Colorectal cancer:
the diagnosis and management of colorectal cancer

Evidence review

November 2011
Developed for NICE by the National Collaborating Centre for Cancer

2. Investigation, diagnosis and staging

2.1. Diagnostic Interventions

2.1.1. What is the most effective diagnostic intervention(s) for patients with suspected colorectal cancer to establish a diagnosis?

Short Summary

The volume of evidence available was variable across the interventions of interest with a large volume of evidence available investigating CT Colonography but little to no evidence for other interventions of interest.

There were some concerns relating to the applicability of the evidence to the population of interest as there was a degree of inconsistency in the types of patients included in studies.

There was some degree of consistency in the results reported in systematic reviews, though as there was a high degree of overlap in the included studies, this was not surprising.

The quality of evidence available varied according to the intervention with high quality evidence available for CT Colonography and very low quality evidence available for Flexible Sigmoidscoopy plus barium enema. No evidence was available for flexible Sigmoidoscopy plus colonoscopy.

From two systematic reviews and meta-analysis (Chaparro et al, 2009 and Halligan et al, 2005), per polyp sensitivity of CT colonography was similar and both reviews reported higher sensitivities for larger polyps.

CT Colonography versus Conventional Colonoscopy

Chaparro (2009) reported sensitivities which ranged from 28-100% for all polyps >6mm with an overall pooled sensitivity of 66% (95% CI 64-68%).

From one systematic review (Chaparro et al, 2009), the per patient sensitivity for CT colonography ranged from 24%-100% across the individual studies and the overall pooled sensitivity was 69% (95% CI, 66%-72%).

Mulhall et al, 2005 reported that per patient sensitivity ranged from 21% to 96% with an overall pooled sensitivity of 70% (95% CI, 53% to 87%).

The overall specificity of CT colonography was reported to be 83% (95% CI, 81%-84%, I^2=89%) (Chaparro et al, 2009).

Sensitivity and specificity of CT Colonography were reported to increase with larger polyp size in all three systematic reviews (Chaparro et al, 2009; Halligan et al, 2005 & Mulhall et al, 2005).

Flexible Sigmoidoscopy plus air contrast barium enema versus conventional colonoscopy

Two randomised trials (Rex et al, 1990 & Rex et al, 1995) provide poor quality evidence comparing flexible sigmoidoscopy plus air contrast barium enema (ACBE) with conventional colonoscopy.

Rex et al (1990) reported that air contrast barium enema was sufficient to rule out major pathology in 157 patients and reasons for unsuccessful ACBE included; inability to distend or fill the right colon adequately in 5 patients, repeatedly inadequate preparation to rule out mass lesions (n=4) and inability to retain the enema adequately in 2 patients.

ACBE findings were normal in 48/168 patients and abnormalities identified included haemorrhoids (n=1), diverticulosis (n=82), any polyp (n=43), stricture (n=3) and cancer (n=4).

Colonoscopy was successful in 151 patients (insertion to the cecum) and reasons for unsuccessful colonoscopy included; obstructing cancers in 6 patients and technical factors in 7 patients. Colonoscopy findings were normal in 18/162 patients (Rex et al, 1990).

From one randomised trial, there was a significant difference between the arms in relation to the proportion of patient's recommended alternative lower GI procedures (p≤0.0001)

53/168 (32%) patients in the flexible sigmoidoscopy group were referred for subsequent colonoscopy due to inadequate study (n=11), for polypectomy (n=38) and for biopsies on lesions outside the reach of flexible sigmoidoscopy.

13/164 (8%) patients in the colonoscopy arm were referred for ACBE because of difficulty advancing the colonoscope to the cecum (Rex et al, 1990).
In the second trial (Rex et al, 1995) patients undergoing flexible sigmoidoscopy were more likely to require an alternative intervention such as colonoscopy than were patients undergoing colonoscopy to require air contrast barium enema (OR=2.07, 95% CI, 1.47-16.4).

Review Protocol

Population	Intervention	Comparison	Outcomes
Patients with symptoms suspected colorectal cancer	• Flexible sigmoidoscopy + Barium Enema • CT colonography • Flexible sigmoidoscopy + colonoscopy	• Colonoscopy + biopsy	• Sensitivity • Specificity • Risk/Safety?

Following a systematic search of relevant data sources (see appendix 1..), the information specialist created a database of potentially relevant studies. All titles and abstracts were sifted by a single reviewer. Queries about inclusion were clarified by the GDG topic subgroup. The full studies were then obtained and reviewed and relevant studies were included in the final evidence review.

All update searches were sifted by a single reviewer and the list of potentially relevant studies was also checked for irrelevant studies by the GDG subgroup. Only studies which all subgroup members were in agreement were excluded. The remaining studies were obtained and reviewed with relevant studies included in the final evidence review.

For this topic, the GDG felt that there should be high quality evidence available for the comparisons of interest and it was decided to look to that in the first instance. Should this not prove to be the case, then the GDG recommended looking to lower quality evidence.

Several date limits were applied to this topic, with certain interventions of interest available much earlier than others and developments in technology rendering earlier versions of interventions inapplicable to the topic. The date limits set by the GDG for each of the interventions of interest were:
Colonoscopy: 1990 onwards (introduction of videoscopes)
Barium Enema: 1965 onwards
CT colongraphy/pneumocolon/virtual colonoscopy: 1997 onwards (technical software)
Flexi sigmoidoscopy: 1990 onwards (introduction of video scopes)

The GDG felt that other specific factors that should be considered while assessing the evidence included complications, radiation risk and extracolonic/incidental findings.

The GDG wanted to be clear about what they meant by diagnostic intervention. The gold standard for making the diagnosis is a biopsy, which can only be achieved by colonoscopy. Equally if the colonoscope cannot pass the cancer the rest of the colon has not been imaged this should be done and the best investigation, barium enema or CT colonography performed. It may be that radiological investigations can make the diagnosis and allow a decision to operate and the histology is obtained from the pathology specimen.

If possible, await results of SIGGAR study before conducting evidence review.

Exclusion criteria for included evidence:
Individual studies included in a systematic review
Comparisons in studies not relevant to PICO
Population in studies not relevant to PICO
Outcomes not relevant to PICO
Sensitivities and Specificities not reported
Foreign Language studies
Expert Reviews

Quality of the included studies
Systematic review of RCTs (n = 0)
Systematic review of combined study designs (n =3)
Randomized controlled trial (n =2)
Prospective cross sectional study (n = 0)
Case Series Studies (n = 2)
Diagnostic Studies (n= 4)

599
possibly relevant
papers identified

529
papers excluded
based on title &
abstract

| 70 papers obtained for appraisal | ☐ | 59 papers excluded |

☐

| 11 papers included in evidence table |
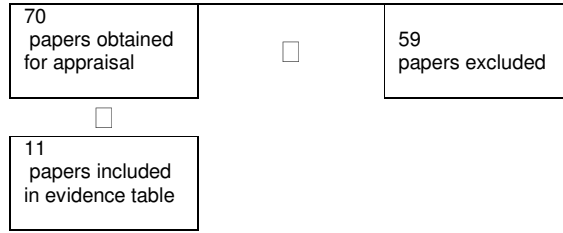
Volume of evidence

The volume of evidence available was variable across the interventions of interest with a large volume of evidence available investigating CT Colonography. The evidence base investigating flexible sigmoidoscopy plus barium enema was less comprehensive, with only 2 studies available and there was no evidence available to assess flexible sigmoidoscopy plus colonoscopy.

Two studies specifically investigated the potential adverse events associated with CT colonography

Applicability

In the main, the available evidence was directly applicable to the PICO in terms of the research question addressed however, there were some concerns that the populations in individual studies were not directly applicable due to the fact that they included asymptomatic patients. This was a particular problem when assessing the systematic reviews as in this situation it is difficult to separate the data from the individual studies included particularly as some studies included mixed populations (symptomatic and asymptomatic).

Consistency

There was a good degree of consistency across the three systematic reviews in relation to the sensitivities and specificities of CT colonography, and all three studies reported higher sensitivities for larger polyps. This degree of consistency is perhaps not surprising given the degree of overlap between the three studies which results in the data used being very similar in all three; with more data available for analysis it could be argued that the results from Chaparro et al (2009) could be considered the most appropriate results on which to base recommendations.

In relation to flexible sigmoidoscopy plus air contrast barium enema, no comment can be made on the consistency of the results as the evidence is drawn from only 2 small randomised trials in which the populations are different.

Evidence Statement

In the diagnosis of colorectal cancer, the gold standard for making the diagnosis is a biopsy, which can only be achieved by colonoscopy and therefore for the purposes of this topic, colonoscopy plus biopsy was considered to be the reference standard.

If the colonoscope cannot pass the cancer the rest of the colon has not been imaged and this should be done using the best alternative investigation, usually barium enema or CT colonography. It may be that radiological investigations can make the diagnosis and allow a decision to operate and the histology is obtained from the pathology specimen.

A large randomised trial to evaluate CT colonography versus colonoscopy or barium enema for diagnosis of colonic cancer in older symptomatic patients (The SIGGAR study) commenced recruitment in March 2004. There was some hope that this study, which is to include an economic evaluation of the interventions of interest, would publish in time to add to the evidence base for this topic, particularly as it is conducted in the UK and so is directly relevant to the population of interest, however this has not been the case and therefore further evidence on this topic is likely to become available in the future which may need consideration.

Quality of Included Studies and Risk of Bias

CT Colonography

The evidence base comparing CT colonography and conventional colonoscopy consists of three systematic reviews (Chaparro et al, 2009, Mulhall et al, 2005 and Halligan et al, 2005). There was a high degree of overlap between the three meta-anlayses in relation to the studies included in each with the more up to date review (Chaparro e al, 2009) including the majority of studies which had been used in the two previous reviews along with a number of studies published since. In total, 85% of studies included in Mulhall, 2005 and 67% of studies included in Halligan, 2005 were included by Chaparro, 2009. Reasons for discrepancies in the included studies might be due to slight differences in research questions in each review or more up to date versions of studies used in the later review, though it is not clear that this is the case.

The evidence base is of generally high quality based on assessment using the QUADAS checklist to evaluate the 47 studies assessed as part of a systematic review (Chaparro et al, 2009). The two remaining systematic reviews did not provide a detailed report of the quality assessment for the included studies though both studies did assess quality using standardised methods. Due to the fact that there was a high degree of overlap in the reviews, the quality assessment provided by Chaparro (2009) was considered an adequate reflection of the quality of evidence from all 3 reviews.

The only area for which the quality of the individual studies was low related to the inadequacy of reporting of uninterpretable results in the majority of studies.

The area of largest uncertainty was whether or not readers of CT colonography and colonoscopy results had access to all relevant clinical information necessary to accurately interpret images as this is not generally reported in studies.
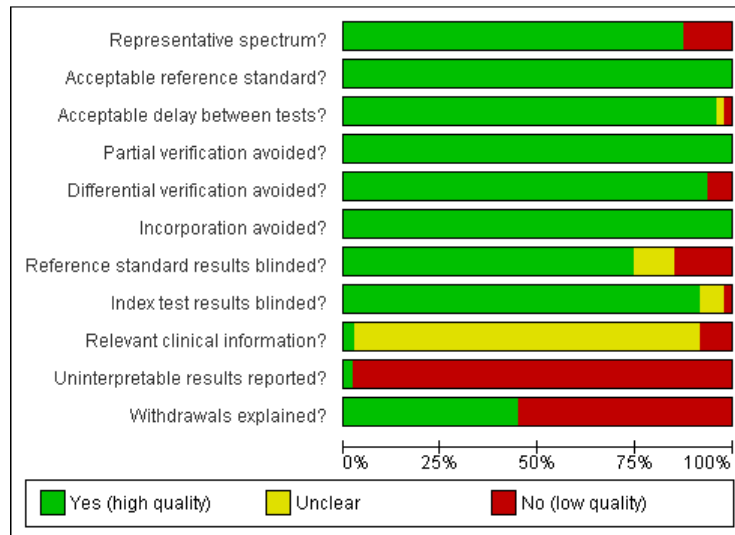
Figure 2.1: Summary of the quality of included studies comparing CT Colonography and Conventional Colonscopy

Diagnostic studies are susceptible to a particular bias known as spectrum bias which describes the effect a change in patient mix may have on the performance of a given test. In the case of the studies used to inform this topic, the majority of the study populations consist of a representative spectrum of the patients that are likely to be referred for diagnostic interventions which would suggest that spectrum bias is not a particular concern for this topic. This does not present the whole picture however as the spectrum of patients referred for a particular intervention may be impacted by local practices and therefore a representative patient population in the UK may not be the same as one in the US and so this should be considered when examining the evidence; for example a patient may be referred for a particular intervention based on the severity of their symptoms. This topic also related to the effectiveness of interventions in symptomatic patients and the studies included in each systematic review included a variety of patients including both symptomatic and asymptomatic patients.

Two retrospective case series' examined the potential adverse effects of CT colonography (Burling et al, 2006 and Sosna et al, 2006).

A small number of individual studies examining the effectiveness of CT colonography which were not included in any of the systematic reviews were identified (Hoppe et al, 2004; Laghi et al, 2002; Pescatore et al, 2000; Reuterskiold et al, 2006). No reason for why these studies were excluded from the most recent systematic review could be found and so an evidence table for each study has been produced and included, though the results reported are not discussed in this summary.

Flexible Sigmoidoscopy plus Air Contrast Barium Enema
Two randomised trials compared flexible sigmoidoscopy plus barium enema with conventional colonoscopy (Rex et al, 1995 and Rex et al, 1990). From figure 2 it can be seen that the quality of the two randomised trials is very low with a high risk of bias in both studies.
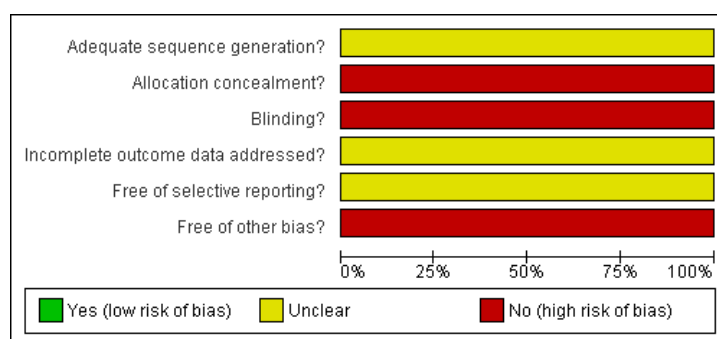
Figure 2.2: Summary of quality of studies comparing flexible sigmoidoscopy plus air contrast barium enema with conventional colonoscopy

CT Colonography

Per Polyp Sensitivity
From two systematic reviews and meta-analysis (Chaparro et al, 2009 and Halligan et al, 2005), per polyp sensitivity of CT colonography was similar and both reviews reported higher sensitivities for larger polyps. Chaparro (2009) reported sensitivities which ranged from 28-100% for all polyps >6mm with an overall pooled sensitivity was 66% (95% CI 64-68%). Halligan et al (2005) did not report an overall pooled sensitivity.

Sensitivity was reported to increase with polyp size with a pooled sensitivity of 59% (95% CI 56%-61%, range 16%-90%) for polyps 6-9mm and a pooled sensitivity of 76% (95% CI 73-79%, range 50-100%) for polyps >9mm.
There was significant heterogeneity between studies in all three comparison groups with the I^2 value >50% for all three groups (Chaparro et al, 2009).
Halligan et al (2005) similarly reported the the performance of CT colonography was affected by polyp size; average sensitivity for large polyps was 77% (95% CI, 70%-83%) and 70% (95% CI 63%-76%) for medium polyps. Due to heterogeneity the data for small polyps were not pooled in this study.

Different thresholds for polyp size were used in both systematic reviews maybe which impact on the outcomes and so ought to be considered when interpreting the results.

Mulhall et al (2005) did not report per polyp sensitivities as it was considered that the per patient outcomes were more important to know for the accuracy of CT Colonography in diagnosis and screening.

Per Patient Sensitivity and Specificity
From one systematic review (Chaparro et al, 2009), the per patient sensitivity for CT colonography ranged from 24%-100% across the individual studies and the overall pooled sensitivity was 69% (95% CI, 66%-72%).
Mulhall et al, 2005 reported that per patient sensitivity ranged from 21% to 96% with an overall pooled sensitivity of 70% (95% CI, 53% to 87%).

Sensitivity again increased with increasing polyp size with a pooled sensitivity of 60% (95% CI 56%-65%) for patients with polyps 6-9mm (range 20%-91%) and 83% (95% CI, 70%-85%) for patients with polyps >9mm (range 46%-100%) (Chaparro et al, 2009).
Again there was significant between studies heterogeneity for each of the analyses groups.
Halligan et al (2005) reported an average per patient sensitivity of 93% (95% CI, 73%-98%) for large polyps (≥1cm), 86% (95% CI 75%-93%) for medium polyps (6-9mm) and did not report an average sensitivity for small polyps (<6mm) due to the heterogeneity of the data across studies.

Sensitivity progressively increased as polyp size increased with sensitivity of 48% (95% CI, 25%-70%, range, 14%-86%) for the detection of polyps <6mm, 70% (95% CI, 55%-84%, range, 30%-95%) for polyps 6-9mm and 85% (95% CI 79%-91%, range, 48%-100%) for polyps >9mm.
Significant statistical heterogeneity was observed for each of these analyses (p<0.001 for each group) with most of the variance attributed to between-study heterogeneity.

The overall specificity of CT colonography was reported to be 83% (95% CI, 81%-84%, I^2=89%) with specificity improving with increasing polyp size; specificity was 90% (95% CI, 89%-91%, I^2=21%) for patients

with polyps 6-9mm in size and increased to 92% (95% CI, 92%-93%, I^2=62%) for polyps >9mm (Chaparro et al, 2009).
Halligan et al (2005) also reported improved specificity with larger polyp size with an average sensitivity of 70% (95% CI, 63%-76%) for medium polyps (6-9mm) increasing to 77% (95% CI, 70%-83%) for large polyps (≥1cm).
Mulhall et al (2005) reported a consistent per patient specificity across polyp sizes though there was significant heterogeneity; overall specificity was reported as being 86% (95% CI, 84%-88%, I^2=92.6%, p=0.001).
When examining specificity according to polyp size no heterogeneity was observed within the groups (though the I^2 statistic was still around 50% for all groups) and specificity improved as polyp size increased; for polyps <6mm pooled specificity was 91% (95% CI, 89%-95%, I^2=47.1%, p=0.15), for polyps 6-9mm in size, pooled specificity was 93% (95% CI, 91%-95%, I^2=50%, p=0.07) and for polyps >9mm, pooled specificity was 97% (95% CI, 96%-97%, I^2=41.8%, p>0.2).

Subgroup Analysis
Two systematic reviews (Chaparro et al, 2009 and Mulhall et al, 2005) examined a number of variables in an effort to explain some of the heterogeneity, the results of which are outlined in table 1. Variables investigated included colonic preparation, use of contrast, use of faecal tagging, collimation width, scanner type, width of reconstruction interval, imaging (2D with 3D confirmation or 3D only), high risk versus average risk patients, study quality, year of publication and type of scanner.

Subgroup	Mean Sensitivity (95% CI)	Comparison	Mean Sensitivity (95% CI)
Chaparro et al (2009)			
Phospho-soda for bowel preparation	83.3% (95% CI, 79%-87%), I^2=73%	No Phospho-soda	62% (95% CI, 58%-66%), I^2=93%
With fecal tagging	88% (95% CI 84%-91%), I^2<50%	Without fecal tagging	59% (95% CI 56%-63%), I^2=91%
Collimation thinner than 5mm	72% (95% CI 68%-76%), I^2=89%	Collimation ≥5mm	65% (95% CI, 68%-76%), I^2=95%
Reconstruction thinner than 3mm	64% (95% CI, 60%-68%), I^2=90%)	Reconstruction ≥3mm	58% (95% CI, 49%-67%), I^2=87%
2-D imaging with 3-D confirmation	64% (95% CI, 60%-67%), I^2=90%	3-D imaging	83% (95% CI, 78%-87%), I^2=84%
Radiation dose <100mA	63% (95% CI, 60%-67%), I^2=95%	Radiation dose >100mA	79% (95% CI, 75%-83%), I^2=83%
Patients at high risk of CRC or polyps	65% (95% CI, 61%-68%), I^2=94%	Patients at average risk	82% (95% CI, 77&-87%), I^2=83%
Other variables	No differences were found in other variables analysed, including study quality		
Mulhall et al (2005)			
Multidetector Scanner	95% (95% CI, 92%-99%), I^2=40%, p>0.2	Single Detector Scanner	82% (95% CI, 76%-92%), I^2=87.1%, p<0.001
2D imaging with 3-D confirmation	81.9% (95% CI, 71%-91%), I^2=87.5%, p=0.02	3-D imaging	91% (95% CI, 83%-99%), I^2=53.1%, p=0.06
Collimation width	Studies using thinner slices for collimation appeared to have better sensitivity and meta-regression appeared to suggest that for every 1mm increase in collomation width there was a decrease in sensitivity of 4.9% (95% CI 0.8%-7.1%)		
Fly through technology	Studies using fly through technology reported a pooled sensitivity of 99% (95% CI, 95%-100%, I^2=47.6%, p=0.17).		
Other Variables	For the other subgroups investigated (year of publication, type of scanner, thickness of reconstruction interval, use of contrast and patient characteristics) no source of possible heterogeneity was found.		

Table 2.1: Subgroup analysis for possible variables contributing to heterogeneity

Likelihood Ratios
Chaparro et al (2009) reported overall positive likelihood ratio was 2.9 (1.8-4) and the overall negative likelihood ratio was 0.38 (0.27-0.53).
For polyps between 6-9mm, the positive likelihood ratio was 3.8 (2.5-5.7) and the negative likelihood ratio was 0.4 (0.27-0.59).
For polyps >9mm, the positive likelihood ratio was 12.3 (7.7-19.4) and the negative likelihood ratio was 0.19 (0.12-0.3).
Likelihood ratios were not reported in either of the other systematic reviews.

Risks and Safety of CT Colonography
Two retrospective case series studies reported on the potential adverse events related to CT colonography (Burling et al (2006) & Sosna et al (2006).

Burling et al (2006) reported that 17,067 CT Colonographic examinations had been performed across 50 centres; which had performed a total of 100 examinations or more.

No deaths were reported and 13 patients (0.08%; 1 in 1313 patients) had experienced potentially serious adverse events believed to be related to CT colonography, 9 of which were luminal perforations giving a perforation rate of 0.05% (1 in 1896 patients). The symptomatic perforation rate was 0.03% (1 in 3413 patients).

8/9 patients with perforation were treated conservatively either as inpatients or outpatients and to the knowledge of the respondents, all patients were alive and well at the time of the survey.

At 29 centres (58%) an inflated balloon catheter was never used, at 7 centres (14%) one was used occasionally and at 14 centres (28%) one was always used.
Overall, 9378 CT Colonographic examinations were performed using an inflated balloon in the rectum and among these there were 6 perforations; 7689 CT colonographic examinations were performed without an inflated balloon with 2 perforations.
At 6 centres (12%) an automated insufflation device was used with 2 perforations associated.
There was no significant difference in the proportion of perforations associated with and without rectal balloon inflation (p=0.3)

Sosna et al (2006) reported 7 colonic perforations at 5 centres for a perforation risk rate of 0.059% (95% CI 0.02%-0.1%), translating to an event occurrence of 1/1695 studies (95% CI 1/974 - 971/6537).

6/7 cases of perforations were in symptomatic patients at high risk of colorectal neoplasia and only 1 occurred in an asymptomatic patient with average risk who underwent screening.
4 cases of perforation were in patients undergoing CT Colonography as completion studies following incomplete conventional colonoscopy.

There were 5 cases of perforation in the sigmoid colon and 2 in the rectum.

6 cases of perforation occurred in patients in whom a rectal tube was inserted and in 5/6 cases the balloon was inflated. In the remaining patient a 16-F Foley catheter was inserted and 5ml of saline was inflated into the balloon.

4/7 patients with perforation required surgical treatment with a one-stage procedure performed in 3 patients and a two-stage procedure performed in 1.
The incidence of surgical intervention was 1/2968 patients (95% CI 1.5 of 10,000 – 14.7 of 10,000).
The remaining 3 patients had multiple comorbidities and were at high risk for surgery and so received conservative treatment without any complications.
No deaths were recorded.

The physicians performing the air insufflation in 2 cases of perforation did not have any experience in the performance of CT colonography at the time of examination with neither having performed unsupervised air insufflation previously nor read images from CT colonographic studies on a regular basis.

Flexible Sigmoidoscopy plus air contrast barium enema versus conventional colonoscopy
Two randomised trials (Rex et al, 1990 & Rex et al, 1995) provide poor quality evidence comparing flexible sigmoidoscopy plus air contrast barium enema (ACBE) with conventional colonoscopy.

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ACBE findings were normal in 48/168 patients and abnormalities identified included haemorrhoids (n=1), diverticulosis (n=82), any polyp (n=43), stricture (n=3) and cancer (n=4).

Colonoscopy was successful in 151 patients (insertion to the cecum) and reasons for unsuccessful colonoscopy included; obstructing cancers in 6 patients and technical factors in 7 patients.
Colonoscopy findings were normal in 18/162 patients (Rex et al, 1990).

In the flexible sigmoidoscopy plus ACBE group, 64 patients had a total of 101 polyps ranging in size from ≤4mm (n=45) to ≥9mm (n=27) and included 4 patients with 7 polyps who also had colorectal cancer. Patients

with polyps ≥5mm were referred for colonoscopy where the polyps in 4/38 patients could not be found; these patients were considered to have false positive ACBE results.

28 patients, including the 4 with cancer, were referred for polypectomy and all had at least 1 adenoma.

33 patients in the flexible sigmoidoscopy plus ACBE group had either cancer or adenoma documented by initial testing or subsequent colonoscopy.

Colonoscopy detected a further 25 polyps not visualised by initial flexible sigmoidoscopy + ACBE; 18 were ≤4mm, 5 were 5-8mm and 2 were ≥9mm.

9 patients in the flexible sigmoidoscopy plus ACBE group had cancer: 3 had Dukes B tumours with serosal involvement, 1 had a Dukes C tumour and 4 had Dukes D tumours. One patient in the group has a negative ACBE and four weeks later underwent colonoscopy which showed a cecal cancer which was resected.

One patient with transverse colon cancer diagnosed on ACBE refused surgery.

In the colonoscopy group, 86 patients had a total of 194 polyps ranging in size from ≤4mm (n=108) to ≥9mm (n=29). 9 patients with a total of 16 polyps also had colorectal cancer. In total, 76/146 patients in the colonoscopy group had colonic adenoma or carcinoma.

13 patients in the colonoscopy group had cancer, 2 patients had Dukes A tumours, 8 had Dukes B, 2 had Dukes D and 1 had transverse colon cancer and refused surgery.

When examining the diagnostic yields with respect to age there was an indication of diversion in polyp and cancer yield for patients aged ≥55 years. There was no significant difference between the two groups within each age group in relation to demographic data, patient history or laboratory variables. The superior detection of polyps in the colonoscopy group was accounted for by the finding of polyps <9mm in patients ≥55years.

Overall, the yield of cancers in patients <55 years was very low at 1% compared with 8% in those aged ≥55years.

Flexible sigmoidoscopy + ACBE found more patients <55 years with polyps ≥9mm than did colonoscopy (p=0.021) (Rex et al, 1990).

Requirement for Alternative Procedures
From one randomised trial, there was a significant difference between the arms in relation to the proportion of patient's recommended alternative lower GI procedures (p≤0.0001)

53/168 (32%) patients in the flexible sigmoidoscopy group were referred for subsequent colonoscopy due to inadequate study (n=11), for polypectomy (n=38) and for biopsies on lesions outside the reach of flexible sigmoidoscopy.

13/164 (8%) patients in the colonoscopy arm were referred for ACBE because of difficulty advancing the colonoscope to the cecum (Rex et al, 1990).

While in the second trial (Rex et al, 1995) patients undergoing flexible sigmoidoscopy were more likely to require an alternative intervention such as colonoscopy than were patients undergoing colonoscopy to require air contrast barium enema (OR=2.07, 95% CI, 1.47-16.4)..

Complications and Risks
No significant difference between the two groups in relation to procedural complications. Phlebitis occurred in 7 patients in the colonoscopy group versus 4 patients in the flexible sigmoidoscopy +ACBE group, this difference was not statistically significant, however the authors state that the study did not have sufficient power to detect a true difference in the incidence of phlebitis of this magnitude (Rex et al, 1990).

No deaths, transfusions, hospitalisations, or prolonged hospital stays were reported in either patient group from either study (Rex et al, 1995 & Rex et al, 1990).

References

Burling D, Halligan S, Slater A, Noakes M and Taylor S (2006) Potentially Serious Adverse Events at CT Colonography in Symptomatic Patients: National Survey of the United Kingdom *Radiology* 239;2:464-471

Chaparro M, Gisbert J, del Campo L, Cantero J, and Mate J (2009) Accuracy of Computed Tomographic Colonography for the Detection of Polyps and Colorectal Tumours: A systematic review and meta-analysis *Digestion* 80:1-17

Halligan S, Altman D, Taylor S, Mallett S, Deeks J, Bartram C, and Atkin W (2005) CT Colonography in the Detection of Colorectal Polyps and Cancer: Systematic Review, Meta-analysis and Proposed Minimum Data Set for Study Level Reporting

Hoppe H, Netzer P, Spreng A, Quattropani C et al (2004) Prospective comparison of contrast enhanced CT colonography for detection of colorectal neoplasms in a single institutional study using second look colonoscopy with discrepant results *American Journal of Gastroenterology* 99;1924-1935

Laghi A, Iannaccone R, Carbone I, Catalano C et al (2002) Computed Tomographic Colonography (Virtual Colonoscopy): Blinded Prospective Comparison with Conventional Colonoscopy for the Detection of Colorectal Neoplasia *Endoscopy* 34;441-446

Mulhall B, Veerappan G & Jackson J (2005) Meta-analysis: Computed Tomographic Colonography *Ann Intern Med* 142;635-650

Pescatore P, Glucker T, Delarive J et al (2000) Diagnostic accuracy and interobserver agreement of CT colonography (virtual colonoscopy) *Gut* 47:126-130

Reuterskiold MH, Lasson A, Svensson E et al (2006) Diagnostic performance of computed tomography colonography in symptomatic patients and in patients with increased risk for colorectal disease *Acta Radiologica* 9;888-898

Rex D, Mark D, Clarke B et al (1995) Flexible sigmoidoscopy plus air contrast barium enema versus colonoscopy for evaluation of symptomatic patients without evidence of bleeding *Gastrointestinal Endoscopy* 42;2:132-138

Rex D, Weddle R, Lehman G et al (1990) Flexible Sigmoidoscopy plus Air Contrast Barium Enema versus Colonoscopy for suspected lower gastrointestinal bleeding *Gastroenterology* 98;855-861

Sosna J, Blachar A, Amitai M, Barmeir E, Peled N, Nahum-Goldberg S, Bar-Ziv J (2006) Colonic Perforation at CT Colonography: Assessment of Risk in a Multicentre Large Cohort *Radiology* 239;2:457-463

Evidence Tables

Citation: Burling D, Halligan S, Slater A, Noakes M and Taylor S (2006) Potentially Serious Adverse Events at CT Colonography in Symptomatic Patients: National Survey of the United Kingdom *Radiology* 239;2:464-471	
Design: Retrospective Clinical Audit	
Country: UK	
Setting:	
Aim: To determine the incidence of potentially serious adverse events associated with computed tomographic colonography performed in patients with symptoms of rectal cancer	
Inclusion criteria Any radiology department offering CT Colonography	
Exclusion criteria	
Sample Size N/A	
Randomisation Method N/A	
Population N=216 UK National Health Service hospitals offering radiology service for adults	
Study Duration Survey carried out in February 2005	
Interventions CT Colonography	
Outcomes Adverse Events	

Results

Responses were received from 138/216 (64%) of departments, of which 50 (36%) provided CT colonography as part of everyday clinical practice.

All patients within the survey underwent CT colonography for symptoms that might have been attributable to colorectal cancer including change in bowel habits, rectal bleeding and weight loss.
No patients were undergoing screening.

Ethical requirements stipulated that no details of patients' age or sex be revealed during the study.

The lead gastrointestinal radiologist in each of the 50 centres where CT colonography was performed was contacted and was asked a series of six questions, read from a study sheet. The questions were as follows:

Approximately how many CT colonographic studies does your department perform on average?	More than one per day, one per day, one per week or one per month
Approximately how many CT colonographic studies has your department performed in total?	Total given
How frequently does your department use inflated rectal balloon catheters for CT colonography?	Never, occasionally (approx. %) of always
Does your department use an automated colonic insufflation device?	Yes/No
To the best of your knowledge, has bowel perforation related to CT colonography occurred?	Yes/No (please give number)
To the best of your knowledge, has there been any other serious adverse event associated with CT colonography? For example, have there been reactions to intravenous contrast or spasmolytic agents?	Yes/No (please give number)

17,067 CT Colonographic examinations had been performed across 50 centres; mean number per centre = 359, range 10-3000.
At 36 centres (72%), a total of 100 examinations or more had been performed.

At the time of the study, more than one examination per day was performed at 5 centres (10%); at 21 centres (42%) one examination per day was performed, at 7 centres (14%) one examination per month was performed and at 3 (6%) CT colonography was no longer performed.

No deaths were reported and 13 patients (0.08%; 1 in 1313 patients) had experienced potentially serious adverse events believed to be related to CT colonography, 9 of which were luminal perforations giving a perforation rate of 0.05% (1 in 1896 patients).
8/9 perforations were discovered during or after the CT procedure; 4 patients were entirely asymptomatic with extraluminal gas discovered incidentally by the reporting radiologist between 6 hours and 4 days after the procedure.

The symptomatic perforation rate was 0.03% (1 in 3413 patients).

8/9 patients with perforation were treated conservatively either as inpatients or outpatients and to the knowledge of the respondents, all patients were alive and well at the time of the survey.

At 29 centres (58%) an inflated balloon catheter was never used, at 7 centres (14%) one was used occasionally (on average, for 14% of the examinations when anal incontinence was encountered; range 1-50%) and at 14 centres (28%) one was always used.
Overall, 9378 CT Colonographic examinations were performed using an inflated balloon in the rectum and among these there were 6 perforations. Further, 7689 CT colonographic examinations were performed without an inflated balloon and among these there were 2 perforations.
At 6 centres (12%) an automated insufflation device was used with 2 perforations associated.
There was no significant difference in the proportion of perforations associated with and without rectal balloon inflation (p=0.3)

At 3/50 centres (6%), contributing 4350 patients to the total, investigators had published peer reviewed indexed articles relating to CT colonography and 2 perforations occurred at one of these centres. No significant difference was observed in the proportion of perforations originating from research and non-research centres (p=0.82).

Citation: Chaparro M, Gisbert J, del Campo L, Cantero J, and Mate J (2009) Accuracy of Computed Tomographic Colonography for the Detection of Polyps and Colorectal Tumours: A systematic review and meta-analysis *Digestion* 80:1-17

Design: Systematic Review and Meta-analysis **Country**: Various **Setting**: **Aim**: To perform a meta-analysis of the diagnostic accuracy of CT-Colonography compared with colonoscopy for the detection of polyps and colorectal tumours.

Inclusion criteria Prospective blinded studies in which the results of CTC were interpreted independently of colonoscopy findings or during surgery. Enrolment of adult patients who were to undergo CTC after a full bowel preparation, followed by complete colonoscopy or surgery and use of at least a single detector scanner with colon insufflation by air or carbon dioxide. If there are multiple studies originating from the same institution, the dates for patient inclusion were evaluated to ensure that there were no patient overlaps.

Exclusion criteria Studies with elevated computer aided detection systems Technical Studies Cost utility studies Studies not reporting on CTC Studies examining patient comfort No appropriate gold standard Not a diagnostic study Reviews Case Reports Studies of preparation Studies of Adverse Events Clinical Practice Guidelines Extracolonic Findings Phantom Studies Not in Humans

Sample Size N/A

Randomisation Method N/A

Population The total population included in the review was 10,546 from 47 studies.

Study Duration N/A

Interventions CT Colonography versus an appropriate Gold Standard

Outcomes Sensitivity Specificity (taken directly from the individual study as reported or calculated through analysis of true positives, true negatives, false positives and false negatives on a per patient and per polyp basis). Positive and negative likelihood ratios and their 95% confidence intervals were calculated for each study. In calculating the likelihood ratios, if any of the cells of a 2x2 table contained a 0 value, 0.5 was added to all the cells. Heterogeneity of all indexes was calculated through examination of forest plots, the X^2 test for homogeneity and through the calculation of the I^2 statistic where a value of >50% was considered substantial heterogeneity.

Results

1,798 articles were identified during initial searches of which 1,751 were excluded for reasons outline above.

From 47 studies, the total patient population was 10,546 with an average of 224 participants per study.

- 16 studies used single detector scanners, 27 used multidetector scanners and 4 studies used both.
- In 44 studies, colonoscopy was the gold standard while in 3 studies surgery was the gold standard.
- 24 studies used 2-D imaging with 3-D imaging on selected slices, 20 studies used both 2-D and 3-D imaging and 2 studies used flythrough imaging with 2-D reconstruction.
- Sodium phosphate was used for bowel preparation in 10 studies and polyethylene glycol was used in 21 studies
- Faecal tagging was used in 6 studies and in 12 studies intravenous contrast was used
- Average collimation was 3.7mm and average reconstruction interval was 2mm
- 41 studies were carried out in high risk populations with the remaining 6 carried out in an average risk population

Quality of included studies

The quality of studies included in the review was assessed using the QUADAS (Quality Assessment of Diagnostic Accuracy Studies) tool which is based on a 14- item questionnaire. The QUADAS tool does not incorporate a global quality score for a number of reasons including the fact that a quality score ignores the importance of individual items and the direction of potential biases associated with these items may vary according to the context in which they are applied.

Sensitivity of CT Colonography

Across the studies, per polyp sensitivity ranged from 28-100% for polyps >6mm. Overall pooled sensitivity was 66% (95% CI 64-68%).
Sensitivity increased with polyp size with a pooled sensitivity of 59% (95% CI 56%-61%, range 16%-90%) for polyps 6-9mm and a pooled sensitivity of 76% (95% CI 73-79%, range 50-100%) for polyps >9mm.
There was significant heterogeneity between studies in all three comparison groups with the I^2 value >50% for all three groups.

The per patient sensitivity for CT colonography ranged from 24%-100% across the individual studies and the overall pooled sensitivity was 69% (95% CI, 66%-72%).
Sensitivity again increased with increasing polyp size with a pooled sensitivity of 60% (95% CI 56%-65%) for patients with polyps 6-9mm (range 20%-91%) and 83% (95% CI, 70%-85%) for patients with polyps >9mm (range 46%-100%).
Again there was significant between studies heterogeneity for each of the analyses groups.

Subgroup	Mean Sensitivity (95% CI)	Comparison	Mean Sensitivity (95% CI)
Phospho-soda for bowel preparation	83.3% (95% CI, 79%-87%), I^2=73%	No Phospho-soda	62% (95% CI, 58%-66%), I^2=93%
With fecal tagging	88% (95% CI 84%-91%), I^2<50%	Without fecal tagging	59% (95% CI 56%-63%), I^2=91%
Collimation thinner than 5mm	72% (95% CI 68%-76%), I^2=89%	Collimation ≥5mm	65% (95% CI, 68%-76%), I^2=95%
Reconstruction thinner than 3mm	64% (95% CI, 60%-68%), I^2=90%)	Reconstruction ≥3mm	58% (95% CI, 49%-67%), I^2=87%
2-D imaging with 3-D confirmation	64% (95% CI, 60%-67%), I^2=90%	3-D imaging	83% (95% CI, 78%-87%), I^2=84%
Radiation dose <100mA	63% (95% CI, 60%-67%), I^2=95%	Radiation dose >100mA	79% (95% CI, 75%-83%), I^2=83%
Patients at high risk of CRC or polyps	65% (95% CI, 61%-68%), I^2=94%	Patients at average risk	82% (95% CI, 77&-87%), I^2=83%
No differences were found in other variables analysed, including study quality			

Results of the sensitivity analyses by subgroup

Specificity of CT Colonography

The overall specificity of CT colonography was 83% (95% CI, 81%-84%, I^2=89%).
Specificity improved with increasing polyp size; specificity was 90% (95% CI, 89%-91%, I^2=21%) for patients with polyps 6-9mm in size and increased to 92% (95% CI, 92%-93%, I^2=62%) for polyps >9mm.

Likelihood Ratios

Overall positive likelihood ratio was 2.9 (1.8-4) and the overall negative likelihood ratio was 0.38 (0.27-0.53).

For polyps between 6-9mm, the positive likelihood ratio was 3.8 (2.5-5.7) and the negative likelihood ratio was 0.4 (0.27-0.59).

For polyps >9mm, the positive likelihood ratio was 12.3 (7.7-19.4) and the negative likelihood ratio was 0.19 (0.12-0.3).

General comments

Not all the studies included in this review are relevant to the current topic as it included studies which are looking at diagnostic accuracy in asymptomatic patients which is not a relevant population group as it relates more to screening.

As the systematic review included the QUADAS assessment and the 2x2 tables both by per-patient and per-polyp analysis where appropriate for all the included studies, the data for the relevant studies was extracted.

Meta-analyses were performed in which the sensitivities and specificities and likelihood ratios of studies in the corresponding pooled indexes were combined using a random effects model.

Subgroup	Categories
Polyp size	6-9mm or >9mm
Colonic Preparation	
Use of Faecal Tagging	Yes or No
Collimation width and reconstruction interval	
Type of scanner	Single detector, multi detector or mixed
Imaging technique	2-D imaging with 3-D confirmation when a lesion was observed or always 3-D imaging
Radiation dose	
Risk of colorectal cancer	

Subgroup analysis comparisons

Citation: Halligan S, Altman D, Taylor S, Mallett S, Deeks J, Bartram C, and Atkin W (2005) CT Colonography in the Detection of Colorectal Polyps and Cancer: Systematic Review, Meta-analysis and Proposed Minimum Data Set for Study Level Reporting
Design: Systematic Review and Meta-analysis **Country**: **Setting:** **Aim**: To assess methodological quality of available data in published reports of CT colonography
Inclusion criteria Studies which focused on the detection of polyps and if the key methods for CT colonography were based on the consensus document presented at the fourth international symposium on virtual colonoscopy (i.e. full bowel preparation should be administered, prone and supine images should be acquired and helical scanners should be used). Inclusion of studies was restricted to full reports Software used for interpretation of CT colonography findings was to be commercially available and allow 2-D interpretation with luminal 3-D rendering for problem solving. Although a primary 3-D interpretation was equally acceptable.
Exclusion criteria Studies using computer aided diagnostic systems Any studies with fewer than 30 patients (in an attempt to diminish the effect of incorporating any learning curve for CT colonography). Studies in which the prevalence of abnormality could be guessed to be excessively high by CT observers because *a priori* patient selection criteria were used. Studies in which patients underwent CT as a result of incomplete colonoscopy due to obstructing tumour unless they formed less than 50% of the patient population group or an identifiable subset that could be excluded during data extraction. Studies without details of polyps and verification with a reference test. Studies with artificially inserted polyps, digital or otherwise Studies in which intravenous iodinated contrast material was routinely administered to patients
Sample Size N/A
Randomisation Method N/A
Population
Study Duration Searches carried out from January 1994 (the point at which CT Colonography was first described) to December 2003.
Interventions CT Colonography with finding to be verified with a within subject reference test. Conventional endoscopy was the standard reference test used, though studies using surgical findings were considered acceptable as an alternative.
Outcomes Per patient detection of colorectal polyps Per polyp detection of colorectal polyps Per patient sensitivity and specificity for different lesion sizes Per polyp sensitivity
Results 1398 citations were identified with 65 considered for inclusion after search criteria were applied. 41/65 were excluded for reasons such as; • Dual positioning not used • Fewer than 30 patients • Intravenous contrast material routinely used • Overlap with other studies • No results detailing neoplasia • Inadequate reference standard

- Bi blind, disease prevalence too high
- Reduced or no bowel preparation
- Custom software, digital polyp library

A total of 24 studies were included in the review for a total of 4181 patients with a prevalence of abnormality ranging from 15% to 72%. Studies were assessed for quality and potential bias according to the Standards for Reporting of Diagnostic Accuracy and Quality Assessment of Studies of Diagnostic Accuracy
A total of 5 studies did not report on small polyps (<6mm)
23/24 studies included symptomatic or a subset of asymptomatic patients with a prior history of colorectal neoplasia, were under surveillance, or had recently had positive findings for a previous screening test.

Studies used between 1 and 4 observers per patient with findings for individual observers were presented in 58% (n=14) of studies and only after consensus in 42% (n=10).
5 studies investigated possible learning effects.
6 studies performed the reference test on the same day in all but 6 patients (from 2 studies).
6 studies used segmental unblinding to modify reference colonoscopy.

CT technique could be replicated from the details provided in all articles while details of reference colonoscopy were insufficiently described in 11 studies.
CT technical failures were reported in 17 studies and 4 more studies explicitly stated that there were no technical failures; the remaining 3 studies provided no details.

11 studies reported on incomplete colonoscopy, 6 stated that colonoscopy was complete in all patients and 7 studies did not provide details.

18 studies measured polyps during colonoscopy and described the method used, 2 studies described measurement but not the method used and 4 studies did not mention colonoscopic measurement.
The recording of lesion location was not described in 6 studies.

Fully populated 2x2 contingency tables for per patient data for any polyp size category could be extracted from 12 studies and data for a further 5 studies were obtained after contacting the authors.
1x2 contingency table for per polyp data for any polyp size category was extracted from all studies, though in one study it was reported for adenomas only.

Per Patient Analysis
Three polyp size categories were defined small (<6mm), medium (6-9mm) and large (≥1cm) and forest plots of sensitivity, specificity and ROC curves of sensitivity versus 1 minus specificity were produced for each category. Summary ROC curves were calculated for the small and medium polyp categories, however considerable heterogeneity between studies meant a summary ROC curve could not be calculated for the category of large polyps.

For large polyps, meta analysis was based on data from 2610 patients from 7 studies and the majority of studies had high sensitivity and all studies had excellent specificity. At least one large polyp was identified in 206 patients.
For medium polyps, meta-analysis was based on data from 1834 patients from 7 studies; 477 of whom were identified as having at least 1 medium polyp.
For small polyps, studies were heterogenous in sensitivity (range: 45%-97%), specificity (range: 26%-97%) and overall performance and so meta-analysis was not performed. From 12 studies with a total of 1361 patients, 650 patients were identified as having at least one small polyp. According to the authors, the variation in the mix of polyp sizes across the studies, in particular, the proportion of patients with only small polyps

Category	Average Sensitivity	95% CI	Range	Average Specificity	95% CI	Range
Large Polyps (≥1cm)	93%	73%-98%	64%-100%	97%	95%-99%	95%-100%
Medium Polyps (6-9mm)	86%	75%-93%	79%-100%	86%	76%-93%	55%-100%

Average Sensitivities and Specificities of the operating point for large and medium polyps (operating point is the point on the summary ROC curve representing the sensitivity and specificity results at the average threshold, together with 95% CI's).

Incorporation bias, which potentially occurs when information from the test being reviewed is included in the reference standard by using a modified reference standard, could have resulted in the over estimation of sensitivity and specificity. Exploratory analysis, comparing studies with and without a modified reference standard and

comparing individual observer agreement with consensus agreement, was attempted however there were too few studies to allow meaningful analysis.

Per Polyp Analysis
The performance of CT deteriorates for smaller polyps with an average sensitivity of 77% (95% CI 70%-83%) for large polyps down to 70% (95% CI 63%-76%) for medium polyps. Data for small polyps was not pooled due to the large amount of heterogeneity.

Cancer Detection
144/150 tumours were detected on CT but no meta-analysis could be performed as the numbers of established cancers per individual studies was too small.
Treating the data as if it were from a single study resulted in sensitivity (detection rate) of 96% (91%-99%).

General comments
Although there were some patients included in this study which were not relevant to the PICO, they were from a single study (Pickhardt et al) however this also represented the largest study in the meta-analysis with 1233 patients and was one of the studies which was included in the per patient meta-analysis and therefore the results of the meta-analysis cannot be considered to be directly relevant to the PICO.

References of Included Studies

Pickhardt P, Choi J, Hwang I et al (2003) Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults *New England Journal of Medicine* 349;2191-2200

Iannaccone R, Laghi A, Catalono C et al (2003) Detection of colorectal lesions: lower dose multi-detector row helical CT colonography compared with conventional colonoscopy *Radiology* 229;775-781

Taylor, S, Halligan S, Vance M et al (2003). Use of multidetector-row CT colonography for detection of colorectal neoplasia in patients referred via the Department of Health "2-week-wait" initiative. *Clinical Radiology* 58;11:855-861.

Taylor S, Halligan S, Vance M et al (2003) Use of multi detector row computed tomographic colonography before flexible sigmoidoscopy in the investigation of rectal bleeding. *British Journal of Surgery* 90;1163-1164

Bruzzi J, Moss A, Brennan D et al (2003) Efficacy of IV buscopan as a muscle relaxant in CT colonography. *Eur Radiol* 13;2264-2270

Ginnerup Pederson B, Christiansen T, Bjerregaard N et al (2003) Colonoscopy and multidetector array computed tomographic colonography: detection rates and feasibility *Endoscopy* 35:736-742

Johnson C, Harmsen W, Wilson L et al (2003) Prospective blinded evaluation of computed tomographic colonography for screen detection of colorectal polyps. *Gastroenterology* 125:311-319

Pineau B, Paskett E, Chen et al (2003) Virtual colonoscopy using oral contrast compared with colonoscopy for the detection of patients with colorectal polyps. *Gastroenterology* 125;304-310

Thomeer M, Carbone I, Bosmans H et al (2003) Stool tagging applied in thin slice multi detector computed tomography colonography. *Journal of Computer Assisted Tomography* 27:132-139

McFarland E, Pilgram T, Brink J et al (2002) CT colonography: multi observer diagnostic performance *Radiology* 225;380-390

Macari M, Bini EJ, Xue X et al (2002) Colorectal neoplasms: prospective comparison of thin section low dose multi detector row CT colonography and conventional colonoscopy for detection *Radiology* 224;383-392

Gluecker, T, Dorta, G, Keller, W, Jornod, P, Meuli, R, and Schnyder, P (2002). Performance of multidetector computed tomography colonography compared with conventional colonoscopy. *Gut* 51;2:207-211.

Van Gelder R, Venema H, Serlie I et al (2002) CT colonography at different radiation dose levels: feasibility of dose reduction *Radiology* 224;25-33

Laghi A, Iannaccone R, Carbone I et al (2002) Detection of colorectal lesions with virtual tomographic colonography *American Journal of Surgery* 183:124-131

Wessling J, Fischbach R, Domagk D et al (2001) Colorectal Polyps: detection with multi-slice CT colonography *Rofo* 173;1069-1071

Yee, J, Akerkar G Hung R et al (2001) Colorectal neoplasia: Performance characteristics of CT colonography for detection in 300 patients. *Radiology* 219;3:685-692

Regge D, Galatola G, Martincich L et al (2000) Use of virtual endoscopy in the identification of colorectal neoplasms: prospective study with symptomatic patients [in Italian] *Radiol Med (Torino)* 99;449-455

Spinzi, G, Belloni, G, Martegani, A, Sangiovanni, A, Del, Favero C, and Minoli, G. (2001) Computed tomographic colonography and conventional colonoscopy for colon diseases: a prospective, blinded study. American Journal of *Gastroenterology* 96;2:394-400.

Mendelson R, Foster N, Edwards J, Wood C, et al (2000) Virtual colonoscopy compared with conventional colonoscopy: a developing technology *Med J Aust* 173;472-475

Morrin M, Farrell R, Kruskal R et al (2000) Raptopoulous v. utility of intravenously administered contrast material at CT colonography *Radiology* 216:704-711

Fletcher J, Johnson C, Welch T et al (2000) Optimisation of CT colonography technique: prospective trial in 180 patients *Radiology* 216;704-711

Macari M, Milano A, Lavelle M (2000) Comparison of time efficient CT colonography with two and three dimensional colonic evaluation for detecting colorectal polyps *Am J Roentgenol* 174;1543-1549

Fenlon H, Nunes D, Schroy P et al (1999) A comparison of virtual and conventional colonoscopy for the detection of colorectal polyps *New England Journal of Medicine* 341;1496-1503

Rex D, Vining S Kopecky K et al (1999) An initial experience with screening for colon polyps using spiral CT with and without CT colonography (virtual colonoscopy) *Gastro-intest Endosc*

Citation: Hoppe H, Netzer P, Spreng A, Quattropani C et al (2004) Prospective comparison of contrast enhanced CT colonography for detection of colorectal neoplasms in a single institutional study using second look colonoscopy with discrepant results *American Journal of Gastroenterology* 99;1924-1935
Design: Prospective Diagnostic Study **Country**: Switzerland **Setting:** **Aim**: to prospectively compare CT colonography with conventional colonoscopy for detection of colorectal neoplasms.
Inclusion criteria Adult patients referred to the gastroenterology clinic for conventional colonoscopy to evaluate symptoms including: Haematochezia Positive haemoccult test result Iron deficiency anaemia Personal or family history of neoplasia
Exclusion criteria No definitive criteria detailed though 8 patients were excluded for reasons including: Residual stool and fluid rendered colonoscopic and CT evaluation impossible Anal sphincter insufficiency Unable to establish a reference standard due to impassable stenosis on flexible colonoscopy
Sample Size No details
Randomisation Method N/A
Population N=100 patients enrolled (62 men, 38 women) N=92
Study Duration N/A
Interventions CT Colonography which was immediately followed by conventional colonoscopy (reference standard)
Outcomes Sensitivity and Specificity by size (using colonic lesion size as determined at colonoscopy as the reference standard) Sensitivity, specificity, positive and negative predictive values (using conventional colonoscopic findings after unblinding as the reference standard)
Results The reference standard for location and size was conventional colonoscopy. When CT colonography detected a lesion missed on initial conventional colonoscopy, results of a second look colonoscopy following unblinding were used as the reference standard. If there was discord between CT colonography and conventional colonoscopy regarding individual lesion status, 2 negative findings on conventional colonoscopy were considere to be a true negative for convention colonoscopy and false positive finding for CT colonography. If initial findings were negative, but second look colonoscopy confirmed the positive CT colonography , the result was considered a true positive for CT colonography. For positive conventional colonoscopy and negative CT colonography, the positive colonoscopy finding was considered to be the true positive with a false negative reported for CT colonography. Complete conventional colonoscopy to the caecum was achieved in 94 patients and failed to demonstrate the entire colon in 6% (6/100) patients. 8 patients were excluded from analysis (see exclusion criteria).

Conventional colonoscopy found 122 lesions which included 8 colorectal carcinomas and colonoscopy results were normal in 43 patients.

		Lesion size at colonoscopy		
Colon Segment	N	≤5mm	6-9mm	≥10mm
Caecum	7	2	0	5
Ascending Colon	14	6	2	6
Transverse Colon	27	14	8	5
Descending Colon	14	8	4	2
Sigmoid	30	13	8	9
Rectum	30	20	6	4
Total	122	63	28	31

Distribution of conventional colonoscopic findings according to lesion size and colonic segment

Second look colonoscopy after unblinding was performed in 19 segments. There were 2 negative looks on conventional colonoscopy in 17 segments considered to be a true-negative for conventional colonoscopy and false positive for CT colonography.
In 2 segments initial colonoscopy was negative but second look colonoscopy confirmed the positive CT colonography findings (true positive for CT colonography).
The by-polyp sensitivity of conventional colonoscopy was 94% (32/34) for the detection of polyps of 6mm and larger.

CT colonography had a sensitivity of 88% (7/8) for the detection of colorectal carcinoma; all carcinomas detected by CT colonography were larger than 10mm, one small carcinoma (7mm) in the ascending colon was not detected.

Using direct polyp matching, the sensitivity of CT colonography fpr polyp detection was 61% (36/59) for all lesions with a 6mm cut-off.
Sensitivity of CT colonography was 71% (22/31) for polyps sized ≥10mm, 50% (14/28) for polyps 6-9mm and 25% (16/63) for polyps 5mm or smaller.
The sensitivity for the detection of histologically confirmed adenomas was 64% (23/36) for the 6mm cut-off and 71% (12/17) for the 10mm cut-off.

CT colonography demonstrated 65 false positive polyps using by-polyp matching, 7 of which were ≥10mm, 25 of which were 6-9mm and 33 were 5mm or smaller.
39 of the false positives were reported in colonic segments that were poorly distended or poorly prepared.

70 polyps found at conventional colonoscopy, 9 of which were ≥10mm, 14 of which were 6-9mm and 47 of which were <5mm, were not found on CT colonography.
40 of the missed lesions were in poorly distended or poorly prepared segments.

36/67 adenomas identified by conventional colonoscopy were not observed on CT colonography; 5/36 were ≥10mm and 4 of these adenomas were in patients who had another polyp correctly identified at CT colonography.

	By Polyp					
	N	TP	FN	FP	PPV (95% CI)	Sensitivity (95% CI)
10mm and larger	31	22	9	7	76% (0.56-0.9)	71% (0.52-0.96)
6mm and larger	59	36	23	32	53% (0.4-0.65)	61% (0.47-0.73)
6-9mm	28	14	14	25	35% (0.21-0.53)	50% (0.31-0.7)
5mm and smaller	63	16	47	33	30% (0.17-0.45)	25% (0.13-0.35)
All sizes	122	52	70	65	44% (0.35-0.54)	43% (0.34-0.51)

CT colonography results for the detection of lesions using by polyp comparison analysis

34 patients had polyps of ≥6mm and16 patients had only 1 polyp while 18 patients had more than one. Using by patient comparisons, the sensitivity and specificity of CT colonography was 76% (26/34) and 88% (51/58) for the detection of patients with at least 1 polyp ≥6mm.
The positive predictive value was 79% (26/33) and the negative predictive value was 86% (51/59).
20 patients had clinically important polyps ≥10mm in size.
Patient sensitivity for polyps ≥10mm was 95% (19/20) and specificity was 98% (65/66).
The negative predictive value of CT colonography was 98% (65/66) for a 10mm cut off.
The positive predictive value of CT colonography for clinically important polyps ≥10mm was 95% (19/20).

The overall sensitivity (comparison analysis) for detecting adenomas using by-patient comparison analysis was 73% (22/30). CT colonography resulted in false positive results in 7 patients for whom conventional colonoscopy results were normal.

	By Patient								
	n	TP	FN	FP	TN	Sensitivity	Specificity	PPV	NPV	p
≥6mm	34	26	8	7	51	76% (0.59-0.89)	88% (0.77-0.95)	79% (0.61-0.91)	86% (0.75-0.94)	<0.0001
≥10mm	20	19	1	1	65	95% (0.75-0.99)	98% (0.92-1.00)	95% (0.75-0.99)	98% (0.92-1.00)	<0.0001

Sensitivity and Specificity of CT Colonography for lesion detection using by patient comparison analysis

Citation: Laghi A, Iannaccone R, Carbone I, Catalano C et al (2002) Computed Tomographic Colonography (Virtual Colonoscopy): Blinded Prospective Comparison with Conventional Colonoscopy for the Detection of Colorectal Neoplasia *Endoscopy* 34;441-446

Design: Prospective blinded diagnostic study

Country: Italy

Setting: gastrointestinal unit

Aim: to evaluate the performance of CTC in a blinded comparison with conventional colonoscopy with suspected colorectal neoplasia

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Inclusion criteria
Symptomatic patients referred for conventional colonoscopy

Exclusion criteria
Patients with suspected inflammatory bowel disease
Patients that were pregnant

Sample Size
No details

Randomisation Method
N/A

Population
N=66

Study Duration
No details

Interventions
CT Colonography
Conventional Colonoscopy (reference standard)

Outcomes
Per polyp analysis (location and size)
Per patient analysis (sensitivity and specificity for polyps of any size)

Results
Conventional colonoscopy
In 32 patients there were 15 colorectal carcinomas and 52 polyps detected and 34/66 patients had normal findings. Conventional colonoscopy failed to visualise the entire colon in 5 patients due to the presence of occlusive neoplastic lesions.
No complications were reported in any patient.
26.9% of polyps were ≥10mm, 25% were 6-9mm and 48.1% were ≤5mm.
26 polyps were removed endoscopically and 26 were removed at surgery in a patient affected by familial polyposis with a coexisting colon carcinoma.

Location	Colorectal Carcinoma	Polyps
Rectum	5	
Sigmoid Colon	7	20
Ascending Colon	1	8
Transverse Colon	2	13
Descending Colon		7
Cecum		4

Location of colorectal carcinoma and polyps on conventional colonoscopy

CT Colonography
There were no reported complications on CT colonography.

Due to previous surgery in 7 patients only 372 colonic segments were considered; the segments were judged as collapsed in 4.8% of cases, poorly distended in 5.3% and optimally distended in 89.7% of cases.

CT colonpgrahy detected all 15 cases of colorectal carcinoma and location and size were correctly documented in all cases.
In the 5 patients with incomplete colonoscopy, CT colonography was able to visualise the whole colon and found

no additional lesions and these findings were confirmed at surgery.

CT colonography identified 30/52 polyps for an overall per polyp sensitivity of 57.6% (95% CI 44%-72%).
CT colonography correctly identified 13/14 polyps ≥10mm for a sensitivity of 92.8 % (95% CI 77%-100%); 11/13 polyps 6-9mm in diameter for a sensitivity of 84.6% (95% CI, 62%-100%) and 6/25 polyps ≤5mm for a sensitivity of 24% (95% CI, 6%-42%).

CT colonography missed 22/52 polyps , 4 due to residual stool, 2 due to collapsed bowel and the remaining 16 could not be identified even retrospectively.

There were 6 lesions seen on CT colonography that were not observed on conventional colooscopy and on re-evaluation of the CT colonography data, these findings were associated with misinterpretaion eith of hypertrophic haustral folds or residual stool.

The per patient senstivity and specificity of CT colonography was 93.7% (95% CI 85%-100%) and 94.1% (CI 86%-100%) respectively.

	CT Colonography
True Positives	30
True Negatives	32
False Positives	2
False Negatives	2

CT colonography performance

General comments
Conventional Colonoscopy was performed with 4 hours of CT colonography.

Per Polyp Analysis
True Positive: lesion detected at CT colonography matched exactly the location and size at conventional colonoscopy.
False Positive: lesion detected at CT colonography not confirmed at conventional colonography.

Per Patients Analysis
True Positive: at least one polyp per patient identified on CT colonography was confirmed on conventional colonoscopy.

Citation: Mulhall B, Veerappan G & Jackson J (2005) Meta-analysis: Computed Tomographic Colonography *Ann Intern Med* 142;635-650

Design: Systematic Review and Meta-analysis

Country:

Setting:

Aim: to assess the test performance of CT colonography compared with colonoscopy or surgery and to assess variables that may impact test performance.

Inclusion criteria
Prospective, blinded design where CT colonography results were interpreted independently of colonoscopy or surgery findings.
Studies which included adult patients that were to undergo CT colonography after full bowel preparation, followed by complete colonoscopy or surgery
Studies which utilised at least a single-detector CT scanner with colon insufflations by air or carbon dioxide
Scan intervals no greater than 5mm
Use of 2D and 3D views

Exclusion criteria
Reasons for excluding studies included:
Not a diagnostic study
Studies of patient comfort
Not on CT colonography
Cost Utility study
Clinical Practice Guideline
Extracolonic findings
Not in humans
Not of CRC screening
Technical studies
Studies of preps
Phantom studies
Case reports/series
No appropriate gold standard
Subset data
Did not meet inclusion criteria

Sample Size
N/A

Randomisation Method
N/A

Population
N=33 studies with a total population of 6393 patients

Study Duration

Interventions

Outcomes
Pooled Sensitivities and specificities on a per patient basis

Subgroup analysis was conducted by year of publication, imaging technique, collimation width and reconstruction interval, type of scanner and use of a contrast agent.

Results
The average number of participants per study was 248 (range 20-1233) and the mean age of participants was 61.9 years.
74% of patients included across the studies were at high risk for colorectal cancer.

CT colonography was compared to a number of reference standards including standard colonoscopy, segmental

unblinded colonoscopy, optimised colonoscopy and surgical findings or results of double contrast barium enema. Several studies used a combination of reference standards.

Potential sources of bias in the included studies were numerous and varied; one important source of bias was the differences in disease severity or prevalence among studies. Another specific source of bias could result from the differential verification of findings. A full table outlining the potential sources of bias can be found in the original publication.

Sensitivity of CT Colonography
Per patient sensitivity ranged from 21% to 96% with an overall pooled sensitivity of 70% (95% CI, 53% to 87%). Sensitivity progressively increased as polyp size increased with sensitivity of 48% (95% CI, 25%-70%, range, 14%-86%) for the detection of polyps <6mm, 70% (95% CI, 55%-84%, range, 30%-95%) for polyps 6-9mm and 85% (95% CI 79%-91%, range, 48%-100%) for polyps >9mm.
Significant statistical heterogeneity was observed for each of these analyses (p<0.001 for each group) with most of the variance attributed to between-study heterogeneity. Several potential sources of heterogeneity were identified by the authors including:
Studies using thinner slices for collimation appeared to have better sensitivity and meta-regression (19 studies) appeared to suggest that for every 1mm increase in collomation width there was a decrease in sensitivity of 4.9% (95% CI 0.8%-7.1%)
In the 7 studies that used multidetector scanners reported homogenously high sensitivities (95% (95% CI, 92%-99%), I^2=40%, p>0.2) compared to the 9 studies using single detector scanners which reported pooled sensitivity of 82% (95% CI, 76%-92%) with statistically significant heterogeneity reported (I^2=87.1%, p<0.001).
From the 10 studies which used 2D imaging with 3D confirmation, the pooled sensitivity was 81.9% (95% CI, 71%-91%, I^2=87.5%, p=0.02) compared with 6 studies using 2D and 3D imaging which reported a pooled sensitivity of 91% (95% CI, 83%-99%, I^2=53.1%, p=0.06). The 2 studies using fly through technology reported a pooled sensitivity of 99% (95% CI, 95%-100%, I^2=47.6%, p=0.17).
For the other subgroups investigated (year of publication, type of scanner, thickness of reconstruction interval, use of contrast and patient characteristics) no source of possible heterogeneity was found.

No evidence of a threshold effect between sensitivity and specificity on calculation of the Spearman statistic or construction of ROC curves.

Specificity of CT Colonography
Per patient specificity was relatively consistent across polyp sizes; from 14 studies, overall specificity was 86% (95% CI, 84%-88%, I^2=92.6%, p=0.001).
Specificity also improved as polyp size increase and there was no heterogeneity in the groups.
4 studies reported specificity for the detection of polyps <6mm with a pooled specificity of 91% (95% CI, 89%-95%, I^2=47.1%, p=0.15).
For polyps 6-9mm in size (from six studies), pooled specificity was 93% (95% CI, 91%-95%, I^2=50%, p=0.07) and for polyps >9mm (15 studies) the pooled specificity was 97% (95% CI, 96%-97%, I^2=41.8%, p>0.2).

General comments
Per patient analysis was considered to be more important than per polyp analysis because it was felt that this was the most important perspective for screening

Citation: Pescatore P, Glucker T, Delarive J et al (2000) Diagnostic accuracy and interobserver agreement of CT colonography (virtual colonoscopy) *Gut* 47:126-130

Design: Prospective Diagnostic Study

Country: Switzerland

Setting:

Aim: to assess the diagnostic accuracy and interobserver agreement of CT colonography for correct patient identification compared with conventional colonoscopy

Inclusion criteria
No specific inclusion criteria were detailed. The population included patients referred for conventional colonoscopy. Indications for colonoscopy included abdominal pain, iron deficiency anaemia of unknown origin, surveillance due to personal history of colon polyps, haematochezia or positive faecal occult blood test, tumour search or personal history of colorectal cancer.

Exclusion criteria
Inflammaory bowel disease
Refusal to give consent

Sample Size
No details

Randomisation Method
N/A

Population
N=50

Study Duration
March 1997-March 1998

Interventions
CT colonography (index test)
Conventional colonoscopy (reference test)

Outcomes
Sensitivity and specificity of CT colonography for correct classification of patients with or without polyps with CT colonography results considered to correlate with conventional colonoscopy findings when polyp size was identical ±3mm, when polyp morphology was similar and when CT colonography located the polyp in the same segment of the colon as conventional colonoscopy.

Results
Conventional colonoscopy found 65 polyps in 24 patients; 46/65 were ≤5mm, 8/65 were 6-9mm and 11/65 were ≥10mm in diameter.

According to histology there were 35 adenomas and 11 hyperplasic polyps ≤5mm, 8 adenomas 6-9mm and 7 adenomas and 4 carcinomas ≥10mm.
Two colonoscopies were incomplete due to stenosing masses.

Interpretation of CT colonography was carried out by two independent investigator teams consisting of a radiologist and a gastroenterologist.

	Team 1	Team 2
Sensitivity (95% CI)	75% (±18%)	71% (±18%)
Specificity (95% CI)	62% (±19%)	69% (±19%)
Positive Predictive Value	72%	72%
Negative Predictive Value	64%	68%

Diagnostic values of CT colonography for the identification of any patient with polyps of any size

	Team 1	Team 2
Sensitivity (95% CI)	37% (±33%)	62% (±33%)
Specificity (95% CI)	74% (±13%)	74% (±13%)
Positive Predictive Value	21%	31%
Negative Predictive Value	86%	91%

Diagnostic values of CT colonography for the identification of any patient with polyps ≥10mm

	Team 1	Team 2
Sensitivity (95% CI)	71% (±19%)	71% (±19%)
Specificity (95% CI)	59% (±18%)	69% (±17%)
Positive Predictive Value	55%	62%
Negative Predictive Value	74%	77%

Diagnostic values of CT colonography for the identification of any patient with polyps <10mm

False negative findings for patients with polyps ≥10mm occurred in 6 cases in team 1 and in 3 cases in team 2.
To try to explain the low sensitivities, all false negative results from polyps ≥10mm were analysed in 6 patients with 11 lesions. 7 lesions, including 3/4 carcinomas were missed by team 1 while team 2 missed 4 lesions, including 1/4 carcinomas.
Reasons for missing lesions in team 1 were primarily perceptive errors (n=4), explained by inadequate analysis of the 2D CT images in 3 cases and the polyp was masked by fluid in 1 case. The 3 remaining polyps missed by team 1 could not be found on a review of the data set and repeated multiplanar reconstructions.

For patients 1-24 sensitivity of CT colonography for the detection of polyps was 100% for team 1 and 92% for team 2 and specificity was 42% for team 1 and 58% for team 2.
For patients 25-50 sensitivity of CT colonography for the identification of polyps was 50% and specificity was 79% for both teams.
There were statistically significant differences in sensitivity between the two study periods for both teams; team 1 p=0.01 and team 2 p=0.04.
Differences in specificity between the two study periods did not differ significantly (team 1, p=0.1 and team 2, p=0.4).

	Sensitivity	
	Team 1	Team 2
Rectum	0%	0%
Left Colon	32%	32%
Transverse Colon	63%	50%
Right Colon	33%	25%

Sensitivity of CT Colonography for individual polyp detection for anatomical location

Kappa values for patients with polyps of any size were 0.56 (0.12) and 0.72 (0.10) for patients with polyps ≥10mm in diameter.

Citation: Reuterskiold MH, Lasson A, Svensson E et al (2006) Diagnostic performance of computed tomography colonography in symptomatic patients and in patients with increased risk for colorectal disease *Acta Radiologica* 9;888-898
Design: Prospective, observer blind diagnostic study **Country**: Sweden **Setting:** Specialist endoscopy department of a university hospital **Aim**: to evaluate diagnostic performance of CT colonography in symptomatic patients and patients at increased risk of colorectal carcinoma on a per lesion and a per patient basis.
Inclusion criteria Patients referred for colonoscopy
Exclusion criteria Women younger than 50 years Patients with acute colitis or colostomy
Sample Size No details
Randomisation Method N/A
Population N=111 (66 men and 45 women)
Study Duration 16 months (no dates given)
Interventions CT Colonography Conventional Colonoscopy (reference standard)
Outcomes Diagnostic performance of CT Colonography on a per lesion and per patient basis Impact of lesion size and histological type of results Impact of observer's diagnostic certainty on results Ability to identify patients in need of further work up
Results Indications for referral for colonoscopy included anaemia and or rectal bleeding and or positive faecal occult blood test (n=48), suspected malignancy without symptoms (n=5), previous findings on barium enema (n=11). Diarrhoea (n=16), history of abdominal pain and/or diverticulitis (n=16), surveillance after polypectomy (n=9) or surveillance due to colitis (n=6). CT colonography was performed immediately before colonoscopy and detailed analysis of the results were carried out by one observer. Examination was complete to the caecum in 101 (91%) of patients; in the remaining patients examination was discontinued in the rectum (n=2), in the sigmoid colon (n=3), in the transverse colon (n=1), in the right flexure (n=1) and in the ascending colon (n=3). Reasons for discontinuation included stenosis (n=3), insufficient bowel preparation (n=2), technical difficulties in combination with pain (n=2) or insufficient bowel preparation (n=1). 108 polyps and carcinomas were identified by colonoscopy and/or CT colonography: 23 of which were ≥10mm, 24 of which were 5-9mm and 61 of which were <5mm. 60/108 lesions were identified by both CT colonography and colonoscopy and 32 /48 of the unmatched lesions were <5m. Matching certainty increased with lesion size; for 30/31 matched lesions≥5mm the matching was 'rather certain' or 'completely certain'. 72/108 lesions were identified at CT colonography. Sensitivity increased with lesion size (p<0.001) and was 83% for lesions ≥5mm and 91% for lesions ≥10mm. Sensitivity in the 5-9mm group was higher concerning adenoma than concerning any lesion (92% (11/12) versus

75% (18/24)).
Sensitivity was 91% (29/32) for the detection of adenoma/carcinoma ≥5mm.

45/11 patients had one or more confirmed lesions with the most advanced lesion identified by CT colonography in 33/45 patients.
Sensitivity increased with lesion size (p=0.01) and was 82% for detection of patients with a lesion ≥5mm.
Sensitivity for the detection of patients with adenoma/carcinoma was 80% (91% for lesions ≤5mm).

There were 10 carcinomas in 10 patients, all ≥20mm and all were correctly identified at both examinations.
There were 43 adenomatous polyps, 30 of which were identified on CT colonography in 20 patients with 14 patients correctly identified on CT colonography.
CT colonography therefore identified 40/53 (75%) clinically important lesions.
27/98 polyps had no histological diagnosis, the majority of which were <5mm (63%) and found in patients with other lesions (23/27).

36 lesions were identified at colonoscopy alone, 2 of which were ≥10mm.
12 lesions were identified at CT colonography and not at colonoscopy, though they were retrospectively confirmed.

There were 5 false positive results at colonoscopy (all <5mm) and 14 findings (all ≥5mm) at CT colonography could be defined as false positives.
Among the remaining 154 unconfirmed findings, 6 were 10-15mm and 101 were <5mm. (These numbers do not fit with anything else in the paper and it is possible that they are an error, however it is not possible to confirm this based on the data provided.)

58/72 (81%) of all confirmed CT colonography findings were classified as being completely certain or rather certain.
12/14 uncertain or very uncertain findings were <5mm.
A weak but statistically significant relationship was found between the size of confirmed CT colonography findings and the level of certainty (r_s=0.33, p=0.005) indicating that qualities other than size were important for diagnostic certainty as the relationship between size and certainty explains 11% of the variability in these variables.

103/168 (61%) of the unconfirmed or false-positive findings were uncertain or very uncertain.
7/13 findings ≥10mm were classified as rather certain, 4 of which turned out to be false positive and 3 remained unconfirmed.

One or more CT colonography findings were made in 77 patients and if all were referred for follow-up, 41/45 patients with confirmed lesions would be identified. However 36/66 patients without any confirmed lesion had CT findings.
Of 24 patients with any 'completely certain' or 'rather certain' CT finding ≥10mm, 17 had a confirmed lesion ≥10mm, 3 had a smaller lesion and 4 had only false positive or unconfirmed lesions. 2 patients with confirmed lesions ≥10mm would have been missed.
The specificity of CT colonography would be 45% (30/66, 95% CI 34%-57%) if patients with findings of any size and any diagnostic certainty were selected for follow-up and 92% (85/92, 95% CI 85%-96%) if only patients with completely certain or rather certain CT findings ≥10mm were selected.

	Per Lesion			Per Patient		
	Lesion Size			Lesion Size		
	<5mm	5-9mm	≥10mm	<5mm	5-9mm	≥10mm
Any Lesion						
Total, n	61	24	23	17	9	19
CC true positive, n	57	19	20	16	8	17
CTC true positive, n	33	18	21	10	5	18
CTC sensitivity	54%	75%	91%	59%	56%	95%
Adenoma or carcinoma						
Total, n	21	12	20	8	5	17
CC true positive, n	20	11	18	8	5	15
CTC true positive, n	11	11	18	4	4	16
CTC sensitivity	52%	92%	90%	50%	80%	94%

Detection Rate according to lesion size, by colonoscopy (CC) and CT colonography (CTC)

	Lesion Size		
Histologic Type	**<5mm (n=61)**	**5-9mm (n=24)**	**≥10mm (n=23)**
Adenocarcinoma, n			9
CC/CTC true positive, n/n			9/9

Squamous cell carcinoma, n			1
CC/CTC true positive n/n			1/1
Adenoma	21	12	10
CC/CTC true positive n/n	20/11	11/11	8/8
Hyperplastic Polyp, n	21	2	1
CC/CTC true positive, n/n	21/9	1/1	1/1
Other polyp, n*	2	1	1
CC/CTC true positive, n/n	2/1	1/0	1/1
No histologic diagnosis, n	17	9	1
CC/CTC true positive, n/n	14/12	6/6	0/1

*including 1 juvenile polyp, 2 inflammatory polyps and 1 lipoma

All confirmed lesions according to size and histologic type and detection rate by colonoscopy and CT colonography

	Lesion Size		
Histologic Type	**<5mm (n=61)**	**5-9mm (n=24)**	**≥10mm (n=23)**
Adenocarcinoma, n			9
CC/CTC true positive, n/n			9/9
Squamous cell carcinoma, n			1
CC/CTC true positive n/n			1/1
Adenoma	8	5	7
CC/CTC true positive n/n	8/4	5/4	5/6
Hyperplastic Polyp, n	6	1	1
CC/CTC true positive, n/n	6/4	1/0	1/1
Other polyp, n*	1	1	1
CC/CTC true positive, n/n	1/1	1/0	1/1
No histologic diagnosis, n	2	2	0
CC/CTC true positive, n/n	1/1	1/1	0/0

All patients with confirmed lesions according to size and histologic type and detection rate by colonoscopy and CT colonography

General comments

Matching of findings was performed jointly by a CT colonography observer and an endoscopist level of matching certainty (completely certain, rather certain, uncertain, very uncertain) were recorded.

All polyps and masses described at conventional colonoscopy were considered to be true positive findings unless histologically confirmed as normal colon mucosa.

CT colonography and conventional colonoscopy findings were considered to be matched when observed lesions were of a similar size and location, or if other characteristics indicated identity.

If the finding was ≥5mm and was graded as completely certain or rather certain on CT colonography and could not be matched to any colonoscopy finding, a review of the colonoscopy video recordings and/or other clinical documentation was performed. CT colonography findings were considered to be false positive if a true lesion could be excluded; true positive if a true lesion could be confirmed and unconfirmed if the analyses was inconclusive or not performed.

Diagnostic performance of CT colonography was analysed in relation to all confirmed lesions identified by either colonoscopy, CT colonography or both.
For per patient analysis the ability of CT colonography to identify the histologically advanced lesion in patients with confirmed lesions was investigated.

Citation: Rex D, Mark D, Clarke B et al (1995) Flexible sigmoidoscopy plus air contrast barium enema versus colonoscopy for evaluation of symptomatic patients without evidence of bleeding *Gastrointestinal Endoscopy* 42;2:132-138

Design: Randomised Trial

Country: USA

Setting: Single Medical Centre

Aim: to investigate the effectiveness and cost-effectiveness of initial diagnostic strategies in patients without evidence of intestinal bleeding

Inclusion criteria
Aged ≥40 years
Patients referred with suspected

Exclusion criteria
Prior colorectal neoplasms or vascular malformations
Patients who had undergone colonoscopy or barium enema within 18 months previous to randomisation
Patients who had hematochezia or significant coagulopathy
Patients unable to give informed consent
Haemoglobin <14 g/100ml in men and <12g/100ml in women

Sample Size
No details provided

Randomisation Method
Randomisation was done using a randomly varying block design with block sizes of two and four. It was stated that randomised patients did not represent consecutive patients for a number of reasons including:
Location of physicians involved in randomisation
Referral of private patients or managed care patients specifically for flexible sigmoidoscopy or colonoscopy
Insufficient space on the endoscopy schedule to perform potential colonoscopy generated by randomisation

Population
N=180 patients randomized (91 to flexible sigmoidoscopy + ACBE and 89 to initial colonoscopy)

Study Duration
No details

Interventions
Initial colonoscopy versus flexible sigmoidoscopy + air contrast barium enema (ACBE)

Outcomes
Not clearly reported appear to be findings in each group and prevalence of neoplasia

Results
149 patients kept their appointments and completed initial tests.
There were no significant differences in baseline information collected from patients.
Reasons for referral included constipation (18%), diarrhoea (6.5%), abdominal pain (17%), weight loss (9.5%) and a combination of these symptoms (49%).

Finding	Flexible Sigmoidoscopy + ACBE (n=75)	Colonoscopy (n=75)
	N (%)	N (%)
Cancer	1 (1)	0 (0)
Diverticulosis	46 (62)	31 (41)
Adenomas	13 (18)	23 (31)
Only adenomas (≤4mm)	4 (5)	8 (11)
Largest adenoma (5-9mm)	7 (9)	10 (13)
Any adenoma ≥1cm	2 (3)	5 (7)
Arteriovenous malformation	0 (0)	1 (1)

Findings for the two patient groups

In the flexible sigmoidoscopy + ACBE group, 1 patient had Dukes A cancer for which endoscopic resection appeared to be definitive and the patient did not undergo surgery.
No patient in the colonoscopy group was diagnosed with cancer.

Significantly fewer patients in the colonoscopy group were diagnosed with diverticulosis compared with the flexible sigmoidoscopy + ACBE group (OR=0.41, 95% CI 0.21-0.87).
More patients undergoing colonoscopy were found to have at least one adenoma (OR=2.07, 95% CI 0.90-4.92).

Patients undergoing flexible sigmoidoscopy were more likely to require an alternative procedure such as colonoscopy than were patients undergoing colonoscopy to require ACBE (OR 4.46, 95% CI 1.47-16.4).

18/75 patients in the flexible sigmoidoscopy group required colonoscopy and in all cases a polypectomy was indicated. 16/18 patients actually underwent colonoscopy and 14 patients had one or more polyps.

5 patients in the colonoscopy group required ACBE due to incomplete colonoscopy; 4 patients underwent ACBE but no additional lesions were detected.

There were no perforations, postpolypectomy bleeds or requirements for hospitalisation in either group.

Citation: Rex D, Weddle R, Lehman G et al (1990) Flexible Sigmoidoscopy plus Air Contrast Barium Enema versus Colonoscopy for suspected lower gastrointestinal bleeding *Gastroenterology* 98;855-861

Design: Randomised Trial

Country: USA

Setting: Single Medical Centre

Aim: to compare colonoscopy with flexible sigmoidoscopy plus air contrast barium enema for the evaluation of suspected lower GI bleeding.

Inclusion criteria
Patients aged ≥40 years who were referred with a clinical suspicion of nonemergent lower GI bleeding

Exclusion criteria
Prior colorectal neoplasia or vascular malformations
Prior colonoscopy or barium enema within the previous 18 months
Patients with significant coagulopathy
Patients who could not give informed consent

Sample Size
The study sample size provided a power of 0.8 at an alpha of 0.05 to detect a 10% difference in cancer prevalence between the two groups.

Randomisation Method
Randomisation was done using a randomly varying block design with block sizes of two and four.
It was stated that randomised patients did not represent consecutive patients for a number of reasons including:
Location of physicians involved in randomisation
Referral of private patients or managed care patients specifically for flexible sigmoidoscopy or colonoscopy
Insufficient space on the endoscopy schedule to perform potential colonoscopy generated by randomisation
The sample of non-consecutive patients was compared with a sample of 100 consecutive patients and was found to be demographically similar.

Population
N=380 (191 to flexible sigmoidoscopy + ACBE and 189 to colonoscopy)

Study Duration
Recruitment: March 1985-November 1987

Interventions
Flexible sigmoidoscopy + ACBE versus colonoscopy

Outcomes
Not clearly reported in the text

Results
332/390 patients kept their appointments and completed initial test: 168 in the flexible sigmoidoscopy group and 164 in the colonoscopy group.

There was no significant difference between the groups in relation to demographic or historical data.

Reasons for referral included haemoccult positive stools, hematochezia and melena with negative upper GI evaluation.

Flexible sigmoidoscopy was successful (insertion to at least 30cm) in 161 patients with a mean depth of insertion of 50cm.
Findings on flexible sigmoidoscopy included haemorrhoids (58%), diverticulosis (19%), any polyps (23%), cancer (4%) and proctitis (2%).

Air contrast barium enema was sufficient to rule out major pathology in 157 patients and reasons for unsuccessful ACBE included; inability to distend or fill the right colon adequately in 5 patients, repeatedly inadequate preparation to rule out mass lesions (n=4) and inability to retain the enema adequately in 2 patients.
ACBE findings were normal in 48/168 patients and abnormalities identified included haemorrhoids (n=1), diverticulosis (n=82), any polyp (n=43), stricture (n=3) and cancer (n=4%).

Colonoscopy was successful in 151 patients (insertion to the cecum) and reasons for unsuccessful colonoscopy

included; obstructing cancers in 6 patients and technical factors in 7 patients.
Colonoscopy findings were normal in 18/162 patients.

In the flexible sigmoidoscopy plus ACBE group, 64 patients had a total of 101 polyps ranging in size from ≤4mm (n=45) to ≥9mm (n=27) and included 4 patients with 7 polyps who also had colorectal cancer. Patients with polyps ≥5mm were referred for colonoscopy where the polyps in 4/38 patients could not be found; these patients were considered to have false positive ACBE results.
28 patients, including the 4 with cancer, were referred for polypectomy and all had at least 1 adenoma.
33 patients in the flexible sigmoidoscopy plus ACBE group had either cancer or adenoma documented by initial testing or subsequent colonoscopy.
Colonoscopy detected a further 25 polyps not visualised by initial flexible sigmoidoscopy + ACBE; 18 were ≤4mm, 5 were 5-8mm and 2 were ≥9mm.

9 patients in the flexible sigmoidoscopy plus ACBE group had cancer: 3 had Dukes B tumours with serosal involvement, 1 had a Dukes C tumour and 4 had Dukes D tumours. One patient in the group has a negative ACBE and four weeks later underwent colonoscopy which showed a cecal cancer which was resected.
One patient with transverse colon cancer diagnosed on ACBE refused surgery.

In the colonoscopy group, 86 patients had a total of 194 polyps ranging in size from ≤4mm (n=108) to ≥9mm (n=29). 9 patients with a total of 16 polyps also had colorectal cancer. In total, 76/146 patients in the colonoscopy group had colonic adenoma or carcinoma.
13 patients in the colonoscopy group had cancer, 2 patients had Dukes A tumours, 8 had Dukes B, 2 had Dukes D and 1 had transverse colon cancer and refused surgery.

There was a significant difference between the arms in relation to the proportion of patients recommended alternative lower GI procedures (p≤0.0001).
53/168 (32%) patients in the flexible sigmoidoscopy group were referred for subsequent colonoscopy due to inadequate study (n=11), for polypectomy (n=38) and for biopsies on lesions outside the reach of flexible sigmoidoscopy.
13/164 (8%) patients in the colonoscopy arm were referred for ACBE because of difficulty advancing the colonoscope to the cecum.

When examining the diagnostic yields with respect to age there was an indication of diversion in polyp and cancer yield for patients aged ≥55 years. There was no significant difference between the two groups within each age group in relation to demographic data, patient history or laboratory variables. The superior detection of polyps in the colonoscopy group was accounted for by the finding of polyps <9mm in patients ≥55years.
Overall, the yield of cancers in patients <55 years was very low at 1% compared with 8% in those aged ≥55years.
Flexible sigmoidoscopy + ACBE found more patients <55 years with polyps ≥9mm than did colonoscopy (p=0.021).

There was no significant difference between the two groups in relation to procedural complications. Phlebitis occurred in 7 patients in the colonoscopy group versus 4 patients in the flexible sigmoidoscopy +ACBE group, this difference was not statistically significant, however the authors state that the study did not have sufficient power to detect a true difference in the incidence of phlebitis of this magnitude.

No deaths, transfusions, hospitalisations, or prolonged hospital stays were reported in either group.

	All patients		
	Flexible Sigmoidoscopy + ACBE (N=168)	Colonoscopy (N=164)	p
	N (%)	N (%)	
Internal or external haemorrhoids	99 (59)	97 (59)	NS
Diverticulosis	85 (51)	56 (34)	0.002
Any colorectal polyp	64 (38)	86 (52)	0.009
Any colorectal polyp ≥5mm	38 (23)	53 (32)	0.048
Any colorectal polyp ≥9mm	21 (13)	22 (13)	NS
Colonic Stricture	3 (2)	3 (2)	NS
Colon cancer	9 (5)	13 (8)	NS
Colitis pr Proctitis	4 (2)	10 (6)	NS
Arteriovenous malformation	0 (0)	9 (5)	0.002

Comparison of Abnormalities on Initial Lower Gastrointestinal Procedures (all patients)

| | Age ≥55 years | | |
| | Flexible Sigmoidoscopy + ACBE | Colonoscopy (N=123) | p |

	(N=127)		
	N (%)	N (%)	
Internal or external haemorrhoids	76 (60)	75 (61)	NS
Diverticulosis	67 (53)	45 (37)	0.01
Any colorectal polyp	50 (39)	74 (60)	0.001
Any colorectal polyp ≥5mm	30 (24)	47 (38)	0.012
Any colorectal polyp ≥9mm	16 (13)	22 (18)	NS
Colonic Stricture	2 (2)	3 (2)	NS
Colon cancer	9 (7)	12 (10)	NS
Colitis pr Proctitis	3 (2)	7 (6)	NS
Arteriovenous malformation	0 (0)	8 (7)	0.003

Comparison of Abnormalities on Initial Lower Gastrointestinal Procedures (patients ≥55 years)

	Age <55 years		
	Flexible Sigmoidoscopy + ACBE (N=43)	Colonoscopy (N=41)	p
	N (%)	N (%)	
Internal or external haemorrhoids	23 (56)	22 (54)	NS
Diverticulosis	18 (44)	11 (26)	NS
Any colorectal polyp	14 (34)	12 (29)	NS
Any colorectal polyp ≥5mm	8 (20)	6 (15)	NS
Any colorectal polyp ≥9mm	5 (12)	0 (0)	0.021
Colonic Stricture	1 (2)	0 (0)	NS
Colon cancer	0 (0)	1 (2)	NS
Colitis pr Proctitis	1 (2)	3 (7)	NS
Arteriovenous malformation	0 (0)	1 (2)	NS

Comparison of Abnormalities on Initial Lower Gastrointestinal Procedures (patients <55 years)

Citation: Sosna J, Blachar A, Amitai M, Barmeir E, Peled N, Nahum-Goldberg S, Bar-Ziv J (2006) Colonic Perforation at CT Colonography: Assessment of Risk in a Multicentre Large Cohort *Radiology* 239;2:457-463
Design: Retropsective Case Series
Country: Israel
Setting: Multicentre
Aim: To assess the incidence, clinical features and treatment of colonic perforation at computed tomographic colonography in a large multicentre cohort.
Inclusion criteria   All patients who underwent CT colonography during a 48 month period (January 2001 – December 2004)
Exclusion criteria   No details
Sample Size   N/A
Randomisation Method   N/A
Population   N=11,870 CT colonographic studies performed in 6837 men and 5033 women
Study Duration   January 2001 – December 2004
Interventions   CT Colonography
Outcomes   Rates of colonic perforation and surgical treatment
Results   7 colonic perforations were identified at 5 centres for a perforation risk rate of 0.059% (95% CI 0.02%-0.1%), translating to an event occurrence of 1/1695 studies (95% CI 1/974 - 971/6537).   6/7 cases of perforations were in symptomatic patients at high risk of colorectal neoplasia and only 1 occurred in an asymptomatic patient with average risk who underwent screening.   4 cases of perforation were in patients undergoing CT Colonography as completion studies following incomplete conventional colonoscopy.   There were 5 cases of perforation in the sigmoid colon and 2 in the rectum.   6 cases of perforation occurred in patients in whom a rectal tube was inserted and in 5/6 cases the balloon was inflated. In the remaining patient a 16-F Foley catheter was inserted and 5ml of saline was inflated into the balloon.   4/7 patients with perforation required surgical treatment with a one-stage procedure performed in 3 patients and a two-stage procedure performed in 1.   The incidence of surgical intervention was 1/2968 patients (95% CI 1.5 of 10,000 – 14.7 of 10,000).   The remaining 3 patients had multiple comorbidities and were at high risk for surgery and so received conservative treatment without any complications.   No deaths were recorded.   3 cases of perforation occurred at 3 medical centres at which 40, 50 and 120 CT colonographic studies had been performed at the time perforation occurred.   4 cases of perforation occurred at non-academic centres, 3 in one centre at which approximately 2,700, 4,000 and 5,200 CT colonographic studies had been performed and one case at a centre at which 2,500 studies had been performed.   The physicians performing the air insufflation in 2 cases of perforation did not have any experience in the performance of CT colonography at the time of examination with neither having performed unsupervised air insufflation previously nor read images from CT colonographic studies on a regular basis.
General comments

The population under investigation included both symptomatic and asymptomatic (screening) and it appears that part of the population is patients referred for CT Colonography following failed/incomplete colonoscopy. It is not possible to separate the population according to the indications/reasons for CT Colonography in order that only data relevant to the population of interest for the PICO can be reported. The results and data reported in this study can be considered indirect evidence of the risk of perforation with CT Colonography.

2.2.   Staging of Colorectal Cancer

2.2.1. For patients diagnosed with primary colorectal cancer, what is the most effective technique(s) in order to accurately stage the disease (excluding pathology)?

Short Summary
There were three systematic reviews of case series studies (Kwok et al. 2000; Bipat et al. 2004 and Dighe et al, 2010) and a large volume of low quality case series studies with which to address this topic (Akin O, 2004 Beets-Tan RGH, 2001, Beynon J, 1986, Bianchi P, 2005, Brown G, 2004, Brown G, 2003, Brown G, 1999, Chun HK, 2006, Dirisamer A, 2010, Fillipone A, 2004, Fuchsjager M, 2003, Halefoglu A, 2008, Kantorova I, 2003, Kim CK, 2007, Kim CK, 2006, Kulinna C, 2004, Kulinna C, 2004, Llamas-Elvira JM, 2007, Low RN, 2003, Mainenti PP, 2006, Mercury Study Group, 2007, Mercury Study Group, 2006, Nicholls R, 1982, Rafaelsen S, 1994, Rao SX, 2007, Salerno G, 2009, Tatli S, 2006, Tateishi U, 2007).

The evidence body relating to colon cancer specifically was poor, with only a single systematic review available for review (Dighe et al, 2010). The remainder of included studies related either to rectal cancer only or to colorectal cancer where it was not possible to separate the colon patients from the rectal patients. There appears to be a large degree of variation across the body of evidence in relation to interventions;, outcomes reported; inclusion and exclusion criteria; the standard to which the interventions were compared and names/terminology used across studies.

<u>Colon Cancer</u>
Dighe et al (2010) investigated the accuracy and limitations of CT in identifying poor prognostic features in colon cancer and reported (from 8 studies) that sensitivity was 92% (95% CI, 87%-95%) and specificity was 81% (95% CI, 70%-89%) for distinguishing between T3 and T4 tumours and for the distinction between T1/T2 and T3/T4 tumours sensitivity was 86% (95% CI 78%-92%) and for lymph node involvement, sensitivity was 70% (95% CI, 59%-80%) and specificity was 78% (95% CI, 66%-86%).

<u>Rectal Cancer</u>
For digital rectal exam, a total of 4 studies reported results (Beynon et al, 1986; The Mercury Study Group (2006); Brown et al (2004) and Rafaelson et al). Reported sensitivities and specificities ranged from 38%-68% and 74%-83% respectively.

 From two systematic reviews (Kwok et al. 2000; Bipat et al. 2004) it appears that /endoluminal ultrasound had the highest sensitivity, specificity and accuracy of the modalities investigated (CT, endoluminal ultrasound and MRI). Kwok et al. (2000) reported a pooled sensitivity, specificity and accuracy for endoluminal ultrasound of 93%, 78% and 87% respectively for wall penetration and 71%, 76% and 74% respectively for nodal involvement. Bipat et al. (2004) reported summary estimates of sensitivity and specificity for endoluminal ultrasound of 94% and 86% respectively for muscularispropria invasion, 90% and 75% respectively for perirectal tissue invasion and 67% and 78% respectively for lymph node involvement compared with sensitivity and specificity for MRI of 90% and 69% respectively for muscularispropria invasion, 82% and 76% respectively for perirectal tissue invasion and 66% and 76% respectively for lymph node involvement. For muscularispropria invasion, endoluminal ultrasound specificity was significantly higher than that of MRI (p=0.02); for perirectal tissue invasion, endoluminal ultrasound sensitivity was significantly higher than that of CT (p<0.001) and MRI (p=0.003).

Specific UK evidence was provided from the Mercury Study group, (Mercury Study Group 2006 and 2007) investigating MRI in the staging of rectal cancer.
The accuracy of MRI for predicting the status of circumferential resection margin (presence/absence of tumour) by initial imaging or imaging after pre-operative treatment was 88% (95% CI, 85%-91%), sensitivity was 59% (95% CI, 46%-72%) and specificity was 92% (95% CI, 90%-95%).
For patients undergoing primary surgery with no pre-operative treatment (n=311), accuracy of prediction of a clear margin was 91% (95% CI, 88%-94%), sensitivity of 42% and specificity of 98%.
For patients undergoing pre-operative chemoradiotherapy or long-course radiotherapy the accuracy of prediction of clear margins on MRI was 77% (95% CI, 69%-86%), sensitivity was 94% and specificity was 73%.

Two studies investigated the use of FDG-PET (Kantorova et al. 2003 and Llamas-Elvira et al. 2007). For lymph node involvement the reported sensitivity ranged from 21%- 29%, specificity ranged from 88%-95% and accuracy ranged from 56%-75% and for liver involvement sensitivity was 78%, specificity was 96% and accuracy was 91%.

Interobserver agreement was not addressed in all studies, though the studies which did evaluate interobserver agreement (Fillipone et al. 2004; Tatli et al. 2006; Kim et al. 2006) reported good to excellent agreement for interventions being investigated.

Review Protocol

Population	Intervention	Comparison	Outcome
Patients with newly diagnosed colorectal cancer	• CT (C, R), chest, abdo, pelvis • CT/PET (C, R) • MRI (R) • Endoanal ultrasound (R) • DRE	Each other	• Sensitivity • Specificity • Adverse reaction to contrast • Reclassification

Following a systematic search of relevant data sources (see appendix .1), the information specialist created a database of potentially relevant studies. All titles and abstracts were sifted by a single reviewer. Queries about inclusion were clarified by the GDG topic subgroup. The full studies were then obtained and reviewed and relevant studies were included in the final evidence review.

All update searches were sifted by a single reviewer and the list of potentially relevant studies was also checked for irrelevant studies by the GDG subgroup. Only studies which all subgroup members were in agreement were excluded. The remaining studies were obtained and reviewed with relevant studies included in the final evidence review.

The review will look to include only high level evidence in the form of randomised trials and meta-anlaysis, though the GDG subgroup suspect that there will be little available and that it will be necessary to look to lower quality study types such as case series.

The date limits for each modality, before which the subgroup felt relevant data would not be available, were as follows:
Digital Examination: 1970
MRI: 1990 onwards
EUS: 1990 onwards
CT: 1990 onwards

Not only should the most effective methods be looked at but a statement about the minimum acceptable level of investigations should be made.
The relevant investigations for this topic are CT (for colon cancer and distant metastatic disease), MR (for local tumour staging of rectal cancer), endoanal/endorectal/transrectal US for staging rectal cancer, and CT-PET for "whole-body" assessment.
It was deemed reasonable to restrict CT to the spiral / helical era.
Relevant MR studies really start around 1995 and endorectal / intracavitary coil MR can be regarded as obsolete.
For nuclear medicine it was determined that the searches should be limited to CT-PET only, as it easily trumps all previous PET techniques.
Abdominal US scan was at one time considered adequate for detecting liver metastases, but it was decided that it has been abandoned since the advent of multislice CT, or at least is practised in very few centres (with the addition of intravascular microbubble contrast agents) and even then probably only in specific circumstances.
There was also a single-author claim that Doppler US of the hepatic artery could predict subsequent development of metastatic disease with uncanny accuracy, however that experience couldn't be replicated elsewhere and GDG subgroup members do not believe it's still used.

Reasons for excluding papers:
Studies included in meta-analysis/systematic review
Studies did not report relevant outcomes
Studies pre 2000 were excluded on the grounds that there were 2 good systematic reviews post 2000 which had adequately searched the relevant literature (Kwok, 2004 and Bipat, 2004).

Studies with less than 20 participants were excluded (this was the criteria for exclusion of studies in one of the systematic reviews).

Quality of the included studies
Systematic review of RCTs (n = 0)
Systematic review of combined study designs (n =3)
Randomized controlled trial (n = 0)

Prospective cross sectional study (n = 0)   Case Series Studies (n = 28)

485 (+132) possibly relevant papers identified	→	312 (+113) papers excluded based on title & abstract
↓		
173 (+19) papers obtained for appraisal	→	156 (+17) papers excluded
↓		
17 (+2) papers included in evidence table +12 papers referred by GDG members		
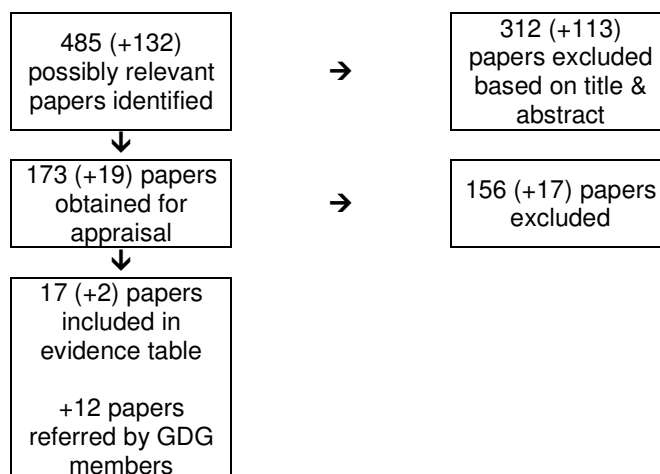
Volume of evidence

There was a large volume of low quality evidence with which to address this question; the evidence body consists primarily of case series studies. In particular the evidence body relating to the staging of colon cancer is quite poor when compared to that relating to the staging of rectal cancer. Two good quality systematic reviews were available for the staging of rectal cancer however the quality of the evidence contained within the reviews was of a low quality. The majority of evidence was drawn from case series studies in which the numbers of cases available to be reviewed is small with little detail provided with regards to factors such as inclusion/exclusion criteria, co-morbidities or other factors that may impact on the outcome of imaging.

One good systematic review compared the effectiveness of CT in identifying poor prognostic features preoperatively in colon cancer. No other evidence was available which looked specifically at colon cancer.

Applicability

Most studies compared two or more of the interventions of interest in relation to sensitivity and specificity. No study reported on adverse reaction to contrast or reclassification as outcomes.

Few studies reported on the impact of the reader/clinician on the outcomes.

All studies used pathological or histological staging as the reference standard and though the sensitivity and specificity of histopathologic staging was not of interest to this topic, it was necessary to review studies using histopathologic staging as the reference standard in order that the results were meaningful.

Histopathologogy is considered the gold standard however obtaining this information requires surgery and the purpose of this topic is to determine whether any of the currently available methods of pre-operativley assessing tumour can provide similar information in order to correctly assign patients to treatment groups and avoid under or over treating patients where possible.Sensitivites, specificities and accuracy results all relate to modality under investigation and it's ability to provide sufficient information to accurately stage the tumour when compared with histopathology data.

Consistency

There appears to be some degree of variation in the methodology employed, the interventions investigated in each study and the factors investigated within each of the studies. There is variation in the inclusion/exclusion criteria, interventions being investigated, factors used for classification and the standard to which each imaging modality was compared and the way in which the results were reported.

Evidence Statement

A table (table 2.2) outlining the studies included in the evidence tables, the imaging modalities investigated, the factors examined for each modality and where available, the sensitivity, specificity and accuracy for each intervention is presented below. The table also reports the number of participants in each of the studies, however it is important to note that not all study partcipants were subject to the same intervention procedures and therefore the number of participants undergoing each intervention may be lower than the number of participants in the study. Where possible, the numbers of participants undergoing each intervention is highlighted in the individual evidence table pertaining to the study in question.

In the individual evidence tables, other outcomes such as positive predictive values, negative predictive values, and degree of overstaging or understaging and likelihood ratios are recorded where relevant.

Colon Cancer

Five studies reported on colorectal cancer (Fillipone et al. (2004); Low et al. (2003); Maineti et al. (2006); Kantorova et al. (2003) and llamas-Elvira et al. (2007)), and provided details of the number of patients in the study group that were diagnosed with rectal cancer and colon cancer. The imaging modalities included in the individual studies included CT colonography, Presurgical abdominal and pelvic MRI, FDG-PET, Sonography and CT. On full review, none of the studies reported the results separated by colon and rectum however, therefore it is not possible to report on the effectiveness of the relevant interventions in staging colon cancer specifically.

Updated Evidence

A single systematic review (Dighe et al, 2010) investigated the accuracy and limitations of CT in identifying poor prognostic factors in colon cancer as well as investigating which CT technique achieved the best results.

The comprehensive review included 19 studies from which relevant data could be extracted and specifically examined the ability of CT to detect muscularispropria invasion enabling the differentiation between T1/T2 and T3/T4 tumours and the detection of lymph node metastases.

For the detection of muscularispropria invasion, sensitivity and specificity measures could be obtained from 17 studies, while for lymph node involvement data could be obtained from 15 studies.

Funnel plots for publication bias showed some evidence that the smaller studies included in the review were associated with a larger diagnostic odds ratio for both tumour invasion and lymph node detection and therefore the evidence provided from smaller studies alone potentially over-estimates the true effect; though this was not statistically significant (p=0.07).

From the systematic review, a significant number of false negatives for muscularispropria invasion resulted in understaging of T3/T4 tumours in 4 of the included studies however the three of the four studies were older and CT was performed without the benefit of spiral or MDCT and with a section thickness of 10mm which may be a factor in the failure to detect small amount of tumour invasion. In the fourth study, the authors of the systematic review reported that there did not appear to be any reason for the high false negative rate other than the possibility that the study population included many patients with microscopic invasion beyond the muscularispropria.

The false positive rate was low in all included studies suggesting that CT can reliably identify T3/T4 tumours.

For nodal involvement, earlier studies showed poor results for similar reasons to those outlined for muscularispropria invasion.

Distinction between T1/T2 and T3/T4 tumours

The systematic review reported that earlier studies did not make the distinction between T3 (tumour extension beyond muscularispropria) and T4 tumours (tumour with perforation, invading adjacent organs, penetrating peritoneal surface) From 8 studies (n=399 patients) for the differentiation between T3 and T4 tumours, sensitivity was 92% (95% CI, 87%-95%) and specificity was 81% (95% CI, 70%-89%).

A summary estimate (derived by bivariate random effects model) and drawing on data from 17 studies (n=784 patients) for differentiating between T1/T2 and T3/T4 tumours was 86% (95% CI 78-92%) for sensitivity and 78% (95% CI 71-84%) for specificity. The diagnostic odds ratio (DOR) was 22.4 (95% CI, 11.9-42.4).

For lymph node detection data were available from 15 studie (n=674 patients) and reported sensitivity was 70% (95% CI, 59%-80%) and specificity was 78% (95% CI, 66%-86%). The DOR was 8.1 (95% CI, 4.7-14.1).

Rectal Cancer

Two good quality systematic reviews of the available evidence (Kwok et al. 2000; Bipat et al. 2004) examined CT, MRI and endorectalsonography for the staging of rectal cancer. Kwok et al. (2000) reported that overall endorectal ultrasound had the highest pooled sensitivity, specificity and accuracy of the three modalities. In assessing wall penetration, MRI with endorectal coil had a pooled sensitivity, specificity and accuracy close to endorectalsonography and in assessing nodal involvement, although endorectalsonography and MRI had similar results overall, subgroup analysis showed MRI with endorectal coil to have the highest pooled sensitivity, specificity and accuracy. CT showed the lowest sensitivity, specificity and accuracy of all three modalities for both wall penetration and nodal involvement.
Bipat et al. (2004) reported that endoluminal ultrasound had a significantly higher specificity than that of MRI for muscularispropria invasion (p=0.02). In relation to perirectal tissue invasion endoluminal ultrasound had a significantly higher sensitivity estimate than CT (p<0.001) and MRI (p<0.003). There was no significant difference in sensitivity and specificity estimates for any modality for adjacent organ invasion or for lymph node involvement.
Subgroup analysis of different techniques for MRI and endoluminal ultrasound for perirectal tissue invasion showed no significant difference in sensitivity or speciticity.

The majority of studies excluded patients that had receiverd radiotherapy, however in one systematic review (Kwok et al. 200), all studies in which patients received radiotherapy were combined, regardless of the regimen and it was observed that patients receiving radiotherapy, preoperative staging with CT and ES had the lowest sensitivity and specificity and MRI appeared to be less affected by radiotherapy when compared to those with no radiotherapy. One other study (Tatli et al. 2006) investigated whether there was any difference between MRI with phased array coil and MRI with endorectal coil in patients receiving chemoradiotherapy and no chemoradiotherapy, but did not report whether differences observed were significant.

In addition to the systematic reviews, a number of smaller and more recent case series were reviewed and for studies investigating the same interventions as the systematic review (EUS, CT and MRI), the results are from these case series areoutlinedbriefly in the tables below with the exception of studies from the UK (Mercury Study Group). Studies which reported on interventions not included in the systematic reviews are reported in more detail for more detailed results from each of the studies, refer to the individual evidence table.

Digital Rectal Exam
Four studies provided information on digital rectal examination (Beynon et al, 1986; The Mercury Study Group (2006); Brown et al (2004) and Rafaelson et al).
From Beynon et al (1986), surgeons were asked to allocate palpable tumours to one of four grades. Digital rectal exam was performed in 35 patients and the study reported an accuracy of 68%, sensitivity of 68% and specificity of 83% in the ability of DRE to preoperatively stage rectal cancer (histology was used as the reference standard).
The Mercury Study group is primarily concerned with investigating the accuracy of MRI to preoperatively stage rectal cancer through the prediction of circumferential resection margins. Patients participating in the study were also required to undergo a clinical exam which, included a DRE and the study reported that DRE resulted in an accuracy of 70% for the prediction of circumferential resection margins and that when DRE showed fixed or tethered tumours, this corresponded to an involved margin in only 15% of cases. Sensitivity and specificity for DRE were 38% and 74% respectively.
Brown et al (2004) evaluated the accuracy of CRE in the identification of favourable, unfavourable and locally advanced rectal carcinoma in 98 patients in order to determine which patients should be offered pre-operative short course or long course radiotherapy or surgery alone.
Compared with pathological findings, DRE correctly identified 71% of patients with favourable prognosis tumours, 36% of patients with unfavourable prognosis tumours and 11% of patients with features indicative of locally advanced tumours. Based on the results of DRE, Brown et al (2004). concluded that 51 patients would have undergone surgery alone, 39 patients would have been offered short-course radiotherapy and 8 patients would have been offered long-course radiotherapy compared with 22, 14, and 3 patients in each group if basing decision on results of histopathology.
Rafaelson et al (1994) aimed to pre-operatively stage rectal cancer by DRE. A total of 107 patients were included in the study though in 13 patients, tumour was beyond the reach of the examining finger. DRE underestimated depth of rectal wall penetration in 28% of patients and overestimated depth of penetration in 26% of cases. Overestimation appeared to occur more often with small tumours versus large tumours and a significant difference in overestimation was observed when comparing tumours located in a single quadrant compared with tumours located in more than one quadrant (p=0.01).
Underestimation of penetration depth on DRE was significantly higher in large tumours versus smaller tumours (p=0.006).

Complete clinical and pathological data were available for 53 patients and palpable lymph nodes were found in one patient on DRE though no metastases were found in the resected specimen. Overall, this study reported that 45% of patients were correctly staged by DRE.

Computed Tomography
A total of 11 studies investigating the use of computed tomography (CT) for the preoperative staging of rectal cancer were identified (Kwok et al (2000), Bipat et al (2004), Filipone et al (2004) Kantarova et al (2003), Kulinna et al (2004a), Kulinna et al (2004b) Mainenti et al (2006), Llamas-Elvira et al (2007), Beynon et al (1986), Kim et al (2007), Dirisamer et al (2010), Nicholls et al (1982) . There was variation across the studies in relation to the factors examined and the type of CT used.
Features investigated by individual studies included depth of rectal wall penetration, nodal involvement, muscularispropria invasion, perirectal tissue invasion, adjacent organ invasion, T stage and presence of liver metastases.
Methods of CT reported across individual studies included CT colonography with transverse images alone or in combination with multi-planar reconstructions (MPRs), multislice CT, axial slice CT with and without coronal and saggital MPRs.

Two good quality systematic reviews (Kwok et al (2000) and Bipat et al (2004)) evaluated the use of CT as a method for the preoperative staging of rectal cancer.
From Kwok et al (2000) 23 studies with a total of 1116 patients, were reported to have used CT in the pre-operative assessment of local tumour penetration (defined as 'through wall' i.e. invading muscularispropria or 'not through wall'). The pooled sensitivity was 78%, pooled sensitivity was 63% and pooled accuracy was 73%.
Of these, 4 studies (n=135 patients) classified wall penetration according to TNM notation and of these 80% were correctly staged, 11% were over-staged and 7% were understaged.
From Bipat et al (2004) depth of tumour pentetration was investigated as three specific subgroups; muscularispropria invasion, perirectal tissue invasion and adjacent organ invasion. There were not enough data available to determine sensitivity and specificity of CT in determining muscularispropria invasion. For perirectal tissure invasion the pooled sensitivity was 72% (95% CI, 64%-79%) and the pooled specificity was 78% (95% CI, 73%-83%). For adjacent organ invasion the pooled sensitivity was 72% (95% CI, 64%-79%) and the pooled specificity was 96% (95% CI, 95%-97%).

For nodal involvement, Kwok et al (2000) reported on data that were drawn from 18 studies (n=945 patients) and the pooled sensitivity was 52%, pooled specificity was 78% and pooled accuracy was 66%.
Bipat et al (2004) reported a pooled sensitivity of 55% (95% CI, 43%-67%) and pooled specificity of (74% (67%-80%) for the detection of lymph node involvement.

Endoluminal Ultrasound (EUS)
A total of 9 studies reported on the use of endoluminal ultrasound (EUS) in the pre-operative staging of rectal cancer including 2 good quality systematic reviews (Kwok et al (2000) and Bipat et al (2004)). Features investigated in order to stage rectal cancer, again varied across the individual studies in relation to the subgroups identified and investigated but again primarily included wall penetration, nodal involvement, presence/absence of liver metastases.
From 53 studies (n=2915 patients) Kwok et al (2000) reported a pooled sensitivity of 93%, pooled specificity of 78% and pooled accuracy of 87% for the detection of wall penetration according to the TNM classification; of these, 84% were correctly staged, 11% were over-staged and 5% were understaged.
Bipat et al (2004) reported a pooled sensitivity of 94% (90%-97%), and pooled specificity of 86% (95% CI, 80%-90%) for muscularispropria invasion; a pooled sensitivity of 90% (95% CI, 88%-92%) and a pooled specificity of 75% (95% CI, 69%-81%) for perirectal tissue invasion and a pooled sensitivity of 70% (95% CI, 62%-77%) and pooled specificity of 97% (95% CI, 96%-98%) for adjacent organ invasion.

In relation to nodal involvement Kwok et al (2000) reported a pooled sensitivity of 71% , pooled specificity of 76% and an accuracy of 74%(36 studies with a total of 2032 patients) while Bipat et al (2004) reported a pooled sensitivity of 67% (95% CI, 60%-73%) and a pooled specificity of 78% (95% CI, 71%-84%).

Magnetic Resonance Imaging (MRI)
MRI as a method of pre-operatively staging rectal cancer was investigated in 18 studies including two good quality systematic reviews (Kwok et al (2000), Bipat et al (2004) and one large multicentre, UK study (Mercury Study Group, 2006 and 2007).
The method of MRI varied across the studies identified and included studies which investigated all types of MRI and studies which investigated subgroups of MRI such as MRI with endorectal coil, MRI with body coil, MRI with and without contrast material and phased array MRI.

From Kwok et al (2000) with a total of 18 studies (n=521 patients and 546 MRI scans) the pooled sensitivity was 86%, pooled specificity was 77% and pooled accuracy was 82% for wall penetration.
Eight studies included in the review reported results using TNM notation (246 patients) and the pooled sensitivity, specificity and accuracy for these studies was 89%, 79% and 84% respectively.
In a subgroup analysis of patients using endorectal surface coil (6 studies; 169 patients) resulted in a pooled sensitivity, specificity and accuracy of 89%, 79% and 84% respectively.
Four studies (124 patients) reported the results according to TNM notation, of these 81% were correctly staged, 12% were overstaged and 6% were understaged.

For muscularispropria invasion, Bipat et al (2004) reported a pooled sensitivity of 90% (95% CI, 89%-97%) and a pooled specificity of 69% (95% CI, 52%-82%); for perirectal tissue invasion the pooled sensitivity was 82% (95% CI, 74%-87%) and pooled specificity was 76% (95% CI, 65%-84% and for adjacent organ invasion the pooled sensitivity was 74% (95% CI, 63-83%) and pooled specificity was 96% (95% CI, 95%-97%).

A total of 15 studies (14 patients) with a total of 436 MRI scans assessed local nodal involvement by MRI. The pooled sensitivity, specificity and accuracy were 65%, 80% and 74% respectively.
A total of 181 patients (6 studies) received MRI with endorectal surface coil; the pooled sensitivity, specificity and accuracy for this subgroup were 82%, 83% and 82% respectively (Kwok et al, 2000).
Pooled sensitivity was 66% (95% CI, 54%-76%) and pooled specificity was 76% (95% CI, 59%-87%) for lymph node involvement (Bipat et al, 2004).

Specific UK evidence was provided from the Mercury Study group, (Mercury Study Group 2006 and 2007) investigating MRI in the staging of rectal cancer.
The accuracy of MRI for predicting the status of circumferential resection margin (presence/absence of tumour) by initial imaging or imaging after pre-operative treatment was 88% (95% CI, 85%-91%), sensitivity was 59% (95% CI, 46%-72%) and specificity was 92% (95% CI, 90%-95%).
For patients undergoing primary surgery with no pre-operative treatment (n=311), accuracy of prediction of a clear margin was 91% (95% CI, 88%-94%), sensitivity of 42% and specificity of 98%.
For patients undergoing pre-operative chemoradiotherapy or long-course radiotherapy the accuracy of prediction of clear margins on MRI was 77% (95% CI, 69%-86%), sensitivity was 94% and specificity was 73%.
Histopathology results showed 58 patients with affected margins, of which MRI correctly identified 32.
A second publication by the same study group (Mercury Study Group, 2007) evaluated the accuracy of MRI in depicting the extramural depth of invasion in patients with rectal cancer with the primary outcome being equivalence between MRI and histopathology in the measurement of extramural depth of tumour invasion. Information on the depth of extramural tumour invasion was available for both histopathology and MRI in 295 patients. Mean extramural depths of invasion at MRI was 2.8mm (SD±4.6mm) and for histopathology was 2.81mm (SD±4.28mm). The mean difference between MRI and histopathologic analysis was 0.05mm±3.85 (95% CI, -0.49mm-0.4mm) resulting more than 95% certainty that the assessments were equivalent (i.e. MRI was as good as histopathology for the measurement of the depth of extramural invasion). Overall, MRI depicted depth of tumour spread in 92.5% of patients to within 5mm of histopathology and in 7.25% of patients MRI resulted in overestimation of depth of tumour spread by more than 5mm which would have resulted in patients being assigned to the wrong prognostic group.
MRI led to underestimation of tumour depth in 13 patients of which 5 were deemed to be interpretation errors due to movement artefact.

FDG-PET
Three studies investigated the use of FDG-PET in the pre-operative staging of rectal cancer (Kantarova et al, 2003, Llamas-Elvira et al 2007, and Dirisamer et al 2010). All three studies were retrospective case series of poor quality with small numbers of patients and little information on methodology and outcomes provided.
Kantarova et al (2003) reported that FDG-PET correctly detected 95% of primary tumours. For the detection of lymph nodes accuracy was 75%, sensitivity was 29% and specificity was 88%. Liver metastases were present in 9 patients and FDG-PET had an accuracy of 91%, sensitivity of 78% and specificity of 96%.
Llamas-Elvira et al (2007) evaluated FDG-PET in the initial staging of colorectal cancer and reported an accuracy of 56%, sensitivity of 21% and specificity of 95% for N0/N+ staging and an accuracy of 92%, sensitivity of 89% and specificity of 93% for M0/M+ staging.
Dirisamer et al (2010) evaluated the diagnostic role of FDG-PET in the staging and restaging of colorectal cancer and reported an overall accuracy of 84%, sensitivity of 85% and specificity of 70%.

Summary of best results for each factor investigated across the individual studies
Tumour Penetration

Tumour penetration was reported in some form in a total of 6 studies (Kwok et al (2000), Bipat et al (2004), Rafaelson et al (1994), Chun et al (2006), Fuchsjager et al (2003) and The Mercury Study Group (2007)) with some reporting wall penetration as a single outcome and some studies reporting subgroups of penetration including; muscularispropria invasion, perirectal tissue invasion and adjacent organ invasion. From one systematic review study using data from a number of studies (Kwok et al. 2000) EUS had the highest sensitivity (93%) specificity (78%) and accuracy (87%) for wall penetration when compared with CT and MRI, though MRI with endorectal coil was quite similar.

Reported sensitivities for all types of penetration ranged from 72%-79% for CT; 79%-100% for MRI and 70%-94% for EUS. No sensitivities or specificities were reported for either DRE or PET though one study (Rafaelson et al) reported that DRE correctly identified tumour penetration in 73% of cases examined.

Specifically for muscularispropria invasion; from two studies (Bipat et al. 2004, Chun et al. 2006), endoluminal ultrasound/endorectalsonography had the highest sensitivity (100%) and specificity (86%, range: 61.1%-86%) for muscularispropria invasion. Accuracy for endorectalsonography was 90.3%, similar to that of 3-T MRI (91.7%) but this was only reported in one study (Chun et al. 2006).

For perirectal tissue invasion; from two studies (Bipat et al. 2004, Chun et al. 2006) endorectalsonography had the highest sensitivity (100%; range 89%-100%) and accuracy (91.7%), whereas MRI had the highest specificity (92.6%; Range 71%-92.6%) compared to endorectalsonography/endoluminal ultrasound (81.5%; Range 75%-81.5%)

Adjacent organ involvement was specifically reported in 1 study and reported sensitivities and specificities ranged from 70% to 74% and 96%-97% respectively. MRI showed the highest sensitivity at 74%.

Mesorectal Fascia Involvement
Three studies reported on circumferential resection margin or mesorectal fascia involvement (Mercury Study Group, 2006, Rao et al, 2007, and Salerno et al, 2009); all studied used MRI and the Mercury Study Group also reported on DRE.
Salerno et al (2009) reported a significant higher rate of positive resection margins in patients with MRI stage T3/T4 tumours compared with patients with MRI stage T1/T2 tumours (36.7% versus 5.6%, p<0.001). Multivariate analysis showed MRI to be a significant predictor of positive margins (OR for stages T3/T4=15.2, p=0.002). The Mercury Study Group (2006) reported a sensitivity of 42%, 98% and accuracy of 92% for MRI in predicting circumferential margin involvement versus a sensitivity of 38%, specificity of 74% and accuracy of 70% for DRE.
Rao et al (2007) reported that mesorectal fascia was observed in all patients on MRI and found to be involved in 15/67 patients. The reported overall accuracy of predicting mesorectal fascia involvement was 88%, sensitivity was 80% and specificity was 90.4%.

T Stage
T-stage was reported in a number of papers (Kulinna et al. 2004; Bianchi et al. 2005; Akin et al. 2004; Fuchsjager et al. 2003; Halefoglu et al. 2008; Tatli et al 2006, Kim et al. 2006; Mainenti et al 2006, Fillipone et al. 2004; Rao et al. 2007), with some reporting results of comparisons for T-stage as a whole and some reporting results of comparisons for specific T stage. For overall T-stage, from five studies MRI had the highest sensitivity (93%; Range 55%-93%), specificity (9.14%; Range 63%-100%) and accuracy (89.7%; Range 43%-89.7%).

N Stage
N-stage was reported in 6 studies (Kulinna et al. 2004; Bianchi et al 2005; Halefoglu et al. 2008; Low et al. 2003; Tatli et al. 2006; Kim et al. 2006) and nodal involvement was reported in four studies (Kwok et al. 2000; Bipat et al. 2004; Chun et al. 2006; Kantorova et al. 2003). MRI has the highest sensitivity (85%; Range 62%-85%), specificity (98%; Range 69%-98%) and accuracy (95%; Range 64%-95%).

Nodal Involvement
Four studies reported nodal involvement (Kwok et al. 2000; Bipat et al. 2004; Chun et al. 2006; Kantorova et al. 2003) and MRI had the highest sensitivity (82%; Range 65%-82%), specificity (92.3%; Range 80%-92.3%) and accuracy (82%; Range 74%-79.2%).

Interobserver Agreement
Three studies reported on interobserver agreement between readers (Fillipone et al. 2004; Tatli et al. 2006;Kim et al. 2006). Fillipone et al. reported 93% agreement between observers for T-stage when evaluating transverse images alone and 98% agreement when evaluating transverse images and MPR's in combination. For N-stage, interonserver agreement was 90% for transverse images alone and 97% for transverse images and MPR's in combination. Tatli et al. (2006) reported excellent agreement between

observers for prediction of T3 tumours (κ=0.85) and good agreement for the prediction of nodal metastases (κ=0.8) for MRI with phased array coil and endorectal coil. Kim et al. (2006) reported interobserver agreement for both T-staging and N-staging as being moderate to substantial for MRI with 3Twhole body system using 6 elements phased array coil.

	Brown et al (2004)	98	DRE	Favourable and unfavourable prognosis tumours and locally advanced tumours	N/R
	Rafaelson et al (1994)	107	DRE	Depth of Penetration of Rectal Wall	N/R
				Nodal Involvement	N/R

Intervention	Study	Total Number in Study	Intervention	Factors	Sen...
CT	Kwok et al. (2000)	1429	CT	Wall penetration	78%
				Nodal Involvement	52%
	Bipat et al. (2004)		CT	MuscularisPropria Invasion	N/A
				Perirectal Tissue Invasion	79%
				Adjacent organ invasion	72%
				Lymph node Involvement	55%
	Fillipone et al. (2004)	41	CT Colonography - Transverse Images Alone	≤ T2	82%
				T3	76%
				T4	100%
				N0	62%
				N1	27%
				N2	89%
			CT Colonography - Transverse Images in combination with MPR's	≤ T2	92%
				T3	88%
				T4	100%
				N0	81%
				N1	73%
				N2	81%
	Kantorova et al. (2003)	38		Liver metastases	67%
	Kulinna et al. (2004)	92	Multi Slice CT	T-Stage	82%
				N-Stage	68%
				UICC Stage	91%
	Mainenti et al. (2006)	52	CT Colonography	Stage ≤ T2	70%
				Stage T3	97%
				Stage T4	100%
				N+	86%
	Llama-Elvira et al. (2007)	104	CT	N0/N+	25%
				M0/M+	44%
	Kim et al (2006)	31	MDCT	≤T2	79%
				T3	73%
				N0	64%
				N1	63%
				N2	75%
	Nicholls et al (1982)	70	CT	Level of tumour	N/R
				Quadrants Involved	N/R
				Morphology	N/R
				Extent of local spread	N/R
				Lymph Node Involvement	N/R
	Dirisamer et al (2010)	73	Ce CT	Staging and restaging of rectal cancer	91%
	Beynon et al (1986)	44	CT	Staging of palpable rectal tumours	86%

Intervention	Study	Total Number in Study	Intervention	Factors	Sen...
MRI	Kwok et al. (2000)		MRI (All)		86%

Intervention	Study	Total Number in Study	Intervention	Factors	Sen
			MRI at ≥ 1.5T		80%
			MRI (All)	Adjacent organ invasion	74%
				Lymph node Involvement	66%
	Akin et al. (2004)	20	Endorectal MRI	T-Stage	
				Lymph nodes > 0.5cm	90.9%
				Lymph nodes > 1cm	80%
	Bianchi et al. (2005)	49	Body-Coil MRI	T-Stage	55%
				N-Stage	62%
			Phased Array MRI	T-Stage	75%
				N-Stage	63%
	Chun et al. (2006)	24	3-T MRI	MuscularisPropria	100%
				Perirectal Tissue Invasion	91.1%
				Lymph Node Involvement	63.6%
	Fuchsjager et al. (2003)	39	Double Contrast MRI -All	T-Stage	
			Double Contrast MRI at 1.0T MR		
			Double Contrast MRI at 1.5T MR		
			Double Contrast MRI -All	Rectal Wall Penetration	100%
				Nodal Disease	81%
	Halefoglu et al. (2008)	34	Phased Array MRI	T-Stage	79.41
				N-Stage	61.6%
	Low et al. (2003)	48	Presurgical abdominal and pelvic MRI	N-Stage	68%
	Rao et al. (2007)	67	1.5T whole body MRI with phased array multi-coil	≤ pT2	70%
				pT3	90.5%
				pT4	100%
				Mesorectal Fascia involvement	80%
	Tatli et al. (2006)	51	MRI with phased array coil and endorectal coil	T-Stage	93%
				N-Stage	85%
	Kim et al. (2006)	35	3T whole body MRI using six elements phased array coil	T1	88%
				T2	86%
				T3	90%
				N-Stage	80%
	Beets-Tan et al. (2001)	76	1.5T MRI	T2	42%
				T3	89%
				T4	88%
	Brown et al. (2003)	42	1.5T MRI with four element pelvic phased array wrap	Nodal Status (≤5mm)	81%
				Nodal Status (>10mm)	3%
				Nodal Detection (≤5mm)	42%
				Nodal Detection (>10mm)	78%
	Kim et al. (2007)	31	3.0T whole body MRI	≤T2	93%
				T3	92%
				N0	89%
				N1	88%
				N2	100%
	Mercury Study Group (2006)	408	High Resolution MRI with body coil	Circumferential resection margin status	59%
	Brown et al. (1999)	28	1.5T MRI with four element surface coil	Extent of tumour infiltration	N/R
	Salerno et al. (2009)	101	High resolution, body coil, phased array MRI	Positive Resection Margins	N/R
	Mercury Study Group (2007)	679	MRI	Depth of tumour invasion	N/R

Intervention	Study	Total Number in Study	Intervention	Factors	Sen
	Kwok et al. (2000)	3640	Endorectal sonography	Wall Penetration	93%
				Nodal Involvement	71%

Intervention	Study	Total Number in Study	Intervention	Factors	Sen
	Chun et al. (2006)	24	Endorectal Sonography	MuscularisPropria Invasion	100%
				Perirectal Tissue Invasion	100%
				Lymph Node Involvement	57.6%
	Fuchsjager et al. (2003)	39	Transrectal Sonography	T-Stage	
				Rectal Wall Penetration (T1/T2 vs. T3/T4)	93%
				Presence/Absence of Nodal Disease	92%
	Halefoglu et al. (2008)	34	Endorectal Ultrasonography	T-Stage	70.59
				N-Stage	52.94
	Kantorova et al. (2003)	38	Sonography	Liver metastases	25%
	Kulinna et al. (2004)	92	TRUS	T-Stage	59%
				N-Stage	55%
				UICC Stage	67%
	Brown et al (2004)	98	EUS	Favourable prognosis tumours	N/R
				Unfavourable prognosis tumours	N/R
				Locally advanced disease	N/R

Intervention	Study	Total Number in Study	Intervention	Factors	Ser
PET	Kantorova et al. (2003)	38	FDG-PET	Lymph Node Involvement	29%
				Liver Metastases	78%
	Llamas-Elvira et al. (2007)	104	FDG-PET	N0/N+	21%
				M0/M+	89%

Intervention	Study	Total Number in Study	Intervention	Factors	Ser
PET/CT	Tateishi et al. (2007)	53	PET/CT with non-enhanced CT	Nodal Status	85%
			PET/CT with enhanced CT		85%

TABLE 2.2

References

Akin O, Nessar G, Agildere AM, Aydog G (2004) Preoperative staging of rectal cancer with endorectal MR imaging: Comparison with histopathologic findings. *Journal of Clinical Imaging* 28;432-438.

Beets-Tan RGH, Beets GL, Vliegen RFA, Kessels AGH, Van Boven H, De Bruine A, von Meyenfeldt MF, Baeten CGMI, van Engelshoven JMA (2001) Accuracy of magnetic resonance imaging in prediction of tumour-free resection margin in rectal cancer surgery *The Lancet* 357;497-504

Beynon J, Mortensen NJ, Foy DMA, Channer JL, Virjee J, Goddard P (1986) Preoperative assessment of local invasion in rectal cancer: digital examination, endoluminalsonography or omputed tomography *British Journal of Surgery* 73;1015-1017

Bianchi P, Ceriami C, Rottoli M, Torzilli G, Pompili G, Malesci A, Ferraroni M, Montorsi M (2005) Endoscopic Ultrasonography and Magnetic Resonance in Preoperative Staging of Rectal Cancer: Comparison with Histological Findings *Journal of Gastrointestinal Surgery* 9;9:1222-1227.

Bipat S, Glas AS, Slors FJM, Zwinderman AH, Bossuyt PMM, Stoker J (2004) Rectal Cancer: Local Staging and Assessment of Lymph Node Involvement with Endoluminal US, CT and MR imaging – A Meta-Analysis *Radiology* 232;773-783.

Brown G, Davies S, Williams et al (2004) Effectiveness of preoperative staging in rectal cancer: digital rectal examination, endoluminal ultrasound or magnetic resonance imaging? *British Journal of Cancer* 91;23-29

Brown G, Richards C, Bourne A, Newcombe R, Radcliffe A, Dallimore N, Williams G (2003) Morphological predictors of lymph node status in rectal cancer with the use of high-spatial resolution MR imaging with histopathological comparison *Radiology* 227;371-377

Brown G, Richard C, Newcombe R et al (1999) Rectal Carcinoma: Thin Section MR Imaging for staging in 28 patients *Radiology* 211;215-222

Chun HK, Choi D, Kim MJ, Lee J, Yun SH, Kim SH, Lee SJ, Kim CK (2006) Preoperative Staging of rectal Cancer: Comparison of 3-T High Field MRI and Endorectal Sonography *American Journal of Roentgenology* 187;6:1557-1562

Dighe S, Purkayastha S, Swift I et al (2010) Diagnostic precision of CT in local staging of colon cancers: a meta-analysis *Clinical Radiology* 65;708-719

Dirisamer A, Halpern B, Flory D et al (2010) Performance of integrated FDG-PET/contrast enhanced CT in the staging and restaging of colorectal cancer: Comparison with PET and enhanced CT *European Journal of Radiology* 73;324-328

Fillipone A, Ambrosini R, Fushi M, Marinelli T, Genovesi D, Bonomo L (2004) Preoperative T and N staging of colorectal cancer: Accuracy of Contrast-enhanced Multi-Detector Row CT Colonography – Initial Experience. Radiology 231; 83-90

Fuchsjager M, Maier A, Schima W, Zebedin E, Herbst F, Mittlbock M, Wrba F, Lechner G (2003) Comparison of transrectal sonography and double-contrast MR imaging when staging rectal cancer *American Journal of Roentgenology* 181;2:421-427.

Halefoglu A, Yildirim S, Avlanmis O, Sakiz D, Baykan A (2008) Endorectal ultrasonography versus phased array magnetic resonance imaging for preoperative staging of rectal cancer *World Journal of Gastroenterology* 14;22:3504-3510

Kantorova I, Lipska L, Belohlavek O, Visokai V, Trubac M, Schneiderova M (2003) Routine ^{18}F-FDG PET Preoperative staging of colorectal cancer: comparison with conventional staging and its impact on treatment decision making *Journal of Nuclear Medicine* 44;11:1784-1788

Kim CK, Kim SH, Choi D, Kim MJ, Chun HK, Lee SJ, Lee JM (2007) Comparison between 3-T Magnetic Resonance Imaging and Multi-Detector Row Computed Tomography for the Preoperative Evaluation of Rectal Cancer *Journal of Computer Assissted Tomography* 31;853-859

Kim CK, Kim SH, Chun HK, Lee WY, Yun SH, Song SY, Choi D, Lim HK, Kim MJ, Lee J, Lee SJ (2006) Preoperative staging of rectal cancer: accuracy of 3-Tesla magnetic resonance imaging *European Radiology* 16;5:972-980

Kulinna C, Eibel R, Matzek W et al (2004a) Staging of rectal cancer: diagnostic potential of multi-planar reformatting with multidetector CT *AJR* 183:421-427

Kulinna C, Scheidler J, Strauss T, Bonel H, Herrmann K, Aust D, Reiser M (2004b) Local staging of rectal cancer: assessment with double contrast multislice computed tomography and transrectalunltrasound*Journal of Computer Assisted Tomography*

Kwok H, Bisset IP, Hill GL (2000) Preoperative Staging of Rectal Cancer *International Journal of Colorectal Disease* 15;1:9-20

Llamas-Elvira JM, Rodriguez-Fernandez A, Gutierrez Sainz J, Gomez-Rio M, Bellon-Guardia M, Ramos Font C, Rebollo Aguirre AC, Cabello Garcia D, FerronOrihuela A (2007) Fluorine-18 fluorodeoxyglucose PET in the preoperative staging of colorectal cancer. *European Journal of Nuclear Medicine and Molecular Imaging* 34;6:859-867

Low RN, McCue M, Barone R, Saleh F, Song (2003) MR staging of primary colorectal carcinoma: comparison with surgical and histopathological findings *Abdominal Imaging* 28;6:784-793

Mainenti PP, Cirillo LC< Camera L, Perscio F, Cantalupo T, Pace L, De Palma GD, Persico G, Alvatore M (2006) Accuracy of single phase contrast enhanced multidetector CT colonography in the preoperative staging of colorectal cancer *European Journal of Radiology* 60;453-459

Mercury Study Group (2007) Extramural Depth of tumour invasion at thin section MR in Patients with rectal cancer: Results of the Mercury Study Radiology 243;1:132-139

Mercury Study Group (2006) Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study

Nicholls R, York Mason A, Morson B et al (1982) The clinical staging of rectal cancer *British Journal of Surgery* 69;404-409

Rafaelsen S, Kronborg O and Fenger C (1994) Digital rectal examination and transrectal ultrasonography in staging of rectal cancer Acta Radiology 35;3:300-304

Rao SX, Zeng MS, Xu JM, Q XU, Chen CZ, Li RC, Hou YY (2007) Assessment of T-staging and mesorectal fascia status using high-resolution MRI in rectal cancer with rectal distention*World Journal of Gastroenterology* 13;30:4141-4146.

Salerno G, Daniels I, Moran B et al (2009) Magnetic Resonance Imaging Prediction of an Involved Surgical Resection Margin in Low Rectal Cancer *Diseases of the Colon and Rectum* 52;4:632-639

Tatli S, Mortele K, Breen E, Bleday R, Silverman S (2006) Local staging of rectal cncer using combined pelvic phased array and endorectal coil MRI *Journal of Magnetic Resonance Imaging* 23;4:534-540

Tateishi U, Maeda T, Morimoto T, Miyake M, Arai Y, Kim, E (2007) Non-enhanced CT versus contrast enhanced CT in integrated PET/CT studies for nodal staging of rectal cancer *European Journal of Nuclear Medicine and Molecular Imaging* 34;10:1627-1634

Evidence Tables

Citation: Akin O, Nessar G, Agildere AM, Aydog G (2004) Preoperative staging of rectal cancer with endorectal MR imaging: Comparison with histopathologic findings. *Journal of Clinical Imaging* 28;432-438.
Design: Prospective Case Series **Country**: Turkey **Aim**: to assess the accuracy of endorectal MR imaging in the preoperative local staging of rectal cancers.
Inclusion criteria None given
Exclusion criteria One patient was excluded due to the endorectal coil not being placed appropriately. One patient was excluded because the neoplasm extended beyond the scope of the endorectal coil One patient was excluded because they refused surgery.
Population N=20
Interventions Endorectal MRI
Outcomes Sensitivity Specificity
Results Endorectal MRI agreed with histopathological staging in 17/20 patients. The overall accuracy of endorectal MRI for determining T stage of rectal tumours was 85%. (table below) **Table: Comparison of staging based on endorectal MRI and histopathologic staging** 2 tumours were identified as T1 histopathologically and on endorectal MRI 4 tumours were histopathologically identified as being T2, with 2 of these identified on endorectal MRI. In one case invasion of the muscularis propria was not detected on endorectal MRI resulting in the tumour being under-staged to T1 and in the second case the tumour was over-staged to T3 due to inflammatory changes mimicking tumour invasion into the perirectal fat. 12 tumours were histopathologically identified as T3, 11 of these were correctly identified as T3 by endorectal MRI which clearly demonstrated tumoural invasion of the perirectal fat. In one case endorectal MRI under-staged to T2 due to there being no obvious signal intensity change in the perirectal fat. In 2 patients with bulky T4 tumours endorectal MRI accurately demonstrated invasion of adjacent pelvic organs and structures. No significant morphological or signal characteristics on endorectal MRI to differentiate metastatic lymph nodes from normal or inflamed ones. Considering all lymph nodes measuring greater than 0.5cm in short axis to be metastatic the sensitivity and specificity of endorectal MRI were 90.9% and 55.5% respectively and when 1cm was considered the upper limit the sensitivity dropped to 80% though the specificity increase to 70%. (table below) **Table: Sensitivity and specificity for the detection of metastatic lymph nodes with endorectal MRI**

		Histopathologic Staging				
		T1	T2	T3	T4	Total
Endorectal MRI staging	**T1**	2	1	-	-	3
	T2	-	2	1	-	3
	T3	-	1	11	-	12
	T4	-	-	-	2	2
	Total	2	4	12	2	20

		Sensitivity	Specificity
Lymph nodes on endorectal MRI	>0.5cm	90.9	55.5
	>1cm	80	70

General comments
Patients underwent surgery within a week of the endorectal MRI and an experienced pathologist with no knowledge of the imaging findings examined all the surgical specimens.

Citation: Beets-Tan RGH, Beets GL, Vliegen RFA, Kessels AGH, Van Boven H, De Bruine A, von Meyenfeldt MF, Baeten CGMI, van Engelshoven JMA (2001) Accuracy of magnetic resonance imaging in prediction of tumour-free resection margin in rectal cancer surgery *The Lancet* 357;497-504

Design: Case-series

Country: The Netherlands

Aim: To assess the accuracy of phased-array MRI for preoperative staging of rectal carcinoma and the accuracy for predicting the distance of the tumour to the circumferential resection margin in a TME.

Inclusion criteria
None given

Exclusion criteria
None given

Population
N=76

Interventions
MRI at 1.5T

Outcomes
Sensitivity
Specificity
Positive Predictive Value (PPV)
Negative Predictive Value (NPV)

Results
- Final histopathologic staging showed 7 T1 tumours, 13 T2 tumours, 40 T3 tumours and 16 T4 tumours.
- For observer 1, MRI stage agreed with histopathologic staging in 83% of cases (63/76) and for observer 2, MRI stage agreed with histological stage in 67% cases (51/76).
- The intraobserver agreement of observer 1 on tumour stage was good (κ=0.80 [0.69-0.91]) and moderate for observer 2 (κ=0.49 [0.34-0.65]).
- Interobserver agreement was moderate (κ=0.53 [0.38-0.69])

	Observer 1	Observer 2
T2		
Sensitivity	38%	46%
Specificity	94%	83%
PPV	56%	35%
NPV	88%	88%
T3		
Sensitivity	95%	83%
Specificity	75%	61%
PPV	81%	70%
NPV	93%	76%
T4		
Sensitivity	100%	75%
Specificity	100%	100%
PPV	100%	100%
NPV	100%	94%

Table: Results for Observer 1 and Observer 2

- The mesorectal fascia was visualised in all patients on MRI with measured distances from tumour ranging from 0mm to 33mm (mean 9.5mm). Both reviewers noted gross involvement of surrounding organs with an involved mesorectal fascia in 12 patients.
- In 29 patients the pathologist reported a tumour free distance to the margin of at least 10mm, Observer 1 correctly predicted a distance of at least 10mm in 28 of these patients and observer 2 correctly predicted a distance of at least 10mm in 27 patients.
- For observer 1, a tumour free resection margin of at least 2.0mm can be predicted with 97.5% certainty when the measured distance on MRI is at least 5.7mm for the first reading and 5.1mm for the second reading and a tumour free resection margin of at least 1.0mm can be predicted with confidence when the measured distances are at least 4.8mm and 4.1mm.
- For the first reading of observer 2 these figures are 5.2mm for a resection margin of 2.0mm and 4.2mm for a resection margin of 1.0mm. The second reading resulted in a much wider 95% prediction interval because of a

single interpretation error.

- A tumour free margin of at least 1.0mm can be predicted with a high degree of certainty when the measured distance on MRI is at least 5.0mm and a margin of 2.0mm when the distance at MRI is at least 6.0mm.

General comments

Histological tumour stage and distance to the mesorectal fascia were taken as the gold standard against which the MRI findings were compared.

| | Citation: Beynon J, Mortensen NJ, Foy DMA, Channer JL, Virjee J, Goddard P (1986) Preoperative assessment of local invasion in rectal cancer: digital examination, endoluminal sonography or omputed tomography *British Journal of Surgery* 73;1015-1017 |

Design: Prospective Case Series

Country: UK

Aim: to determine whether digital examination (DRE) endorectal sonography (ELU) or CT is the most accurate assessment in the preoperative staging of rectal cancer when compared with postoperative histopathology.

Inclusion criteria
Patients with primary rectal cancer

Exclusion criteria
None given

Population
N=44

Interventions
Digital Rectal Exam (DRE)
Endorectal Sonography (ELU)
CT

Outcomes
Accuracy
Sensitivity
Specificity
Positive Predictive Value (PPV)
Negative Predictive Value (NPV)

Results
- Surgeons were asked to allocate palpable tumours to one of four grades; grade 1 (tumour mobile over the rectal wall), grade 2 (tumour mobile not separable from the rectal wall), grade 3 (slightly fixed) or grade 4 (fixed).
- Digital exam was not possible in 10 patients due to tumour location and DRE was performed in 25 patients as part of an examination under anaesthetic or immediately prior to definitive operation.
- Accuracy of DRE dropped to 52% if non-palpable tumours were included and rose to 73% for prediction of tumours confined to rectal wall or spread beyond.
- There was a high degree of correlation of endoluminal ultrasound with post-operative histology (0.87, p<0.001).

	DRE (n=34)	ELU	CT
Accuracy	68%	91%	82%
Sensitivity	68%	94%	86%
Specificity	83%	87%	62%
Positive Predictive Value	100%	97%	91%
Negative Predictive Value	46%	78%	50%

Table: Results for DRE, ELU and CT

Design: Case Series

Country: Italy

Aim: To comparatively assess the ability of EUS, body coil MRI (BC-MRI) and phased array MRI (PA-MRI) in the preoperative staging of rectal carcinoma using histological findings on the specimen as gold standard.

Inclusion criteria
Patients with resectable rectal carcinoma

Exclusion criteria
Patients undergoing emergency surgery
Patients who underwent previous chemotherapy or radiotherapy

Population
N=49

Interventions
Endoscopic ultrasonography
Body coil MRI
Phased array MRI

Outcomes
Sensitivity
Specificity
Positive Predictive Value
Negative Predictive Value
95% confidence interval of the accuracy of the estimates of the T and N stages

Results
There was no significant difference in the accuracies of T staging for EUS (70%, 95% CI; 65%-90%), BC-MRI (43%, 95% CI; 39%-75%) and PA-MRI (71%, 95% CI; 52%-91%).
There was no significant difference in the accuracies of N staging for EUS (63%, 95% CI; 50%-80%), BC-MRI (64%, 95% CI; 47%-82%) and PA-MRI (76%, 95% CI; 58%-94%).

	T-Stage		N-Stage	
	Sensitivity	**Specificity**	**Sensitivity**	**Specificity**
EUS	0.8	0.67	0.47	0.8
BC-MRI	0.55	0.63	0.62	0.8
PA-MRI	0.75	0.67	0.63	0.8

Table: Sensitivity and Specificity of each imaging modality

	T-Stage		N-Stage	
	Positive Predictive Value	**Negative Predictive Value**	**Positive Predictive Value**	**Negative Predictive Value**
EUS	0.85	0.64	0.67	0.64
BC-MRI	0.79	0.36	0.73	0.71
PA-MRI	0.79	0.57	0.75	0.77

Table: positive and negative predictive values for each imaging modality

	T-Stage		N-Stage	
	Overstaged	**Understaged**	**Overstaged**	**Understaged**
EUS	0.17	0.12	0.1	0.27
BC-MRI	0.25	0.32	0.14	0.21
PA-MRI	0.14	0.14	0.09	0.14

Table: proportions of cases overstaged and understaged by each imaging modality

General comments
Patients with T1-T3 disease were included in the analysis while patients with T4 disease were excluded as they received neoadjuvant therapy.

The mean time from preoperative staging to surgery was 7.5 days.

Authors Conclusions: EUS and PA-MRI provide similar results in assessing the T-stage of rectal cancer, in addition PA-MRI allows good assessment of tumour penetration, provides good visualization of rectal wall layers, is less operator dependent than EUS and is not influenced by tumour size of location.
MRI techniques have slightly better sensitivity and accuracy compared to EUS when it comes to lymph node evaluation.

Citation: Bipat S, Glas AS, Slors FJM, Zwinderman AH, Bossuyt PMM, Stoker J (2004) Rectal Cancer: Local Staging and Assessment of Lymph Node Involvement with Endoluminal US, CT and MR imaging – A Meta-Analysis *Radiology* 232;773-783.
Design: Systematic review and Meta-analysis **Country**: Netherlands **Aim**: to perform meta-analysis to compare endoluminal US, CT and MR imaging in the staging of rectal cancer.
Inclusion criteria Studies were selected for inclusion if they fulfilled the following criteria: • More than 20 patients with histologically proven rectal carcinoma or adenocarcinoma which was not treated with pre-operative chemotherapy and/or radiation therapy • Histopathologic findings were used as the reference standard • Sufficient data were presented to enable the construction of a 2x2 contingency table of the imaging modalities compared with the reference standard for invasion of the submucosa, muscularis propria, perirectal tissue or adjacent organs or lymph node involvement (raw 2x2 data or sensitivity and/or specificity with the absolute numbers of positive and negative findings or standard errors).
Exclusion criteria Reviews, letters, comments, case reports and articles that did not present raw data. Studies where the data was reported elsewhere in more detail
Population 357 articles identified 146 articles potentially eligible 31 articles were excluded due to small numbers (n<20) 1 article was excluded due to a lack or reference standard 19 articles were excluded due to incomplete or inconclusive data 5 articles were excluded due to more detailed reporting of data elsewhere *90 fulfilled the criteria for inclusion*
Interventions Endoluminal ultrasound: type of probe and frequency of transducer CT: type of contrast material (oral, rectal, intravenous), section thickness and use of spiral mode MRI: magnetic field strength, sequence, intravenous contrast material and coil type
Outcomes Summary estimates of sensitivity and specificity

Results

General Study Characteristics

Stage	Imaging Modality	No of data sets	No of patients	Prevalence (%)	Years of Publication
T2	EUS	39	2881	73.1	1985-2002
	CT	2	65	96.9	1986, 1994
	MRI	13	630	83.5	1993-2002
T3	EUS	61	3904	52.7	1985-2002
	CT	18	994	61.1	1985-2002
	MRI	17	746	58.2	1993-2002
T4	EUS	37	2686	7.4	1985-2002
	CT	9	397	6.6	1985-2002
	MRI	11	537	8.4	1993-2002
N	EUS	55	3879	39.9	1986-2002
	CT	18	1123	40.8	1985-2002
	MRI	19	1003	32.5	1986-2002

Table: Study and patient characteristics

From 90 articles, 299 data sets were extracted.
64% of data sets suffered from selective patient sampling
77% suffered suboptimal interpretation of results
73% had poorly described reference standards
90% had complete verification of results
66% had sufficient description of patient populations
89% had sufficient description of diagnostic tests

50% of included data were prospectively collected

Bivariate analysis with covariates was performed to determine whether study results were significantly affected by heterogeneity between individual studies. Variables were considered to be explanatory if their regression coefficients were statistically significant (P<0.05).
Backwards stepwise regression analysis revealed a number of variables as significant predictors of the diagnostic performance of endoluminal ultrasound, CT and MRI for the evaluation of invasion of the muscularis propria, perirectal tissue and adjacent organs and lymph node involvement from rectal cancer. For this stage variables were considered statistically significant if P<0.1

Summary ROC Curves
Summary ROC Curves indicated no difference in diagnostic performance of imaging modalities for lymph node involvement; however curves for perirectal tissue invasion indicated differences in diagnostic performance, with EUS appearing to the better of the three modalities.

Due to the homogeneity of either the sensitivity or specificity values, no intercepts or slopes could be defined for data for invasion in the muscularis propria and adjacent organs.

Summary Estimates of Sensitivity and Specificity

Muscularis propria invasion
No analysis could be performed for CT due the small number of data sets available
No significant variables were identified for MRI
Publication year and sample size (>50 patients) were included as co-variates for endoluminal ultrasound

Perirectal tissue invasion
Covariates in the final model included consecutive patient selection for endoluminal ultrasound, publication year for CT and prospective data collection for MRI.

Adjacent organ invasion
The final model included year of publication and sample size (>50) patients as covariates for endoluminal ultrasound, and publication year for MRI. No significant covariates were identified for CT.

Lymph node involvement
Year of publication and prospective data collection for endoluminal ultrasound, complete verification for CT and year of publication and blind interpretation of results for MRI were included in the final model.

Stage	Imaging Modality	Sensitivity (95% CI)	Specificity (95% CI)
Muscularis propria invasion	EUS	94% (90, 97)	86% (80, 90)
	CT	NA	NA
	MRI	90% (89, 97)	69% (52, 82)
Perirectal tissue invasion	EUS	90% (88, 92)	75% (69, 81)
	CT	79% (74, 84)	78% (73, 83)
	MRI	82% (74, 87)	76% (65, 84)
Adjacent organ invasion	EUS	70% (62, 77)	97% (96,98)
	CT	72% (64, 79)	96% (95, 97)
	MRI	74% (63, 83)	96% (95, 97)
Lymph node involvement	EUS	67% (60, 73)	78% (71, 84)
	CT	55% (43, 67)	74% (67, 80)
	MRI	66% (54, 76)	76% (59, 87)

Table: Summary estimates of sensitivity and specificity in the staging of rectal cancer

- Endoluminal ultrasound specificity was significantly higher than that of MRI for muscularis propria invasion (p =0.02).
- For perirectal tissue invasion the sensitivity estimate for endoluminal ultrasound was significantly higher than for CT (p<0.001) and MRI (p=0.003). The specificity estimates did not differ significantly for any of the modalities.
- Sensitivity and specificity estimates did not differ significantly for any modality for adjacent organ invasion.
- There was no significant difference in sensitivity or specificity in relation to lymph node involvement.

Imaging Modality and Technique	Sensitivity (95% CI)	Specificity (95% CI)
MRI with body coil	83 (70, 91)	75 (54,88)
MRI with body coil and additional coil	79 (68, 87)	73 (57, 84)
MRI without contrast material	80 (61, 91)	76 (52, 90)
MRI with contrast material	81 (72, 87)	71 (59, 81)

MRI at <1.5T	86 (70, 94)	73 (48, 89)
MRI imaging at >= 1.5T	80 (70, 87)	74 (60, 84)
Endoluminal US at <7.5 MHz	91 (85, 94)	79 (76, 82)
Endoluminal US at >=7.5 MHz	89 (85, 92)	79 (71, 85)

Table: Subgroup analysis of MRI and EUS for perirectal tissue invasion

No significant difference was observed between the different techniques for MRI or EUS on subgroup analysis for perirectal tissue invasion.

General comments
The following study design characteristics were scored:
- Patient selection (consecutive, non-consecutive)
- Interpretation of test results (blinded, not blinded)
- Verification (complete or partial, if more than 10% of the study group was not subjected to the reference test the study was scored as applying partial verification)
- Methods of data collection (prospective, retrospective or unknown)
- Reporting of study population (sufficient or insufficient – a description was deemed sufficient if at least age and male to female ratio of participants were included)
- Reporting of diagnostic tests (sufficient or insufficient)
- Reporting of reference tests (sufficient or insufficient)
- Year of publication
- Sample size (number of patients)
- Mean patient age

Citation: Brown G, Davies S, Williams et al (2004) Effectiveness of preoperative staging in rectal cancer: digital rectal examination, endoluminal ultrasound or magnetic resonance imaging? *British Journal of Cancer* 91;23-29
Design: Prospective diagnostic Case Series
Country: UK
Setting:
Aim: to determine to accuracy of MRI, DRE and EUS in the identification of favourable, unfavourable and locally advanced rectal carcinoma compared with pathologic findings.
Inclusion criteria Patients with biopsy diagnosed rectal cancer
Exclusion criteria None given
Sample Size N/A
Randomisation Method N/A
Population N=98
Study Duration No details
Interventions DRE MRI EUS
Outcomes Preoperative identification of favourable prognosis tumours, unfavourable prognosis tumours and locally advanced tumours.
Results *Favourable Prognosis Tumours* DRE correctly identified 71%(22/31) of patients with favourable prognosis tumours; 4 tumours were not identified due to location (beyond the reach of DRE), in 3 cases apparent tethering indication more extensive extramural spread was not confirmed on histologic examination, in 2 cases bulky tumours deemed fixed on clinical assessment were found to be confined to the rectal wall on subsequent histopathologic examination. EUS identified 45% (14/31) of patients with favourable prognosis tumours; in 15 patients, failure to reach the tumour using the EUS probe was the reason for failure. MRI correctly identified all patients with favourable prognosis tumours, however in 9 patients there was overlap between MRI and histology assessment. *Unfavourable Prognosis Tumours* Clinical assessment (DRE) correctly identified 36% (14/39) of patients with tumour extension into perirectal fat and/or node positive status. In 22/39 patients clinical assessment judged tomours as mobile and 9/22 showed tumour spread >5mm into perirectal fat that were not clinically tethered. In 3/39 patients, clinical assessment suggested tumour fixation. EUS assessment correctly identified 82% (32/39) and MRI correctly identified 85% (33/39) of patients with unfavourable prognosis tumours. *Locally advanced tumours* 3/28 of patients with features indicative of locally advanced disease were identified by DRE with the remainder classified as unfavourable (n=18) or favourable (n=7). EUS identified 1 locally advanced case with tumour unassessable in 12 patients and in the remaining 15 patients, tumour deposits involving the mesorectal fascia resulting in positive CRM had not been identified.

MRI correctly identified 22/28 locally advanced tumours. In 4 cases, nodes close to the mesorectal fascia had not been detected and in 2 cases tumour was thought to have breached the wall anteriorly by <1mm though histopathologic examination showed stage pT4 peritoneal infiltration by tumour.

There was a high degree of agreement between MRI and histological assessment of tumour favourability (94%, κ=0.81, SE=0.05, weighted κ=0.83)
There was poor agreement between DRE and histological assessment (65%, κ=0.08, SE=0.068, weighted κ=0.16).
There was poor agreement between EUS and histological assessment (69%, κ=0.17, SE=0.065, κ=0.17).

Treatments
Based on the results of DRE, 51 patients would have had surgery alone, 39 patients would have had short course radiotherapy and 8 patients would have had long-course radiotherapy versus 22, 14 and 3 patients in each treatment group when basing the results on histopathologic assessment. The remainder of the patients would have been over or under treated.
On EUS staging 48% of patients would have been correctly selected while on MRI staging 88% of patients would have been correctly selected.

Citation: Brown G, Richards C, Bourne A, Newcombe R, Radcliffe A, Dallimore N, Williams G (2003) Morphological predictors of lymph node status in rectal cancer with the use of high-spatial resolution MR imaging with histopathological comparison *Radiology* 227;371-377

Design: Case Series

Country: UK

Aim: To evaluate signal intensity and border characteristics of lymph nodes at high-spatial resolution magnetic resonance imaging in patients with rectal cancer and to compare the findings with size in prediction of nodal status.

Inclusion criteria
Patients who underwent total mesorectal excision of the rectum with a biopsy to determine whether they had rectal carcinoma.

Exclusion criteria
None given

Population
N=42

Interventions
MRI at 1.5T with a four element pelvic phased array wrap around surface coil

Outcomes
Sensitivity
Specificity

Results
437 lymph nodes were harvested from 42 patients, of these 102; all with diameters less than 3mm were not identified on MRI. An additional 51 (7 containing metastasis) lymph nodes were above the area imaged by MRI leaving a total of 284 lymph nodes available for evaluation.

Nodal Size Criteria
The size of lymph nodes containing metastases varied greatly at MRI; 58% (35/60) of positive lymph nodes had a diameter of less than 5mm.
MRI measurement of nodal diameter ranged from 2-10mm in 119 benign nodes from 20 patients with node-negative status and from 3-15mm in 60 cancerous nodes from 22 patients with node-positive status.
In 71% of patients with lymph node metastases, the size of normal or reactive nodes was similar to or greater than the smallest positive node in the same specimen.

	Sensitivity	Specificity
≤5mm		
Nodal Status	81%	68%
Nodal Detection	42%	87%
>10mm		
Nodal Status	3%	100%
Nodal Detection	78%	59%

Table: Sensitivity and Specificity

The overall predictive value of MR size is poor due to substantial overlap in size between nodes that are benign and malignant.

Signal Intensity and Border Characteristics
- The signal intensity and border characteristics could not be evaluated further due to image degradation caused by motion artefact in 3/284 nodes depicted by MRI.
- 75 of the remaining 281 nodes were hyper-intense on MRI and of these 3 (4%) were malignant.
- 91 nodes were iso-intense on MRI with 7 (8%) malignant.
- 83 nodes were hypo-intense on MRI, with 11 (13%) malignant.
- 32 nodes showed mixed signal intensity on MRI, with 29 (91%) malignant.
- Using mixed signal intensity alone as a marker for nodal involvement gave a sensitivity of 48% and specificity of 99%.
- 15/232 nodes with smooth borders contained metastases compared with 45/49 nodes with irregular borders thus giving a sensitivity of 75% and a specificity of 98%.
- Defining a positive node as one with either irregular border or mixed signal intensity gave a sensitivity of 85%

(95% CI: 74%, 92%) and specificity of 98% (95% CI: 95%, 99%).
- Using lymph node contour and MR signal intensity to identify patients with nodal metastases resulted in a sensitivity of 77% (95% CI: 57%, 90%) and a specificity of 95% (95% CI: 76%, 99%)
- A comparison of nodal sensitivity and specificity between the assessment of morphology (irregular border or mixed signal intensity) and node size (cut-off of >5mm) showed a significant difference in both sensitivity (43%; 95% CI: 28%, 56%) and specificity (11%; 95% CI: 6%, 16%) in favour of morphology.

General comments
MR images of the nodes were characterized according to nodal size and border contour and signal intensity.
Nodal size criteria – maximum diameter of the lymph node was measured in millimeters
Border Contour and Signal Intensity – borders of each node were classified as smooth and well-defined or as irregular and ill-defined.

Citation: Brown G, Richard C, Newcombe R et al (1999) Rectal Carcinoma: Thin Section MR Imaging for staging in 28 patients *Radiology* 211;215-222

Design: Prospective Case Series

Country: UK

Setting:

Aim: To evaluate the accuracy of thin-section MRI in the preoperative assessment of extramural tumour infiltration.

Inclusion criteria Patients with rectal carcinoma proven by means of endoluminal biopsy using snare forceps at the time of initial clinical presentation
Exclusion criteria None given
Sample Size N/A
Randomisation Method N/A
Population N=28 (8 females and 20 males)
Study Duration No details given
Interventions MRI with a 1.5T whole body system using a four element flexible wrapping around surface coil performed 7 days before surgery and within 4 weeks of initial assessment and biopsy.
Outcomes Diagnostic Accuracy of MRI using a four element surface coil, in determining the extent of tumour infiltration compared with histopathology

Results

All patients received preoperative short course radiotherapy followed by total mesorectal excision or abdominoperineal excision.

Each MR image was interpreted by two experienced readers independently and without the knowledge of clinical and histopathologic data.

MRI allowed visualisation and delineation of the layers of the rectal wall and mesorectal fascia in all patients and tumour was identified as having higher signal intensity than the circular and longitudinal muscle layers but a lower intensity than the submucosa.

The primary criterion for the differentiation between T1 and T2 lesions was the lack of extension of the tumour into the circular muscular layer.
The primary criterion for the differentiation between T2 and T3 tumours was infiltration of perirectal fat, further defined as extension beyond the contour of the interface between muscle and fat with a rounded or nodular advancing margin.

Tumour Staging of Rectal Carcinoma
Histopathologic examination showed 5 T", 18 T3 and 2 T4 tumours
3 patients had tumour present at the circumferential excision margins of a portion of the specimen, indicating incomplete excision but no positive histologic evidence of adjacent organ invasion and so these patients were not included in the tumour staging analysis.

There was complete agreement between both readers and MRI correctly predicted the overall histopathologic stage of every completely excised tumour.

11 patients were found to have discrete extraluminal deposits not in continuity with the main tumour; none could be proved to be within lymph nodes though 7/11 had unequivocal involvement of other lymph nodes.

5/17 patients without extramural deposits on MRI were found to have lymph node metastases.

Extramural deposits were found in every patient with involved resection margins.

Measurement of the Depth of Extramural tumour Penetration
23 patients had extramural tumour spread and there appeared to be good agreement between the measured depth visible on preoperative MRI and the corresponding histopathologic slices.

Preoperative MR assessment of extramural penetration in incompletely excised specimens
5/11 patients with extraluminal deposits did not have complete excision at the circumferential margin.
2 patients had involvement of the posterior mesorectal margin and the same two patients represented the greatest measured depth of extramural invasion visible on preoperative MRI (45mm and 30mm compared with a median of 6mm and range of 1-19mm in patients with posterior extramural spread in whom local excision was complete).
The remaining 3 patients had low rectal tumours with anterior margin involvement; 2 were men with seminal vesicle invasion resulting in a histopathologic classification of stage T4. The measured extramural tumour penetration visible on preoperative MRS was 4mm and 5mm compared with <1mm in 2 men with completely excised low anterior tumours.
The remaining female patient had extramural penetration measured at 14mm, no other women had low anterior rectal tumours.

Citation: Chun HK, Choi D, Kim MJ, Lee J, Yun SH, Kim SH, Lee SJ, Kim CK (2006) Preoperative Staging of rectal Cancer: Comparison of 3-T High Field MRI and Endorectal Sonography *American Journal of Roentgenology* 187;6:1557-1562
Design: Case Series
Country: South Korea
Aim: to compare phased-array 3-T MRI and endorectal sonography in the preoperative staging of rectal cancer
Inclusion criteria
Exclusion criteria
Population N=24 patients with rectal cancer
Interventions 3-T MRI Endorectal sonography
Outcomes Sensitivity Specificity Diagnostic Accuracy
Results For local invasion, sensitivity and specificity of endorectal sonography and MRI were calculated as follows: for muscularis propria invasion, stage T2 or higher versus stage T1, for perirectal tissue invasion, stage T3 or higher versus stage T2 or lower and for invasion of adjacent organs, stage T4 versus stage T3 or lower. All rectal cancers were identified on both endorectal sonography and MRI For local invasion, histopathological examinations revealed 6 T1 cancers, 3 T2 cancers and 15 T3 cancers *Local Invasion* *Muscularis Propria* Mean sensitivity and specificity of MRI for all observers was 100% and 66.7% respectively and for endorectal sonography the mean sensitivity and specificity for all observers was 100% and 61.1% respectively. There was no significant difference in the mean sensitivities or specificities for either modality. The positive predictive value of MRI was 90% and for endorectal sonography was 88.5% and the negative predictive values for both modalities were 100%. The accuracies of MRI and endorectal sonography for all observers were 91.7% and 90.3% respectively. Results of ROC assessment of pooled data from three observers, the Az value of MRI and endorectal sonography showed no statistically significant difference in diagnostic accuracy. *Perirectal tissue invasion* The mean sensitivity and specificity of MRI for all observers was 91.1% and 92.6% respectively and for endorectal sonography the mean sensitivity and specificity for all observers was 100% and 81.5% respectively. There was no significant difference in the mean sensitivities or specificities for either modality. The positive predictive value of MRI was 95.3% and for endorectal sonography was 90% and the negative predictive values for both modalities 86.2% for MRI and 100% for endorectal sonography. The accuracies of MRI and endorectal sonography for all observers were 91.7% and 93.1% respectively. Results of ROC assessment of pooled data from three observers the Az value of endorectal sonography had higher diagnostic accuracy than that of MRI (p=0.028). *Lymph Node Involvement* From histopathological examination 225 lymph nodes from the rectal cancer specimens of 21 patients that underwent total mesorectal excision were identified. 35/225 (15.6%) were found to be metastatic; 13 had N0 disease, 7 had N1 disease and 4 had N2 disease. The mean sensitivity and specificity of MRI for lymph node involvement was 63.6% and 92.3% respectively and for endorectal sonography the mean sensitivity and specificity for all observers was 57.6% and 82.1% respectively. There was no significant difference in the mean sensitivities or specificities for either modality. The positive predictive value of MRI was 87.5% and of endorectal sonography was 73.1% and the negative predictive values for both modalities were 75% for MRI and 69.6% for endorectal sonography.

The accuracies of MRI and endorectal sonography were 79.2% and 70.8% respectively.
There was no significant difference in diagnostic accuracy for the three observers on ROC assessment of pooled data.

Performance Measures by Imaging Technique	Muscularis Propria Invasion	Perirectal Tissue Invasion	Lymph Node Involvement
Sensitivity			
3-T MRI	100% (54/54)	91.1% (41/45)	63.6% (21/33)
Endorectal Sonography	100% (54/54)	100% (45/45)	57.6% (19/33)
Specificity			
3-T MRI	66.7% (12/18)	92.6% (25/27)	92.3% (36/39)
Endorectal Sonography	61.1% (11/18)	81.5% (22/27)	82.1% (32/39)
Diagnostic Accuracy (Az)			
3-T MRI	0.971 +/- 0.018	0.938 +/- 0.028	0.776 +/- 0.056
Endorectal Sonography	0.978 +/- 0.015	0.996+/- 0.007	0.721 +/- 0.061

Table: Mean sensitivity, specificity and diagnostic accuracy of 3-T MRI and Endorectal Sonography in Preoperative staging of Rectal Cancer by three observers.

Interobserver agreement
The kappa values for muscularis propria invasion showed good or excellent agreement for both imaging techniques. For perirectal tissue invasion the kappa values among observers showed excellent agreement for both techniques. In relation to lymph involvement showed moderate agreement for MRI and good or excellent agreement for endorectal sonography.

Imaging Technique	Muscularis Propria Invasion	Perirectal Tissue Invasion	Lymph node Involvement
3-T MRI			
Observer 1 vs. Observer 2	0.7	0.83	0.503
Observer 1 vs. Observer 3	0.7	0.83	0.417
Observer 2 vs. Observer 3	1	0.822	0.417
Endorectal Sonography			
Observer 1 vs. Observer 2	1	0.903	0.798
Observer 1 vs. Observer 3	0.833	0.903	1
Observer 2 vs. Observer 3	0.833	1	0.798

Table: Interobserver agreement in preoperative staging of rectal cancer

Citation: Dighe S, Purkayastha S, Swift I et al (2010) Diagnostic precision of CT in local staging of colon cancers: a meta-analysis *Clinical Radiology* 65;708-719
Design: Systematic Review
Country: **Setting:** **Aim**: to determine the accuracy and limitations of CT in identifying poor prognostic factors (muscularis propria invasion and detection of malignant lymph nodes) in colon cancers and to determine which CT technique achieved the best results.
Inclusion criteria CT used to stage colonic tumours preoperatively Provided information on the tumour invasion beyond the muscularis propria and presence of malignant lymph nodes (N stage) Histopathologic analysis as the reference standard Sufficient per patient data was provided in order that the 2x2 tables could be extracted.
Exclusion criteria No clear exclusion criteria given however studies were excluded for a variety of reasons including: Studies in which the majority of tumours analysed were rectal lesions 2x2 tables could not be extracted No English translation No histology results No differentiation between T2 and T3 lesions
Sample Size N/A
Randomisation Method N/A
Population N=19 studies from which the requisite data could be extracted
Study Duration N/A
Interventions Preoperative CT
Outcomes Sensitivity and specificity of CT to differentiate between T1/T2 and T3/T4 tumours and lymph node involvement
Results 19 studies with a total of 907 patients were considered for analysis. Sensitivity and specificity for the detection for muscularis propria invasion could be derived from 17 studies (n=784 patients) and overall sensitivity and specificity for detection of malignant lymph nodes could be derived from 15 studies (n=674 patients). There was evidence from the funnel plots that smaller studies were associated with a larger diagnostic odds ratio for both tumour invasion and lymph node detection, though this was not statistically significant (p=0.07). *False Positives and False Negatives* A significant number of false negatives for muscularis propria invasion resulted in understaging of T3/T4 tumours in 4 studies however the three of the four studies were older and CT was performed without the benefit of spiral or MDCT and with a section thickness of 10mm which may be a factor in the failure to detect small amount of tumour invasion. In the fourth study, there did not appear to be any reason for the high false negative rate other than the possibility that the study population included many patients with microscopic invasion beyond the muscularis propria. The false positive rate was low in all included studies suggesting that CT can reliably identify T3/T4 tumours. For nodal involvement, earlier studies showed poor results for similar reasons.

Distinction between T1/T2 and T3/T4 tumours
Earlier studies did not make the distinction between T3 (tumour extension beyond muscularis propria) and T4 tumours (tumour with perforation, invading adjacent organs, penetrating peritoneal surface).

A summary estimate (derived by bivariate random effects model) for differentiating between T1/T2 and T3/T4 tumours was 86% (95% CI 78-92%) for sensitivity and 78% (95% CI 71-84%) for specificity.

From eight studies, the summary estimate for differentiating between T3 and T4 disease was 92% for sensitivity and 81% for specificity

	Studies (n)	Patients (n)	Sensitivity (95% CI)	Specificity (95% CI)	Diagnostic Odds Ratio (95% CI)	P value for publication bias
All Studies Combined	17	784	0.86 (0.78-0.92)	0.78 (0.71-0.84)	22.4 (11.9-42.4)	0.07
Quadas Score ≥12	9	448	0.92 (0.83-0.97)	0.84 (0.73-0.91)	58.3 (19-179.2)	0.11
Assessment of TNM staging (distinction between T3 and T4)	8	399	0.92 (0.87-0.95)	0.81 (0.7-0.89)	48.6 (22.9-103.1)	0.51
Section thickness ≤5mm	7	272	0.95 (0.88-0.98)	0.84 (0.74-0.91)	95.3 (38-238.6)	0.63
Rectal insufflations with air or water	8	336	0.95 (0.9-0.97)	0.86 (0.76-0.92)	104.5 (44.8-243.9)	0.43
Oral contrast	6	255	0.84 (0.63-0.94)	0.79 (0.66-0.88)	20.1 (5.7-70.5)	0.22
Spiral CT or MDCT	13	590	0.93 (0.86-0.96)	0.81 (0.72-0.87)	53.5 (24-119.7)	0.04
Studies after 2000	10	499	0.92 (0.84-0.96)	0.8 (0.7-0.88)	46.6 (19.4-112.2)	0.11
Studies before 2004	8	406	0.92 (0.81-0.97)	0.81 (0.68-0.89)	44.9 (15.4-130.7)	0.18
Spiral CT	7	384	0.92 (0.82-0.97)	0.74 (0.63-0.82)	32.7 (12.1-88.5)	0.21
MDCT	6	206	0.93 (0.85-0.97)	0.86 (0.75-0.93)	48.6 (22.9-103.1)	0.64

Table: Tumour Invasion

	Studies (n)	Patients (n)	Sensitivity (95% CI)	Specificity (95% CI)	DOR (95%CI)	p-value for publication bias
Overall Analysis	15	674	0.70 (0.59-0.8)	0.78 (0.66-0.86)	8.1 (4.7-14.1)	0.07
Quadas score ≥12	8	354	0.78 (0.69-0.84)	0.79 (0.66-0.88)	113 (5.6-30.2)	0.09
Section thickness ≤5mm	6	220	0.82 (0.68-0.91)	0.75 (0.62-0.84)	13.6 (4.7-39.7)	0.048
Rectal insufflations with air or water	8	366	0.78 (0.69-0.85)	0.78 (0.64-0.87)	12.6 (5-31.9)	0.14
Oral contrast	6	316	0.66 (0.51-0.79)	0.79 (0.53-0.92)	7.1 (3.1-16.7)	0.45
Spiral CT or MDCT	11	480	0.76 (0.68-0.83)	0.75 (0.65-0.84)	9.7 (4.9-19.3)	0.045
Studies after 2000	6	266	0.75 (0.62-0.85)	0.77 (0.64-0.87)	10.4 (4.2-25.5)	0.25
Studies before 2004	5	206	0.79 (0.65-0.88)	0.8 (0.65-0.9)	15.1 (6.7-33.6)	0.97
Spiral CT	7	346	0.69 (0.6-0.77)	0.78 (0.64-0.88)	8 (3.3-19.4)	0.27
MDCT	4	134	0.87 (0.77-0.93)	0.7 (0.55-0.83)	15.3 (6.15-38.19)	0.39

Table: Subgroup Analysis for Nodal Detection

Citation: Dirisamer A, Halpern B, Flory D et al (2010) Performance of integrated FDG-PET/contrast enhanced CT in the staging and restaging of colorectal cancer: Comparison with PET and enhanced CT *European Journal of Radiology* 73;324-328
Design: Retrospective analysis of diagnostic exams **Country**: USA **Setting:** **Aim**: to evaluate the diagnostic role of 18-FDG-PET/CT including a contrast enhanced CT component compared with FDG PET and CECT alone.
Inclusion criteria Biopsy proven primary colorectal cancer, suspected recurrent CRC or suspected distant disease recurrence on the basis of other imaging tests, tumour markers or clinical symptoms.
Exclusion criteria Patients who had received chemotherapy or radiotherapy within 4 weeks prior to PET CT scan. Patients with co-existent non-colorectal disease
Sample Size N/A
Randomisation Method N/A
Population N=73
Study Duration Patients were examined between July 2004 and May 2007
Interventions 18-FDG PET/CT
Outcomes Sensitivity Specificity Positive Predictive Value Negative Predictive Value Accuracy
Results Patients image data sets were blinded and separated into CT, PET and PET-CT images PET images were interpreted by an experienced nuclear medicine physician; CT images were interpreted by a radiologist who was blinded to the PET findings. Lesion by lesion and patient by patient analysis were conducted performed with PPET/CT images reviewed 6 weeks after reading the PET and CT datasets. The accuracy of the imaging findings was determined by histological verification or patient follow-up which included histopathologic evaluation of lesions found by imaging or clinical follow-up with available clinical data. For bone metastasis, follow-up examinations were scintigraphy and/or CT/MRI. Mean clinical follow-up was 18 months. 26/73 patients underwent PET/CT for staging and 47/73 for restaging. A total of 266 lesions were identified based on histopathology or clinical/imaging follow-up demonstrating either disease progression or response. On a lesion by lesion basis PET/CT identified 28 metastatic lesions not detected on ce-CT alone and 40 lesions not detected on PET alone. PET/CT correctly identified 266 lesions and was false positive in 2 lesions. PET detected only 14/41 lung metastases, the majority of which were smaller than 8mm. CT detected only 48/72 lymph node metastases with the missed lesions smaller than 12mm in the short axis.

PET/CT correctly identified 107 liver lesions while CT alone detected 103 and PET alone detected 99 lesions.

On a patient basis, every 73 patients were correctly diagnosed with PET/CT.

	Number of Lesions	Staging	Restaging	PET/CT	ce-CT	PET
Local Recurrence	34		34	35	34	35
Lymph Nodes	72	24	48	72	48	72
Liver	107	55	52	108	103	99
Lung	41	10	31	41	41	14
Peritoneal Carcinomatosa	9	3	6	9	9	4
Bone	3	3	0	3	3	3

Table: Summary of Malignant lesion and lesion detection of each modality

	PET	ce-CT	PET/CT
Sensitivity	85%	91%	100%
Specificity	70%	100%	81%
PPV	97%	100%	99%
NPV	25%	33%	100%
Accuracy	84%	86%	99%

Table: Diagnostic Value of PET, ce-CT and PET/CT in the staging and restaging of colorectal cancer

Citation: Fillipone A, Ambrosini R, Fushi M, Marinelli T, Genovesi D, Bonomo L (2004) Preoperative T and N staging of colorectal cancer: Accuracy of Contrast-enhanced Multi-Detector Row CT Colonography – Initial Experience. *Radiology* 231; 83-90

Design: Prospective Case Series

Country: Italy

Aim: To evaluate the accuracy of contrast material-enhanced multidetector row computed tomographic (CT) colonography for preoperative staging of colorectal cancer.

Inclusion criteria
Patients with histopathologically proven colorectal cancer

Exclusion criteria
None given

Population
N=41

Interventions
CT Colonography

Outcomes
Sensitivity
Specificity
Accuracy
Positive Predictive Value
Negative Predictive Value

All of the above were calculated for transverse images alone and in combination with MPRs for T and N staging.

Differences in accuracy for T and N staging were calculated.

Results
All 41 colorectal cancers were identified on contrast-enhanced CT colonography as a wall thickening of more than 0.5cm.
Tumours were correctly located in the rectum in 26 patients, the sigmoid colon in 8 patients, the descending colon in 3 and the ascending colon in 4 patients.

T Staging
At histopathological examination, 3/41 neoplasms were staged as pT1, 10/41 as pT2, 25/41 as pT3 and 3/41 as pT4. Overall accuracy of CT colonography was 73% (30/41) when evaluating transverse images alone and improved to 83% (34/41) when evaluating transverse and MPR images in combination.
Over-staging occurred in 22% (9/41) and under-staging occurred in 5% (2/41) patients when using transverse images. When using combined transverse images and MPRs, over-staging occurred in 12% (5/41) patients and under-staging occurred in 5% (2/41) patients.

Stage		Accuracy	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
≤T2 (n=13)	Transverse Images Alone	90%	82%	93%	82%	93%
	Transverse and MPR images combined	93%	92%	93%	86%	96%
T3 (n=25)	Transverse Images Alone	85%	76%	100%	100%	73%
	Transverse and MPR images combined	90%	88%	94%	96%	83%
T4 (n=3)	Transverse Images Alone	80%	100%	79%	27%	100%
	Transverse and MPR images combined	98%	100%	97%	75%	76%

Table: Results for contrast enhanced CT colonography for each T-stage

N-Staging
At histopathological examination 21/41 neoplasms were staged as pN0, 11/41 as pN1 and 9/41 as pN2. Overall accuracy of N-stage assessment on contrast enhanced multi detector row CT colonography was 59%.
Over-staging occurred in 29% of patients and under-staging occurred in 12% of patients. When using combined transverse images and MPRs, overall accuracy increased to 80% and over-staging occurred in 12% of patients and under-staging occurred in 7% of patients. The difference between transverse images alone and transverse images

in combination with MPRs was statistically significant (p<0.01).

Stage		Accuracy	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
N0 (n=21)	Transverse Images Alone	71%	62%	80%	76%	67%
	Transverse and MPR images combined	85%	81%	90%	89%	82%
N1 (n=11)	Transverse Images Alone	63%	27%	77%	30%	74%
	Transverse and MPR images combined	83%	73%	87%	67%	90%
N2 (n=9)	Transverse Images Alone	83%	89%	81%	57%	96%
	Transverse and MPR images combined	93%	89%	94%	80%	97%

Table: Results for contrast enhanced CT colonography for each N-stage

Nodal metastases were detected in 80% (16/20) of patients using transverse images alone and in 90% (18/20) of patients when using combined images. 59% of patients without nodal metastases were correctly classified using transverse images alone and 77% were correctly classified using transverse images and MPR's in combination.

Interobserver Agreement
Two independent readers were partially blinded to endoscopic results and completely blinded to lesion size, macroscopic features and stage of colorectal cancer. Blinded consensus was used to resolve disagreements between radiologists. For T-stage, overall there was 93% agreement when evaluating transverse images alone and 98% agreement when evaluating transverse images and MPRs in combination. For N-stage, overall agreement was 90% for transverse images alone and 97% for transverse images and MPRs combined.

General comments
CT readers considered three T stages; ≤T2 (to account for known limitations of CT in distinguishing T1 and T2 lesions), T3 (defined as tumours with rounded or nodular advancing margins) and T4.

For N stage, N1 was defined as a cluster of three nodes, independent of size or if fewer than three lymph nodes were present with at least one of them measuring at least 1cm in long axis. N2 was defined as more than three perivisceral lymph nodes regardless of size and N3 was considered to be the presence of enlarged retroperitoneal lymph nodes (≥1cm in long axis).

Citation: Fuchsjager M, Maier A, Schima W, Zebedin E, Herbst F, Mittlbock M, Wrba F, Lechner G (2003) Comparison of transrectal sonography and double-contrast MR imaging when staging rectal cancer *American Journal of Roentgenology* 181;2:421-427.
Design: Prospective Case Series
Country: Austria
Aim: to assess the accuracy of double contrast MR imaging compared with transrectal sonography in the preoperative staging of rectal cancer.
Inclusion criteria None given
Exclusion criteria None given
Population N=39
Interventions Double contrast MRI Transrectal sonography
Outcomes Sensitivity Specificity

Results
Overall
In 28 patients that underwent both MRI and transrectal sonography, the overall accuracies for MRI were 57% for T-stage and 79% for bowel wall penetration, for transrectal sonography the overall accuracies were 64% for T-stage and 83% for bowel wall penetration. There was no significant difference between MRI and transrectal sonography with regard to T-stage (p=0.6).

Transrectal Sonography
It was not possible to do endosonographic imaging in 28% of patients either due to the tumour being located to high in the rectum or because the tumour was stenotic.
In the remaining patients transrectal sonography had an overall accuracy of 64% for T-stage.
For rectal wall penetration for stages T1 and T2 versus T3 and T4, transrectal sonography showed a sensitivity of 93% (95% CI, 66.1-99.8%), a specificity of 71% (95% CI, 41.9%-91.6%) and an accuracy of 82% (Dukes Classification).
7 patients were over-staged, 6 of whom had undergone preoperative radiation; 3 T1 tumours were over-staged as T2 and 3 T2 tumours were classified as T3.

Accuracy for patients who underwent preoperative radiotherapy (15/28) was 60% for T-staging and 73% for bowel penetration (Dukes Classification). For patients without preoperative radiotherapy the accuracy was 69% for T stage and 92% for bowel wall penetration. There was no statistically significant difference in accuracies between the two groups (p=0.71).

Accuracy of transrectal sonography was 81%, sensitivity was 92% (95% CI, 64-99.8%) and specificity was 71% (95% CI, 41.9-91.6%) for the presence or absence of nodal disease.

Double Contrast MRI
MRI correctly staged 25/39 tumours for an accuracy of 64% for T stage; accuracy for MRI at the 1.0-T MR unit was 67% and for MRI at the 1.5-T MR unit was 62% (p=0.54).
Disease was overstaged in 10 patients, 7 of whom underwent pre-operative radiation and was understaged in 4 patients.
Double contrast MRI showed 100% sensitivity (95% CI, 88.3-100%) and 60% specificity (95% CI, 32.3-83.7%) and an accuracy of 85% (Dukes classification) for rectal wall penetration.

Accuracy for patients who underwent preoperative radiotherapy (19/39) was 53% for T-stage and 68% for bowel wall penetration. For patients that did not undergo preoperative radiotherapy (20/39) the accuracy was 75% for T-stage and 100% for bowel wall penetration. The differences between the two groups were not statistically significant.

Accuracy of MRI was 70%, sensitivity was 81% (95% CI, 54.4-96%) and specificity was 62% (95% CI, 38.4-81.9%) for the presence or absence of nodal disease.

Citation: Halefoglu A, Yildirim S, Avlanmis O, Sakiz D, Baykan A (2008) Endorectal ultrasonography versus phased array magnetic resonance imaging for preoperative staging of rectal cancer *World Journal of Gastroenterology* 14;22:3504-3510

Design: Case Series

Country: Turkey

Aim: to compare diagnostic accuracy of pelvic phased-array magnetic resonance imaging (MRI) and endorectal sonography (ERUS) in the preoperative staging of rectal carcinoma.

Inclusion criteria
Patients with biopsy proven rectal cancer

Exclusion criteria
Patients who previously underwent chemotherapy or radiotherapy

Population
N=34

Interventions
Endorectal Ultrasonography
MRI

Outcomes
Accuracy
Sensitivity
Specificity

Results
Histopathological evaluation of resected tumours revealed adenocarcinoma for all patients; pathological T-stage of tumours was pT1 in 1 patient, pT2 in 9 patients, pT3 in 21 patients and pT4 in 3 patients and pathological N-stage was pN0 in 19 patients pN1 in 9 patients and pN2 in 6 patients.

All tumours could be detected by both ERUS and MRI

T-staging
MRI
The accuracy of T-staging was 89.7%, the sensitivity was 79.41% and the specificity was 93.14%. MRI correctly identified invasion in 23 patients and no invasion in 6 patients for an overall accuracy of 85.29%, sensitivity of 95.8% and specificity of 60% for discriminating between p-T1-pT2 and pT3-pT4 tumours.
The positive and negative predictive values were 85.19% and 85.7% respectively.

ERUS
The accuracy of T-staging was 85.29%, the sensitivity was 70.59% and specificity was 90.20%. ERUS correctly identified invasion in 21 patients and no invasion in 5 patients for an overall accuracy of 76.47%, sensitivity of 76.47% and specificity of 50% for discriminating between p-T1-p-T2 and pT3-pT-4 tumours. The positive and negative predictive values were 80.77% and 62.5% respectively.

N-Staging
The accuracy of phased array MRI for the detection of lymph node metastases was 74.5%, the sensitivity was 61.6% and specificity was 80.88%.
For ERUS, the accuracy for the detection of lymph node metastases was 76.47%, the sensitivity was 52.94% and specificity was 84.31%.

		p-T1	p-T2	p-T3	p-T4
MRI	**MR-T1**	1	0	0	0
	MR-T2	0	5	1	0
	MR-T3	0	4	18	0
	MR-T4	0	0	2	3
	No. of cases	1	9	21	3
ERUS	**ERUS-T1**	0	0	0	0
	ERUS-T2	1	4	3	0
	ERUS-T3	0	5	18	1

ERUS-T4	0	0	0	2
No. of cases	1	9	21	3

Table: T-staging evaluation by MRI and ERUS

		p-N0	p-N1	p-N2
MRI	**N0**	8	1	1
	N1	11	8	0
	N2	0	0	5
ERUS	**N0**	7	2	2
	N1	12	7	0
	N2	0	0	4

Table: N-staging evaluation by MRI and ERUS

	T-Stage		N-Stage	
	Overstaged	**Understaged**	**Overstaged**	**Understaged**
MRI	6	1	11	2
ERUS	6	4	12	4

Table: Comparison of overstaged and understaged cases by MRI and ERUS

Citation: Kantorova I, Lipska L, Belohlavek O, Visokai V, Trubac M, Schneiderova M (2003) Routine ^{18}F-FDG PET Preoperative staging of colorectal cancer: comparison with conventional staging and its impact on treatment decision making *Journal of Nuclear Medicine* 44;11:1784-1788

Design: Case Series

Country: Czech Republic

Aim: to assess the potential clinical benefit of ^{18}F-FDG PET in the routine staging of colorectal cancer

Inclusion criteria Patients with histologically proven colorectal cancer
Exclusion criteria
Population N=38
Interventions ^{18}F-FDG PET Sonograpy CT Chest X-ray
Outcomes Sensitivity Specificity Accuracy

Results
^{18}F-FDG PET correctly detected 95% (35/37) of primary tumours compared to CT which detected 49% and sonography which detected 14%.

Lymph nodes were involved in 7 patients; the sensitivity of ^{18}F-FDG PET was 29% (2/7), specificity was 88% (22/25) and accuracy was 75% (24/32). PET findings were false negative in 5/7 patients and false positive in 3/25 patients. CT and sonography did not detect any lymph node involvement.

Liver metastases were present in 9 patients.

	^{18}F-FDG PET	CT	Sonography
Sensitivity	78%	67%	25%
Specificity	96%	100%	100%
Accuracy	91%	91%	81%

Table: Results for each modality in relation to liver metastases

General comments
There is not a lot of data or information in this paper and the main focus appeared to be how management/treatment decisions were affected by ^{18}F-FDG PET rather than how useful it was for staging.

Citation: Kim CK, Kim SH, Choi D, Kim MJ, Chun HK, Lee SJ, Lee JM (2007) Comparison between 3-T Magnetic Resonance Imaging and Multi-Detector Row Computed Tomography for the Preoperative Evaluation of Rectal Cancer *Journal of Computer Assissted Tomography* 31;853-859

Design: Prospective Case Series

Country: South Korea

Aim: To compare between 3-T magnetic resonance imaging (MRI) and multi-detector row computed tomography (MDCT) for the local staging of rectal cancer.

Inclusion criteria
Patients who underwent both MRI and computed tomographic imaging with histopathologically proven rectal cancer.

Exclusion criteria
Patients that had received preoperative radiation or chemotherapy
Patients that refused surgery
Patients that were inoperable
Patients that underwent MRI only
Patients that had anal fistula
Patients with endometriosis in the rectum

Population
N=31

Interventions
3.0T whole body MRI
Multi-detector row CT

Outcomes
Accuracy
Sensitivity
Specificity
Positive Predictive Value (PPV)
Negative Predictive Value (NPV)

Results
- MR and CT imaging allowed visualisation of tumours in all patients.
- Rectal wall layers seen on MDCT could not be discriminated in all patients with rectal cancer.
- Histopathologic staging revealed 8 patients with T1 tumour, 6 patients with T2 tumour and 17 patients with T3 tumour.
- There was a significant difference between MRI and CT in relation to overall accuracy for ≤T2 staging (p=0.01) and for T3 staging (p=0.001).
- The mean false positive rate and false negative rate for ≤T2 staging for three reviewers using MRI were 12% and 24% respectively compared to 17% and 21% respectively for CT.
- The mean false positive rate and false negative rate for T3 staging for three reviewers using MRI were 7% and 17% respectively compared to 8% and 27% respectively for CT.
- The interobserver agreement for perirectal invasion of rectal cancer on MRI was moderate to substantial, while for CT interobserver agreement was fair.
- 294 lymph nodes were harvested from the rectal cancer resection specimens of 26 patients; 14 were N0, 8 were N1 and 4 were N2 stage.
- There was no statistically significant difference between MRI and CT for the detection of lymph node metastasis.

Stage		≤T2 (n=14)		T3 (n=17)	
		CT	MRI	CT	MRI
Reviewer 1	Sensitivity	79%	100%	71%	88%
	Specificity	76%	88%	79%	100%
	PPV	73%	88%	80%	100%
	NPV	81%	100%	69%	88%
	Accuracy	77%	94%	74%	94%
Reviewer 2	Sensitivity	71%	93%	71%	94%
	Specificity	76%	88%	79%	93%

	PPV	71%	87%	80%	94%
	NPV	76%	94%	69%	93%
	Accuracy	74%	90%	74%	94%
Reviewer 3	Sensitivity	86%	86%	76%	94%
	Specificity	76%	94%	93%	86%
	PPV	75%	92%	93%	88%
	NPV	87%	89%	76%	86%
	Accuracy	81%	90%	83%	90%
Mean	Sensitivity	79%	93%	73%	92%
	Specificity	76%	88%	83%	93%
	PPV	73%	89%	84%	94%
	NPV	81%	94%	71%	89%
	Accuracy	77%	91%	78%	92%

Table: Results for ≤T2, T3 and N staging

	N0 (n=14)		N1 (n=8)		N2 (n=4)	
	MR	CT	MR	CT	MR	CT
Sensitivity	89%	64%	88%	63%	100%	75%
Specificity	92%	83%	89%	61%	100%	91%
PPV	92%	90%	78%	42%	100%	60%
NPV	85%	69%	94%	79%	100%	95%
Accuracy	88%	77%	88%	62%	100%	88%

Table: Results for N staging

General Comments

Three experienced reviewers, who were blinded to each other and to the histopathologic results, prospectively assessed the MR and MDCT images.

Citation: Kim CK, Kim SH, Chun HK, Lee WY, Yun SH, Song SY, Choi D, Lim HK, Kim MJ, Lee J, Lee SJ (2006) Preoperative staging or rectal cancer: accuracy of 3-Tesla magnetic resonance imaging *European Radiology* 16;5:972-980

Design: Case Series

Country: South Korea

Aim: to evaluate the accuracy of 3-telsa magnetic resonance imaging for the preoperative staging of rectal cancer

Inclusion criteria
Histopathologically proven rectal cancer

Exclusion criteria
Patients receiving preoperative radiation or chemotherapy
Patients refusing surgery
Patients that were inoperable
Anal fistula
Endometriosis in the rectum

Population
N=35

Interventions
MRI with 3T whole body system using six elements phased array coil.

Outcomes
Sensitivity
Specificity
Accuracy

Results
Three experienced observers who were blinded to each other and to the histopathological results examined the MR images prospectively.
All 35 rectal cancers were identified on MRI and in all patients MRI allowed visualisation and delineation of the layers of both the rectal wall and mesorectal fascia.

T-Staging

		Observer 1	Observer 2	Observer 3	Mean
T1 (n=8)	**Sensitivity**	88%	88%	88%	88%
	Specificity	100%	100%	100%	100%
	Accuracy	97%	97%	97%	97%
T2 (n=7)	**Sensitivity**	100%	85%	71%	86%
	Specificity	89%	86%	93%	89%
	Accuracy	91%	86%	89%	89%
T3 (n=20)	**Sensitivity**	90%	85%	95%	90%
	Specificity	100%	93%	87%	96%
	Accuracy	94%	89%	91%	91%
Total (n=35)	**Mean Accuracy**	94%	90%	92%	

Table: Prediction of sensitivity, specificity and accuracy of staging with MRI by three independent observers

Observer performance was investigated by analysing the ROC curve with diagnostic accuracy measured using the area under the curve (Az). The Az values in all three observers were high and there was no significant difference among the Az values in the three observers.

	Observer 1	Observer 2	Observer 3
Az	0.973	0.927	0.920
95% CI	0.853, 0.995	0.786, 0.986	0.77, 0.983
Sensitivity	90%	85%	95%
Specificity	100%	93%	87%

Table: Prediction for performance in depicting perirectal invasion of rectal cancers

N-Staging
The number of lymph nodes in each specimen varied from three to 26 at histopathologic examination, with a total of 310 lymph nodes revealed in 30 patients. Of these, 53 nodes, all less than 3mm in diameter were not identified on MRI.

	Sensitivity	Specificity	PPV	NPV	Accuracy
Observer 1	78% (31/40)	98% (213/217)	89% (31/35)	96% (213/222)	95%
Observer 2	80% (32/40)	98% (212/217)	86v (32/37)	96% (212/220)	95%
Observer 3	83% (33/40)	97% (211/217)	85% (33/39)	97% (211/218)	95%
Mean	80%	98%	86%	96%	95%

Table: Prediction of nodal metastases of rectal cancer between 3 observers

Interobserver Agreement
The interobserver agreement for T-staging was; observer 1 vs. observer 2 κ=0.55; observer 2 vs. observer 3 κ=0.8 and observer 1 vs. observer 3 κ=0.63.
Interobserver agreement for determining the presence of perirectal invasion was moderated to substantial.

The interobserver agreement for N-staging was; observer 1 vs. observer 2 κ=0.63; observer 2 vs. observer 3 κ=0.72 and observer 1 vs. observer 3 κ=0.51.
Interobserver agreement for determining the presence of regional lymph node metastasis was moderate to substantial.

General comments
Tumours were classified as follows:
T1: tumour signal intensity is confined to the submucosal layer and has a relatively low signal compared with the high signal intensity of surrounding submucosa
T2: tumour signal intensity extends to the muscle layer leading to an irregular or thickened muscle layer but without perirectal infiltration.
T3: tumour signal intensity extends through the muscular layer into the perirectal fat or an angiolymphatic tumour invasion in the mesorectum.
T4: tumour signal intensity extends to adjacent organs, mesorectal fascia or bowel.

Most staging failures with MRI occur in the differentiation of T2 stage and borderline T3 stage due to over-staging and therefore observers scored the MR images independently for tumour penetration into the perirectal fat using a confidence level scoring system. The appearance of nodules, interruption of the outer rectal wall, or irregularly thickened speculation were considered to be indicators of perirectal invasion. The following confidence intervals were used for T3 staging; 1 definitely absent, 2 probably absent, 3 possibly present, 4 probably present and 5 definitely present.

Citation: Kulinna C, Scheidler J, Strauss T, Bonel H, Herrmann K, Aust D, Reiser M (2004) Local staging of rectal cancer: assessment with double contrast multislice computed tomography and transrectal ultrasound *Journal of Computer Assisted Tomography*

Design: prospective case series

Country: Germany

Aim: to evaluate the accuracy of multislice computed tomography (MSCT) with double-contrast technique and transrectal ultrasound (TRUS) in staging of rectal carcinoma compared with histopathological confirmation.

Inclusion criteria

Exclusion criteria

Population
N=92

Interventions
MSCT
TRUS

Outcomes
Accuracy
Sensitivity
Specificity

Results

Stage	MSCT (n=92)	Accuracy	TRUS (n=63)	Accuracy	Pathology
T-Stage					
<T2	32/38	84%	15/31	48%	38
T3	44/50	84%	23/32	72%	50
T4	2/4	50%	0		4
All	76/92	83%	38/63	60%	92
N-Stage					
N0	47/59	80%	29/39	74%	59
N+	25/33	76%	12/24	50%	33
All	72/92	78%	41/63	65%	92

Table: Results of MSCT and TRUS compared with pathology

T-Staging
There was a significant difference between MSCT and TRUS in determining T-stage (p=0.0001), with MSCT being more sensitive, specific and accurate than TRUS.

	Sensitivity	Specificity	PPV	NPV	Accuracy
Overall					
MSCT (n=92)	82%	84%	88%	76%	83%
TRUS (n=63)	59%	63%	72%	48%	60%
Comparison of findings for MSCT and TRUS of same patients					
MSCT (n=63)	85%	87%	88%	84%	86%
TRUS (n=63)	59%	63%	72%	48%	60%

Table: Results for MSCT and TRUS for determining T-stage

N-Staging
There was no significant difference between MSCT and TRUS in detecting metastatic nodes.

	Sensitivity	Specificity	PPV	NPV	Accuracy
Overall					
MSCT (n=92)	68%	85%	75%	79%	78%
TRUS (n=63)	55%	71%	50%	74%	65%
Comparison of findings for MSCT and TRUS of same patients					
MSCT (n=63)	75%	85%	75%	85%	81%
TRUS (n=63)	55%	71%	50%	74%	65%

Table: Results for MSCT and TRUS for determining N-stage

UICC-Staging

UICC staging includes T-stage and N-stage and is useful in determining which patients benefit from preoperative radiotherapy. Preoperative radiotherapy is effective for UICC >1 (T3 and/or N1) but not for UICC = 1 (T2N0). In the current study, 80% of patients receiving preoperative radiotherapy were correctly staged with MSCT compared with 69% correctly staged with TRUS. For patients not receiving preoperative radiotherapy, 94% were correctly staged with MSCT compared with 68% with TRUS. The overall accuracy rating was significantly better with MSCT than with TRUS (p<0.0001), when looking at only patients that had undergone both MSCT and TRUS (n=63).

	Sensitivity	Specificity	PPV	NPV	Accuracy
MSCT (n=63)	91%	86%	89%	89%	89%
TRUS (n=63)	67%	67%	83%	44%	66%

Table: Results for UICC-staging with MSCT and TRUS in the same patients

Citation: Kulinna C, Eibel R, Matzek W et al (2004) Staging of rectal cancer: diagnostic potential of multi-planar reformatting with multidetector CT *AJR* 183:421-427

Design: Prospective Diagnostic Case Series

Country: Germany

Setting:

Aim: to evaluate whether the addition of coronal and saggital MPRs to axial slices alone could improve UICC staging.

Inclusion criteria
Biopsy proven rectal carcinoma

Exclusion criteria
None given

Sample Size
N/A

Randomisation Method
N/A

Population
N=55

Study Duration
No details

Interventions
MDCT

Outcomes
Sensitivity, specificity, positive predictive value, negative predictive value and accuracy for:

Detectability of tumour
Tumour location
Depth of tumour infiltration
Regional lymph nodes

Results
Results of histopathologic examination showed that 24 patients had pT2 tumours, 30 patients had pT3 tumours and 1 patient had pT4 tumour.
N staging showed 36 patients without lymph node metastasis, 16 patients with pN1 and 3 patients with pN2.

23 patients with UICC stage 1 and 32 patients with UICC stage 2 were identified histologically.

Inter-observer variability was good to excellent; the lowest inter-observer variability was found fro UICC staging in saggital reconstructions (κ=0.881) and the highest inter-observer variability was observed on coronal reconstructions in N staging (κ=0.606).

T-staging
There was a statistically significant difference between acial and coronal reconstructions (p=0.006) and between axial and sagittal reconstructions (p=0.02) but only for reviewer 1.

Type of Image	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)
Reviewer 1					
Axial	81% (63%-92%0	58% (36%-77%)	71% (53%-85%)	70% (45%-88%)	71% (57%-82%)
Coronal	98% (88%-100%)	75% (53%-90%)*	84% (68%-93%)	97% (81%-100%)	89% (77%-95%)*
Saggital	98% (88%-100%)	83% (62%-95%)*	87% (73%-96%)	97% (83%-100%)	93% (82%-98%)*
Reviewer 2					
Axial	77% (77%-87%)	67% (44%-84%)	75% (56%-88)	70% (47%-86%)	72% (59%-83%)
Coronal	88% (87%-96%)	62% (40%-81%)	75% (57%-87%)	79% (54%-93%)	76% (63%-86%)
Saggital	90% (74%-98%)	79% (57%-92%)	85% (68%-94%)	86% (65%-97%)	85% (73%-93%)

*p<0.05
Table: Overall T stage assessment in rectal cancer (n=55)

N Staging
There were statistically significant differences between axial and coronal reconstructions (p=0.006) and between axial and saggital reconstructions (pp=0.01) but again only with reviewer 1.

Type of Image	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)
Reviewer 1					
Axial	84% (60%-96%)	67% (49%-81%)	57% (37%-75%)	89% (69%-98%)	73% (59%-83%)
Coronal	98% (82%-100%)	86% (70%-95%)	79% (57%-92%)	98% (88%-100%)	91% (80%-97%)*
Saggital	97% (82%-100%)	94% (81%-99%)	95% (69%-98%)	98% (89%-100%)	96% (87%-99%)*
Reviewer 2					
Axial	80% (54%-93%)	67% (44%-84%)	61% (35%-74%)	86% (67%-96%)	71% (57%-82%)
Coronal	90% (69%-98%)	61% (43%-76%)	55% (36%-72%)	91% (73%-99%)	71% (57%-82%)
Saggital	98% (82%-100%)	70% (Not given)	63% (43%-80%)	95% (67%-100%)	80% (67%-89%)

*p<0.05
Table: assessment of N staging rectal cancer (n=55)

UICC Staging
There were statistically significant differences between axial and coronal reconstructions (reviwer 1 p=0.01; reviewer 2 p=0.04) and between axial and sagittal reconstructions (reviewer 1 p=0.001; reviewer 2 p=0.012) for both reviewers.

Type of Image	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)
Reviewer 1					
Axial	78% (60%-90%)	39% (19%-46%)	64% (47%-78%)	56% (29%-80%)	62% (47%-74%)
Coronal	98% (89%-100%)*	74% (61%-89%)*	84% (68%-94%)	97% (80%-100%)	89% (77%-95%)*
Saggital	98% (89%-100%)*	87% (66%-97%)*	91% (76%-98%)	96% (83%-100%)	95% (84%-98%)*
Reviewer 2					
Axial	78% (60%-97%)	52% (30%-73%)	69% (51%-83%)	63% (38%-83%)	67% (53%-79%)
Coronal	87% (71%-96%)*	52% (30%-73%)	72% (55%-85%)	75% (47%-92%)	73% (59%-83%)*
Saggital	97% (83%-99%)*	78% (56%-92%)	86% (70%-95%)	95% (74%-99%)	89% (77%-95%)*

*p<0.05)
Table: Assessment for UICC staging in rectal cancer (n=55)

General comments
Tumours on MDCT were classified by a modified TNM stage:
Tumours confined to the bowel wall were classified as T1 or T2
An indistinct or speculated border between the outer rectal wall and the surrounding fat at the level of the tumour was considered to be evidence of perirectal invasion (T3).
Tumour infiltration into adjacent organs was considered to be T4

Lymph nodes were considered to be positive for metastases if at least one perirectal lymph node with a short-axis diameter of more than 3mm was found.

Citation: Kwok H, Bisset IP, Hill GL (2000) Preoperative Staging of Rectal Cancer *International Journal of Colorectal Disease* 15;1:9-20
Design: Systematic Review **Country**: New Zealand **Aim**: to evaluate computed tomography (CT), endorectal sonography (ES) and magnetic resonance imaging (MRI) as preoperative staging methods in rectal cancer.
Inclusion criteria Studies presenting (1) pathological staging of rectal cancer as a gold standard; (2) a minimum of 20 patients in the whole study; (3) sufficient raw data to allow data extraction and (4) original data. If only a subset of patients within the study met the inclusion criteria, only this subset were included.
Exclusion criteria Reviews, comments and editorials which presented no new data Papers with internal inconsistency
Population N=4879 patients from 83 studies
Interventions CT ES MRI
Outcomes *Bowel penetration and nodal status* Accuracy Sensitivity Specificity Positive Predictive Value Negative Predictive Value Positive likelihood ratio Negative likelihood ratio *T stage* Accuracy Percentage under-staged Percentage over-staged
Results *Studies included* 275 studies identified from Medline and citation lists 86 excluded as irrelevant 40 excluded due to small patient numbers (<20) 15 excluded due to insufficient data 20 excluded because data was included in subsequent papers 36 excluded because they presented no new data **83 studies reporting data on 4879 patients were included in the review, the overall numbers of patients receiving pre-operative staging by CT, ES and MRI were 1429, 3640 and 665 respectively.** *Wall Penetration* 23 studies (22 papers) used CT in the pre-operative assessment of local tumour penetration and a total of 1116 patients met the inclusion criteria. The pooled sensitivity, specificity and accuracy were 78%, 63% and 73% respectively. Four studies with a total of 135 patients classified wall penetration according to TNM notation, of these 80% were correctly staged, 13% were over-staged and 7% were under-staged. 53 studies (48 papers) with a total of 2915 eligible patients, assessed wall penetration with ES. The pooled sensitivity, specificity and accuracy were 93%, 78% and 87% respectively. 31 studies, representing a total of 1852 patients reported wall penetration according to TNM notation, of these 84% were correctly staged, 11% over-staged and 5% were understaged.

18 studies (15 papers) with a total of 521 patients and 546 MRI scans (some patients were evaluated by more than one type of MRI) assessed wall penetration with MRI. The pooled sensitivity, specificity and accuracy were 86%, 77% and 82% respectively.

8 studies, representing 246 patients reported results using TNM notation, of these 74% were correctly staged, 13% were overstaged and 13% were under-staged.

Subgroup analysis on patients using endorectal surface coil (6 studies; 169 patients) resulted in a pooled sensitivity, specificity and accuracy of 89%, 79% and 84% respectively.

4 studies (124 patients) reported the results according to TNM notation, of these 81% were correctly staged, 12% were overstaged and 6% were understaged.

Nodal Involvement

18 studies (17 papers) with a total of 945 patients assessed nodal status by CT. The pooled sensitivity, specificity and accuracy were 52%, 78% and 66% respectively.

38 studies (36 papers) with a total of 2032 patients assessed nodal involvement by ES. The pooled sensitivity, specificity and accuracy were 71%, 76% and 74% respectively.

15 studies (14 patients) with a total of 436 MRI scans assessed local nodal involvement by MRI. The pooled sensitivity, specificity and accuracy were 65%, 80% and 74% respectively.

181 patients (6 studies) received MRI with endorectal surface coil; the pooled sensitivity, specificity and accuracy for this subgroup were 82%, 83% and 82% respectively.

	Sensitivity	Specificity	Accuracy	Positive Predictive Value (PPV)	Negative Predictive Value (NPV)	Positive likelihood ratio (PLR)	Negative likelihood ratio (NLR)
Wall Penetration							
CT	78%	63%	73%	82%	58%	2.11	0.35
ES	93%	78%	87%	87%	87%	4.31	0.09
MRI (all)	86%	77%	82%	83%	81v	3.7	0.19
MRI (endorectal coil)	89%	79%	84%	82%	86%	4.22	0.14
Nodal Involvement							
CT	52%	78%	66%	68%	64%	2.38	0.61
ES	71%	76%	74%	69%	78%	2.99	0.38
MRI (all)	65%	80%	74%	72%	75%	3.27	0.43
MRI (endorectal coil)	82%	83%	82%	76%	87%	4.7	0.22

Table: Pooled sensitivity, specificity, accuracy, PPV, NPV, PLR and NLR for all modalities

Comparing CT, ES and MRI
- Overall ES had the highest sensitivity, specificity and accuracy of the three modalities.
- MRI assessment of wall penetration had lower sensitivity, specificity and accuracy than ES although subgroup analysis of those patients undergoing MRI with endorectal coil had a sensitivity, specificity and accuracy close to that of ES.
- In assessing nodal involvement, MRI performed with an endorectal coil has the highest sensitivity, specificity and accuracy, ES had similar results to MRI overall.
- CT showed the lowest sensitivity, specificity and accuracy for both wall penetration and nodal involvement.

Radiotherapy
All studies in which patients received radiotherapy were combined irrespective of the regimen. In patients receiving radiotherapy preoperative staging using CT and ES had the lowest sensitivity and specificity and MRI seemed less affected by radiotherapy when compared with those with no radiotherapy.

General Comments
Medline was searched for papers published between January 1980 and November 1998 and the resulting list was supplemented by searching the citations for any further papers. No information on any other databases searched was provided.

Data extracted from each of the studies included; the study type, year of publication and investigation, patient demographics, details of examination technique, examiner blinding, tumour factors and use of radiotherapy.

Wall penetration was defined as 'through wall' (invading the muscularis propria) or 'not through wall' and where possible according to the T component of the TNM staging system. Patients staged by other systems were reclassified according to the conversion matrix established by the 1990 World Congress of Gastroenterology Working Party on Clinicopathological Staging.

Nodal involvement was defined as either 'positive' or 'negative'

Citation: Llamas-Elvira JM, Rodriguez-Fernandez A, Gutierrez Sainz J, Gomez-Rio M, Bellon-Guardia M, Ramos Font C, Rebollo Aguirre AC, Cabello Garcia D, Ferron Orihuela A (2007) Fluorine-18 fluorodeoxyglucose PET in the preoperative staging of colorectal cancer. *European Journal of Nuclear Medicine and Molecular Imaging* 34;6:859-867

Design: Case Series

Country: Spain

Aim: to evaluate the utility of FDG-PET in the initial staging of patients with colorectal cancer in comparison with conventional staging methods and to determine it's impact on therapeutic decisions.

Inclusion criteria

Exclusion criteria

Population
N=104

Interventions
CT
FDG-PET

Outcomes
Sensitivity
Specificity
Positive Predictive Value
Negative Predictive Value
Accuracy

Results
Both FDG-PET and CT showed changes at the level of the primary lesion that were compatible with tumour status; most primary tumours showed FDG uptake, with only 1 small, well-differentiated mucinous adenocarcinoma showing no significant uptake.

Lymphatic spread was studied in 90 patients to evaluate the presence or absence of involved lymph nodes. CT correctly detected the presence/absence of lymph node involvement in 54 patients with 36 false negative and 2 false positive results. FDG-PET correctly detected presence/absence of lymph node involvement in 50 patients, with 38 false negatives and 2 false positive results.

	FDG-PET	CT	FDG-PET	CT + Chest X Ray
	N0/N+		M0/M+	
Sensitivity	21% (11-35%)	25% (14-40%)	89% (64-98%)	44% (22-69%)
Specificity	95% (83-99%)	100% (83-99%)	93% (85-97%)	95% (88-98%)
Overall Accuracy	56% (45-66%)	60% (49-70%)	92% (85-96%)	87% (78-92%)
PPV	83% (51-97%)	100% (70-99%)	73% (50-88%)	67% (35-89%)
NPV	51% (40-63%)	54% (42-65%)	98% (91-100%)	89% (80-94%)

Table: Diagnostic Accuracy in N0/N+ and M0/M+ staging

General comments
Diagnostic validity of CT and FDG-PET in N and M staging was analysed by comparing the information in the reposts of each examination with the reference criteria, solely considering N0-N+ and M0-M+ categories.

Citation: Low RN, McCue M, Barone R, Saleh F, Song (2003) MR staging of primary colorectal carcinoma: comparison with surgical and histopathological findings *Abdominal Imaging* 28;6:784-793

Design: Retrospective Case Series

Country: USA

Aim: to evaluate the accuracy of magnetic resonance imaging in staging colorectal cancer and assessing local tumour extent, nodal involvement and distant abdominal and pelvic metastases.

Inclusion criteria

Exclusion criteria

Population
N=48 patients (21 patients with rectal cancer and 27 patients with colon cancer)

Interventions
Presurgical abdominal and pelvic MRI

Outcomes
Sensitivity
Specificity

Results
Abdominal and pelvic imaging was performed with body in 27 patients and with combination body coil for abdomen and phased array surface coil for pelvis in 19 patients. (Note: There appear to be 2 patients unaccounted for here.)

Overall Staging
MRI agreed with surgical and pathologic stagin in 85% (41/48) patients. Over-staging occurred in 1 patient and under-staging occurred in 6 patients with the largest category of staging error occurring in stage 3 tumours.

	Surgical/Histopathologic TNM stage					
	Overall	**0**	**1**	**2**	**3**	**4**
MRI	**0**	0				
	1		12			
	2			8	5	1
	3		1		8	
	4					13

Table: Comparison of MRI and surgical/pathological staging

Depth of Tumour Penetration (T-staging)
Depth of tumour penetration into the bowel wall could not be evaluated in 4 patients. In 86% (38/44) of patients depth of tumour penetration on MRI agreed with surgical and pathologic findings. In 95% of patients, MRI correctly distinguished tumour confined to the bowel wall.

	Surgical/Histopathologic TNM stage					
	T-Stage	**0**	**1**	**2**	**3**	**4**
MRI	**0**	1				
	1		1			
	2		2	9	1	
	3			1	22	2
	4					5

Table: Comparison of MRI and surgical/pathologic staging for T-stage

Nodal Metastases (N-staging)
MRI showed a sensitivity of 68%, specificity of 96% and accuracy of 83% for the identification of local and regional nodal metastases.

Distant Metastases (M-staging)
Surgical exploration confirmed colorectal cancer with distant metastases in 14/48 patients with MRI correctly depicting metastatic tumour in 13/14 patients.

Rectal Cancer
MRI staging agreed with surgical/pathologic staging in 20/21 patients with rectal cancer. Depth of tumour penetration

was correctly estimated on MRI in 16/19 patients and nodal metastasis was correctly depicted in 8/9 patients.

Colon Cancer
MRI staging agreed with surgical/pathologic staging in 21/27 patients. Depth of tumour penetration was correctly estimated in 22/25 patients and nodal metastasis was correctly depicted in 7/13 patients.

General comments
Surgical staging occurred in all patients within 5 weeks of MRI
Staging of colon carcinoma was based on TNM classification

Citation: Mainenti PP, Cirillo LC< Camera L, Perscio F, Cantalupo T, Pace L, De Palma GD, Persico G, Alvatore M (2006) Accuracy of single phase contrast enhanced multidetector CT colonography in the preoperative staging of colorectal cancer *European Journal of Radiology* 60;453-459
Design: Case Series
Country: Italy
Aim: to assess the value of single portal venous phase contrast enhanced multidetector CT colonography (CE CTC) in the preoperative staging of colorectal cancer
Inclusion criteria   Histologically proven colorectal adenocarcinoma   Highly suspected colorectal cancer on conventional colonoscopy
Exclusion criteria   None given
Population   N=52 (20 with histologically proven colorectal adenocarcinoma, 32 with highly suspected diagnosis of colorectal cancer on conventional colonoscopy)
Interventions   CT colonography
Outcomes   Accuracy   Sensitivity   Specificity   Positive Predictive Value   Negative Predictive Value

Results

All 52 colorectal cancers were identified on CE-CTC with a total of 56 adenocarcinomas present and correctly located with CE-CTC.

Site	Number
Rectum	11
Rectal-sigmoid colon junction	5
Sigmoid colon	24
Splenic flexure	1
Transverse Colon	4
Hepatic flexure	3
Ascending colon	2
Cecum	4
Anastomosis in patients with previous colic resection	2

Table: site and number of tumours detected on CE-CTC

	Stage ≤T2 (n=10)	Stage T3 (n=41)	Stage T4 (n=5)	N+ (n=29)
Accuracy (95% CI)	93 (86, 100%)	93 (86, 100%)	100 (99.9, 100%)	71 (59, 83%)
Sensitivity (95% CI)	70 (40, 100%)	97 (92, 100%)	100 (99.9, 100%)	86 (73, 99%)
Specificity (95% CI)	98 (94, 100%)	80 (59, 100%)	100 (99.9, 100%)	55 (36, 74%)
Positive Predictive Value (95% CI)	87 (62, 100%)	93 (85, 100%)	100 (99.9, 100%)	68 (53, 83%)
Negative Predictive Value (95% CI)	94 (87 (100%)	92 (77, 100%)	100 (99.9, 100%)	79 (60, 98%)

Table: Results for CT Colonography for T and N stage

General comments

Pathological findings served as the reference standard for depth of tumour invasion and nodal involvement.
The radiologists reading the results were blinded to the surgical and pathological findings.

Citation: Mercury Study Group (2006) Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study
Design: Prospective Case Series **Country**: Europe (four countries) **Aim**: To assess the accuracy of preoperative staging of rectal cancer with MRI to predict surgical circumferential resection margins.
Inclusion criteria
Exclusion criteria Pregnant patients History of pelvic malignancy Pelvic radiotherapy or pelvic floor surgery for faecal incontinence or rectal prolapse. Patients that were unable to undergo MRI because of metal fragments of implanted metal devices with the body
Population N=408
Interventions Clinical Assessment including digital rectal exam and rigid sigmoidoscopy Radiological Assessment including MRI with a body coil and a high resolution protocol
Outcomes Accuracy of MRI in predicting a curative resection based on histological yardstick of presence or absence of tumour at the margins of the specimen.
Results MRI prediction of circumferential resection margin MRI predicted clear margins in 349 patients that underwent surgery, of these 327 had clear margins (94%, 95% CI; 91% to 96%). Accuracy for predicting the status of circumferential resection margin by initial imaging or imaging after pre-operative treatment in 408 patients was 88% (95% CI; 85% to 91%). 311/408 patients underwent primary surgery and the accuracy for prediction of a clear margin was 91% (95% CI; 88% to 94%) with a negative predictive value of 93% (95% CI; 90%-96%) compared to an accuracy of 77% (95% CI; 69% to 86%) and negative predictive value of 98% in 97 patients that underwent preoperative chemoradiotherapy or long course radiotherapy. Patients with a curative resection on histopathology 354 patients had clear margins on histopathology, 327 of which were correctly predicted on MRI resulting in a specificity of 92% (89% to 95%). 27 patients were incorrectly diagnosed as having involved margins on MRI; 21 patients received chemoradiotherapy or long course radiotherapy and the appearance of tumour at the margins on their scans after treatment correspond to changes related to treatment. Patients with non-curative resection on histopathology 54/508 patients showed affected margin on histopathology, 32 of which were correctly predicted on MRI. 22/54 patients were not predicted to have involved margins on MRI due to perforation of tumour during surgery which could not have been predicted by MRI; in 7 patients the affected margin was not due to direct spread of tumour but to the presence of nodes containing tumour that had not been detected by the scan; in 1 patient, changes on the scan were interpreted as post-radiotherapy fibrosis at the margin and in 3 patients, although the local extent of tumour had been correctly documented compared with pathology, the distance to the mesorectal fascia had been over-estimated by the radiologist. Accuracy of digital rectal examination versus MRI MRI resulted in more accurate information than did digital rectal examination (DRE). The accuracy for circumferential resection margin status in patients who underwent primary surgery was 70% for DRE and 92% for MRI (p<0.001). When DRE showed fixed or tethered tumour this corresponded to an involved circumferential margin in only 15% of patients.

	MRI
Accuracy (95% CI)	88% (85% to 91%)
Sensitivity (95% CI)	59% (46% to 72%)
Specificity (95% CI)	92% (90% to 95%)
Positive Predictive Value (95% CI)	54% (42% to 67%)
Negative Predictive Value (95% CI)	94% (91% to 96%)

Table: Results for MRI by margin status

	MRI	
	Primary Surgery/short course radiotherapy	**After Chemotherapy**
Accuracy (95% CI)	91%	77%
Sensitivity (95% CI)	42%	94%
Specificity (95% CI)	98%	73%
Positive Predictive Value (95% CI)	71%	45%
Negative Predictive Value (95% CI)	93%	98%

Table: Result for MRI by treatment

	MRI	DRE
Accuracy	92%	70%
Sensitivity	42%	38%
Specificity	98%	74%
Positive Predictive Value	73%	15%
Negative Predictive Value	93%	91%

Table: Results for MRI versus DRE prediction at circumferential resection margin

Citation: Mercury Study Group (2007) Extramural Depth of tumour invasion at thin section MR in Patients with rectal cancer: Results of the Mercury Study *Radiology* 243;1:132-139
Design: Prospective Diagnostic Study Country: UK Setting: Aim: to evaluate the accuracy of MRI in depicting the extramural depth of invasion in patients with rectal cancer
Inclusion criteria ≥18 years Able to provide written consent Recently diagnosed adenocarcinoma of the rectum (the distal 15cm region of the large bowel) Patients scheduled to undergo preoperative short-course radiotherapy only
Exclusion criteria Pregnancy Previous history of pelvic malignancy, pelvic radiation therapy or pelvic floor surgery for faecal incontinence or rectal prolapsed Patients unable to undergo MRI due to claustrophobia or metal fragments or implanted metal devices in the body. Patients referred for palliative care only Patients who received treatment at locations other than the study centres Patients who had or were scheduled to undergo local excision of primary tumour Patients scheduled to undergo chemoradiotherapy or long course radiotherapy
Sample Size 277 patients were required (β=0.025, α=2β=0.05)
Randomisation Method N/A
Population N=679
Study Duration Patient Recruitment: February 2002 – November 2003
Interventions MRI
Outcomes Equivalence between MRI measurement of extramural depth of tumour invasion and histopathologic measurement after primary surgery.
Results 428 histopahtologic specimens were available Values of tumour height (defined as measured distance of the tumour from the anal verge) were 0-5cm in 137 cases, 5.1-10cm in 152 cases and >10.1cm in 105 cases. Measurements were missing in 34 cases. 311 patients (183 men and 128 women, median age 67 years, range 33-92 years) underwent primary surgery and 97 underwent surgery following treatment with either chemoradiotherapy or long-course radiotherapy. Anterior resection was performed in 302/428 cases and the hartmann procedure in 25 cases. Overall, 266 mesorectal specimens were graded as complete, 81 were graded as moderate and 23 were graded as incomplete. The specimen grade was not available in 58 cases. The median number of nodes found per specimen was 13 (range 1-50). Overall, 311 patients were eligible for primary end-point assessment of extra mural depth of tumour spread. MRI versus Histopathological Measurement of Extramural Depth of Tumour Invasion Measurement of extramural depth of invasion was available for both histopathology and MRI in 295/311 patients (95%) who underwent primary surgery.

Mean extramural depths of invasion at MRI was 2.80mm (SD±4.6mm) and for histopathologic analysis was 2.81mm (SD±4.28mm).
The mean difference between MRI and histopathologic assessments of extramural depth of invasion was -0.05mm±3.85 (95% CI -0.49mm-0.4mm) resulting in more than 95% certainty that the mean difference was within the predefined 0.5mm boundary and thus that the assessments were equivalent.

In 92.5% of patients, depth of tumour spread depicted on the thin-section MRI was with 5mm of the histopathologic measurements.
In 7.5% of patients, MRI resulted in apparent over-estimation of extramural depth of invasion by more than 5mm which would have resulted in patients being assigned to an incorrect prognostic group.

In 4 of the 22 patients, the presence of transacted tumour at the circumferetial margin likely represented pathologic under-estimation.

Review of the images showed that in 7 of the remaining 18 patients there were image interpretation errors and 11 overestimations due to incorrect angulation of the imaging plane in tumours in the very low region of the rectum and tumours above the peritoneal reflection.

MRI led to underestimation of tumour depth in 4.4% (13/295) of patients; at review of these patients imaged it was noted that there were 5 impterpretation errors due to movement artefact.

General comments
 MRI and histopathologic results were considered to be equivalent when the 95% CI of the difference between them was within ±0.5mm, giving a less than 5% probability that of a false claim of equivalence if the true mean difference between MRI and histopathologic results exceeded ±0.5mm.

Citation: Nicholls R, York Mason A, Morson B et al (1982) The clinical staging of rectal cancer *British Journal of Surgery* 69;404-409

Design: Case Series Study

Country: UK

Setting:

Aim: to investigate the ability of digital rectal examination to recognise significant stages of local extent and lymph node involvement in adenocarcinoma of the lower two thirds of the rectum

Inclusion criteria None Given

Exclusion criteria None Given

Sample Size N/A

Randomisation Method N/A

Population N=70

Study Duration No details provided

Interventions DRE CT Pathology (Reference)

Outcomes Not clear from the study

Results

Level of tumour
Digital estimations of the level of tumour from the anal verge in patients having total rectal excisions were within 2cm of the pathologist's measurements on the lower border to the dentate line in 70% of cases examined by clinician 1, 82% of cases examined by clinician 2 and 82% of cases examined by clinician 3.

Quadrants
The number of involved quadrants was correctly assessed in 77%, 69% and 71% of cases examined by clinician 1, 2 and 3 respectively.
Tumours occupying three or more quadrants were correctly identified in 96%, 80% and 67% of cases examined by clinician 1, 2 and 3 respectively.
A relationship was observed between the number of quadrants judged to be involved by the clinician and extent of local spread.

Morphology
All 3 non-ulcerated carcinomas were correctly identified by all clinicians.

Extent of Local Spread

	Clinical assessment by Clinicians 1, 2 and 3											
	Nil			Slight			Moderate			Extensive		
	1	2	3	1	2	3	1	2	3	1	2	3
Patients Examined	5	11	18	23	23	14	12	10	21	20	19	11
Pathological Assessment												
Nil	4	8	8	5	3	4	0	0	1	0	0	0
Slight	1	2	8	13	14	5	5	2	5	3	2	1
Moderate	0	0	2	4	4	3	4	4	8	8	8	6
Extensive	0	1	0	1	2	2	3	4	6	8	7	4
No specimen (deemed inoperable)	0	0	0	0	0	0	0	0	1	1	1	0
Concordance of clinical with pathological	80	73	44	56	61	36	33	40	38	45	42	36

Table: Digital Assessment of Local Spread in 70 Patients

	Clinical assessment by clinicians 1, 2 and 3					
	Nil and Slight			Moderate and Extensive		
	1	2	3	1	2	3
Patients examined	28	34	32	32	29	32
Pathological assessment						
Nil and Slight	23	27	25	8	4	7
Moderate and extensive	5	7	7	24	24	25
Concordance of clinical and pathological assessments (%)	82	79	78	75	83	78

Table: Digital Assessment of Local Spread in 70 Patients (grouped by nil/slight and moderate/extensive)

Lymph Node Involvement
Full pathological examination of lymph nodes was available for 64 tumours

	Clinical Assessment by clinicians 1, 2 and 3					
	Involved			Not Involved		
	1	2	3	1	2	3
Patients examined	36	34	53	18	23	3
Pathological assessment						
Not Involved	24	22	30	6	8	1
Involved	12	12	23	12	15	2
Concordance of clinical and pathological assessments (%)	67	65	57	67	65	67

Table: Digital Assessment of Pararectal Lymph Nodes in 64 patients

Tumours underassessed as confined
Clinician 1 wrongly assessed 1 patient, clinician 2 wrongly assessed 2 patients and clinician 3 wrongly assessed 10 patients.
1 patient was wrongly assessed as confined by all 3 clinicians.

Computed Tomography
Extrarectal spread was seen on CT in 2/18 tumours with nil or slight spread and in 13/18 tumours with moderate or extensive spread.
CT showed higher sensitivity than clinical examination in identifying extensive local spread; 89% of tumours deemed extensive (8/9) were found to have extrarectal spread greater than 1.5cm compared with sensitivities of 71%, 56% and 33% obtained by clinicians 1, 2 and 3 respectively.
CT was not more reliable than clinical examination for growths with moderate spread with extrarectal spread seen on in 55% (5/9) of cases.
Nodes were seen on CT in 28% of Dukes C tumours compared with 27%, 58% and 8% respectively for clinicians 1, 2 and 3.

Choice of Treatment
31/69 resectable tumours were treated by total rectal excision and 38/69 were treated by sphincter preserving operation.
A relationship was observed between choice of operation and level of tumour and also selection by surgeon in charge based on local extent.
Patients with tumours between 5-8cm from the anal verge appeared more likely to be treated with a sphincter preserving operation if local spread was assessed to be nil or slight and by total rectal excision when local spread was considered moderate or extensive.

Citation: Rafaelsen S, Kronborg O and Fenger C (1994) Digital rectal examination and transrectal ultrasonography in staging of rectal cancer *Acta Radiology* 35;3:300-304
Design: A prospective, blind study
Country: Denmark
Setting:
Aim: Not clearly stated in the paper, it appears that the aim was to stage rectal cancer pre-operatively by digital rectal exam and transrectal linear ultra sonography (TRUS) and to compare the results with pathology.
Inclusion criteria Patients with rectal carcinoma
Exclusion criteria None given
Sample Size N/A
Randomisation Method N/A
Population N=107 (50 males and 57 females)
Study Duration 1989-1992
Interventions Clinical Examination (Digital rectal evaluation of mobility, consistency, number of quadrants involved, depth of rectal wall penetration and palpable perirectal lymph nodes) Rigid Sigmoidoscopy TRUS
Outcomes
Results TRUS was performed immediately following clinical examination and the ultrasonographer was informed that the patient had a tumour. Comment: The study was apparently blinded, though if the ultrasonographer was aware that a tumour was present prior to carrying out TRUS then they are not blinded. 31/107 patients were treated by local excision, 58/107 were treated by low anterior resection and 18/107 were treated by abdominoperineal excision Primary Tumour

Pathological Specimen	TRUS	
	Penetration	No Penetration
Penetration	65	3
No Penetration	9	30
Total	74	33

Table: Penetration of the rectal wall in 107 patients as evaluated by TRUS and pathology

Pathological Specimen	TRUS		Digital Rectal Exam	
	Penetration N=66	No Penetration N=28	Penetration N=76	No Penetration N=18
Penetration (n=61)	59	2	56	5
No Penetration (n=33)	7	26	20	13

Table: Penetration of rectal wall in 94 patients as evaluated by TRUS, digital examination and pathology

In 13 patients, tumour was beyond the reach of the finger; digital examination underestimated penetration in 5/18 patients versus 2/28 by TRUS (p=0.09).
Overestimation of penetration occurred in 20/76 patients on DRE versus 7/66 patients on TRUS (p=0.02).

The clinician expressed doubt about 8/76 patients considered to have penetration on DRE and further investigation found no penetration in 6/8 of these patients, 5 of which were correctly identified on TRUS. Excluding the 8 patients resulted in overestimation of penetration by DRE of 14/68 versus 6/65 by TRUS (p=0.09).

Overestimation of penetration appeared to occur more often in small tumours compared with larger tumours (p=0.07).
There was a significant difference in overestimation when comparing tumours located in a single quadrant and those located in more than one quadrant (p=0.01).
Underestimation of penetration was significantly higher with DRE in larger tumours versus smaller tumours (<2cm diameter) (p=0.006).
Hard tumours were significantly more likely to be underestimated than soft tumours (p=0.006).

The majority of specimens with tumour penetration were correctly identified by DRE and also by TRUS although not in more than 13 of the same 33 patients examined by DRE (p=0.001). The difference remained significant when patients with uncertain results were excluded (p=0.02).

Overestimation of tumours with a diameter ≥4cm occurred in 5/41 patients on TRUS versus 8/49 patients on DRE (p=0.64).
27 tumours involved 4 quadrants and none were confined to the rectal wall by pathological exam and neither were they overestimated by TRUS or DRE.

Perirectal Lymph Node Status

	N	DRE			TRUS		
Pathology Dukes Stage		**A**	**B**	**C**	**A**	**B**	**C**
A	9	1	8	0	7	1	1
B	25	1	23	1	1	17	7
C	19	1	18	0	0	8	11

Table: Characteristics of 53 patients having complete clinical and pathological examination and complete TRUS

Complete clinical and pathological staging could be obtained from 53 patients and palpable lymph nodes were found in one patient on DRE but no metastases were found in the resected specimen.
TRUS correctly identified 11/19 patients with lymph node metastases.

TRUS correctly staged 35/53 patients versus 24/53 correctly staged by DRE (p=0.05)

Citation: Rao SX, Zeng MS, Xu JM, Q XU, Chen CZ, Li RC, Hou YY (2007) Assessment of T-staging and mesorectal fascia status using high-resolution MRI in rectal cancer with rectal distention *World Journal of Gastroenterology* 13;30:4141-4146.

Design: Case Series

Country: China

Aim: to assess the accuracy of MRI for pre-operative T staging of rectal cancer and the distance to the mesorectal fascia with rectal distention.

Inclusion criteria
Patients with histopathologically proven rectal cancer by means of endoluminal biopsy

Exclusion criteria

Population
N=67

Interventions
MRI using 1.5T whole body systems and a phased array multi-coil.

Outcomes
Accuracy
Sensitivity
Specificity
Positive predictive value
Negative predictive value

Results
T1 and T2 tumours were combined to represent on T stage ≤T2 due to the limitations of MRI in distinguishing between T1 and T2 tumours.
At histopathological examination 20 of 67 neoplasms were staged ≤pT2, 42/67 were classified as pT3 and 5/67 were classified as pT4.
The overall accuracy of MRI was 85.1%; over-staging occurred in 9/67 patients and under-staging occurred in 1/67 patients. Accuracy for each T-stage was 89.6% for ≤T2, 85.1% for T3 and 95.5% for T4.

	≤pT2 (n=20)	pT3 (n=42)	pT4 (n=5
Accuracy	89.6% (60/67)	85.1% (57/67)	95.5% (64/67)
Sensitivity	70% (14/20)	90.5% (38/42)	100% (5/5)
Specificity	97.9% (46/47)	76% (19/25)	95.2% (59/62)
PPV	93.3% (14/15)	86.4% (38/44)	62.5% (5/8)
NPV	88.5 % (46/52)	82.6% (19/23)	100% (59/59)

Table: Results for MRI

Mesorectal fascia was visualised on MRI in all patients and found to be involved in 15 patients by pathologists using a cut-off distance of 2mm between a tumour and the mesorectal fascia. Overall accuracy of predicting mesorectal fascia involvement on MRI was 88%. The sensitivity was 80%, specificity was 90.4%, PPV was 70.6% and NPV was 94%.

Citation: Salerno G, Daniels I, Moran B et al (2009) Magnetic Resonance Imaging Prediction of an Involved Surgical Resection Margin in Low Rectal Cancer *Diseases of the Colon and Rectum* 52;4:632-639

Design: Diagnostic Case Series

Country: UK

Setting:

Aim: to assess positive resection margin prediction by using MRI staging

Inclusion criteria
A subgroup of patients with low rectal cancer already part of the MERCURY study comprised the population for this study.
Patients forming the subgroup were those with:
Full pathology and MRI data available
Tumours ≤5cm from the anal verge
MRI scans available for review

Exclusion criteria
Patients with tumours >5cm above the anal verge

Sample Size
N/A

Randomisation Method
N/A

Population
N=101

Study Duration
No details

Interventions
High resolution, body coil, phased array MRI.

Outcomes

MRI Stage 1	Tumour on MRI appears confined to the bowel wall but not through full thickness
MRI Stage 2	Tumour on MRI replaces the muscle coat but does not extend into the intersphincteric plane
MRI Stage 3	Tumour on MRI invading into the intersphincteric plane or laying within 1mm or levator muscle
MRI Stage 4	Tumour invading into the external anal sphincter and infiltrating or extending beyond the levators with or without invasion of adjacent organs

Outcomes of the study are not clearly stated, it appears to be the ability of MRI to assign one of the above stages to tumour.

Results
A single experienced MRI radiologist who was blinded to the pathologic and surgical outcomes reviewed images of 101 patients

45/70 patients undergoing abdominoperineal excision received preoperative chemoradiotherapy; 29 of these patients had pre and post treatment MRI scans available for analysis of tumour regression grade (TRG).
10/31 patients undergoing low anterior resection received either preoperative chemoradiotherapy or short-course radiotherapy. Only 1 patient had pre-treatment and post-treatment MRI scans available for analysis of tumour regression grade.

Median age of patients eligible for analysis was 68 years (range 29-88); 70 patients underwent APE and 31 underwent LAR. 27% (27/101) had pathologically involved margins.

Significantly more patients with MRI stage 3 to 4 had positive resection margins (24/47, 36.7%) compared with patients with MRI stage 1 to 2 (3/54, 5.6%) (p<0.001).

Patients with anterior tumours had a higher risk of positive margins versus patients with a posterior tumour (36.7% versus 17.3%, p=0.026).

Patients with a tumour regression grade of 1 to 2 had a significantly higher risk of positive margins compared with

patients with tumour regression grade of 3 to 5 (73.3% versus 13.3%, p=0.001).

There was no significant difference between operation type or between patients that did and did not have any preoperative therapy.

On multivariate analysis, MRI stage remained a significant predictor of positive margins (OR for stages 3-4, 15.2, p=0.002) but tumour location (anterior versus posterior) was no longer significant (p=0.095).

Results of multivariate logistic regression analysis suggested that thumour regression grade and quadrant were predictive of positive margins however the authors deemed the results unreliable and chose not to present them in this study.

Citation: Tatli S, Mortele K, Breen E, Bleday R, Silverman S (2006) Local staging of rectal cancer using combined pelvic phased array and endorectal coil MRI *Journal of Magnetic Resonance Imaging* 23;4:534-540

Design: Case Series

Country: USA

Aim: to assess the accuracy of MRI using a pelvic phased array coil and an endorectal coil for preoperative local staging of rectal cancer.

Inclusion criteria
Patients with biopsy proven adenocarcinoma of the rectum

Exclusion criteria
Patients in whom endorectal coil could not be used

Population
N=51

Interventions
MRI with phased array coil and endorectal coil

Outcomes
Accuracy
Sensitivity
Specificity
Positive Predictive values
Negative Predictive values

Results
At pathological examination, 25% of patients had T1, 29% had T2 and 29% had T3. In 16% of patients no residual tumour was identified on pathological examination.
Overall MRI-based T-staging was identical to pathology based T-staging in 45/51 (88%) patients according to retrospective reading of images.
MRI correctly identified 31/36 (86%) of T0-T2 tumours and 14/15 (93%) of T3 tumours.
Blinded retrospective MRI reading correctly identified lymph node involvement in 29/39 patients.

	Total	Chemoradiotherapy	No chemoradiotherapy
Accuracy	88%	81%	96%
Sensitivity	93%	100%	80%
Specificity	86%	69%	100%
PPV	74%	67%	100%
NPV	97%	100%	95%

Table: Blinded retrospective reader interpretation of MRI for T-staging of rectal cancer

	Total	Chemoradiotherapy	No chemoradiotherapy
Accuracy	74%	81%	69%
Sensitivity	85%	100%	33%
Specificity	69%	69%	80%
PPV	58%	67%	33%
NPV	90%	100%	80%

Table: Blinded retrospective reader interpretation of MRI for N-staging of rectal cancer

Interobserver agreement between blinded retrospective reading (single reader) and prospective readings (seven radiologists) from radiological experts were excellent (κ=0.85) for prediction of T3 tumour and good (κ=0.80) for prediction of nodal metastasis.

General comments
An experienced radiologist without knowledge of the results of the pathological examination and surgical stage of the tumours evaluated all MRI images retrospectively.

Tumours were classified as:
T1 = confined to the mucosa and submucosa
T2 = muscularis propria invasion
T3 = mesorectal fat extension
T4 = adjacent organ invasion

N0 = no nodal involvement

N1 = one to three regional nodes positive for tumour
N2 = four or more regional nodes positive for tumour
Where a lymph node ≥5mm was deemed positive.

Citation: Tateishi U, Maeda T, Morimoto T, Miyake M, Arai Y, Kim, E (2007) Non-enhanced CT versus contrast enhanced CT in integrated PET/CT studies for nodal staging of rectal cancer *European Journal of Nuclear Medicine and Molecular Imaging* 34;10:1627-1634

Design: Retrospective Case Series

Country: Japan

Aim: to determine the diagnostic accuracy of non-enhanced CT and contrast enhanced CT in integrated PET/CT studies for preoperative nodal staging of rectal cancer.

Inclusion criteria
Patients with histologically proven rectal cancer
Performances Status (PS) PS0: fully active, able to carry on all pre-disease performance without restriction or PS1: restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature.

Exclusion criteria
Evidence of distant metastasis
Diabetes
Pregnancy or lactation in women

Population
N=53

Interventions
PET/CT with non-enhanced CT
PET/CT with enhanced CT

Outcomes
Accuracy
Sensitivity
Specificity
Positive Predictive Value
Negative Predictive Value

Results
Nodal status of regional lymph nodes was examined in all patients and a total of 106 lymph nodes were pathologically metastatic nodes. On the CT portion of non-enhanced PET/CT, nodal status was correctly determined in 17 (32%) patients versus 27 patients (51%) on CT of the contrast-enhanced PET/CT.
Nodal stage was correctly diagnosed in 37 (70%) of patients on non-enhanced PET/CT and in 42 patients (79%) in contrast-enhanced PET/CT.
There was no significant difference in accuracy of contrast enhanced PET/CT and non-enhanced PET/CT for nodal staging (p=0.063).

	Contrast Enhanced PET/CT	Non-enhanced PET/CT
Sensitivity	85%	85%
Specificity	68%	42%
Positive Predictive Value	83%	73%
Negative Predictive Value	72%	62%
Accuracy	79%	70%

Table: Results of nodal staging for contrast enhanced PET/CT and non-enhanced PET/CT

Contrast enhanced PET/CT determined the pararectal nodal status, internal iliac nodal involvement and obturaror nodal status more accurately than did non-enhanced PET/CT
Contrast enhanced PET/CT was significantly more accurate that non-enhanced PET/CT in the staging of regional lymph node metastasis.

Lymph Nodes	Non-enhanced PET/CT	Contrast enhanced PET/CT	P value
Pararectal Nodes			
Correct	35 (66%)	45 (85%)	0.002
Overstaged	10 (19%)	5 (9%)	
Understaged	8 (15%)	3 (6%)	
Internal Iliac Nodes			
Correct	35 (66%)	44 (83%)	0.004
Overstaged	7 (14%)	5 (9%)	
Understaged	11 (21%)	4 (8%)	
Obturator Nodes			

Correct	33 (62%)	47 (89%)	<0.0001
Overstaged	16 (30%)	2 (4%)	
Understaged	4 (8%)	4 (8%)	

Table: Staging performance for non-enhanced PET/CT and contrast enhanced PET/CT in respect of regional lymph nodes

	Contrast Enhanced PET/CT			Non-enhanced PET/CT		
	Pararectal Nodes	**Internal Iliac Nodes**	**Obturator Nodes**	**Pararectal Nodes**	**Internal Iliac Nodes**	**Obturator Nodes**
Sensitivity	73% (22/30)	60% (9/15)	50% (5/10)	90% (27/30)	73% (11/15)	80% (8/10)
Specificity	57% (13/23)	82% (31/38)	84% (36/43)	78% (18/23)	87% (33/38)	91% (39/43)
PPV	69% (22/32)	56% (9/16)	42% (5/12)	84% (27/32)	69% (11/16)	67% (8/12)
NPV	62% (13/21)	84% (31/37)	87% (31/37)	86% (18/21)	89% (33/37)	95% (39/41)
Accuracy	66% (35/53)	75% (40/53)	77% (41/53)	85% (45/53)	83% (44/53)	89% (47/53)

Table: Diagnostic accuracy of contrast enhanced and non-enhanced PET/CT with respect of regional lymph node status.

General comments

Total mesorectal resection and lymphadenectomy were performed in all patients and histopathologic results used as the reference standards.

Authors Conclusion: Contrast enhanced PET/CT shows a trend towards more accurate N‑staging of rectal cancer compared with non-enhanced PET/CT.

3. Management of Local Disease

3.1. Preoperative Management of the Patients Primary Tumour

3.1.1. For patients with operable rectal cancer, what is the effectiveness of preoperative short course radiotherapy or chemoradiotherapy?

Short Summary

Preoperative radiotherapy versus surgery alone
The evidence for this comparison comprised a systematic review (Wong *et al.,* 2007) and data from long term follow-up of two randomised trials (Peeters *et al.*, 2007 and Birgisson *et al.,* 2005). In addition there was a systematic review (Birgisson *et al.,* 2007) which addressed the late adverse effects of pre-operative (and post-operative) radiotherapy (RT) in patients treated for rectal cancer.

Wong *et al.* (2007) calculated a pooled hazards ratio for overall survival from fourteen studies of HR: 0.93 (95%CI: 0.87-1.0) (p=0.04) in favour of pre-operative RT versus surgery only, but this could not be replicated using individual patient data. Long term data from the Dutch TME trial also found no significant difference in the rate of overall survival between patients who had pre-operative RT compared with those patients who had surgery only (64.2% versus 63.5%) (Peeters *et al.*2007).

Pooled data for disease-specific survival indicated an advantage of pre-operative RT in reducing the risk of disease-free survival (HR: 0.87 (95%CI: 0.78-0.98) (p=0.02)) but there was high between studies heterogeneity so the results may not be reliable. The data for local recurrence were highly heterogeneous and were not appropriate for pooling. However, good data showed an overall reduction in the rate of second malignancies in favour of pre-operative RT (HR: 0.89 (95%CI: 0.82-0.97) (p<0.001). The most common side effect of pre-operative RT was diarrhoea. Patients in the surgery only group experienced more post-surgical toxicity.

Peeters *et al.* (2007) analysed long term data from the Dutch TME trial and found no significant difference in the rate of overall survival between patients who had pre-operative RT compared with those patients who had surgery only (64.2% versus 63.5%).
 They also found no significant difference in 5 year cancer specific survival in irradiated versus non-irradiated patients (75.4% versus 72.4%). However, there was a 49% reduction in local disease recurrence (p<0.001) for irradiated patients but no significant difference in the rate of distant recurrence after 5 years of follow-up.

Quality of life comparisons showed a non-significant trend towards worse outcomes in irradiated patients. There was more scarring of the anal sphincters in this group (33%) when compared with the non-irradiated group (13%) and most also suffered some degree of incontinence. The maximum resting and squeezing pressures were significantly lower in the irradiated group (Wong *et al.*, 2007). Birgisson *et al.* (2005) observed an increased risk of infections among irradiated patients during the first 6 months after treatment (RR: 7.67 (95%CI: 1.76-33.39)) and similarly in gastrointestinal diagnoses (RR: 2.57 (95%CI: 1.55-4.26)). There was an increase in the risk of non-specific infections (n=10; RR: 8.06 (95%CI: 1.02-63.69) in the irradiated group although the risk of cardiac arrhythmia was reduced (RR: 0.57 (95%CI: 0.36-0.91). In relation to gastrointestinal diagnoses, increased relative risks were observed in irradiated patients for bowel obstruction, nausea and non-specific abdominal pain whereas the risk for inguinal hernia was lower.

Pre-operative chemoradiotherapy versus pre-operative radiotherapy
The evidence for this comparison comprised four papers (Pietrzak *et al.,* 2007, Bujko *et al.,* 2004, Bujko *et al.,* 2005 and Bujko *et al.,* 2006) reporting different outcomes from the same trial comparing conventionally fractionated pre-operative chemoradiotherapy (chemoRT) with short course pre-operative RT (RT).

Bujko *et al.* (2006) reported no significant difference in the rate of 4 year survival (HR: 1.01 (95%CI: 0.69-1.48) or 4 year disease free survival (HR: 0.96 (95%CI: 0.69-1.35) between patients having received chemoRT compared with RT. There was also no significant difference in the 4 year incidence of local recurrence (HR: 0.65 (95%CI: 0.32-1.28), the crude incidence of distant metastases, late toxicity (RR: 1.05 (95%CI: 0.72-1.53) or late severe toxicity (RR: 1.43 (95%CI: 0.67-3.07). Bujko *et al.* (2004) found no significant difference in the rate of sphincter preservation between patients having had RT and those having had chemoRT (61% versus 58%). Bujko *et al.* (2005) found no significant difference in the rate of post-operative complications or severe complications, including death, between comparators but, unfortunately,

as this was not the primary outcome of the trial, the study was underpowered to have detected a difference between the interventions had one existed.

(Pietrzak *et al.,* 2007) specifically addressed quality of life (QoL) and observed no significant difference in the mean scores for the global health/quality of life status (p=0.22) or for anorectal and sexual function in patients having had chemoRT or RT. Approximately two thirds of patients complained of faecal and gas incontinence, urgency and inability to differentiate between stool and gas. Approximately two-thirds of respondents stated that the disturbances in anorectal function had a negative impact on their QoL, with approximately 20% stating the impact was considerable. Anorectal function was estimated as being 'good' or 'very good' by 41% of patients in the RT group and by 37% of patients in the chemoRT group (p=0.52). Two percent (n=2) of patients scored anorectal function as being 'unacceptable' and regretted that a stoma had not been performed. There was no significant difference between the two groups in relation to the impact on sexual function (p=0.56 for males; p=0.1 for females).

Updated Evidence
Stephens *et al.* (2010) conducted a quality of life study within a randomised controlled trial that had compared short course radiotherapy then surgery (PRE) with surgery and post-operative chemotherapy (if tumour was within 1mm of resection margin) (SEL POST). Study participants completed two questionnaires (MOS SF-36 and QLQ-CR38) at baseline (N=1,208), every 3 months for the first year and every 6 months to 3 years (N=563 at 2 years). The main, irreversible treatment effect that reduced QoL was sexual dysfunction (P<0.001 for men, regardless of group, between baseline and 3 months) caused primarily by surgery but exacerbated by RT (P<0.001 at 6 months between groups). There were insufficient responses from females to measure this outcome. Bowel function in patients without a stoma (or in those who had a stoma reversal) was not significantly different between treatment arms. However, sub group analysis suggested that patients in the PRE group may have experienced an increase in the 'unintentional release of stools' even at 2 years post-treatment (P=0.007). Generally, there were no significant differences in treatment groups in overall general health or QoL. Although the quality of the trial from which these data may have been good, the non-specific nature of the questionnaires applied may have rendered them less sensitive to detecting differences in outcomes.

Fiorica *et al.* (2010) presented a systematic review and meta-analysis of long term follow-up data from seven trial reports, including one abstract, comparing pre-operative chemoradiotherapy and pre-operative radiotherapy in patients with resectable rectal cancer. The conclusions of the study were that the addition of chemotherapy to pre-operative radiotherapy reduced the risk of local recurrence (RR: 1.05; 95%CI: 1.01-1.10; P=0.02) but did not improve overall survival (RR: 1.02; 95%CI: 0.94-1.09; P=0.68) or the risk of distant metastases (RR: 0.97; 95%CI: 0.93-1.02; P=0.21). Treatment associated toxicity was also higher with the combined modality.

Review Protocol

Population	Intervention	Comparison	Outcomes
Patients with operable rectal cancer	• Pre-operative short course radiotherapy • Pre-operative chemoradiotherapy	Surgery alone and with each other	• Survival • Local Control • Morbidity from early studies • Quality of Life • Second malignancies

Following a systematic search of relevant data sources (see appendix .1), the information specialist created a database of potentially relevant studies. All titles and abstracts were sifted by a single reviewer. Queries about inclusion were clarified by the GDG topic subgroup. The full studies were then obtained and reviewed and relevant studies were included in the final evidence review.

All update searches were sifted by a single reviewer and the list of potentially relevant studies was also checked for irrelevant studies by the GDG subgroup. Only studies which all subgroup members were in agreement were excluded. The remaining studies were obtained and reviewed with relevant studies included in the final evidence review.

The GDG felt that there should be high level evidence available to address this topic and advised looking at these studies only

The date limit set by the GDG was from 1990 onwards as it was considered that this was when relevant data for current practice became available

Other issues identified by the GDG to be addressed included the long term effects of treatment and effects on bowel function

Exclusion criteria for included evidence:
Comparisons in studies not relevant to PICO
Population in studies not relevant to PICO
Outcomes not relevant to PICO
Foreign Language studies
Expert Reviews

Quality of the included studies
Systematic review of RCTs (n = 3)
Systematic review of combined study designs (n =0)
Randomized controlled trial (n =7)
Prospective cross sectional study (n =0)
Case Series Studies (n = 0)
Diagnostic Studies (n= 0)

813(+68) possibly relevant papers identified	□	781 (+62) papers excluded based on title & abstract	
□			
32 (+6) papers obtained for appraisal	□	23 (+4) papers excluded	
□			
9 (+2) papers included in evidence table			
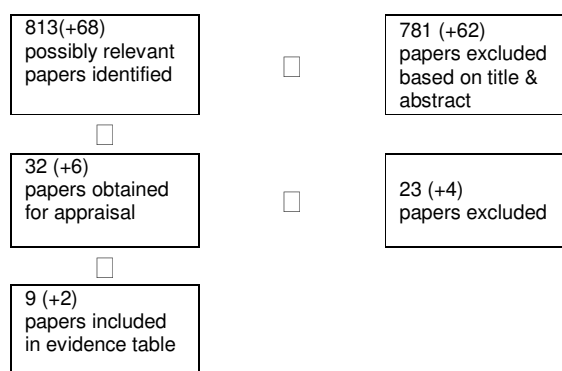
Evidence Summary

Survival
Overall survival
Wong *et al.* (2007) calculated a pooled hazards ratio from fourteen studies of HR: 0.93 (95%CI: 0.87-1.0) (p=0.04) in favour of pre-operative RT. However, when using individual patient data published by the Cochrane Colorectal Cancer Group (2001), the difference between pre-operative RT and surgery lost statistical significance (HR: 0.95 (5%CI: 0.89-1.02) (p=0.13). The largest study of the fourteen in this group (Swedish RCT, 1997) showed that the magnitude of any benefit with pre-operative RT was just 2% after both 5 years (from 75% to 77% survival) and 8 years (from 60% to 62% survival) follow-up. Subgroup analyses showed that non total mesorectal excision (TME) studies, higher biological effective dose (BED) and treatment fields focused to the posterior pelvis were each associated with significant survival benefit. Peeters *et al.* (2007) analysed long term data from the Dutch TME trial and found no significant difference in the rate of overall survival between patients who had pre-operative RT compared with those patients who had surgery only (64.2% versus 63.5%).

Disease specific survival
The pooled hazards ratio (from five studies) was HR: 0.87 (95%CI: 0.78-0.98) (p=0.02) in favour of pre-operative RT, however there was significant heterogeneity between the relatively low number of studies (I^2=54%) and the results should therefore be considered with some caution (Wong *et al.,* 2007). Peeters *et al.* (2007) found no significant difference in 5 year cancer specific survival in irradiated versus non-irradiated patients (75.4% versus 72.4%).

Local control
Local recurrence
Local recurrence rates ranged greatly, from 11% to 54% in thirteen pooled studies (Wong *et al.,* 2007). Although all but one study individually reported a benefit in favour of pre-operative RT, very significant, unexplained between studies heterogeneity was observed (I^2=84%) which negated the value of pooling data. Nevertheless, the authors reported RR: 0.71 (95%CI: 0.64-0.78) (p<0.00001) in favour of pre-operative RT. Peeters *et al.* (2007) found a 49% reduction in local disease recurrence (rate in irradiated patients 5.6% versus 10.9% in irradiated patients (p<0.001)) from 5 year follow-up of the Dutch TME trial.

Second malignancies
Any recurrence
From the review (Wong *et al.,* 2007) the pooled hazards ratio (from eight studies) was HR: 0.89 (95%CI: 0.82-0.97) (p<0.001), an overall reduction of recurrences in favour of pre-operative radiotherapy. Peeters *et al.* (2007) could not demonstrate a significant difference in the rate of distant recurrence after 5 years of follow-up (irradiated patients 25.8% versus 28.3% in irradiated patients)

Curative and overall resectability
From fifteen studies, Wong *et al.* (2007) reported a pooled risk ratio for curative resectability of RR: 1.02 (95%CI: 1-1.05) in favour of pre-operative RT but which was not of statistical significance (p=0.06). The data for overall resectability could not be pooled due to high between studies heterogeneity (I^2=72%).

Morbidity
Acute post-radiotherapy toxicity
The proportion of patients with post-RT toxicities ranged from 20% to 84%. The most common reported side effect was diarrhoea (20%) (Wong *et al.,*2007).

Post surgical morbidity
The surgery only group had fewer patients without post-surgical toxicities than the pre-operative RT group; from six studies the risk ratio was RR: 0.88 (95%CI: 0.82-0.94) (p=0.00015) (Wong *et al.,* 2007).

Sphincter sparing surgery
From fifteen studies, the pooled risk ratio (Wong *et al.,* 2007) for sphincter sparing surgery was RR: 0.96 (95%CI: 0.88-1.04) (p=0.27) which was not statistically significant. There was high between studies heterogeneity (I^2=40%) which could not be explained by the authors.

Longer term adverse effects
Late treatment morbidity
Quality of life comparisons showed a non-significant trend towards worse outcomes in irradiated patients. There was more scarring of the anal sphincters in the irradiated group (33%) when compared with the non-

irradiated group (13%) confirmed by endoanal ultrasound. This outcome was related to functional outcome with 11/12 patients suffering some degree of incontinence symptoms.

Maximum resting pressure and maximum squeezing pressure were significantly lower in the irradiated group (Wong *et al.,* 2007). Birgisson *et al.* (2007) reviewed the late adverse effects of radiotherapy treatment and concluded that these included bowel obstructions, bowel dysfunction and sexual problems in both males and females. They did point out that the more recent improvements in technique had resulted in fewer adverse events being reported.

Birgisson *et al.* (2005) observed an increased risk of infections among irradiated patients during the first 6 months after treatment (RR: 7.67 (95%CI: 1.76-33.39)) and similarly in gastrointestinal diagnoses (RR: 2.57 (95%CI: 1.55-4.26)). An increase in relative risk among irradiated patients was observed for non-specific infections (n=10; RR: 8.06 (95%CI: 1.02-63.69). The risk of cardiac arrhythmia was reduced in the irradiated group (RR: 0.57 (95%CI: 0.36-0.91). In relation to gastrointestinal diagnosis, increased relative risks were observed in irradiated patients for bowel obstruction, nausea and unspecific abdominal pain whereas the risk for inguinal hernia was lower among irradiated patients.

Hospital admissions after surgery
Birgisson *et al.* (2005) compared the occurrence of sub-acute and late adverse effects in irradiated and non-irradiated patients that had participated in two randomised trials of rectal cancer treatment in Sweden. The authors reported that 73% (n=661) of patients analysed were admitted to hospital at least once after treatment of primary rectal cancer. More patients from the irradiated group were admitted both in the early and late post-operative periods but there was no difference in relative risk (RR: 1.07 (95%CI: 0.91-1.26)). There was however, an increase in relative risk for early admissions in irradiated patients (RR: 1.64 (95%CI: 1.21-2.22)) but not in late admissions (RR: 0.95 (95%CI: 0.8-1.12)).

Pre-operative radiotherapy no. of patients	Surgery alone no. of patients	Relative Effect (95% CI)	Absolute Effect
Overall survival (Wong *et al.,* 2007) (p=0.15)			
2027/3997 (50.7%)	1880/4635 (40.6%)	HR 0.93 (0.87 to 1)[1]	22 fewer per 1000 (from 42 fewer to 0 more)
5 year overall survival rate (Peeters *et al.,* 2007) (p=0.39)			
64.2%	63.5%	N/A	N/A
Cause specific mortality (Wong *et al.,* 2007) (p=0.016)			
467/1119 (41.7%)	508/1136 (44.7%)	HR 0.87 (0.78 to 0.98)[1]	44 fewer per 1000 (from 7 fewer to 77 fewer)
5 year cancer-specific survival rate (Peeters *et al.,* 2007) (p=0.26)			
75.4%	72.4%	N/A	N/A
Any recurrence (Wong *et al.,* 2007) (p=0.0056)			
955/2576 (37.1%)	1091/2601 (41.9%)	HR 0.89 (0.82 to 0.97)[1]	36 fewer per 1000 (from 10 fewer to 60 fewer)
5 year distant disease recurrence rate (Peeters *et al.,* 2007) (p=0.39)			
25.8%	28.3%	N/A	N/A
Local recurrence (Wong *et al.,* 2007) (p<0.00001)			
681/3709 (18.4%)	1034/3758 (27.5%)	HR 0.71 (0.64 to 0.78)[1]	71 fewer per 1000 (from 53 fewer to 89 fewer)
5 year local recurrence rate (Peeters *et al.,* 2007) (p<0.001)			
5.6%	10.9%	N/A	N/A
Curative resectability (Wong *et al.,* 2007) (p=0.059)			
3290/4228 (77.8%)	3203/4254 (75.3%)	RR 1.02 (1 to 1.05)	15 more per 1000 (from 0 fewer to 38 fewer)
Sphincter sparing surgery (Wong *et al.,* 2007)			
1592/3950 (40.3%)	1657/3967 (41.8%)	RR 0.96 (0.88 to 1.04)	17 fewer per 1000 (from 50 fewer to 17 more)
Acute post surgery toxicity (Wong *et al.,* 2007) (p=0.00015)			
962/1836 (52.4%)	1128/1879 (60%)	RR 0.88 (0.82 to 0.94)	72 fewer per 1000 (from 36 fewer to 108 fewer)
Adverse events – risk of infection within 6 months of surgery (Birgisson *et al.,* 2005) (p<0.01)			
-	-	RR 7.67 (1.76 to 33.39)	-

Pre-operative radiotherapy no. of patients	Surgery alone no. of patients	Relative Effect (95% CI)	Absolute Effect
Adverse events – risk of gastrointestinal diagnosis (Birgisson *et al.,* 2005) (p<0.01)			
-	-	RR 2.57 (1.55 to 4.26)	-
Adverse events – risk of hospital admission, all admissions (Birgisson *et al.,* 2005) (NSD)			
-	-	RR 1.07 (0.91 to 1.26)	-
Adverse events – risk of hospital admission, early admissions (Birgisson *et al.,* 2005) (p<0.05))			
-	-	RR 1.64 (1.21 to 2.22)	-

Table 3.1 GRADE summary of findings (pre-operative radiotherapy versus surgery)

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Quality
Overall survival (Wong *et al.,* 2007)						
14	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	⊕⊕⊕⊕ HIGH
5 year overall survival rate (Peeters *et al.,* 2007)						
1	randomised trial	serious[2]	N/A	N/A	N/A	⊕⊕⊕ MODERATE
Cause specific mortality (Wong *et al.,* 2007)						
4	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	⊕⊕⊕⊕ HIGH
5 year cancer-specific survival rate (Peeters *et al.,* 2007)						
1	randomised trial	serious[2]	N/A	N/A	N/A	⊕⊕⊕ MODERATE
Any recurrence (Wong *et al.,* 2007)						
8	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	⊕⊕⊕⊕ HIGH
5 year distant disease recurrence rate (Peeters *et al.,* 2007)						
1	randomised trial	serious[2]	N/A	N/A	N/A	⊕⊕⊕ MODERATE
Local recurrence (Wong *et al.,* 2007)						
13	randomised trials	no serious limitations	serious[3]	no serious indirectness	no serious imprecision	⊕⊕⊕ MODERATE
5 year local recurrence rate (Peeters *et al.,* 2007)						
1	randomised trial	serious[2]	N/A	N/A	N/A	⊕⊕⊕ MODERATE
Curative resectability (Wong *et al.,* 2007)						
15	randomised trials	no serious limitations	serious	no serious indirectness	no serious imprecision	⊕⊕⊕⊕ HIGH
Sphincter sparing surgery (Wong *et al.,* 2007)						
15	randomised trials	no serious limitations	serious[4]	no serious indirectness	no serious imprecision	⊕⊕⊕ MODERATE

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Quality
Acute post surgery toxicity (Wong *et al.,* 2007)						
6	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	⊕⊕⊕⊕ HIGH
Adverse events – risk of infection within 6 months of surgery (Birgisson *et al.,* 2005)						
1	randomised trial	no serious limitations	N/A	N/A	N/A	⊕⊕⊕⊕ HIGH
Adverse events – risk of gastrointestinal problems (Birgisson *et al.,* 2005)						
1	randomised trial	no serious limitations	N/A	N/A	N/A	⊕⊕⊕⊕ HIGH
Adverse events – risk of hospital admission, all admissions (Birgisson *et al.,* 2005)						
1	randomised trial	no serious limitations	N/A	N/A	N/A	⊕⊕⊕⊕ HIGH
Adverse events – risk of hospital admission, early admissions (Birgisson *et al.,* 2005)						
1	randomised trial	no serious limitations	N/A	N/A	N/A	⊕⊕⊕⊕ HIGH

[1] The Cochrane Review (Wong *et al.,* 2007) states that hazards ratios were calculated with RevMan software however it was unclear what data were used in the analyses.
[2] Central randomisation was adequate, blinding was not feasible and allocation was unclear.
[3] Differences in recurrence rates ranged from 11% to 54% (I^2 = 84%) i.e. the studies were highly heterogeneous and hence results should be interpreted with caution.
[4] Data were heterogeneous (I^2 = 40%) across the studies for sphincter sparing surgery.

Table 3.2 GRADE quality assessment table (pre-operative radiotherapy versus surgery)

Pre-operative chemoradiotherapy versus pre-operative radiotherapy - summary

The evidence for this comparison comprised four papers (Pietrzak *et al.,* 2007, Bujko *et al.,* 2004, Bujko *et al.,* 2005 and Bujko *et al.,* 2006) reporting different outcomes from the same trial comparing conventionally fractionated pre-operative chemoradiotherapy with short course pre-operative RT. Where possible, study quality was assessed for each outcome by means of GRADE methodology (see tables iii and iv). For outcomes assessed in this way, the quality was assessed to be 'high'.

Updated evidence
Fiorica *et al.* (2010) presented a systematic review and meta-analysis of long term follow-up data from seven trial reports, including one abstract, comparing pre-operative chemoradiotherapy and pre-operative radiotherapy in patients with resectable rectal cancer. Stephens *et al.* (2010) conducted a quality of life study within a randomised controlled trial that had compared short course radiotherapy then surgery with surgery and post-operative chemotherapy (if tumour was within 1mm of resection margin).

Survival
The conclusions of Fiorica *et al.* (2010) were that the addition of chemotherapy to pre-operative radiotherapy did not improve overall survival (RR: 1.02; 95%CI: 0.94-1.09; P=0.68).

Bujko *et al.* (2006) reported no significant difference in the rate of 4 year survival between patients in the pre-operative chemoradiotherapy arm when compared with the pre-operative RT arm (HR: 1.01 (95%CI: 0.69-1.48) and no significant difference in the rate of 4 year disease free survival between patients in the pre-operative RT arm when compared with those patients in the pre-operative chemoradiotherapy arm (HR: 0.96 (95%CI: 0.69-1.35).

Local control
Fiorica *et al* (2010) found that, compared with pre-operative radiotherapy, pre-operative chemoradiotherapy significantly reduced the risk of local recurrence (RR: 1.05; 95%CI: 1.01-1.10; P=0.02). Conversely, Bujko *et al.* (2006) reported no significant difference in the 4 year incidence of local recurrence between patients in the pre-operative RT arm when compared with patients in the pre-operative chemoradiotherapy arm (HR: 0.65 (95%CI: 0.32-1.28).

Second malignancies
Fiorica *et al.*(2010) found that, compared with pre-operative radiotherapy, pre-operative chemoradiotherapy did not reduce the risk of distant metastases (RR: 0.97; 95%CI: 0.93-1.02; P=0.21). Bujko *et al.* (2006) reported no significant difference in the crude incidence of distant metastases between patients in the pre-operative RT arm when compared with patients in the pre-operative chemoradiotherapy arm (31.45% versus 34.6%).

Morbidity
Fiorica *et al.* (2010) found that treatment associated toxicity was higher for patients having received the combined modality of pre-operative chemoradiotherapy compared with the effects of pre-operative radiotherapy alone.

Sphincter preservation
Bujko *et al.* (2004) found no significant difference in the rate of sphincter preservation between patients having had pre-operative RT and those having had pre-operative chemoradiotherapy (61% versus 58%).

Post surgical morbidity
Bujko *et al.* (2005) found no significant difference in the rate of post-operative complications or severe complications, including death, between patients having had pre-operative RT and those having had pre-operative chemoradiotherapy. Unfortunately, as this was not the primary outcome of the trial, the study was underpowered to have detected a difference between the interventions had one existed.

Long term effects

Late treatment morbidity
Bujko *et al.* (2006) reported no significant differences in the relative risk of late toxicity (RR: 1.05 (95%CI: 0.72-1.53) nor in late severe toxicity (RR: 1.43 (95%CI: 0.67-3.07) between pre-operative RT and pre-operative chemoradiotherapy.

Quality of life

One randomised trial (Pietrzak *et al.,* 2007), specifically addressing quality of life as an outcome observed no significant difference between the two groups in relation to mean scores for the global health/quality of life status (p=0.22). The same trial did note however, that a significantly higher number of patients in the short-term RT went on to receive post-operative chemotherapy compared with the chemotherapy group (p=0.002).

In relation to anorectal and sexual function, Pietrzak *et al.* (2007) observed no significant difference between the two groups in relation to any of the questions posed. Approximately two thirds of patients complained of faecal and gas incontinence, urgency and inability to differentiate between stool and gas. Approximately two-thirds of respondents stated that the disturbances in anorectal function had a negative impact on their quality of life, with approximately 20% stating the impact was considerable.

Anorectal function was estimated as being 'good' or 'very good' by 41% of patients in the short-course pre-operative RT group and by 37% of patients in the chemoradiotherapy group (p=0.52).
Two percent (n=2) of patients scored anorectal function as being 'unacceptable' and regretted that a stoma had not been performed. There was no significant difference between the two groups in relation to the impact on sexual function (p=0.56 for males; p=0.1 for females).

Stephens *et al.* (2010) reported the outcomes from a trial in which participants had been randomised to receive short course radiotherapy then surgery or surgery and post-operative chemotherapy. Patients had completed two questionnaires regarding health outcomes (MOS SF-36 and QLQ-CR38) at baseline (N=1,208), every 3 months for the first year and every 6 months to 3 years (N=563 at 2 years). The main, irreversible treatment effect that reduced QoL was sexual dysfunction (P<0.001 for men, regardless of group, between baseline and 3 months) caused primarily by surgery but which was exacerbated by pre-operative RT (P<0.001 at 6 months between groups). There were insufficient responses from females to measure this outcome. Bowel function in those patients without a stoma (or in those who had a stoma reversal) was not significantly different between treatment arms. However, sub group analysis suggested that patients in the pre-operative RT group may have experienced an increase in the 'unintentional release of stools' even at 2 years post-treatment (P=0.007). Generally, there were no significant differences in treatment groups in overall general health or QoL. The quality of the trial from which these data are taken was high; however, the non-specific nature of the questionnaires applied may have rendered them less sensitive to detecting differences in outcomes.

Pre-operative chemoradiotherapy no. of patients	Pre-operative radiotherapy no. of patients	Relative effect (95% CI)	Absolute effect
Sphincter preservation rate (Bujko *et al.,* 2004) (p=0.57)[1]			
91/157 (58.0%)	95/155 (61.2%)	OR 0.93 (0.59 to 1.47)	1 fewer per 1000 (from 5 fewer to 6 more)
Acute post RT grade III-IV toxicity (Bujko *et al.,* 2004) (p<0.001)[1]			
29/157 (18.5%)	5/155 (3.2%)	OR 6.8 (2.56 to 18.07)	70 more per 1000 (from 20 more to 180 more)
Post-operative morbidity (Bujko *et al.,* 2005) (p=0.27)[1]			
31/157 (21%)	39/155 (27%)	OR 0.73 (0.43 to 1.25)	61 fewer per 1000 (from 134 fewer to 52 more)
4 year risk of death (Bujko *et al.,* 2006) (NSD)			
53/157 (33.8%)	52/155 (33.5%)	HR 1.01 (0.69 to 1.48)	0 fewer per 1000 (from 4 fewer to 6 more)
4 year risk of death or relapse (Bujko *et al.,* 2006) (NSD)			
44.4%	41.6%	HR 1.12 (0.64 to 1.96)[2]	4 more per 1000 (from 91 fewer to 202 more)

Pre-operative chemoradiotherapy no. of patients	Pre-operative radiotherapy no. of patients	Relative effect (95% CI)	Absolute effect
4 year risk of local recurrence (Bujko *et al.,* 2006) (NSD)			
15.6%	10.6%	HR 1.56 (0.68 to 3.60)[2]	53 more per 1000 (from 32 fewer to 221 more)
Rate of distant metastases (Bujko *et al.,* 2006) (NSD)			
34.6%	31.4%	-	-
Rate of late toxicity (Bujko *et al.,* 2006) (NSD)			
27%	28.3%	RR 0.94 (0.66 to 1.35)[2]	17 fewer per 1000 (from 97 fewer to 99 more)
Rate of severe late toxicity (Bujko *et al.,* 2006) (NSD)			
7.1%	10.1%	RR 0.68 (0.33 to 1.41)[2]	33 fewer (from 69 fewer to 42 more)
Risk of permanent stoma (Bujko *et al.,* 2006) (NSD)			
51.6%	56.9%	RR 0.91 (0.74 to 1.12)[2]	52 fewer (from 149 fewer to 69 more)
QOL, anorectal and sexual function (Pietrzak *et al.,* 2007) (NSD)[3]			
-	-	-	-

Short course pre-operative radiotherapy number of responses	Post-operative chemoradiotherapy number of responses	Mean QoL scores (higher scores : poorer QoL)	Absolute effect
QOL, male sexual function between baseline and 3 months (Stephens *et al.,* 2010) (P<0.001 for all patients)			
351 baseline 165 at 3 months	307 baseline 171 at 3 months	28.6% baseline versus 28.2% at 3 months for all patients NSD between groups	-
QOL, male sexual function between at 2 years (Stephens *et al.,* 2010)			
154 at 2 years	146 at 2 years	65.7% versus 57.4% P=0.058 between groups	-
QOL, physical function at 3 months (Stephens *et al.,* 2010)			
310 at 3 months	343 at 3 months	58.4% versus 62.6% P=0.028 between groups	-
QOL, unintentional release of stools at 2 years (Stephens *et al.,* 2010)			

Short course pre-operative radiotherapy number of responses	Post-operative chemoradiotherapy number of responses	Mean QoL scores (higher scores : poorer QoL)	Absolute effect
141 at 2 years	153 at 2 years	53.2% versus 37.3% P=0.007 between groups	-

Pre-operative chemoradiotherapy number of patients	Pre-operative radiotherapy number of patients	Relative effect (95% CI)	Absolute effect
5 year overall survival (pooled, random effect model) (Fiorica *et al.,* 2010) (P=0.068)			
1392	1395	RR: 1.02 (0.94 to1.09)	-
5 year local control (pooled, random effect model) (Fiorica *et al.,* 2010) (P=0.02)			
1390	1395	RR: 1.05 (1.01 to 1.10)	-
5 year local control (pooled, fixed effect model) (Fiorica *et al.,* 2010) (P<0.0001)			
1390	1395	RR: 1.06 (1.03 to 1.10)	-
5 year distant metastases (pooled, random effect model) (Fiorica *et al.,* 2010) (P=0.21)			
1390	1395	RR: 0.97 (0.93 to 1.02)	-
Risk of toxicity related mortality (pooled, random effect model) (Fiorica *et al.,* 2010) (P=0.08)			
1340	1383	RR: 1.63 (0.95 to 2.82)	-

Table 3.3-3.5 GRADE summary of findings table (pre-operative chemoradiotherapy versus pre-operative radiotherapy)

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Quality
Sphincter preservation rate (Bujko *et al.,* 2004) (p=0.57)[1]						
1	randomised trial	no serious limitations	N/A	N/A	N/A	⊕⊕⊕⊕ HIGH
Acute post RT grade III-IV toxicity (Bujko *et al.,* 2004) (p<0.001)						
1	randomised trial	no serious limitations	N/A	N/A	N/A	⊕⊕⊕⊕ HIGH
Post-operative morbidity (Bujko *et al.,* 2005*)* (p=0.27)						

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Quality
1	randomised trial	no serious limitations	N/A	N/A	N/A	⊕⊕⊕⊕ HIGH

4 year risk of death (Bujko *et al.,* 2006) (NSD)

| 1 | randomised trial | no serious limitations | N/A | N/A | N/A | ⊕⊕⊕⊕ HIGH |

4 year risk of death or relapse (Bujko *et al.,* 2006) (NSD)

| 1 | randomised trial | no serious limitations | N/A | N/A | N/A | ⊕⊕⊕⊕ HIGH |

4 year risk of local recurrence (Bujko *et al.,* 2006) (NSD)

| 1 | randomised trial | no serious limitations | N/A | N/A | N/A | ⊕⊕⊕⊕ HIGH |

Rate of distant metastases (Bujko *et al.,* 2006) (NSD)

| 1 | randomised trial | no serious limitations | N/A | N/A | N/A | ⊕⊕⊕⊕ HIGH |

Rate of late toxicity (Bujko *et al.,* 2006) (NSD)

| 1 | randomised trial | no serious limitations | N/A | N/A | N/A | ⊕⊕⊕⊕ HIGH |

Rate of severe late toxicity (Bujko *et al.,* 2006) (NSD)

| 1 | randomised trial | no serious limitations | N/A | N/A | N/A | ⊕⊕⊕⊕ HIGH |

Risk of permanent stoma (Bujko *et al.,* 2006) (NSD)

| 1 | randomised trial | no serious limitations | N/A | N/A | N/A | ⊕⊕⊕⊕ HIGH |

QOL, anorectal and sexual function (Pietrzak *et al.,* 2007) (NSD)[3]

| 1 | randomised trial | no serious limitations | N/A | N/A | N/A | ⊕⊕⊕⊕ HIGH |

QOL, all outcomes (Stephens *et al.,* 2010) [4]

| 1 | randomised trial | - | - | - | - | – |

All outcomes (Fiorica *et al.,* 2010) [5]

| 7 | randomised trial | - | - | - | - | – |

[1] Odds ratios reported by Ceelen *et al.,* 2009
[2] Ratios were calculated from the data reported in order to provide consistency by comparing chemoradiotherapy with radiotherapy, rather than the reverse.
[3] No data suitable to put into GRADE. All included studies are from a single RCT of high quality.
[4] Original study data were reported by Sebag-Montefiore *et al.,* 2009 which was not appraised in this review since only one comparator was appropriate to the topic.
[5] Although Fiorica *et al*., 2010 reported assessment of individual study quality, the resulting data could not be accessed in order to complete a GRADE analysis.

Table 3.6 GRADE quality assessment table (pre-operative chemoradiotherapy versus pre-operative radiotherapy)

References

Birgisson H, Pahlman L, Gunnarsson U, Glimelius B, Swedish Rectal Cancer Trial Group. (2005) Adverse effects of preoperative radiation therapy for rectal cancer: long-term follow-up of the Swedish Rectal Cancer Trial. *J Clin Oncol*; **23(34):**8697-8705.

Birgisson H, Pahlman L, Gunnarsson U, Glimelius B. (2007) Late adverse effects of radiation therapy for rectal cancer - a systematic overview. *Acta Oncol*; **46(4):**504-516.

Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Ko M et al. (2004) Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy. *Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology*; **72(1):**15-24.

Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. (2006) Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg*; **93(10):**1215-1223.

Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M et al. (2005) Long-term results of a randomised trial comparing preoperative short-course radiotherapy vs. preoperative conventionally fractionated chemoradiation for rectal cancer. *Ejc Suppl*; **3(2):**169.

Ceelen W, Fierens K, Van NY, Pattyn P. (2009) Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer: a systematic review and meta-analysis. *Int J Cancer*; **124(12):**2966-2972.

Fiorica F, Cartei F, Licata A, Enea M, Ursino S and Colosimo C et al. (2010) Can chemotherapy concomitantly delivered with radiotherapy improve survival of patients with resectable rectal cancer? A meta-analysis of literature data. *Cancer Treat Rev* **36(7):** 539-549

Peeters KC, Marijnen CA, Nagtegaal ID, Kranenbarg EK, Putter H, Wiggers T et al. (2007) The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. *Ann Surg*; **246(5):**693-701.

Pietrzak L, Pietrzak,L, Bujko,K, Nowacki MP, Kepka L, Oledzki J, Rutkowski A, Szmeja J, Kladny J, Dymecki D, Wieczorek A, Pawlak M, Lesniak T, Kowalska T, Richter P, Polish Colorectal Study Group (2007) Quality of life, anorectal and sexual functions after preoperative radiotherapy for rectal cancer: Report of a randomised trial. *Radiother Oncol*; **84(3):**217-225.

Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S, Quirke P, Couture J, de MC, Myint AS, Bessell E, Griffiths G, Thompson LC and Parmar M (2009). Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. *Lancet.* **373:** 811-820. (not appraised)

Stephens RJ, Thompson LC, Quirke P, Steele R, Grieve R, Couture J, Griffiths GO and Sebag-Montefiore D. (2010) Impact of short-course preoperative radiotherapy for rectal cancer on patients' quality of life: data from the Medical Research Council CR07/National Cancer Institute of Canada Clinical Trials Group C016 randomized clinical trial. *J Clin Oncol.* **28 [27]:** 4233-4239.

Wong RK, Tandan V, De SS, Figueredo A. (2007) Pre-operative radiotherapy and curative surgery for the management of localized rectal carcinoma. *Cochrane DB Sys Rev*; **(2):**CD002102.

Evidence Tables

Reference: Birgisson H, Pahlman L, Gunnarsson U, Glimelius B. (2007) Late adverse effects of radiation therapy for rectal cancer - a systematic overview. *Acta Oncol*; **46(4):**504-516

Design: Systematic review

Country: Multiple

Aim: to present a comprehensive overview of published studies on late adverse effects related to radiotherapy for rectal cancer.

Inclusion criteria:

· Meta-analyses, reviews, randomised trials and clinical trials
· External beam radiotherapy
· Chemoradiotherapy
· Pre-operative and post-operative radiotherapy.

Exclusion criteria:

· Editorials, letters and practice guidelines
· Intraoperative radiotherapy, brachytherapy.

Population:

People with rectal cancer.

Intervention(s) and comparator(s):

Radiotherapy (variable schedules).

Outcomes:

Gastrointestinal disorders, neurological problems, anal, rectal, urinary and sexual dysfunction, pelvic or hip fractures, thromboembolic diseases and secondary cancers. In some studies, quality of life was also addressed.

Results:

The majority of studies examining late adverse effects of radiotherapy were using pre-operative 5x5Gy schedule with the exception of four trials.

The small bowel was affected most often by pelvic irradiation while the colon, rectum and anus were also affected. Resulting symptoms included diarrhoea, bleeding, abdominal pain and obstruction due to stenosis, adhesions or rarely malabsorption, necrosis, perforation and fistulation.

Anal and rectal dysfunction:

Study	Type	Follow-up	Adverse Effects	RT	CRT	No RT	P value
Dahlberg *et al.* (1998)	Q	5 yrs	Bowel Frequency > 4 times a day	20%		8%	?
-do-			Incontinence to loose stools	50%		24%	p<0.05
-do-			Incontinence to solid stools	14%		3%	p<0.05

Study	Type	Follow-up	Adverse Effects				P Value
-do-			Faecal incontinence (night)	14%		8%	nsd
-do-			Emptying difficulties	52%		36%	?
Pollack *et al.* (2006b)	RCT follow-up	14-year	Faecal incontinence	57%		26%	p<0.05
-do-			Soiling	38%		16%	?
Peeters *et al.* (2005)	RCT	5-year	Faecal incontinence	62%		38%	p<0.05
-do-			Faecal incontinence (night)	32%		17%	p<0.05
Pietrzak *et al.* (2006)	RCT		Faecal incontinence to loose stools	72%	65%		nsd
-do-			Difficulty discriminating between gas and stools	59%		66%	nsd

Abbreviations: RCT randomised controlled trial; Q questionnaire; RT radiotherapy; CRT chemoradiotherapy

Bowel Obstruction:

Study	Type	Follow-up	Adverse Effects	RT	No RT	P Value
Holm *et al.* (1996)	RCT	5	Small bowel obstruction	13%	8.5%	?
Birgisson *et al.* (2005)	RCT	13	Small bowel obstruction	9%	4%	?
Peeters *et al.* (2005)	RCT	5	Small bowel obstruction	11% of patients suffered small bowel obstruction with no difference between the groups.		nsd

Abbreviations: RCT randomised controlled trial; RT radiotherapy

Other Gastrointestinal Disorders:

The Stockholm Trials reported an increased risk for fistulas in irradiated patients (Holm *et al.,* 1996) and there was an increased risk of anastomotic strictures with post-operative chemoradiotherapy when compared with pre-operative chemoradiotherapy (12% compared with 4%, p=0.003).

Urinary Tract Dysfunction:

One small study (Prabhudesai *et al.,* 2005) reported more urinary dysfunction problems in irradiated patients compared with non-irradiated patients. Late follow-up of the Stockholm trials (Pollack *et al.,* 2006a) showed increased urinary incontinence in the irradiated patients.

From larger trials however there did not appear to be a difference in effects on urinary tract in irradiated patients versus non-irradiated patients (Sauer *et al.,* 2004; Peeters *et al.,* 2005; Birgisson *et al.,* 2005; Holm *et al.,* 1996

and Frykholm *et al.,* 1993).

In the Western Norwegian trial (Dahl *et al.,* 1990) late urinary tract symptoms were reported in 4% of all patients and in 3% of all patients in the Uppsala trial (Frykholm *et al.,* 1993). Bladder problems were reported in 2% of pre-operatively treated and 4% of post-operatively treated patients (p=0.21) (Sauer *et al.,* 2004).

Sexual Dysfunction:

From one trial (Marijnen *et al.,* 2005), sexual activities of male patients still active pre-operatively decreased to 67% in irradiated patients and 76% in non-irradiated patients. In female patients there was a reduction to 72% in the irradiated group and 90% in the non-irradiated group.

Second Cancers:

One study concluded that irradiated patients had increased risk of developing secondary cancers compared to those treated with surgery only; follow up time was 14 years and second cancers occurred in 9.5% of irradiated patients compared with 4.3% of non-irradiated patients.

Fractures:

Long-term follow-up revealed a higher risk for femoral neck and pelvic fractures in irradiated patients when analysing the Stockholm I and II trials together though the difference was not significant (Holm *et al.,* 1996). Long-term follow up of two trials did not reveal any increased risk of fractures in irradiated patients (Peeters *et al.,* 2005; Birgisson *et al.,* 2005).

Thromboembolic Disorders:

From the Stockholm I and II trials, venous thromboembolism was more common in the irradiated group when compared to the non-irradiated group (Holm *et al.,* 1996). No difference was observed between the treatment groups regarding venous or arterial or cardiovascular diseases (Peeters *et al.,* 2005; Birgisson *et al.,* 2005).

Mortality:

There was no increased death rate in irradiated patients compared with non-irradiated patients (Folkesson *et al.,* 2005).

Quality of Life:

There were no studies on quality of life measuring the late adverse effects of radiotherapy for rectal cancer and only a small number measuring early adverse effects.

Quality of life was analysed mainly in relation to bowel function; Dahlberg *et al.* (1998) commented that 30% of irradiated patients reported restrictions to social life compared to only 10% of non-irradiated patients.

Marijnen *et al.* (2005) reported no difference between irradiated and non-irradiated patients in relation to quality of life.

Follow-up:

N/A

General comments:

A search was conducted of Medline, PubMed, Cochrane database and reference lists from primary and review articles. The search was limited to English language articles and the key terms were listed. Details of the study selection procedure were not given.

Late adverse events were defined as adverse effects persisting or occurring more than six months from the start of radiotherapy. The grading systems were based on a severity scale from 'no symptoms' (grade 0) to 'death' (grade 5). Study design influenced whether mild symptoms (grade 1-2) were detected, with questionnaire and interview based studies detecting the milder symptoms while register or hospital record based studies only

detected the more severe symptoms.

The review authors concluded that fewer late adverse effects had been reported in more recent studies in which smaller irradiated volumes and better techniques had been used although one study has shown an increased risk of secondary cancers in irradiated patients.

Studies included in the review:

(The studies underlined reported on short course 5x5Gy pre-operative radiotherapy vs. either surgery only or chemoradiotherapy)

Bakx *et al.* (2006); Birgisson *et al.* (2005a); Birgisson *et al.* (2005b); Birnbaum *et al.* (1994); Birnbaum *et al.* (1994); Bujko *et al.* (2006); Caffo *et al.* (2002); Caffo *et al.* (2002); Camilleri-Brennan *et al.* (1998); Coia *et al.* (1995); Colorectal Cancer Collaborative Group (2001); Cummings *et al.* (1986); Dahl *et al.* (1990); Dahlberg *et al.* (1998); Dehni *et al.* (2002); Dehni *et al.* (2002); Fajardo *et al.* (2005); Frykholm *et al.* (1993); Geckenberger and Flentje (2005); Gerard *et al.* (1995); Glimelius *et al.* (2003); Holm *et al.* (1996); Johnston *et al.* (2003); Kollmorgan *et al.* (1994); Kollmorgan *et al.* (1994); Letschert *et al.* (1990); Letschert *et al.* (1995); Lewis *et al.* (1995); Lewis *et al.* (1995); Lundby *et al.* (1997); Lundby *et al.* (2005); Mak *et al.* (1994); Mak *et al.* (1994); Marjinen *et al.* (2004); Miller *et al.* (1999); Miller *et al.* (1999); Minsky *et al.* (1995); Minsky *et al.* (1995); Mohiuddin *et al.* (2006); MRC-2 (1996); MRC-3 (1996); Olagne *et al.* (2000); Olagne *et al.* (2000) ; Pollack *et al.* (2006); Ooi *et al.* (1999); Peeters *et al.* (2005); Pietrzak *et al.* (2006); Pollack *et al.* (2006); Prabhudesai *et al.* (2005); Sauer *et al.* (2004); Temple *et al.* (2003); Van Duijvendijk *et al.* (2002); Wagman *et al.* (1998); Wagman *et al.* (1998).

Reference:. Birgisson H, Pahlman L, Gunnarsson U, Glimelius B, Swedish Rectal Cancer Trial Group. (2005) Adverse effects of preoperative radiation therapy for rectal cancer: long-term follow-up of the Swedish Rectal Cancer Trial. *J Clin Oncol*; **23(34):**8697-8705.

Design: Randomised Controlled Trial

Country: Sweden

Aim: To analyse the occurrence of sub-acute and late adverse effects in patients treated with pre-operative irradiation for rectal cancer within the Swedish Rectal Cancer Trial (1987-1990).

Inclusion criteria:

Not recorded.

Exclusion criteria:

Not recorded.

Population:

In the original trial, 118/572 of patients in group A had been treated with non-curative surgery and 121/575 in group B. The remaining patients with whom hospital records admission records were matched were:

Group A: n=188 females and 266 males. Median age: 69 years (range: 51-78 years)

Group B: n=178 females and 276 males. Median age: 69 years (range: 49-78 years)

Interventions:

Group A: 5x5Gy pre-operative irradiation given in one week followed by surgery within 7 days

Group B: Surgery without prior irradiation.

Outcomes:

Occurrence of late adverse events due to irradiation assessed by analysing hospital admissions of Swedish Rectal Study participants.

Results:

Early and late admissions were defined as admissions occurring before and after 6 months from resection of primary rectal cancer. To avoid confounding from diagnoses related to the presence of cancer, admissions for non-curatively treated patients and admissions during the three months before diagnosis of a local recurrence or metastasis were excluded.

For the 908 patients in the Rectal Study who had received surgery with curative intent, there were 3,442 hospital admissions in the analysis; 2,021 for patients who had been randomised to Group A and 1, 421 from Group B.

More patients were excluded from the non-irradiated group than from the irradiated group.
A larger proportion of the irradiated patients survived for more than 5 and 10 years than did the non-irradiated group, thus the number of person-years at risk for hospital admissions was higher in the irradiated group.

73% (n=661) of all patients analysed were admitted to hospital at least once after treatment of primary rectal cancer; more patients from the irradiated group were admitted both in the early and late post-operative periods.

Incidence of hospital admission (irradiated versus non-irradiated):
All admissions: RR: 1.07 95%CI: 0.91-1.26 (NSD)
Early admissions: RR: 1.64 95%CI: 1.21-2.22 (p<0.05)
Late admissions RR: 0.95 95%CI: 0.8-1.12 (NSD)

Admissions according to condition (irradiated versus non-irradiated):

Non-specific infections: RR: 8.06 95%CI: 1.02-63.69 (NSD)
Cardiac arrhythmia: RR: 0.57 95%CI: 0.36-0.91
Bowel obstruction: RR: 1.88 95%CI: 1.10-3.20 (p=0.02)
Nausea: RR: 4.04 95%CI: 1.16-14.06 (p=0.03)
Abdominal pain: RR: 1.92 95%CI: 1.14-3.23 (p=0.01)
Inguinal hernia: RR: 0.26 95%CI: 0.07-0.96 (p=0.04)

Early admissions (<6 months) (irradiated versus non-irradiated):

Infection (RR: 7.67 95%CI: 1.76-33.39) (p<0.01)
Gastrointestinal diagnoses (RR: 2.57 95%CI: 1.55-4.26) (p<0.01).

Follow-up:

General comments:

This study was not included in the Cochrane Review (Wong *et al.,* 2007) although it fell within the timelines for the literature search. The paper describes an analysis of late adverse events in persons who participated in the Swedish Rectal Study which ran from 1987 to 1990.

Patients were matched against the Swedish Hospital Discharge Register which includes all hospital admissions in Sweden and records primary and secondary diagnosis, date of admission and discharge, and the hospital and department.

The authors concluded that overall there was no difference in the risk of hospital admission between irradiated and non-irradiated patients but that early admissions, mainly due to gastrointestinal disorders, were significantly higher for patients who had received radiotherapy as part of their treatment for rectal cancer. Of these, bowel obstruction was identified as being of the greatest importance.

Reference: Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. (2006) Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg*; **93(10):**1215-1223.

Design: Randomised Trial

Country: Poland

Aim: to determine whether pre-operative short-term irradiation offers an advantage with respect to survival, local control and late toxicity when compared with pre-operative conventionally fractionated chemoradiation.

Inclusion criteria:

· Pathological confirmation of rectal adenocarcinoma
· T3 or T4 resectable tumour
· No evidence of involvement of sphincters and an inferior margin of the tumour palpable on digital rectal exam
· No evidence of distant metastases
· WHO performance score of 0-2
· Age ≤75 years
· Written informed consent of the patient.

Exclusion criteria:

· Patients with a fixed tumour
· Inadequate potential for follow-up
· Previous malignancy

NB: There were no exclusion criteria listed in this study, however as this is the same trial as Bujko *et al*. (2004, 2005) it is assumed that the same exclusion criteria apply.

Population:

Group A: n=55 female and 100 males. Mean age: 60 years (range: 30-75 years)

Group B: n=54 females and 103 males. Mean age: 59 years (range: 34-73 years)

296 patients underwent surgery, 147 in group A and 149 in group B.

Interventions:

Group A: 5x5Gy pre-operative irradiation given in one week, followed by surgery within 7 days

Group B: Chemoradiotherapy to a total dose of 50.4Gy (1.8Gy per fraction in 5.5 weeks) concomitantly with two courses of 5'-fluorouracil and leucovorin followed by surgery within 4-6 weeks.

Outcomes:

Survival, local control and the incidence of late toxicity.

Results:

Survival:

The actuarial 4-year overall survival was 67.2% in the radiotherapy group and 66.2% in the chemoradiotherapy group (p=0.960). The hazard ratio of death in the chemoradiotherapy group compared with the radiotherapy group was HR 1.01 (95% CI: 0.69–1.48).

The actuarial 4-year disease free survival in the radiotherapy group was 58.4% compared with 55.6% in the chemoradiation group (p=0.820). The hazard ratio of death or relapse in the radiotherapy group compared with the chemoradiotherapy group was HR 0.96 (95% CI: 0.69–1.35).

Local Control:

The rate of local control was calculated in 295 patients that underwent resection with or without microscopic residual tumour. The crude rate of local recurrence was 9% in the radiotherapy group and 14.2% in the chemoradiotherapy group (p=0.17).

The actuarial 4-year cumulative incidence of local recurrence was 10.6% in the radiotherapy group and 15.6% in the chemoradiation group (p=0.210). The hazard ratio for local recurrence in the radiotherapy group compared to the chemoradiation group was HR 0.65 (95% CI: 0.32–1.28).

The crude incidence of local failure was 14.4% in the radiotherapy group and 18.6% in the chemoradiation group (p=0.32). The crude incidence of distant metastases was 31.4% in the radiotherapy group and 34.6% in the chemoradiation group (p=0.54).

Late Toxicity:

The crude overall incidence of late toxicity was 28.3% in the radiotherapy group and 27% in the chemoradiation group (p=0.81). The relative risk of late toxicity in the radiotherapy group compared with the chemoradiation group was RR 1.05 (95% CI: 0.72–1.53).

The crude incidence of severe late toxicity for was 10.1% in the radiotherapy group and 7.1% in the chemoradiotherapy group (p=0.36). The relative risk of severe late toxicity in the radiotherapy group compared with the chemoradiation group was RR 1.43 (95% CI: 0.67–3.07).

Permanent Stoma:

The crude incidence of permanent stoma was 56.9% in the radiotherapy group and 51.6% in the chemoradiation group (p=0.35). The relative risk of a permanent stoma in the radiotherapy group compared with the chemoradiation group was RR 1.10 (95% CI: 09–1.35).

Follow-up:

The median follow-up time was 48 months (range: 31-69 months) with 97.5% of patients having a follow-up time of more than 3 years and 14.9% having follow-up time of more than 5 years. No patients were lost to follow-up with regard to vital status; 3 patients were lost with regard to relapse and 14 with regard to late toxicity.

General comments:

This paper, which is the second in a series of three (Bujko *et al*. 2004, 2005 and 2006), describes the final results from a randomised controlled trial of pre-operative chemoradiation versus short course pre-operative radiotherapy only. Participants were recruited between April 1999 and February 2002. In this paper the authors report data on survival, local control and the incidence of late toxicity

Randomisation was performed by telephone to a central office and was based on the minimisation method. Patients were stratified according to the centre, character of the tumour (mobile or tethered) and the declared type of surgery (anterior resection/abdominoperineal resection). Data were analysed according to the intention to treat principle.

Post-operative chemotherapy was optional and was more common in the radiotherapy group than in the chemoradiation group.

The authors concluded that treatment with pre-operative short course radiotherapy did not increase survival, local control or the incidence of late toxicity compared with pre-operative conventionally fractionated chemoradiation.

Reference: Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M et al. (2005) Long-term results of a randomised trial comparing preoperative short-course radiotherapy vs. preoperative conventionally fractionated chemoradiation for rectal cancer. *Ejc Suppl*; **3(2):**169.
Design: Randomised Trial **Country**: Poland **Aim:** to determine whether pre-operative short-term irradiation offers an advantage with respect to the incidence of post-operative complications when compared with pre-operative conventionally fractionated chemoradiation.
Inclusion criteria: · Pathological confirmation of rectal adenocarcinoma · T3 or T4 resectable tumour · No evidence of involvement of the sphincter · Lower tumour margin determined by digital rectal examination · No evidence of distant metastases · WHO performance score of 0-2 · Age ≤75 years · Written informed patient consent
Exclusion criteria: · Patients with a fixed tumour · Inadequate potential for follow-up · Previous malignancy
Population: Group A: n=55 females and 100 males. Mean age: 60 years (range: 30-75 years) Group B: n=54 females and 103 males. Mean age: 59 years (range: 34-73 years) 296 patients underwent surgery with tumour resection: 147 in group A and 149 in group B.
Interventions: Group A: 5x5Gy pre-operative irradiation given in one week, followed by surgery within 7 days Group B: Chemoradiotherapy to a total dose of 50.4Gy (given with 1.8Gy per fraction in 5.5 weeks) concomitantly with two courses of 5'-fluorouracil and leucovorin followed by surgery within 4-6 weeks.
Outcomes: The primary outcome for this study was the incidence of post-operative complications.
Results: 95% of patients received therapy according to the allocated schedule; 2 patients from group A and 7 patients from group B did not receive pre-operative radiotherapy; 6 patients in group B were treated according to the radiotherapy schedule and one patient from group A was treated according to the chemoradiation schedule. There was no significant difference between the treatment groups in relation to the rates of post-operative complications (p=0.27). Expressing the values in terms of number of events (rather than number of patients with complications) the rate of complications for radiotherapy versus chemoradiation was 31% versus 22% respectively (p=0.06). For severe complications the event rates were 10% in the radiotherapy group and 11% in the chemoradiotherapy group (p=0.85) for death and 12% in the radiotherapy group versus 11% in the chemoradiotherapy group for complications that required surgical intervention (p=0.85). There was no statistically significant difference between the two groups in relation to anastomotic leakage or

delayed perineal wound healing.

Duration of hospital stay for the two groups differed, though not significantly; duration of hospital stay ranged from 7–93 days for patients in the radiotherapy group as compared with a range of 6–51 days for patients in the chemoradiotherapy group (p=0.09). For patients in the radiotherapy group, there was no association between overall treatment time and the risk of post-operative complications.

For patients in the chemoradiotherapy group, there was a trend towards a higher risk of post-operative complications for patients with a longer overall treatment time. Median OTT was 84 days for patients with complications and 78 days for those without (p=0.054).

Follow-up: N/A

General comments:

This paper, which is the second in a series of three (Bujko *et al.* 2004, 2005 and 2006), describes the preliminary results from a randomised controlled trial of pre-operative chemoradiation versus short course pre-operative radiotherapy only. Participants were recruited between April 1999 and February 2002. In this paper the authors report on the incidence of post-operative complications, a secondary outcome of the trial.

Randomisation was performed by telephone to a central office and was based on the minimisation method. Patients were stratified according to the centre, character of the tumour (mobile or tethered) and the declared type of surgery (anterior resection/abdominoperineal resection). Data were analysed according to the intention to treat principle.

The authors concluded that they had been unable to demonstrate a statistically significant difference in the rate of post-operative complications between patients having had short course radiotherapy and patients having had chemoradiation. However, it was noted that their initial power calculation meant that they only had sufficient study participants in each arm to have detected a difference of 15% or more between groups.

Reference: Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Ko M et al. (2004) Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy. *Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology*; **72(1):**15-24.

Design: Randomised Trial

Country: Poland

Aim: to determine whether pre-operative short-term irradiation offers an advantage with respect to sphincter preservation when compared with pre-operative conventionally fractionated chemoradiation.

Inclusion criteria:

· Pathological confirmation of rectal adenocarcinoma
· T3 or T4 resectable tumour
· No evidence of involvement of sphincters and an inferior margin of the tumour palpable on digital rectal exam
· No evidence of distant metastases
· WHO performance score of 0-2
· Age ≤75 years
· Written informed consent of the patient.

Exclusion criteria:

· Patients with a fixed tumour
· Inadequate potential for follow-up
· Previous malignancy.

Population:

Group A: n=55 females and 100 males. Mean age: 60 years (range: 30-75 years)

Group B: n=54 females and 103 males. Mean age: 59 years (range: 34-73 years)

296 patients underwent surgery with tumour resection: 147 in group A and 149 in group B.

Interventions:

Group A: 5x5Gy pre-operative irradiation given in one week, followed by surgery within 7 days

Group B: Chemoradiotherapy to a total dose of 50.4Gy (given with 1.8Gy per fraction in 5.5 weeks) concomitantly with two courses of 5'-fluorouracil and leucovorin followed by surgery within 4-6 weeks.

Outcomes:

The primary outcome for this study was the effect of treatment on sphincter preservation. Other outcomes included acute post irradiation toxicity and post-operative pathology.

Results:

Protocol violations:

There were a number of protocol violations in both arms;
· 6 patients randomised to group B were treated according to group A while 1 patient randomised to group A was treated according to group B
· 4 patients did not receive radiotherapy and surgery
· 9 patients were operated on without pre-operative radiotherapy
· 3 patients underwent radiotherapy but did not have surgery
· There were 3 deviations from the protocol in group A and 16 deviations in group B
· In group B, 17 patients did not undergo the second course of chemotherapy

Surgery:

Prior to surgery, complete clinical response was reported in 2% of patients in the radiation arm and in 13% in the chemoradiation arm (p<0.001). For patients that underwent tumour resection, the sphincter preservation rate for a lesion located with 2-3cm of the anal verge was 12% (n=4/34); for 4-5cm was 45% (n=46/102), for 6-7cm was 82% (n=83/101) and for >7cm was 96% (n=52/55). Sphincter preservation rate in the radiation arm was 61% compared with 58% for the chemoradiation arm (p=0.57).

The rates of patients with all post-operative complications was 23% for the radiation group versus 15% for the chemoradiation group (p=0.12) and for severe complications (death or complications requiring surgical intervention) was 12% for the radiation group versus 9% for the chemoradiation group (p=0.38).

Acute post irradiation toxicity:

There were 2 sudden deaths due to cardiac arrest in group B. The rates of patients with all complications was 24% in group A versus 85% in group B (p<0.001) and for grade III and IV complications (including death) the rate was 3% in group A versus 18% in group B (p<0.001).

Post-operative pathology:

There was a better tumour response in patients receiving short-term irradiation with more microscopic complete responses in the radiotherapy group (16%) compared with the chemoradiotherapy group (1%), p<0.001.

Follow-up: N/A

General comments:

This paper, which is the first in a series of three (Bujko *et al.* 2004, 2005 and 2006), describes the preliminary results from a randomised controlled trial of pre-operative chemoradiation versus short course pre-operative radiotherapy only. Participants were recruited between April 1999 and February 2002. In this report the authors report primarily on post-operative sphincter preservation.

The type of surgery anticipated (anterior resection (AR) or abdominoperineal resection (APR)) was declared prior to randomisation. Randomisation was performed by telephone to the central trial office and was based on the minimisation method. Patients were stratified according to the centre, character of the tumour (mobile or tethered) and the declared type of surgery (anterior resection/abdominoperineal resection). Data were analysed according to the intention to treat principle.

It was agreed that the final decision on whether or not to perform sphincter sparing surgery would be based on tumour status at the time of surgery, not prior to irradiation. However, the procedure for surgery based on the clinical status after chemoradiation was not addressed and subsequently, despite an apparent complete clinical response in 5 patients in group B, AR was performed. This suggests that the surgeons made a subjective judgement based on pre-therapy tumour volume rather than on tumour status at surgery. Additionally, 30% of patients were anticipated by surgeons to receive AR regardless of their group allocation.

The authors concluded that, despite downsizing of tumours, pre-operative short-term radiotherapy did not result in enhanced sphincter preservation rates compared with chemoradiotherapy prior to surgery.

Citation: Fiorica F, Cartei F, Licata A, Enea M, Ursino S and Colosimo C et al. (2010) Can chemotherapy concomitantly delivered with radiotherapy improve survival of patients with resectable rectal cancer? A meta-analysis of literature data. *Cancer Treat Rev* **36(7):** 539-549.
Design: Systematic review and meta-analysis **Country**: Italy **Aim**: To provide a comprehensive and reliable summary of the effects of chemoradiotherapy (chemoRT) on 5-year overall mortality, local recurrence, distant metastases and toxicity.
Inclusion criteria **Studies:** Randomised controlled trials published up to April 2009. Only the relevant results from this study are reported here i.e. comparisons between patients having received chemoRT or RT before surgery for resectable rectal cancer. **Population:** Patients with histologically proven rectal adenocarcinoma but no metastatic disease and for whom 5-year survival had been reported.
Exclusion criteria **Studies:** Trials with surgery only as the control group, partially or non-randomised studies or preliminary reports where final papers were available. Observational studies.
Population N=2,787. Mean age > 60 years (range: ~59-65 years). The majority of patients were males (range: ~47-73%).
Interventions Pre-operative chemoradiotherapy versus pre-operative radiotherapy (variable regimes).
Outcomes 5-year survival, 5-year local control, 5-year distant metastases, toxicity.
Results **Pooled estimate 5-year overall survival - random effects model** **Pre-op chemoRT (N=1,392) versus pre-op RT (N=1,395):** RR: 1.02 (95%CI: 0.94-1.09) (P=0.68) I^2 = 37.2% **Pooled estimate 5-year local control - random effects model** **Pre-op chemoRT (N=1,390) versus pre-op RT (N=1,395):** RR: 1.05 (95%CI: 1.01-1.10) (P=0.02) I^2 = 55.3% (numbers needed to treat = 17) **Pooled estimate 5-year local control - fixed effects model** **Pre-op chemoRT (N=1,390) versus pre-op RT (N=1,395):**

RR: 1.06 (95%CI: 1.03-1.10) (P<0.0001)

Pooled 5-year distant metastases - random effects model
Pre-op chemoRT (N=1,390) versus pre-op RT (N=1,396):

RR: 0.97 (95%CI: 0.93-1.02) (P=0.21) I^2 = 0%

Risk of toxicity-related mortality - random effects model
Pre-op chemoRT (N=1,340) versus pre-op RT (N=1,383):

RR: 1.63 (95%CI: 0.95-2.82) (P=0.08) I^2 = 0%

Toxic events >Grade 2:
ChemoRT group (N=477) versus RT group (N=190) (P<0.00001) (number needed to harm = 4)

General comments

This paper was a systematic review and meta-analysis on the comparison between pre-operative chemoradiotherapy and pre-operative radiotherapy for patients with resectable rectal cancer. The authors conducted a thorough literature search from the Cochrane controlled trials register, Cochrane library, Medline, Embase and Cancerlit databases using search terms not fully described in the report. The quality of included studies was assessed by two independent reviewers using the JADAD scoring system. Differences were resolved by discussion. The data on study quality was published as an online appendix which was not retrievable.

For the purposes of reporting outcomes between chemoRT and RT, seven studies, including one abstract, were identified. It should be noted that one study (Frykholm *et al*) included only patients with non-resectable disease.

The authors noted that, for patients having had RT only, no dose reductions were required and all patients in that group tolerated the treatment well whereas, in the chemoRT group, 31 patients required a reduction in RT dose. Adding chemotherapy to the RT reduced compliance from 88.5% to just 30.6%. The conclusions of the study were that the addition of chemotherapy to pre-operative radiotherapy reduced the risk of local recurrence but did not improve overall survival or the risk of distant metastases. Treatment associated toxicity was also higher with the combined modality.

References of Included Studies (For systematic reviews):

Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, Daban A, Bardet E, Beny A, Ollier JC and EORTC Radiotherapy Group (2006). Chemotherapy with preoperative radiotherapy in rectal cancer. *N.Engl.J.Med.* **355:** 1114-1123.

Boulis-Wassif S, Gerard A, Loygue J, Camelot D, Buyse M and Duez N (1984). Final results of a randomized trial on the treatment of rectal cancer with preoperative radiotherapy alone or in combination with 5-fluorouracil, followed by radical surgery. Trial of the European Organization on Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group. *Cancer.* **53:** 1811-1818.

Braendengen M, Tveit KM, Berglund A, Birkemeyer E, Frykholm G, Pahlman L, Wiig JN, Bystrom P, Bujko K and Glimelius B (2008). Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. *J.Clin.Oncol.* **26:** 3687-3694.

Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M, Oledzki J, Szmeja J, Kladny J and Pietrzak L (2005). Long-term results of a randomised trial comparing preoperative short-course radiotherapy vs. preoperative conventionally fractionated chemoradiation for rectal cancer. *Ejc Supplements.* **3:** 169-169.

Frykholm GJ (2001). Combined chemo- and radiotherapy vs. radiotherapy alone in the treatment of primary, nonresectable adenocarcinoma of the rectum. *International Journal of Radiation Oncology Biology Physics.* **50:** 433-440.

Gerard JP, Conroy T, Bonnetain F, Bouche O, Chapet O, Closon-Dejardin MT, Untereiner M, Leduc B, Francois E, Maurel J, Seitz JF, Buecher B, Mackiewicz R, Ducreux M and Bedenne L (2006). Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. *J.Clin.Oncol.* **24:** 4620-4625.

Rouanet P, Rivoire M, Lelong B *et al.* (2006). Sphincter preserving surgery after preoperative treatment for ultra-low rectal carcinoma. A French mulicenter prospective trial: GRECCAR 1. *J Clin Oncol.* **2006: 18S:** 3527.

Reference: Peeters KC, Marijnen CA, Nagtegaal ID, Kranenbarg EK, Putter H, Wiggers T et al. (2007) The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. *Ann Surg*; **246(5):**693-701.

Design: Randomised controlled trial

Country: The Netherlands

Inclusion criteria:

Patients with resectable rectal cancer (defined as 15cm from anal verge, below S1-2).

Exclusion criteria:

Patients who had received previous pelvic radiotherapy (RT) or chemotherapy or who had been previously treated for rectal cancer.

Population:

Group A: n=324 females and 573 males. Median age: 65 years (range: 26-88 years). Stage 0 (n=11), stage I (n=264), stage II (n=251), stage III (n=299), stage IV (n=62).

Group B: n=330 females and 578 males. Median age: 66 years (range: 23-92 years). Stage 0 (n=17), stage I (n=243), stage II (n=245), stage III (n=325), stage IV (n=61).

Intervention(s) and comparator(s):

Group A: 5x5Gy pre-operative irradiation given in one week followed by surgery within 7 days.

Group B: Surgery without prior irradiation.

Surgery: total mesorectal excision (TMA).

Outcomes:

The primary outcome was local control. The study reported on 5 year local recurrence and overall survival rates.

Results:

16/897 eligible patients in group A and 29/908 in group B, had no resection and twelve patients had incomplete local excision with involved margins. Ninety-five patients (47 in group A and 48 in group B) were found to have distant metastases during work-up or surgery. 1,478 patients had a macroscopically complete resection.

Local recurrence risk (RT before TME versus TME alone):

At the conclusion of follow-up, 129 patients had local disease recurrence (83 patients also had distant disease).

5 year rate of local disease recurrence: 5.6% versus 10.9% (p<0.001). Risk reduction: 49% in favour of pre-operative radiotherapy.

Independent predictors of local recurrence risk by multivariate analysis were: treatment group assignment, tumour location, type of surgery, TNM stage and resection margin.

Distant recurrence risk (RT before TME versus TME alone)*:*

At the conclusion of follow-up, 201 patients had experienced distant recurrence in group A and 222 patients in group B.

5 year rate of distant disease recurrence: 25.8% versus 28.3% (p=0.39).

Overall survival (RT before TME versus TME alone)*:*

5 year overall survival rate: 64.2% versus 63.5% (p=0.9). 5 year cancer-specific survival rate: 75.4% versus 72.4% (p=0.26).
Follow-up: Median: 6.1 years (range: 1.2-9.5 years). By November 2005 748 patients had died of which 374 (50.2%) had distant disease.
General comments: This moderate quality study reported long term recurrence and survival rates from the Dutch TME Trial (Kapiteijn *et al.,*1999) the initial results of which were published in 2001 and analysed within the systematic review by Wong *et al.* (2007). Participants were recruited between January 1996 and December 1999 and follow-up was concluded in November 2005. The authors compared the reduction in the risk of recurrence of 49% with pre-operative radiotherapy at 5 years to that observed after 2 years (71%) and pointed out that the majority (78/87) of local recurrences in patients assigned to group A had occurred after 3 years. They inferred that the delayed recurrence with patients generally was because, when compared with similar studies, TME resulted in a lower residual tumour burden than conventional surgery (for example, as used in the Swedish trials). The authors concluded that, despite improved long term local control with pre-operative radiotherapy, this was not sufficient to lead to an improvement in overall survival. Further, they suggested that prevention of distant metastases could be addressed with adjuvant chemotherapy.

Reference: Pietrzak L, Pietrzak,L, Bujko,K, Nowacki MP, Kepka L, Oledzki J, Rutkowski A, Szmeja J, Kladny J, Dymecki D, Wieczorek A, Pawlak M, Lesniak T, Kowalska T, Richter P, Polish Colorectal Study Group (2007) Quality of life, anorectal and sexual functions after preoperative radiotherapy for rectal cancer: Report of a randomised trial. *Radiother Oncol*; **84(3):**217-225.

Design: Randomised Trial

Country: Poland

Aim: to determine whether large doses per fraction of short-course pre-operative radiotherapy result in more severe anorectal and sexual dysfunction or impairment of quality of life compared with pre-operative conventionally fractionated chemoradiation.

Inclusion criteria:

· Pathological confirmation of rectal adenocarcinoma
· T3 or T4 resectable tumour
· No evidence of involvement of sphincters and an inferior margin of the tumour palpable on digital rectal exam
· No evidence of distant metastases
· WHO performance score of 0-2
· Age ≤75 years
· Written informed consent of the patient.

Exclusion criteria:

· Patients with a fixed tumour
· Inadequate potential for follow-up
· Previous malignancy

NB: There were no exclusion criteria listed in this study, however as this is the same trial as Bujko *et al.* (2004, 2005) it is assumed that the same exclusion criteria apply.

Population:

Group A: n=55 female and 100 males. Mean age: 60 years (range: 30-75 years)

Group B: n=54 females and 103 males. Mean age: 59 years (range: 34-73 years)

296 patients underwent surgery, 147 in group A and 149 in group B.

256 patients were alive and disease-free 7 months after surgery and form the study group for this paper.

Interventions:

Group A: 5x5Gy pre-operative irradiation given in one week, followed by surgery within 7 days

Group B: Chemoradiotherapy to a total dose of 50.4Gy (1.8Gy per fraction in 5.5 weeks) concomitantly with two courses of 5'-fluorouracil and leucovorin followed by surgery within 4-6 weeks.

Outcomes:

· Quality of Life (QOL) assessed by Quality of Life Questionnaire Core 30 items (QLQ-C30) of the European Organisation for Research and Treatment of Cancer
· Anorectal and sexual function assessed by a self administered, non-validated 19 item questionnaire.

Results:

QOL Evaluation:

221/256 patients, alive and disease free 7 months after surgery, completed the QLQ-C30 questionnaire. The median time interval between surgery and questionnaire completion was 12 months (range: 3-65 months).

A significantly higher number of patients in the short-term radiotherapy went on to receive post-operative chemotherapy compared with the chemoradiotherapy group (p=0.002). However, there was no significant difference between the two groups in relation to mean scores for the global health/QOL status (p=0.22).

Anorectal and Sexual Functions Evaluation:

118/137 patients, alive, disease free and with no stoma, completed the questionnaire on anorectal function and 116 answered the question relating to sexual function. The median time interval between surgery and questionnaire completion was 13 months (range: 4-74 months).

There was no significant difference between the two groups in relation to any of the questions posed. Approximately two thirds of patients complained of faecal and gas incontinence, urgency and inability to differentiate between stool and gas.

Approximately two-thirds of respondents stated that the disturbances in anorectal function had a negative impact on their QOL, with approximately 20% stating the impact was 'considerable'. Anorectal function was estimated as being 'good' or 'very good' by 41% of patients in the short-course chemotherapy group and by 37% of patients in the chemoradiotherapy group (p=0.52).

2% (n=2) patients scored anorectal function as being 'unacceptable' and regretted that a stoma had not been performed.

There was no significant difference between the two groups in relation to the impact on sexual function (p=0.56 for males; p=0.1 for females).

Follow-up: N/A

General comments:

This paper reports data from the same randomised controlled trial as Bujko *et al.* (2004, 2005 and 2006) comparing treatment outcomes between short course pre-operative radiotherapy and conventionally fractionated pre-operative chemoradiation. Participants were recruited between April 1999 and February 2002. In this paper the authors report data on anorectal & sexual functions and QOL.

Randomisation was performed by telephone to a central office and was based on the minimisation method. Patients were stratified according to the centre, character of the tumour (mobile or tethered) and the declared type of surgery (anterior resection/abdominoperineal resection). Data were analysed according to the intention to treat principle.

The authors concluded that they did not find a statistically significant difference between the outcomes of QOL, anorectal or sexual functioning in patients receiving the different treatment regimes. Approximately two thirds of patients who had received irradiation combined with surgery experienced subsequent anorectal dysfunction and the majority of those expressed the view that their QOL had been adversely affected.

Citation: Stephens RJ, Thompson LC, Quirke P, Steele R, Grieve R, Couture J, Griffiths GO and Sebag-Montefiore D. (2010) Impact of short-course preoperative radiotherapy for rectal cancer on patients' quality of life: data from the Medical Research Council CR07/National Cancer Institute of Canada Clinical Trials Group C016 randomized clinical trial. *J Clin Oncol.* **28 [27]:** 4233-4239.
Design: Randomised controlled trial (Medical Research Council CR07/National Cancer Institute of Canada Clinical Trials Group C016 trial (CR07/C016). **Country**: United Kingdom **Aim**: To record changes in patient reported quality of life (QoL) before and after pre-operative radiotherapy followed by surgery (and adjuvant chemotherapy in selected patients) for rectal cancer.
Inclusion criteria Histologically confirmed, resectable adenocarcinoma of the rectum with no evidence of metastases.
Exclusion criteria -
Population Baseline: N=1,208 completed (879 males) with median age 66 years (inter-quartile range: 58-72 years). 66 in Pre group and 597 in SEL POST group. 2 years: N=563 completed (404 males) with median age 66 years (inter-quartile range: 58-71 years). 281 in PRE group and 282 in SEL POST group.
Interventions [1] Short course radiotherapy of 25Gy in 5 fractions followed by surgery within 7 days (PRE). [2] Surgery followed by post-operative chemoradiotherapy in selected patients (those with microscopic tumour within 1mm of the circumferential resection margin) (SEL POST) According to circumferential resection margin and lymph node status, patients in either arm may have received adjuvant chemotherapy of 5'FU and leucovorin according to centre policy. Questionnaires were completed at baseline, every 3 months for the first year and every 6 months to 3 years from randomisation.
Outcomes Patient reported QoL assessed by questionnaires MOS SF-36 and QLQ-CR38. MOS SF-36 is a general health questionnaire with 36 items in eight scales: physical function, role-physical, bodily pain, general health, vitality, social function, role-emotional and mental health. QLQ-CR38 is sub-divided into four function scales: body image, sexual function, sexual enjoyment and future perspective with sub-scales including sexual dysfunction).
Results There was no significant difference in QoL scores between the PRE and SEL POST groups at baseline. **Male sexual dysfunction (MSD):**

Mean score at baseline: 28.4
Mean score after 3 months: 59.3 (P<0.001)
There was no difference between treatment groups.

Mean score at 6 months PRE: 65.9
Mean score at 6 months SEL POST: 56.0 (P=0.004)

Mean score at 2 years PRE: 65.7
Mean score at 2 years SEL POST: 57.4 (P=0.058)
The impact of surgery was, therefore >30 % points but pre-operative RT made only a small impact. The authors claim that the increase in sexual dysfunction at 3 months was not due to chemoradiotherapy given to selected patients in the SEL POST arm, or to adjuvant chemotherapy.

There were insufficient responses from women for sexual dysfunction analyses.

Defecation function (for patients without a stoma):

Mean score at 2 years PRE: 22.6
Mean score at 2 years SEL POST: 24.6 (P=0.42) NSD

Unintentional release of stools:

Mean score at 2 years PRE: 53.2
Mean score at 2 years SEL POST: 37.3 (P=0.007)
Most of the significance in the different scores between groups was seen in the severity level of this outcome: 'a little' PRE: 43 versus SEL POST: 29.

Physical function:

Mean score at 3 months PRE: 58.4
Mean score at 3 months SEL POST: 62.6 (P=0.028)
This difference was lost thereafter, returning to baseline for both groups.

General health:

No significant changes were seen over time for this outcome. Adjuvant chemotherapy made little impact on general health, physical or MSD function. Post-operative chemoradiotherapy had a significant effect on bowel function at 2 years.

General comments

The authors concluded that the general health of patients undergoing curative treatment for rectal cancer was good. The main, irreversible adverse effect experienced by men was sexual dysfunction, caused primarily by surgery, although this was exacerbated by RT. There were insufficient responses from females to measure sexual dysfunction. Bowel function in those patients without a stoma (or in those who had a stoma reversal) was not significantly different between treatment arms. However, sub group analysis suggested that patients in the PRE group may have experienced an increase in the 'unintentional release of stools' even at 2 years post-treatment. Generally, there were no significant differences in treatment groups in overall general health or QoL. This suggested to the authors that either the questionnaires may not have been sensitive enough to have detected any differences or that perhaps in an older patient group the observed adverse events were accepted as an unavoidable cost of treatment.

Reference: Wong RK, Tandan V, De SS, Figueredo A. (2007) Pre-operative radiotherapy and curative surgery for the management of localized rectal carcinoma. *Cochrane DB Sys Rev*; **(2):**CD002102.

Design: Systematic Review

Country: Various

Aim: To determine if pre-operative radiotherapy improves outcomes for patients with localised, resectable cancer.

Inclusion criteria:

Randomised trials with a pre-operative radiotherapy arm versus surgery alone, or other neoadjuvant or adjuvant strategies, targeted patients with localised rectal cancer planned for radical surgery were included.

Studies where the intended surgery was radical (e.g. Hartmann procedure, anterior resection, abdominal peritoneal resection, total mesorectal excision (TME)). Subgroup analysis was performed to examine the impact of TME specifically.

Exclusion criteria:

Studies where the intended surgery was local resection.

Population:

Nineteen studies addressing pre-operative radiotherapy versus surgery alone.

Interventions:

· Pre-operative radiotherapy
· Surgery

Outcomes:

Overall mortality was the primary outcome for the review. Secondary outcomes included; cause specific mortality, any recurrence, local recurrence, probability of downstaging, overall resectability, curative resectability, sphincter sparing resections, acute radiotherapy toxicity, operative morbidity and perioperative mortality (90 day mortality), late toxicity, functional outcome, quality of life, and compliance with the assigned therapy.

Results:

Included studies:

Three studies defined rectal cancer as 'below the sacral promontory'; One study used 'below the pelvic brim'; Three studies stated 'rectal cancer' but provided no additional criteria; One study used the requirement of 'abdominal perineal resection'; A number of studies used 'distance from anal verge' ranging from 12cm to within 16cm; Two studies provided no details.
One trial specifically required the use of TME.

The average proportion of patients with stage A (Dukes A) disease in the control arm (surgery alone) was 17% (range: 0.7-37.0%). In general, any patient with resectable disease was eligible for inclusion.

Twelve studies employed doses above 30Gy[10]; Six studies employed doses below 30Gy[10]; One study used 30Gy but did not specify the dose. Ten studies had a one week interval between radiotherapy and surgery. Longer intervals of between two and four weeks were employed in other studies and one study reported a mean interval of eleven days between radiotherapy and surgery.

Overall mortality (RT before surgery versus surgery alone. n=8,163, all data):

From fourteen studies, the pooled hazards ratio HR: 0.93 (95%CI: 0.87-1) in favour of pre-operative radiotherapy, although this was not statistically significant (X^2 p=0.15). When using the CCCG data (individual patient data) plus the published data, the pooled Peto OR: 0.95 (95%CI: 0.89-1.02).

The magnitude of survival benefit was modest; when taking the overall mortality curve from the single largest study in the analysis (with an eight year follow-up) to calculate the magnitude of benefit this translated into a 2% survival improvement (75-77%) at five years and 2% (60-62%) at eight years.

Subgroup analysis suggests that non TME studies, higher BED and treatment fields focused to the posterior pelvis showed significant benefit.

Subgroup/sensitivity analysis on overall mortality / (number of studies):

Non TME (n=19) HR: 0.92 (95%CI: 0.86-0.99)
TME (n=1) HR: 1.02 (95%CI: 0.84-1.26)
BED ≥ 30Gy^{10} (n=9) HR: 0.91 (95%CI: 0.84-0.98)
BED < 30Gy^{10} (n=7) HR: 0.99 (95%CI: 0.89-1.12)
Treatment fields focused to the posterior pelvis (n=4) HR: 0.85 (95%CI: 0.76-0.95)
Other (n=16) HR: 0.99 (95%CI: 0.91-1.07)

Cause specific mortality (RT before surgery versus surgery alone. n=2,255):

From five studies, the pooled HR: 0.87 (95%CI: 0.78-0.98) but heterogeneity I^2=54%, so the result should be interpreted with caution.

Any recurrence (n=5,177):

From eight studies, the pooled HR: 0.89 (95%CI: 0.82-0.97) suggesting an overall reduction of recurrence in favour of pre-operative radiotherapy (heterogeneity I^2=0%).

Local recurrence (n=7,467):

Recurrence rates in the control arms ranged from 11% to 54%. All but one study showed a benefit in favour of pre-operative radiotherapy although the data were highly variable across the available studies (heterogeneity I^2=84%) indicating differences in the magnitude of effect. The absolute rate of local recurrence in the control group was variable. From twelve studies, the pooled HR: 0.71 (95%CI: 0.64-0.78). Examining the data for factors which may be sources of heterogeneity, all radiotherapy characteristics showed interaction with local recurrence; however significant heterogeneity remained within each of the subgroups. It is likely that the difference in baseline risk of recurrence is in part responsible for this variability.

Subgroup/sensitivity analysis on local recurrence / (number of studies):

Non TME (n=12) HR: 0.73 (95%CI: 0.66-0.81)
TME (n=1) HR: 0.42 (95%CI: 0.26-0.67)
BED ≥ 30Gy^{10} (n=8) HR: 0.50 (95%CI: 0.44-0.57)
BED < 30Gy^{10} (n=5) HR: 1.03 (95%CI: 0.89-1.18)
Treatment fields focused to the posterior pelvis (n=5) HR: 0.49 (95%CI: 0.41-0.58)
Other (n=16) HR: 0.85 (95%CI: 0.75-0.96)

Curative and overall resectability (RT before surgery versus surgery alone. n=8,482):

From fifteen studies, for curative respectability pooled RR: 1.02 (95% CI 1-1.05) in favour of pre-operative treatment (heterogeneity I^2=6%). The data for overall resectability could not be pooled due to high heterogeneity (I^2=72%).

Sphincter sparing surgery (RT before surgery versus surgery alone. n=7,917):

From fifteen studies, for sphincter sparing surgery pooled RR: 0.96 (95%CI: 0.88-1.04) in favour of pre-operative treatment (but heterogeneity I^2=40%). None of the factors specified *a priori* could explain the observed heterogeneity for this outcome.

Acute radiotherapy side effects:

The proportion of patients experiencing no toxicity ranged from 20% to 84% with the most common reported side effect being diarrhoea (20%).

Acute toxicity post surgery:

The proportion of patients with no post-operative toxicity favoured the surgery alone group; from 6 studies RR: 0.88 (95%CI: 0.82-0.94).

Late toxicity:

Quality of life comparisons showed no significance between study arms. There was more scarring of the anal sphincter in the irradiated group (33%) compared with the non-irradiated group (13%) when confirmed by endoanal ultrasound. This outcome was related to functional outcome with 11/12 patients suffering some degree of incontinence. Maximum resting pressure and maximum squeezing pressure were significantly lower in the irradiated group.

Follow-up:

General comments:

This paper was a well conducted Cochrane systematic review. The literature search was designed to find studies published between 1966 and December 2006

The review looked at a number of different treatment comparisons, some of which are not relevant to the current PICO. Therefore this evidence table contains information pertaining only to the relevant comparisons – pre-operative radiotherapy versus surgery alone. The quality of each included study was assessed by two authors using a fourteen point checklist. Any discrepancy was resolved by consensus and the range of quality scores was 0.29 to 0.88 (maximum possible score = 1.0).

The biological effective dose (BED) was calculated to facilitate comparison between regimens using $BED=30Gy^{10}$ as the point to divide studies into lower versus higher doses for subgroup/sensitivity analyses.

In the text of this review, results are presented as hazards ratios whereas the forest plots within the publication are labelled with as Peto odds ratios because the version of Review Manager© used for the analysis labels the resulting plot in this way by default. It should be noted that the results from this review could not be replicated in Review Manager© from the data and information provided.

The review authors concluded that pre-operative radiotherapy, compared with surgery alone, provides a 'modest improvement' in overall survival, 'definite improvement' in local recurrence and a 'modest increase' in the proportion of patients undergoing surgery with curative intent. These improvements are, however, at the cost of an increase in problems with acute and late rectal & sexual function.

3.1.2. For patients presenting with a) non-metastatic locally advanced colon cancer is pre-operative chemotherapy followed by surgery more effective than immediate surgery and for patients presenting with b) locally advanced rectal cancer is preoperative radiotherapy, preoperative chemotherapy or pre-operative chemoradiotherapy more effective than immediate surgery?

Short Summary
There was no evidence with which to address the issue of pre-operative chemotherapy versus surgery alone in patients with locally advanced colon cancer. There was a large volume of evidence of a variety of quality with which to address the issue of pre-operative treatment (radiotherapy, chemoradiotherapy or chemotherapy) versus immediate surgery, though the volume and quality of evidence was dependent on the particular comparison under investigation. In relation to pre-operative chemoradiotherapy versus pre-operative radiotherapy alone, a Cochrane review (Ceelen et al, 2009) was available along with a number of randomised trials.

In relation to preoperative chemoradiotherapy versus surgery alone there were a number of case series studies available. One Cochrane review (Wong et al, 2007) was available to provide evidence for pre-operative radiotherapy versus surgery alone.

There was no evidence available to address the issue of pre-operative chemotherapy versus surgery alone or chemoradiotherapy versus surgery alone in patients with locally advanced rectal cancer. Nor were there any studies comparing pre-operative chemotherapy with preoperative radiotherapy for patients with locally advanced rectal cancer.

In relation to preoperative chemoradiotherapy versus radiotherapy alone a pooled analysis showed no significant difference between the two treatments for overall survival (OR=1.06, 95% CI; 0.74 – 1.36) but a significant difference in favour of chemoradiotherapy for local recurrence (OR=0.53, 95% CI; 0.39 – 0.72).

Preoperative chemotherapy versus surgery alone in patients with locally advanced colon cancer
There was no evidence with which to determine the benefits, if any, of pre-operative chemotherapy versus surgery alone in patients with locally advanced colon cancer

Preoperative Chemoradiotherapy versus Preoperative Radiotherapy Alone
Overall Survival
No significant difference was observed between the treatment groups in terms of overall survival (pooled odds ratio, 1.00; 95% CI, 0.74-1.36)

Local Recurrence
A significant difference in the rates of local recurrence at 5 years was observed for patients in the radiotherapy group compared to patients in the chemoradiotherapy group (OR 0.53, 95% CI 0.39-0.72, p<0.001)

Cancer Specific Survival
From Braendengen et al (2008), a significant difference in cancer specific survival in favour of the chemoradiotherapy group; OR, 2.15, 95% CI, 1.2-3.84; p=0.01.

Disease Free Survival
Using data from 2 studies, Ceelen et al, 2009 reported no significant difference in 5-year disease free survival between the radiotherapy and chemoradiotherapy groups (OR 1.11, 95% CI 0.92-1.34, p=0.27)

Pathologic Complete Response
Pooled analysis showed a significant difference in pathologic complete response in favour of chemoradiotherapy: OR, 3.46,(95% CI, 2.46-4.86); p<0.00001.

Toxicity
Pooled analysis showed significantly higher rates of grade III/IV toxicity in the chemoradiotherapy group; OR, 4.51 (95% CI, 2.15-9.49), p<0.005 although there was significant heterogeneity on pooling (I^2=77%)

Preoperative Chemoradiotherapy versus Immediate Surgery
Overall Survival
No significant difference in either overall survival (p=0.09) or relapse free survival (p=0.1) between patients experiencing major complications and those with no major complications was observed, no numbers were given for the groups, therefore overall survival for the whole population cannot be calculated. (Chessin et al, 2005).

From a second case series study (Coco et al, 2006), the actuarial overall survival at 5-years was 75.5% %, at 7 years was 67.8% and at 10 years was 60.4%; actuarial cancer-related survival at 5 years was 77.9%, at 7 years was 70% and at 10 years was 65.8%. Mermershtain et al (2005) reported a 5-year overall survival of 70% and 8-year overall survival of 58% in a retrospective case series of 30 people. One retrospective case series (Twu et al, 2009) compared patients that responded to chemoradiotherapy with patients that did not respond and found no significant difference between the two groups in relation to overall survival, though a significant difference in local recurrence rate was observed in favour of the patients responding to chemoradiotherapy (p=0.002).

Relapse Free Survival/Disease Free Survival
Chessin et al (2005) did not report a significant difference in relapse free survival between patients experiencing major post-operative complications and patients not experiencing major post-operative complications.
In a retrospective case series of 43 patients (Twu et al, 2009), disease free survival was higher in the group of patients responding to chemoradiotherapy compared with those patients not responding to chemoradiotherapy (p=0.06).

Chemoradiotherapy with Capecitabine
9 phase II trials with a total of 470 patients, all with similar inclusion/exclusion criteria, were available to address this section (Elwanis et al, 2009; DeBruin et al, 2008; De Paoli et al, 2006; Desai et al, 2007; Kim et al, 2005; Koeberle et al, 2008, Machiels et al, 2005; Rodel et al, 2003; Velenik et al, 2006).

From 9 studies grade III/IV toxicity was reported in 13.2% (62/470) of patients (range 1-43%), one study reported no grade III/IV toxicity (Elwanis et al, 2009; DeBruin et al, 2008; Desai et al, 2007; Kim et al, 2005; Koeberle et al, 2008; Machiels et al, 2005; Rodel et al, 2003; Velenik et al, 2006). The most commonly reported toxicity was diarrhoea; other reported toxicities included anaemia, radiation dermatitis and leucocytopenia.

Sphincter preservation rate was reported in 4 studies and ranged from 36% to 74%, though in the study reporting 74% it is unclear whether this is the rate of sphincter sparing surgery or the success rate of sphincter sparing surgery (Elwanis et al, 2009; Kim et al, 2005; Rodel et al, 2003; Velenik et al, 2006).

Preoperative Radiotherapy versus Surgery Alone
Overall Mortality
Wong et al (2007) reported a pooled Hazards Ratio from 14 studies of 0.93 (0.87-1) in favour of preoperative radiotherapy. The magnitude of survival benefit was modest at 2% survival improvement at 5 years and 2% improvement at 8 years.
Subgroup analysis suggested that non TME studies, higher BED and treatment fields focused to the posterior pelvis showed significant benefit.

Local recurrence
Recurrence rates ranged from 11% to 54%. All but one study included in the Cochrane review (Wong et al, 2007) reported a benefit in favour of preoperative radiotherapy though again significant heterogeneity was observed between studies (p<0.05). The pooled Hazards Ratio was 0.71 (0.95% CI 0.64-0.78).

Curative and Overall Resectability
From 15 studies, Wong et al (2007) reported a pooled Risk Ratio (RR) for curative respectability was 1.02 (95% CI 1-1.05) in favour of preoperative treatment (Homogeneity X^2=14.94; p=0.38; I^2=6%).
The data for overall resectability could not be pooled due to heterogeneity (Homogeneity X^2=39.59; p=0.00004; I^2=72%).

Acute Radiotherapy Side Effects
The proportion of patients experiencing no toxicities ranged from 20% to 84% with the most common reported side effect being diarrhoea (20%) (Wong et al, 2007).

Acute Toxicities Post Surgery
The proportion of patients with no toxicities post-operatively favoured the surgery alone group; from 6 studies the Risk Ratio=0.88 (95% CI; 0.82-0.94) (Wong et al, 2007).

Updated Evidence
A retrospective review of 390 patients treated for rectal cancer presenting with T3 or T4 disease and/or involved lymph nodes received neoadjuvant chemoradiotherapy (5'-FU) before total mesorectal excision

(TME) whereas patients with T1 and T2 disease and no suspicion of involved nodes received TME directly. The time to death, local or distant recurrence was not significantly different between groups but the prognosis was more unfavourable for those patients who had positive nodes regardless of group (Klos *et* al 2010).

Stephens *et al* (2010) conducted a quality of life study within a randomised controlled trial that had compared short course radiotherapy then surgery (PRE) with surgery and post-operative chemotherapy (if tumour was within 1mm of resection margin) (SEL POST). Study participants completed two questionnaires (MOS SF-36 and QLQ-CR38) at baseline (N=1,208), every 3 months for the first year and every 6 months to 3 years (N=563 at 2 years). The main, irreversible treatment effect that reduced QoL was sexual dysfunction (P<0.001 for men, regardless of group, between baseline and 3 months) caused primarily by surgery but exacerbated by RT (P<0.001 at 6 months between groups). . Bowel function in those patients without a stoma (or in those who had a stoma reversal) was not significantly different between treatment arms. However, sub group analysis suggested that patients in the PRE group may have experienced an increase in the 'unintentional release of stools' even at 2 years post-treatment (P=0.007). Generally, there were no significant differences in treatment groups in overall general health or QoL.

Review Protocol

Population	Intervention	Comparison	Outcomes
Patients with locally advanced **colon** cancer	Pre operative Chemotherapy	Immediate surgery	• Quality of surgery (stoma, +/- margins, lymph node harvest)
Patients with locally advanced **rectal** cancer	Pre operative radiotherapy, chemotherapy or chemoradioatherapy	Immediate surgery and each other	• Risks/Safety • Quality of life • Local recurrence • Survival

Following a systematic search of relevant data sources (see appendix .1), the information specialist created a database of potentially relevant studies. All titles and abstracts were sifted by a single reviewer. Queries about inclusion were clarified by the GDG topic subgroup. The full studies were then obtained and reviewed and relevant studies were included in the final evidence review.

All update searches were sifted by a single reviewer and the list of potentially relevant studies was also checked for irrelevant studies by the GDG subgroup. Only studies which all subgroup members were in agreement were excluded. The remaining studies were obtained and reviewed with relevant studies included in the final evidence review.

It was felt by the GDG that evidence for this topic should focus on high level in the first instance if not available then look to lower level as randomised studies are probably limited.

Date limit set for this topic was 1997 onwards as effective chemotherapy not available until then

There is not likely to be evidence for part A of this topic so the GDG recommend that we look at evidence provided as the rationale for the FOxTROT trial and the protocol for the FOxTROT trial.
For rectal cancer especially may need to consider whether defunctioning colostomy or stent is needed before chemo or radiotherapy.
Also should look to see if any evidence for incidence of surgical intervention as an emergency if initial chemo/radiotherapy is chosen as the primary treatment modality.

There are a number of ways in which these patients can be treated depending on whether they have colon or rectal cancer; this topic will only address those over which there is a need for guidance.
- o Radiotherapy versus surgery alone
- o Chemoradiotherapy versus surgery alone
- o Chemotherapy versus surgery alone
- o Radiotherapy versus Chemoradiotherapy/Chemotherapy
- o Chemoradiotherapy versus Chemotherapy

Reasons for excluding studies:
Not relevant to topic
Not a relevant comparison
Not randomised trials
Foreign language papers with no translations
Expert Reviews
Abstract Only

Quality of the included studies
Systematic review of RCTs (n = 3)
Systematic review of combined study designs (n = 0)
Randomized controlled trial (n = 7)
Prospective cross sectional study (n = 0)
Case Series Studies (n = 7)
Other Study types (n=10)
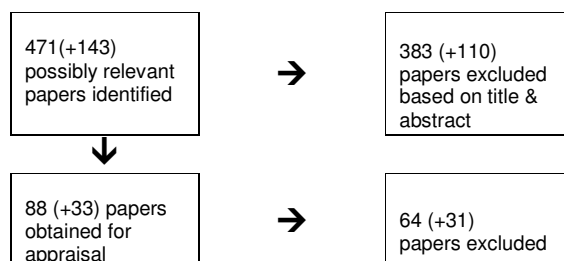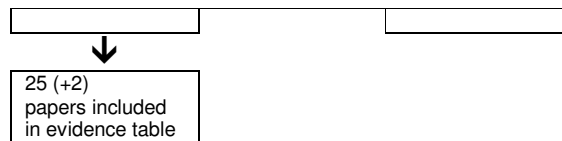
| 471(+143) possibly relevant papers identified | → | 383 (+110) papers excluded based on title & abstract |
| 88 (+33) papers obtained for appraisal | → | 64 (+31) papers excluded |

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┌──────────────┐              ┌────────────────┐
└──────────────┘              └────────────────┘
       ↓
┌─────────────────┐
│ 25 (+2)         │
│ papers included │
│ in evidence table│
└─────────────────┘
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Volume of evidence
There was no evidence with which to address the issue of pre-operative chemotherapy versus surgery alone in patients with locally advanced colon cancer.
There was a large volume of evidence of a variety of quality with which to address part B of this topic, though the volume and quality of evidence was dependent on the particular comparison under investigation. In relation to pre-operative chemoradiotherapy versus pre-operative radiotherapy alone, a Cochrane review (Ceelen et al, 2009) was available along with a number of randomised trials. In relation to preoperative chemoradiotherapy versus surgery alone there were a number of case series studies available. Also falling under the chemoradiotherapy section were studies relating to the use of capecitabine in the pre-operative setting for which there were a number of phase II trials addressing the issue of safety and efficacy of capecitabine as part of pre-operative chemoradiotherapy.
One Cochrane review (Wong et al, 2007) was available to provide evidence for pre-operative radiotherapy versus surgery alone.
There was no evidence available to address the issue of pre-operative chemotherapy versus surgery alone or chemoradiotherapy versus surgery alone in patients with locally advanced rectal caner. Nor were there any studies comparing pre-operative chemotherapy with preoperative radiotherapy for patients with locally advanced rectal cancer

Applicability
For some comparisons directly applicable evidence was available while for other comparisons, little or no direct evidence was available.

Other factors
Due to the number of possible comparisons relevant to this topic, the GDG were asked to prioritise those which were considered to be of most clinical importance, these prioritised comparisons then formed the basis for this topic.

Evidence Statement
The evidence is presented by section, with each section relating to a specific comparison identified as part of this topic.

Preoperative chemotherapy versus surgery alone in patients with locally advanced colon cancer
There was no evidence with which to determine the benefits, if any, of pre-operative chemotherapy versus surgery alon in patients with locally advanced colon cancer. Pre-operative chemotherapy is considered to be an attractive concept for colon cancer due to the potential for it to impact on both local and distant failure as well as the potential to eradicate micrometastases which might otherwise become irreversibly established during the period from surgery to post-operative treatment. Pre-operative therapy may also have beneficial effects on the primary tumour and regional spread by potentially reducing tumour cell shedding at the time of surgery, a process thought to contribute to the dissemination of tumour cells at the time of operation. It is also possible that the administration of pre-operative treatment may allow drug benefits to be achieved with relatively short exposures with resulting quality of life and cost benefits.
Reasons why the effects of pre-operative chemotherapy have not been studied in colon cancer include; drug therapy gave low response rates leaving significant risk of tumour growth during treatment phase; inaccurate radiological staging and unproven value of chemotherapy in node-negative disease which together made it difficult to exclude patients from treatment that would be managed better by surgery alone. Recent advances in radiology and chemotherapy mean that it is now possible to investigate neoadjuvant treatment for patients with colon cancer. The FOxTROT trial is a randomised trial part of which is aiming to establish whether an optimum combination of chemotherapy prior to surgery improves the probability of cure for patients with high-risk operable colon cancer. The trial is to be two stage, first assessing the feasibility, safety and tolerance of pre-operative therapy for patients treated with 24 weeks oxaliplatin plus modified de Gramont infusional fluoruouracil (OxMdG) in 150 patients, followed by the randomisation of a further 900 patients receiving either OxMdG or OxCap (oxaliplatin plus capecitabine) (FOxTROT Protocol).
Primary objectives of the FOxTROT Trial are:

1. to determine if neoadjuvant chemotherapy +/- panitumumab followed by deferred surgery and completion of chemotherapy post-operatively can reduce 2 year recurrence as compared to surgery and post-operative chemotherapy +/- panitumumab.
2. To determine if adding panitumumab in the neoadjuvant treatment of patients with KRAS wildtype tumours produces a measureable increase in anti-tumour efficacy as measured by tumour shrinkage

Relevant secondary objectives are to assess the tolerability of the neo-adjuvant therapies and to assess the nature and frequency of surgical complications.

The FOxTROT trial is to be a four arm trial, the two arms of relevance to this topic will be:
1. 6 weeks of preoperative oxaliplatin/fluoropyrimidine (OxFP) chemotherapy followed by surgery and 18 weeks of post-operative OxFP chemotherapy
2. Surgery followed by 24 weeks of post-operative OxFP chemotherapy

This trial will not report during the development of the current guideline on colorectal cancer so this section of the topic should be revisited once the FOxTROT trial reports results.

Preoperative Chemoradiotherapy versus Preoperative Radiotherapy Alone
There was one Cochrane Review (Ceelen et al, 2009), one systematic review (Birgisson et al, 2007) and four randomised trials (Braendengen et al, 2008; Pietrzak et al, 2007; Bujko et al, 2005, Bujko et al, 2004) available to address this section. Where possible the results from the individual trials have been added to the results from the Cochrane Review for a more complete picture of currently available evidence.
The systematic review (Birgisson et al, 2007) reported on the late adverse effects of radiation therapy for rectal cancer, however the results are discussed in a narrative fashion and so have not been presented here; full details of the study can be found in the accompanying evidence tables.
Two trials (Bujko et al, 2005 & 2004) reported on post-operative complications in patients irradiated pre-operatively for rectal cancer and sphincter presentation following preoperative radiotherapy for rectal cancer respectively. It was determined that there is a strong possibility that these two studies represent the same population as the more recent study included in the Cochrane Review (Ceelen et al, 2009) which reported long term results of a randomised trial comparing pre-operative short course radiotherapy with preoperative conventionally fractionated chemoradiotherapy (Bujko et al, 2006) and for this reason details have not been reported here, thought the studies are both included in the accompanying evidence tables.

Overall Survival
No significant difference was observed between the treatment groups in terms of overall survival (pooled odds ratio, 1.00; 95% CI, 0.74-1.36) (Figure 1) and GRADE (Figure 2).
Ceelen et al, 2009 included 4 studies in a Cochrane review, For overall survival using data from 3 studies, no statistically significant difference in 5-year survival was observed between patients in the radiotherapy group and patients in the chemoradiotherapy group (OR 0.95, 95% CI; 0.79-1.14, p=0.58). Braendengen et al, 2008 reported no significant difference in 5-year overall survival between patients in the radiotherapy group and patients in the chemoradiotherapy group (log-rank p=0.09).
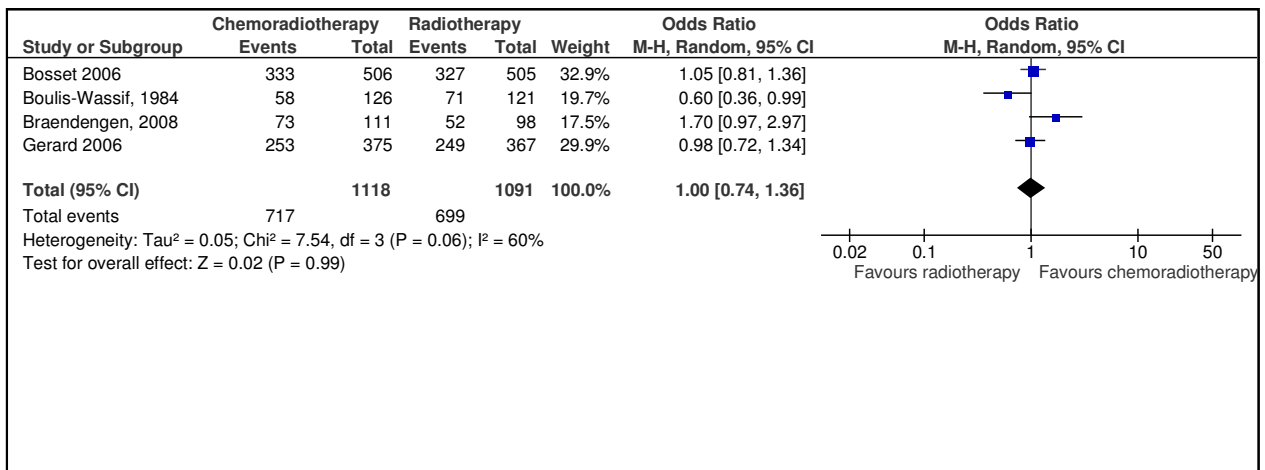
Figure 3.1: Overall Survival (RevMan)

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	preoperative chemotherapy, radiotherapy and chemoradiotherapy	immediate surgery	Relative (95% CI)	Absolute	Quality
Quality assessment							**Summary of findings**				
							No of patients		**Effect**		
Chemoradiotherapy versus Radiotherapy) (follow-up 5-7 years[1])											
4	randomised trials	serious[2]	no serious inconsistency[3]	no serious indirectness	no serious imprecision[4]	none	717/1118 (64.1%)	699/1091 (64.1%)	OR 1.01 (0.85 to 1.2)[5]	5 more per 1000 (from 72 fewer to 87 more)	⊕⊕⊕O MODERATE
								64.1%		5 more per 1000 (from 72 fewer to 87 more)	

[1] Boulis-Wassif et al, 1984 follow-up: available up to 7 years; Gerard et al, 2006 follow-up: median of 81 months and Bosset et al, 2006 follow-up: median of 5.4 years, Braendengen et al, 2008 follow-up: median of 61 months.
[2] None of the studies were described as being double blinded or using blinded outcome assessment.
[3] The Isquared value was 60% which suggests that these studies should not be pooled as the degree of heterogeneity is quite high, though not significant (p=0.06), Two studies, with similar numbers both found similar results, whereas the second two trials (one older and both with much smaller numbers) found a benefit for radiotherapy (Boulis-Wassif) and a benefit for chemoradiotherapy

(Braendengen) though the results were not significant. One possible reason for the difference in results, is that newer trial (Braendengen et al, 2008) looked at non-resectable patients whereas both Bosset et al 2006 and Gerard et al, 2006 excluded non-resectable patients.
[4] Although the pooled estimates confidence interval crosses the line of no effect there were more than 300 events recorded.
[5] p=0.95

Table 3.7 Overall Survival (GRADE)

Local Recurrence

A significant difference in the rates of local recurrence at 5 years was observed for patients in the radiotherapy group compared to patients in the chemoradiotherapy group (OR 0.53, 95% CI 0.39-0.72, p<0.001) (Figure 3) and GRADE (Figure 4): (Ceelen et al, 2009).

Braendengen et al (2008) reported local recurrence in 5% of patients in the chemoradiotherapy group compared with 7% in the radiotherapy group for patients undergoing R0 or R1 resection.

Study or Subgroup	Chemoradiotherapy Events	Total	Radiotherapy Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bosset 2006	22	253	43	252	33.0%	0.46 [0.27, 0.80]
Boulis-Wassif, 1984	19	126	18	121	13.1%	1.02 [0.51, 2.04]
Braendengen, 2008	5	85	8	81	6.5%	0.57 [0.18, 1.82]
Gerard 2006	30	375	61	367	47.5%	0.44 [0.27, 0.69]
Total (95% CI)		839		821	100.0%	0.53 [0.39, 0.72]
Total events	76		130			

Heterogeneity: Chi² = 4.26, df = 3 (P = 0.23); I² = 30%
Test for overall effect: Z = 4.14 (P < 0.0001)

Odds Ratio M-H, Fixed, 95% CI
0.01 0.1 1 10 100
Favours chemoradiotherapy   Favours radiotherapy

Figure 3.2: Local Recurrence (RevMAN)

	Quality assessment						Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	preoperative chemotherapy, radiotherapy and chemoradiotherapy	immediate surgery	Relative (95% CI)	Absolute	Quality
Local Recurrence (follow-up 5-7 years)											
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	76/839 (9.1%)	130/821 (15.8%)	OR 0.53 (0.39 to 0.72)[3]	69 fewer per 1000 (from 40 fewer to 92 fewer)	⊕⊕⊕O MODERATE
								15.8%		69 fewer per 1000 (from 40 fewer to 92 fewer)	

[1] None of the studies were described as being double blinded or using blinded outcome assessment.
[2] Pooled Estimate: 95% CI do not cross the line of no effect
[3] p<0.0001

Table 3.8: Local Recurrence (GRADE)

Cancer specific Survival

Braendengen et al (2008), reported a significant difference in cancer specific survival in favour of the chemoradiotherapy group (log-rank p=0.09). To maintain consistency and as the study reported only a p value, the data from this study were entered into RevMan to calculate the odds ratio (OR, 2.15, 95% CI, 1.2-3.84; p=0.01), which was then used in the GRADE table (Figures 5&6).

	Quality assessment						Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	preoperative chemotherapy, radiotherapy and chemoradiotherapy	immediate surgery	Relative (95% CI)	Absolute	Quality

Cancer Specific Survival at 5 years (follow-up median 61 months)										
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	71/98 (72.4%)	60/109 (55%)	OR 2.15 (1.20 to 3.84)[2,3]	359 more per 1000 (from 77 more to 661 more)	⊕⊕⊕O MODERATE
								55%		359 more per 1000 (from 77 more to 661 more)	

[1] None of the studies were described as being double blinded or using blinded outcome assessment.

[2] Braendengen et al (2008) did not report Odds Ratios, however to remain consistant with the results for the rest of this section, the odds ratio was calculated using RevMan.

[3] p=0.01

Table 3.9: Cancer Specific Survival (GRADE)

Disease Free Survival

Using data from 2 studies, Ceelen et al, 2009 reported no significant difference in 5-year disease free survival between the radiotherapy and chemoradiotherapy groups (OR 1.11, 95% CI 0.92-1.34, p=0.27) (Figures 7&8).

Study or Subgroup	Chemoradiotherapy Events	Total	Radiotherapy Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bosset 2006	284	506	275	505	59.1%	1.07 [0.83, 1.37]
Gerard 2006	223	375	204	367	40.9%	1.17 [0.88, 1.57]
Total (95% CI)		881		872	100.0%	1.11 [0.92, 1.34]
Total events	507		479			

Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 1.10 (P = 0.27)
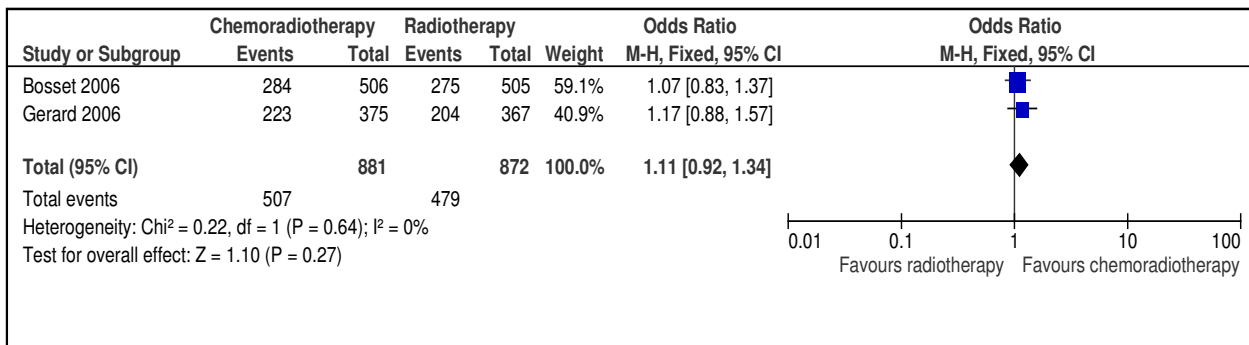
Figure 3.3: Disease Free Survival (RevMan)

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	preoperative chemotherapy, radiotherapy and chemoradiotherapy	immediate surgery	Relative (95% CI)	Absolute	Quality
Quality assessment							**Summary of findings**				
							No of patients		**Effect**		
Disease Free Survival at 5 years (follow-up 5-7 years)											
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	507/881 (57.5%)	479/872 (54.9%)	OR 1.11 (0.92 to 1.34)	43 more per 1000 (from 33 fewer to 127 more)	⊕⊕⊕O MODERATE
								54.9%		43 more per 1000 (from 33 fewer to 127 more)	

[1] None of the studies were described as being double blinded or using blinded outcome assessment.

Table 3.10: Disease Free Survival (GRADE)

Pathologic Complete Response

Pooled analysis showed a significant difference in pathologic complete response in favour of chemoradiotherapy: OR, 3.46,(95% CI, 2.46-4.86); p<0.00001 (Figure 9) and GRADE (Figure 10):. From the Cochrane review (Ceelen et all, 2009) there was a significant difference in pathologic complete response in favour of the chemoradiotherapy group (OR 3.65, 95% CI 2.52-5.27, p<0.0001). Braendengen et al, 2008 also observed a significant difference in pathologic complete response rates in favour of patients receiving chemoradiotherapy (p=0.04).

Study or Subgroup	Chemoradiotherapy Events	Total	Radiotherapy Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bosset 2006	60	473	22	476	47.0%	3.00 [1.81, 4.97]
Boulis-Wassif, 1984	6	126	3	121	7.2%	1.97 [0.48, 8.05]
Braendengen, 2008	16	98	8	109	15.6%	2.46 [1.00, 6.04]
Bujko, 2006	22	138	1	148	2.0%	27.88 [3.70, 209.90]
Gerard 2006	41	359	13	360	28.2%	3.44 [1.81, 6.54]
Total (95% CI)		1194		1214	100.0%	3.46 [2.46, 4.86]
Total events	145		47			

Heterogeneity: Chi² = 5.58, df = 4 (P = 0.23); I² = 28%
Test for overall effect: Z = 7.17 (P < 0.00001)

Odds Ratio M-H, Fixed, 95% CI — 0.01 0.1 1 10 100 — Favours radiotherapy Favours chemoradiotherapy

Figure 3.4: Pathologic Complete Response (RevMan)

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	preoperative chemotherapy, radiotherapy and chemoradiotherapy	immediate surgery	Relative (95% CI)	Absolute	Quality
			Quality assessment				Summary of findings				
							No of patients		Effect		
Pathologic Complete Response (follow-up 5-7 years)											
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	145/1194 (12.1%)	47/1214 (3.9%)	OR 3.46 (2.46 to 4.86)[3]	84 more per 1000 (from 52 more to 127 more)	⊕⊕⊕O MODERATE
								3.9%		85 more per 1000 (from 52 more to 127 more)	

[1] None of the studies were described as being double blinded or using blinded outcome assessment.
[2] Pooled Estimate: 95% CI do not cross the line of no effect
[3] p<0.00001

Table 3.11: Pathologic Complete Response (GRADE)

Sphincter Preservation Rate
Pooled analysis showed no significant difference between the two treatment groups for sphincter preservation rate; OR, 1.15 (95% CI, 0.97-1.36); p=0.1 (Figure 11) and GRADE (Figure 12): From the Cochrane Review (Ceelen et al, 2009), no significant difference was observed in the sphincter preservation rate (OR 1.1, 95% CI 0.92-1.131, p=0.29). Braendengen et al (2008) reported that 53% of resected patients in the chemoradiotherapy group had sphincter preserving surgery compared with 36% in the radiotherapy group (p=0.03).

Study or Subgroup	Chemoradiotherapy Events	Total	Radiotherapy Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Bosset 2006	263	473	249	475	42.9%	1.14 [0.88, 1.47]	
Boulis-Wassif, 1984	13	124	6	121	2.1%	2.24 [0.82, 6.11]	
Braendengen, 2008	46	87	32	88	5.8%	1.96 [1.07, 3.59]	
Bujko, 2006	87	157	87	155	15.2%	0.97 [0.62, 1.52]	
Gerard 2006	188	357	185	357	34.0%	1.03 [0.77, 1.39]	
Total (95% CI)		**1198**		**1196**	**100.0%**	**1.15 [0.97, 1.36]**	
Total events	597		559				

Heterogeneity: Chi² = 5.77, df = 4 (P = 0.22); I² = 31%
Test for overall effect: Z = 1.62 (P = 0.10)

0.01   0.1   1   10   100
Favours Radiotherapy   Favours Chemoradiotherapy

Figure 3.5: Sphincter Preservation Rate (RevMan)

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	preoperative chemotherapy, radiotherapy and chemoradiotherapy	immediate surgery	Relative (95% CI)	Absolute	Quality
			Quality assessment				No of patients		Effect		
									Summary of findings		
Sphincter Preservation (follow-up 5-7 years)											
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	597/1198 (49.8%)	559/1196 (46.7%)	OR 1.15 (0.97 to 1.36)[2]	51 more per 1000 (from 11 fewer to 117 more)	⊕⊕⊕O MODERATE
								46.7%		51 more per 1000 (from 11 fewer to 117 more)	

[1] None of the studies were described as being double blinded or using blinded outcome assessment.
[2] p=0.1

Table 3.12: Sphincter Preservation Rate (GRADE)

Postoperative Mortality and Morbidity
From the Cochrane Review (Ceelen et al, 2009) there was no statistically significant difference in 30 day postoperative mortality (OR 1.48, 95% CI 0.84-2.6, p=0.17).

There was no significant difference between the groups in relation to 30 day postoperative morbidity (OR 0.84, 95% CI 0.68-1.03, p=0.1) (Ceelen et al, 2009). Braendengen et al reported no significant difference in postoperative complications between the groups, though infections were more common in the chemoradiotherapy group (23%) than the radiotherapy group (12%) p=0.03.

In relation to anastomatic leak rates, Ceelen et al did not observe a significant difference between the groups (OR 1.03, 95% CI 0.57-1.85, p=0.93). Nor did Bujko et al (2005) record a significant difference in anastomotic leak rate or delayed perineal wound healing.

Study or Subgroup	Chemoradiotherapy Events	Total	Radiotherapy Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Bosset 2006	111	487	112	483	42.8%	0.98 [0.73, 1.32]
Braendengen, 2008	20	87	11	88	4.2%	2.09 [0.93, 4.68]
Bujko, 2006	31	152	39	153	15.3%	0.75 [0.44, 1.28]
Gerard 2006	75	359	97	360	37.8%	0.72 [0.51, 1.01]
Total (95% CI)		1085		1084	100.0%	0.89 [0.73, 1.09]
Total events	237		259			

Heterogeneity: Chi² = 6.62, df = 3 (P = 0.09); I² = 55%
Test for overall effect: Z = 1.14 (P = 0.26)

Odds Ratio M-H, Fixed, 95% CI
0.01 0.1 1 10 100
Favours chemoradiotherapy   Favours radiotherapy

Figure 3.6: Postoperative Morbidity (RevMan)

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	preoperative chemotherapy, radiotherapy and chemoradiotherapy	immediate surgery	Relative (95% CI)	Absolute	Quality
							No of patients		**Effect**		
Post-operative Morbidity											
4	randomised trials[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision[3]	none	237/1085 (21.8%)	259/1084 (23.9%)	OR 0.89 (0.73 to 1.09)[4]	22 fewer per 1000 (from 57 fewer to 18 more)	⊕⊕⊕O MODERATE
								23.9%		22 fewer per 1000 (from 57 fewer to 18 more)	

The top header row spans "Quality assessment" over Design–Other considerations and "Summary of findings" over the patient/effect/quality columns.

[1] 3 trials from the Cochrane Review report 3- day post-operative morbidity, another single trial reports post-operative infections.
[2] None of the studies were described as being double blinded or using blinded outcome assessment.
[3] Although the pooled estimates confidence interval crosses the line of no effect there were more than 300 events recorded.
[4] p=0.26

Table 3.13: Postoperative Morbidity (GRADE)

Toxicity
Pooled analysis showed significantly higher rates of grade III/IV toxicity in the chemoradiotherapy group; OR, 4.51 (95% CI, 2.15-9.49), p<0.005 although there was significant heterogeneity on pooling (I²=77%) Ceelen et al (2009) observed a statistically significant difference in the occurrence of Grade III/IV toxicity (OR 4.1, 95% CI 1.68-10, p=0.002) though there was significant heterogeneity between the studies which remained after using reanalyses using the random effects assumption. A second randomised trial (Braendengen et al, 2008) also reported more grade III/IV toxicity in the chemoradiotherapy group compared with the radiotherapy group (p=0.001). (Figure) and GRADE (Figure):

Study or Subgroup	Chemoradiotherapy Events	Total	Radiotherapy Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Bosset 2006	67	483	37	495	30.5%	1.99 [1.31, 3.04]
Braendengen, 2008	27	98	6	109	22.0%	6.53 [2.56, 16.63]
Bujko, 2006	29	157	5	155	21.3%	6.80 [2.56, 18.07]
Gerard 2006	55	375	10	367	26.2%	6.14 [3.08, 12.24]
Total (95% CI)		1113		1126	100.0%	4.51 [2.15, 9.49]
Total events	178		58			

Heterogeneity: Tau² = 0.43; Chi² = 12.86, df = 3 (P = 0.005); I² = 77%
Test for overall effect: Z = 3.97 (P < 0.0001)

Odds Ratio M-H, Random, 95% CI — scale: 0.01 0.1 1 10 100 — Favours chemoradiotherapy / Favours radiotherapy

Figure 3.7: Toxicity (RevMan)

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	preoperative chemotherapy, radiotherapy and chemoradiotherapy	immediate surgery	Relative (95% CI)	Absolute	Quality
Quality assessment							**Summary of findings**				
							No of patients		**Effect**		
Toxicity (Grade III/IV (follow-up 5-7 years)											
4	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision[3]	none	178/1113 (16%)	58/1126 (5.2%)	RR 4.51 (2.15 to 9.49)[4]	181 more per 1000 (from 59 more to 437 more)	⊕⊕OO LOW
								5.2%		183 more per 1000 (from 60 more to 441 more)	

[1] None of the studies were described as being double blinded or using blinded outcome assessment.
[2] Significant Heterogeneity between studies (p=0.005)
[3] Pooled Estimate: 95% CI do not cross the line of no effect
[4] p<0.0001

Table 3.14: Toxicity (GRADE)

Quality of Life
One randomised trial (Pietrzak et al, 2007), specifically addressing quality of life as an outcome observed no significant difference between the two groups in relation to mean scores for the global health/quality of life status (p=0.22).
The same trial did note however, that a significantly higher number of patients in the short-term radiotherapy went on to receive post-operative chemotherapy compared with the chemoradiotherapy group (p=0.002).

In relation to anorectal and sexual function, Pietrzak et al (2007) observed no significant difference between the two groups in relation to any of the questions posed. Approximately two thirds of patients complained of faecal and gas incontinence, urgency and inability to differentiate between stool and gas.
Approximately two-thirds of respondents stated that the disturbances in anorectal function had a negative impact on their quality of life, with approximately 20% stating the impact was considerable.
Anorectal function was estimated as being good or very good by 41% of patients in the short-course chemotherapy group and by 37% of patients in the chemoradiotherapy group (p=0.52).
2% (n=2) patients scored anorectal function was being unacceptable and regretted that a stoma had not been performed.
There was no significant difference between the two groups in relation to the impact on sexual function (p=0.56 for males; p=0.1 for females).

Preoperative Chemoradiotherapy versus Immediate Surgery
In relation to this comparison, there was little evidence available and all available evidence was drawn from a small number of case series studies, both prospective and retrospective. Numbers included in the studies

were small for the most part and reporting of aims and outcomes was not clear or detailed in many cases. The evidence for this section should be interpreted and used with caution.

Complications and Toxicity
From one prospective case series (Chessin et al, 2005), there is evidence that some patients receiving chemoradiotherapy will suffer major post-operative complications, with 98/297 patients recording at least one major complication. In this study, bowel obstruction and wound infection were the most common major complications.
A retrospective case series (Mermershtain et al, 2005) reported no serious toxicities related to chemoradiotherapy and only mild to moderate radiation dermatitis was observed in 3 patients, grade II diarrhoea in 4 patients. No haematological or genitourinary grade III/IV toxicities were encountered during chemoradiotherapy, nor was any long term radiation induced toxicity observed.

| No of studies | Quality assessment | | | | | | Summary of findings | | | | Quality |
| | | | | | | | No of patients | | Effect | | |
	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative Chemoradiotherapy	Surgery Alone	Relative (95% CI)	Absolute	
Postoperative complications and Toxicity (Chessin et al, 2005) (follow-up median 43.9 months)											
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	98/297 (33%)[3]	0/0 (0%)	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕OOO VERY LOW
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)	
Postoperative Morbidity and Toxicity (Mermershtain et al, 2005) (follow-up median 73 months)											
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/0 (0%)	0/0 (0%)	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕OOO VERY LOW
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)	

[1] Not a randomised Trial
[2] Imprecision cannot be assessed
[3] 98/297 patients reported at least one major post-operative complication
Table 3.15 GRADE Quality Assessment and Summary of Findngs

Overall Survival
No significant difference in either overall survival (p=0.09) or relapse free survival (p=0.1) between patients experiencing major complications and those with no major complications was observed, no numbers were given for the groups, therefore overall survival for the whole population cannot be calculated. (Chessin et al, 2005).
From a second case series study (Coco et al, 2006), the actuarial overall survival at 5-years was 75.5% %, at 7 years was 67.8% and at 10 years was 60.4%; actuarial cancer-related survival at 5 years was 77.9%, at 7 years was 70% and at 10 years was 65.8%. Mermershtain et al (2005) reported a 5-year overall survival of 70% and 8-year overall survival of 58% in a retrospective case series of 30 people. One retrospective case series (Twu et al, 2009) compared patients that responded to chemoradiotherapy with patients that did not respond and found no significant difference between the two groups in relation to overall survival, though a significant difference in local recurrence rate was observed in favour of the patients responding to chemoradiotherapy (p=0.002).

| No of studies | Quality assessment | | | | | Other considerations | Quality |
	Design	Limitations	Inconsistency	Indirectness	Imprecision		
Overall Survival (Chessin et al, 2005) (follow-up median 43.9 months[1])							
1	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	⊕OOO VERY LOW
Overall Survival (Coco et al, 2006) (follow-up median 108 months)							
1	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	⊕OOO VERY LOW
Overall Survival (Memershtain et al, 2005)							
1	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	⊕OOO VERY LOW

Overall Survival (Twu et al, 2009) (follow-up median 1.5 years[5])							
1	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	⊕OOO VERY LOW

[1] Median Follow-up was given under the results of post-operative morbidity. No other mention of follow-up duration was made for other outcomes, therefore it is assumed that this was the median follow up for all outcomes.
[2] Not a randomised Trial
[3] Imprecision cannot be assessed
[4] no significant difference between patients with serious post-operative morbidity and patients without (p=0.09)
[5] Median follow-up time was longer than 1.5 years, but the study does not report actual median follow-up time.

Table 3.16 GRADE Quality Assessment and Summary of Findings

Relapse Free Survival/Disease Free Survival
Chessin et al (2005) did not report a significant difference in relapse free survival between patients experiencing major post-operative complications and patients not experiencing major post-operative complications.
In a retrospective case series of 43 patients (Twu et al, 2009), disease free survival was higher in the group of patients responding to chemoradiotherapy compared with those patients not responding to chemoradiotherapy (p=0.06).

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Quality assessment							**Quality**
Relapse and Disease Free Survival (Chessin et all, 2005) (follow-up median 43.9 months)							
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	⊕OOO VERY LOW
Relapse and Disease Free Survival (Twu et al, 2009) (follow-up median 1.5 years[4])							
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	⊕OOO VERY LOW

[1] Not a randomised Trial
[2] Imprecision cannot be assessed
[3] Relapse free survival did not differ significantly between patients with major postoperative complications and those without (p=0.1)
[4] Median follow-up time was longer than 1.5 years, but the study does not report actual median follow-up time.
[5] Disease free survival was higher in the patients responding to preoperative chemoradiotherapy than in patients not responding (p=0.06)

Table 3.17 GRADE Quality Assessment and Summary of Findings

Pathologic Complete Response
From one retrospective case-series of 100 patients (Habr-Gama et al, 2004) pathologic complete response occurred in 12% of patients treated with preoperative chemoradiotherapy; a second retrospective case series of 30 patients (Mermershtain et al, 2005) reported pathologic complete response in 13% of patients and partial response in 17% and progression in 13% of patients and a third retrospective case series of 43 patients (Twu et al, 2009) reported complete pathologic response in 12% of patients and Tulchinsky et al (2008) reported that 26% of patients had either a complete or near complete pathologic response with the rate of pathologic complete response increased with longer time to surgery interval (p=0.03).

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative Chemoradiotherapy	Surgery Alone	Relative (95% CI)	Absolute	Quality
Quality assessment							**Summary of findings**				
							No of patients		**Effect**		
Pathologic Complete Response (Habr-Gama et al, 2004)											
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	6/50 (12%)[3]	0/50 (0%)[4]	RR 0 (0 to 0)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕OOO VERY LOW
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)	
Pathologic Complete Response (Mermershtain et al, 2005) (follow-up median 73 months)											
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/0 (0%)	0/0 (0%)	RR 0 (0 to 0)[5]	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕OOO VERY LOW
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)	
Pathologic Complete Response (Tulchinsky et al, 2008)											
1	observational	very	no serious	no serious	serious[2]	none	22/132 (16.7%)[6]	46/132	RR 0 (0	348 fewer per	⊕OOO

| studies | serious[1] | inconsistency | indirectness | | | | (34.8%)[7] | to 0)[8] | 1000 (from 348 fewer to 348 fewer) | VERY LOW |
| | | | | | | | 0% | | 0 fewer per 1000 (from 0 fewer to 0 fewer) | |

[1] Not a randomised Trial
[2] Imprecision cannot be assessed
[3] patients treated with preoeprative chemoradiotherapy
[4] patients with surgery alone
[5] Pathologic complete response occurred in 4 patients (13%)
[6] Complete or near complete pathologic response in patients with less than seven weeks to surgery
[7] Complete or near complete pathologic response in patients with more than seven week time interval to surgery
[8] p=0.03

Table 3.18 GRADE Quality Assessment and Summary of Findings

Sphincter Preservation Rate

From one retrospective case series of 100 patients (Habr-Gama et al, 2004) reported that 86% of patients in the surgery group were treated with abdomino-perineal resections and 14% by anterior resections. In the chemoradiotherapy group, 68% were treated by abdomino-perineal resection and 32% by anterior resection (p=0.03)

Quality assessment						Summary of findings				
						No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Preoperative Chemoradiotherapy	Surgery Alone	Relative (95% CI)	Absolute	Quality
Sphincter Preservation Rate (Habr-Gama et al, 2004)											
1	observational studies	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	16/50 (32%)[3]	7/50 (14%)[4]	RR 0 (0 to 0)[5]	140 fewer per 1000 (from 140 fewer to 140 fewer)	⊕OOO VERY LOW
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)	

[1] Not a randomised Trial
[2] Imprecision cannot be assessed
[3] patients receiving preoperative chemoradiotherapy undergoing anterior resection
[4] Patients with surgery alone undergoing anterior resection
[5] p=0.03

Table 3.19 GRADE Quality Assessment and Summary of Findings

Chemoradiotherapy with Capecitabine

The body of evidence for this intervention is comprised of phase II trials primarily examining the efficacy and toxicity of chemoradiotherapy with Capecitabine in patients with locally advanced rectal cancer.
9 phase II trials with a total of 470 patients, all with similar inclusion/exclusion criteria, were available to address this section (Elwanis et al, 2009; DeBruin et al, 2008; De Paoli et al, 2006; Desai et al, 2007; Kim et al, 2005; Koeberle et al, 2008, Machiels et al, 2005; Rodel et al, 2003; Velenik et al, 2006).

From 9 studies grade III/IV toxicity was reported in 13.2% (62/470) of patients (range 1-43%), one study reported no grade III/IV toxicity (Elwanis et al, 2009; DeBruin et al, 2008; Desai et al, 2007; Kim et al, 2005; Koeberle et al, 2008; Machiels et al, 2005; Rodel et al, 2003; Velenik et al, 2006). The most commonly reported toxicity was diarrhoea; other reported toxicities included anaemia, radiation dermatitis and leucocytopenia.

Compliance with treatment regimens was reported in 6 studies and was presented in one of two ways; compliance with each part of the regimen (radiotherapy, chemotherapy, capecitabine) or as an overall treatment compliance with the regimen as a whole. Reported treatment compliance ranged from 93% compliance with radiotherapy, 87% compliance with oxaliplatin and 92% compliance with capecitabine in one study (Koeberle et al, 2008) to 100% compliance for radiotherapy and 97% compliance for chemotherapy in one study (De Bruin et al, 2008) to 98% compliance with whole treatment regimen (Velenik et al, 2006).

From 8 studies, mean complete pathologic response rate was 12.7% (range: 4% - 23%); overall downstaging was recorded in 5 studies and ranged from 55% to 85% (Elwanis et al, 2009; DeBruin et al, 2008; De Paoli et al, 2006; Desai et al, 2007; Kim et al, 2005; Koeberle et al, 2008, Rodel et al, 2003; Velenik et al, 2006).

Sphincter preservation rate was reported in 4 studies and ranged from 36% to 74%, though in the study reporting 74% it is unclear whether this is the rate of sphincter sparing surgery or the success rate of sphincter sparing surgery (Elwanis et al, 2009; Kim et al, 2005; Rodel et al, 2003; Velenik et al, 2006).

Preoperative Radiotherapy versus Surgery Alone

There was one Cochrane Review (Wong et al, 2007) and one randomised trial (Birgisson et al, 2005) available to address this section.

Overall Mortality

Wong et al (2007) reported a pooled Hazards Ratio from 14 studies of 0.93 (0.87-1) in favour of preoperative radiotherapy. The magnitude of survival benefit was modest at 2% survival improvement at 5 years and 2% improvement at 8 years.

Subgroup analysis suggested that non TME studies, higher BED and treatment fields focused to the posterior pelvis showed significant benefit.

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	preoperative radiotherapy	surgery alone	Relative (95% CI)	Absolute	Quality
Quality assessment							**Summary of findings**				
							No of patients		**Effect**		
Overall Mortality											
14	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	2027/3997 (50.7%)	1880/4635 (40.6%)	HR 0.93 (0.87 to 1)[1]	22 fewer per 1000 (from 42 fewer to 0 more)	⊕⊕⊕⊕ HIGH
								40.6%		22 fewer per 1000 (from 42 fewer to 0 more)	

[1] The Cochrane Review states that Hazards Ratios were calculated in RevMan, however the results cannot be replicated as the analysis appears to use an older version of RevMan which labels HR as Peto Odds Ratio. In addition, the data provided in the review is not enough to allow replication of results in the newer version of RevMan. It is unclear what data were used in the analysis.

Table 3.20 GRADE Quality Assessment and Summary of Findings

Cause Specific Mortality

The Hazards Ratio (from 5 studies) was 0.87 (095% CI; 0.78-0.98) in favour of radiotherapy, however there was significant heterogeneity between studies (p=0.07) and so the results should be considered with caution (Wong et al, 2007).

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	preoperative radiotherapy	surgery alone	Relative (95% CI)	Absolute	Quality
Quality assessment							**Summary of findings**				
							No of patients		**Effect**		
Cause Specific Mortality											
4	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	467/1119 (41.7%)	508/1136 (44.7%)	HR 0.87 (0.78 to 0.98)	44 fewer per 1000 (from 7 fewer to 77 fewer)	⊕⊕⊕⊕ HIGH
								44.7%		44 fewer per 1000 (from 7 fewer to 77 fewer)	

Table 3.21 GRADE Quality Assessment and Summary of Findings

Any Recurrence

From the Cochrane review (Wong et al, 2007) Hazards Ratio (from 8 studies) was 0.89 (95% CI; 0.82-0.97) suggesting an overall reduction of recurrences in favour of pre-operative radiotherapy.

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	preoperative radiotherapy	surgery alone	Relative (95% CI)	Absolute	Quality
Quality assessment							**Summary of findings**				
							No of patients		**Effect**		
Any Reccurence											
8	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	955/2576 (37.1%)	1091/2601 (41.9%)	HR 0.89 (0.82 to 0.97)	36 fewer per 1000 (from 10 fewer to 60 fewer)	⊕⊕⊕⊕ HIGH
								41.9%		36 fewer per 1000 (from 10 fewer to 60 fewer)	

Table 3.22 GRADE Quality Assessment and Summary of Findings

Local recurrence

Recurrence rates ranged from 11% to 54%. All but one study included in the Cochrane review (Wong et al, 2007) reported a benefit in favour of preoperative radiotherapy though again significant heterogeneity was observed between studies (p<0.05). The pooled Hazards Ratio was 0.71 (0.95% CI 0.64-0.78).

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	preoperative radiotherapy	surgery alone	Relative (95% CI)	Absolute	Quality
Quality assessment							**Summary of findings**				
							No of patients		**Effect**		
Local Recurrence											
13	randomised trials	no serious limitations	serious[1]	no serious indirectness	no serious imprecision	none	681/3709 (18.4%)	1034/3758 (27.5%)	HR 0.71 (0.64 to 0.78)	71 fewer per 1000 (from 53 fewer to 89 fewer)	⊕⊕⊕O MODERATE
								27.5%		71 fewer per 1000 (from 53 fewer to 89 fewer)	

[1] Differences in recurrence rates ranged from 11% to 54%

Table 3.23 GRADE Quality Assessment and Summary of Findings

Curative and Overall Resectability
From 15 studies, Wong et al (2007) reported a pooled Risk Ratio (RR) for curative respectability was 1.02 (95% CI 1-1.05) in favour of preoperative treatment (Homogeneity X^2=14.94; p=0.38; I^2=6%). The data for overall resectability could not be pooled due to heterogeneity (Homogeneity X^2=39.59; p=0.00004; I^2=72%).

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	preoperative radiotherapy	surgery alone	Relative (95% CI)	Absolute	Quality
Quality assessment							**Summary of findings**				
							No of patients		**Effect**		
Curative and Overall Resectability											
15	randomised trials	no serious limitations	serious[1]	no serious indirectness	no serious imprecision	none	3290/4228 (77.8%)	3203/4254 (75.3%)	RR 1.02 (1.00 to 1.05)	15 more per 1000 (from 0 more to 38 more)	⊕⊕⊕O MODERATE
								75.3%		15 more per 1000 (from 0 more to 38 more)	

[1] Data were heterogenous across the studies for overall resectability which precluded pooling.

Table 3.24 GRADE Quality Assessment and Summary of Findings

Sphincter Sparing Surgery
From 15 studies, the pooled Risk Ratio (RR) for sphincter sparing surgery was 0.96 (95% CI; 0.88-1.04) in favour of pre-operative treatment (Homogeneity X^2=23.47; p=0.05; I^2=40%). None of the factors specified *a priori* could explain the observed heterogeneity for this outcome (Wong et al, 2007).

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	preoperative radiotherapy	surgery alone	Relative (95% CI)	Absolute	Quality
Quality assessment							**Summary of findings**				
							No of patients		**Effect**		
Sphincter Saving Surgery											
15	randomised trials	no serious limitations	serious[1]	no serious indirectness	no serious imprecision	none	1592/3950 (40.3%)	1657/3967 (41.8%)	RR 0.96 (0.88 to 1.04)	17 fewer per 1000 (from 50 fewer to 17 more)	⊕⊕⊕O MODERATE
								41.8%		17 fewer per 1000 (from 50 fewer to 17 more)	

[1] Results were heterogenous across the studies

Table 3.25 GRADE Quality Assessment and Summary of Findings

Acute Radiotherapy Side Effects

The proportion of patients experiencing no toxicities ranged from 20% to 84% with the most common reported side effect being diarrhoea (20%) (Wong et al, 2007).

Acute Toxicities Post Surgery
The proportion of patients with no toxicities post-operatively favoured the surgery alone group; from 6 studies the Risk Ratio=0.88 (95% CI; 0.82-0.94) (Wong et al, 2007).

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	preoperative radiotherapy	surgery alone	Relative (95% CI)	Absolute	Quality
Acute Post Surgery Toxicity											
6	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	962/1836 (52.4%)	1128/1879 (60%)	RR 0.88 (0.82 to 0.94)	72 fewer per 1000 (from 36 fewer to 108 fewer)	⊕⊕⊕⊕ HIGH
								60%		72 fewer per 1000 (from 36 fewer to 108 fewer)	

Table 3.26 GRADE Quality Assessment and Summary of Findings

Late Toxicities
Quality of life comparisons showed a non-significant trend towards worse outcomes in irradiated patients. There was more scarring of the anal sphincters in the irradiated group (33%) when compared with the non-irradiated group (13%) confirmed by endoanal ultrasound. This outcome was related to functional outcome with 11/12 patients suffering some degree of incontinence symptoms.
Maximum resting pressure and maximum squeezing pressure were significantly lower in the irradiated group (Wong et al, 2007).

Postoperative Complications and Adverse Events
A single study compared irradiated and non-irradiatated patients that had been part of two randomised trials in Sweden (Birgisson et al, 2005) with the aim of analysing the occurrence of sub acute and late adverse effects in patients treated with preoperative irradiation for rectal cancer.
The study reported that 73% (n=661) of patients analysed were admitted to hospital at least once after treatment of primary rectal cancer; more patients from the irradiated group were admitted both in the early and late post-operative periods.
There was no difference in relative risk (RR=1.07; 95% CI, 0.91-1.26) between the irradiated and non-irradiated groups. There was however, an increase in relative risk for early admissions in irradiated patients (RR=1.64; 95% CI, 1.21-2.22). No difference was observed between the groups for late admissions (RR=0.95; 95% CI, 0.8-1.12).

An increase in relative risk among irradiated patients during the first 6 months was observed for infections (RR=7.67; 1.76-33.39) and gastrointestinal diagnoses (RR=2.57; 95% CI, 1.55-4.26).
An increase in relative risk among irradiated patients was observed for non-specific infections (n=10; RR=8.06; 95% CI 1.02-63.69).
The risk of cardiac arrhythmia was reduced in the irradiated group (RR=0.57; 95% CI, 0.36-0.91).
In relation to gastrointestinal diagnosis, increased relative risks were observed in irradiated patients for bowel obstruction, nausea and unspecific abdominal pain, whereas the risk for inguinal hernia was lower among irradiated patients.

Updated Evidence
Klos *et* al (2010) described a retrospective review of 390 patients treated for rectal cancer at a single general hospital. Patients presenting with T3 or T4 disease and/or involved lymph nodes received neoadjuvant chemoradiotherapy (5'-FU) before total mesorectal excision (TME) whereas patients with T1 and T2 disease and no suspicion of involved nodes received TME directly. Adjuvant treatment was offered based on the resulting pathology and to all patients who had received neoadjuvant therapy. The time to death, local or distant recurrence was not significantly different between groups but the prognosis was more unfavourable for those patients who had positive nodes regardless of group. A retrospective, non-randomised study is, by design, of low evidential value plus the surgical protocols, surgeons and histologists varied between patients.

Stephens *et al* (2010) conducted a quality of life study within a randomised controlled trial that had compared short course radiotherapy then surgery (PRE) with surgery and post-operative chemotherapy (if tumour was within 1mm of resection margin) (SEL POST). Study participants completed two questionnaires (MOS SF-36 and QLQ-CR38) at baseline (N=1,208), every 3 months for the first year and every 6 months to 3 years (N=563 at 2 years). The main, irreversible treatment effect that reduced QoL was sexual dysfunction

(P<0.001 for men, regardless of group, between baseline and 3 months) caused primarily by surgery but exacerbated by RT (P<0.001 at 6 months between groups). There were insufficient responses from females to measure this outcome. Bowel function in those patients without a stoma (or in those who had a stoma reversal) was not significantly different between treatment arms. However, sub group analysis suggested that patients in the PRE group may have experienced an increase in the 'unintentional release of stools' even at 2 years post-treatment (P=0.007). Generally, there were no significant differences in treatment groups in overall general health or QoL. The quality of the trial from which these data are taken was high; however, the non-specific nature of the questionnaires applied may have rendered them less sensitive to detecting differences in outcomes.

References

FOxTROT Protocol: http://www.foxtrot.bham.ac.uk/FOxTROT_Protocol_v4.pdf

Braendengen M, Tveit KM, Berglund A, Birkemeyer E, Frykholm G, Pahlman L, Wiig JN, Bystrom P, Bujko K, Glimelius B (2008) Randomised Phase II Study Comparing Preoperative Radiotherapy with Chemoradiotherapy in Nonresectable Rectal Cancer *Journal of Clinical Oncology* 26;22: 3687-3694

Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M (2006) Long-term Results of a randomised trial comparing preoperative short course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer *British Journal of Surgery* 93;1215-1223

Bujko K, Nowacki MP, Kepka L, Oledzki J, Bebeneki M, Kryj M (2005) Postoperative complications in patients irradiated pre-operatively for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs. chemoradiation *Colorectal Disease* 7;4:410-416

Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Pudelko M, Kryj M, Oledzki J, Szmeja J, Sluszniak J, Serkies K, Kladny J, Pamucka M, Kkolowicz (2004) Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy *Radiotherapy and Oncology* 72;15-24

Birgisson H, Pahlman L, Gunnersson U, Limelius B (2007) Late adverse effects of radiation therapy for rectal cancer – a systematic overview *Acta Oncologica* 46;504-516

Birgisson H, Pahlman L, Gunnersson U, Glimlelius B (2005) Adverse Effects of Preoperative Radiation Therapy for Rectal Cancer: Long-Term Follow-up of the Swedish Rectal Cancer Trial *Journal of Clinical Oncology* 23;34:8697-8705

Ceelen WP, Van Nieuwenhove Y, Fierens K (2009) Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer (Review) *Cochrane Database of Systematic Reviews*

Chessin D, Enker W, Cohen A, Paty P, Weiser M, Saltz L, Minsky B, Wong WD, Guillem JG (2005) Complications after preoperative combines modality therapy and radical resection of locally advanced rectal cancer: a 14 year experience from a specialty service *Journal of the American College of Surgeons* 200;6:876-882

Coco C, Valentini V, Manno A, Mattana C, Verbo A, Cellini N, Gambacorta M, Covino M, Mantini G, Micciche F, Pedretti G, Petito L, Rizzo G, Cosimelli M, Impiombato F, Picciocchi A (2006) Long-term results after neoadjuvant radiochemotherapy for locally advanced resectable extraperitoneal rectal cancer *Diseases of the Colon and Rectum* 49;3:311-318

De Bruin AFJ, Nuyttens JJ, Ferenschild FTJ, Planting AST, Verhoef C, de Wilt JHW (2008) Preoperative chemoradiation with capecitabine in locally advanced rectal cancer *Netherlands Journal of Medicine* 66;2:71-76

De Paoli A, Chiara S, Luppi G, Friso ML, Beretta GD, Del Prete S, Pasetto L, Santantonio M, Sarti E, Mantello G, Innocente R, Frusctaci S, Corvo R, Rosso R (2006) Capecitabine in combination with preoperative radiation therapy in locally advanced, resectable, rectal cancer: a multicentric phase II study *Annals of Oncology* 17;2:246-251

Desai SP, El-Rayes BF, Ben-Josef E, Greenson JK, Knol JA, Huang EH, Griffith KA, Philip PA, McGinn CJ, Zalupski MM (2007) A phase II study of preoperative capecitabine and radiation therapy in patients with rectal cancer *American Journal of Clinical Oncology* 30;4:340-345

Elwanis MA, Maximous DW, Elsayed MI Mikhail NNH (2009) Surgical treatment for locally advanced lower third rectal cancer after neoadjuvant chemoradiation with capecitabine; prospective phase II trial *Worl Journal of Surgical Oncology* 7;52

Habr- Gama A, Perez RO, Kiss DR, Rawet V, Scanavini A, Santinho PM, Nadalin W (2004) Preoperative chemoradiation therapy for low rectal cancer. Impact on downstaging and sphincter saving operations *Hepato Gastroenterology* 51;60:1703-1707

Kim JC, Kim TW, Kim JH, Yu CS, Kim HC, Chang HM, Ryu MH, Park JH, Ahn SD, Lee S, Shin SS, Kim JS, Choi EK (2005) Preoperative concurrent radiotherapy with capecitabine before total mesorectal excision in locally advanced rectal cancer *Journal of Radiation Oncology, Biology, Physics* 63;2:346-353

Klos CL, Shellito PC, Rattner DW, Hodin RA, Cusack JC, Bordeianou L, Sylla P, Hong TS, Blaszkowsky L, Ryan DP, Lauwers GY, Chang Y and Berger DL. (2010). The effect of neoadjuvant chemoradiation therapy on the prognostic value of lymph nodes after rectal cancer surgery. *Am J Surgery* **200 [4]**: 440-445.

Koeberle D, Burkhard R, von Moos R, Winterhalder R, Hess V, Heitzmann F, Ruhstaller T, Terraciano L, Neuweiler J, Bieri G, Rust C, Toepfer M (2008) Phase II study of capecitabine and oxaliplatin given prior to and concurrently with preoperative pelvic radiotherapy in patients with locally advance rectal cancer *British Journal of Cancer* 98;7:1204-1209

Machiels JP, Duck L, Honhon B, Coster B, Coche JC, Scalliet P, Humblet Y, Aydin S, Kerger J, Remouchamps V, Canon JL, van Maele P, Gilbeau L, Laurent S, Kirkove C, Octave-Prignot M, Baurain JF, Kartheuser A, Sempoux C (2005) Phase II study of preoperative oxaliplatin, capecitabine and external beam radiotherapy in patients with rectal cancer: the RadiOxCape study *Annals of Oncology* 16;12:1898-1905

Mermershtain W, Gluzman A, Gusakova I, Walfish S, Cohen Y, Ariad S (2005) Preoperative radio-chemotherapy treatment in locally advanced rectal carcinoma. Results of 8 year follow-up *Onkologie* 28;5:267-269

Pietrzak L, Bujko K, Nowacki MP, Kepka L, Oledzki J, Rutkowski A, Szmeja J, Kladny J, Dymecki D, Wieczorek A, Pawlak M, Lesnial T, Kowalska T, Richter P (2007) Quality of life, anorectal and sexual functions after preoperative radiotherapy for rectal cancer: report of a randomised trial

Rodel C, Grabenbauer G, Papadopoulos T, Hohenberger W, Schmoll HJ, Sauer R (2003) Phase I/II Trial of capecitabine, oxaliplatin and radiation for rectal cancer *Journal of Clinical Oncology* 21;16:3098-3104

Stephens RJ, Thompson LC, Quirke P, Steele R, Grieve R, Couture J, Griffiths GO and Sebag-Montefiore D. (2010) Impact of short-course preoperative radiotherapy for rectal cancer on patients' quality of life: data from the Medical Research Council CR07/National Cancer Institute of Canada Clinical Trials Group C016 randomized clinical trial. *J Clin Oncol.* **28 [27]:** 4233-4239.

Twu CM, Wang HM, Chen JB, Chao TH, Mar HF (2009) Neoadjuvant concurrent chemoradiotherapy in treating locally advance rectal cancer. *Journal of the Chinese Medical Association* 72;4:179-182

Tulchinsky H, Shmueli E, Figer A, Klausner J, Rabau M (2008) An interval >7 weeks between neoadjuvant therapy and surgery improves pathologic complete response and disease-free survival in patients with locally advanced rectal cancer *Annals of Surgical Oncology* 15;10:2661-2667

Velenik V, Anderluh F, Oblak I, Strojan P, Zakotnik B (2006) Capecitabine as a radio-sensitising agent in neoadjuvant treatment of locally advanced resectable rectal cancer: prospective phase II trial *Croatian Medical Journal* 47;5:693-700

Wong RKS, Tandan V, DeSilva S, Figueredo A (2007) Pre-operative radiotherapy and curative surgery for the management of localized rectal carcinoma (Review) *Cochrane Database of Systematic Reviews*

Evidence Tables

Citation: Braendengen M, Tveit KM, Berglund A, Birkemeyer E, Frykholm G, Pahlman L, Wiig JN, Bystrom P, Bujko K, Glimelius B (2008) Randomised Phase II Study Comparing Preoperative Radiotherapy with Chemoradiotherapy in Nonresectable Rectal Cancer *Journal of Clinical Oncology* 26;22: 3687-3694

Relevant Comparison
Preoperative Chemoradiotherapy versus Preoperative Radiotherapy Alone

Design: Randomised Trial

Country: Norway

Aim: to investigate whether chemotherapy, within a combined modality treatment, could improve survival and reduce recurrence rates.

Inclusion criteria
Patients with primary, nonresectable or locally recurrent rectal carcinoma after major surgery.
Patients aged 75 years and younger with a WHO performance status of 0-2, no distant metastases, haemoglobin of at least 100g/l, WBC of at least $3.0x10^9$/l, platelet count of at least $100x10^9$/l, creatinine less than 150µmol/l and bilirubin less than 30µmol/l.

Exclusion criteria
Patients with another malignancy (except nonmelanoma skin cancer), previous RT to the pelvis or medical contraindication to the planned treatment.

Population
N=209

Interventions
Chemoradiotherapy versus radiotherapy alone

Outcomes
5-year Survival
Reduction of relapse rates (distant and local)
Local Control
Toxicity
Quality of Life

Results
All patients completed radiotherapy as planned, 85% of patients in the chemoradiotherapy group received all three cycles of concomitant chemotherapy.

- There were more anterior resections in the chemoradiotherapy group than in the radiotherapy group (47% versus 29% respectively; p=0.009).
- Complications did not differ significantly between the two groups, though infection was more common in the chemoradiotherapy group (23% versus 12%; p=.03).
- An R0 resection was achieved more often in the chemoradiotherapy group than in the radiotherapy group (84% versus 68% respectively; p=0.009).
- An R0+R1 resection was achieved in 87% of patients in the chemoradiotherapy group and in 74% in the radiotherapy group (p=0.03).
- A pathological complete response was achieved in 16% of patients in the chemoradiotherapy group and in 7% of the radiotherapy group (p=0.04). If non-resected patients were excluded, the proportions were 18% versus 9%.

Time to treatment failure (TTF) and survival
- The median follow-up for living patients was 61 months in January 2007.
- There was a statistically significant difference in TTF at five years with 63% of patients in the chemoradiotherapy group failure free versus 44% in the radiotherapy group (log-rank p=0.003).
- Cancer specific survival (CsS) at five years was statistically significantly different between the two groups; 72% in the chemoradiotherapy group versus 55% in the radiotherapy group (log-rank p=0.09).
- There was no significant difference between the two groups at 5-years for overall survival; 66% in the chemoradiotherapy group versus 53% in the radiotherapy group (log-rank p=0.09).

Local Tumour Control

- Local tumour control was higher in the chemoradiotherapy group compared with the radiotherapy group

Acute and late Toxicity
- Grade 1 and 2 diarrhoea was the most frequently reported toxicity.
- There was more grade 3 or 4 toxicity in the chemoradiotherapy group compared with the radiotherapy group (28% versus 6%; p=0.001)

General comments
Patients were recruited from March 1996 to November 2003

Follow up investigations were every 3 months during the first two years, every 6 months for the following 2 years and annually thereafter.

The mean dose of radiotherapy was more than 49Gy in both arms (range 8-56Gy).

Citation: Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M (2006) Long-term results of a randomised trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer *British Journal of Surgery* 93; 1215-1223

Relevant Comparison
Preoperative radiotherapy versus preoperative chemoradiotherapy

Design: Randomised Trial

Country: Poland

Aim: to compare survival, local control and late toxicity in two treatment groups

Inclusion criteria
- Pathological confirmation of rectal adenocarcinoma
- T3 or T4 resectable tumour
- No evidence of involvement of sphincters and an inferior margin of the tumour palpable on digital rectal exam
- No evidence of distant metastases
- WHO performance score of 0-2
- Age ≤75 years
- Written informed consent of the patient

Exclusion criteria
- Patients with a fixed tumour
- Inadequate potential for follow-up
- Previous Malignancy

Note: there were no exclusion criteria listed in this study, however as this is the same trial as the previous reported one, it is assumed that the exclusion criteria apply here too.

Population
N=312 patients included in analysis (155 in the radiotherapy arm and 157 in the chemoradiotherapy arm).

Interventions
Preoperative short-course radiotherapy versus chemoradiotherapy

Outcomes
Survival
Local Control
Late Toxicity

Results
The median follow-up time was 48 months (range: 31-69 months) with 97.5% of patients having a follow-up time of more than 3 years and 14.9% having follow-up time of more than 5 years.
No patients were lost to follow-up with regard to vital status, 3 patients were lost with regard to relapse and 14 with regard to late toxicity.

Survival
The actuarial 4-year overall survival was 67.2% in the radiotherapy group and 66.2% in the chemoradiotherapy group (p=0.960).
The hazard ratio of death in the radiotherapy group compared with the chemoradiotherapy group was 1.01 (95% CI; 0.69 – 1.48).
Actuarial 4-year disease free survival in the radiotherapy group was 58.4% compared with 55.6% in the chemoradiation group (p=0.820).
The hazard ratio of death or relapse in the radiotherapy group compared with the chemoradiotherapy group was 0.96 (95% CI; 0.69 – 1.35).

Local Control
The rate of local control was calculated in 295 patients that underwent resection with or without microscopic residual tumour. The crude rate of local recurrence was 9% in the radiotherapy group and 14.2% in the chemoradiotherapy group (p=0.17).
The actuarial 4-year cumulative incidence of local recurrence was 10.6% in the radiotherapy group and 15.6% in the chemoradiation group (p=0.210).
The hazard ratio for local recurrence in the radiotherapy group compared to the chemoradiation group was 0.65 (95% CI; 0.32 – 1.28).
The crude incidence of local failure was 14.4% in the radiotherapy group and 18.6% in the chemoradiation group

(p=0.32).
The crude incidence of distant metastases was 31.4% in the radiotherapy group and 34.6% in the chemoradiation group (p=0.54).

Late Toxicity
The crude overall incidence of late toxicity was 28.3% in the radiotherapy group and 27% in the chemoradiation group (p=0.81).
The relative risk of late toxicity in the radiotherapy group compared with the chemoradiation group was 1.05 (95% CI; 0.72 – 1.53).
The crude incidence of severe late toxicity for was 10.1% in the radiotherapy group and 7.1% in the chemoradiotherapy group (p=0.36).
The relative risk of severe late toxicity in the radiotherapy group compared with the chemoradiation group was 1.43% (95% CI; 0.67 – 3.07).

Permanent Stoma
The crude incidence of permanent stoma was 56.9% in the radiotherapy group and 51.6% in the chemoradiation group (p=0.35).
The relative risk of a permanent stoma in the radiotherapy group compared with the chemoradiation group was 1.10 (95% CI; 09 – 1.35).

General comments
Postoperative chemotherapy was optional and was more common in the radiotherapy group than in the chemoradiation group.

Citation: Bujko K, Nowacki MP, Kepka L, Oledzki J, Bebeneki M, Kryj M (2005) Postoperative complications in patients irradiated pre-operatively for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs. chemoradiation *Colorectal Disease* 7;4:410-416
Relevant Comparisons **Chemoradiotherapy versus Radiotherapy**
Design: Randomised Trial **Country**: Poland **Aim**: To compare post-operative complications in patients receiving pre-operative chemoradiotherapy and patients receiving pre-operative radiotherapy alone.
Inclusion criteria Pathological confirmation of rectal adenocarcinoma T3 or T4 resectable tumour No evidence of involvement of the sphincter Lower tumour margin determined by digital rectal examination No evidence of distant metastases WHO performance score of 0-2 Age ≤75 years Written informed patient consent
Exclusion criteria Patients with a fixed tumour Inadequate potential for follow-up Previous Malignancy
Population 312 patients randomised to receive short-term radiotherapy (155) or chemoradiation (157). 305 patients underwent surgery 153 had received short-term radiotherapy and 152 received chemoradiation 95% of patients received therapy according to the allocated schedule; 2 patients from the radiotherapy group and 7 patients from the chemoradiotherapy group did not receive pre-operative radiotherapy; 6 patients in the chemoradiation group were treated according to the radiotherapy schedule and one patient from the radiotherapy group was treated according to the chemoradiation schedule.
Interventions 5x5Gy preoperative radiotherapy followed by total mesorectal excision within 7 days *versus* chemoradiation (50.4Gy, 1.8Gy per fraction plus bolus 5-fluorouracil and Leucovorin) followed by total mesorectal excision after 4-6 weeks.
Outcomes Post-operative complications
Results There was no significant difference between the treatment groups in relation to the rates of post-operative complications (p=0.27). Expressing the values in terms of number of events (rather than number of patients with complications) the rate of complications for radiotherapy versus chemoradiation was 31% versus 22% respectively (p=0.06). For severe complications the event rates were 10% in the radiotherapy group and 11% in the chemoradiotherapy group (p=0.85) for death and 12% in the radiotherapy group versus 11% in the chemoradiotherapy group for complications that required surgical intervention (p=0.85). There was no statistically significant difference between the two groups in relation to anastomotic leakage or delayed perineal wound healing. Duration of hospital stay for the two groups differed, though not significantly; duration of hospital stay ranged from 7 – 93 days for patients in the radiotherapy group as compared with a range of 6 – 51 days for patients in the chemoradiotherapy group (p=0.09). For patients in the radiotherapy group, there was no association between overall treatment time and the risk of post-operative complications. For patients in the chemoradiotherapy group, there was a trend towards a higher risk of post-operative complications for patients with a longer overall treatment time. Median OTT was 84 days for patients with complications and 78 days for those without (p=0.054).
General comments Comparing post-operative complications was a secondary outcome in a trial comparing the rates of sphincter

preservation in patients receiving pre-operative chemoradiation or pre-operative radiotherapy alone.

Randomisation was performed by telephone to a central office and was based on the minimisation method. Patients were stratified according to the centre, character of the tumour (mobile or tethered) and the declared type of surgery (anterior resection/abdominoperineal resection)

Citation: Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Pudelko M, Kryj M, Oledzki J, Szmeja J, Sluszniak J, Serkies K, Kladny J, Pamucka M, Kkolowicz (2004) Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy *Radiotherapy and Oncology* 72;15-24

Relevant Comparison **Chemoradiotherapy versus Radiotherapy**

Design: Randomised Trial **Country**: Poland **Aim**: to verify whether preoperative conventionally fractionate chemoradiation offers an advantage in sphincter preservation in comparison with pre-operative short-term irradiation

Inclusion criteria
- Pathological confirmation of rectal adenocarcinoma
- T3 or T4 resectable tumour
- No evidence of involvement of sphincters and an inferior margin of the tumour palpable on digital rectal exam
- No evidence of distant metastases
- WHO performance score of 0-2
- Age ≤75 years
- Written informed consent of the patient

Exclusion criteria
- Patients with a fixed tumour
- Inadequate potential for follow-up
- Previous Malignancy

Population
312 patients were randomised; 155 to Arm A and 157 to Arm B.

Interventions
Patients were randomised to Arm A (5x5Gy preoperative irradiation given in one week followed by surgery to be performed within 7 days) or Arm B (radiochemotherapy to total dose of 50.4Gy given with 1.8Gy per fraction in 5.5 weeks concomitantly with two courses of 5-fluorouracil and Leucovorin followed by surgery within 4-6 weeks.

Outcomes
The primary outcome for this study was the effect of treatment on sphincter preservation
Other outcomes included acute postirradiation toxicity and postoperative pathology

Results
Protocol Violations
There were a number of protocol violations in both arms;
- 6 patients randomised to arm B were treated according to arm A while 1 patient randomised to arm A was treated according to arm B
- 4 patients did not receive radiotherapy and surgery
- 9 patients were operated on without preoperative radioatherapy
- 3 patients underwent radiotherapy but did not have surgery
- There were 3 deviations from the protocol in arm A and 16 deviations in arm B
- In arm B, 17 patients did not undergo the second course of chemotherapy

Surgery
Prior to surgery, complete clinical response was reported in 2% of patients in the radiation arm and in 13% in the chemoradiation arm (p<0.001).
For patients that underwent tumour resection, the sphincter preservation rate for a lesion located with 2-3cm of the anal verge was 12% (4/34); 4-5cm was 45% (46/102), 6-7cm was 82% (83/101) and >7cm was 96% (52/55).
Sphincter preservation rate in the radiation arm was 61% compared with 58% for the chemoradiation arm (p=0.57).
The rates of patients with all postoperative complications was 23% for the radiation group versus 15% for the chemoradiation group (p=0.12) and for severe complications (death or complications requiring surgical intervention) was 12% for the radiation group versus 9% for the chemoradiation group (p=0.38).

Acute Postirradiation Toxicity
There were 2 sudden deaths due to cardiac arrest in the arm B

The rates of patients with all complications was 24% in arm A versus 85% in arm B (p<0.001) and for grade III and IV complications (including death) the rate was 3% in arm A versus 18% in arm B (p<0.001).

Postoperative Pathology
The was better tumour response in patients receiving short-term irradiation
There were more microscopic complete responses in the radiotherapy group (16%) compared with the chemoradiotherapy group (1%), p<0.001

General comments
The final decision on sphincter preservation was based on tumour status at the time of surgery and not before irradiation.

Randomisation was performed by telephone to the central trial office and based on the minimisation method.

Citation: Birgisson H, Pahlman L, Gunnersson U, Limelius B (2007) Late adverse effects of radiation therapy for rectal cancer – a systematic overview *Acta Oncologica* 46;504-516

Relevant Comparison
Radiotherapy and chemoradiotherapy

Design: Systematic Review

Country: Multiple

Aim: to provide a comprehensive overview of published studies on late adverse effects related to radiotherapy for rectal cancer

Inclusion criteria
Meta-analyses, reviews, randomised trials and clinical trials
External beam radiotherapy
Chemoradiotherapy
Preoperative and postoperative

Exclusion criteria
Editorials, letters and practice guidelines
Intraoperative and bracytherapy

Population

Interventions

Outcomes
Late adverse effects due to radiotherapy included gastrointestinal disorders, neurological problems, anal, rectal, urinary and sexual dysfunction, pelvic or hip fractures, thromboembolic diseases and secondary cancers. In some studies, quality of life was also addressed.

Results
Anal and rectal dysfunction
Anal and rectal dysfunction relates to symptoms such as gas, liquid or solid faeces, incontinence, rectal emptying problems, frequent bowel movements and diarrhoea.

Gastrointestinal tract
The majority of studies examining late adverse effects were preoperative 5x5Gy radiotherapy, though 4 trials did not use this regimen.
The small bowel was affected most often by pelvic irradiation while the colon, rectum and anus were also affected. Resulting symptoms included diarrhoea, bleeding, abdominal pain and obstruction due to stenosis, adhesions or rarely malabsorption, necrosis, perforation and fistulation.

Anal and Rectal Dysfunction

	Type	Follow-up	Adverse Effects	Irradiated Patients (radiotherapy only)	Irradiated Patients (chemoradiotherapy)	Non-irradiated patients	P Value
Dahlberg et al (1998)	Questionnaire	5-year	Bowel Frequency more than 4 times a day	20%		8%	
			Incontinence to loose stools	50%		24%	
			Incontinence to solid stools	14%		3%	
			Emptying difficulties	52%		36%	
Pollack et al. (2006b)	Randomised Trials – Follow-up	14-year	Faecal incontinence	57%		26%	P<0.05
			Soiling	38%		16%	
Peeters et al (2005)	Randomised Trial	5-year	Faecal incontinence	62%		38%	P<0.05
			Faecal	32%		17%	P<0.05

			incontinence (night)				
Pietrzak et al (2006)	Randomised Trial		Faecal incontinence to loose stools	72%	65%		
			Difficulty discriminating between gas and stools	59%		66%	
Lundby et al (2005)	Randomised Trial	17-year	Faecal incontinence	60%		8%	P<0.05
			Urgency	53%		0%	
			Increased bowel frequency (>2 stools per day)	80%		23%	
Kollmorgan et al (1994)	Retrospective Case Series	3-year	Bowel Frequency (<4 bowel movements per day)		22%	83%	
			Faecal incontinence		56%	7%	

Bowel Obstruction

Study	Type	Follow-up	Adverse Effects	Irradiated Patients (radiotherapy only)	Non-irradiated patients	P Value
Holm et al (1996)	Randomised Trial	5-year	Small bowel obstruction	13%	8.5%	
Birgission et al (2005)	Randomised Trial	13-year	Small bowel obstruction	9%	4%	
Peeters et al (2005)	Randomised Trial	5-year	Small bowel obstruction	11% of patients suffered small bowel obstruction with no difference between the groups.		

Other Gastrointestinal Disorders
The Stockholm Trials reported and increase risk for fistulas in irradiated patients (Holm et al, 1996); there was an increased risk of anastomotic strictures with postoperative chemoradiotherapy when compared with preoperative chemoradiotherapy (12% compared with 4%, p=0.003).

Urinary Tract Dysfunction
One small study (Prabhudesai et al, 2005) reported more urinary dysfunction problems in irradiated patients compared with non-irradiated patients. Late follow-up of the Stockholm trials (Pollack et al, 2006a) showed increased urinary incontinence in the irradiated patients.
From larger trials however there did not appear to be a difference in effects on urinary tract in irradiated patients versus non-irradiated patients (Sauer et al, 2004; Peeters et al, 2005; Birgisson et al, 2005; Holm et al, 1996 and Frykholm et al, 1993).
In the Western Norwegian trial (Dahl et al, 1990) late urinary tract symptoms were reported in 4% of all patients and in 3% of all patients in the Uppsala trial (Frykholm et al, 1993). Bladder problems were reported in 2% of preoperatively treated and 4% of postoperatively treated patients (p=0.21) (Sauer et al, 2004).

Sexual Dysfunction
From one trial (Marijnen et al, 2005), sexual activities of male patients still active preoperatively decreased to 67% in irradiated patients and 76% in non-irradiated patients. In female patients there was a reduction to 72% in the irradiated group and 90% in the non-irradiated group.

Second Cancers
One study concluded that irradiated patients had increased risk of developing secondary cancers compared to those treated with surgery only; follow up time was 14 years and second cancers occurred in 9.5% of irradiated patients compared with 4.3% of non-irradiated patients.

Quality of Life
There were no studies on quality of life measuring the late adverse effects of radiotherapy for rectal cancer and only a small number measuring early adverse effects.
Quality of life was analysed mainly in relation to bowel function; Dahlberg et al (1998) commented that 30% of irradiated patients reported restrictions to social life compared to only 10% of non-irradiated patients.

Marijnen et al (2005) reported no difference between irradiated and non-irradiated patients in relation to quality of life.

Fractures
Long-term follow-up revealed a higher risk for femoral neck and pelvic fractures in irradiated patients when analysing the Stockholm I and II trials together though the difference was not significant (Holm et al, 1996). Long-term follow up of two trials did not reveal any increased risk of fractures in irradiated patients (Peeters et al, 2005; Birgisson et al, 2005).

Thromboembolic Disorders
From the Stockholm I and II trials, venous thromboembolism was more common in the irradiated group when compared to the non-irradiated group (Holm et al, 1996). No difference was observed between the treatment groups regarding venous or arterial or cardiovascular diseases (Peeters et al, 2005; Birgisson et al, 2005).

Mortality
There was no increased death rate in irradiated patients compared with non-irradiated patients (Folkesson et al, 2005).

General comments
The search was limited to English language articles
Late adverse events were defined as adverse effects persisting or occurring more than 6 months from the start of radiotherapy.
The grading systems were based on a severity scale from no symptoms (grade 0) to death (grade 5).
Study design influenced whether mild symptoms (grade 1-2) were detected, with questionnaire and interview based studies detecting the milder symptoms while register or hospital record based studies only detected the more severe symptoms.

References of Included Studies (For systematic reviews):
Full citations in review

Colorectal Cancer Coolaborative Group (2001)	Temple et al (2003)	Sauer et al (2004)	Birnbaum et al (1994)
Glimelius et al (2003)	Fajardo et al (2005)	Birgisson et al (2005)	Kollmorgan et al (1994)
Bakx et al (2006)	Geckenberger and Flentje (2005)	Birgisson et al (2005)	Mak et al (1994)
Cummings et al (1986)	Dahl et al (1990)	Marjinen et al (2004)	Lewis et al (1995)
Gerard et al (1995)	Frykholm et al (1993)	Peeters et al (2005)	Minsky et al (1995)
Letschert et al (1995)	Holm et al (1996)	Lundby et al (2005)	Wagman et al (1998)
Coia et al (1995)	MRC-2 (1996)	Pollack et al (2006)	Miller et al (1999)
Camilleri-Brennan et al (1998)	MRC-3 (1996)	Pollack et al (2006)	Olagne et al (2000)
Ooi et al (1999)	Lundby et al (1997)	Bujko et al (2006)	Caffo et al (2002)
Johnston et al (2003)	Dahlberg et al (1998)	Letschert et al (1990)	Dehni et al (2002)
Birnbaum et al (1994)	Lewis et al (1995)	Miller et al (1999)	Dehni et al (2002)
Kollmorgan et al (1994)	Minsky et al (1995)	Olagne et al (2000)	Van Duijvendijk et al (2002)
Mak et al (1994)	Wagman et al (1998)	Caffo et al (2002)	Prabhudesai et al (2005)
Mohiuddin et al (2006)			

Citation: Birgisson H, Pahlman L, Gunnersson U, Glimlelius B (2005) Adverse Effects of Preoperative Radiation Therapy for Rectal Cancer: Long-Term Follow-up of the Swedish Rectal Cancer Trial *Journal of Clinical Oncology* 23;34:8697-8705
Relevant Comparison **Preoperative Radiotherapy versus surgery alone**
Design: Randomised Trial **Country**: Sweden **Aim**: To analyze the occurrence of sub acute and late adverse effects in patients treated with preoperative irradiation for rectal cancer
Inclusion criteria Patients participating in the Swedish Rectal Cancer Trial (1987-1990)
Exclusion criteria Patients participating in the Swedish Rectal Cancer Trial (1987-1990)
Population N=1147 patients randomised to preoperative radiotherapy or surgery alone
Interventions 5x5Gy radiotherapy with surgery a week later versus surgery alone
Outcomes
Results Early and late admissions were defined as admissions occurring before and after 6 months from the resection of the primary rectal cancer. To avoid confounding from diagnoses related to the presence of cancer, admissions for non-curatively treated patients and admissions during the 3 months before diagnosis of a local recurrence or metastasis were excluded. For the 1,147 patients matched to the Swedish Hospital Discharge Register, 6496 admissions were registered of which 999 were excluded as the related to the non-curatively treated patients. 1,712 were excluded due to cancer recurrence and 343 were excluded due to secondary malignancy. More patients were excluded from the non-irradiated group than from the irradiated group. A larger proportion of the irradiated patients survived for more than 5 and 10 years than did the non-irradiated group, thus the number of person-years at risk for hospital admissions was higher in the irradiated group. 73% (n=661) of patients analysed were admitted to hospital at least once after treatment of primary rectal cancer; more patients from the irradiated group were admitted both in the early and late post-operative periods. There was no difference in relative risk (RR=1.07; 95% CI, 0.91-1.26) between the irradiated and non-irradiated groups. There was however, an increase in relative risk for early admissions in irradiated patients (RR=1.64; 95% CI, 1.21-2.22). No difference was observed between the groups for late admissions (RR=0.95; 95% CI, 0.8-1.12). An increase in relative risk among irradiated patients during the first 6 months was observed for infections (RR=7.67; 1.76-33.39) and gastrointestinal diagnoses (RR=2.57; 95% CI, 1.55-4.26). An increase in relative risk among irradiated patients was observed for non-specific infections (n=10; RR=8.06; 95% CI 1.02-63.69). The risk of cardiac arrhythmia was reduced in the irradiated group (RR=0.57; 95% CI, 0.36-0.91). In relation to gastrointestinal diagnosis, increased relative risks were observed in irradiated patients for bowel obstruction, nausea and unspecific abdominal pain, whereas the risk for inguinal hernia was lower among irradiated patients.
General comments This study was not included in the Cochrane Review (Wong et al 2007) although it fell within the timelines for the literature search. Patients were matched against the Swedish Hospital Discharge Register which includes all hospital admissions in Sweden and records primary and secondary diagnosis, date of admission and discharge, and the hospital and department.

Citation: Ceelen WP, Van Nieuwenhove Y, Fierens K (2009) Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer (Review) *Cochrane Database of Systematic Reviews*

Relevant Comparisons
Preoperative Chemoradiotherapy versus preoperative radiotherapy alone

Design: Systematic Review

Country:

Aim: To compare preoperative radiotherapy with preoperative chemoradiotherapy in patients with resectable stage II and stage III rectal cancer

Inclusion criteria
Studies which randomised resectable stage II and stage III rectal cancer patients to at least one arm of preoperative radiotherapy alone or at least one arm of preoperative chemoradiotherapy.

Exclusion criteria

Population
N = 4 studies

Interventions
Preoperative Radiotherapy or Preoperative Chemoradiotherapy using fractionated external radiotherapy, followed by surgery with curative intent (rectal amputation or sphincter preserving anterior resection using open or laparoscopic approach).

Outcomes
Primary: Overall survival at 5 years
　　　　　Local recurrence at 5 years

Secondary: Disease free survival (DFS)
　　　　　Metastasis Rate
　　　　　Pathological Complete Response Rate
　　　　　Clinical Response Rate
　　　　　Sphincter Preservation Rate
　　　　　Acute Toxicity
　　　　　Postoperative Mortality and Morbidity
　　　　　Anastomotic Leak Rate

Results
Risk of Bias in included studies
- Randomisation was adequately performed in all four included studies using communication with a central office.
- Randomisation was based on the minimisation method in three studies and not specified in the fourth study (Bujko, 2006; Gerard, 2006; Bosset, 2006).
- None of the studies were described as being double blinded or using blinded outcome assessment.
- There were no imbalances between treatment arms in the number of patients that did not undergo the complete trial procedure.
- Three of the included trials were performed on an intention to treat basis (Bujko, 2006; Gerard, 2006; Bosset, 2006).

Overall Survival
From 3 studies (Boulis-Wassif, 1984; Gerard, 2006; Bosset, 2006) there was no statistically significant difference in survival at 5 years between patients in the radiotherapy group (647/993; 65.2%) and patients in the chemoradiation group (644/1007; 63.9%): Odds Ratio 0.95, 95% CI 0.79-1.14, p=0.58. No significant hetereogeneity was observed between the studies (X^2=3.78, p=0.15, I^2=47%), this may be explained by the different findings from one study (Boulis-Wassif, 1984) as the results from the two more recent trials are in close agreement and are both much larger than the older trial.

Local Recurrence
From 3 studies (Boulis-Wassif, 1984; Gerard, 2006; Bosset, 2006), there was significant difference in the rates of local recurrence at 5 years in patients in the radiotherapy group (122/740; 16.5%) compared with patients in the chemoradiation group (71/754; 9.4%): Odds Ratio 0.53, 95% CI 0.39-0.72, p<0.001. There was no significant heterogeneity between the studies, though this was borderline and the I^2 value was above 50% (X^2=4.24, p=0.12, I^2=53%), again this could be explained by the different findings of the one study (Boulis-Wassif, 1984) as the

results from the two more recent trials are in close agreement and are both much larger than the older trial.

Disease Free Survival
From 2 studies (Bosset, 2006 and Gerard, 2006) the 5 year disease free survival was 57.5% in the chemoradiotherapy group and 54.9% in the radiotherapy group (OR 1.11, 95% CI 0.92-1.34, p=0.27). There was no significant heterogeneity between the studies (X^2=1.10, p=0.64, I^2=0%)

Grade III or IV Toxicity
From 3 studies (Bujko, 2006; Gerard, 2006; Bosset, 2006), there was a statistically significant difference in the occurrence of Grade III or IV toxicity (OR 4.1, 95% CI 1.68-10, p=0.002). There was significant heterogeneity between the studies (Tau^2=0.49, X^2=10.57, p=0.01, I^2=81%) which remained after reanalyses using the random effect assumption.

Sphincter Preservation Rate
There was no significant difference in the sphincter preservation rates, with sphincter preservation possible in 551/1111 (49.6%) patients in the chemoradiotherapy group compared with 527/1108 (47.6%) patients in the radiotherapy group (OR 1.1, 95% CI 0.92-1.31, p=0.29).

Postoperative Mortality and Morbidity
Postoperative 30 day mortality was observed in 31/1112 (2.8%) patients in the chemoradiotherapy group and in 21/1117 (1.9%) patients in the radiotherapy group though there was no statistically significant difference (OR 1.48, 95% CI 0.84-2.6, p=0.17).
Similarly the differences between the two groups in relation to postoperative 30 day morbidity or anastomotic leak rate were not statistically significant (OR 0.84, 95% CI 0.68-1.03, p=0.1 and OR 1.03, 95% CI 0.57-1.85, p=0.93 respectively).

Pathological Complete Response
From 4 studies, pathological complete response was 11.8% in the chemoradiotherapy group and 3.5% in the radiotherapy group (OR 3.65, 95% CI 2.52-5.27, p<0.0001) and no significant heterogeneity was observed between the studies.

General comments
- Search dates for the review were 1975 – 2007 and included such databases as Embase, Web of Science, Cochrane Trial register and Pubmed.
- Methodological details considered relevant for potential bias included sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome.
- Radiotherapy dose was converted to biologically equivalent dose (BED)
- Heterogeneity analysis was performed using the Q test, with significance accepted when p<0.1

References of Included Studies (For systematic reviews):
Bousset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, Daban A, bardet E, Beny A, Ollier JC, EORTC Radiotherapy Group Trial 22921 (2006) Chemotherapy with Preoperative Radiotherapy in rectal cancer *The New England Journal of Medicine*; 355:1114-1123

Boulis-Wassif S, Gerard A, Loygue J, Camelot D, Buyse M, Duez N (1984) Final results of a Randomised Trial on the Treatment of Rectal Cancer with Preoperative Radiotherapy Alone or in Combination with 5-Fluorouracil, Followed by Radical Surgery *Cancer*;53:1811-1818

Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M (2006) Long-term Results of a randomised trial comparing preoperative short course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer *British Journal of Surgery* 93;1215-1223

Gerard JP, Conroy T, Bonnetain F, Bouche O, Chapet O, Closon-Dejardin MT, Untereiner M, Leduc B, Francois E, Maurel J, Seitz JF, Buecher B, Mackiewicz R, Ducreux M, Bedenne L (2006) Preoperative Radiotherapy With or Without Concurrent Fluorouracil and Leucovorin in T3-T4 Rectal Cancers: Results of FFCD 9203 *Journal of Clinical Oncology* 24;4620-4625

Citation: Chessin D, Enker W, Cohen A, Paty P, Weiser M, Saltz L, Minsky B, Wong WD, Guillem JG (2005) Complications after preoperative combines modality therapy and radical resection of locally advanced rectal cancer: a 14 year experience from a specialty service *Journal of the American College of Surgeons* 200;6:876-882
Relevant Comparison   **Preoperative Chemoradiotherapy versus Surgery Alone**
Design: Prospective Case Series   **Country**: USA   **Aim**: to determine the incidence of post-operative complications and associated clinicopathological factors
Inclusion criteria   Locally advanced primary rectal adenocarcinoma (T3 to 4 or N1, clinically bulky or both)   Biopsy proven rectal adenocarcinoma (median distance from anal verge 6cm; range 0-15cm)
Exclusion criteria   Patients with recurrent rectal cancer
Population   N=297
Interventions   Preoperative chemoradiation   277 patients received 5-FU based chemotherapy either by bolus (n=259) or continuous infusion (n=18)   20 patients had preoperative chemotherapy with irinotecan hydrochloride (CPT-11).   External beam radiotherapy (EBRT) was delivered with a median dose of 5,040cGy; range 1,980-5400cGy.
Outcomes   Postoperative Morbidity   Factors associated with postoperative morbidity   Pelvic infectious morbidity   Low anterior resection and proximal faecal diversion   Relapse Free survival   Overall survival
Results   Postoperative Morbidity   Median follow-up was 43.9 months (range 0.8 to 128.6 months).   No postoperative mortalities within 30 days of operation were reported for the study population.   173 complications were reported, 145 of which were classed as major complications with 98 patients recording at least one major complication.   The most common major postoperative complication was small bowel obstruction (11%) and wound infection (10%).   Factors Associated with postoperative morbidity   Major preoperative comorbidities such as heart, lung, liver disease or diabetes were predictive of major postoperative complications (p=0.02).   Gender, procedure, distance of tumour from the anal verge, preoperative endorectal ultrasound stage and postoperative pathologic tumour stage were not predictive of postoperative morbidity.   Pelvic Infectious Morbidity   There were 8 (4%) anastomotic leaks and 9 pelvic abscesses (4%) in patients treated with low anterior resection and faecal diversion occurred in 2/53 patients with tumour located 0 to 5cm from the anal verge and in 4/66 patients with tumour located 6 to 10 cam from the anal verge.   Pelvic sepsis with no faecal diversion occurred in 4/10 patients with tumour located 0 to 5cm from the anal verge and in 7/76 patients with tumour located 6 to 10cm from the anal verge.   No pelvic septic complications were reported for patients with tumour located 11cm or more from the anal verge.   Perineal wound complications occurred in 24% of patients undergoing abdominoperineal resection.   LAR and proximal faecal diversion   In patients treated with LAR and proximal faecal diversion there was a significantly increased rate of small bowel obstruction when compared with patients undergoing LAR and no faecal diversion (p=0.04) but no significant difference in rates of anastomotic leak or pelvic abscess.

	Median Tumour Level	Small Bowel Obstruction		Anastomotic Leak		Pelvic Abscess	
		n	%	n	%	n	%
Diversion	6	21	18	3	3	3	3
No Diversion	8	7	8	5	6	6	7
P Value		0.04		N/S		N/S	

Table: Relationship between faecal diversion after LAR and major postoperative complications

The significant difference in rates of small bowel obstruction was accounted for by an increased rate of hospital readmission for nonoperative management of small bowel obstruction.

	Diversion (n=119)	No Diversion (n=91)	P Value
Operative, n (%)	7 (6)	2 (2)	NS
Nonoperative (readmission), n (%)	14(12)	4(4)	0.04
Nonoperative (no readmission), n (%)	0(0)	1(1)	NS

Table: Management of postoperative small bowel obstruction in patients with and without faecal diversion after low anterior resection

Relapse Free Survival
Relapse free survival was not significantly different between the groups that did or did not experience a major postoperative complication (p=0.1).

Overall Survival
Median overall survival in the group experiencing major postoperative complications was 90 months and in the group not experiencing major postoperative complications was 95 months.
Overall survival did not differ significantly between the groups that did or did not experience a major post-operative complication (p=0.09).

Citation: Coco C, Valentini V, Manno A, Mattana C, Verbo A, Cellini N, Gambacorta M, Covino M, Mantini G, Micciche F, Pedretti G, Petito L, Rizzo G, Cosimelli M, Impiombato F, Picciocchi A (2006) Long-term results after neoadjuvant radiochemotherapy for locally advanced resectable extraperitoneal rectal cancer *Diseases of the Colon and Rectum* 49;3:311-318	

Relevant Comparison
Preoperative Chemoradiotherapy versus Surgery Alone

Design: Case Series

Country: Italy

Aim: to evaluate the long-term outcome in locally advance resectable extraperitoneal rectal cancer treated by preoperative radiochemotherapy.

Inclusion criteria
Patients with locally advanced rectal cancer, extramural spread (T3), with or without lymph node involvement: N0-N+.

Exclusion criteria
Distant metastases

Population
N=87

Interventions
Concomitant radiochemotherapy: bolus IV mytomycin C, 10mg/m^2, day 1 plus 24 hour continuous infusion IV 5-flourouracil (5-FU) 1000 mg/m^2, days 1-4 and concurrent external beam radiotherapy (37.8Gy with conventional fractionation of 1.8Gy/day for 5 sessions per week).

Outcomes
Overall Survival
Cancer-related survival
Local and distal recurrence rates

Results
Median follow-up was 108 months (range 10-169) with complete follow-up for living patients of at least nine years. 14 patients developed local recurrence, of which 6 developed recurrence at two years, 10 at five years and 14 at ten years (cumulative).
At univariate analysis, pathologic T stage was the only factor that influenced the occurrence of local relapse but it was not statistically significant (T0-2 vs. T3-4; p=0.094).

Distant metastases occurred in 21 patients, 9 in the liver, 8 in the chest and 1 each in the brain, lumboaortic nodes and liver and chest together. 19 cases occurred within five years after surgery and 2 occurred more than 5 years after surgery.
At univariate analysis, clinical stage and lymph node invasion were positively correlated to distant metastasis (stage 2 vs. stage 3 and No vs. N+; p=0.028 in both cases). Other factors potentially affecting distant metastasis are listed below (table 1)

Factor	Comparison	P value
Lymph node involvement	N0 vs. N+	0.004
pTNM stage	stage 0-1 vs. stage 2-3	0.003
pT stage	pT0-pT2 vs. pT3	0.006
pN stage	pN0 vs. pN+	<0.001

Table 1: results of univariate analysis of factors potentially influencing distant metastases (significant factors only)

On multivariate analysis only pT stage (p=0.025) and pN stage (p=0.001) remained significantly positively correlated to the occurrence of distant metastases.

Actuarial overall survival at 5 years was 75.5%, at 7 years was 67.8% and at 10 years was 60.4%; actuarial cancer-related survival at 5 years was 77.9%, at 7 years was 70% and at 10 years was 65.8%. At univariate analysis, factors found to be correlated with survival were TNM stage at clinical restaging after neoadjuvant therapy and in particular, lymph node involvement as well as pTNM, pT stage and pN stage. On multivariate analysis pTNM (p=0.049), pT (p=0.007) and pN (p=0.003) were found to influence survival when considered separately.

Factor	Comparison	P value
TNM post RCT	Stage 0-2 vs. stage 3	0.041
N stage post RCT	N0 vs. N+	0.002
pTNM	Stage 0-1 vs. stage 2-3	0.041
pT	pT0-pT2 vs. pT3	0.033
pN	pN0 vs. pN+	0.002

Table 2: Results of univariate analysis of factors potentially influencing survival

General comments

All patients in this case series were treated with chemoradiotherapy and there is therefore nothing to compare the results to making it difficult to determine whether there is any benefit to chemoradiotherapy over other preoperative treatments.

Citation: De Bruin AFJ, Nuyttens JJ, Ferenschild FTJ, Planting AST, Verhoef C, de Wilt JHW (2008) Preoperative chemoradiation with capecitabine in locally advanced rectal cancer *Netherlands Journal of Medicine* 66;2:71-76
Relevant Comparison **Preoperative Chemoradiotherapy** **Capecitabine**
Design: Phase II Trial **Country**: The Netherlands **Aim**: To evaluate the toxicity and efficacy of preoperative chemoradiation using oral 5-Fu prodrug capecitabine in locally advanced rectal cancer.
Inclusion criteria Histologically proven adenocarcinoma of the rectum Patients with large T_3 or T_4, N_x or any T_3, N_{1-2} rectal adenocarcinoma ECOG performance status ≤2 Aged between 18 and 80 years Adequate liver, renal and bone marrow function (full details provided in the paper)
Exclusion criteria Severe comorbidity such as cardiomyopathy or other cardiovascular disease Known risk of adverse reaction to fluoropyrimidines Patients participating in other trials or receiving any investigational drugs
Population N=60
Interventions 825mg/m^2 capecitabine was administered orally twice a day on radiotherapy days (2 hours before and 12 hours after). Radiotherapy was delivered in 25 fractions of 2.0Gy. Surgery was performed 6 to 10 weeks after completing chemoradiation

Outcomes
Primary: Toxicity (haematological and nonhaematological)
       Grade of tumour down staging
       Pathological complete response
 	
Secondary: Rate of Sphincter Preservation
       Post-operative complications

Results All patients completed radiotherapy; 2 patients, in one male patient reporting severe chest pain while taking capecitabine and in one female experiencing grade III diarrhoea requiring intravenous fluid replacement. *Toxicity* Toxicity was moderate, no patient suffered grade IV toxicity and 5% suffered grade III toxicity (radiation dermatitis 3% and diarrhoea 2%). Haematological toxicity was mild with grade II anaemia in 7%, leucocytopenia in 12% and neutropenia in 3% of patients. *Response* All patients underwent definitive surgery, 19 had abdominal perineal resection, 16 had Hartmanns resection and 25 had low anterior resection. A complete pathological response was achieved in 13% (8) patients; overall tumour and nodal downstaging occurred in 85% of patients, tumour downstaging was observed in 67% of patients and overall nodal downstaging occurred in 84% of patients. No tumour progression was observed during chemoradiation. Final pathology demonstrated T_0 in 13% of patients, T_1 in 10% of patients, T_2 in 23% of patients, T_3 in 45% and T_4 in 8% of patients.

Citation: De Paoli A, Chiara S, Luppi G, Friso ML, Beretta GD, Del Prete S, Pasetto L, Santantonio M, Sarti E, Mantello G, Innocente R, Frusctaci S, Corvo R, Rosso R (2006) Capecitabine in combination with preoperative radiation therapy in locally advanced, resectable, rectal cancer: a multicentric phase II study *Annals of Oncology* 17;2:246-251
Relevant Comparison **Preoperative Chemoradiotherapy** **Capecitabine**
Design: Phase II Trial **Country**: Italy **Aim**: to evaluate tolerance and efficacy of preoperative treatment with capecitabine in combination with radiation therapy (RT) in patients with locally advanced, resectable rectal cancer.
Inclusion criteria Histologically confirme diagnosis of locally advanced, resectable clinical stage T_3, or T_4, N_0 or N_{1-2}, M_0 suitable for preoperative combined radiochemotherapy. ECOG performance status ≤2 Age between 18 and 80 years Adequate haematological, liver and renal function.
Exclusion criteria Previous radiotherapy on the pelvic region Previous chemotherapy Patients with serious illness or medical conditions including significant cardiac disease History of significant neurological or psychiatric disorders Serious uncontrolled active infection Pregnant or lactating women and women of child-bearing age unless using a reliable method of contraception Sexually active males unwilling to practice contraception during the study Patients with a history of previous malignancy except cured non-melanoma skin cancer and in-situ cervical carcinoma Patients with absolute neutrophil count $<2x10^{-9}$/l or platelet count $<100x10^{-9}$/l, total bilirubin >1.5 times the upper normal limits of the institutional normal values, transaminase or alkaline phosphatase >1.5 times the upper normal levels and creatinine >1.6 mg/dl.
Population N=53
Interventions 825mg/m^2 capecitabine administered orally twice a day throughout the course of radiotherapy (2hours before and 12 hours after). Radiation dose of 45Gy, followed by a boost of 5.4Gy limited to the tumour and corresponding mesorectum for a total dose of 50.4Gy. Radiotherapy was delivered in 1.8Gy/day fractions for 5 days over 5.5 weeks.
Outcomes Pathological complete response Clinical response rate Safety
Results *Toxicity and compliance to treatment* 15 patients require dose adjustment of capecitabine and capecitabine treatment was discontinued in 3 of the 15 patients. 72% of patients received the full capecitabine dose, 17% received 81-95% of the dose and 11% had 48-74% of the planned dose of capecitabine. Radiotherapy compliance was 96% (2 patients did not complete the planned radiotherapy dose) There were no grade IV toxicities or treatment related deaths reported Non haematological toxicity of grade I or II occurred most commonly with diarrhoea (40%) and procitis (34%) the most common Haematological toxicity was observed most commonly in this study; 42% of patients experienced grade I and 26% experienced grade II leucopenia. *Clinical response* The overall response rate was 58%; 4% had a complete pathological response, 54% had a partial response and 42% had minor or stable disease. There was no disease progression on primary tumour in any patient, though 2

patients had liver metastases at preoperative restaging or at operation with pathologic response on the primary tumour.

Surgery
51/53 patients underwent surgical resection; 48 had a radical R_0 resection and 3 had a trans anal full thickness excision.
Sphincter saving surgery was achieved in 36/51 patients.
59% (20/34) of patients with tumour distance of ≤5cm received sphincter saving surgery

Pathologic response and down staging
Overall tumour down staging was reported in 57% of patients (29/51).
Nodal down staging was observed in 78% of operated patients (22/28) with clinical N_1-N_2 disease.
There was no evidence of nodal involvement in 79% of patients (38/48) undergoing radical surgery.

Citation: Desai SP, El-Rayes BF, Ben-Josef E, Greenson JK, Knol JA, Huang EH, Griffith KA, Philip PA, McGinn CJ, Zalupski MM (2007) A phase II study of preoperative capecitabine and radiation therapy in patients with rectal cancer *American Journal of Clinical Oncology* 30;4:340-345
Relevant Comparison **Preoperative Chemoradiotherapy** **Capecitabine**
Design: Phase II Trial **Country**: USA **Aim**: to evaluate the safety and efficacy of preoperative capecitabine and radiation therapy in patients with locally advanced rectal cancer
Inclusion criteria Pathologic confirmation of adenocarcinoma of the rectum. Distal extent of tumour to be within 12cm of the anus as measured by sigmoidoscopy with disease staged as ≥UT3 of N1 as determined by physical examination, endoscopic ultras sound and CT scan of the pelvis. Age 18 years or older Zubrod performance status of ≤2 Adequate organ function
Exclusion criteria Pregnant or lactating patients History of pelvic irradiation or chemotherapy within 6 months prior to enrollment No other active systemic malignancy or serious co-morbid medical or psychiatric condition that may interfere with delivery of treatment
Population N=30
Interventions 5.5 weeks of radiation therapy in 28 daily fraction plus six weeks of capecitabine, taken twice a day, 7 days a week at a total daily dosage of 1330 mg/m^2. Surgery was planned for 6-8 weeks after completion of chemoradiotherapy
Outcomes Safety Toxicity Evaluation of efficacy
Results *Treatment received and associated toxicity* Preoperative chemoradiotherapy was generally well tolerated and there were no treatment related deaths. 28/30 patients (93%) completed the full planned course of chemoradiotherapy. 1 patient discontinued chemotherapy due to grade III diarrhoea, but continued with radiotherapy 1 patient discontinued chemoradiotherapy due to grade IV diarrhoea requiring hospitalisation. 29% of patients required treatment interruptions, commonly due to diarrhoea, hand-foot syndrome or radiation dermatitis. Surgical resection was performed on 90% of patients (27/30). *Pathologic and Clinical Response* 3/27 patients that underwent surgical resection had a complete pathologic response (11.1%, 95% CI; 2.4-29.2); 7/27 patients (25.9%, 95% CI; 11.1-46.3) had minimal microscopic evidence of tumour present in the pathologic specimen for an overall grade I response rate of 37% (95% CI; 19.4-57.6). *Follow-up* As of May 2006, 24 patients were known to be alive with a median follow-up of 23 months; 18 have no evidence of disease, 1 patient has local recurrence, 5 patients have developed distant disease. Of the 25 patients enrolled without metastatic disease 94.1% (95% CI; 65-99.1) were progression free at 2 years and 71.7% (95% CI; 40.5-88.5) were progression free at 3 years. Patients achieving a grade I pathologic response to neoadjuvant therapy appeared more likely to remain disease free as compared with grade 2 or 3 responses though the difference was not statistically significant (p=0.3709).

Citation: Elwanis MA, Maximous DW, Elsayed MI Mikhail NNH (2009) Surgical treatment for locally advanced lower third rectal cancer after neoadjuvant chemoradiation with capecitabine; prospective phase II trial *Worl Journal of Surgical Oncology* 7;52
Relevant Comparison **Preoperative Chemoradiotherapy** **Capecitabine**
Design: Prospective Phase II Trial **Country**: Egypt **Aim**: To evaluate the rate of anal sphincter preservation in low lying, resectable, locally advance rectal cancer and the resectability rate in unresectable cases after preoperative chemoradiation with oral Capetcitabine
Inclusion criteria Patients with lower third rectal carcinoma with no clinical evidence of metastases Patients with T3-T4, N0-N1 disease Patients with ECOG performance status ≤2
Exclusion criteria Previous pelvic irradiation History of Malignant Disease Any other serious illness and/or major organ dysfunction Pregnancy or Lactation
Population N=43
Interventions Preoperative combined chemoradiation 45Gy in 25 fractions over 5 weeks + 826mg/m^2 oral Capecitabine twice a day on radiotherapy days (administered 2 hours before and 12 hours after radiotherapy).

Outcomes
Primary: Grade of tumour down staging
       Rate of Sphincter preservation
 	
Secondary: Toxicity
       Postoperative Complications

Results A complete pathological response was found in 4 patients (9.3%, 95% CI 3-23.1). Overall down staging was achieved in 32 patients (74.4%, 95% CI 58.5-85%). No tumour progression was observed T_0 disease was observed in 4 patients, T_1 disease in 11 patients, T_2 in 8 patients, T_3 in 11 patients and T_4 in 9 patients. Overall sphincter preservation rate was 46.5% (20/43, 95% CI; 31.5 – 62.2). Sphincter sparing procedures were performed in 75% of patients with clinical T_3 disease and in 21.7% of patients with clinical T_4 disease, 19 patients underwent abdominoperineal resection. Four patients with clinical T_4n_1 rectal cancer showed no response to chemoradiation. Sphincter preservation was achieved in the 55.6% of patients with an initial tumour located 5-≤10cm from the anal verge and in 31.3% of patients with tumour located <5cm from the anal verge. After median follow-up of 25 months (range: 12-30 months), the 2-year overall survival was 79%. The two year recurrence free survival rate was 75%. Toxicity was moderate with no occurrences of grade 3 or 4 toxicity. Haematological toxicity was mild with grade II anaemia in 9.3% of patients (95% CI; 3-23%) and grade II leucopenia in 4.7% of patients (95% CI; 0.8-17). Grade II radiation dermatitis occurred in 9.3% of patients (95% CI; 3-23.1) and diarrhoea occurred in 2.3% of patients (95% CI; 0.1-13.8%).
General comments Surgery was performed between 4 and 6 weeks after the end of chemoradiation treatment following a physical exam, laboratory investigation and radiological study to assess suitability for surgery.

Citation: Klos, C. L., Shellito, P. C., Rattner, D. W., Hodin, R. A., Cusack, J. C., Bordeianou, L., Sylla, P., Hong, T. S., Blaszkowsky, L., Ryan, D. P., Lauwers, G. Y., Chang, Y., and Berger, D. L. - The effect of neoadjuvant chemoradiation therapy on the prognostic value of lymph nodes after rectal cancer surgery. - American Journal of Surgery 200[4], 440-445. 2010.

Relevant Comparison
Preoperative Chemoradiotherapy versus Surgery Alone

Design: Retrospective Case Series

Country: United States of America

Aim: In those patients who have had neoadjuvant chemoradiotherapy, to define the importance of the total number and prognostic value of lymph nodes harvested after resection of a rectal tumour.

Inclusion criteria
-

Exclusion criteria
Patients with synchronous distant metastases to lung, liver or bones. Also, patients who had been treated with polypectomy by hot snare/scope, transanal excision. Short-course radiotherapy (RT)

Population
N=390 consecutive patients treated surgically for rectal cancer at a single general hospital between February 2000 and December 2008. Few useful patient demographics presented.

Interventions
[Group 1] Neoadjuvant therapy (N=221): patients with clinically advanced rectal cancer stages T3 or T4 and/or those with lymph node involvement. These patients received a fractionated dose (45 or 50.4 Gy) of RT over 6 weeks and 5'FU-based chemotherapy.

[Group 2] Surgery only (N=164): patients with T1 or T2 cancer without suspicious lymph nodes.

All patients received total mesorectal excision (TME). Patients having received neoadjuvant therapy had surgery 4-8 weeks after completion. According to the distance of the tumour from the anal verge, surgical procedures included abdominal perineal resection or low anterior resection. Adjuvant treatment was offered based on the resulting pathology and to all patients who had received neoadjuvant therapy.

Outcomes
Time to death, local recurrence or distant recurrence.

Results

Death:
Group 1 versus group 2: HR: 0.97 (95%CI: 0.63-1.51) P=0.90

Local recurrence:
Group 1 versus group 2: HR: 0.82 (95%CI: 0.27-2.45) P=0.72

Distant recurrence:
Group 1 versus group 2: HR: 0.65 (95%CI: 0.31-1.37) P=0.25

The average number of lymph nodes harvested in patients who had neoadjuvant therapy was 13 compared with 14 in the surgery only group. Positive lymph nodes were found more frequently in the surgery only group

but the differences in time to death, local or distant recurrence between groups were not significant.

Patients with positive lymph nodes had a significantly shorter survival time (HR: 2.09 (95%CI: 1.32-3.30) P=0.002), shorter time to local recurrence (HR: 3.49 (95%CI: 1.07-11.43) P=0.039) and time to distant recurrence (HR: 2.80 (95%CI: 1.32-5.94) P=0.007) compared to patients having negative nodes.

Patients in the neoadjuvant treatment group having one or more positive lymph nodes experienced a significantly shorter time to survival (HR: 2.89 (95%CI: 1.46-5.74) P=0.002) and local recurrence (HR: 6.36 (95%CI: 1.18-34.29) (P=0.031) than patients in this group with negative lymph nodes. Time to distant recurrence was not significantly different between groups. It should be noted that the width of the 95% confidence intervals suggests high variance within these data.

General comments
This paper describes a retrospective review of patients treated for rectal cancer at a single general hospital between 2000 and 2008. Based on stage at presentation, patients with more advanced disease received neoadjuvant therapy whereas patients with T1 and T2 disease were directed straight to surgery. The outcomes for these patients are compared but this is not a randomised trial and hence may be biased and should be interpreted with caution. Median follow-up was 3 years.

The authors suggest that treatment with neoadjuvant therapy could potentially have reduced the number of lymph nodes harvested and thus the chance of missing a positive node could be more significant, potentially leading to understaging. This appears not to be this case in these patients, however, since the mean number of nodes removed was not significantly different between groups. The authors concluded that, following neoadjuvant therapy and surgery, positive lymph nodes were associated with significantly poorer outcomes but that the total number of lymph nodes harvested had made no impact on prognosis.

There are quality considerations with this retrospective study. The surgical component of treatment was conducted by various individuals and with numerous different protocols. In addition, the histological analysis of the resected specimens was carried out by a variety of pathologists.

Citation: Habr- Gama A, Perez RO, Kiss DR, Rawet V, Scanavini A, Santinho PM, Nadalin W (2004) Preoperative chemoradiation therapy for low rectal cancer. Impact on downstaging and sphincter saving operations *Hepato Gastroenterology* 51;60:1703-1707
Relevant Comparison **Preoperative Chemoradiotherapy versus Surgery Alone**
Design: Retrospective Case Series
Country: Brazil
Aim: No clear aim was provided by the authors
Inclusion criteria Patients with palpable adenocarcinoma of the distal rectum (0-7cm from the anal verge) considered to be resectable by means of physical exam, CT, colonoscopy or proctoscopy.
Exclusion criteria Patients with distant metastases
Population N=100
Interventions Preoperative chemoradiotherapy (325mg/m^2 5FU and 20mg/m^2 leucovorin by bolus infusion on days 1-5 and 29-33 delivered concurrently with at least 45-50Gy pelvic radiation followed by surgery 8 weeks later).
Outcomes Not clear from the paper, though appear to be factors such as: Pathologic Stage Sphincter Preservation

Results

Pathologic Stage

18% of patients in the surgery group had stage I (TI-2, N0), 40% had stage II (T3-4, N0) and 42% had stage III (T1-3, N1-2) disease.

In the preoperative chemotherapy group, pathologic complete response occurred in 12% (n=6) of patients, 42% of patients had stage I (TI-2, N0), 24% had stage II (T3-4, N0) and 22% had stage III (T1-3, N1-2) disease.

	Group 1	Group 2
	Number of Patients (%)	
Stage 0	0(0%)	6(12%)
Stage I	9(18%)	21(42%)
Stage II	20(40%)	12(24%)
Stage III	21(42%)	11(22%)

Table: Pathologic Stage (p<0.001)

	Group 1 pN1-2	Group 2 pN1-2
	Number of Patients (%)	
pT0		0/6(0%)
pT1	0/2(0%)	0/4(0%)
pT2	4/11(36%)	6/23(22%)
pT3	16/36(44%)	5/16(31%)
pT4	1/1(100%)	0/1(0%)

Table: Correlation between pT Stage and pN Stage (p<0.003)

No primary tumours progressed during chemoradiotherapy and none of the tumours showed distant metastasis at surgery in both groups.

The mean tumour size before chemoradiation was estimated to be 4.4cm (range; 2-9cm) and the mean tumour size after chemoradiotherapy was 3.3cm (range: 1-7cm), corresponding to a mean reduction of 27.3%. Reduction in tumour size was observed in 58% of patients in this group.

Sphincter Preservation

86% of patients in the surgery group were treated with abdomino-perineal resections and 14% by anterior resections. In the chemoradiotherapy group, 68% were treated by abdomino-perineal resection and 32% by anterior resection (p=0.03)

General comments
The actual dose of radiation is unclear in the paper – written as 45-50,4Gy

Citation: Kim JC, Kim TW, Kim JH, Yu CS, Kim HC, Chang HM, Ryu MH, Park JH, Ahn SD, Lee S, Shin SS, Kim JS, Choi EK (2005) Preoperative concurrent radiotherapy with capecitabine before total mesorectal excision in locally advanced rectal cancer *Journal of Radiation Oncology, Biology, Physics* 63;2:346-353
Relevant Comparison **Preoperative Chemoradiotherapy** **Capecitabine**
Design: Phase II Trial **Country**: South Korea **Aim**: To evaluate the toxicity and efficacy of oral capecitabine when used with preoperative radiation therapy
Inclusion criteria Histologically proven rectal adenocarcinoma Distal margin of tumour located within 10cm from the anal verge on colonofiberoscopy Extension of primary tumour through the bowel wall or positive lymph nodes without evidence of distant metastatic disease (T3-4, or N positive and M0) on EUS and CT scanning. Aged 18-75 years ECOG performance status of ≤2 Adequate bone marrow reserve Adequate renal function
Exclusion criteria Patients with other tumour types Prior cancer chemotherapy or radiotherapy Other serious medical condition Familial history of rectal cancer
Population N=95
Interventions Preoperative radiation therapy for weeks with concurrent use of capecitabine (full details of regimen provided in the paper) Surgery was performed 4-6 weeks after treatment was completed
Outcomes Treatment Compliance and acute toxicity Surgical Complications Rate of complete resection Downstaging effect Rate of pathologic complete response Sphincter preservation rate in lower anterior resection cases
Results *Treatment Compliance and Toxicity* 95% of patients completed the preoperative chemoradiation as initially planned; chemotherapy does was reduced due to leukocytopenia in 2 patients, a radiation dose of 50Gy was not delivered in 2 patients for non-treatment related reasons, 1 patient finished radiotherapy at a dose of 44Gy because of mechanical ileus symptoms. There was no interruption of more than 2 days related to treatment. 3% of patients suffered Grade III diarrhoea and 1% of patients suffered grade III neutropenia, there were no Grade IV adverse events. The majority of adverse events were mild to moderate in intensity and no treatment related mortality was observed. One patient developed lung and liver metastases identified on a preoperative CT scanning and curative surgical resection was performed in 99% of patients. *Tumour Response and Sphincter Preservation* <u>Clinical response on EUS</u> Full evaluation of T and N stage was possible in 81 patients and partial assessment was possible in 8 patients. Down staging in T-category was observed in 37% of patients (31/84) and in N-category in 68% of patients (39/57). In total, comparison of T and N status pre and post operatively was possible in 79 patients and down-staging was observed in 71% of patients (56/79).

Surgical Resection
Complete resection was performed in 98% of patients (92/94) resected.

Pathologic Response
Complete disappearance of the primary tumour was observed on the pathology specimen in 13% of patients and 64% of patients showed no tumour cells in their lymph node specimen.
The pathologic stage was lower than initial clinical stage in 57% of T-category, 69% of N-category and in 76% in the combined TN category in resected patients.

Sphincter Preservation
Sphincter preservation was possible in 74% of patients with tumours located within 5cm from the anal verge. Preoperative chemoradiotherapy enabled elevation of the distal tumour margin from the anal verge by 0.8±1.3cm (mean ± SD; range 0-5.5cm). Distal resection margin was maintained as ≥0.5cm for T1 and ≥2cm for T2-4 in 37%. Rectal manometry was performed in 71/77 patients and loss of recto-anal inhibitory reflex was observed in 27% of these patients.

Citation: Koeberle D, Burkhard R, von Moos R, Winterhalder R, Hess V, Heitzmann F, Ruhstaller T, Terraciano L, Neuweiler J, Bieri G, Rust C, Toepfer M (2008) Phase II study of capecitabine and oxaliplatin given prior to and concurrently with preoperative pelvic radiotherapy in patients with locally advance rectal cancer *British Journal of Cancer* 98;7:1204-1209
Relevant Comparison **Preoperative Chemoradiotherapy** **Capecitabine**
Design: Phase II Trial **Country**: Switzerland **Aim**: to evaluate the safety and efficacy of preoperative capecitabine plus oxaliplatin and radiotherapy in patients with locally advanced rectal cancer (T3/T4 rectal adenocarcinoma with or without nodal involvement).
Inclusion criteria Histologically confirmed rectal adenocarcinoma Evidence of T3 or T4 disease with or without perirectal nodal involvement by EUS or MRI of the pelvis. ECOG performance status 0-2 Adequate haematological, renal and liver function.
Exclusion criteria Patients with metastatic disease Previous chemotherapy fro colorectal cancer or prior radiotherapy to the pelvis History of another malignancy within the last 5 years Any contraindication to radiotherapy Clinically significant cardiac disease Malabsorption syndrome Peripheral neuropathy ≥ grade 1 according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 Serious uncontrolled infection Concomitant treatment with any nucleoside analogue Known dihydropyrimidine dehydrogenase deficiency Psychiatric disorders or conditions interfering with compliance for oral drug intake Pregnant or lactating women
Population N=60
Interventions 45Gy with a daily fraction of 1.8Gy 5 days a week for five weeks. If treatment was interrupted, the dose was increased by 1-2 fractions. Single cycle of Xelox (oral capecitabine) at 1,000mg/m^2 twice daily on days 1-14 plus a 2 hour intravenous infusion of oxaliplatin 130mg/m^2 on day one, followed by CAPOX combined with radiotherapy (capecitabine 825mg/m^2 twice daily on days 22-35 and 43-56 and oxaliplatin 50mg/m^2 on days 22, 29, 43 and 50.
Outcomes Pathological complete tumour response Rate of sphincter preservation R0 resection inpatients with T$_4$ tumours Down staging Safety
Results All 60 patients were included in the safety and intention to treat (ITT) analysis despite 1 patient withdrawing consent and 1 patient dying prior to surgery, resulting in 97% of enrolled patients (58/60) undergoing chemoradiotherapy and surgery. *Dose intensity and Safety* 92% of patients received all three cycles of capecitabine (mean relative dose intensity 97%) and 87% of patients received all five planned oxaliplatin doses (mean relative dose intensity 97%). 93% of patients received at least 25 fractions of radiotherapy as planned (45Gy). Grade III/IV lymphocytopenia was observed in 43% of patients and diarrhoea was the most frequently occurring grade III/IV non-haematological adverse effect (20% of patients). 13% of patients recorded at least one serious adverse event. 7% of patients had one adverse event leading to the

discontinuation of capecitabine and 5% had adverse effects leading to discontinuation of oxaliplatin.

Efficacy and surgical parameters
81% of patients underwent TME, 16% underwent abdominoperineal extirpation and 3% underwent some other type of surgery.
Median time between end of radiotherapy and surgery was 42 days (range 24-59 days).
R0 resection was achieved in 98% of patients, including all T_4 patients and sphincter preservation was achieved in 84% of patients.
Down staging with respect to tumour stage was observed in 47% of patients in the ITT population and downstaging with respect to nodal stage was observed in 48% of patients.
Complete tumour regression was achieved in 7 patients and an additional 7 patients showed near complete regression. According to predefined criteria, the pCR rate was 23% (95% CI 13-36%).

Citation: Machiels JP, Duck L, Honhon B, Coster B, Coche JC, Scalliet P, Humblet Y, Aydin S, Kerger J, Remouchamps V, Canon JL, van Maele P, Gilbeau L, Laurent S, Kirkove C, Octave-Prignot M, Baurain JF, Kartheuser A, Sempoux C (2005) Phase II study of preoperative oxaliplatin, capecitabine and external beam radiotherapy in patients with rectal cancer: the RadiOxCape study *Annals of Oncology* 16;12:1898-1905

Design: Phase II trial

Country: Belgium

Aim: No clear aim provided

Setting
The study was conducted in community based hospitals

Inclusion criteria
Histologically proven rectal adenocarcinoma stage T_3-T_4 or/and N_1-N_2 by transrectal ultrasound (or locally staged by MRI of transrectal ultrasound was not possible).
Age >18 years
ECOG performance status ≤2
Acceptable liver, renal and haematological parameters

Exclusion criteria
Prior pelvic irradiation
Active second malignancy during the previous 5 years (except non-melanomatous skin cancer or in-situ cervical cancer).
Pregnancy and lack of contraception
Presence of any psychological, familial, sociological or geographical condition potentially hampering the compliance with the study protocol and follow-up schedule.
Prior of concurrent evidence of peripheral neuropathy
Inflammatory bowel disease
Malabsorption syndrome
Synchronous colic and rectal tumours
Uncontrolled severe disease precluding administration of chemotherapy and radiotherapy

Population
N=40

Interventions
Radiotherapy; 45Gy in 25 fractions (1.8Gy) five days a week for five weeks
Chemotherapy; 50mg/m^2 oxaliplatin intravenously over 2hours on days 1, 8, 15, 22 and 29.
Adequate haematological parameters were required before each oxaliplatin infusion and radiotherapy was performed within 2 hours of oxaliplatin infusion.
Capecitabine; 825mg/m^2 twice a day orally on radiotherapy days

Outcomes
Safety and Efficacy as assessed by the pathological complete response

Results
One patient was not evaluated due to rectal stenosis and was staged T_3N+ by MRI.

Acute adverse events and dose intensity
- No grade III/IV febrile neutropenia or diarrhoea was recorded in the first 6 patients enrolled in the study and therefore accrual continued.
- The most frequent grade III/IV adverse event was diarrhoea (30%)
- 10/40 (25%) of patients had transient dysesthesia with cold or parasthesia.
- No parasthesia with pain or functional impairment was noted
- No hand-foot syndrome was recorded
- The relative dose intensities of oxaliplatin and capecitabine in the intention to treat population were 85% and 84% respectively.
- The main reason for reducing chemotherapy doses was diarrhoea, occurring in the fourth or fifth week of treatment.
- In multivariate analysis, increasing age was significantly correlated with grade III/IV diarrhoea (p<0.01)

Efficacy
36 patients were evaluable for pathologic assessment of tumours and nodes with pathologic complete response observed in 14% of patients.
Good regression, as defined by Dworak grade 3 (very few tumour cells in fibrotic tissue) was observed in 16% of patients while good regression as defined by Wheeler grade 1 (sterilisation or only macroscopic foci of adenocarcinoma remaining with marked fibrosis) was observed in 58% of patients.
Circumferential margin (defined as <2mm between tumour and surgical margin) was tumour free in 83% of patients.

Surgery and surgical morbidity
Surgery was performed in all patients bar 2 and median time spent in hospital was 15 days (range; 8-38).
12 patients had an abdominoperineal resection with permanent colostomy; low anterior resection with colorectal or coloanal anastomosis was performed in the other patients.
Post-surgical morbidities reported included; anastomotic fistula (n=4), pelvic abscess (n=2), delay in perineal healing (n=2), cutaneous necrosis (n=1) and suture dehiscence (n=1).
A second surgical procedure was required in 5 patients.

Follow-up
Median follow-up at the time of publication was 14 months (range 9-20).
No local relapses were observed among the 36 evaluable patients.
2 patients developed distant metastasis at 6 and 10 months respectively

Citation: Mermershtain W, Gluzman A, Gusakova I, Walfish S, Cohen Y, Ariad S (2005) Preoperative radio-chemotherapy treatment in locally advanced rectal carcinoma. Results of 8 year follow-up *Onkologie* 28;5:267-269

Relevant Comparison
Preoperative Chemoradiotherapy versus Surgery Alone

Design: Retrospective Case Series

Country: Israel

Aim: to retrospectively analyse the effectiveness and toxicity of preoperative pelvic radiotherapy in combination with 5-fluorouracil in locally advanced rectal cancer.

Inclusion criteria
Patients with locally advanced rectal adenocarcinoma

Exclusion criteria
Patients with a prior history of cancer or pelvic irradiation

Population
N=30

Interventions
Chemoradiotherapy followed by surgical resection

Outcomes
Not clear from the study what the outcomes are – appear to be pathologic response, overall survival and treatment toxicity.

Results
All patients completed a full course of chemoradiotherapy and had surgery 2-4 weeks after. 15 patients underwent abdominoperineal resection, 11 underwent anterior resection, 1 patient underwent trans-anal resection, 1 patient received explorative laparotomy and 2 patients refused surgery.

Complete Remission N (%)	Partial Remission N (%)	No Change N (%)	Progression N (%)
4 (13)	5 (17)	17 (57)	4 (13)

Table: Pathologic evaluation after chemoradiotherapy and surgery

Necrosis was noted as a prominent histopathologic feature.
Relapses were classed as local, regional or distant with 3 patients having local recurrence, 9 developing distant metastases.

The overall 5-year survival was 70% and 8 year survival was 58%.

No serious toxicities related to chemoradiotherapy were recorded and no chemotherapy or radiotherapy total doses were modified as a result of treatment related toxicities.

Mild to moderate transient radiation dermatitis was observed in 3 patients and grade II diarrhoea in 4 patients. There were no haematological or genitourinary grade III/IV toxicities encountered during chemoradiotherapy. No long-term radiation induced toxicity was observed.

General comments
Very low quality evidence; small numbers and more narrative in reporting.

Citation: Pietrzak L, Bujko K, Nowacki MP, Kepka L, Oledzki J, Rutkowski A, Szmeja J, Kladny J, Dymecki D, Wieczorek A, Pawlak M, Lesnial T, Kowalska T, Richter P (2007) Quality of life, anorectal and sexual functions after preoperative radiotherapy for rectal cancer: report of a randomised trial
Relevant Comparison **Preoperative radiotherapy versus preoperative chemoradiotherapy**
Design: Randomised Trial **Country**: Poland **Aim**: to determine whether large doses per fraction of short-course schedule result in more sever anorectal and sexual dysfunction and quality of life impairment
Inclusion criteria Trial details are outlined in the above evidence table (Bujko et al, 2004)
Exclusion criteria
Population N=256 patients alive 7 months after surgery
Interventions Quality of Life Questionnaire Core 30 items (QLQ-C30) of the European Organisation for Research and Treatment of Cancer Self administered, non-validated 19 item questionnaire on anorectal function, with a single question designed to assess sexual function.
Outcomes Quality of Life (QoL) Anorectal Function Sexual Function
Results 221/256 patients alive and disease free 7 months after surgery completed the QLQ-C30 questionnaire 118/137 patients alive, disease free and with no stoma completed the questionnaire on anorectal function and 116 answered the question relating to sexual function. The median time interval between surgery and completing the QLQ-C30 questionnaire was 12 months (3-65 months) and 13 months (4-74 months) for the anorectal-sexual function questionnaire. *QoL Evaluation* A significantly higher number of patients in the short-term radiotherapy went on to receive post-operative chemotherapy compared with the chemoradiotherapy group (p=0.002). There was no significant difference between the two groups in relation to mean scores for the global health/quality of life status (p=0.22). *Anorectal and Sexual Functions Evaluation* There was no significant difference between the two groups in relation to any of the questions posed. Approximately two thirds of patients complained of faecal and gas incontinence, urgency and inability to differentiate between stool and gas. Approximately two-thirds of respondents stated that the disturbances in anorectal function had a negative impact on their quality of life, with approximately 20% stating the impact was considerable. Anorectal finction was estimated as being good or very good by 41% of patients in the short-course chemotherapy group and by 37% of patients in the chemoradiotherapy group (p=0.52). 2% (n=2) patients scored anorectal function was being unacceptable and regretted that a stoma had not been performed. There was no significant difference between the two groups in relation to the impact on sexual function (p=0.56 for males; p=0.1 for females).

Citation: Rodel C, Grabenbauer G, Papadopoulos T, Hohenberger W, Schmoll HJ, Sauer R (2003) Phase I/II Trial of capecitabine, oxaliplatin and radiation for rectal cancer *Journal of Clinical Oncology* 21;16:3098-3104
Relevant Comparison **Preoperative Chemoradiotherapy** **Capecitabine**
Design: Phase I/II Trial **Country**: Germany **Aim**: to establish the feasibility and efficacy of preoperative radiotherapy with concurrent capecitabine and oxaliplatin in patients with rectal cancer
Inclusion criteria Histologically proven rectal adenocarcinoma classified as either T_4M_0 or locally recurrent disease or any T M_1 disease requiring surgery of the primary tumour. Patients with low-lying lesions who were declared by the surgeon as needing abdominoperineal resection but sought sphincter preservation. ECOG performance status ≤2 Adequate haematologic, liver and renal function
Exclusion criteria Prior radiotherapy to the pelvic region or previous cytotoxic chemotherapy Other synchronous cancers Patients suffering from inflammatory bowel disease, malabsorption syndrome, ischemic heart disease, peripheral neuropathy, psychiatric disorders or psychological disorders thought to adversely affect treatment compliance Pregnant of lactating patients and women with childbearing potential who lacked effective contraception.
Population N=32
Interventions XELOX-RT All patients received a total radiotherapy dose of 50.4Gy with daily fractions of 1.8Gy on 5 consecutive days per week. Capecitabine was delivers orally at a fixed dose of 825mg/m^2 twice daily on days 1-14 and 22-35 of radiotherapy; the first dose was administered 2 hours prior to radiotherapy and the second dose 12 hours later. Oxaliplatin was administered as a 2-hour infusion on days 1, 8, 22 and 29 beginning with a dose level of 50mg/m^2/d with planned escalation steps of 10mg/m^2/d to a maximum of 80mg/m^2/d.
Outcomes Phase I – determine a suitable oxaliplatin dose when combined with preoperative radiotherapy and capecitabine Phase II – R0 resection rate in T_4 rectal cancer
Results *Dose Escalation and DLTs* In 3 patients treated with 50mg/m^2/d oxaliplatin no DLT's were observed. A total of 6 patients were included at the 60mg/m^2/d and increasing the dose to 60mg/m^2/d resulted in grade III diarrhoea and grade II vomiting in 1 with recurrent disease during the second cycle of chemotherapy. In the third week 1 patient with primary T_4 tumour developed grade III diarrhoea with fever and increase of laboratory infection parameters and radiographic signs of paralytic ileus. Oxaliplatin dose escalation stopped at 60mg/m^2/d and 6 additional patients were treated at 50mg/m^2/d with no grade III toxicity observed; therefore all subsequent patients were treated at 50mg/m^2/d. *Toxicity and Compliance with the regimen* At the lower dose level there 4 patients suffered grade III toxicities (perineal skin toxicity and diarrhoea). Grade I/II gastrointestinal toxicities occurred in approximately half of patients and consisted primarily of diarrhoea and nausea. Mild grade I neurologic toxicity manifested as painless dysesthesias of the hands in f5 patients receiving 50mg/m^2/d and in 1 patient receiving 60mg/m^2/d. Grade I hand-foot syndrome was observed in 2 patients and there was 1 case of angina pectoris in a patient with no previous history of cardiac disease. There was no grade III/IV haematological toxicity; 69% of patients suffered grade I/II leukopenia. All patients received the full radiotherapy dose apart from 2 patients with DLT's Compliance with oxaliplatin at 50mg/m^2/d was 89% and compliance with radiotherapy was 100% for patients

receiving oxaliplatin at $50mg/m^2/d$

Efficacy
There was no local or metastatic progression during or after treatment.
2/5 patients with metastatic disease showed partial response.
1 patient with recurrent extraluminal diffuse disease was deemed inoperable
31 patients underwent surgery; in 94% locally radical resection was achieved with negative margins, 6% (2 patients both with locally advanced T_4 tumours) had microscopically involved margins on pathologic examination.
Sphincter sparing surgery could be performed in 36% of patients with tumours that extended ≤2cm from the dentate line before treatment.
Downs staging was observed in 75% of patients with cT_4 tumours, 40% of patients with cT_3 tumours and 50% of patients with cT_2 tumours.
68% of patients that underwent surgery had negative lymph node involvement; nodal status down staging was observed in 61% (11/18) patients.
Complete tumour regression was observed in 19% of patients and in 39% of patients only a few tumour cells were observed within fibrotic tissues.

Citation: Stephens, R. J., Thompson, L. C., Quirke, P., Steele, R., Grieve, R., Couture, J., Griffiths, G. O., and Sebag-Montefiore, D. Impact of short-course preoperative radiotherapy for rectal cancer on patients' quality of life: data from the Medical Research Council CR07/National Cancer Institute of Canada Clinical Trials Group C016 randomized clinical trial. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 28[27], 4233-4239. 2010.
Design: Randomised controlled trial (Medical Research Council CR07/National Cancer Institute of Canada Clinical Trials Group C016 trial (CR07/C016).   **Country**: United Kingdom   **Aim**: To record changes in patient reported quality of life (QoL) before and after pre-operative radiotherapy followed by surgery (and adjuvant chemotherapy in selected patients) for rectal cancer.
Inclusion criteria   Histologically confirmed, resectable adenocarcinoma of the rectum with no evidence of metastases.
Exclusion criteria   -
Population   Baseline: N=1,208 completed (879 males) with median age 66 years (inter-quartile range: 58-72 years). 66 in Pre group and 597 in SEL POST group.   2 years: N=563 completed (404 males) with median age 66 years (inter-quartile range: 58-71 years). 281 in PRE group and 282 in SEL POST group.
Interventions   [1] Short course radiotherapy of 25Gy in 5 fractions followed by surgery within 7 days (PRE).   [2] Surgery followed by post-operative chemoradiotherapy in selected patients (those with microscopic tumour within 1mm of the circumferential resection margin) (SEL POST)   According to circumferential resection margin and lymph node status, patients in either arm may have received adjuvant chemotherapy of 5'FU and leucovorin according to centre policy.   Questionnaires were completed at baseline, every 3 months for the first year and every 6 months to 3 years from randomisation.
Outcomes   Patient reported QoL assessed by questionnaires MOS SF-36 and QLQ-CR38. MOS SF-36 is a general health questionnaire with 36 items in eight scales: physical function, role-physical, bodily pain, general health, vitality, social function, role-emotional and mental health. QLQ-CR38 is sub-divided into four function scales: body image, sexual function, sexual enjoyment and future perspective with sub-scales including sexual dysfunction).
Results   There was no significant difference in QoL scores between the PRE and SEL POST groups at baseline.   **Male sexual dysfunction (MSD):**   Mean score at baseline: 28.4   Mean score after 3 months: 59.3 (P<0.001)   There was no difference between treatment groups.   Mean score at 6 months PRE: 65.9   Mean score at 6 months SEL POST: 56.0 (P=0.004)   Mean score at 2 years PRE: 65.7

Mean score at 2 years SEL POST: 57.4 (P=0.058)

The impact of surgery was, therefore >30 % points but pre-operative RT made only a small impact. The authors claim that the increase in sexual dysfunction at 3 months was not due to chemoradiotherapy given to selected patients in the SEL POST arm, or to adjuvant chemotherapy.

There were insufficient responses from women for sexual dysfunction analyses.

Defecation function (for patients without a stoma):
Mean score at 2 years PRE: 22.6
Mean score at 2 years SEL POST: 24.6 (P=0.42) NSD

Unintentional release of stools:
Mean score at 2 years PRE: 53.2
Mean score at 2 years SEL POST: 37.3 (P=0.007)
Most of the significance in the different scores between groups was seen in the severity level of this outcome: 'a little' PRE: 43 versus SEL POST: 29.

Physical function:
Mean score at 3 months PRE: 58.4
Mean score at 3 months SEL POST: 62.6 (P=0.028)
This difference was lost thereafter, returning to baseline for both groups.

General health:
No significant changes were seen over time for this outcome. Adjuvant chemotherapy made little impact on general health, physical or MSD function. Post-operative chemoradiotherapy had a significant effect on bowel function at 2 years.

General comments
The authors concluded that the general health of patients undergoing curative treatment for rectal cancer was good. The main, irreversible adverse effect experienced by men was sexual dysfunction, caused primarily by surgery, although this was exacerbated by RT. There were insufficient responses from females to measure sexual dysfunction. Bowel function in those patients without a stoma (or in those who had a stoma reversal) was not significantly different between treatment arms. However, sub group analysis suggested that patients in the PRE group may have experienced an increase in the 'unintentional release of stools' even at 2 years post-treatment. Generally, there were no significant differences in treatment groups in overall general health or QoL. This suggested to the authors that either the questionnaires may not have been sensitive enough to have detected any differences or that perhaps in an older patient group the observed adverse events were accepted as an unavoidable cost of treatment.

Citation: Twu CM, Wang HM, Chen JB, Chao TH, Mar HF (2009) Neoadjuvant concurrent chemoradiotherapy in treating locally advance rectal cancer. *Journal of the Chinese Medical Association* 72;4:179-182
Relevant Comparison **Preoperative Chemoradiotherapy versus Surgery Alone**
Design: Retrospective Case Series **Country**: Taiwan **Aim**: No clear aim given
Inclusion criteria Patients with locally advanced rectal cancer who received concurrent chemoradiotherapy
Exclusion criteria None given
Population N=46 N=43 included in analysis
Interventions 5-FU 400mg/m^2 plus Leucovorin 20mg/m^2 intravenously for 1 hour on days 1-4 and 29-32 concurrent with radiotherapy (200cGy/day, Mon-Fri for 5 weeks)
Outcomes None given
Results 3 patients achieved complete clinical response, confirmed by CT scan and physical exam leaving 43 patients for analysis 12% of patients achieved complete pathologic response, 67% had partial response for and overall response rate of 79%. • Curative resection rate (R0 resection) was higher in the patients that responded to chemoradiotherapy when compared with the patients that did not respond 97% vs. (66.7%, p=0.024) • Local recurrence rate was low in the responding group compared to the non-responding group (p=0.002). • Disease free survival was higher in the responding group compared with the none-responding group (p=0.06) • There was no significant difference between the two groups in relation to overall survival. • The rate of anastomotic leak was up to 25% for both groups. • Mean hospital stay was 11.5 days with no significant difference between the groups. • Risk factors for local recurrence were high Dukes grade and incomplete resection.
General comments Short paper, very sparse on details Comparator was patients responding to chemoradiotherapy versus patients not responding to chemoradiotherapy but there were only small numbers included overall.

Citation: Tulchinsky H, Shmueli E, Figer A, Klausner J, Rabau M (2008) An interval >7 weeks between neoadjuvant therapy and surgery improves pathologic complete response and disease-free survival in patients with locally advanced rectal cancer *Annals of Surgical Oncology* 15;10:2661-2667
Relevant Comparison **Preoperative Chemoradiotherapy versus Surgery Alone**
Design: Retrospective Case Series
Country: Israel
Aim: to asses whether the time interval between neoadjuvant therapy and surgery affects the operative and postoperative morbidity and mortality, the pathologic complete response rate and disease recurrence in locally advanced rectal cancer
Inclusion criteria None have been explicitly stated though it appears to be patients with confirmed locally advanced low and mid rectal adenocarcinoma who underwent preoperative therapy followed by radical resection with total mesorectal excision.
Exclusion criteria None have been explicitly identified however 14 patients were excluded from analysis due to a number of factors such as the presence of liver metastases at surgery, R2 resection, pelvic exenteration and receiving only radiotherapy as preoperative therapy.
Population N=132
Interventions High-dose radiation therapy of 45-50.4Gy with concomitant 5FU based chemotherapy
Outcomes Patterns of disease recurrence Overall survival Disease Free Survival
Results The chemoradiotherapy to surgery time interval ranged from 13 – 173 days (median 56 days) with 98% of patients operated on between 4 – 17 weeks after treatment. Type of surgery, operative time, number of blood transfusions given during surgery, length of hospital stay and use of diverting stoma in patients undergoing sphincter procedures were not influenced by the interval length. Patients that were operated on ≤7 weeks had a complication rate of 48% compared with 36% for patients who were operated after more than 7 weeks though the difference was not significant (p=0.17). Factors Predictive of Tumour Response to Neoadjuvant Therapy 26% (n=37) of patients had complete pathologic response (n=26) or near pathologic response (n=11). Preoperative treatment to surgery time interval was the only independent predictor of pCR and near pCR; the rate of pCR increased with longer time interval to surgery for patients with an interval ≤7 weeks to surgery the rate was 17% vs. 35% for patients with an interval <7 weeks (p=0.03). Factors Prognostic for Disease-free and Overall Survival Median follow-up was 33 months (range 6-80 months). 17% of patients had disease recurrence of which two-thirds had a time to surgery interval of <7 weeks (p=0.03). 15 patients died, two-thirds of whom had a time to surgery interval of <7 weeks (p=0.04) On analysis, time to surgery interval was the only independent prognostic factor. There was significantly improved disease free survival in patients with >7 week time to surgery interval compared to patients with ≤7 week times to surgery interval (p=0.05). There was no significant difference in overall survival rates between the two groups (p=0.07).
General comments Low Quality evidence Not directly applicable though may go toward quality and success rates for surgery. The study does not mention the impact of time interval on the quality of the subsequent surgery which would have been a useful outcome to report.

Citation: Velenik V, Anderluh F, Oblak I, Strojan P, Zakotnik B (2006) Capecitabine as a radio-sensitising agent in

neoadjuvant treatment of locally advanced resectable rectal cancer: prospective phase II trial *Croatian Medical Journal* 47;5:693-700

Design: Prospective Phase II Trial

Country: Slovenia

Aim: To evaluate the efficacy and toxicity of preoperative chemoradiotherapy with capecitabine in locally advanced rectal cancer

Inclusion criteria
Histologically confirmed adenocarcinoma of the rectum, clinical TNM stage II or III
WHO performance status <2
Age 18 or older
Adequate bone marrow, liver, renal and cardiac function

Exclusion criteria
Prior radiotherapy and/or chemotherapy
History of ischaemic heart disease
History of prior malignancies other than non-melanoma skin cancer or in-situ carcinoma of the cervix

Population
N=57

Interventions
Radiotherapy: 45Gy in 25 fractions over 5 weeks once a day, 5 days a week.
Chemotherapy: administered concomitantly with radiotherapy and consisting of oral capecitabine at a daily dose of 1650mg/m^2 in 2 equal doses given 12 hours apart one dose to be given 2 hours prior to radiotherapy.
Chemotherapy started on the first day of radiotherapy and finished on the last day of radiotherapy including weekends. If radiotherapy was interrupted, chemotherapy was not administered.

Outcomes
Pathologically determined complete remission rate of local and regional disease
Rate of sphincter preservation in low-sited tumours
Overall down staging rate
Toxicity

Results
Treatment compliance
1/57 patients due to pulmonary embolism after receiving 27Gy radiotherapy, this was not thought to be treatment related.
98% of patients (56/57) completed preoperative chemoradiotherapy according to the protocol, receiving a total dose of 45Gy in 25 fractions of 1.8Gy.
After chemotherapy definitive surgery was performed in 55/56 patients. Median time to surgery was 45 days (range: 13 – 87 days) from the last day of preoperative chemoradiotherapy. 58.2% of patients underwent low anterior resection, 30.9% underwent abdominoperineal resection, 7.3% underwent anterior resection, 1.8% underwent exenteration of the small pelvis and 1.8% underwent Hartmann's resection.

Toxicity
Preoperative chemoradiotherapy was well tolerated in the majority of patients and no treatment related mortality was observed.
Grade III dermatitis occurred in 34.5% of patients.
Weight loss occurred in 52.7% of patients with maximum body weight loss of 17.5% (median 3.8%; range 1.2 – 17.5%). 34.5% of patients maintained a constant weight and 11% of patients gained weight during treatment.
1 patient died of sepsis in the early perioperative period while non-lethal complications were recorded in 24/55 patients including delayed wound healing (21.8%), febrile episode (9.1%), ileus (5.5%), chronic diarrhoea (5.5%) and anastomotic leakage (1.8%).

Tumour Response
2/55 patients were found to have liver metastases during operation (no signs of liver metastases had been recorded in preoperative radiological studies).
Overall down staging rate was 49.1%, decrease in T stage was observed in 40% (n=22) of patients while decrease

in N stage was observed in 52.9% (n=18) of patients while increase in T and/or N stage was recorded in 10.9% (n=6) of patients.

Complete pathologic response was recorded in 9.1% of patients (95% CI, 3%-20%) all of whom received more than 90% of the planned capecitabine dose and did not have any interruption of radiotherapy.

The difference in pathologic complete response rates for patients with and without radiotherapy interruptions was significant, though marginally (Fishers exact test, P=0.056) whereas there was no significant difference between patients receiving more than 90% of planned capecitabine dose compared with those receiving less than 90% of planned dose.

Sphincter Preservation

Rate of sphincter sparing surgery was 65.5% (33/35 planned); in a subgroup of patients with tumours located within the anal opening, sphincter preservation was possible in 37% (n=10).

Citation: Wong RKS, Tandan V, DeSilva S, Figueredo A (2007) Pre-operative radiotherapy and curative surgery for the management of localized rectal carcinoma (Review) *Cochrane Database of Systematic Reviews*
Relevant Comparisons: **Preoperative radiotherapy versus Surgery alone** **Preoperative radiotherapy versus Preoperative Chemoradiotherapy**
Design: Systematic Review **Country**: **Aim**: To determine if pre-operative radiotherapy improves outcomes for patients with localised, resectable cancer and how it compares with other adjuvant and neoadjuvant strategies.
Inclusion criteria Randomised trials with a pre-operative radiotherapy arm versus surgery alone, or other neoadjuvant or adjuvant strategies, targeted patients with localised rectal cancer planned for radical surgery were included. Studies where the intended surgery was radical (e.g. Hartmann procedure, anterior resection, abdominal peritoneal resection, total mesorectal excision (TME)). Subgroup analysis was performed to examine the impact of TME specifically.
Exclusion criteria Studies where the intended surgery was local resection
Population 19 studies addressing preoperative radiotherapy versus surgery alone
Interventions Pre-operative radiotherapy Surgery Alone Pre-operative chemoradiotherapy
Outcomes Overall mortality was the primary outcome for the review Secondary outcomes included; cause specific mortality, any recurrence, local recurrence, probability of downstaging, overall respectability, curative respectability, sphincter sparing resections, acute radiotherapy toxicities, operative morbidity and perioperative mortality (90 day mortality), late toxicities, functional outcome, quality of life, and compliance to the assigned therapy.
Results Defining rectal cancer 3 studies used below the sacral promontory 1 study used below the pelvic brim 3 studies stated rectal cancer but provided no additional criteria 1 used the requirement of abdominal perineal resection A number of studies used defined distance from anal verge ranging from 12cm to within 16cm 2 studies provided no details Total Mesorectum Excision as part of the study requirement 1 study specifically required TME Stage Distribution The average proportion of patients with stage A (Dukes A) disease in the control arm (surgery alone) was 17% (0.7% to 37%). In general, any patients with resectable disease were eligible for inclusion. Radiotherapy Details 12 studies employed doses above 30Gy[10] 6 studies employed doses below 30Gy[10] 1 study used 30Gy but did not specify the dose. 10 studies had a 1 week interval between radiotherapy and surgery. Longer intervals of between 2 and 4 weeks were employed in other studies and one study reported a mean interval of 11 days between radiotherapy and surgery. **Preoperative Radiotherapy versus Surgery Alone**

Overall Mortality
From 14 studies, the pooled Hazards Ratio (HR) was 0.93 (0.87-1) in favour of preoperative chemotherapy, though this was not statistically significant (Chi sq. p=0.15). When using the CCCG data (individual patient data) plus the published data, the pooled POR was 0.95 (0.89-1.02).
The magnitude of survival benefit was modest; when taking the overall mortality curve from the single largest study in the analysis (with an 8 year follow-up) to calculate the magnitude of benefit this translated into a 2% survival improvement (75% to 77%) at 5 years and 2% (60% to 62%) at 8 years.
Subgroup analysis suggests that non TME studies, higher BED and treatment fields focused to the posterior pelvis showed significant benefit.

	Number of Studies	Hazards Ratio (95% CI)
Non TME	19	0.92 (0.86-0.99)
TME	1	1.02 (0.84-1.26)
BED ≥ 30Gy^{10}	9	0.91 (0.84-0.98)
BED < 30Gy^{10}	7	0.99 (0.89-1.12)
Treatment fields focused to the posterior pelvis	4	0.85 (0.76-0.95)
Other	16	0.99 (0.91-1.07)

Table: Subgroup/Sensitivity Analysis on overall mortality

Cause Specific Mortality
From 5 studies, the pooled HR was 0.87 (95% CI 0.78-0.98) but the homogeneity X^2 =8.70; p=0.07, so the result should be interpreted with caution.

Any Recurrence
From 8 studies, the pooled HR was 0.89 (0.82-0.97) suggesting and overall reduction of recurrences in favour of pre-operative radiotherapy (Homogeneity X^2 =6.94; p=0.44; I^2=0.0%).

Local Recurrence
Recurrence rates in the control arms raged from 11% to 54%. All but one study showed a benefit in favour on preoperative radiotherapy, though the data were heterogeneous across the available studies (Homogeneity X^2=68.71; p<0.05; I^2 = 84%) indicating differences in the magnitude of effect across the individual studies. The absolute rate of local recurrence in the control group was variable across the studies. From 12 studies, the pooled HR was 0.71 (95% CI 0.64-0.78). Examining the data for factors which may be sources of heterogeneity, all radiotherapy characteristics showed interaction with local recurrence; however significant heterogeneity remained within each of the subgroups. It is likely that the difference in baseline risk of recurrence is in part responsible for this variability.

	Number of Studies	Hazards Ratio (95% CI)
Non TME	12	0.73 (0.66-0.81)
TME	1	0.42 (0.26-0.67)
BED ≥ 30Gy^{10}	8	0.50 (0.44-0.57)
BED < 30Gy^{10}	5	1.03 (0.89-1.18)
Treatment fields focused to the posterior pelvis	5	0.49(0.41-0.58)
Other	8	0.85 (0.75-0.96)

Table: Subgroup/Sensitivity Analysis on local recurrence

Curative and Overall Resectability
From 15 studies, the pooled Risk Ratio (RR) for curative respectability was 1.02 (95% CI 1-1.05) in favour of preoperative treatment (Homogeneity X^2=14.94; p=0.38; I^2=6%).
The data for overall resectability could not be pooled due to heterogeneity (Homogeneity X^2=39.59; p=0.00004; I^2=72%).

Sphincter Sparing Surgery
From 15 studies, the pooled Risk Ratio (RR) for sphincter sparing surgery was 0.96 (95% CI; 0.88-1.04) in favour of pre-operative treatment (Homogeneity X^2=23.47; p=0.05; I^2=40%). None of the factors specified *a priori* could explain the observed heterogeneity for this outcome.

Acute Radiotherapy Side Effects
The proportion of patients experiencing no toxicities ranged from 20% to 84% with the most common reported side effect being diarrhoea (20%).

Acute Toxicities Post Surgery
The proportion of patients with no toxicities post-operatively favoured the surgery alone group; from 6 studies the Risk Ratio=0.88 (95% CI; 0.82-0.94).

Late Toxicities
Quality of life comparisons showed a non-significant trend towards worse outcomes in irradiated patients. There was more scarring of the anal sphincters in the irradiated group (33%) when compared with the non-irradiated group (13%) confirmed by endoanal ultrasound. This outcome was related to functional outcome with 11/12 patients suffering some degree of incontinence symptoms.
Maximum resting pressure and maximum squeezing pressure were significantly lower in the irradiated group.

Preoperative Radiotherapy versus preoperative chemoradiotherapy
The data for this comparison were not pooled, rather a brief summary of results from each of the individual, relevant studies was provided. As there is a more recent Cochrane review which addresses this comparison specifically, it was deemed unnecessary to include the results presented in the current review.

General comments
Literature search conducted from 1966 – December 2006

This review looks at a number of different treatment comparisons, some of which are not relevant to the current PICO. Therefore this evidence table contains information pertaining only to the relevant comparisons – pre-operative radiotherapy versus surgery alone and pre-operative radiotherapy versus pre-operative chemoradiotherapy.

The review did not use individual patient data for any of the analysis.

NOTE: In the text of this review, results are presented as Hazards Ratios whereas in the tables the results are listed either as Peto Odds Ratios as the version of RevMan used for the analysis labels the results as Peto Odds Ratios by default. It should be noted that the results from this review could not be replicated in RevMan from the data and information provided.

Risk of bias in included studies
The quality of each study was assessed by two authors using a 14 point checklist, with any discrepancy resolved by consensus and the range of quality scores was 0.29 to 0.88 (max 1).

Special considerations for radiotherapy dose fractionation
Biological effective dose (BED) was calculated and used to facilitate comparison between regimens using BED=30Gy[10] to divide studies into lower versus higher doses for subgroup/sensitivity analysis.

References of Included Studies (For systematic reviews):
Refer to review for full details of studies included in the review

3.2. Colonic Stents

3.2.1. For patients presenting with acute large bowel obstruction as first presentation of colorectal cancer, what are the indications for stenting as a bridge to elective surgery?

Short Summary

There was very little evidence of any type with which to address this topic. There are no directly applicable studies and so in assessing the body of evidence, consideration was given to the possibility that relevant evidence may not be directly available and so studies which compared stenting as a bridge to surgery, stenting for palliative purposes or immediate emergency surgery were also reviewed to check whether these studies contained information relevant to the topic. Despite this consideration, very little evidence of relevance was found from these studies and what was available was of very poor quality.

In relation to the use of CT for the diagnosis of colorectal cancer in the emergency setting, 2 studies (Beattie et al, 2007; Maras-Simunic et al, 2009) comprised the body of evidence.

Beattie et al. (2007) reported a sensitivity, specificity, positive predictive value and negative predictive value of 91% for the use of CT in the diagnosis of large bowel obstruction. The positive likelihood ratio was 10.1 and the negative likelihood ratio was 0.10. There were 4 reported CT errors for the presence of mechanical obstruction, 2 false positive and 2 false negative.

Maras-Simunic et al. (2009) reported that the use of multi-detector CT colonography correctly identified all obstructions resulting from colorectal cancer (41/47). MDCT colonography gave 1 false positive result in a population of 44 patients with obstruction. Overall MDCT correctly established diagnosis in 97.9% of patients and located all obstructive cancers correctly (46/47).

The evidence body for the indications and timing for stenting consisted of one pooled analysis of case series studies (Sebastian et al, 2004) and 2 case series (Song et al, 2007 and Ripici et al, 2008).

Technical Failure

From one pooled analysis with a total of 1198 patients (Sebastian et al, 2004) there was a 5.8% failure rate on attempted placement of rectosigmoid stents, 14.5% failure rate for descending colon placement and 15.38% failure rate for more proximal colon stent placement.

Clinical Failure

Pooled analysis (Sebastian et al. 2004) showed that clinical success was achieved in 88.56% (1061/1198) of patients with 52 failures in the left colon and 4/5 patients with stent placement in the right colon not achieving clinical success. Causes of clinical failure included malposition, migration, proximal obstruction, stool impaction, perforation and persistent obstructive symptoms.

Perforation

From one pooled analysis (Sebastian et al. 2004) there were 45 perforations related to stent placement (3.76%) with all but one occurring at the rectosigmoid junction. Predilation was significantly associated with perforation and thought to be responsible in 16 instances. 64.4% (29/45) required emergency surgical intervention while 10 patients were treated with intravenous antibiotics and one patient had a new stent placed.

Migration

Migration occurred in 11.81% (n=132) of cases of successfully inserted stents; occurring within a week in 7.25% (n=81) patients and more than a week after insertion in the remaining 41 patients (Sebastian et al. 2004).

Stents inserted as a palliative measure migrated more often (116/791) than those inserted as a bridge to surgery (16/407) (p=0.01).

There was a significant difference in the number of covered stent (52/170) and uncovered stent migration (p=0.04).

Mortality

The cumulative mortality rate was 0.58% (n=7 deaths), three of which had documented colonic perforations. Six of the deaths occurred in patients stented for palliative purposes (Sebastian et al. 2004).

Bridging to Surgery

The rate of successful bridging to surgery was 100% (95% CI, 85%-100%).
Median time from SEMS placement to surgery was 5 days (95% CI, 5.4-5.6 days)

In all patients, stents were removed en bloc with the tumour without any surgical complications.
2 patients experienced post-operative complication; 1 pulmonary embolism and 1 wound infection (Repici et al. 2008).

Updated Evidence
On update searches, a further two studies were found to be relevant to the current topic (Iverson et al, 2011 and Vemulapalli et al, 2010).

Comparing SEMS insertion with emergency surgery, no difference in technical success of relieving colonic obstruction was observed between the two modalities (94% vs. 100%, p=0.07).
Patients in the SEMS group had a significantly shorter median hospital stay (2 days, range 1-24 days) compared with patients in the surgery group (8 days, range 2-43 days) (p<0.001).
Patients with SEMS had significantly fewer acute complications compared with the surgery group (8% vs. 30%, p=0.03) (Vemulapalli et al, 2010).
Hospital mortality for the SEMS group was 0% versus 8.5% in patients that underwent surgical decompression (p=0.04).
The number of patients with SEMS who presented with late complications (22%) was higher than in the surgery group (9%) though this difference was not statistically significant (p=0.06).
Overall survival did not differ significantly between the groups; median survival time in the SEMS group was 24 weeks (range: 2-196) compared with 23 weeks (range: 1-124) in the surgery group (p=0.76) (Vemulapalli et al, 2010).

From Iverson et al (2011) SEMS insertion was successful in all 34 patients for a technical success rate of 100%. 31/34 attempted SEMS insertions were performed or supervised by a colorectal surgeon.
Four patients had events which classified the procedure as a clinical failure resulting in a clinical success rate of 88%. Clinical failure occurred equally in patients with tumours located in the transverse colon or splenic flexure (1/11) and descending/sigmoid colon (3/23).

Overall perforation rate was 12% (4/34) and was comparable for tumours located in the transverse colon or splenic flexure (1/11) and descending/sigmoid colon (3/23).

Median follow-up was 33.7 months independent of oncological outcome and timing of surgery; 2 year survival for the 34 patients with potentially curable disease was 85% (68%-94%) and 3 year survival was 74% (53%-86%).
Median survival was 4.5 years (3.1 to 6.0 years).

Curative outcome was achieved in 88% of patients (30/34); 2 and 3 year survival rates after surgery with curative outcome were 90% (72%-97%) and 77% (54%-89%).

Review Protocol

Population	Intervention	Comparison	Outcomes
Patients presenting with acute large bowel obstruction as a first presentation of colorectal cancer	CT Scan	No CT Scan	• Detection rates • Management

Population	Factors		Outcomes
Patients presenting with acute large bowel obstruction as a first presentation of colorectal cancer	• Prognostic Factors (e.g. age, co-morbidities) • Timing of intervention • Degree of obstruction • T stage • Level of tumour in colon		• Post-procedure mortality (colonic perforation, stent failure) • Quality of surgery (stoma, +/- margins, lymph node harvest) • Morbidity

Following a systematic search of relevant data sources (see appendix .1), the information specialist created a database of potentially relevant studies. All titles and abstracts were sifted by a single reviewer. Queries about inclusion were clarified by the GDG topic subgroup. The full studies were then obtained and reviewed and relevant studies were included in the final evidence review.

All update searches were sifted by a single reviewer and the list of potentially relevant studies was also checked for irrelevant studies by the GDG subgroup. Only studies which all subgroup members were in agreement were excluded. The remaining studies were obtained and reviewed with relevant studies included in the final evidence review.

The GDG identified two key areas in this topic where there is a need for guidance and as such this topic comprises two parts:
  a) Should all patients presenting with obstruction as a symptom of colorectal cancer have a CT scan to confirm diagnosis and provide evidence of metastases?
  b) What are the indications for stenting patients and the optimal timing for stenting to occur?

Reasons for Excluding Studies
Expert Reviews
Abstracts Only
Studies did not report on outcomes of interest
Stenting/Surgery not in the emergency setting
Foreign Language with no translation
Population not relevant to PICO
Interventions not relevant to PICO

Quality of the included studies
Systematic review of RCTs (n =0)
Systematic review of combined study designs (n = 1)
Randomized controlled trial (n =0)
Prospective cross sectional study (n =0)
Case Series Studies (n = 5)
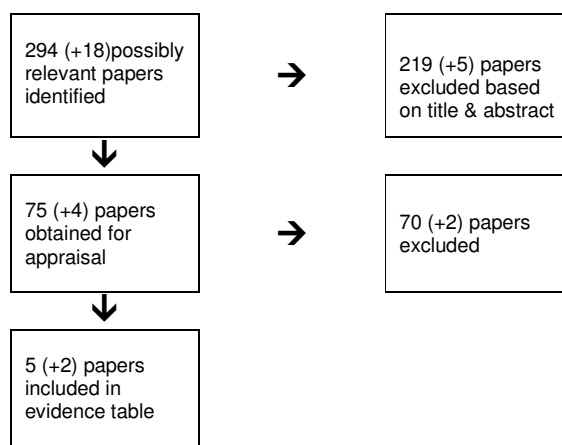
294 (+18)possibly relevant papers identified → 219 (+5) papers excluded based on title & abstract

↓

75 (+4) papers obtained for appraisal → 70 (+2) papers excluded

↓

5 (+2) papers included in evidence table

Volume of evidence

There was very little evidence with which to address this topic.

Applicability
No studies identified in the searches were relevant to the topic; a small volume of indirect evidence may be of use in discussing this topic.

Consistency
Unable to comment on consistency of the evidence body given that it is so sparse

Other factors
In assessing the evidence, consideration was given to the possibility that relevant evidence may not be directly available and so studies which compared stenting as a bridge to surgery, stenting for palliative purposes or immediate emergency surgery were also reviewed to ensure that these studies did not contain information relevant to the topic.

Evidence Statement
No studies were identified which were deemed directly applicable to this topic and despite consideration being given to the possibility of evidence being available indirectly, very little of relevance was found from studies comparing stenting as a bridge to surgery, stenting for palliative purposes or immediate emergency surgery.

Should all patients presenting with obstruction as a symptom of colorectal cancer have a CT scan to confirm diagnosis and provide evidence of metastases?
Two studies (Beattie et al, 2007; Maras-Simunic et al, 2009) provided low quality evidence for the use of CT or CT colonography in the diagnosis of large bowel obstruction.
Beattie et al. reported a sensitivity, specificity, positive predictive value and negative predictive value of 91%. The positive likelihood ratio was 10.1 and the negative likelihood ratio was 0.10. There were 4 reported CT errors for the presence of mechanical obstruction, 2 false positive and 2 false negative.
Maras-Simunic et al. reported that the use of multi-detector CT colonography correctly identified all obstructions resulting from colorectal cancer (41/47). MDCT colonography gave 1 false positive result in a population of 44 patients with obstruction. Overall MDCT correctly established diagnosis in 97.9% of patients and located all obstructive cancers correctly (46/47).
MDCT colonography correctly identified T-stage in 40/41 lesions (accuracy: 97.6%); in relation to the classification of T3 lesions only, sensitivity was 100%, specificity was 75%, accuracy was 97.6%, positive predictive value was 97.4% and negative predictive value was 100%.
Histopathological classification of nodal status of the 41 lesions showed 19 without lymph node involvement and 22 with lymph node metastases. MDCT correctly identified lymph node involvement in 30/41 patients with an overall accuracy of 73.2%.
MDCT correctly identified all cases of metastases (8/41).

What are the indications for stenting patients and the optimal timing for stenting to occur?
A total of 3 studies provided some indirect evidence of low quality with which to address this topic (Sebastian et al, 2004; Song et al, 2007; Repici et al, 2008).

Technical Failure
From one pooled analysis with a total of 1198 patients (Sebastian et al, 2004) there was a 5.8% failure rate on attempted placement of rectosigmoid stents, 14.5% failure rate for descending colon placement and 15.38% failure rate for more proximal colon stent placement.
From one multi-centre prospective study (Song et al. 2007) fluoroscopic negotiation of a guide wire was considered a technical failure in 13/151and was significantly higher in cases with complete obstruction compared with patients with partial obstruction (p=0.034). No statistically significant difference between sites was observed (p=0.106 for fluoroscopic technical failure and p=0.244 for the technical failure rate.
In one prospective cohort study (Ripici et al, 2008), SEMS were placed as a bridge to surgery in 19 patients and with palliative intent in 23 patients; 36 patients received 1 stent each, 6 patients had 2 stents placed due to long strictures and 1 patient had 2 stents due to malpositioning of the initial stent.
No patient underwent balloon dilation before or after stent placement.
Spanning of the strictures was accomplished in 39/42 patients for a technical success rate of 93% (95% CI, 81%-99%)
The SEMS could not be passed through a hepatic flexure stricture in one patient, stent failed to expand in one patient after placement within a severe angulation of the rectosigmoid junction which was compressed by a large neoplastic mass and the third technical failure was the result of malpositioning of the stent

proximal to the stricture, though a second overlapping SEMS was placed during the same procedure in this patient.

Clinical Failure
Pooled analysis (Sebastian et al. 2004) showed that clinical success was achieved in 88.56% (1061/1198) of patients with 52 failures in the left colon and 4/5 patients with stent placement in the right colon not achieving clinical success. Causes of clinical failure included malposition, migration, proximal obstruction, stool impaction, perforation and persistent obstructive symptoms.
Ribici et al (2008) reported that 40/42 patients had relief of obstructive symptoms within 24 hours of stent placement for a clinical success rate of 95% (95% CI, 84%-99%).
During initial follow-up, there were 8 additional clinical failures in patients in the palliation group.
In the palliative group median time at risk for clinical failure was 99 days (42-212 days) and at 6 months, the rate of clinical success was 58%.
No difference was observed for maintenance of clinical success over time for patients presented with complete versus subtotal occlusion (p=0.12) or for patients with strictures distal to the splenic flexure versus more proximal sites (p=0.8).

Perforation
From one pooled analysis (Sebastian et al. 2004) there were 45 perforations related to stent placement (3.76%) with all but one occurring at the rectosigmoid junction. Predilation was significantly associated with perforation and thought to be responsible in 16 instances. 64.4% (29/45) required emergency surgical intervention while 10 patients were treated with intravenous antibiotics and one patient had a new stent placed.
Song et al. (2004) reported perforation in 22% of patients (11/50) in the bridge to surgery group and in 5% (5/95) patients in the palliative group. Perforation was significantly higher in the bridge to surgery group compared to the palliative group (p=0.004). In multivariate analysis, complete obstruction was the only significant independent factor of perforation (OR, 6.88, 95% CI 2.04-23.17, p=0.002). Age, sex, site of obstruction, length of obstruction, source of malignancy and balloon dilation before and after stent placement were not related to the likelihood of perforation.

Migration
Migration occurred in 11.81% (n=132) of cases of successfully inserted stents; occurring within a week in 7.25% (n=81) patients and more than a week after insertion in the remaining 41 patients (Sebastian et al. 2004).
125 of migrations were distal and in many there was spontaneous expulsion of the stents per anus.
10.5% (n=96) of recto-sigmoid stents migrated as compared with 23.9% (n=29) of the descending colon stents and 26.9% (n=7) of proximal colon stents.
Stents inserted as a palliative measure migrated more often (116/791) than those inserted as a bridge to surgery (16/407) (p=0.01).
There was a significant difference in the number of covered stent (52/170) and uncovered stent migration (p=0.04).
Risks for increased rate of stent migration included use of laser treatment, dilation prior to stent insertion, and use of chemotherapy and radiotherapy.

Mortality
The cumulative mortality rate was 0.58% (n=7 deaths), three of which had documented colonic perforations. Six of the deaths occurred in patients stented for palliative purposes (Sebastian et al. 2004).

Reobstruction
There were 82 clinically significant episodes of reobstruction documented (7.34%) with median time to obstruction reported as being 24 weeks (range: 1-52 weeks).
Reobstruction rate was significantly lower in patients with covered stents compared with patients with uncovered stents (4.7% vs. 7.81%, p=0.003).
Reasons for reobstruction included tumour ingrowth, faecal impaction, mucosal prolapse, migration, tumour overgrowth and peritoneal seeding (Sebastian et al. 2004).

Follow-up
9/50 patients in the bridge to surgery group died 40-378 days (mean 171.2 days) after stent placement as a result of colon perforation, myocardial infarction of cancer recurrence. The remaining patients were still alive 15-1608 days (mean 434.2 days) after stent placement.
62/95 patients in the palliative group died 5-706 days (mean 109.3 days) after stent placement due to progression of disease, myocardial infarction, bleeding or sepsis. The remaining patients were alive 21-683 days (mean 210.5 days) after stent placement.

Median survival period was 263.8 days (95% CI 96.4 days to 331.3 days); 30 day survival was 87%, 60 day survival was 78%, 90 day survival was 62% and 180 day survival was 42% (Song et al, 2007).

Survival
All patients with operable tumours survived until elective surgery and throughout the post-operative follow-up period; median follow-up time after stent placement was 528 days (range 445-634).
In the palliative group, 30% (7/23) patients were still alive at the end of follow-up (January 2007); median survival was 208 days (95% CI, 93-232 days).
No difference in survival was observed between patients with complete versus subtotal occlusion at baseline (p=0.31) (Repici et al. 2008).

Bridging to Surgery
The rate of successful bridging to surgery was 100% (95% CI, 85%-100%).
Median time from SEMS placement to surgery was 5 days (95% CI, 5.4-5.6 days)
In all patients, stents were removed en bloc with the tumour without any surgical complications.
2 patients experienced post-operative complication; 1 pulmonary embolism and 1 wound infection (Repici et al. 2008).

Cost Effectiveness
From the pooled analysis, 3 studies reported on the cost-benefit ratio of stent insertion (Sebastian et al, 2004); one European study reported a 50% reduction in estimated costs of managing a palliative case and 12% in the bridge to surgery group, a second study reported a significant reduction in overall cost in stented patients as compared to the conventional surgery group and the group where stent insertion failed. A third study reported the overall costs were 19.7% lower in the stent group and in patients in whom curative surgery was planned, the cost reduction was reported to be 28.8%.
Cost reductions were attributed to shorter hospital stays, fewer days in intensive care units and fewer surgical procedures.

Updated Evidence
On update searches, a further two studies were found to be relevant to the current topic (Iverson et al, 2011 and Vemulapalli et al, 2010).

Vemulapalli et al (2010) compared the use of SEMS with emergency surgery in patients with incurable metastatic colorectal cancer. Though the topic was related to the use of stents as a bridge to surgery for potentially curative outcomes, thus this study should be considered to be indirect evidence as the population consists solely of patients for whom treatment is being carried out with palliative intent.
It is included here for the purposes of providing evidence on the comparative outcomes of SEMS versus immediate emergency surgery for a topic where there is a lack of comparative evidence.
Iverson et al (2011) evaluated the outcomes in patients with potentially curable colorectal cancer treated with SEMS as a bridge to surgery.

Vemulapalli et al (2010) reported that SEMS were successfully placed and relieved obstruction in 50/53 patients and were unable to be deployed in 3 patients due to altered colonic anatomy caused by the tumour. These patients underwent surgical decompression.
There were no procedure related deaths; two patients developed peritonitis and day 1 and 3 respectively, due to delayed colonic perforation by the stent.
Two patients had stent migration while hospitalised and re-obstructed; these patients underwent a second stent placement across the lesion.

Late complications were recorded in 11 patients; 4 patients developed peritonitis from colonic perforation and required surgery with a stoma.
Stent migration occurred in 2 patients after 6 and 8 months respectively, both of these patients were receiving chemotherapy which resulted in tumour shrinkage and they remained unobstructed until death.
Four patients re-obstructed at the primary tumour site as a result of SEMS occlusion.
Median time from SEMS placement to occlusion was 8 months (range: 4-15 months).

In the surgery group, surgery was successful in relieving obstruction in all 70 patients.
There were 6 post-operative deaths and early post-surgical complications occurred in 26 patients (within 30 days of surgery) and late complications occurred in 6 patients.

No difference in technical success of relieving colonic obstruction was observed between the two modalities (94% vs. 100%, p=0.07).

Patients in the SEMS group had a significantly shorter median hospital stay (2 days, range 1-24 days) compared with patients in the surgery group (8 days, range 2-43 days) (p<0.001).
Patients with SEMS had significantly fewer acute complications compared with the surgery group (8% vs. 30%, p=0.03) (Vemulapalli et al, 2010).
Hospital mortality for the SEMS group was 0% versus 8.5% in patients that underwent surgical decompression (p=0.04).
The number of patients with SEMS who presented with late complications (22%) was higher than in the surgery group (9%) though this difference was not statistically significant (p=0.06).

Overall survival did not differ significantly between the groups; median survival time in the SEMS group was 24 weeks (range: 2-196) compared with 23 weeks (range: 1-124) in the surgery group (p=0.76) (Vemulapalli et al, 2010).

From Iverson et al (2011) SEMS insertion was successful in all 34 patients for a technical success rate of 100%. 31/34 attempted SEMS insertions were performed or supervised by a colorectal surgeon.
Four patients had events which classified the procedure as a clinical failure resulting in a clinical success rate of 88%. Clinical failure occurred equally in patients with tumours located in the transverse colon or splenic flexure (1/11) and descending/sigmoid colon (3/23).

Overall perforation rate was 12% (4/34) and was comparable for tumours located in the transverse colon or splenic flexure (1/11) and descending/sigmoid colon (3/23).

29 patients had an elective resection (including the 3 patients that stayed in hospital until scheduled surgery); elective surgery was performed a median of 35 days (range: 6-100 days) after SEMS insertion.
There were no post-operative deaths, though 3 patients developed severe post-operative complications.

Overall 30 day mortality rate after technical success was 0; of the 5 patients that had acute surgery, 1 patient dies 7 days later for a cumulative 30-day mortality after SEMS and surgery of 3% (1/34).

Outcome
28/34 patients were stoma free after surgery.
Median follow-up was 33.7 months independent of oncological outcome and timing of surgery; 2 year survival for the 34 patients with potentially curable disease was 85% (68%-94%) and 3 year survival was 74% (53%-86%).
Median survival was 4.5 years (3.1 to 6.0 years).

Curative outcome was achieved in 88% of patients (30/34); 2 and 3 year survival rates after surgery with curative outcome were 90% (72%-97%) and 77% (54%-89%).

Liver metastases were detected in 3 patients; curative liver resection was possible in 1/3 patients.

Two patients had a palliative outcome; both had incurable peritoneal disease at bowel resection.

References

Beattie G, Peters R, Guy S, Mendelson R (2007) Computed Tomography in the Assessment of Suspected Large Bowel Obstruction *Anz Journal or Surgery 77;160-165*

Iverson L, Kratmann M, Boje M & Laurberg S (2011) Self-expanding metallic stents as bridge to surgery in obstructing colorectal cancer *British Journal of Surgery* 98;275-281

Maras-Simunic M, Druzijanic N, Simunic M, Roglic J (2009) Use of modified multidetector CT colonography for the evaluation of acute and subacute colon obstruction caused by colorectal cancer: a feasibility study

Repici A, DeCaro G, Luigiano C, Fabbri C, Pagano N, Preatoni P, Danese S, Fucci L, Consolo P, Malesci A, D'Imperio N, Cennamo V (2008) Wallfles colonic stent placement for the management of malignant colorectal obstruction: a prospective study at two centres *Gastrointetinal Endoscopy* 67;1:77-84

Song HY, Kim JH, Shin JH, Kim HC, Yu CS, Kim JC, Kang SG, Yoon CJ, Lee JY, Koo JH, Lee KH, Kim JK, Kim DH, Shin TB, Jung GS, Han YM (2007) A dual design expandable colorectal stent for malignant colorectal obstruction: results of a multi-centre study *Endoscopy* 39;5:448-454

Sebastian S, Johnstone S, Geoghegan T, Torreggiani W, Buckley M (2004) Pooled analysis of the efficacy and safety of self-expanding metal stenting in malignant colorectal obstruction *American Journal of Gastroenterology*

Vemulapalli R, Lara L et al (2010) A comparison of palliative stenting or emergent surgery for obstructing incurable colon cancer *Dig Dis Sci* 55;1732-1737

Evidence Tables

Citation: Beattie G, Peters R, Guy S, Mendelson R (2007) Computed Tomography in the Assessment of Suspected Large Bowel Obstruction *Anz Journal or Surgery 77;160-165*
Design: Retrospective Case Series **Country**: Australia **Aim**: to assess the efficacy of computed tomography (CT) scanning in the diagnosis of acute large bowel obstruction
Inclusion criteria Patients with suspected large bowel obstruction (LBO) both clinically and with suspicious plain radiological features who required further imaging
Exclusion criteria Patients in which LBO was not the primary diagnosis for exclusion but was incidentally diagnosed on routine CT Patients in whom flatus tubes had been passed before imaging Patients who had received rectal contrast
Population N=44 patients were scanned
Interventions LBO scanning CT protocol
Outcomes Management Sensitivity Specificity Positive Predictive Value (PPV) Negative Predictive Value (NPV) Positive Likelihood Ratios Negative Likelihood Ratios
Results 22 patients had proven mechanical acute LBO of whom 18 had obstructing carcinoma, 2 had diverticular stricture, 1 had endometriosis and 1 had sigmoid volvulus. 17/18 patients underwent surgical resection, one elderly patient opted not to undergo surgery and instead underwent stenting. 22 patients had no evidence of mechanical obstruction, 15 of which were scanned in more than one position. Sensitivity, specificity, PPV and NPV were each 91%; positive likelihood ratio was 10.1 and negative likelihood ratio was 0.10. There were four CT errors for the presence of mechanical obstruction, 2 false positive and 2 false negative.

Citation: Iverson L, Kratmann M, Boje M & Laurberg S (2011) Self-expanding metallic stents as bridge to surgery in obstructing colorectal cancer *British Journal of Surgery* 98;275-281
Design: Retrospective Case Series **Country**: Denmark **Setting:** Emergency Setting **Aim**: to evaluate the outcomes in patients with potentially curable colorectal cancer treated with SEMS as a bridge to surgery
Inclusion criteria Details not clear – appears to be patients with potentially curable colorectal cancer in whom SEMS placement had been attempted due to bowel obstruction
Exclusion criteria Patients with distant metastases detected before or after the SEMS attempt Patients unfit for surgery due to comorbidity or advanced age Patients that were transferred to their primary hospital for evaluation and treatment.
Sample Size N/A
Randomisation Method N/A
Population N=34
Study Duration Recruitment: January 2004 and August 2007 Follow-up: until death or December 1st 2009 (whichever came first).
Interventions SEMS
Outcomes Technical Success (defined as accurate SEMS placement with adequate stricture coverage). Clinical Success (defined as decompression and relief of obstructive symptoms without further interventions during the hospital stay) Perforation (diagnosed at surgery) Bridge to Surgery (scheduled elective surgery, independent of time between SEMS insertion and surgery) Cumulative 30 day mortality after SEMS insertion and bridge to surgery (based on deaths within 30 days after SEMS insertion and bridge to surgery respectively and calculated on an intention to treat basis).
Results *Technical Success Rate* SEMS insertion was successful in all 34 patients for a technical success rate of 100%. 31/34 attempted SEMS insertions were performed or supervised by a colorectal surgeon. *Clinical Success Rate* Four patients had events which classified the procedure as a clinical failure resulting in a clinical success rate of 88%. Clinical failure occurred equally in patients with tumours located in the transverse colon or splenic flexure (1/11) and descending/sigmoid colon (3/23). Three patients had scheduled elective surgery during hospital stay and were classified and having a bridge to surgery. A total of 27 patients had a functioning SEMS in place on discharge or death; the median hospital stay was 3 days. Two patients needed surgical intervention while awaiting elective surgery due to SEMS migration and tumour perforation. Overall perforation rate was 12% (4/34) and was comparable for tumours located in the transverse colon or

splenic flexure (1/11) and descending/sigmoid colon (3/23).

A total of 5 patients had acute surgery after SEMS insertion.

Elective Bridge to Surgery
29 patients had an elective resection (including the 3 patients that stayed in hospital until scheduled surgery); elective surgery was performed a median of 35 days (range: 6-100 days) after SEMS insertion.
There were no post-operative deaths, though 3 patients developed sever post-operative complications.

Cumulative 30 day Mortality
Overall 30 day mortality rate after technical success was 0; of the 5 patients that had acute surgery, 1 patient dies 7 days later for cumulative 30-day mortality after SEMS and surgery of 3% (1/34).

Outcome
28/34 patients were stoma free after surgery.
Median follow-up was 33.7 months independent of oncological outcome and timing of surgery; 2 year survival for the 34 patients with potentially curable disease was 85% (68%-94%) and 3 year survival was 74% (53%-86%).
Median survival was 4.5 years (3.1 to 6.0 years).

Curative outcome was achieved in 88% of patients (30/34); 2 and 3 year survival rates after surgery with curative outcome were 90% (72%-97%) and 77% (54%-89%).

Liver metastases were detected in 3 patients; curative liver resection was possible in 1/3 patients.

Two patients had a palliative outcome; both had incurable peritoneal disease at bowel resection.

Citation: Maras-Simunic M, Druzijanic N, Simunic M, Roglic J (2009) Use of modified multidetector CT colonography for the evaluation of acute and subacute colon obstruction caused by colorectal cancer: a feasibility study
Design: Diagnostic Case Series **Country**: Croatia **Aim**: to evaluate the feasibility of using CT colonography with a modified procedural protocol for diagnosis and cancer staging in patients with patients with suspected acute or subacute colon obstruction caused by colorectal cancer.
Inclusion criteria Patients seen in the emergency setting with significant suspicion of acute colon obstruction caused by colorectal cancer based on medical history, clinical evaluation and a plain abdominal radiograph.
Exclusion criteria Patients with acute colon obstruction suspected to be caused by diverticulitis or diverticular strictures, volvulus or adhesions. Agitated patients Patients with progressive malignancies Patients with severe concomitant disease Patients with obstructions and perforations
Population N=47
Interventions CT Colonography
Outcomes Technical Fesibility Diagnosis of Colorectal Cancer TNM Classification
Results Technical Feasibility CT colonography was performed in 87.2% of patients Diagnosis of Colorectal Cancer In 44/47 patients colon distension was caused by obstruction and pathological examination confirmed colorectal cancer in 41/47 patients. MDCT colonography indicated a tumour as the cause of obstruction in 42/44 patients giving one false positive diagnosis of obstructive cancer. MDCT correctly established diagnosis in 97.9% of patients (46/47) and located all obstructive cancers correctly. Evaluation of all the identified colorectal lesions indicated lesion diameters from 2-9cm as measured by MDCT and 2-10.5cm as measured by pathologists after surgery. There was no significant difference in measurement of lesion size (p=0.809). TNM Classification MDCT correctly identified T stage in 40/41 lesions with an accuracy of 97.6%. For the classification of T3 lesions, sensitivity was 100%, specificity was 75%, accuracy 97.6%, positive predictive value 97.4% and negative predictive value 100%. Histopathological classification of nodal status of the 41 colorectal lesions showed 19 without lymph node metastases and 22 with lymph node metastases. MDCT correctly identified lymph node involvement in 30/41 patients with an overall accuracy of 73.2%. MDCT correctly identified all patients with metastatic disease (8/41)

Citation: Repici A, DeCaro G, Luigiano C, Fabbri C, Pagano N, Preatoni P, Danese S, Fucci L, Consolo P, Malesci A, D'Imperio N, Cennamo V (2008) Wallfles colonic stent placement for the management of malignant colorectal obstruction: a prospective study at two centres *Gastrointetinal Endoscopy* 67;1:77-84
Design: Prospective Clinical Cohort Study **Country**: Italy **Aim**: to evaluate the effectiveness and safety of a novel large diameter SEMS (WallFlex) designed for delivery through the endoscope in treating malignant colonic obstruction
Inclusion criteria The presence of large bowel obstruction secondary to malignancy as confirmed by erect and supine abdominal radiograph imaging and CT. Consecutive patients who are ≥18 years requiring stents for palliation or a bridge to surgery
Exclusion criteria Benign stricture Perforated colon Concurrent radiotherapy for the colorectal stricture Treatment with an investigational drug or device within the preceding 4 weeks Placement of another metal stent for the same stricture Any terminal condition
Population N=42
Interventions TTS WallFlex colonic stent
Outcomes Technical Success (accurate SEMS deployment across the stricture on the first attempt) Clinical Success (complete relief of bowel obstruction as judged by clinical symptoms and radiographic observations without complications) Survival Bridging to Surgery
Results 64% of patients were aged 70 years or older 83% of strictures were situated distal to the splenic flexure Technical Success SEMS were placed as a bridge to surgery in 19 patients and with palliative intent in 23 patients; 36 patients received 1 stent each, 6 patients had 2 stents placed due to long strictures and 1 patient had 2 stents due to malpositioning of the initial stent. No patient underwent balloon dilation before or after stent placement. Spanning of the strictures was accomplished in 39/42 patients for a technical success rate of 93% (95% CI, 81%-99%) The SEMS could not be passed through a hepatic flexure stricture in one patient, stent failed to expand in one patient after placement within a severe angulation of the rectosigmoid junction which was compressed by a large neoplastic mass and the third technical failure was the result of malpositioning of the stent proximal to the stricture, though a second overlapping SEMS was placed during the same procedure in this patient. Clinical Success 40/42 patients had relief of obstructive symptoms within 24 hours of stent placement for a clinical success rate of 95% (95% CI, 84%-99%). During initial follow-up, there were 8 additional clinical failures in patients in the palliation group. In the palliative group median time at risk for clinical failure was 99 days (42-212 days) and at 6 months, the rate of clinical success was 58%. No difference was observed for maintenance of clinical success over time for patients presented with complete versus subtotal occlusion (p=0.12) or for patients with strictures distal to the splenic flexure versus more proximal sites (p=0.8). Survival All patients with operable tumours survived until elective surgery and throughout the post-operative follow-up period; median follow-up time after stent placement was 528 days (range 445-634).

In the palliative group, 30% (7/23) patients were still alive at the end of follow-up (January 2007); median survival was 208 days (95% CI, 93-232 days).
No difference in survival was observed between patients with complete versus subtotal occlusion at baseline (p=0.31).

Bridging to Surgery
The rate of successful bridging to surgery was 100% (95% CI, 85%-100%).
Median time from SEMS placement to surgery was 5 days (95% CI, 5.4-5.6 days)
In all patients, stents were removed en bloc with the tumour without any surgical complications.
2 patients experienced post-operative complication; 1 pulmonary embolism and 1 wound infection

General comments
The assignment of patients to palliation rather than surgery was based on unacceptable surgical risk due to factors such as advanced age, comorbidities or the presence of locally advanced disease or distant metastases.

Citation: Sebastian S, Johnstone S, Geoghegan T, Torreggiani W, Buckley M (2004) Pooled analysis of the efficacy and safety of self-expanding metal stenting in malignant colorectal obstruction *American Journal of Gastroenterology*
Design: Systematic Review/Pooled Analysis **Country**: Ireland **Aim**: to review the efficacy and safety of self-expanding metal stents in the setting of malignant colorectal obstruction.
Inclusion criteria English and foreign language studies are included
Exclusion criteria Studies with inadequate data reported (even after contacting the author) on outcome variables or adverse events. Studies with data included in a subsequent publication Stenting done for benign stenosis
Population 54 trials including a total of 1,198 patients
Interventions Self expanding metal stents
Outcomes *Efficacy* Technical Success/Failure Clinical Success/Failure *Safety Data* Perforation Migration Mortality Reobstruction Cost effectiveness
Results Pooled median age of patients was 68 years (range 41-48) Stenting was performed as definitive palliative procedure in 791 (66%) and as a bridge to surgery in 407 (34%) patients. Technical Success/Failure Technical success was achieved at first attempt in 93.4% of patients (1,117/1,198); in individual series the success rates ranged from 64% to 100%. In the palliative group, the technical success was 93.35% and in the 'bridge to surgery' group it was 91.9% (p=0.34). There was a 5.8% failure on attempted placement of rectosigmoid stents, 14.5% failure for descending colon placement and 15.38% for more proximal colon stent placement. Clinical Success/Failure Pooled data showed that clinical success was achieved in 88.56% of patients (1,061/1,198) with the clinical success rates from individual series ranging from 55% to 100% (median 91%). In the left colon there were 52 failures. 4/5 patients who had stents placed in the right colon did not achieve clinical success. Causes of clinical failure included malposition, migration, proximal obstruction, stool impaction, perforation and persistent obstructive symptoms. Outcome in 'bridge to surgery' group 407 patients from 21 series underwent stenting as a bridge to surgery, with technical success in 374 (91.9%) patients and clinical success in 292 (71.7%) patients (clinical success was defined as the ability to perform a single stage surgery with primary anastomosis). Reasons for the requirement of a colostomy stoma in the stented patients included locally advanced tumour, inadequate preparation, perforation and migration.

Perforation
There were 45 perforations related to stent placement (3.76%) with all but one occurring at the rectosigmoid junction. Predilation was significantly associated with perforation and thought to be responsible in 16 instances. 64.4% (29/45) required emergency surgical intervention while 10 patients were treated with intravenous antibiotics and 1 patient had a new stent placed.

Migration
Migration occurred in 11.81% (n=132) of cases of successfully inserted stents; occurring within a week in 7.25% (n=81) patients and more than a week after insertion in the remaining 41 patients.
125 of migrations were distal and in many there was spontaneous expulsion of the stents per anus.
10.5% (n=96) of recto-sigmoid stents migrated as compared with 23.9% (n=29) of the descending colon stents and 26.9% (n=7) of proximal colon stents.
Stents inserted as a palliative measure migrated more often (116/791) than those inserted as a bridge to surgery (16/407) (p=0.01).
There was a significant difference in the number of covered stent (52/170) and uncovered stent migration (p=0.04).
Risks for increased rate of stent migration included use of laser treatment, dilation prior to stent insertion, and use of chemotherapy and radiotherapy.

Mortality
The cumulative mortality rate was 0.58% (n=7 deaths), three of which had documented colonic perforations. Six of the deaths occurred in patients stented for palliative purposes.

Reobstruction
There were 82 clinically significant episodes of reobstruction documented (7.34%) with median time to obstruction reported as being 24 weeks (range: 1-52 weeks).
Reobstruction rate was significantly lower in patients with covered stents compared with patients with uncovered stents (4.7% vs. 7.81%, p=0.003).
Reasons for reobstruction included tumour ingrowth, faecal impaction, mucosal prolapse, migration, tumour overgrowth and peritoneal seeding.

Cost Effectiveness
3 studies reported on the cost-benefit ratio of stent insertion; one European study reported a 50% reduction in estimated costs of managing a palliative case and 12% in the bridge to surgery group, a second study reported a significant reduction in overall cost in stented patients as compared to the conventional surgery group and the group where stent insertion failed. A third study reported the overall costs were 19.7% lower in the stent group and in patients in whom curative surgery was planned, the cost reduction was reported to be 28.8%.
Cost reductions were attributed to shorter hospital stays, fewer days in intensive care units and fewer surgical procedures.

Citation: Song HY, Kim JH, Shin JH, Kim HC, Yu CS, Kim JC, Kang SG, Yoon CJ, Lee JY, Koo JH, Lee KH, Kim JK, Kim DH, Shin TB, Jung GS, Han YM (2007) A dual design expandable colorectal stent for malignant colorectal obstruction: results of a multi-centre study *Endoscopy* 39;5:448-454

Design: Multi-centre prospective study

Country: Korea

Aim: to prospectively investigate the technical feasibility, clinical effectiveness and safety of a dual-design colorectal stent (consisting of an outer stent and an inner bare nitinol stent) in patients with malignant colorectal obstruction.

Inclusion criteria
Documented malignancy
Colorectal obstruction as defined by symptoms resulting in difficulty in defecation
Expandable metallic stent placement

Exclusion criteria
Nonsymptomatic patients with malignant colorectal obstruction
Clinical evidence of perforation or peritonitis combined with multiple small-bowel obstructions
Cecal or ascending colon obstruction (due to the shortness of the length of the stent delivery system)
Extension of rectal cancer to the anal sphincter

Population
N=151 consecutive patients with symptomatic malignant colorectal obstruction

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Interventions
fluoroscopic dual stent placement

Outcomes
Procedural Results
Functional Results
Complications
Follow-up

Results
Dual stent placement was attempted as a bridge to surgery in 50 patients and as palliative treatment in 101 patients.

Procedural Results
Fluoroscopic negotiation of a guide wire was considered a technical failure in 13/151 patients and was significantly higher in cases of complete obstruction than in partial obstruction (p=0.034); technical failure was also higher in patients with complete obstruction compared to patients with partial obstruction (p=0.034).
No statistically significant difference between sites was observed (p=0.106 for fluoroscopic technical failure rate and p=0.244 for the technical failure rate.

Functional Results
In the bridge to surgery group with technical success (48/50) complete expansion of the stent occurred and bowel obstruction was resolved within 2 days.
The mean interval between stent placement and surgery was 7 days (range 1-30 days).
In the palliative group, 87/95 patients showed complete decompression.

Complications
Perforation
Colon perforation occurred in 22% of patients (11/50) in the bridge to surgery group and in 5% (5/95) patients in the palliative group. Perforation rate was significantly higher in the bridge to surgery group compared with the palliative group (p=0.004).
In multivariate analysis with forward stepwise selection, complete obstruction was the only significant independent factor for perforation (odds ratio 6.88, 95% CI 2.04-23.17, p=0.002). Age, sex, site and length of obstruction, source of malignancy and balloon dilation before and after stent placement were not related to the likelihood of perforation.
Stent Migration
There were no stent migrations in the bridge to surgery group and there were 4 stent migrations in the palliative group 32-636 days after stent placement (mean 273 days).
Bleeding
Bleeding occurred after stent placement in 2 patients in the bridge to surgery group and in 6 patients in the

palliative group, all of which resolved spontaneously.
Pain
5/34 patients with stent placed in the rectum complained of sever rectal pain 2-22 hours after stent placement requiring analgesics.
Tumour overgrowth
Tumour overgrowth occurred in none of the bridge to surgery group and in 5 patients in the palliative group 61-393 days after stent placement (mean 195 days).

Follow-up
9/50 patients in the bridge to surgery group died 40-378 days (mean 171.2 days) after stent placement as a result of colon perforation, myocardial infarction of cancer recurrence. The remaining patients were still alive 15-1608 days (mean 434.2 days) after stent placement.
62/95 patients in the palliative group died 5-706 days (mean 109.3 days) after stent placement due to progression of disease, myocardial infarction, bleeding or sepsis. The remaining patients were alive 21-683 days (mean 210.5 days) after stent placement.
Median survival period was 263.8 days (95% CI 96.4 days to 331.3 days); 30 day survival was 87%, 60 day survival was 78%, 90 day survival was 62% and 180 day survival was 42%.

General comments
This study is aimed at assessing a particular type of stent and may not be relevant to the UK clinical setting.

Citation: Vemulapalli R, Lara L et al (2010)A comparison of palliative stenting or emergent surgery for obstructing incurable colon cancer *Dig Dis Sci* 55;1732-1737
Design: Retrospective Case Series **Country**: USA **Setting:** Emergency Setting **Aim**: to review experience with self-expanding metal stents (SEMS) compared to emergent surgery as initial therapy for the management of patients with incurable obstructing colon cancer.
Inclusion criteria Patients with stage 4 colorectal cancer who underwent stent insertion or surgery for acute total or subtotal colonic obstruction
Exclusion criteria Patients with clinical and/or radiological evidence of bowel perforation, peritonitis or massive gastrointestinal bleeding
Sample Size N/A
Randomisation Method N/A
Population N=123 (53 patients underwent stent insertion and 70 patients underwent surgery)
Study Duration May 2002 to December 2008
Interventions Self-expanding metal stents (SEMS) Emergency Surgery
Outcomes Relief of obstruction Technical success of procedure Duration of Hospital Stay Early and long term complications Overall Survival
Results All patients had unresectable metastatic colorectal cancer and the groups were comparable in regards to age, gender and tumour site. *SEMS Group* SEMS were successfully placed and relieved obstruction in 50/53 patients and were unable to be deployed in 3 patients due to altered colonic anatomy caused by the tumour. These patients underwent surgical decompression. There were no procedure related deaths; two patients developed peritonitis and day 1 and 3 respectively, due to delayed colonic perforation by the stent. Two patients had stent migration while hospitalised and re-obstructed; these patients underwent a second stent placement across the lesion. Late complications were recorded in 11 patients; 4 patients developed peritonitis from colonic perforation and required surgery with a stoma. Stent migration occurred in 2 patients after 6 and 8 months respectively, both of these patients were receiving chemotherapy which resulted in tumour shrinkage and they remained unobstructed until death. Four patients re-obstructed at the primary tumour site as a result of SEMS occlusion. Median time from SEMS placement to occlusion was 8 months (range: 4-15 months). *Surgery Group* Surgery was successful in relieving obstruction in all 70 patients. There were 6 post-operative deaths and early post-surgical complications occurred in 26 patients (within 30

days of surgery).
Late complications occurred in 6 patients.

SEMS versus Surgery
No difference in technical success of relieving colonic obstruction was observed between the two modalities (94% vs. 100%, p=0.07).
Patients in the SEMS group had a significantly shorter median hospital stay (2 days, range 1-24 days) compared with patients in the surgery group (8 days, range 2-43 days) (p<0.001).
Patients with SEMS had significantly fewer acute complications compared with the surgery group (8% vs. 30%, p=0.03).

Hospital mortality for the SEMS group was 0% versus 8.5% in patients that underwent surgical decompression (p=0.04).
The number of patients with SEMS who presented with late complications (22%) was higher than in the surgery group (9%) though this difference was not statistically significant (p=0.06).

Overall survival did not differ significantly between the groups; median survival time in the SEMS group was 24 weeks (range: 2-196) compared with 23 weeks (range: 1-124) in the surgery group (p=0.76).

Citation: Tilney HS, Lovegrove RE, Purkayastha S, Sains P (2007) Comparison of colonic stenting and open surgery for malignant large bowel obstruction *Surgical Endoscopy* 21;225-233
Design: Systematic Review

Country:

Aim: to compare outcomes of stents and open surgery in the management of malignant large bowel obstruction

Inclusion criteria Studies comparing colonic stents with open surgery for malignant large bowel obstruction reporting on at least one outcome of interest
Exclusion criteria Studies where analysis of interest were not reported or where they could not be calculated Studies reporting on stents for benign strictures and the where the outcomes for these patients could not be separated from those patients with malignant obstruction Studies where a zero cell was displayed for the outcomes of interest for both the stenting and open resection groups and if the standard deviation of the mean or range for continuous outcomes was not reported
Population N=10 studies included
Interventions Stent versus open surgery
Outcomes Treatment details (including length of stay, intensive care bed usage, cost of admission and success rates for the colonic stent procedure) Functional recovery (time to first bowel movement and time to toleration of an oral diet) Short term adverse events (operative mortality, medical complications, surgical complications and stent related complications Lon term outcomes (the proportion of patients in each group with a stoma at some point in their treatment as well as long term survival)

Results
Obstruction was attributable to colorectal cancer in 8 studies; extrinsic compression secondary to ovarian cancer was included in one study and some patients were treated for ovarian cancer or disseminated upper gastrointestinal malignancy in another.

Study types included: 2 randomised trials, one case matched study, 3 prospective case series and 4 retrospective case series.
Seven studies scored five or more stars on the Newcastle-Ottawa scale

Studies included reported outcomes for a total of 451 patients, 244 of whom had undergone attempted stent insertion.
Stents were successfully inserted in 226 patients (92.6%) with success rates for individual studies ranging from 88%-100%.
There were 14 deaths in the stent group compared with 25 deaths in the emergency surgery group

Treatment Details
Length of hospital stay was shorter in the stent group by almost 8 days (WMD, -7.72; 95% CI, -11.42 to -4.02; p<0.001) but there was significant between studies heterogeneity (HG=97.29; p<0.001)
From 3 studies, significantly fewer patients required ICU care after colonic stenting (OR 0.07; 95% CI 0.01 – 0.31; p<0.001).

Short-term Adverse Events
For post-procedural medical complications there was a significant benefit for patients in the stent group (OR 0.18, 95% CI 0.08 – 0.4; p<0.001); there was no significant heterogeneity associated with this outcome (no details reported).
For post-procedure mortality there was a significant benefit for stented patients (OR 0.45, 95% CI 0.22 – 0.91, p=0.03).

Long-term outcomes
Of the patients in whom colonic stenting was attempted, 20 went on to require a stoma at some point in in their treatment.

Stented patients had significantly lower chanced of undergoing stoma formation at any point in their treatment (OR 0.02; 95% CI, 0.0.1 – 0.08; p<0.001) but this finding was associated with significant heterogeneity (HG=17.58, p=0.01).
No difference was observed between the two treatment groups for overall survival (data for this outcome was poor)

Sensitivity Analysis
High Quality Studies
For studies scoring 5 or more stars on the modified Newcastle-Ottawa scale were analysed, a reduction of 5.45 days in hospital stay was shown for the stent group (95% CI, -6.15 to -4.75, p<0.001) with no significant between studies heterogeneity.
There was no significant difference in mortality between the groups
Fewer medical complications were observed in stented patients (OR 0.22; 95% CI 0.09 – 0.55; p=0.001).
The overall need for a stoma at some point during treatment was lower in stented patients (OR 0.01; 95% CI 0.00 – 0.09) there was significant between studies heterogeneity (HG=15.98; p=0.007).

Colorectal Cancer Studies Only
Significant benefits for stented patients were seen in terms of mortality (OR 0.4, 95% C, 0.19-0.86, p=0.02) and medical complications (OR, 0.17, 95% CI, 007 – 0.44, p<0.001).
The long term stoma rate was significantly lower for the stent group (OR 0.04; 95% CI 0.01-0.13; p<0.001 and for this group the length of hospital stay was significantly shorter by 6.59 days (95% CI -10.31 to -2.88; p<0.001) but there was significant heterogeneity associated with these findings.

Studies with more than 35 patients
A significant reduction in length of hospital stay (WMD, -5.33, 95% CI, -8 to -2.67, p<0.001); mortality rate (OR, 0.39; 95% CI, 0.18-0.87; p=0.02); medical complications (OR 0.14; 95% CI, 0.04-0.50, p=0.003) and need for stoma (OR, 0.07; 95% CI, 0.02-0.23; p<0.001).
No significant between studies heterogeneity was observed.

Studies using intention to treat analysis
In this subgroup, a significantly reduced length of hospital stay (WMD, -6.94; 95% CI, -10.76 to -3.13; p<0.001); mortality rate (OR, 0.35; 95% CI, 0.16-0.79; p=0.01); medical complications (OR 0.15; 95% CI, 0.04-0.5; p=0.002) and long term need for stoma (OR, 0.06; 95% CI 0.02-0.18; p<0.001).
There was significant between studies heterogeneity for length of hospital stay (HG=89.13; p<0.001)

Functional Recovery
From two studies stented patients tolerated an oral diet an average of 5 days earlier than those treated by defunctioning colostomy.

Cost of treatment
From one study the cost of colonic stent insertion was 6.9% higher than for stoma creation with the cost of materials 36.6% higher in the stent group
A second study reported an overall saving of £1,760 per stented patients

General comments
No bridge to surgery group, therefore the usefulness of this study is questionable particularly in relation to long-term outcomes and functional recovery as the intention would be for patients to progress to elective surgery as soon as possible.

Assessment of publication bias for all studies reporting on length of hospital stay after colonic stent versus immediate surgery found three studies lie outside the 95% CI (on funnel plots) and was associated with significant heterogeneity (HG=97.29; p<0.001). When considering only high quality studies all studies were found to lie within the confidence intervals suggesting a lack of publication bias with no significant heterogeneity observed (HG=0.99; p=0.61).

References of Included Studies (For systematic reviews):
Xinopoulos D et al (2004) Stenting or stoma creation for patients with inoperable malignant colonic obstructions? Results of a study and cost effectiveness analysis. *Surg Endosc* 18 421-426

Osman HS et al (2000) The cost effectiveness of self-expanding metal stents in the management of malignant left sided large bowel obstruction *Colorectal Dis 2* 233-237

Baque P et al (2004) Colostomy vs self-expanding metal stents: comparison of the two techniques in actual

tumoral left colonic obstruction *Ann Chir* 129: 353-358

Carne PW et al (2004) Stents or open operation for palliation of colorectal cancer: a retrospective cohort study of perioperative outcome and long-term survival *Dis Colon Rectum* 47;14455-1461

Fiori E et al (2004) Palliative management of malignant rectosigmoidal obstruction: colostomy vs. Endoscopic stenting: a randomised prospective trial *Anticancer Res* 24:265-268

Johnson R et al (2004) A comparison of two methods of palliation of large bowel obstruction due to irremovable colon cancer *Ann R Coll Surg Engl* 86;99-103

Law WL et al (2003) Comparison of stenting with emergency surgery as palliative treatment for obstructing primary left sided colorectal cancer *Br J Surg* 90;1429-1433

Martinez-Sanchez C et al (2002) self-expandable stent before elective surgery versus emergency surgery for the treatment of malignant colorectal obstructions: comparison of primary anastomosis and morbidity rates *Dis Colon Rectum* 45;401-406

Saida Y et al (2003) Long term prognosis of preoperative "bridge to surgery" expandable metallic stent insertion for obstructive colorectal cancer: comparison with emergency operation *Dis Colon Rectum* 46: S44-S49

Tomiki Y et al (2004) Comparison of stent placement and colostomy as palliative treatment for inoperable malignant colorectal obstruction *Surg Endosc* 18;1572-1577

3.3. Stage I Colorectal Cancer

3.3.1. For patients who have undergone local excision and diagnosed stage I colorectal cancer, including/or polyp cancer and with/without neoadjuvant treatment for low rectal tumours, what is the most effective next treatment?

Short Summary

The purpose of this topic was to try to identify which treatment was the next best treatment for patients that had undergone local excision of stage 1 colorectal cancer (including polyps) and subsequently found to have unfavourable prognostic features. If possible, the topic aimed to indentify whether treatment efficacy was impacted by specific prognostic features.

There was no evidence with which to answer this question as much of the literature concentrates on identifying the unfavourable prognostic features rather than focusing on the long term outcomes related to such features or which type of treatment is best for patients with specific unfavourable characteristics.

A small number of studies examining the outcomes of further treatment in patients with poor prognostic features following local excision were identified. These were however, non-comparative, case series of a poor quality and did not provide any insight to the best treatment option for patients.

Review Protocol

Population	Interventions	Factors	Outcomes
Patients with stage I colorectal cancer or polyp cancer following local excision (colorectal) with/without neoadjuvant treatment (low rectum)	• Radical Resection(C&R) • Radiotherapy? (R) • TEMS • No further treatment	• Prognostic factors (e.g. age, comorbidities) • Involved margins • Tumour size?	• Survival after treatment (surgery or radiotherapy) • Local control after surgery or radiotherapy) • Recurrence (local & distant) • Quality of Life

Following a systematic search of relevant data sources (see appendix .1), the information specialist created a database of potentially relevant studies. All titles and abstracts were sifted by a single reviewer. Queries about inclusion were clarified by the GDG topic subgroup. The full studies were then obtained and reviewed and relevant studies were included in the final evidence review.

All update searches were sifted by a single reviewer and the list of potentially relevant studies was also checked for irrelevant studies by the GDG subgroup. Only studies which all subgroup members were in agreement were excluded. The remaining studies were obtained and reviewed with relevant studies included in the final evidence review.

The GDG members set a number of date limits for the searches:
Surgery-1965 onwards
Radiotherapy-1985
TEMS-1990

Other issues highlighted by the GDG for consideration included:
Survival data
Involved lymph nodes in surgical resection specimens
Sessile vs. Pedunculated polyps

The GDG felt that there was a need to consider accuracy of staging. As if a tumour is not resected surgically there will be no information on lymph node status. A percentage therefore will not be cured out of this early stage group.

They also felt that there was a need to distinguish between cancers in-situ and unexpected finding of malignancy in endoscopically-resected polyp

Reasons for Excluding Studies
Expert Reviews
Abstracts Only
Studies did not report on outcomes of interest
Foreign Language with no translation
Population not relevant to PICO
Interventions not relevant to PICO

Quality of the included studies
Systematic review of RCTs (n =0)
Systematic review of combined study designs (n = 0)
Randomized controlled trial (n =0)
Prospective cross sectional study (n =0)
Case Series Studies (n = 0)

534 (+66)
possibly relevant
papers identified

→

449 (+64)
papers excluded
based on title &
abstract

85 (+2)
papers obtained
for appraisal

→

85 (+2)
papers excluded

0 (+0)
papers included
in evidence table
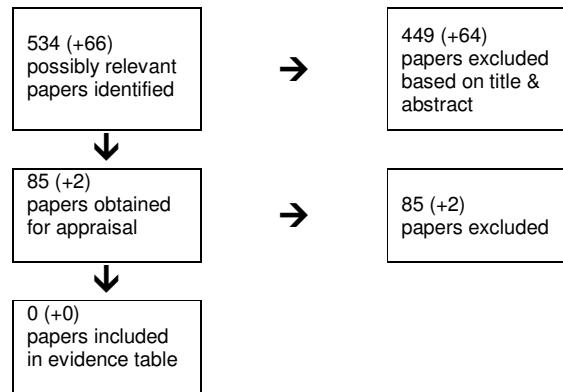
Volume of evidence
There was no evidence with which to address this topic.

Applicability
No studies identified in the searches were relevant to the topic; a small number of non-comparative case series studies were initially considered though subsequently excluded on the basis that they did not provide comparative data on the relative efficacy of different treatments.

Evidence Statement
The purpose of this topic was to try to identify which treatment was the next best treatment for patients that had undergone local excision of stage 1 colorectal cancer (including polyps) and subsequently found to have unfavourable prognostic features. If possible, the topic aimed to indentify whether treatment efficacy was impacted by specific prognostic features.

There was no evidence with which to answer this question as much of the literature concentrates on identifying the unfavourable prognostic features rather than focusing on the long term outcomes related to such features or which type of treatment is best for patients with specific unfavourable characteristics.

A small number of studies examining the outcomes of further treatment in patients with poor prognostic features following local excision were identified. These were however, non-comparative, case series of a poor quality and did not provide any insight to the best treatment option for patients.

3.4. Adjuvant Chemotherapy in Rectal Cancer

3.4.1. In patients with clinical or pathological stage II and III rectal cancer, what is the effectiveness of adjuvant chemotherapy following surgery?

Short Summary

There was a moderate volume of evidence with which to address this topic consisting primarily of randomised trials and pooled analysis of trials (Quasar Collaborative Group (2007), Bosset JF et al (2006), Cionini et al (2001), Fisher B et al (1988), Akasu T (2006), Sakamoto J et al (2004), Sakamoto J (1999), Glimelius B (2005))

There was one systematic review (Germond, 1998 which was conducted as part of guideline development, available for this topic, though the results from this review should be considered to be indirect as not all studies included in the analysis were directly relevant to the current topic. For this reason, the relevant studies were extracted and appraised individually and where possible included in a pooled analysi. A Cochrane Review protocol (Kirkeby LT, 2002), and a second trial protocol (Glynne-Jones R et al, 2007) which although do not add to the body of evidence, would suggest that there is a need to address the issue of adjuvant chemotherapy specifically in patients with rectal cancer.

The evidence included in the review was directly applicable to the topic in terms of the comparisons in each study and the population of interest, however the treatments evaluated in some of the older trials are not be currently clinically relevant and, although there were a number of studies investigating adjuvant chemotherapy in colorectal cancer patients, the topic relates specifically to rectal cancer patients and therefore if the results for rectal cancer patients alone were not presented, these studies were excluded from the review.

One systematic review identified three randomised trials comparing adjuvant chemotherapy to surgery alone reporting an Odds Ratio (OR) of 0.64 (95% CI; 0.48-0.85) in favour of adjuvant chemotherapy, representing an absolute increase in 5 year survival of 9% (Germond et al, 1998). An update of the systematic review (1998-2001) identified 4 meta-analysis and 3 randomised trials however no further updates were done on the meta-analysis.

Despite evaluating the effect of adjuvant chemotherapy, no recommendations were made in the guideline relating to the use of adjuvant chemotherapy in patients with resected rectal cancer.

A total of three trials provided data which allowed a pooled analysis to be conducted for overall survival and disease/recurrence free survival (Bosset et al, 2006; Fisher et al, 1988 and QUASAR, 2007). The quality of the studies included in the pooled analysis was considered to be moderate according to GRADE assessment with the only area of concern relating to the reporting of factors such as concealment and bias in the individual studies.

Pooled analysis of trial data gave a hazards ratio (HR) of 0.0.8 (95% CI; 0.69 – 0..92) for overall survival in favour of adjuvant chemotherapy although none of the individual trials showed a statistically significant benefit of adjuvant chemotherapy. Using the 5-year overall survival for the control arm (63.2%) from Bosset et al (2006), this translates to an absolute reduction in the risk of death within 5 years of 4.3% (95% CI; 2.4% - 9.7%) for patients receiving adjuvant chemotherapy.

The number needed to treat (NNT) was 23 (95% CI; 10.3 – 42) to prevent one additional death within 5 years.

For disease/recurrence free survival, pooled analysis resulted in a hazards ratio (HR) of 0.77 (95% CI; 0.68-0.88) which translates into an absolute reduction in risk of recurrence within 5 years of 8.4% (95% CI; 4.2% - 12%); using the reported 5-year disease free survival of 52.2%for the control arm of Bosset et al. (2006) and the pooled analysis hazard ratio. The number needed to treat was 12 (95% CI; 9 – 24) to prevent one additional recurrence within 5 years.

One trial reported quality of life as a study outcome, though this was reported for the whole population (colon and rectal); quality of life measurements directly related to expected toxicity (e.g. diarrhoea, nausea, vomiting, mouth pain, fatigue, appetite loss and social functioning) were worse in the chemotherapy group than in the observation group (p<0.01) though only during the course of chemotherapy treatment.

Updated Evidence

An update search was conducted but no further relevant evidence was found for inclusion.

Review Protocol

Population	Intervention	Comparison	Outcomes
Patients with clinical or pathological stage II and III **rectal** cancer -patients who have had primary surgery - patients who have had pre op radiotherapy -patients who have had pre op chemoradiotherapy	• Adjuvant chemotherapy following surgery	• No chemotherapy	• Survival • Recurrence • Complications • Quality of life

Following a systematic search of relevant data sources (see appendix .1), the information specialist created a database of potentially relevant studies. All titles and abstracts were sifted by a single reviewer. Queries about inclusion were clarified by the GDG topic subgroup. The full studies were then obtained and reviewed and relevant studies were included in the final evidence review.

All update searches were sifted by a single reviewer and the list of potentially relevant studies was also checked for irrelevant studies by the GDG subgroup. Only studies which all subgroup members were in agreement were excluded. The remaining studies were obtained and reviewed with relevant studies included in the final evidence review.

It was felt by the GDG that there would be high level evidence with which to address this topic and therefore only randomised trials, systematic reviews and meta-analysis were to be included in the evidence review.

The literature was to be searched from 1985 onwards as this is when the clinically relevant data started

Other issues to consider in this topic were whether or not patients have had pre-op radiotherapy (long or short course) and whether they had pre-op chemo/radiotherapy

Reasons for excluding papers:
Not Relevant to PICO
Not randomised trials
Foreign Language with no translation available
No rectal cancer data presented separately
Studies investigating adjuvant chemoradiotherapy
Studies with no surgery alone comparison group
Studies included in pooled analysis/meta-analysis
unless reasonable to evaluate the individual trials.

Quality of the included studies
Systematic review of RCTs (n=1)
Systematic review of combined study designs (n=0)
Randomized controlled trial (including pooled analyses) (n=8)
Prospective cross sectional study (n=0)
Case Series Studies (n=0)
Study Protocol/Comment (n=3)

472 (+33) possibly relevant papers identified		391(+28) papers excluded based on title & abstract
81 (+5) papers obtained for appraisal		68 (+5) papers excluded
13 papers included in evidence table		
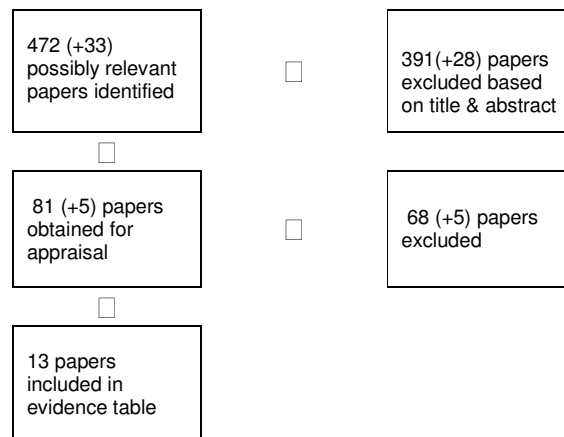
Volume of evidence

There was a small volume of evidence with which to address this topic consisting primarily of randomised trials and pooled analysis of trials. There was one systematic review (Germond, 1998), conducted as part of guideline development available for this topic, though the guideline did not make any recommendations regarding the use of adjuvant chemotherapy in patients with rectal cancer and could be considered to be out of date as the literature review was last updated in 2001 and the results of the meta-analysis relate to the original 1998 publication.

Applicability

In the case of the randomised trials and systematic review, the evidence included was directly applicable to the topic in terms of the comparisons in each study and the population of interest, however the treatments evaluated in some of the older trials are not be currently clinically relevant. A large number of trials examined the effects of adjuvant chemotherapy in colorectal cancer patients and as this topic was specifically interested in rectal cancer patients, studies where the results for the rectal cancer patients could not be separated and assessed in isolation, the studies were excluded from the review.

Only one trial (Bosset et al, 2006) gave consideration to the possible differing benefits of adjuvant chemotherapy in patients receiving different preoperative treatment (radiotherapy versus chemoradiotherapy).

Consistency

There was a good degree of consistency across the studies in terms of the patients included however; although all studies compared adjuvant chemotherapy to surgery alone, there was a degree of variation in terms of the chemotherapy administered in each study.

There appeared to be a good degree of consistency across the results of the individual studies in relation to the potential benefits of adjuvant chemotherapy despite the fact that the studies were looking at a variety of chemotherapy drugs and regimens.

Evidence Statement

There was a small volume of evidence with which to address this topic consisting primarily of randomised trials, the results of which are pooled where possible to give a single estimate. One systematic review (Germond et al, 1998), conducted as part of a guidelines program, evaluated the role of post-operative radiotherapy and/or chemotherapy for patients with stage II or III rectal cancer in terms of improving survival and delaying recurrence. Four studies (Quasar Collaborative Group (2007); Bosset et al (2006); Sakamoto et al (2004) and Fisher et al (1998)) were identified from which data could be extracted and used to perform a pooled analysis (see below) of trial data in an attempt to provide a single estimate of the benefits of adjuvant chemotherapy in patients with rectal cancer. The results from each of these studies is also presented separately and an evidence table for each study has been included (refer to evidence table document). Further studies identified which were relevant but did not present sufficient data to enable inclusion in the pooled analysis included the preliminary results of a randomised study assessing the value of concomitant chemoradiotherapy as preoperative treatment and of postoperative chemotherapy in locally advanced rectal cancer (Cionini et al, 2001 (poster)); a meta-analysis of individual patient data (Sakamoto et al, 1999) which evaluated the effect of oral fluoropyrimidines in rectal cancer and a joint analysis of randomised trials (Glimelius et al, 2005) which aimed to assess adjuvant chemotherapy in the various sites and stages of colorectal cancer, including rectal.

Survival

One systematic review identified three randomised trials comparing adjuvant chemotherapy to surgery alone reporting an Odds Ratio (OR) of 0.64 (95% CI; 0.48-0.85) in favour of adjuvant chemotherapy, representing an absolute increase in 5 year survival of 9% (Germond et al, 1998). One of the trials (Krook et al, 1991) included in the meta-analysis compared post-operative chemoradiotherapy to radiotherapy alone and for this reason the results from the meta-analysis should be considered with caution as the comparators in this trial were not relevant to the PICO. An update of the systematic review (1998-2001) identified 4 meta-analysis and 3 randomised trials however no further updates were done on the meta-analysis.

Despite evaluating the effect of adjuvant chemotherapy, no recommendations were made in the guideline relating to the use of adjuvant chemotherapy in patients with resected rectal cancer.

The Quasar Trial (Quasar Collaborative Group, 2007) randomised 3,329 patients of who 948 had rectal or colon and rectal cancer; of these 424 patients each were randomised to adjuvant chemotherapy or surgery alone.

The relative risk of death from any cause in patients with rectal cancer was 0.77 (95% CI 0.54-1.00; p=0.05) though subgroup investigations (rectal only and colon only) of mortality were less reliable than for recurrence due to the lesser treatment effect.

Bosset et al (2006) reported no significant interaction between the effects of preoperative and postoperative treatments on overall survival (p=0.43) or disease free survival (p=0.50).
5 year overall survival rate was 64.8% for the two groups receiving preoperative radiotherapy and 65.8% in the two groups receiving preoperative chemoradiotherapy. The survival curves did not differ significantly (p=0.84).
The hazards ratio for death in the preoperative chemoradiotherapy groups compared with the preoperative radiotherapy groups was 1.02 (95% CI; 0.83-1.26).
5-year overall survival rate was 63.2% in the two groups that did not receive adjuvant chemotherapy and 67.2% in the groups that did receive adjuvant chemotherapy (p=0.12).
The hazard ratio for death in the adjuvant chemotherapy groups was 0.85 (95% CI; 0.68-1.04).

5-year disease free survival rate in the two preoperative radiotherapy groups was 54.4% and in the preoperative chemoradiotherapy groups was 56.1% (p=0.52).
The hazard ratio was 0.84 (95% CI; 0.78-1.13) for preoperative chemoradiotherapy as compared with preoperative radiotherapy.
5-year disease free survival rate in the two no-adjuvant chemotherapy groups was 52.2% and in the adjuvant treatment groups was 58.2% (p=0.13).
The Hazard Ratio was 0.87 (95% CI; 0.72-1.04) for adjuvant chemotherapy as compared with no adjuvant chemotherapy.

From Fisher et al (1988) 191 patients were randomised to surgery alone and 193 patients were randomised to receive adjuvant chemotherapy. There was an overall improvement in disease free survival in the chemotherapy (p=0.006). Comparing chemotherapy to surgery alone the cumulative odds at 5 years was 1.5 (95% CI; 1.13-1.99). There was an overall survival advantage with chemotherapy (p=0.05).
The cumulative odds at 5 years comparing the survival times in the chemotherapy group to those in the surgery group was 1.3 (95% CI; 0.95-1.79).

Sex and age showed a statistically significant interaction with treatment in regard to disease free survival; age, sex and Dukes stage showed a statistically significant interaction in regard to overall survival.
There was a significant benefit from chemotherapy in the disease free survival and overall survival in males but no such advantage was observed in females.
When testing males for age trend, chemotherapy was observed to be more effective in younger patients; disease free survival (p=0.08) and survival (p=0.03) with the observed advantage evident throughout the 5 years of follow-up.
Patients with both Dukes B and C tumours demonstrated a benefit from chemotherapy in disease-free survival and patients with Dukes B tumours showed as survival advantage.

From one pooled analysis of trial data (Sakamoto et al, 2004) overall survival Hazard Ratio (HR) was 0.89 (95% CI; 0.8 – 0.99, p=0.04) with no significant heterogeneity between the treatment effects in different trials. The benefit of oral fluorinated pyrimidines was seen in both rectal and colon locations; HR for rectal cancer was 0.92 (95% CI; 0.79-1.07).
There was a trend towards larger treatment effects in earlier Dukes stages (p=0.077); a trend towards smaller benefits in older patients with a negative effect observed in patients older than 70 years, this trend was not consistent in younger patients (p=0.4).
There was no statistically significant difference in benefit of the various oral fluoropyrimidines (p=0.8) but the trials used different agents depending on tumour site and so this comparison may be confounded by other differences in trial characteristics.
A proportional hazard regression model of survival confirmed the benefit of treatment and the lack of significant treatment by covariate interactions, except for a trend toward larger benefit in earlier Dukes stage. The best survival model excluded sex, site or type of oral fluoropyrimidine and included Dukes stage (p<0.0001), age (p=0.001), treatment (p=0.026) and the interaction between treatment and Dukes stage (p=0.066).

Sakamoto et al (2004) reported a disease free survival (DFS) HR of 0.85 (95% CI; 0.77 – 0.93, p<0.001) with no significant heterogeneity between the treatment effects in different trials .
The benefit of oral fluoropyrimidines on DFS was similar in rectal and colon locations; HR for rectal was 0.83 (95% CI; 0.73 – 0.95).
There was a trend towards a larger benefit in earlier Dukes stage, though this failed to reach statistical significance (p=0.1).
The best DFS model retained the same covariates as the survival model: Dukes stage (p<0.0001), age (p=0.012), treatment (p=0.021) and the interaction between treatment and Dukes Stage (p=0.095).

In this meta-analysis, two trials tested UFT (7-1-R and 15-R) and one trial tested HCFU (7-2-R). One trial (trial 15 had a third treatment arm consisting of the non-specific immunopotentiator OK-432, which was discontinued by the Ministry of Health and Welfare of Japan at the end of 1989. As of January 1990, random assignment to this study was performed on a 2:1 ratio (two treatments to one control) and so for the purposes of the meta-analysis this trial was considered as two separate trials labelled 15-1 (three arm study) or 15-2 (two arm study). It is unclear from this quite how the trial was split into two or whether some or all of the patients are being double counted in this situation. For this reason, the individual results reported for each trial (7-1-R, 7-2-R, 15-1 and 15-2) were used in the pooled analysis rather than the overall HR calculated.

Cionini et al (2001) reported overall survival at 5 years of 67.3% with significant prognostic factors including initial T-stage, APR, downstaging and pN+.
A meta-analysis of individual patient data (Sakamoto et al, 1999) reported a RR for disease free survival for rectal cancer was 0.767 (95% CI; 0.6560-00.882, p=0.0003).
Significant differences in disease free survival were observed in rectal cancers in both Dukes B (p=0.0001) and Dukes C (p=0.0003) patients. The RR for survival for rectal cancer was 0.857 (95% CI; 0.734-0.999, p=0.049).
Analysis by Dukes stage showed a significant effect of oral fluoropyrimidines for survival in Dukes C (p=0.0124) but not in Dukes B (p=0.1088) for rectal cancers.
Glimelius et al (2005) reported no significant difference in survival between surgery and chemotherapy groups for either stage II rectal cancer (p=0.09) or for stage III rectal cancer (p=0.91).

Recurrence
From the Quasar trial (Quasar Collaborative Group, 2007), the relative risk for recurrence in the first 2 years after randomisation with chemotherapy in patients with stage III rectal cancer was 0.44 (95% CI; 0.18-1.06, p=0.02) and for patients with stage II rectal cancer was 0.57 (95% CI; 0.38-0.89, p=0.007).
The proportional reduction in recurrence with chemotherapy versus observation alone was similar in patients with stage II and III and in patients with colon cancer and those with rectal cancer.
The relative risk of recurrence with chemotherapy compared with observation alone in patients with rectal cancer was 0.68 (95% CI; 0.52-0.88, p=0.004). Although in this study, the outcome was referred to as recurrence; it was judged to refer to recurrence/disease free survival and was therefore included in the pooled analysis under disease free survival.
There was no reduction in recurrence for patients aged over 70 years and for patients under 70 years the relative risk of recurrence in the 2 years following randomisation was 0.58 (95% CI; 0.38-0.93, p=0.01) for those with stage II rectal cancer.

Bosset et al (2006) reported local recurrences separately for the four treatment groups due to indications of an interaction between preoperative and postoperative chemotherapy (p=0.09),

	Local recurrences	95% Confidence Interval
Preoperative Radiotherapy	17.1%	12.3 – 21.9
Preoperative Chemoradiotherapy	8.7%	4.9 – 12.6
Preoperative Radiotherapy with adjuvant chemotherapy	9.6%	5.7 – 13.5
Preoperative Chemoradiotherapy with adjuvant chemotherapy	7.6%	4.2 – 11

Table3.27: Cumulative incidences of local recurrences as a first event at 5 years

P=0.002 for the comparison between the group receiving preoperative radiotherapy alone and the other three treatment groups.
Treatment effect appeared homogenous regardless of the distance from the tumour to the anal verge (≤5cm vs. >5cm, p=0.74) though this was tested with low statistical power.
The cumulative incidence of distant metastases did not differ significantly according to the preoperative (p=0.14) or postoperative (p=0.62) treatment.
Overall the 5 year cumulative incidence of distant metastases was 34.4% (95% CI, 31.3 – 37.6%).

Cionini et al (2001) reported no significant difference in recurrence rate with 71 recurrences in each arm;

Sakamoto et al (1999) reported recurrence in 30.1% of patients allocated to surgery alone compared with 25.5% of patients in the adjuvant chemotherapy group.

Quality of Life

Results for QoL relate to the whole study population and not just to rectal cancer patients, though it is likely that the results would be applicable and relevant to the rectal cancer subgroup alone (Quasar collaborative group, 2007).

Quality of life measurements directly related to expected toxicity (e.g. diarrhoea, nausea, vomiting, mouth pain, fatigue, appetite loss and social functioning) were worse in the chemotherapy group than in the observation group (p<0.01), though only during the course of chemotherapy.

The proportion of patients with grade 3/4 nausea, oral adverse events, neutropenia and any grade 3/4 toxicity was significantly greater with 4-week courses of chemotherapy compared with once weekly delivery (p<0.001).

Pooled Analysis
As part of this evidence review, data from individual trials were pooled where possible to provide a single estimate of effect of adjuvant chemotherapy. Although the majority of individual trials included in the pooled analysis do not show a statistically significant benefit of chemotherapy, when pooled there is a statistically significant benefit of adjuvant chemotherapy for both overall survival and disease/recurrence free survival. The pooled analysis calculated Hazards Ratios (an expression of the hazard or chance of events occurring in the treatment arm as a ratio of the hazard of the events occurring in the control arm).

There were only two outcomes for which pooled analysis could be performed, mortality and disease free survival.

The X^2 test for heterogeneity is not significant (p=0.73 for mortality and p=0.2 for disease free survival) and I^2 is 0% for mortality and 39% for disease free survival, suggesting that there is no heterogeneity between studies and that is was therefore appropriate for the individual study results to be pooled in this instance, however it should be noted that each study used different treatment regimens and in some cases different chemotherapy drugs, in addition there are differences in the way in which patients were treated during the trials in relation to factors such as preoperative treatments and surgery types and therefore, although the results suggest no between studies heterogeneity, these differences should be considered.

Data included in the pooled analysis for this topic were taken from Fisher et al (1988), Quasar Collaborative Group (2007), Bosset et al (2006).The results of the meta-analysis (Germond et al, 1998) were not included in the pooled analysis as the results were not updated when the literature review was updated, also one of the trials included in the original meta-analysis was not relevant to the current topic. It was therefore deemed more appropriate to assess the individual trials reported and include any relevant data in the pooled analysis. On review of the individual trials, only one (Fisher et al, 1988) was determined to be appropriate for inclusion.

Studies Included in Pooled Analysis
- Fisher et al (1988): Data included in the pooled analysis included the number of patients analysed, number of events, log rank p value for survival and disease free survival, O-E and variance were calculated using methodology from Tierney et al (2007), the lowest O-E and highest variance values were used in the analysis
- Quasar Study (2007): The data were taken from the paper as reported with no further calculations or analysis performed.
- Bosset (2006): Hazards Ratios were presented in the paper with confidence intervals; O-E and variance calculated using HR and 95% CI for overall survival using methodology from Tierney et al (2007).
- Absolute reduction in risk of death and recurrence and the numbers needed to treat (NNT) were calculated using methods from Tierney et al (2007).

Studies Excluded from Pooled Analysis
- Sakamoto (2004): meta analysis, This study was not included in the pooled analysis as following discussion with the GDG members it was determined that the data were unreliable due to the fact that is was not possible to entirely elucidate where the data from each individual study in the meta-analysis were drawn from and there was a strong possibility that the data were duplicated. It was determined that it was acceptable not to spend time trying to address these issues in order that the data might be included as the GDG subgroup felt that the practices investigated in the studies were not applicable to the UK setting and so would not provide any additional evidence of relevance.

Mortality
From the pooled analysis (figure 3.8), it can be seen that despite none of the individual studies being statistically significant, the HR for the pooled results is 0.80 (95% CI; 0.69-0.92). Using the 5-year overall survival rate (63.2%) from the control arm of one of the included trials (Bosset et al, 2006) and the pooled hazard ratio, this translates to an absolute reduction in the risk of death within 5 years of 4.3% (95% CI; 2.4% - 9.7%) for patients receiving adjuvant chemotherapy.

The number needed to treat (NNT) was 23 (95% CI; 10.3 – 42) to prevent one additional death within 5 years.
The GRADE table for mortality shows that the quality of evidence included in the pooled analysis was moderate, with only serious questions raised over the methodology of the individual trials in relation to factors such as allocation concealment or blinding (table 3.28).

Disease Free Survival/Recurrence
From the pooled analysis (figure 3.9), the hazards ratio for recurrence is 0.77 (95% CI; 0.68 – 0.88) which translates into an absolute reduction in risk of recurrence within 5 years of 8.4% (95% CI; 4.2% - 12%); using the reported 5-year disease free survival from Bosset et al. (2006) and the pooled analysis hazard ratio. The number needed to treat was 12 (95% CI; 9 – 24) to prevent one additional recurrence within 5 years.
The GRADE table for mortality shows that the quality of evidence included in the pooled analysis was moderate, with only serious questions raised over the methodology of the individual trials in relation to factors such as allocation concealment or blinding (table 3.29).

There are no systematic reviews or meta-analyses of recent trials and though in many trials the data for rectal cancer patients are recorded, analysis of the data often does not separate the colon and rectal cancer patients. In a comment to the Lancet, Bujko et al (2008) stated that there is a need for a meta-analysis to resolve the issue of whether adjuvant chemotherapy produces worthwhile benefits for patients with rectal cancer who receive preoperative or postoperative radiotherapy.
There is currently one Cochrane Review Protocol, published in 2002, the objective of which is to evaluate the effect of postoperative adjuvant chemotherapy after radical rectal surgery compared to surgery alone in Dukes C rectal cancer on mortality, recurrence, adverse effects, quality of life and cost effectiveness assessment.
An ongoing trial (Glynne-Jones et al, 2007) the Chronicle trial, is an open-label phase III multicentre randomised trial examining the benefit of a non-cross-resistant chemotherapy to patients who have previously received neoadjuvant 5-FU based chemoradiotherapy combination with primary end point of 3-year disease free survival and the secondary end points of overall survival and toxicity of postoperative chemotherapy.

Study or Subgroup	Adjuvant Chemotherapy Events	Total	Observation Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Bosset, 2006*	0	506	0	505	-13.83	85.12	45.7%	0.85 [0.69, 1.05]	
Fisher, 1988	78	187	95	116	-12.83	43.25	23.2%	0.74 [0.55, 1.00]	
QUASAR, 2007	103	474	129	474	-15	58	31.1%	0.77 [0.60, 1.00]	
Total (95% CI)		**1167**		**1095**			**100.0%**	**0.80 [0.69, 0.92]**	
Total events	181		224						

Heterogeneity: Chi² = 0.62, df = 2 (P = 0.73); I² = 0%
Test for overall effect: Z = 3.05 (P = 0.002)

0.2 0.5 1 2
Favours experimental   Favours control

...e calculated from the paper,
...numbers from the other
...e event data were not used to

Summary of findings

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Adjuvant Chemotherapy	control	Relative (95% CI)	Absolute	Quality
Mortality (follow-up median 5.5 years[1])											
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	181/1167 (15.5%)	224/1095 (20.5%)	HR 0.8 (0.69 to 0.92)	37 fewer per 1000 (from 15 fewer to 58 fewer)	MODERATE
								31.6%		54 fewer per 1000 (from 21 fewer to 85 fewer)	

[1] The median follow-up from three studies was at least five years but ranged from 0-10.9 years.
[2] Lack of clarity in the individual trials regarding factors such as concealment and bias
[3] The total events for one study were not reported, however as the HR was not calculated using this missing data does not impact the overall results.

Table 3.28: Mortality (GRADE)

Total (95% CI)		1167	1163	**100.0%**	**0.77 [0.68, 0.88]**
Total events	195		245		
Heterogeneity: Chi² = 3.26, df = 2 (P = 0.20); I² = 39%					
Test for overall effect: Z = 3.85 (P = 0.0001)					

0.2   0.5   1
Adjuvant Chemotherapy   Obse
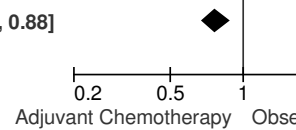
*The number of events could not be calculated from Bosset et al.

Figure 3.9: Pooled analysis of disease free survival/recurrence data

As the number of events from one of the trials (Bosset et al, 2006) could not be calculated from the paper, the numbers in the adjuvant chemotherapy and control columns are based on numbers from the other included trials only. This does not affect the Hazards Ratio calculations and the event data were not used to calculate HR.

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Adjuvant Chemotherapy	control	Relative (95% CI)	Absolute	Quality
Recurrence (follow-up median 5 years[1])											
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	195/1167 (16.7%)[3]	245/1163 (21.1%)[3]	HR 0.77 (0.68 to 0.88)	44 fewer per 1000 (from 23 fewer to 62 fewer)	MODERATE
								0%		0 fewer per 1000 (from 0 fewer to 0 fewer)	
								39.4%		74 fewer per 1000 (from 38 fewer to 105 fewer)	

[1] The median follow-up from three studies was at least five years but ranged from 0-10.9 years.
[2] Lack of clarity in the individual trials regarding factors such as concealment and bias
[3] The total events for one study were not reported, however as the HR was not calculated using this missing data does not impact the overall results.

Table 3.29: Disease free survival/Recurrence free survival (GRADE)

References

Akasu T, Moriya Y, Ohashi Y, Yoshida S (2006) Adjuvant Chemotherapy with uracil-tegafur for pathological stage III rectal cancer after mesorectal excision with selective lateral pelvic lymphadenectomy: a multicentre randomised controlled trial *Japanese Journal of Clinical Oncology* 36;4:237-244

Bosset JF, Collette L, Calais G, Mineur L, Maingon (2006) Chemotherapy with preoperative radiotherapy in rectal cancer *New England Journal of Medicine* 355;11:1114-1123

Bujko et al (2008) adjuvant Chemotherapy for Rectal Cancer *Lancet* 371;9623:1502-1503

Cionini L. et al (2001) Randomised study of postoperative chemotherapy after preoperative chemoradiation in locally advanced rectal cancer. Preliminary Results European Journal of Cancer 37 S6; S300

Fisher B, Wolmark N, Rockette H, Redmond C (1988) Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-01 *Journal of the National Cancer Institute* 80;1:21-29

Germond C, Figueredo A, Taylor BM (1998) Postoperative adjuvant radiotherapy and/or chemotherapy for resected stage II or III rectal cancer (DARE structured abstract)

Glimelius B, Dahl O, Cedermark B, Jakobsen A (2005) Adjuvant Chemotherapy in colorectal cancer: a joint analysis of randomised trials by the Nordic Gastrointestinal Tumour Adjuvant Therapy Group *Acta Oncologica* 44;8:904-912

Glynne-Jones R et al (2007) Chemotherapy or no chemotherapy in clear margins after neoadjuvant chemoradiation in locally advanced rectal cancer: CHRONICLE. A randomised phase III trial of control vs. Capecitabine plus oxaliplatin *Clinical Oncology* 19;5:327-329

Kirkeby LT et al (2002) Postoperative adjuvant chemotherapy for radically operated Dukes C rectal cancer (protocol) *Cochrane Database of Systematic Reviews* 4;4

Quasar Collaborative Group (2007) Adjuvant Chemotherapy versus observation in patients with colorectal cancer: a randomised study *Lancet* 370:9604;2020-2029

Sakamoto J, Ohasi Y, Hamada C, Buyse M (2004) Efficacy of oral adjuvant therapy after resection of colorectal cancer: 5 year results from three randomised trials *Journal of Clinical Oncology* 22;3:484-492

Sakamoto J (1999) Adjuvant therapy with oral fluoropyrimidines as main chemotherapeutic agents after curative resection for colorectal cancer: individual patient data meta-analysis of randomised trials *Jpn Journal of Clinical Oncology* 2;29:78-86

Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR (2007) Practical methods for incorporating summary time-to-event data into meta-analysis *Trials* 8:16

Evidence Tables

Citation: Akasu T, Moriya Y, Ohashi Y, Yoshida S (2006) Adjuvant Chemotherapy with uracil-tegafur for pathological stage III rectal cancer after mesorectal excision with selective lateral pelvic lymphadenectomy: a multicentre randomised controlled trial *Japanese Journal of Clinical Oncology* 36;4:237-244
Design: Randomised Trial **Country**: Japan **Setting:** Multicentre **Aim**: to evaluate the efficacy of postoperative adjuvant chemotherapy with a combination of uracil and tegafur taken orally after standardised mesorectal excision with selective lateral oelvic lymphadenectomy in stage III rectal cancer
Inclusion criteria • Patients who underwent a microscopically verified complete resection of pathological stage III adenocarcinoma of the rectum according to the TNM classification of Malignant tumours by standardised mesorectal excision with selective lateral pelvic lymphadenectomy • Centre of the tumour being located between the levels of the first sacral bone and the anal canal • Age 20-75 years • Absence of preoperative anticancer treatment • Previous cancer and synchronous multiple c ancers • ECOG performance status of 0-2 • Adequate blood counts (see paper for full details) • An absence of severe postoperative complications uncontrolled by the time of registration
Exclusion criteria None Given
Sample Size The study was designed to detect a hazard ratio for relapse or death of 0.67 in the uracil-tegafur group compared with the control group with 80% power at a two-sided α-level of 0.05. Assuming a 5 year relapse free survival rate of 50% in the surgery alone group, a 2 year accrual period and a 5 year follow-up period the target sample was 400. In April 2000 the accrual period was extended to 5 years based on actual accrual rate.
Randomisation Method An open label study design was used, with patients assigned to postoperative adjuvant treatment or surgery alone. Randomisation was performed by telephone/fax at the central trial office with 42 days of operation with patients allocated by the minimisation method with adjustment for inter-institutional imbalance.
Population N=276
Study Duration October 1996-April 2001 (+ follow up time)
Interventions Uracil-tegafur; 400 mg/m^2 per day in the form of 100 mg units (100mg tegafur + 224mg uracil) was given orally twice daily for 5 consecutive days every weekday for 1 year, starting 6 weeks postoperatively. Dose rounded up or down to the nearest 100mg.
Outcomes Relapse Free Survival Overall Survival
Results The study group stopped recruitment in April 2001 because a further rapid enrolment could not be expected and evaluation of treatment would be possible through a meta-analysis* of data obtained from this study and existing data.
General comments All patients were evaluated every 4 months for the first 2 years after surgery and every 6 months for the next 3 years; evaluation included physical exam, blood counts, blood chemistry, serum tumour markers, chest roentgenography and abdominal ultrasonography or computed tomography.

A pelvic computed tomography was performed every 6 months
Patients receiving uracil-tegafur had a physical exam, complete blood count and blood chemical tests ever month during the fist year.

References of Included Studies (For systematic reviews):
*Meta-analysis group of the Japanese Society for Cancer of the Colon and Rectum and the Meta-analysis Group in Cancer (2004) Efficacy of oral adjuvant therapy after resection of colorectal cancer: 5 year results from three randomised trials *J Clin Oncol* 22;484-492

Citation: Bosset JF, Collette L, Calais G, Mineur L, Maingon (2006) Chemotherapy with preoperative radiotherapy in rectal cancer *New England Journal of Medicine* 355;11:1114-1123

Design: Randomised Trial

Country: Unclear

Setting: Unclear

Aim: to evaluate the addition chemotherapy to preoperative radiotherapy and the use of postoperative chemotherapy in the treatment of rectal cancer

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Inclusion criteria
T3 or resectable T4M0 adenocarcinoma of the rectum (according to the 1987 UICC staging system)
Located within 15cm of the anal verge
WHO performance status of 0 or 1
Age 80 or less

Exclusion criteria
History of cancer (except nonmelanoma skin cancer)
Angina pectoris
Inflammatory disease of the ileum or colon

Sample Size
The authors calculated that 1011 patients would need to be included in order to have 80% statistical power to detect a difference in survival of 10 percentage points at 5 years, with a two sided significance level of 0.05.

Randomisation Method
Randomisation was done using the minimisation technique and stratification according to institution, sex, T-stage and distance from the tumour to the anal verge.

Population
1011 patients underwent randomisation

Preoperative Radiotherapy: 252
Preoperative Chemoradiotherapy: 253
Preoperative Radiotherapy and Postoperative Chemotherapy: 253
Preoperative Chemoradiotherapy and Postoperative Chemoradiotherapy: 253

Study Duration
April 1993 – March 2003

Interventions
Preoperative Radiotherapy
Preoperative Chemoradiotherapy
Preoperative Radiotherapy and Postoperative Chemotherapy
Preoperative Chemoradiotherapy and Postoperative Chemoradiotherapy

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Outcomes
Overall Survival
Disease Free Survival
Local Recurrence
Distant Recurrence

Results
Preoperative Treatment
Preoperative radiotherapy was delivered in 98% of assigned (495/505) patients and in 95% (483/506) of patients assigned to chemoradiotherapy.
82% of patients received planned doses fluorouracil

Toxicity
Grade 2 acute toxic effects were reported in 29.7% of patients receiving preoperative radiotherapy and in 38.4% of patients receiving preoperative chemoradiotherapy; grade 3 toxicity or higher toxic effects occurred in 7.4% and 13.9% of patients respectively (p for trend <0.001).
Grade 2 diarrhoea or higher occurred in 17.3% of patients receiving preoperative radiotherapy and in 37.6% of patients receiving preoperative chemoradiotherapy (p<0.001).

<u>Surgery</u>
979/1011 patients underwent surgery with tumour resected in 964 (95.4%)
Liver metastases were found in 42 patients
Sphincter sparing surgery was performed in 255 patients who were assigned to preoperative radiotherapy and in 267 patients assigned to preoperative chemoradiotherapy (p=0.47).
Rates of postoperative complications were 23.3% in the radiotherapy group and 22.8% in the chemoradiotherapy group.

<u>Postoperative Treatments</u>
136/506 patients (26.9%) did not start postoperative chemotherapy due to postoperative complications, disease progression, patient refusal, no surgery/tumour resection, toxic effects of preoperative treatment and other reasons.
217 patients (42.9%) received 95 – 105% of the planned dose of fluorouracil without delays.
Acute toxic effects of any grade were observed in 214 patients (57.8%), there were 111 patients with grade II or higher toxicity; there were no deaths from toxic effects.

<u>Late Side Effects</u>
97/1011 patients experienced grade 2 or higher diarrhoea (9.6%).
47/522 patients that underwent sphincter sparing surgery reported some form of faecal incontinence with 2 patients requiring colostomy.
31 patients had a stricture of the anastomosis with 11 patients requiring colostomy.
14 patients required surgery for small bowel complications
There was no significant difference in the incidence of late side effects among the four treatment groups

<u>Events During Follow-up</u>
As of April 2005, surviving patients were followed for a median of 5.4 years (range 4 months to 10.9 years); follow-up did not differ significantly among treatment groups (p=0.96).
264/347 (76.1%) deaths occurring during follow-up were due to rectal cancer
Local recurrences occurred in 127 patients and distant recurrences in 326.

<u>Survival</u>
There was no significant interaction between the effects of preoperative and postoperative treatments on overall survival (p=0.43) or disease free survival (p=0.50).
5 year overall survival rate was 64.8% for the two groups receiving preoperative radiotherapy and 65.8% in the two groups receiving preoperative chemoradiotherapy. The survival curves did not differ significantly (p=0.84).
The hazards ratio for death in the preoperative chemoradiotherapy groups compared with the preoperative radiotherapy groups was 1.02 (95% CI; 0.83-1.26).
5-year overall survival rate was 63.2% in the two groups that did not receive adjuvant chemotherapy and 67.2% in the groups that did receive adjuvant chemotherapy (p=0.12).
The hazard ratio for death in the adjuvant chemotherapy groups was 0.85 (95% CI; 0.68-1.04).

5-year disease free survival rate in the two preoperative radiotherapy groups was 54.4% and in the preoperative chemoradiotherapy groups was 56.1% (p=0.52).
The hazard ratio was 0.84 (95% CI; 0.78-1.13) for preoperative chemoradiotherapy as compared with preoperative radiotherapy.
5-year disease free survival rate in the two no-adjuvant chemotherapy groups was 52.2% and in the adjuvant treatment groups was 58.2% (p=0.13).
The Hazard Ratio was 0.87 (95% CI; 0.72-1.04) for adjuvant chemotherapy as compared with no adjuvant chemotherapy.

<u>Local and Distant Recurrences</u>
Due to indications of an interaction between preoperative and postoperative chemotherapy (p=0.09), local recurrences are reported separately for the four treatment groups.

	Local recurrences	95% Confidence Interval
Preoperative Radiotherapy	17.1%	12.3 – 21.9
Preoperative Chemoradiotherapy	8.7%	4.9 – 12.6
Preoperative Radiotherapy with adjuvant chemotherapy	9.6%	5.7 – 13.5
Preoperative Chemoradiotherapy with adjuvant chemotherapy	7.6%	4.2 – 11

Table: Cumulative incidences of local recurrences as a first event at 5 years

P=0.002 for the comparison between the group receiving preoperative radiotherapy alone and the other three treatment groups.

Treatment effect appeared homogenous regardless of the distance from the tumour to the anal verge (≤5cm vs. >5cm, p=0.74) though this was tested with low statistical power.

The cumulative incidence of distant metastases did not differ significantly according to the preoperative (p=0.14) or postoperative (p=0.62) treatment.
Overall the 5 year cumulative incidence of distant metastases was 34.4% (95% CI, 31.3 – 37.6%).

Citation: Cionini L. et al (2001) Randomised study of postoperative chemotherapy after preoperative chemoradiation in locally advanced rectal cancer. Preliminary Results *European Journal of Cancer* 37 S6; S300
Design: Randomised Trial **Country**: Italy **Setting:** Multicentre **Aim**: to assess the value of concomitant chemoradiotherapy as preoperative treatment and of postoperative chemotherapy in LARC
Inclusion criteria Tumour invading the perirectal fat at DRE (fixed or tethered) or at intrarectal ultrasound Age below 76 years Tumour origin lower 2/3 Adenocarcinoma
Exclusion criteria None given
Sample Size Details not provided
Randomisation Method Details not provided
Population N=632 Surgery + Observation: 309 Surgery + Postoperative Chemotherapy: 326
Study Duration Ongoing at the time of publication – preliminary results only
Interventions Observation versus postoperative chemotherapy
Outcomes Compliance to preoperative chemoradiotherapy Toxicity Tumour Downstaging Freedom from local and distant recurrences Survival
Results Compliance to Preoperative Chemoradiotherapy 584/632 (92%) of patients had full chemoradiotherapy, 3 patients had radiotherapy only, 44 patients had one course of chemotherapy and 7 patients had neither chemotherapy nor radiotherapy preoperatively. Surgery 562/632 patients (88.5%) of patients underwent surgery; 15 patients were inoperable, 4 patients refused surgery, 7 patients died before surgery for intercurrent death, 2 patients died before surgery for disease, 3 patients died as a result of toxicity and 42 there was missing data for 42 patients. Type of Surgery 188 patients underwent APR, 340 patients underwent LAR, 24 patients underwent TEM and 10 patients underwent palliative procedures. Clinical downsizing 353 (64.2%) patients had tumour downsizing of >50% Downstaging 96 (17.4%) patients were downstaged to T0, 210 (36.5%) patients were downstaged to T1-T2, and 253 patients were T3. 122 (22.2%) patients were N+ and 16 (2.9%) patients had positive margins

Compliance to postoperative chemotherapy
149/326 patients received 6 cycles of chemotherapy, 37/326 patients received <6 cycles, 54/326 patients refused chemotherapy and 66/326 patients had missing data.

Follow-up
Data were available for 536 patients; median length of follow-up was 24.8 months.

28 patients (5.2%) had local recurrence, 114 patients (21.3%) had distant metastases and 19 patients (3.5%) had local and distant metastases.

Overall survival at 5 years was 67.3%
Significant prognostic factors included initial T stage (p<0.02), APR (p<0.05), downstaging (p<0.05) and pN+ (p<0.05).
There was no difference in recurrence rate (71 recurrences in each arm) or in survival (63.5% in Arm A and 67.5% in Arm B) between the two arms.

General comments
This data is taken from a poster and represents only preliminary results from the trial.

Citation: Fisher B, Wolmark N, Rockette H, Redmond C (1988) Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-01 *Journal of the National Cancer Institute* 80;1:21-29
Design: Randomised Trial **Country**: **Setting:** Multicentre **Aim**: to evaluate whether there is a benefit from adjuvant chemotherapy for the management of rectal cancer
Inclusion criteria Rectal tumours which penetrated through the muscularis propria into the pericolic adipose tissue without evidence of regional lymph node metastases (Dukes B) or penetrated the bowl wall to any depth and the lymph nodes removed contained tumour (Dukes C). Patients with intestinal obstruction treated by prior or concomitant colostomy. Patients whose tumours involved adjacent structures that could be removed 'en bloc' so the surgery could be deemed curative. Patients with a performance status and haematological profile that would allow them to be eligible for chemotherapy
Exclusion criteria Tumours that failed to extend into the pericolic tissue and lymph nodes (Dukes A) or those that had extended beyond the scope of surgical excision (Dukes D)
Sample Size Details not given
Randomisation Method Patients were entered into the study by telephone communication with the NSABO Biostatistical Centre, they were stratified according to Dukes Stage, age (<65, ≥65) and sex.
Population
Study Duration
Interventions Arm A: Surgery Alone Arm B: Surgery followed by FUra, semustine and VCR Arm C: Surgery and postoperative radiotherapy
Outcomes
Results 191 patients were randomised to surgery alone and 193 patients were randomised to receive adjuvant chemotherapy. The median time in on study was 63.5 months for the surgery group and 64.3 months for the adjuvant chemotherapy group. Follow-up was every 10 weeks for the first 30 months after surgery with patients undergoing a complete physical exam, blood counts and blood chemistries. Chest X-ray and CEA determinations were performed every 20 weeks. Treatment failure was diagnosed by taking biopsy specimens There was an overall improvement in disease free survival in the chemotherapy (p=0.006). Comparing chemotherapy to surgery alone the cumulative odds at 5 years was 1.5 (95% CI; 1.13-1.99). There was an overall survival advantage with chemotherapy (p=0.05). The cumulative odds at 5 years comparing the survival times in the chemotherapy group to those in the surgery group was 1.3 (95% CI; 0.95-1.79). Sex and age showed a statistically significant interaction with treatment in regard to disease free survival; age, sex and Dukes stage showed a statistically significant interaction in regard to overall survival. There was a significant benefit from chemotherapy in the disease free survival and overall survival in males but no

such advantage was observed in females.

When testing males for age trend chemotherapy was observed to be more effective in younger patients; disease free survival (p=0.08) and survival (p=0.03) with the observed advantage evident throughout the 5 years of follow-up.

Patients with both Dukes B and C tumours demonstrated a benefit from chemotherapy in disease-free survival and patients with Dukes B tumours showed as survival advantage.

General comments

Chemotherapy regimen: FUra, 325mg/m^2 was given iv in a bolus on days 1-5 of a treatment cycle and then FUra, 375 mg/m^2 was given on days 36-40 of the cycle. Semustine (130mg/m^2) was administered orally on day 1 and VCR (1mg/m^2; to 2mg maximum dose) was given iv on days 1 and 36 prior to other chemotherapy.

Each chemotherapy cycle was to be repeated every 10 weeks until 8 cycles were administered or until evidence of treatment failure was documented.

Follow Up: Every 10 weeks for the first 30 months following surgery – patients had a complete physical examination, blood counts and blood chemistry assessment. Chest x-ray and CEA determinations were performed every 20 weeks.

Citation: Germond C, Figueredo A, Taylor BM (1998) Postoperative adjuvant radiotherapy and/or chemotherapy for resected stage II or III rectal cancer (DARE structured abstract)

Design: Systematic Review and meta-analysis **Country**: **Setting:** **Aim**: To evaluate the role of postoperative adjuvant radiotherapy and/or chemotherapy for patients with resected stage II or III rectal cancer in terms of improving survival and delaying local recurrence
Inclusion criteria Syntheses of evidence in the form of evidence-based practice guidelines or systematic overviews and randomised controlled trials with appropriate comparison groups Studies that enrolled patients with stage II or III rectal carcinoma who had undergone rectal resection with curative intent. Studies which included patients with colorectal cancer were only included if the report presented data for patients with rectal carcinoma separately from the data for patients with colon cancer.
Exclusion criteria
Sample Size N/A
Randomisation Method N/A
Population 3 randomised controlled trials were identified for chemotherapy versus observation in the original searches (up to April 1997) 4 meta-analyses and 3 randomised controlled trials were identified during updates (1998-2001)
Study Duration
Interventions
Outcomes
Results From one meta-analysis of 3 randomised trials comparing chemotherapy and observation in rectal cancer, the mortality OR was 0.64 (95% CI; 0.48 – 0.85) in favour of adjuvant chemotherapy, representing an absolute increase in 5-year survival of 9%. There was difficulty interpreting the meta-analysis because one of the trials compared chemotherapy + radiotherapy to radiotherapy alone. A second meta-analysis of individual patient data (4960 patients) with colorectal cancer who participated in 3 randomised trials of adjuvant chemotherapy with fluoropyrimidines (5-FU, tegafur or carmofur) after curative resection compared with surgery alone. Subgroup analysis of patients with rectal cancer (n=2310) the mortality RR was 0.857 (95% CI; 0.734 – 0.999; p=0.049) and the disease free survival RR was 0.767 (95% CI; 0.656 – 0.882, p=0.0003) in favour of adjuvant chemotherapy with oral fluoropyrimidines. Preliminary results from a the Netherlands Adjuvant Colorectal Cancer Project (NACCP) observed no significant difference in disease-free or overall survival in the subgroups of patients with rectal cancer when comparing 5FU + Lavamisole for one year with observation after a median follow-up of three years. From one study of pooled individual data (n=614) for disease-free survival for rectal cancer patients the RR was 0.72 (95% CI; 0.47-1.09, p=0.107); when stratified by Dukes stage a highly significant effect (p=0.0004) was shown for carmofur over observation in Dukes C rectal cancer (RR=0.48, 95% CI; 0.32 – 0.73)

For overall survival the RR was 0.67 (95% CI; 0.43 – 1.06) and when stratified by Dukes stage, a highly significant effect was shown for Carmofur over observation in Dukes C rectal cancer (RR=0.54, 95% CI; 0.35 – 0.84, p=0.0004)

Meta-analysis of Randomised Trials
Pooled results from 3 studies showed a significant survival benefit for chemotherapy (OR (for death); 0.65, 95% CI; 0.51 – 0.83, p=0.0006) but no benefit in local control (OR (for local failure); 0.71, 95% CI; 0.44 – 1.16, p=0.17).

General comments
Results of the updated version are presented here as they are more relevant.

Data were pooled to estimate the overall effect on survival and local control of chemotherapy versus observation. Results for patients with stage II and III rectal cancer were combined in the meta-analysis. When survival and disease free survival were not reported, they were estimated from published graphs and where the actual number of events were reported, these data were used in the analysis.
Data on local control reported at the time of follow-up in each study were pooled even though follow-up times were different across studies. Combining data in this way assumes a constant hazard ratio of risks between the groups being compared.

No additional pooling of data was performed at updates.

References of Included Studies (For systematic reviews):

Individual study results
Fisher B et al (1988) Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-01 *Journal of the National Cancer Institute* 80;1:21-29

Thomas PRM et al (1988) Adjuvant postoperation radiotherapy and chemotherapy in rectal carcinoma: a review of the Gastrointestinal Tumour Study Group experience *Radiother Oncol* 13;245-52

Colorectal Cancer Chemotherapy Study Group of Japan (1995) Five year results of a randomised controlled trial of adjuvant chemotherapy for curatively resected colorectal carcinoma *Jpn J Clinical Oncol* 25;91-103

Dube S, et al (1997) Adjuvant Chemotherapy in Colorectal Carcinoma: results of a meta-analysis *Diseases of the Colon and Rectum* 40;35-41

Sakamoto J et al (1999) Adjuvant therapy with oral fluoropyrimidines as main chemotherapeutic agents after curative resection for colorectal cancer: individual patient data meta-analysis of randomised trials. *Jpn J Clin Oncol* 29;78-86

Zoetmulder FAN et al (1999) Adjuvant 5FU plus Levamisole improves survival in stage II and stage III colonic cancer, but not in rectal cancer. Interim analysis of the Netherlands Adjuvant Colorectal Cancer Project (NACCP) [abstract] *Proc Annu Meet Am Soc Clin Oncol* 18;266a:Abstract 1021

Sakamoto J et al (2001) An individual patient data meta-analysis of long supported adjuvant chemotherapy with oral carmofur in patients with curatively resected colorectal cancer *Oncol Rep* 8;697 - 703

Citation: Glimelius B, Dahl O, Cedermark B, Jakobsen A (2005) Adjuvant Chemotherapy in colorectal cancer: a joint analysis of randomised trials by the Nordic Gastrointestinal Tumour Adjuvant Therapy Group *Acta Oncologica* 44;8:904-912
Design: Pooled Analysis **Country**: Norway/Sweden/Denmark **Setting**: **Aim**: to confirm or refute clinically meaningful gains from adjuvant chemotherapy in the various stages and sites of colorectal cancer.
Inclusion criteria Patients with curatively resected stage II or stage III adenocarcinoma of the colon or rectum Age <76 years
Exclusion criteria Varied between trials but included: Patients with another malignancy apart from squamous cell carcinoma of the skin and stage 0 cervical cancer Patients who had received previous chemotherapy or radiotherapy Patients with severe cardiopulmonary disease and no major laboratory abnormalities
Sample Size
Randomisation Method
Population N=2,224 patients randomized, 13 patients excluded therefore analysis based on 2,211 patients N= 691 patients with stage II or III rectal cancer
Study Duration
Interventions Adjuvant Chemotherapy versus observation Chemotherapy Regimens: 5FU+Levamisole 5FU+Leucovorin (a) 5FU+Leucovorin (b) 5FU+Leucovorin+Levamisole (a) 5FU+Leucovorin+Levamisole (b)
Outcomes Survival
Results Minimum follow-up was 5 years For patients with stage II rectal cancer there was no significant difference in survival between the surgery and chemotherapy groups (p=0.09) and similarly for patients with stage III colon cancer there was no significant difference in 5 year survival between the surgery and chemotherapy groups (p=0.91).
General comments Early randomisation and initiation of treatment was emphasised in all trials though the time limits were different for each trial: Norway – treatment to start within 42 days Denmark – randomisation to occur within 30 days and treatment to start within 40 days Sweden – Stockholm treatment to start within 10 weeks and the rest of Sweden to start as soon as possible, preferably within 49 days. There was insufficient data in this pooled analysis to be able to include the results in the RevMan analysis. It was unclear from the paper whether the individual trials were published separately therefore these could not be reviewed.

Citation: Quasar Collaborative Group (2007) Adjuvant Chemotherapy versus observation in patients with colorectal cancer: a randomised study *Lancet* 370:9604;2020-2029

Design: Randomised Trial **Country**: N/A **Setting:** Multicentre study patients drawn from 150 centres in 19 countries **Aim**: to determine the size and duration of any survival benefit from adjuvant chemotherapy for patients with colorectal cancer at low risk of recurrence, for whom the indication for such treatment is unclear

Inclusion criteria • Patients who were thought to have complete resection of colon or rectal cancer with no evidence of distant metastases • No definite contraindications to chemotherapy • No prior chemotherapy other than 1 week post-operative portal vein infusion for fluorouracil

Exclusion criteria None Given (implicit in the inclusion criteria?)

Sample Size Target recruitment was at least 2,500 patients to give a more than 80% chance of detecting a 5% improvement in survival at a significance level of less than 0.05.

Randomisation Method A minimised randomisation procedure was used with randomisation done by telephone call to a central office

Population N=3,329 Randomised: 1617 patients to observation alone and 1622 patients to receive chemotherapy Observation Group: 6/1617 patients received chemotherapy Chemotherapy Group: 45/1622 did not start chemotherapy Observation Group: 474/1617 (29%) with rectal or colon and rectal cancer Chemotherapy Group: 474/1622 (29%) with rectal or colon and rectal cancer

Study Duration May 1994 – Dec 2003

Interventions • Chemotherapy until Oct 1997: fluorouracil plus either high or low dose folinic acid, combined with levamisole or placebo • Chemotherapy after Oct 1997: fluorouracil plus low dose folinic acid • No Chemotherapy

Outcomes • All cause mortality • Death from colorectal cancer • Recurrence

Results • Prior hypotheses were that the monthly 5-day schedule would be more effective than the once weekly schedule and that chemotherapy within six weeks of surgery would be more effective than later. • Groups were well balanced with respect to baseline characteristics • Median follow-up of surviving patients was 5.5 years (range 0-10.6 years) • There were 311 deaths in the chemotherapy arm and 370 in the observation arm • The relative risk of death from any cause with chemotherapy versus observation was 0.82 (95% CI; 0.701-0.95; p=0.008) while the relative risk of death from colorectal cancer was 0.81 (95% CI; 0.68-0.96, p=0.01) • There were 293 recurrences in the chemotherapy group and 359 in the observation group

- The relative risk of recurrence with chemotherapy versus observation over the whole study period was 0.78 (95% CI; 0.67-0.91, p=0.001).
- There was significant heterogeneity in treatment effect by period of follow-up with 149 (9.2%) recurrences in the chemotherapy in the first 2 years after randomisation, compared with 227 (14%) in the observation group (p=0.004). The relative risk of recurrence in the first 2 years with chemotherapy versus observation was 0.64 (95% CI; 0.52-0.78, p<0.0001).
- There was no benefit or loss of benefit with 144/1127 (12.8%) in the chemotherapy group and 132/1040 patients in the observation group experiencing a recurrence after 2 years (p=0.94).
- The relative risk for recurrence in the first 2 years after randomisation with chemotherapy in patients with stage III rectal cancer was 0.44 (95% CI; 0.18-1.06, p=0.02) and for patients with stage II rectal cancer was 0.57 (95% CI; 0.38-0.89, p=0.007).
- The proportional reduction in recurrence with chemotherapy versus observation alone was similar in patients with stage II and III and in patients with colon cancer and those with rectal cancer.
- The relative risk of recurrence with chemotherapy compared with observation alone in patients with rectal cancer was 0.68 (95% CI; 0.52-0.88, p=0.004)
- There was no reduction in recurrence for patients aged over 70 years, though this was not significant; for patients under 70 years the relative risk of recurrence in the 2 years following randomisation was 0.58 (95% CI; 0.38-0.93, p=0.01) for those with stage II rectal cancer.

Subgroup investigations of mortality were less reliable than for recurrence due to the lesser treatment effect; the relative risk of death from any cause in patients with rectal cancer was 0.77 (95% CI 0.54-1.00; p=0.05)

Results for QoL relate to the whole study population and not just to rectal cancer patients, though it is likely that the results would be applicable and relevant to the rectal cancer subgroup alone.
Quality of life measurements directly related to expected toxicity (e.g. diarrhoea, nausea, vomiting, mouth pain, fatigue, appetite loss and social functioning) were worse in the chemotherapy group than in the observation group (p<0.01), though only during the course of chemotherapy.
The proportion of patients with grade 3/4 nausea, oral adverse events, neutropenia and any grade 3/4 toxicity was significantly greater with 4-week courses of chemotherapy compare with once weekly delivery (p<0.001).

General comments
- With regard to the inclusion criteria, the indication for chemotherapy was decided by each patient's clinician following consultation with the patient rather than by any per-patient protocol definition. In practice, lymph node status was the key discriminator with 70% of those deemed to have a clear indication for chemotherapy having stage III disease while 91% with unclear indication had stage II disease. It is unclear from the text whether the treating physicians had any influence over which group their own patients were assigned to.
- No mention is made as to whether the investigators were blinded to the study groups (it would not be possible to blind the participants in a trial such as this).

Note: The results presented here are the results stated in the paper; there are some discrepancies when trying to replicate the results in RevMan and therefore when completing the GRADE tables for this topic, the results generated in RevMan will be used and where there are discrepancies, these will be noted as a footnote in the GRADE file.

Citation: Sakamoto J, Ohasi Y, Hamada C, Buyse M (2004) Efficacy of oral adjuvant therapy after resection of colorectal cancer: 5 year results from three randomised trials *Journal of Clinical Oncology* 22;3:484-492
Design: Meta-analysis of randomised trials **Country**: Japan **Setting:** Multi-centre **Aim**: to assess the survival and disease free survival benefits of treating patients after surgical resection of a primary colorectal tumour with oral fluoropyrimidines for 1 year
Inclusion criteria Trials that randomised patients to either long-term administration of oral fluorinated pyrimidines or no further treatment after curative resection of colorectal tumours, providing the trial was initiated before 1990 and the randomisation technique used was one that precluded the possibility of prior knowledge of the treatment to be allocated.
Exclusion criteria Trials using sealed envelope method of randomisation
Sample Size N/A
Randomisation Method N/A
Population
Study Duration N/A
Interventions Two trials tested UFT (and one trial tested HCFU (Carmofur)
Outcomes Survival Disease Free Survival
Results All patients had been followed up through 5 years in each individual trial, therefore overall survival and disease free survival data were not available beyond 5 years. Survival Overall Hazard Ratio (HR) was 0.89 (95% CI; 0.8 – 0.99, p=0.04) with no significant heterogeneity between the treatment effects in different trials. The benefit of oral fluorinated pyrimidines was seen in both rectal and colon locations; HR for rectal was 0.92 (95% CI; 0.79-1.07). There was a trend towards larger treatment effects in earlier Dukes stages (p=0.077); a trend towards smaller benefits in older patients with a negative effect observed in patients older than 70 years, this trend was not consistent in younger patients (p=0.4). There was no statistically significant difference in benefit of the various oral fluoropyrimidines (p=0.8) but the trials used different agents depending on tumour site and so this comparison may be confounded by other differences in trial characteristics. A proportional hazard regression model of survival confirmed the benefit of treatment and the lack of significant treatment by covariate interactions, except for a trend toward larger benefit in earlier Dukes stage. The best survival model excluded sex, site or type of oral fluoropyrimidine and included Dukes stage (p<0.0001), age (p=0.001), treatment (p=0.026) and the interaction between treatment and Dukes stage (p=0.066). Disease Free Survival Overall HR was 0.85 (95% CI; 0.77 – 0.93, p<0.001) with no significant heterogeneity between the treatment effects in different trials. The benefit of oral fluoropyrimidines on DFS was similar in rectal and colon locations; HR for rectal was 0.83 (95% CI; 0.73 – 0.95). There was a trend towards a larger benefit in earlier Dukes stage, though this failed to reach statistical significance (p=0.1).

The best DFS model retained the same covariates as the survival model: Dukes stage (p<0.0001), age (p=0.012), treatment (p=0.021) and the interaction between treatment and Dukes Stage (p=0.095).

General comments
All three included trials had separate randomisations for patients with rectal cancer and colon cancer.

References of Included Studies (For systematic reviews):
Kodaira S, Kikuchi K, Yasutomi M et al (1998) Postoperative adjuvant chemotherapy with mytomycin C and UFT for curatively resected rectal cancer: Individual patient data meta-analysis of randomised trials *International Journal of Clinical Oncology* 3;6:357-364

Yasutomi M, Takahashi T, Kodaira S et al (1997) Prospective controlled study of the usefulness of Carmofur as a postoperative adjuvant chemotherapy for colorectal cancer *Gan To Kagaku Ryoho* 24;1953-1960

Citation: Sakamoto J (1999) Adjuvant therapy with oral fluoropyrimidines as main chemotherapeutic agents after curative resection for colorectal cancer: individual patient data meta-analysis of randomised trials *Jpn Journal of Clinical Oncology* 2;29:78-86

Design: Meta Analysis of individual patient data

Country: Japan

Setting:

Aim: To evaluate the effect of oral fluoropyrimidines in rectal cancer

Inclusion criteria
Randomised Trials which began recruiting before January 1988
Adjuvant Chemotherapy by oral fluoropyrimidines with curative intent
At least 5-years of follow-up
Control arm consisting of surgery alone

Exclusion criteria

Sample Size
N/A

Randomisation Method
N/A

Population
N=4960 patients randomised

Study Duration

Interventions
SGCCC Trial: 5-FU
SGACCS Trial: Tegafur
TSGHCFU Trial: Carmofur

Outcomes
Disease Free Survival
Survival

Results
Objective recurrences were observed in 572/1900 (30.1%) of patients allocated to the surgery alone control group and 688/2702 (25.5%) of patients allocated to the adjuvant chemotherapy group.

The RR for disease free survival for rectal cancer was 0.767 (95% CI; 0.6560-00.882, p=0.0003).
Significant differences in disease free survival were observed in rectal cancers in both Dukes B (p=0.0001) and Dukes C (p=0.0003) patients.

Deaths were recorded in 500/1900 (26.3%) of patients allocated to surgery alone and in 664/2702 (24.2%) of patients allocated to adjuvant chemotherapy.
The RR for survival for rectal cancer was 0.857 (95% CI; 0.734-0.999, p=0.049).

Analysis by Dukes stage showed a significant effect of oral fluoropyrimidines for survival in Dukes C (p=0.0124) but not in Dukes B (p=0.1088) for rectal cancers.

General comments
No patient had prior chemotherapy or radiotherapy before surgery
All patients received resection for colorectal cancer with curative intent between 1984 and 1988.

The data presented is not of sufficient quality or detail to allow inclusion in the pooled analysis

3.5. Adjuvant Chemotherapy for High Risk Stage II Colon Cancer

3.5.1. For patients with high-risk stage II colon cancer what is the effectiveness of adjuvant chemotherapy after surgery?

Short Summary

There was very little evidence with which to address this topic and what was available consisted primarily of poor quality, indirect evidence. There were three pooled analyses (non-systematic pooling of specific trial data) which provided some indirect evidence (Erlichman C, 1999; Labianca R, 1995; Mamounas E, 1999), a single randomised trial (O'Connell MJ, 1997) and two case-series studies (one prospective and one retrospective) which added limited, poor quality and indirect evidence (Lin CC, 2009, Yoshimatsu K, 2006)). All of the available evidence was considered to be low to moderate quality for all outcomes on GRADE assessment, primarily due to the indirect nature of the evidence and the small number of patients in each of the relevant studies.

The lack of evidence available to address this question may partly be a result of the fact that there is no standard definition for 'high-risk' patients thus making it difficult to identify these patients, there is however a list of prognostic factors which are used to identify potentially high risk patients including extra mural vascular invasion, grade 3/poor differentiation, T4 stage/perforation, peri-neural invasion, obstructive tumours, mucinous tumours, micro-satellite instability, tumour budding. The available evidence does not specifically address high-risk patients, rather in most cases the studies present some data which is possibly relevant to high-risk patients as a secondary analysis to the main purpose of the study.

From one prospective study (Lin CC, 2009), there was no significant difference in survival for stage II patients receiving adjuvant chemotherapy compared with patients that did not receive adjuvant chemotherapy, however in the subgroup of patients with high risk factors, there was a significant 3-year disease free survival benefit (96.4% vs. 84.7%, p=0.045) and 5-year overall survival benefit (100% vs. 86.4%, p=0.015) in favour of adjuvant chemotherapy.

Considering patients with tumour exposed at the serosa or invasion of other organ as high risk and patients with tumour invasion under the serosa low risk, one retrospective case series observed that for patients in the high risk group there was a significant difference in 5-year survival for patients receiving adjuvant chemotherapy (75.8%) and patients not receiving chemotherapy (44%) (p=0.0008) (Yoshimatsu, 2006).

The American Society for Clinical Oncology (ASCO) recommended that the optimal approach is to encourage patients with high-risk stage II disease to participate in randomised trials as there is no direct evidence that adjuvant chemotherapy converys a survival benefit in high risk patients (Benson et al, 2004).

The toxic effects of chemotherapy were gastrointestinal and consisted primarily of nausea, stomatitis and diarrhoea (Erlichman et al, 1999; Labianca et al, 1995; O'Connell et al, 1997). There were no treatment related deaths in any of the included studies and most of the symptoms of toxicity were manageable.

Review Protocol:

Population	Intervention	Comparison	Outcomes
Patients with high risk stage II **colon** cancer	• Adjuvant chemotherapy following surgery	• No chemotherapy	• Survival • Quality of life Recurrence/disease free survival • toxicity

Following a systematic search of relevant data sources (see appendix .1), the information specialist created a database of potentially relevant studies. All titles and abstracts were sifted by a single reviewer. Queries about inclusion were clarified by the GDG topic subgroup. The full studies were then obtained and reviewed and relevant studies were included in the final evidence review.

All update searches were sifted by a single reviewer and the list of potentially relevant studies was also checked for irrelevant studies by the GDG subgroup. Only studies which all subgroup members were in agreement were excluded. The remaining studies were obtained and reviewed with relevant studies included in the final evidence review.

High risk was defined by the GDG as being patients with any one or a number of the following characteristics: extra mural vascular invasion, grade 3/poor differentiation, T4 stage/perforation, peri-neural invasion, obstructive tumours, mucinous tumours, micro-satellite instability, tumour budding.

The question will not define 'high-risk' groups, however if there is evidence relating to certain individual characteristics deemed to be indicative of high risk, then this evidence will be presented.

It is felt that high level evidence will exist for this topic and the date limit set by the GDG is 1985 as this is when clinically relevant data will be available from.

Reasons for excluding studies:
Did not report on 'high-risk' patients
Did not report on outcomes of interest
Did not separate 'high-risk' patients from other patients in the study
Did not report on stage II patients
Focuses on identifying prognostic features
Foreign Language with no translation
Abstracts Only
Expert Review

Quality of the included studies
Systematic review of RCTs (n =2)
Unsystematic review of RCTs (n =3)
Systematic review of combined study designs (n =0)
Randomized controlled trial (n = 2)
Prospective cross sectional study (n =0)
Case Series Studies (n = 2)

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┌─────────────────┐        ┌─────────────────┐
│ 466 (+43)       │        │ 379 (+39) papers │
│ possibly relevant│  →     │ excluded based   │
│ papers identified│        │ on title & abstract│
└─────────────────┘        └─────────────────┘
         ↓
┌─────────────────┐        ┌─────────────────┐
│ 87 (+4) papers  │        │ 78 (+4) papers  │
│ obtained for    │  →     │ excluded        │
│ appraisal       │        │                 │
└─────────────────┘        └─────────────────┘
         ↓
┌─────────────────┐
│ 9 papers included│
│ in evidence table│
└─────────────────┘
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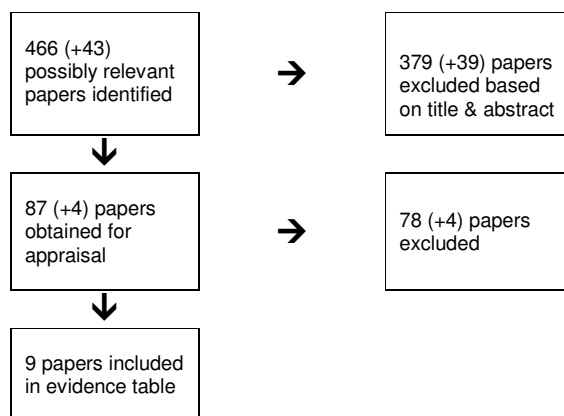
Volume of evidence

There was very little evidence with which to address this topic and what was available consisted primarily of poor quality, indirect evidence. There were three pooled analyses (non-systematic pooling of specific trial

data) which provided some indirect evidence, a single randomised trial, a systematic review (des Guetz, 2009) and two case-series studies (one prospective and one retrospective) which added limited, poor quality and indirect evidence. The American Society of Clinical Oncology (ASCO) have produced recommendations on the use of adjuvant chemotherapy for stage II colon cancer (Benson et al, 2004) which include recommendations on the use of adjuvant chemotherapy in high-risk patients.

Applicability
There was very little direct evidence with which to address this topic, this may partly be a result of the fact that there is no standard definition for 'high-risk' patients thus making it difficult to identify these patients. A number of clinical factors have been identified as being indicators of high risk and small number of studies presented pooled data analyses from randomised trials (Erlichman C, 1999; Labianca R, 1995; Mamounas E, 1999) from which some relevant evidence could be extracted, a single randomised trial (O'Connell MJ, 1997) provided further indirect evidence and one recent prospective case-series study (Lin CC, 2009) provided some direct evidence. One systematic review (Des Guetz, 2009) compared patients with microsatellite instability receiving and not receiving adjuvant chemotherapy.
There was also one set of guidelines from the American Society of Clinical Oncology (Benson AB, 2004) which provide recommendations on the use of adjuvant chemotherapy in high risk patients.

Consistency
Due to the fact that so little evidence was available relating to this topic, it is difficult to comment on consistency of the results. The available evidence does not specifically address high-risk patients, rather in some cases the studies present some data which is possibly relevant to high-risk patients as a secondary analysis to the main purpose of the study. The factors considered to define high risk patients appear to be relatively consistent across the studies though the way in which such patients are grouped and analysed differs, making it difficult to consider any of the studies together. There is variation in treatment regimens in trials included in pooled analysis as well as in the methodology across studies.

Other factors
As the majority of the available evidence is indirect, consisting primarily of secondary outcomes and subgroup analysis in trials, all types of studies potentially addressing high-risk patients were considered for this topic.

Evidence Statement
This topic aimed to address the benefits, if any, for high-risk stage II colon cancer patients of adjuvant chemotherapy. There is currently no standard definition of high-risk stage II patients, however there a number of prognostic factors that are considered to be indicative of high-risk patients including extra mural vascular invasion, grade 3/poor differentiation, T4 stage/perforation, peri-neural invasion, obstructive tumours, mucinous tumours, micro-satellite instability and tumour budding.

Overall Survival, Recurrence/Disease Free Survival
From one pooled analysis (Labianca, 1995) designed to determine the efficacy of fluorouracil and high-dose folinic acid after surgery in Dukes B and C stage colon cancer it was observed that fluorouracil plus folinic acid significantly increased overall survival and event free survival. For Dukes B patients alone (which would include Dukes B2, but not separated from the overall Dukes B) the unstratified event free survival Hazards Ratio (unstratified) was 0.84 (0.62-1.12) and the overall survival hazards ratio (unstratified) was 0.91 (0.63-1.34).

From a second pooled analysis of trials comparing fluorouracil plus folinic acid as adjuvant therapy with no adjuvant therapy in Dukes B2 ($T_{3-4}N_0M_0$) colon cancer patients (Erlichman, 1999) there was no significant difference in event free or overall survival between patients receiving adjuvant chemotherapy and those not receiving adjuvant chemotherapy. Tumour grade was an independent predictor for both overall survival (overall adjusted HR 0.86, 90% CI; 0.68-1.07, p=0.13) and event free survival (overall adjusted HR 0.88, 90% CI; 0.72-1.07, p=0.137) though not statistically significant. When EFS and OS were analysed according to treatment arm and corrected for age and tumour grade, no difference was observed between the treatment arms.
There was a statistically significant difference in event free survival (p<0.001. two-sided) and overall survival (p<0.01, two-sided) between patients with well/moderately differentiated tumours and patients with poorly differentiated tumours.
This study was included as it looked at the benefits of adjuvant chemotherapy in B2 ($T_{3-4}N_0M_0$) colon cancer; T4 stage is one of the factors considered high-risk and so this study provides some indirect evidence that high-risk patients do not benefit from adjuvant chemotherapy. It does not present separate results for T4

stage however, nor does it separate the results of other factors of interest (tumour grade or differentiation) according to treatment/control groups, simply providing a Hazards Ratio for the whole population group.

A third pooled analysis compared whether patients with Dukes B disease benefit from adjuvant chemotherapy and evaluated the magnitude of benefit compared with Dukes C patients (Mamounas, 1999). The analysis included a number of trials, but only two of the included trials were relevant to this topic due to them being the only two relevant to the PICO (comparing adjuvant chemotherapy to surgery alone), therefore the results of the individual trials are reported here. In addition, however the overall results from the pooled analysis in relation to high-risk characteristics are reported for information purposes but care should be taken when interpreting the overall result,   which has been derived by splitting individual trial populations into two treatment groups; group 1 consisted of the treatment groups from each trial with inferior overall, disease free and recurrence free survival for all patients while group 2 consisted of the treatment groups with superior overall, disease free and recurrence free survival for all patients.
From one included trial, administration of adjuvant semustine, vincristine and 5-FU resulted in a 7% absolute improvement in survival over surgery alone (p=0.07). For Dukes B patients the absolute improvement in survival was 3% (p=0.73) compared with 9% (p=0.05) for Dukes C patients.
Administration of adjuvant chemotherapy resulted in a 7% reduction in mortality for Dukes B patients compared with a 26% reduction for Dukes C.
In the second relevant trial, administration of peri-operative PVI of 5-FU resulted in a 7% absolute improvement in survival over surgery alone (p=0.08). There was a 12% improvement in survival for Dukes B patients (p=0.005) and a 2% improvements for Dukes C (p=0.81) with peri-operative PVI compared with surgery alone.
Administration of 7-days perioperative PVI of 5-FU resulted in a 51% reduction in mortality for Dukes B patients compared with a 4% reduction for Dukes C patients.
In the total population (from all four trials), 26% of Dukes B and 28% of Dukes C patients had high risk characteristics (obstruction, perforation, extention of tumour into adjacent organs). In Dukes B patients without high-risk characteristics there was a 32% reduction in mortality (cumulative OR 0.68; 95% CI 0.5-0.92; p=0.01) compared with a 20% reduction in mortality (cumulative OR 0.8; 95% CI 0.55-1.17; p=0.26). The reduction in mortality translated into an absolute improvement in survival of 5% for each risk category.

From a randomised trial examining the efficacy of intensive fluorouracil plus low dose Leucovorin (O'Connell et al 1997), patients were stratified according to extent of invasion, presence/absence of intestinal obstruction, presence/absence of regional peritoneal metastases resected en bloc and extent of regional lymph node metastases
For tumour relapse, no significant interaction between treatment and any of the prognostic variables .

From one prospective case series (Lin, 2009) univariate analysis showed T4 lesion (p=0.024), lymphovascular invasion (p=0.022), obstruction at presentation (p=0.008) and mucinous component more than 50% (p=0.032) were significantly associated with decreased disease free survival. On multivariate analysis, lymphovascular invasion and obstruction were independent factors associated with decreased disease free survival (no data provided).
When considering patients with at least one risk factor (T4 lesion, lymphovascular invasion, obstruction at presentation or mucinous component more than 50%) to be high risk a significant difference in 3 year disease free survival was observed between the patients with high risk factors (84.7%) and patients without (95%) (p=0.001).
A significant difference in disease free survival was observed for patients with no high risk factor, patients with one high-risk factor and patients with more than one high risk factor (p=0.003).
There was no significant difference in survival for stage II patients receiving adjuvant chemotherapy compared with patients that did not receive adjuvant chemotherapy, however in the subgroup of patients with high risk factors, there was a significant 3-year disease free survival benefit (96.4% vs. 84.7%, p=0.045) and 5-year overall survival benefit (100% vs. 86.4%, p=0.015) in favour of adjuvant chemotherapy.

One retrospective case series with 229 patients (Yoshimatsu, 2006) observed that depth of invasion, number of dissected nodes and adjuvant chemotherapy were prognostic factors in Dukes B with depth of invasion the most significant (p=0.0186). Considering patients with tumour exposed at the serosa or invasion of other organ as high risk and patients with tumour invasion under the serosa low risk, it was observed that for patients in the high risk group there was a significant difference in 5-year survival for patients receiving adjuvant chemotherapy (75.8%) and patients not receiving chemotherapy (44%) (p=0.0008).
This study did not compare outcomes for patients in the high risk group compared with patients in the low risk group.

From one meta-analysis (Des Guetz, 2009), evaluation of whether MSI-H and MSS patients benefit similarly from adjuvant chemotherapy found statistically significant interaction meaning that chemotherapy had no

effect among MSI-H patients compared with a beneficial effect in MSS patients (HR for relapse free survival 0.77; 95% CI 0.68-0.87, p<0.001). This study included patients with colon and rectal cancer as well as stage II and stage III patients however, so it's usefulness in making providing evidence for this topic is questionable.

From one systematic review (Des Guetz, 2009), survival was analysed among MSI-H patients reveiving and not receiving chemotherapy and no benefit was observed among MSI-H patients receiving chemotherapy. From 6 studies, global HR for overall survival was 0.7 (95% CI: 0.44-1.09) and from 5 studies, global HR for relapse free survival was 0.96 (95% CI: 0.62-1.49)
Evaluation of whether MSI-H and MSS patients benefit similarly from adjuvant chemotherapy found statistically significant interaction meaning that chemotherapy had no effect among MSI-H patients compared with a beneficial effect in MSS patients (HR for relapse free survival 0.77; 95% CI 0.68-0.87, p<0.001).

Subgroup analysis could not be performed for stage II and stage III patients as the majority of included studies did not separate the stages for analysis.
Two studies included in the systematic review treated patients with Levamisole which is not currently used in the UK and therefore the results of such studies contribute the the indirectness of the evidence base.

Quality assessment						Summary of findings			
						No of patients		Effect	
Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Adjuvant Chemotherapy	Surgery Alone	Relative (95% CI)	
...vival (Erlichman, 1999) (follow-up median 5.75 years)									
...andomised ...ials	no serious limitations[1]	no serious inconsistency[2]	serious[3]	serious[4]	none	98/507 (19.3%)	120/509 (23.6%)	HR 0.81 (0.64 to 1.01)[5]	40 fewer per 1000 (from 78 fewer to 2 more)
							23.6%		40 fewer per 1000 (from 78 fewer to 2 more)
...vival (Mamounas, 1999)									
...andomised ...ials	no serious limitations[1]	serious[6]	serious[3]	serious[4]	none	116/351 (33%)	150/375 (40%)[7]	not pooled	not pooled
							40%		not pooled
...vival (Mamounas, 1999)									
...andomised ...ials	no serious limitations[1]	serious[6]	serious[3]	serious[4]	none	89/340 (26.2%)	113/343 (32.9%)[8]	not pooled	not pooled
							32.9%		not pooled
...vival (Labianca, 1995) (follow-up median 37 months[9])									
...andomised ...ials	no serious limitations[1]	no serious inconsistency[10]	serious[3]	very serious[4]	none	0/0 (0%)	0/0 (0%)	HR 0.91 (0.63 to 1.34)[11]	0 fewer per 1000 (from 0 fewer to 0 more)
							0%		0 fewer per 1000 (from 0 fewer to 0 more)
...Survival (Erlichman, 1999) (follow-up median 5.75 years)									
...andomised ...ials	no serious limitations[1]	no serious inconsistency[2]	serious[3]	serious[4]	none	101/507 (19.9%)	110/509 (21.6%)	HR 0.83 (0.68 to 1.01)	33 fewer per 1000 (from 64 fewer to 2 more)
							21.6%		33 fewer per 1000 (from 63 fewer to 2 more)
...Survival (Labianca, 1995) (follow-up median 37 months[9])									
...andomised ...ials	no serious limitations[1]	no serious inconsistency[10]	serious[3]	no serious imprecision	none	193/754 (25.6%)	262/736 (35.6%)	HR 0.84 (0.62 to 1.12)[12]	47 fewer per 1000 (from 117 fewer to 33 more)
							35.6%		47 fewer per 1000 (from 117 fewer to 33 more)

...m the individual trial methodologies were not given in the paper.
...to be an updated version of Labianca, 1995 with more trials added and using individual patient data for analysis.
...did not look at the high-risk population specifically
...300 events
...esented is the unadjusted HR; the adjusted HR was 0.86, 90% CI; 0.68-1.07 (adjusted for age and tumour grade).
...rials included had different treatment regimens and comparators. No other information is given.

llow-up for the treatment group was 40 months and for the intervention group was 37 months.
from the study that individual patient data were used from a central database of three trials with representatives of each of the trial groups writing a protocol for the pooled co

unstratified HR for overall survival. The HR stratified by country was 0.93, 95% CI; 0.63-1.37. The HR relates to the Dukes B population only.
resented is the unstratified HR and relates to the stage B population only, the HR stratified for by country was 0.93 95% CI; 0.63-1.37

0 GRADE Quality Assessment and Summary of Findings

Toxicity

The toxic effects of chemotherapy were gastrointestinal and consisted primarily of nausea, stomatitis and diarrhoea (Erlichman et al, 1999; Labianca et al, 1995; O'Connell et al, 1997). There were no treatment related deaths in any of the included studies and most of the symptoms of toxicity were manageable.

The American Society of Clinical Oncology (ASCO) have produced recommendations on the use of adjuvant chemotherapy for stage II colon cancer (Benson et al, 2004) which include recommendations on the use of adjuvant chemotherapy in high-risk patients. The recommendations are based on a systematic review and meta-analysis of available data, and for high risk patients the evidence base considered included included final reports of early stage II and III adjuvant chemotherapy trials that include risk factor data, large scale National Caner Data Base (NCDB) analyses of nodal status and prognosis, a secondary analysis of data from a large intergroup randomised trial to demonstrate the association between number of nodes recovered and overall survival, a recent pooled analysis of prognostic and predictive factors in colorectal cancer, a College of American Pathologists consensus statement on prognostic factors in colorectal cancer and selected studies on emerging molecular markers.

The recommendations for patients with any number of poor prognostic features (T4 lesion, perforation or poorly differentiated histology) suggest that such patients might be suitable candidates for adjuvant chemotherapy however it should be made clare that although these characteristics may be prognostic, there is no data to suggest that they are predictive of response to adjuvant chemotherapy and that the magnitude of risk conferred by these characteristics, relative to nodal status, cannot be estimated from current data.

With no direct evidence demonstrating a survival benefit of adjuvant chemotherapy in high risk patients and the toxic effects associated with adjuvant chemotherapy, it would be reasonable to recommend against the use of adjuvant treatment.

Patients and Oncologists who are prepared to accept results from stage III diseases as indirect evidence of the benefits of adjuvant chemotherapy are justified in considering the use of such therapy in stage II patients provided they appreciate that the magnitude of benefit as measured in absolute improvement in survival, is small.

The optimal approach recommended is to encourage patients with high-risk stage II disease to participate in randomised trials.

References

Benson AB, Schrag D, Somerfield MR, Cohen AM, Figueredo AT, Flynn PJ, Krzyzanowska MK, Maroun J, McAllister P, Van Cutsem E, Brouwers M, Charette M, Haller DG (2004) American Society of Clinical Oncology Recommendations on adjuvant chemotherapy for stage II colon cancer (review) *Journal of Clinical Oncology* 22;16:3408-3419

Des Guetz G, Schischmanoff O, Nicola P, Perret GY, Morere JF, Uzzan B (2009) Does microsatellite instability predict the efficacy of adjuvant chemotherapy in colorectal cancer? A systematic review with meta-analysis *European Journal of Cancer* 45;10:1890-1896

Erlichman, C. (1999) Efficacy of adjuvant fluorouracil and folinic acid in B2 colon cancer *Journal of Clinical Oncology* 17;5:1356-1363

Figeuredo A, Charette, ML, Maroun J, Brouwers MC, Zuraw L (2004) Adjuvant Therapy for Stage II Colon Cancer: A Systematic Review from the Cancer Care Ontario Program in Evidence-Based Care's Gastrointestinal Cancer Disease Site Group *Journal of Clinical Oncology* 22;16:3395-3407

Labianca R (1995) Efficacy of adjuvant fluorouracil and Folinic acid in colon cancer *Lancet* 345;8955:939-944

Lin CC, Lin JK, Chang SC, Wang HS, Yang SH, Jiang JK, Chen WS, Lin TC (2009) Is adjuvant chemotherapy beneficial to high risk stage II colon cancer? Analysis at a single institute *International Journal of Colorectal Disease* 24;6:665-676

Mamounas E, Wieand S, Wolmark N, Bear HD, Atkins JN, Song K, Jones J, Rockette H (1999) Comparative Efficacy of Adjuvant Chemotherapy in Patients with Dukes B versus Dukes C colon Cancer: Results from Four National Surgical Adjuvant Breast and Bowel Project Adjuvant Studies (C-01, C-02, C-03 and C-04) *Journal of Clinical Oncology* 17:5;1349-1355

O'Connell MJ, Mailliard JA, Kahn MJ, Macdonald JS, Haller DG, Mayer RJ, Wieand HS (1997) Controlled Trial of Fluorouracil and Low Dose Leucovorin Given for 6 Months as Postoperative Adjuvant Therapy for Colon Cancer *Journal of Clinical Oncology* 15;1:246-250

Yoshimatsu K, Umehara A, Ishibashi K, Yokomizo H, Yoshida K, Fujimoto T, Watanabe K, Ogawa K (2006) Indication and Efficacy of Adjuvant Chemotherapy with Oral Fluorouropyrimidines for Dukes B Colorectal Cancer *Anticancer Research* 26;3089-3094

Evidence Tables

Citation: Benson AB, Schrag D, Somerfield MR, Cohen AM, Figueredo AT, Flynn PJ, Krzyzanowska MK, Maroun J, McAllister P, Van Cutsem E, Brouwers M, Charette M, Haller DG (2004) American Society of Clinical Oncology Recommendations on adjuvant chemotherapy for stage II colon cancer (review) *Journal of Clinical Oncology* 22;16:3408-3419
Design: Literature based meta-analysis **Country**: USA **Aim**: to address whether all medically fit patients with curatively resected stage II colon cancer should be offered adjuvant chemotherapy as part of routine clinical practice, to identify patients with poor prognosis characteristics and to describe strategies for oncologists to use to discuss adjuvant chemotherapy in practice.
Inclusion criteria Randomised Controlled Trials with appropriate control groups Meta-analyses of RCTs comparing adjuvant therapy with observation in patients with stage II colon cancer who had undergone surgery with curative intent.
Exclusion criteria
Population
Interventions
Outcomes
Results Should patients with Curatively Resected Stage II Colon Cancer and with Identifiable Characteristics that Predict for a Poor Prognosis (i.e. high-risk patients) be Offered Adjuvant Chemotherapy? The evidence base considered included final reports of early stage II and III adjuvant chemotherapy trials that include risk factor data, large scale National Caner Data Base (NCDB) analyses of nodal status and prognosis, a secondary analysis of data from a large intergroup randomised trial to demonstrate the association between number of nodes recovered and overall survival, a recent pooled analysis of prognostic and predictive factors in colorectal cancer, a College of American Pathologists consensus statement on prognostic factors in colorectal cancer and selected studies on emerging molecular markers. Patients with a small number of sampled lymph nodes can be considered inadequately staged and at greater risk of having microscopic residual disease and could therefore be offered adjuvant chemotherapy. Patients with any of a number of poor prognostic features (T4 lesion, perforation or poorly differentiated histology) might be considered suitable candidates for adjuvant chemotherapy. It should be made clear however, that these tumour characteristics may be prognostic but there is no data to suggest that they are predictive of response to adjuvant chemotherapy. It should also be noted that the magnitude of risk conferred by these characteristics, relative to nodal status, cannot be estimated from the currently available data. There is no direct evidence to demonstrate a survival benefit of adjuvant chemotherapy in high-risk patients. As the small numbers of such patients evaluated in trials; the potential benefits have not been tested and there are toxic effects associated with adjuvant chemotherapy it is therefore reasonable to recommend against the use of adjuvant treatment. Patients and Oncologists who are prepared to accept results from stage III diseases as indirect evidence of the benefits of adjuvant chemotherapy are justified in considering the use of such therapy in stage II patients provided they appreciate that the magnitude of benefit as measured in absolute improvement in survival, is small. The optimal approach is to encourage patients with high-risk stage II disease to participate in randomised trials.

General comments
This guideline document used an updated version (Figueredo, 2004) of an earlier published review from the Cancer Care Ontario Program (Figueredo, 1997).

The guideline has been assessed using the AGREE Tool for the appraisal of guidelines. The completed assessment is available for review if required.

Only the information for the section on high-risk patients has been presented here as it is all that is relevant to the topic.

Some of the evidence has been drawn from studies which have used Levamisole as part of the treatment regimen and therefore recommendations should be considered with caution as they may draw on evidence that is not relevant to current clinical practice in the UK.

References of Included Studies (For systematic reviews):
Moertel CG, Fleming TR, MacDonald JS, et al (1995) Intergroup study of fluorouracil plus levamisole as adjuvant therapy for stage II/Dukes B2 colon cancer *Journal of Clinical Oncology* 13:2936-2943

Moertel CG, Fleming TR, MacDonald JS, et al (1995) Fluorouracil plus levamisole as effective adjuvant therapy after resection of stage III colon carcinoma: A final report *Annals of International Medicine* 122:321-326

Swanson RS, Compton CC, Stewart AK et al (2003) The prognosis of T3N0 colon cancer is dependent on the number of lymph nodes examined *Annals of Surgical Oncology* 10:65-71

Greene FL, Stewart AK, Norton HJ (2002) A new TNM staging strategy for node-positive (stage III) colon cancer: An analysis of 50,042 patients *Annals of Surgery* 236:416-421

Le Voyer TE, Sigurdson ER, Hanlon AL et al (2003) Colon Cancer survival is associated with increasing number of lymph nodes analyzed: A secondary survey of intergroup trial INT-0089 *Journal of Clinical Oncology* 21:2912-2919

Gill S, Loprinzi C, Sargent D et al (2004) Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: Who benefits and by how much? *Journal of Clinical Oncology* 22:1797-1806

Compton CC, Fielding LP, Burgart LJ et al (2000) Prognostic Factors in Colorectal Cancer College of American Pathologists Consensus Statement 1999. *Arch Pathol Lab Med* 124;979-994

Graziano F, Cascinu S, Staccioli MP et al. Potential Role and Chronology of abnormal expression of the deleted in colon cancer (DCC) and the p53 proteins in the development of gastric caner
http://www.biomedcentral.com/content/pdf/1471-2407-1-9.pdf

Ribic CM, Sargent DJ, Moore MJ et al (2003) Tumour micro-satellite instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer *New England Journal of Medicine* 349;247-257

Figuerdo A, Germond C, Maroun J (1997) Adjuvant therapy for stage II colon cancer after complete resection. Provincial Gastrointestinal Disease Site Group *Cancer Prevention and Control* 1;5:379-392

Figuerdo A, Charette ML, Maroun J (2004) Adjuvant therapy for stage II colon caner: a systematic review from the Cancer Care Ontario Program in evidence-based care's gastrointestinal cancer disease site group (Review) *Journal of Clinical Oncology* 22;16:3395-3407

Citation: Des Guetz G, Schischmanoff O, Nicola P, Perret GY, Morere JF, Uzzan B (2009) Does microsatellite instability predict the efficacy of adjuvant chemotherapy in colorectal cancer? A systematic review with meta-analysis *European Journal of Cancer* 45;10:1890-1896
Design: Systematic Review/Meta-analysis **Country**: France **Aim**: to assess the predictive values of MSI-H status among patients receiving or not receiving adjuvant chemotherapy for colorectal cancer.
Inclusion criteria Studies dealing with colon or rectum assessing the relationship between MSI status, chemotherapy and recurrence free survival or overall survival for localised disease.
Exclusion criteria Studies where survival data were not available
Population 7 studies representing a population of 3690 patients 1345 men and 1198 women (1147 missing data) 1777 colon cancer and 213 rectum (1700 missing data) 810 Stage II and 2444 stage III (436 missing data)
Interventions Adjuvant chemotherapy
Outcomes Not clearly defined
Results 7 studies assessed two cohorts; one receiving adjuvant chemotherapy and one not receiving adjuvant chemotherapy; two of the studies included samples from RCTs evaluating the potential benefit of adjuvant chemotherapy. Most patients were treated with 5Fu-based chemotherapy with or without folinic acid or levamisole. MSI-high was found in 454 patients and microsatellite stable (MSS) was found in 2871 patients (365 missing data). The number of microsatellite markers analysed differed greatly across studies (range 1-17). There was no significant heterogeneity between the studies (pHet=0.3 for overall survival and pHet=0.4 for recurrence free survival, I^2=16% and 4% respectively) No benefit of chemotherapy was observed among MSI-H patients. From 6 studies, global HR for overall survival was 0.7 (95% CI: 0.44-1.09) and from 5 studies, global HR for relapse free survival was 0.96 (95% CI: 0.62-1.49) Subgroup analysis could not be performed for stage II and stage III patients as the majority of included studies did not separate the stages for analysis. Evaluation of whether MSI-H and MSS patients benefit similarly from adjuvant chemotherapy found statistically significant interaction meaning that chemotherapy had no effect among MSI-H patients compared with a beneficial effect in MSS patients (HR for relapse free survival 0.77; 95% CI 0.68-0.87, p<0.001).
General comments Although this topic was not to include papers looking at levamisole, this study is a meta-analysis of studies with mixed treatments (including levamisole) for an area of particular interest (MSI) and so is included here. Searches were conducted on PubMed, EMBASE, Cochrane Database, there was no start date given for the searches, but searches ran up to February 2008. Determination of MSI status was always done retrospectively A pooled random HR estimate and 95% CI was calculated using a fixed effects model due to the absence of

heterogeneity between the studies.

Citation: Erlichman, C. (1999) Efficacy of adjuvant fluorouracil and folinic acid in B2 colon cancer *Journal of Clinical Oncology* 17;5:1356-1363

Design: Pooled Analysis

Country: Various

Aim: To determine whether fluorouracil (FU) and folinic acid (leucovorin) is an effective adjuvant therapy for patients after potentially curative resection of colon cancer in patients with B2 tumours.

Inclusion criteria
- Adenocarcinoma of the colon
- T3 or T4, N0 M0 colon cancer
- Chemo therapy to start between 21 and 56 days after surgery

Exclusion criteria
Patients for whom adequate staging data were not available or that were incorrectly staged (N=9)

Population
N=1016 patients from 5 trials

Interventions
Fluorouracil (FU) combined with Folinic Acid (Leucovorin, LV); all trials used a regimen of FU 370-425 mg/m^2 plus LV 20-200 mg/m^2 daily for 5 days every 28-35 days. 4/5 trials administered treatment for six cycles and 1/5 for 12 cycles (Francini, 1994).

Outcomes
Event free survival (EFS), defined as time from randomisation to first event (first recurrence, second tumour or death from any cause).
The number of events required for this analysis was estimated from the data in a previous publication (Labianca, 1995) in which a 3-year EFS was reported to be 76% for the control population, 5-year EFS (assuming exponential lifetime) was estimated to be 63%. It was determined that 168 events were required in order to have an 80% chance of detecting a 10% improvement in EFS at 5-years for the FU+LV arm.

Results
Median follow-up time was 5.75 years (range 5.17-8.54 years)
Follow up times for the individual studies were: 5.17, 5.29, 5.89, 6.41 and 8.54 years
Median FU dose for the whole population was 11.1g/m^2 (range 9.5-24g/m^2)

- There were 110 relapses in the control arm (22%) and 101 in the FU+LV arm (20%); there was no statistically significant difference between the control arm and treatment arms (HR 0.83, 90% CI 0.68-1.01, p=0.061, one-sided).
- Kaplan-Meier OS curves showed no statistically significant difference in survival between the two arms (HR 0.81,90% CI; 0.64-1.01, p=0.057, one-sided).
- Multivariate Cox analysis revealed age and tumour grade to be independent predictors for both overall survival (OS) (overall adjusted HR 0.86, 90% CI; 0.68-1.07, p=0.13, one-sided) and event free survival (EFS) (overall adjusted HR 0.88, 90% CI; 0.72-1.07, p=0.137, one-sided).
- When EFS and OS were analysed according to treatment arm and corrected for age and tumour grade, no difference was observed between the treatment arms.
- There was a statistically significant difference in EFS (p<0.001, two-sided) and OS (p<0.01, two-sided) between patients with well/moderately differentiated tumours and patients with poorly differentiated tumours.

	Hazards Ratio	
	Control	FU+LV
5-year EFS	0.73	0.76
SE	0.02	0.02
5-year OS	0.80	0.82
SE	0.02	0.02

Table: Differences in Event Free Survival and Overall Survival between control and treatment arms

- The commonest adverse events were gastrointestinal. Grade 3 and 4 nausea occurred in 4% of patients, stomatitis in 11% and diarrhoea in 8%.
- Leukopenia and thrombocytopenia grade 3 or 4 occurred in 2% of patients.

General comments

There were no details provided as to the methodology employed for the pooling of the data from different trials; a protocol outlining the criteria for the pooling of study patients into one common data set, standard definitions and coding for events and patient characteristics, minimum clinical difference to be tested, required statistical power, duration of follow-up and appropriate timing for the main comparison and the analytical approach were outlined in other papers.

None of the individual trials were designed to address *a priori* the question of whether FU+LV was effective in the individual subsets of B2 and C.

Author Conclusions

Individual studies have not clearly demonstrated a statistically significant benefit from adjuvant chemotherapy in patients with B2 colon cancer, neither has the pooled analysis of over 1,000 patients from 5 separate trials shown a statistically significant benefit to FU+LV in patients with B2 colon cancer. It is unlikely that the lack of effect was due to an imbalance of events other than colon cancer favouring the control arm as the two arms in the data set were equally balanced for relapse rate, second malignancy and deaths from any cause.

Some of the trials are not referenced therefore it is difficult to tell which publication in the reference list relates to which trial in the analysis.

The first row of table 4 is titled 5-year EFS; it is assumed that this is a typo and the table should read 5-year OS as table 4 relates to overall survival rather than event free survival.

References of Included Studies (For systematic reviews):

Labianca R (1995) Efficacy of adjuvant fluorouracil and folinic acid in colon cancer *Lancet* 345;8955:939-944

Francini G, Petrioli R, Lorenzini L, Mancini S, Armenio S, Tanzini G, Marsili S, Aquino A, Marzocca G, Civitelli S, Mariani L, deSando D, Bovenga S, Lorenzi M (1994) Folinic Acid and 5-fluorouracil as adjuvant chemotherapy in colon cancer *Gastroenterology* 106;4:899-906

O'Connell MJ, Mailliard JA, Kahn MJ et al. (1997) Controlled trial of fluorouacil and low-dose Leucovorin given for six months as postoperative adjuvant therapy for colon cancer *Journal of Clinical Oncology* 15:246-250

Citation: Figeuredo A, Charette, ML, Maroun J, Brouwers MC, Zuraw L (2004) Adjuvant Therapy for Stage II Colon Cancer: A Systematic Review from the Cancer Care Ontario Program in Evidence-Based Care's Gastrointestinal Cancer Disease Site Group *Journal of Clinical Oncology* 22;16:3395-3407

Design: Systematic Review

Country: USA

Aim: To address the question of whether stage II colon cancer patients should receive adjuvant chemotherapy

Inclusion criteria
Randomised Controlled trials or meta-analyses of RCTs involving patients with stage II colon cancer who had undergone surgery with curative intent that compared adjuvant therapy with observation

Exclusion criteria
Trials published before 1987 as a previous study summarised the results of randomised trials up to that point (Buyse et al, 1988). The current meta-analysis provides a summary of this previous study.

Population
Data on Stage II colon cancer patients were available for pooling from 18 studies using survival curves to estimate the number of events.
Data on specific subgroups (high-risk vs. low risk) were not available

Interventions
Adjuvant Chemotherapy following surgery with curative intent versus surgery alone/observation

Outcomes
Survival
Disease Free Survival

Results
Buyse et al, 1988
• 17 English (British?) trials comparing adjuvant therapy in patients with all stages of colorectal cancer with a total of 6791 patients.
• The pooled results showed no statistically significant difference in the odds of death between treatment and observation groups (OR, 0.96; 95% CI 0.87 – 1.06).
• There was a significant decrease in the odds of death for patients treated with 5FU compared with patients in the observation group (OR, 0.83; 95% CI 0.7 – 0.98; p=0.03) (Subgroup analysis).

Trials after 1987
• Patients with stage II colon cancer had undergone surgery with curative intent and were randomised to receive adjuvant therapy or observation in all trials reviewed.
• In most trials, adjuvant therapy started within 5 to 6 weeks postoperatively, though in studies where portal vein infusion (PVI) was the treatment under investigation, treatment began immediately after surgery.
• Patients were eligible for entry into the individual trials if they had good performance status or general health, no active comorbidity or previous malignancy apart from skin cancer and good haematological, renal and hepatic functions.
• Median age for participants was in the mid-60's.

Results of adjuvant treatment for stage II colon cancer are derived mainly from clinical trials that also included patients with stage III and in some cases, stage I as well as patients with rectal cancer. The results are therefore based primarily on subgroup analysis and should thus the generalisability of the results may be open to interpretation.

Systemic Adjuvant Chemotherapy: FU combined with Semustine
From one trial, no significant difference was reported for either overall survival or disease free survival for whole population or for the subgroup of Stage II patients (Panettiere et al, 1988).
A second trial did not provide separate results for stage II patients, however the results stated that there was no significant interaction between treatment effect and stage although there was a significant improvement in both disease free and overall survival favouring adjuvant chemotherapy for the whole patient group (Wolmark et al, 1988).

Systemic Adjuvant Chemotherapy: FU and folinic Acid (Leucovorin)
Five trials, three of which have published individually, tested the combination of FU modulated by folinic acid (Leucovorin).
The best data were available from one pooled analysis; using individual patient data for stage II patients, no significant difference was observed in 5-year event free survival (HR 0.83, 90% CI 0.72-1.07 (these results differ from the actual publication – it appears that the HR for the unadjusted model has been paired with the confidence interval for the adjusted model) or overall survival (HR 0.86; 90% CI 0.68 – 1.07) (IMPACT).

Regional Chemotherapy: PVI
Although 14 randomised trials and two meta-analyses were found, only 6 papers reported data specific to stage II patients (Taylor et al, 1985; Fielding et al, 1992; Beart et al, 1990, Gray et al, 1987; SAKK, 1995 and Schlag et al, 1990).
Taylor et al reported a significant improvement in 5-year overall survival for PVI of FU compared with observation in the subgroup of patients with stage II colon cancer (95% vs. 65%, p=0.002) and for all subgroups combined (78% vs. 58%, p=0.002).
A 7-day PVI of FU and heparin was tested in eight subsequent trials, with data on stage II patients presented separately in 3 (Fielding et al, 1992; Beart et al, 1990 and Gray et al 1987) none of which reported significant differences in overall or disease free survival.
From two trials (Ryan et al, 1988 and SAKK) the addition of mitomycin C to the standard PVI reported no significant difference in disease free or overall survival.
From one trial (Schlag et al, 1990) no significant difference between adjuvant floxuridine delivered by PVI and observation was observed in the subgroup of stage II patients or in the whole population.

Regional Chemotherapy: IP chemotherapy
From one trial (Vaillant et al, 2000) reported improved 5-year disease-free survival in the treatment group in patients with stage II cancer (89% vs. 73%, p=0.05) for patients receiving a full dose of intraperitoneal FU (n=58) compared to patients receiving surgery alone (n=77). When all stage II patients were considered, the difference was not significant.
From one trial (Scheithauer et al, 1995), no significant difference in disease free or overall survival in stage II patients was observed.

Regional Chemotherapy: hepatic arterial infusion
From one trial (Sadahiro et al, 2001), three year disease-free survival (86% vs. 76%; p=0.002) and overall survival (91% vs. 83%; p=0.03) were significantly improved in patients receiving chemotherapy though this result was for stage II and stage III colon cancer patients.

Oral FU or analogs
Data specific to stage II patients were available from a single trial (CCCSGJ) comparing a combination of mitomycin and FU to observation. No significant differences in disease free or overall survival were reported for the subgroup of stage II patients.
From a meta-analysis using individual patient data from three trials of oral FU and its prodrugs (tegafur, carmofur) (Sakamoto J, 1999) there was no significant difference in overall survival (p=0.721) or disease free-survival (p=0.296) for adjuvant chemotherapy compared with surgery after a median follow-up of almost 5 years. An update which included 9,819 patients from six trials subgroup analysis found a significant difference for disease-free (RR 0.78, 95% CI 0.68 to 0.88, p<0.001) and overall survival (RR 0.84, 95% CI 0.72 – 0.97, p=0.017) for oral agents versus surgery alone in Stage II patients (Sakamoto, 2001).

General comments
Quality of Life data and data on treatment toxicities were excluded from the analysis due to the inconsistencies in reporting methods.

References of Included Studies (For systematic reviews):
Buyse M, Zeleniuch-Jacquotte A, Chalmers TC (1988) Adjuvant therapy of colorectal cancer: Why we still don't know *JAMA* 259:3571-3578.

Panettiere FJ, Goodman PJ, Costanzi JJ et al (1988) Adjuvant therapy in large bowel adenocarcinoma: Long term results of a Southwest Oncology Group Study *Journal of Clinical Oncology* 6:947-954

Wolmark N, Fisher B, Rockette H et al (1988) Postoperative adjuvant chemotherapy of BCG for colon caner: results from NSABP protocol C-01. *Journal of National Cancer Institute* 80;30-36

IMPACT: International Multicentre Pooled Analysis of B2 Colon Cancer Trials (IMPACT B2) Investigators (1999) Efficacy of adjuvant fluorouracil and folinic acid in B2 colon cancer *Journal of Clinical Oncology* 17:1356-1363

Taylor I, Machin D, Mullee M et al (1985) A randomised controlled trial of adjuvant portal vein cytotoxic perfusion after curative resection for colorectal adenocarcinoma British Journal of Surgery 72:359-363

Fielding LP, Hittinger R, Grace RH et al (1992) Randomised controlled trial of adjuvant chemotherapy by portal vein perfusion after curative resection for colorectal adenocarcinoma *Lancet* 340:502-506

Beart RW, Moertel CG, Wieand HS et al (1990) Adjuvant therapy for resectable colorectal carcinoma with fluorouracil administered by portal vein infusion: A study of the Mayo Clinic and the North Central Cancer Treatment Group *Archives of Surgery* 125:897-901

Gray BN, deZwart J, Fisher R et al (1987) The Australia and New Zealand Trial of adjuvant chemotherapy in colon cancer, in, Salmon SE (ed): Adjuvant Therapy of Cancer. New York, NY, Grune-Stratton pp537-554

Swiss Group for Clinical Cancer Research (SAKK) (1995) Long term results of single course of adjuvant intraportal chemotherapy for colorectal cancer *Lancet* 345;349-353

Schlag P, Saeger HD, Friedl P et al (1990) Adjuvant intraportal FUDR-chemotherapy in colon cancer patients, in, Salmon SE (ed) (1990) Adjuvant Therapy of Cancer. New York, NY, Grune-Stratton pp439-445

Ryan J, Weiden P, Crowley J et al (1988) Adjuvant portal vein infusion for colorectal cancer; a 3-arm randomised trial. *Proc Am Soc Clin Oncol* 7;95 abstract 361

The Colorectal Cancer Chemotherapy Study Group of Japan (1995) Five-year results of a randomised controlled trial of adjuvant chemotherapy for curatively resected colorectal canrcinoma *Japanese Journal of Clinical Oncology* 25:91-103

Sakamoto J, Hamada C, Kodaira S et al (1999) adjuvant therapy with oral fluoropyrimidines as main chemotherapeutic agents after curative resection for colorectal cancer: Individual patient data meta-analysis of randomised trials *Japanese Journal of Clinical Oncology* 29;78-86

Sakamoto J, Hamada C, Yasutomi M et al (2001) Adjuvant therapy with oral fluorinated pyrimidines after curative resection for colorectal cancer: Individual patient data meta-analysis of randomised trials *Proc Am Soc Clin Oncol* 20;147a:abstract 583

Citation: Labianca R (1995) Efficacy of adjuvant fluorouracil and Folinic acid in colon cancer *Lancet* 345;8955:939-944

Note: The three trials pooled here are included in the Erlichman pooled analysis but the numbers of patients included in this analysis (3 trials) is smaller than that included in the Erlichman pooled analysis (5 trials).

Design: Pooled Analysis

Country: Multiple

Aim: To determine the efficacy of fluorouracil and high-dose folinic acid after surgery for Dukes B and C stage colon cancer.

Inclusion criteria
Each trial included in the analysis had their own inclusion/eligibility criteria which included such factors as Duke's Stage, Age, Tumour Site, Performance Status and Chemotherapy start following surgery (days).

Exclusion criteria
Of the initial patients randomised, 33 were excluded before analysis for the following reasons:
Incorrect histology (3)
Wrong stage (25)
Other (not specified) (5)

Population
N=1526 randomised
N=1493 eligible for analysis (756 in the treatment arm and 757 in the control arm)

Interventions
All three trials used a regimen of fluorouracil 370-400 mg/m^2 plus folinic acid 200 mg/m^2 daily for 5 days every 28 days for 6 cycles. In one trial the racemic form of Folinic acid was used initially but about 150 patients were treated with pure L-form at a dose of 100 mg/m^2 due to the racemic mixture not being available.

Outcomes
3-year Event free survival
3-year Overall Survival

Results
Median follow-up time for the treatment group was 40 months and for the control group was 37 months (inter quartile range was 29-48 for both groups).

Survival
Fluorouracil plus folinic acid significantly increased survival and event free survival and results were consistent with and without stratification. The global test for interaction of treatment effect with stage and country was not significant for either EFS (p=0.176) or OS (p=0.254).

	Stage B	Stage C	Total	P
3-year EFS				
Control	0.76 (0.04)	0.44 (0.06)	0.62 (0.03)	
FU/FA	0.79 (0.03)	0.62 (0.04)	0.71 (0.03)	
HR for EFS (95% CI)				
Unstratified	0.84 (0.62-1.12)	0.55 (0.44-0.70)	0.67 (0.56-0.80)	P<0.0001
Stratified by country	0.84 (0.62-1.13)	0.55 (0.43-0.70)	0.67 (0.56-0.81)	P<0.0001
Stratified by stage and country			0.65 (0.54-0.78)	P<0.0001
3-year OS				
Control	0.90 (0.02)	0.64 (0.04)	0.78 (0.02)	
FU/FA	0.88 (0.02)	0.76 (0.03)	0.83 (0.02)	
HR for OS (95% CI)				
Unstratified	0.91 (0.63-1.34)	0.70 (0.53-0.92)	0.77 (0.62-0.96)	P=0.018
Stratified by country	0.93 (0.63-1.37)	0.71 (0.54-0.94)	0.79 (0.63-0.98)	P=0.034
Stratified by stage and country			0.78 (0.62-0.97)	0.029

Table: Event free survival (EFS) and overall survival (OS)

Multivariate Cox analyses revealed nodal status to be an independent predictor for EFS and OS, and age was significantly associated with OS.

	Event Free Survival		Overall Survival	
	Hazard Ratio (95% CI)	P	Hazard Ratio (95% CI)	P
Treatment Group				
Control	Reference Category, not retained in the final model (p>0.05)			
FU/FA	0.65 (0.54-0.78)	P<0.0001	0.76 (0.61-0.96)	P=0.018
Age				
≤65	NR			
>65			1.27 (1.01-1.59)	P=0.039
Stage				
B, 0 positive nodes	Reference Category, not retained in the final model (p>0.05)			
C 1-4 positive nodes	2.01 (1.63-2.47)		2.17 (1.67-2.80)	
C >4 positive nodes	4.05 (3.13-5.23)	P<0.0001	5.40 (4.01-7.27)	p<0.0001

Table: Cox analysis of prognostic factors

First Events

There were 394 relapses overall, with the pattern of relapse differing slightly between treatment groups (X^2 for heterogeneity=6.997, p=0.072).

The crude relapse rate for hepatic recurrence as a first event was twice as high in the control group as in the treatment group.

Deaths unrelated to the tumour were equally distributed in the two groups.

Toxic Effects

The most common adverse effect of treatment was gastrointestinal with substantial variation among the three trials (p<0.001 for the association of side-effects with trial site).

General comments

It seems that the folinic acid used in the included trials was Leucovorin.

Event free survival was defined as time from randomisation to the first event; events being first recurrence, second tumour, death with no relapse or date of last observation.

Survival was defined as time from randomisation to death from any cause

Citation: Lin CC, Lin JK, Chang SC, Wang HS, Yang SH, Jiang JK, Chen WS, Lin TC (2009) Is adjuvant chemotherapy beneficial to high risk stage II colon cancer? Analysis at a single institute *International Journal of Colorectal Disease* 24;6:665-676
Design: Prospective Case Series **Country**: Taiwan **Aim**: To identify the risk factors of tumour recurrence in stage II colon cancer and to investigate the benefit of adjuvant chemotherapy for high-risk stage II.
Inclusion criteria None Given – appears to be all stage II colon cancer patients that underwent surgery with curative intent
Exclusion criteria None Given
Population N=375 patients with stage II colon cancer
Interventions Adjuvant chemotherapy following surgery with curative intent
Outcomes Survival
Results 375 patients underwent surgery with curative intent of which 66 patients received 5FU based adjuvant chemotherapy either oral or IV form. 66 patients were lost to follow-up in 3-years and the follow-up rate was 83.7%. Median follow-up time was 48.5 months (0.7-96.6 months). Recurrence occurred in 35 patients (9.3%), 8 of whom had received adjuvant chemotherapy (22.9%). The most frequent site of recurrence was the liver (62.9%) followed by lung and peritoneum. Univariate analysis showed that T4 lesion (p=0.024), lymphovascular invasion (p=0.022), obstruction at presentation (p=0.008) and mucinous component more than 50% (p=0.032) were significantly associated with decreased disease free survival. Multivariate analysis showed that lymphovascular invasion and obstruction were independent factors predicting disease free survival. Patients with at least one risk factor (T4 lesion, lymphovascular invasion, obstruction at presentation or mucinous component more than 50%) were considered as high-risk group. There was a significant difference in disease free survival between patients with high-risk factor and patients without (3-year disease free survival 84.7% and 95% respectively, p=0.001) There was a significant difference in disease free survival for patients with no high risk factor, patients with one high risk factor and patients with more than one risk factor (p=0.003). There was no significant difference in survival for stage II patients receiving adjuvant chemotherapy compared with patients that did not receive adjuvant chemotherapy, however in the subgroup of patients with high risk factors, there was a significant 3-year disease free survival benefit (96.4% vs. 84.7%, p=0.045) and 5-year overall survival benefit (100% vs. 86.4%, p=0.015) in favour of adjuvant chemotherapy.

Citation: Mamounas E, Wieand S, Wolmark N, Bear HD, Atkins JN, Song K, Jones J, Rockette H (1999) Comparative Efficacy of Adjuvant Chemotherapy in Patients with Dukes B versus Dukes C colon Cancer: Results from Four National Surgical Adjuvant Breast and Bowel Project Adjuvant Studies (C-01, C-02, C-03 and C-04) *Journal of Clinical Oncology* 17:5;1349-1355

Note: This study presents results from four trials, however only two of the trials (C-01 and C-02) included are of potential relevance to the PICO (adjuvant chemotherapy versus surgery alone) and as such the results of those two studies are presented here.

Design: Pooled Analysis

Country: USA

Aim: To determine whether patients with Dukes' B disease benefit from adjuvant chemotherapy and to evaluate the magnitude of benefit compared with that observed in Dukes' C patients.

Inclusion criteria
Eligible patients in C-01, C-03 and C-04 included:
- Patients with adenocarcinoma of the colon resected with curative intent with no evidence of gross residual or metastatic disease at the time of laparotomy.
- Patients with pathologically confirmed tumour extension into adjacent organs, provided all tumour was removed en bloc with negative resection margins

Eligible patients in C-02 included:
- Patients were required to have a potentially curable adenocarcinoma – documented by barium enema or endoscopic biopsy

Eligible patients in all trials included :
- Patients presenting with obstruction of contained perforation
- Patients with adequate hepatic or renal function and adequate WBC counts and platelet counts
- Patients with ECOC performance status of 0, 1 or 2

Exclusion criteria
Patients presenting with free perforation

Population
- 4,006 patients recruited in the four studies
- N=3,820 patients eligible for analysis; 1,565 Dukes' B and 2,255 Dukes' C
- C-01: N=726; 316 Dukes' B and 410 Dukes' C
- C-02: N=683; 389 Dukes' B and 294 Dukes' C

Interventions
C-01: Adjuvant semustine, vincristine and 5-FU (MOF) regimen versus surgery alone
C-02: Peri-operative administration of a portal venous infusion (PVI) of 5-FU versus surgery alone

Outcomes
5-Year Overall Survival

Results
C-01
The administration of the MOF regimen resulted in a 7% absolute improvement in survival over surgery alone (p=0.07).
For Dukes' B patients and Dukes' C patients, the administration of MOF resulted in an absolute improvement in survival of 3% (p=0.73) and 9% (p=0.05) respectively over surgery alone.
Similar results were observed for disease-free and recurrence free survival but these results were not shown.
The administration of the MOF regimen resulted in a 7% reduction in mortality for Dukes' B patients compared with a 26% reduction for Dukes' C patients.

C-02*
The administration of peri-operative PVI of 5-FU resulted in a 7% absolute improvement in survival over surgery alone (p=0.08).
There was a 12% improvement in survival for Dukes' B patients (p=0.005) and a 2% improvement for Dukes' C patients (p=0.81) with peri-operative PVI compared with surgery alone.
The administration of 7-days perioperative PVI of 5-FU resulted in a 51% reduction in mortality for Dukes' B patients compared with a 4% reduction for Dukes' C patients.

The individual trial data were presented to demonstrate that all four trials showed similar treatment effects between Dukes' B and Dukes' C patients but due to limited numbers in each trial any one individual could not rule out a substantial difference in treatment effect according to Dukes' stage so the authors combined the data from the four trials into two treatment groups. Treatment 1 consisted of the treatment groups from each trial with the inferior overall, disease free and recurrence free survival for all patients and treatment 2 consisted of the treatment groups with the superior overall, disease free and recurrence free survival for all patients.

Treatment 1	Treatment 2
Operation (C-01)	MOF (C-01)
Operation (C-02)	5-FU PVI (C-02)
MOF (C-03)	5-FU + LV (C-03)
5-FU + Levamisole (C-04)	5-FU + LV C-04)

Table: Treatment Groups

In the total population, 26% of Dukes' B and 28% of Dukes' C patients had high-risk characteristics defined as the presence of obstruction, bowel perforation (contained), or extension of tumour into adjacent organs. It could not be elucidated from the paper what percentage of patients from each of the individual trials had high risk characteristics so the results for the high risk group represent the whole population, including from the trials that were not relevant; results should therefore be interpreted with caution.

In Dukes' B patients without high-risk characteristics there was a 32% reduction in mortality (cumulative OR 0.68; 95% CI 0.5-0.92; p=0.01) compared with a 20% reduction in mortality (cumulative OR 0.8; 95% CI 0.55-1.17; p=0.26) for patients with high-risk characteristics. This reduction in mortality translated into an absolute improvement in survival of 5% in each risk category (treatment 2, 87% vs. treatment 1, 82% in the low risk group and treatment 2, 75% vs. treatment 1, 70% in the high risk category).

*The protocol for C-02 was designed to use a one-sided test for the final conclusions and to maintain consistency across protocols, a two-sided test for p-values was used in this study.

General comments
Patients were classified as Dukes' B if the tumour demonstrated full-thickness penetration of the bowel wall (through the serosa or into the pericolic fat) with no regional lymph node involvement on pathological examination. Patients were classified as Dukes' C if there was evidence of involvement of the regional lymph nodes on pathological examination.

The follow-up requirements for all trials were similar:
- First 2 years - Investigators were required to submit patient follow-up forms every three months which reported results of a physical exam, complete blood cell count and chemistry profile, including liver function test. A chest x-ray and carcinoembryonic antigen levels were required every six months and a barium enema and/or colonoscopy was required yearly.
- Years to 5 – A physical exam, including weight and performance status, complete blood cell count, chemistry profile including liver function tests, chest x-ray and carcinoembryonic antigen levels required every six months. A barium enema and/or colonoscopy were required yearly.
- After year 5 – status of the disease to be reported on a yearly basis

Citation: O'Connell MJ, Mailliard JA, Kahn MJ, Macdonald JS, Haller DG, Mayer RJ, Wieand HS (1997) Controlled Trial of Fluorouracil and Low Dose Leucovorin Given for 6 Months as Postoperative Adjuvant Therapy for Colon Cancer *Journal of Clinical Oncology* 15;1:246-250

Design: Randomised Trial

Country: USA

Aim: To determine the efficacy of intensive course fluorouracil (5FU) plus low dose Leucovorin given for 6 months following potentially curative resection of colon cancer

Inclusion criteria
- Histological proof of adenocarcinoma of the colon
- Undergone complete resection of the primary tumour without gross or microscopic evidence of residual disease
- Patients at high risk of relapse as indicated by one or more of the following features:
  - Regional Lymph Node Metastases
  - Transmural Penetration of the muscular wall of the bowel with evidence of bowel obstruction, perforation, adherence, or invasion of adjacent organs
  - Regional peritonela or mesenteric implants resected en bloc.
- The inferior margin had to be above the peritoneal reflection
- Patients had to be ambulatory and maintaining adequate oral nutrition

Exclusion criteria
- White blood cell count less than 3,500/μL
- Platelet count less than 100,000/μL
- Prior or concurrent radiation or chemotherapy for colon cancer
- Concurrent or previous second malignant disease within the preceding three years
- Pregnancy or lactation

Population
N=317

N=309 included in the statistical analysis

Interventions
5FU given by rapid intravenous infusion at a dose of 425 mg/m^2/d for 5 consecutive days with Leucovorin at a dose of 20mg/m^2 immediately preceding each dose of 5FU.
Courses were repeated at 4 weeks, 8 weeks and then every 5 weeks for a total of six cycles

Outcomes

Results
Median follow-up duration was 72 months
195/205 patients still alive at the time of the study had at least 4 years of follow-up evaluation

Tumour Relapse
41% (62/151) of patients in the control group and 27% (43/158) of patients in the chemotherapy group relapsed. The proportion of patients that were relapse-free at 5-years was 0.74 in the chemotherapy group and 0.58 in the control group. The difference in time to relapse between the two groups was significant (p=0.004 before adjusting for covariates and p=0.001 after adjusting for covariates).
When stratification factors, age and sex were combined with treatment in a multivariate proportional hazards model, older age, increased nodal involvement and the presence of regional implants resected en bloc were significantly associated with increased risk of tumour relapse. There was no significant interaction between treatment and any of the prognostic variables.
The 95% confidence intervals for the relative risk of relapse for control patients versus chemotherapy patients was 1.19 – 2.60 for the unadjusted model and 1.29 – 2.82 for the adjusted model.

Survival
40% of patients in the control group and 28% of patients in the treatment group had died at the time of analysis.
The proportion of patients alive at 5-years was 0.74 for patients in the chemotherapy group and 0.63 for patients in

the control group. The difference in survival between the two groups was significant (p=0.02 before adjusting for covariates and p=0.01 after adjusting for covariates).
When stratification factors plus age and sex were combined with treatment in a multivariate proportional hazards model, extent of nodal involvement and presence of regional implants were significantly associated with an increased risk of death.
The 95% confidence interval for the relative risk of death for patients in the control group versus the treatment group was 1.06 – 2.31 with no covariate and 1.12 – 2.45 after covariate adjustment.

Toxicity
There were no deaths associated with chemotherapy.
Toxicities were generally tolerable and manageable by reducing the dosage of 5-FU on subsequent cycles.

General comments
Patients were stratified according to the extent of primary tumour invasion, presence/absence of intestinal obstruction, presence/absence of regional peritoneal metastases resected en bloc and extent of regional lymph node metastases
Details of Randomisation Method is not provided
Statistical analysis details note that proportional hazards models were use for all multivariate analysis and therefore the results should refer to Hazards Ratios (HR), however the results refer to Relative Risks (RR) and it is not clear whether they are using RR in place of HR as there is a tendency in literature to use two terms interchangeably although they are not the same thing. The actual relative risk values have not been included in the results, just the 95% CI.

Citation: Yoshimatsu K, Umehara A, Ishibashi K, Yokomizo H, Yoshida K, Fujimoto T, Watanabe K, Ogawa K (2006) Indication and Efficacy of Adjuvant Chemotherapy with Oral Fluorouropyrimidines for Dukes B Colorectal Cancer *Anticancer Research* 26;3089-3094
Design: Retrospective Case Series **Country**: Japan **Aim**: to examine retrospectively the prognostic value of routinely assessable clinicopathological factors to identify subgroups of Dukes B colorectal cancer patients at high risk of recurrence and death and to assess adjuvant chemotherapy with oral fluoropyrimidines for the high-risk subgroup.
Inclusion criteria Patients with Dukes B colorectal cancer who had undergone curative resection between 1991 and 2000
Exclusion criteria None Given
Population N=229
Interventions Oral fluorouropyrimidines versus surgery alone
Outcomes Survival
Results • The average age of patients was 64.8 and ranged from 29-93 years. • There were 127 males and 102 females • The 5-year cancer related survival rate was 83.5% and recurrence rate was 20.1%. • CEA, CA19-9, histological type, lymphatic invasion, venous invasion, depth of invasion, number of dissected nodes and adjuvant chemotherapy were found to be significantly correlated with cancer-related survival on univariate analysis. • On multivariate analysis depth of invasion, number of dissected nodes and adjuvant chemotherapy were prognostic factors in Dukes B and as depth of invasion was the most significant prognostic factor (p=0.0186), patients with tumour exposed at the serosa or invasion of other organ were identified as high-risk (n=64) while patients with tumour invasion under the subserosa were considered low risk (n=161). • 44 patients in the high risk group had chemotherapy with oral fluoropyrimidines compared with 114 in the low risk group. The 5-year survival rates in the low risk group were 91.8% for patients receiving adjuvant chemotherapy and 87.9% for patients without chemotherapy. In the high risk group there was a significant difference in 5-year survival for patients receiving adjuvant chemotherapy (75.8%) and patients not receiving chemotherapy (44%); p=0.0008. • In patients treated with adjuvant chemotherapy there was a significant decrease in recurrence rate, especially in the liver and lung; 4.5% for patients with chemotherapy compared to 25% for patients without chemotherapy, p=0.0346).
General comments Retrospective study which does not represent very high quality evidence, one of the key factors here is that the study does not compare survival between the high-risk and low-risk groups.

4. Management of Metastatic Disease

4.1. Management of Patients Presenting in Stage IV

4.1.1. In patients with colorectal cancer presenting with overt synchronous metastatic disease, what is the effectiveness of treating metastatic disease before, after or at the same time as treating the primary tumour?

Short Summary

There was very little evidence with which to address this topic and what was available consisted primarily of retrospective studies. There were 2 systematic reviews of retrospective studies (Hillingso et al, 2007 and Scheer et al, 2007), one randomised trial (Nordlinger et al, 2008) and 3 retrospective case series studies, two case matched (Moug et al, 2010 and Benoist et al, 2005) and one non-matched case series (Mentha et al, 2008).

Synchronous resection versus staged resection

A well conducted systematic review of which included 16 studies (Hillingso et al, 2007) and a more recent case series study (Moug et al, 2010) compared outcomes in patients undergoing synchronous resection and patients undergoing staged resection of primary tumour and liver metastases.

Length of Hospital Stay

A pooled estimate was possible from 8/11 studies reporting on length of hospital stay. The mean difference reported was -3.10 days (95% CI, -6.76-0.56) for patients undergoing synchronous resection indicating no significant difference between the two procedures in relation to the length of hospital stay. There was however significant statistical heterogeneity when pooling the studies (I^2=92%; X^2=82.85, p<0.00001) indicating that it may not be appropriate to conduct pooled analysis.

Morbidity

The results of the pooled analysis show that synchronous resection to be significantly better than staged resection in relation to post-operative morbidity (OR=0.68, 95% CI 0.49-0.81).

Mortality

On calculating the risk difference, there is no significant difference in the risk of mortality between the two groups (RD, 0.01, 95% CI -0.01-0.04).

5 year overall survival

There was no significant difference in 5 year survival for patients undergoing synchronous resection versus patients undergoing staged resection.

Preoperative Chemotherapy followed by surgery versus surgery alone

For chemotherapy followed by surgery versus immediate surgery, a single systematic review included only 7 studies (Scheer et al, 2007) deemed to be relevant and not all included studies were case matched meaning there was no comparison within the individual study. This, coupled with a non-matched case series study (Mentha et al, 2007) and a randomised trial investigating only progression free survival comprised the evidence base examining chemotherapy versus immediate surgery for patients with colorectal cancer and liver metastases.

Outcomes for which data were available included Length of hospital stay, tumour related complications in patients treated initially with chemotherapy, overall survival and progression free survival.

Length of Hospital Stay

One retrospective case series (Benoist et al, 2005) aimed at determining the best treatments strategy for patients with asymptomatic primary tumour and irresectable metastases reported mean hospital stay in the chemotherapy group was 11 days (SD=10 days, range=2-52 days) versus 22 days (SD=15 days, range=5-75 days) in the resection group (p=0.003).

Tumour Related Complications in patients receiving chemotherapy as initial treatment

The rate of intestinal obstruction reported in the included studies ranged from 5.6%-29%; the pooled proportion of patients developing bowel obstruction was 13.9% (95% CI 9.6% - 18.8%) (Scheer et al, 2007).

Haemorrhage due to primary tumour was reported in 4/7 studies included in the systematic review and ranged from 0%-3.7%; the pooled proportion of patients experiencing bleeding due to primary tumour was 3% (95% CI 0.95% - 6%) (Scheer et al, 2007).

Outcomes Related to Surgery
Postoperative mortality ranged from 0% to 4.6%; meta-analysis of the four studies showed a mortality of 2.7% (95% CI 1.1% - 5%) (Scheer et al, 2007).

Overall Survival
Scheer et al (2007) reported that for patients that underwent resection of the primary tumour median survival range from 14-23 months versus 8.2-22 months for patients treated with chemotherapy as first treatment.

Progression Free Survival
Hazard ratio for progression free survival was 0.79 (95.66% CI 0.62-1.02, p=0.058) which corresponds to a 7.3% increase in the rate of progression free survival at 3 years from 28.1% (21.3-35.3) to 35.4% (28.1-42.7) with chemotherapy and an increase in median progression free survival from 11.7 months to 18.7 months (Nordlinger et al, 2008).

Review Protocol

Population	Intervention	Comparison	Outcomes
Patients presenting with operable primary colorectal tumour,with synchronous a) operable metastatic disease b) non operable metastatic disease	Surgery for primary Chemotherapy Surgery for metastases	Sequence of interventions synchronous versus staged surgery	Survival Quality of life Local Control Risks/Safety Complications

Following a systematic search of relevant data sources (see appendix .1), the information specialist created a database of potentially relevant studies. All titles and abstracts were sifted by a single reviewer. Queries about inclusion were clarified by the GDG topic subgroup. The full studies were then obtained and reviewed and relevant studies were included in the final evidence review.

All update searches were sifted by a single reviewer and the list of potentially relevant studies was also checked for irrelevant studies by the GDG subgroup. Only studies which all subgroup members were in agreement were excluded. The remaining studies were obtained and reviewed with relevant studies included in the final evidence review.

In this topic, there is a need to consider if the synchronous metastatic disease is potentially operable (both at presentation and after chemotherapy).
In the event of inoperable metastatic disease, is there any role for surgery on primary or only in the case of obstruction?
Is there any evidence that lack of surgery results in worse prognosis (or increased morbidity)?
In the event of operable is there evidence of the optimum order of surgery (on primary or metastases first)?
There is a need to consider whether patients had pre-op chemo/radiotherapy.

Reasons for Exclusions:
Studies not relevant to PICO on full review
Studies included in a systematic review
Expert Review
Quality of the study reporting meant that there was uncertainty surrounding the accuracy of the results contained within the study.
Foreign Language with no translation

Quality of the included studies
Systematic review of RCTs (n=0)
Systematic review of combined study designs (n = 2)
Randomized controlled trial (n=1)
Prospective cross sectional study (n = 0)
Case Series Studies (n = 3)
Guidelines (n=1)
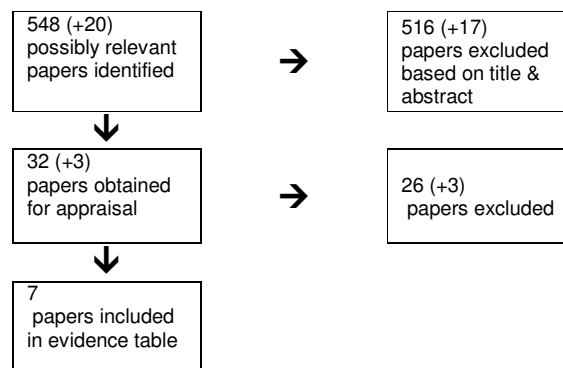
548 (+20) possibly relevant papers identified → 516 (+17) papers excluded based on title & abstract

↓

32 (+3) papers obtained for appraisal → 26 (+3) papers excluded

↓

7 papers included in evidence table

Volume of evidence

There was very little evidence with which to address this topic and what was available consisted primarily of retrospective studies. There were 2 systematic reviews of retrospective studies (Hillingso et al, 2007 and Scheer et al, 2007), one randomised trial (Nordlinger et al, 2008) and 3 retrospective case series studies, two case matched (Moug et al, 2010 and Benoist et al, 2005) and one non-matched case series (Mentha et al, 2008).

The body of evidence comparing synchronous resection to staged resection of primary tumour and operable liver metastases is greater than that comparing chemotherapy as intial treatment with surgery as initial treatment. A well conducted systematic review of which included 16 studies (Hillingso et al, 2007) and a more recent case series study (Moug et al, 2010) compared outcomes in patients undergoing synchronous resection and patients undergoing staged resection of primary tumour and liver metastases.

In contrast, for chemotherapy followed by surgery versus immediate surgery, despite appearing to comprise a similar volume of evidence, a single systematic review included only 7 studies (Scheer et al, 2007) deemed to be relevant and not all included studies were case matched meaning there was no comparison within the individual study. This, coupled with a non-matched case series study (Mentha et al, 2007) and a randomised trial investigating only progression free survival comprised the evidence base examining chemotherapy versus immediate surgery for patients with colorectal cancer and liver metastases.

Applicability

The available evidence is directly applicable to the population of interest, though in some cases there are studies included that were not case matched, for example studies evaluating chemotherapy as a first approach appear to more commonly be non-matched case series studies. Non comparator studies generally would not provide any evidence in favour of one or other treatment or course of treatments, though in this case, where the quality of evidence is generally very low and where a randomised controlled trial is not likely to be conducted it could be argued that these studies do add to the overall body of evidence and allow some indirect inferences to be made.

One set of evidence based guidelines (Bipat et al, 2007) made recommendations on the use if simultaneous surgery and also on the use of neoadjuvant chemotherapy for patients with liver metastases.

Consistency

There was a good degree of consistency in the results of the evidence reviewed, though the evidence base was quite limited, with some outcomes drawing on single studies for evidence; this appears to be particularly the case with studies examining chemotherapy as a first treatment option.

Evidence Statement

Synchronous resection versus staged resection

Length of hospital stay

The body of evidence for length of hospital stay for synchronous resection versus staged resection consists of a single systematic review of observational studies (Hillingso et al 2009) and 1 retrospective case matched study (Moug et al 2010) comparing length of hospital stay in patients undergoing a staged resection procedure with patients undergoing a simultaneous resection procedure.

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Length of Hospital Stay							
8[1]	observational studies	serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	Very Low
4[1]	observational studies	serious[2]	serious[4]	no serious indirectness	no serious imprecision	none	

A total of 11 studies included in the systematic review reported on length of hospital stay;
[1]8/11 reported mean length of hospital stay with standard deviations, while 3 studies reported median length of hospital stay (Reddy et al, 2007; Turini et al, 2007; Yan et al, 2007). A single retrospective case matched study which was not included in the systematic review as it was published later, also reported median length of hospital stay (Moug et al, 2010).

[2] All studies included in the systematic review (Hillingso et al, 2009) were retrospective controlled studies with 2 studies based on prospective databases and the remainder on retrospective analysis of patient data. The methodological quality of the studies included in the systematic review was evaluated using the Newcastle-Ottawa scale and only studies with a score of 8 or more were included in the review; despite this as observational studies rather than randomised trials it is considered that there are serious limitations in study design.

[3] There was significant statistical heterogeneity on pooled analysis, which may have been explained by the differences in populations undergoing each treatment. For example, the review reports that the majority of included studies reported differences between the two patient groups in relation to surgery, primary cancer and metastatic disease.
In patients undergoing resection of primary colonic tumour, all included studies reported that right-sided cancer or minor curative liver resections (wedge or segmentectomies) due to fewer, smaller and uni-lobar metastases, more often resulted in a combined procedure while in patients undergoing staged resections, metastases were more often larger and more numerous. The review also reports that from the included studies, there appeared to be a tendency towards extending the criteria for synchronous resections over time and newer studies reported a greater number of major hepatectomies in more recent years (i.e. more than three segments).

[4]There is inconsistency between the 4 studies reporting median length of hospital stay with 3/4 studies reporting that the median length of hospital stay was lower in the synchronous resection group while 1 study (Turini et al, 2007) reported a shorter median length of hospital stay in the staged resection group, though in this study, median length of hospital stay was similar for both groups; 15 days in the staged resection group and 18 days in the synchronous resection group.

Table 4.1: Quality assessment of studies reporting length of hospital stay (days)

Study or Subgroup	Synchronous Resection Mean	SD	Total	Staged Resection Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Chua et al (2004)	11.4	6.7	64	22.4	17.6	32	10.2%	-11.00 [-17.32, -4.68]
Thelen et al (2007)	20.05	8	40	19.85	30.78	179	11.3%	0.20 [-4.95, 5.35]
Tanaka et al (2004)	25.6	10.4	39	23.1	10.3	37	11.8%	2.50 [-2.15, 7.15]
Capussotti et al (2007b)	13.9	10	31	20.5	8	48	12.2%	-6.60 [-10.78, -2.42]
Weber et al (2003)	17	9	35	16	7	62	12.9%	1.00 [-2.45, 4.45]
Vassiliou et al (2007)	12	6	25	20	8	78	13.3%	-8.00 [-10.95, -5.05]
Martin et al (2003)	12	6	45	18	4	76	14.0%	-6.00 [-7.97, -4.03]
Jaeck et al (1999)	17	3.1	28	15	2.2	31	14.3%	2.00 [0.62, 3.38]
Total (95% CI)			307			543	100.0%	-3.10 [-6.76, 0.56]

Heterogeneity: Tau² = 23.96; Chi² = 82.85, df = 7 (P < 0.00001); I² = 92%
Test for overall effect: Z = 1.66 (P = 0.10)

Figure 4.1: Length of hospital stay (days)

From the systematic review a pooled estimate was possible from 8/11 studies reporting on length of hospital stay. The mean difference reported was -3.10 days (95% CI, -6.76-0.56) for patients undergoing synchronous resection indicating no significant difference between the two procedures in relation to the length of hospital stay. There was however significant statistical heterogeneity when pooling the studies (I^2=92%; X^2=82.85, p<0.00001) indicating that it may not be appropriate to conduct pooled analysis.

The reason for the remaining three studies not being included in the pooled analysis appears to be that the individual studies did not report mean length of hospital stay, instead reporting median length of hospital stay. An additional study, not included in the systematic review also reported median length of hospital stay (Moug et al, 2010). From these 4 studies, the median length of hospital stay ranged from 7-18 days in the synchronous resection group and from 14-20 days in the staged resection group.

Morbidity
The body of evidence for morbidity for synchronous resection versus staged resection consists of a single systematic review of observational studies (Hillingso et al 2009) and 1 retrospective case matched study (Moug et al 2010). comparing post-operative morbidity in patients undergoing a staged resection procedure with patients undergoing a simultaneous resection procedure. Morbidity appears to relate to postoperative complications and immediate inhospital morbidity though neither the systematic review (Hillingso et al, 2009) nor the case series (Moug et al, 2010) clearly define what they mean by morbidity.

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Morbidity							
13[1]	observational	serious[2]	no serious	no serious	no serious	none	Very Low

	studies		inconsistency	indirectness	imprecision		

[1]A total of 12 studies in the systematic review reported on postoperative morbidity and an additional study (Moug et al, 2010) published after the systematic review also reported post-operative morbidity and was included in the evidence assessment and forest plot.

[2] All studies included in the systematic review (Hillingso et al, 2009) were retrospective controlled studies with 2 studies based on prospective databases and the remainder on retrospective analysis of patient data. The methodological quality of the studies included in the systematic review was evaluated using the Newcastle-Ottawa scale and only studies with a score of 8 or more were included in the review; despite this as observational studies rather than randomised trials it is considered that there are serious limitations in study design.

Table 4.2: Quality assessment of studies reporting post-operative morbidity

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
Capussotti et al (2007a)	10	31	27	48	7.2%	0.37 [0.14, 0.95]	
Chua et al (2004)	30	64	21	32	8.3%	0.46 [0.19, 1.11]	
Jaeck et al (1999)	5	28	5	31	3.5%	1.13 [0.29, 4.41]	
Martin et al (2003)	27	45	53	76	10.8%	0.65 [0.30, 1.41]	
Moug et al, 2010	11	32	19	32	6.2%	0.36 [0.13, 0.99]	
Reddy et al (2007)	49	135	27	70	18.1%	0.91 [0.50, 1.65]	
Tanaka et al (2004)	11	39	6	37	5.1%	2.03 [0.66, 6.21]	
Thelen et al (2007)	7	40	45	179	8.2%	0.63 [0.26, 1.53]	
Turrini et al (2007)	12	57	19	62	9.2%	0.60 [0.26, 1.39]	
Vassiliou et al (2007)	18	25	59	78	6.2%	0.83 [0.30, 2.28]	
Vogt et al (1991)	1	19	3	17	1.1%	0.26 [0.02, 2.77]	
Weber et al (2003)	8	35	20	62	7.1%	0.62 [0.24, 1.61]	
Yan et al (2007)	42	103	20	30	8.8%	0.34 [0.15, 0.81]	
Total (95% CI)		653		754	100.0%	0.63 [0.49, 0.81]	
Total events	231		324				

Heterogeneity: Tau² = 0.00; Chi² = 11.99, df = 12 (P = 0.45); I² = 0%
Test for overall effect: Z = 3.57 (P = 0.0004)

0.01 0.1 1 10 100
Favours Synchronous   Favours Staged

Figure 4.2: Post-operative morbidity

The results of the pooled analysis show that synchronous resection to be significantly better than staged resection in relation to post-operative morbidity (OR=0.68, 95% CI 0.49-0.81).
In the systematic review (Hillingso et al, 2009), no pooled analysis was undertaken as the authors felt that there was too much heterogeneity, however on pooled analysis the I^2 was 0% and the X^2 was insignificant (p=0.45) suggesting no significant statistical heterogeneity. It is possible that the clinical heterogeneity identified by the authors of the original systematic review was the reason that no pooled analysis was performed.

Mortality
The body of evidence for mortality for synchronous resection versus staged resection consists of a single systematic review of observational studies (Hillingso et al 2009) and 1 retrospective case matched study (Moug et al 2010) comparing mortality in patients undergoing a staged resection procedure with patients undergoing a simultaneous resection procedure. Mortality has not been clearly defined in either the systematic review (Hillingso et al, 2009) nor the case series (Moug et al, 2010) though as both studies also report on long term survival separately it is likely that mortality relates to deaths resulting from the surgical procedure and is limited to a certain time frame after surgery though this information is not provided.

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Mortality							
14[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Very Low

[1]A total of 13 studies in the systematic review reported on mortality and an additional study (Moug et al, 2010) published after the systematic review also reported mortality and was included in the evidence assessment and forest plot.

Table 4.3: Quality assessment of studies reporting post-operative mortality

Study or Subgroup	Synchronous Events	Total	Staged Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
Bolton and Fuhrman (2000)	12	50	4	115	27.8%	8.76 [2.67, 28.81]	
Capussotti et al (2007a)	1	31	0	48	7.8%	4.77 [0.19, 120.90]	
Chua et al (2004)	0	64	0	32		Not estimable	
Jaeck et al (1999)	0	28	0	31		Not estimable	
Martin et al (2003)	2	45	3	76	18.0%	1.13 [0.18, 7.04]	
Moug et al, 2010	0	32	0	32		Not estimable	
Reddy et al (2007)	4	135	0	70	9.2%	4.83 [0.26, 90.91]	
Tanaka et al (2004)	0	39	0	37		Not estimable	
Thelen et al (2007)	4	40	2	179	19.2%	9.83 [1.73, 55.73]	
Turrini et al (2007)	2	57	3	62	18.0%	0.72 [0.12, 4.44]	
Vassiliou et al (2007)	0	25	0	78		Not estimable	
Vogt et al (1991)	0	19	0	17		Not estimable	
Weber et al (2003)	0	35	0	62		Not estimable	
Yan et al (2007)	0	73	0	30		Not estimable	
Total (95% CI)		673		869	100.0%	3.56 [1.32, 9.60]	
Total events	25		12				

Heterogeneity: Tau² = 0.55; Chi² = 7.99, df = 5 (P = 0.16); I² = 37%
Test for overall effect: Z = 2.51 (P = 0.01)

Figure 4.3: Mortality (Odds Ratio)

Of the 14 studies reporting mortality, only 6 studies recorded any events and the pooled analysis from these six studies indicates that mortality was significantly lower in the staged resection group, however this does not present the whole picture, as in many studies no mortality was recorded and as zero event data cannot be included, these results are not reflected in the pooled analysis.

Study or Subgroup	Synchronous Events	Total	Staged Events	Total	Weight	Risk Difference M-H, Random, 95% CI	Risk Difference M-H, Random, 95% CI
Bolton and Fuhrman (2000)	12	50	4	115	2.7%	0.21 [0.08, 0.33]	
Capussotti et al (2007a)	1	31	0	48	5.4%	0.03 [-0.05, 0.11]	
Chua et al (2004)	0	64	0	32	9.5%	0.00 [-0.05, 0.05]	
Jaeck et al (1999)	0	28	0	31	7.0%	0.00 [-0.06, 0.06]	
Martin et al (2003)	2	45	3	76	5.8%	0.00 [-0.07, 0.08]	
Moug et al, 2010	0	32	0	32	7.6%	0.00 [-0.06, 0.06]	
Reddy et al (2007)	4	135	0	70	11.6%	0.03 [-0.01, 0.07]	
Tanaka et al (2004)	0	39	0	37	9.0%	0.00 [-0.05, 0.05]	
Thelen et al (2007)	4	40	2	179	4.1%	0.09 [-0.01, 0.18]	
Turrini et al (2007)	2	57	3	62	6.1%	-0.01 [-0.08, 0.06]	
Vassiliou et al (2007)	0	25	0	78	8.1%	0.00 [-0.06, 0.06]	
Vogt et al (1991)	0	19	0	17	3.7%	0.00 [-0.10, 0.10]	
Weber et al (2003)	0	35	0	62	10.0%	0.00 [-0.04, 0.04]	
Yan et al (2007)	0	73	0	30	9.3%	0.00 [-0.05, 0.05]	
Total (95% CI)		673		869	100.0%	0.01 [-0.01, 0.04]	
Total events	25		12				

Heterogeneity: Tau² = 0.00; Chi² = 24.31, df = 13 (P = 0.03); I² = 47%
Test for overall effect: Z = 1.23 (P = 0.22)

Figure 4.4: Mortality (Risk Difference)

Calculating the risk difference instead of odds ratio allows the zero counts to be included in the analysis and indicates that there is no significant difference in the risk of mortality between the two groups (RD, 0.01, 95% CI -0.01-0.04). Risk difference is the comparson between the two groups in terms of the absolute difference (i.e. the risk in one group minus the risk in the other) and is calculated as risk in the experimental group minus risk in the control group. In this case, the risk difference indicates that there is a 1% increase in risk of mortality in the synchronous resection group, though this is not statistically significant.

5 year overall survival
The body of evidence for 5 year survival for synchronous resection versus staged resection consists of a single systematic review of observational studies (Hillingso et al 2009) and 1 retrospective case matched study (Moug et al 2010) comparing 5 year survival in patients undergoing a staged resection procedure with patients undergoing a simultaneous resection procedure.

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
5-year survival							
12[1]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Very Low

[1] A total of 11 studies in the systematic review reported on 5 year survival and an additional study (Moug et al, 2010) published after the systematic review also reported 5 year survival and was included in the evidence assessment and forest plot.

[2] All studies included in the systematic review (Hillingso et al, 2009) were retrospective controlled studies with 2 studies based on prospective databases and the remainder on retrospective analysis of patient data. The methodological quality of the studies included in the systematic review was evaluated using the Newcastle-Ottawa scale and only studies with a score of 8 or more were included in the review; despite this as observational studies rather than randomised trials it is considered that there are serious limitations in study design.

Table 4: 4 year surviva

Study or Subgroup	Synchronous Events	Total	Staged Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Capussotti et al (2007a)	27	70	26	57	12.8%	0.75 [0.37, 1.52]
Chua et al (2004)	19	64	14	32	9.2%	0.54 [0.23, 1.31]
Jenkins et al (1997)	3	22	12	24	3.8%	0.16 [0.04, 0.68]
Moug et al, 2010	25	32	24	32	5.8%	1.19 [0.37, 3.79]
Scheele et al (1995)	15	58	14	38	9.1%	0.60 [0.25, 1.45]
Tanaka et al (2004)	21	39	17	37	8.8%	1.37 [0.56, 3.38]
Thelen et al (2007)	13	40	47	179	12.0%	1.35 [0.64, 2.84]
Turrini et al (2007)	18	57	16	62	10.7%	1.33 [0.60, 2.94]
Vassiliou et al (2007)	7	25	24	78	7.5%	0.88 [0.32, 2.37]
Vogt et al (1991)	10	19	5	17	4.2%	2.67 [0.67, 10.58]
Weber et al (2003)	7	35	13	62	7.1%	0.94 [0.34, 2.64]
Yan et al (2007)	26	73	11	30	9.1%	0.96 [0.39, 2.31]
Total (95% CI)		534		648	100.0%	0.92 [0.68, 1.24]
Total events	191		223			

Heterogeneity: Tau² = 0.05; Chi² = 13.35, df = 11 (P = 0.27); I² = 18%
Test for overall effect: Z = 0.55 (P = 0.58)

Figure 4.5: 5 year Overall Survival

There was no significant difference in 5 year survival for patients undergoing synchronous resection versus patients undergoing staged resection.

Preoperative Chemotherapy followed by surgery versus surgery alone
Length of hospital stay (days)
One retrospective case series (Benoist et al, 2005) aimed at determining the best treatments strategy for patients with asymptomatic primary tumour and irresectable metastases reported mean hospital stay in the chemotherapy group was 11 days (SD=10 days, range=2-52 days) versus 22 days (SD=15 days, range=5-75 days) in the resection group (p=0.003). The study states that the difference in mean hospital stay was related to hospital stay for primary tumour resection.

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Length of Hospital Stay							
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Very Low

[1]Benoist et al is a single retrospective, case matched study with a total population of 59 patients and similarly to the previous studies it is considered that a retrospective study design results in serious limitations in study design. This study is included in a systematic review (Scheer et al, 2007) however length of hospital stay for patients undergoing surgery of primary tumour was not an outcome of interest for the systematic review hence the study is evaluated independently of the systematic review for the purpose of this outcome.

Table 4.5: Quality assessment of studies reporting length of hospital stay (days)

Outcome Measures in Patients initially treated with Chemotherapy
Tumour related complications
The most important tumour related complication was intestinal obstruction, details of which were reported in 6/7 studies in the systematic review (Scheer et al, 2007); other complications reported included haemorrhage and peritonitis and fistula.

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Tumour Related Complications							
6	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	Very Low
Haemorrhage							
4	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	Very Low
Peritonitis and Fistula							
2	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	Very Low

[1] Studies included in the systematic review were retrospective studies and consisted of both comparative and non-comparative studies
[2] with some studies describing only the results of initial chemotherapy included in the systematic review, no information on treatment sequence was provided by these studies.

Table 4.6: Quality Assessment for studies reporting tumour related complications

The rate of intestinal obstruction reported in the included studies ranged from 5.6%-29%; the pooled proportion of patients developing bowel obstruction was 13.9% (95% CI 9.6% - 18.8%) (Scheer et al, 2007).

Haemorrhage due to primary tumour was reported in 4/7 studies included in the systematic review and ranged from 0%-3.7%; the pooled proportion of patients experiencing bleeding due to primary tumour was 3% (95% CI 0.95% - 6%) (Scheer et al, 2007).

A total of 2 studies included in the systematic review (Scheer et al, 2007) reported on peritonitis and fistula due to the unresected tumour; one study reported that 6.1% of patients developed peritonitis or fistulae. It appears that the second study reported that no patients developed fistulae or peritonitis thought this is somewhat unclear from the text.

Also from the systematic review (Scheer et al, 2007), a single study included reported that 37% of patients initially treated with chemotherapy experienced grade 3-4 toxicities.

Curative Resection
From one systematic review (Scheer et al, 2007), 3/7 studies reported on patients in whom curative resection of primary tumour and metastases was attempted as a result of downstaging by chemotherapy;

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality

Curative Resection							
3	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	Very Low
1	Observational study	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Very Low

[1] Studies included in the systematic review were retrospective studies and consisted of both comparative and non-comparative studies

[2] with some studies describing only the results of initial chemotherapy included in the systematic review, no information on treatment sequence was provided by these studies.

[3]This was a small (n=35) retrospective case series study with very little information provided in the publication as it was an update of an initial series.

Table 4.7: Quality Assessment for studies reporting curative resection rates

One study reported that curative resection was successful in 6/13 patients with 3 undergoing one-stage resection and 3 undergoing staged resection. The success rate for resection was not reported in the second study and in the third study only as single patient underwent curative resection (Scheer et al, 2007).

From a single case series study (Mentha et al, 2008), 30 patients were treated with chemotherapy prior to liver surgery; primary tumour could be removed at the same time as the liver metastases in 7 patients (or at the same time as first liver resection for patients undergoing 2-step hepatectomies).

Outcome Measures or Resection of Primary Tumour as Initial Therapy
From 1 systematic review (Scheer et al, 2007), 5/7 studies described the results of primary tumour resection with postoperative morbidity described in 4 studies.
Postoperative morbidity ranged from 18.8% to 47% though these results included complications of variable severity; major complications included obstruction, haemorrhage and sepsis and pooled analysis resulted in 11.8% (95% CI 4.4% - 22%) of patients experiencing major complications after surgery.
A total of 3 studies reported minor complications with the most common complications being wound infection (5.5%-10.6%) and urinary tract infection (2.4%-6.1%); pooled analysis resulted in an overall 20.6% (95% CI 15.6%-26%) of patients who had minor complications following surgery.

Postoperative mortality ranged from 0% to 4.6%; meta-analysis of the four studies showed a mortality of 2.7% (95% CI 1.1% - 5%).

Overall Survival

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Overall Survival							
6	observational studies	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	Very Low
1	Observational study	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Very Low

[1] Studies included in the systematic review were retrospective studies and consisted of both comparative and non-comparative studies

[2] with some studies describing only the results of initial chemotherapy included in the systematic review, no information on treatment sequence was provided by these studies.

[3]This was a small (n=35) retrospective case series study with very little information provided in the publication as it was an update of an initial series.

Table 4.8: Quality Assessment for studies reporting overall survival

From one systematic review (Scheer et al, 2008), median survival was addressed in 6/7 studies and for patients that underwent resection of the primary tumour median survival range from 14-23 months versus 8.2-22 months for patients treated with chemotherapy as first treatment.

Two studies included in the review reported a statistically significant difference in survival between resected and unresected patients. One study described a median survival of 14 months for patients treated with resection versus 8.2 months in the group initially treated by chemotherapy though multivariate analysis revealed that performance status and a presence of peritoneal or omental metastases were significant factors affecting survival and that resection status of the primary tumour was not significantly associated with survival.

The second reported a median survival of 16 months for patients initially treated with resection versus 9 months for patients treated with chemotherapy, though again on univariate analysis, resection status was not significantly associated with survival while number of distant sites involved, metastatic disease confined to the liver and volume of hepatic replacement by the tumour were significant factors (Scheer et al, 2007).

From a single case series (Mentha et al, 2008) examining the effect of chemotherapy followed by liver surgery, the overall actuarial survival rates were 91% at 1 year, 82% at 2 years, 54% at 3 years, 41% at 4 years and 30% at 5 years from start of treatment in 35 patients (intent to treat).
Median survival was 44 months.

Progression free survival
One randomised trial (Nordlinger et al, 2008) compared perioperative chemotherapy and surgery versus surgery alone. Median follow up was 3.9 years and there were 254 recorded events of progression free survival in all patients (intent to treat).

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Progression Free Survival							
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	Low

[1] The intervention under investigation meant that the study was subject to lead time bias, though steps were taken to address this.
[2] The number of events did not accumulate at the expected rate resulting in an under-powered study.

Table 4.9: Quality Assessment for studies reporting progression free survival

Hazard ratio for progression free survival was 0.79 (95.66% CI 0.62-1.02, p=0.058) which corresponds to a 7.3% increase in the rate of progression free survival at 3 years from 28.1% (21.3-35.3) to 35.4% (28.1-42.7) with chemotherapy and an increase in median progression free survival from 11.7 months to 18.7 months.

When applying the usual definition of progression free survival (those not operated or not resected were not penalised as events until further disease progression or death), the hazards ratio was 0.76 (0.59-0.98, p=0.023) corresponding to a 7.3% increase in the rate of progression free survival at 3 years from 28.6% (21.7-35.8) to 37.9% (30.5-45.3) with chemotherapy and adjustment of primary analysis for stratification factors did not change the results.

Conclusions
Hillingso et al, 2009 conclude that a randomised trial would be the best way to provide strong evidence on which to base recommendations, however their sample size calculations indicate that more than 1,000 patients would need to be treated in each group in order that a clinically relevant difference in post-operative morbidity be observed. It was felt that to achieve this, a large multi-centre trial would be required and it presented a possible ethical dilemma in that persuading patients, particularly those with the least disseminated disease to the staged arm would be difficult. It was therefore concluded that such a trial would never be performed.

On the basis of weak evidence (resulting from bias and apparent heterogeneity) Hillingso et al, 2010 recommended that combined resection be undertaken in selected patients provided surgeons specialised in colorectal and hepatobiliary surgery are available as the data suggest that this approach leads to shorter hospital stay and less post operative morbidity but there was no difference in 5 year survival for either procedure.

One set of evidence based guideline for Dutch patients (Bipat et al, 2007) recommended that the use of simultaneous resection of colorectal cancer and liver metastases should be avoided due to a high complication rate despite the fact that survival after simultaneous resection was comparable to that for staged resection. The recommendation was based on what the guideline classed as evidence level 3 (generally randomised trials of low quality or other non randomised comparative studies such as cohort and case control studies or poor quality descriptive studies).

The guideline also made recommendations on the use of neoadjuvant chemotherapy. Due to controversial data, the guideline recommends that neoadjuvant chemotherapy be used only in clinical research populations; again this was based on level 3 evidence.
Based on leverl 2 evidence, the guideline recommended that adjuvant chemotherapy should not be used routinely after curative surgery as it's role is unclear. Level 2 evidence was described as being either low quality randomised trials or other non randomised comparative studies such as cohort and case control studies or a systematic r eview of these types of studies).

References

Benoist S, Pautrat K, MItry E, Rougier P, Penna C and Nordlinger B (2005) Treatment strategy for patients with colorectal cancer and synchronous irresectable liver metastases *British Journal of Surgery* 92:1155-1160

Bipat S, van Leeuwen MS, IJzermans JN et al (2007) Evidence based guideline on management of colorectal liver metastases in the Netherlands (Review) *Netherlands Journal of Medicine* 65;1:5-14

Hillingso J and Wille-Jorgensen P (2009) Staged or simultaneous resection of synchronous liver metastases from colorectal cancer – a systematic review *Colorectal Disease* 11;1:3-10

Mentha G, Roth A, Terraz S, et al (2008) 'Liver First' Approach in the treatment of colorectal cancer with synchronous liver metastases *Digestive Surgery*25;430-435

Moug SJ, Smith D, Leen E, Roxburgh C, and Horgan PG (2010) Evidence for a synchronous operative approach in the treatment of colorectal cancer with hepatic metastases: A case matched study *European Journal of Surgical Oncology* 36;4:365-370

Nordlinger B, Sorbye H, Glimlius B, Poston G et al (2008) Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial

Scheer MG, Sloots CE, van der Wilt GJ and Ruers TJM (2008) Management of patients with asymptomatic colorectal cancer and synchronous irresectable metastases *Annals of Oncology* 19;11:1829-1835

Evidence Tables

Citation: Benoist S, Pautrat K, Mltry E, Rougier P, Penna C and Nordlinger B (2005) Treatment strategy for patients with colorectal cancer and synchronous irresectable liver metastases *British Journal of Surgery* 92:1155-1160

Design: Retrospective Case matched study **Country**: France **Setting:** **Aim**: to determine the best treatment strategy for patients with asymptomatic colorectal cancer and irresectable metastases.

Inclusion criteria Patients with colorectal cancer and irresectable synchronous lever metastases that were treated with chemotherapy as initial treatment with minimal or no symptoms related to the primary tumour and a performance status allowing treatment by systemic chemotherapy. Patients were matched with all (one or more) similar patients with asymptomatic colorectal cancer and irresectable liver metastases who had undergone resection of the primary tumour as initial treatment

Exclusion criteria No details

Sample Size No details

Randomisation Method N/A

Population N=59

Study Duration Data were collected between 1997 and 2002

Interventions Chemotherapy – started less than 21 days after diagnosis Surgical resection of primary followed by chemotherapy at least 3 weeks after uneventful surgical procedures

Outcomes Overall survival rate at 2 years Morbidity and mortality rates following surgical resection of the primary tumour (surgery group) Complications related to primary tumour and toxicity of chemotherapy (chemotherapy group) Overall duration of hospital stay Rate of curative liver resection after tumour downstaging by chemotherapy

Results Clinical data and the characteristics of metastases were comparable between the two groups. In the chemotherapy group, the mean interval between diagnosis and start of treatment was 15 days (SD=3 days) and in the resection group the mean interval between surgery and start of chemotherapy was 44 days (SD=22 days). Median survival time from time of diagnosis was 22 months (range1-38) and the 2 year actuarial survival rate was 41% in the chemotherapy group and median survival time 23 months (range 3-42 months) and the 2 year actuarial survival rate was 44% in the resection group. At the end of follow-up, 21 patients in the chemotherapy group died of progressive disease versus 24 in the surgery group (p=0.753). 3 patients in the chemotherapy group and 8 patients in the surgery group were alive with progressive or stable disease (p=0.538) and 3 patients in the chemotherapy group were alive with no evidence of recurrent disease after liver resection.

6/32 patients in the surgery group experienced post-operative complications including wound infection (n=2), pleural effusion (n=1), pulmonary embolism (n=1), urinary tract infection (n=1) and intra-abdominal abscess (n=1). 4/27 patients in the chemotherapy group experienced intestinal complications related to the unresected primary tumour including bowel obstruction requiring emergency surgery including subtotal colectomy (n=1), diverting stoma (n=2), and bypass (n=1).

26 patients in total experienced grade 3 or 4 toxicity, 10 in the chemotherapy group and 16 in the resection group (p=0.466).

Mean hospital stay was 11 days (SD=10 days, range 2-52) in the chemotherapy group versus 22 days (SD=15 days, range 5-75) in the resection group (p=0.003).The difference between the two groups was related to hospital stay for primary tumour resection.

Curative resection was attempted in 13 patients in the chemotherapy group and in 11 patients in the surgery group after shrinkage of initially irresectable liver metastases by chemotherapy (p=0.783). Resection or local ablation of liver metastases was successful in 12 patients, 6 in each group (p=0.699).
In the chemotherapy group, 3 patients underwent staged resection of primary tumour combined with radiofrequency ablation of small liver deposits in one lobe followed by resection of liver deposits in the opposite lobe 2 months later, while the other three underwent simultaneous resection of the colorectal primary and metastases.
In the resection group curative resection was performed in 5 patients and the remaining patient had radiofrequency ablation combined with resection.

Citation: Hillingso J and Wille-Jorgensen P (2009) Staged or simultaneous resection of synchronous liver metastases from colorectal cancer – a systematic review *Colorectal Disease* 11;1:3-10

Design: Systematic Review

Country: Denmark

Setting:

Aim: To systematically review the literature to determine the level of evidence available for recommending a treatment strategy by identifying differences in length of hospital stay, morbidity, mortality and 5 year survival between staged and simultaneous resection of synchronous liver metastases.

Inclusion criteria
Randomised and controlled clinical trials or observations
Studies undertaken over a fixed period comparing patients undergoing combined or delayed resection of synchronous metastases.

Exclusion criteria
Studies dealing with either combined resection or staged resection alone (i.e. no comparator)

Sample Size
N/A

Randomisation Method
N/A

Population
N=16 studies fit the criteria

Quality of Included Studies
All included studies were controlled, retrospective studies with 2 studies based on prospective databases and the remainder on retrospective analysis of patient charts, for this reason methodological quality of the studies was assessed according to the Newcastle-Ottawa scale which evaluates studies on factors such as patient selection, comparability of patient groups and assessments of outcomes with a score of 8 or more required for inclusion (maximum available score was 9).

Study Duration
Literature search conducted until 5th November, 2007 (no start date was given)

Interventions
Staged or simultaneous resection of synchronous liver metastases

Outcomes
Outcome measures included:
- length of hospital stay
- surgical morbidity
- perioperative mortality
- 5 year survival

Results
Length of Hospital Stay
11 studies with a total of 850 patients (307 undergoing synchronous resection and 543 undergoing staged resection) addressed the length of hospital stay; a tendency towards shorter hospital stay was observed in the synchronous resection group.

Study or Subgroup	Synchronous Resection Mean	SD	Total	Staged Resection Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
Chua et al (2004)	11.4	6.7	64	22.4	17.6	32	10.2%	-11.00 [-17.32, -4.68]	
Thelen et al (2007)	20.05	8	40	19.85	30.78	179	11.3%	0.20 [-4.95, 5.35]	
Tanaka et al (2004)	25.6	10.4	39	23.1	10.3	37	11.8%	2.50 [-2.15, 7.15]	
Capussotti et al (2007b)	13.9	10	31	20.5	8	48	12.2%	-6.60 [-10.78, -2.42]	
Weber et al (2003)	17	9	35	16	7	62	12.9%	1.00 [-2.45, 4.45]	
Vassiliou et al (2007)	12	6	25	20	8	78	13.3%	-8.00 [-10.95, -5.05]	
Martin et al (2003)	12	6	45	18	4	76	14.0%	-6.00 [-7.97, -4.03]	
Jaeck et al (1999)	17	3.1	28	15	2.2	31	14.3%	2.00 [0.62, 3.38]	
Total (95% CI)			307			543	100.0%	-3.10 [-6.76, 0.56]	

Heterogeneity: Tau² = 23.96; Chi² = 82.85, df = 7 (P < 0.00001); I² = 92%
Test for overall effect: Z = 1.66 (P = 0.10)

-100 -50 0 50 100
Favours Synchronous   Favours Staged

Reproduced using the data in the forest plot in the original review: the original review did not conduct a pooled analysis to give a single overall estimate due to heterogeneity (I²=92%). The paper states that the 11 studies encompass a population of 850 patients though in actuality, 850 is the population from the 8 studies for which a mean difference was calculable. The pooled result for the 8 studies was -3.10 (95% -6.75-0.56).

Morbidity
From 14 studies with a total of 1,384 patients, 224/641 (35%) of patients undergoing synchronous resection experienced complications versus 301/743 (41%) of patients undergoing staged resection.

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Odds Ratio M-H, Random, 95% CI
Capussotti et al (2007a)	10	31	27	48	7.7%	0.37 [0.14, 0.95]	
Chua et al (2004)	30	64	21	32	8.9%	0.46 [0.19, 1.11]	
Jaeck et al (1999)	5	28	5	31	3.7%	1.13 [0.29, 4.41]	
Martin et al (2003)	27	45	53	76	11.5%	0.65 [0.30, 1.41]	
Reddy et al (2007)	49	135	27	70	19.3%	0.91 [0.50, 1.65]	
Tanaka et al (2004)	11	39	6	37	5.5%	2.03 [0.66, 6.21]	
Thelen et al (2007)	7	40	45	179	8.8%	0.63 [0.26, 1.53]	
Turrini et al (2007)	12	57	19	62	9.8%	0.60 [0.26, 1.39]	
Vassiliou et al (2007)	18	25	59	78	6.7%	0.83 [0.30, 2.28]	
Vogt et al (1991)	1	19	3	17	1.2%	0.26 [0.02, 2.77]	
Weber et al (2003)	8	35	20	62	7.6%	0.62 [0.24, 1.61]	
Yan et al (2007)	42	103	20	30	9.4%	0.34 [0.15, 0.81]	
Total (95% CI)		621		722	100.0%	0.65 [0.50, 0.85]	
Total events	220		305				

Heterogeneity: Tau² = 0.00; Chi² = 10.73, df = 11 (P = 0.47); I² = 0%
Test for overall effect: Z = 3.18 (P = 0.001)

0.01 0.1 1 10 100
Favours Synchronous   Favours Staged

Forest plot is reproduced using the data in the systematic review, again there is a discrepancy between text and graphs with the text stating that 14 studies with a total of 1,384 patients reported morbidity whereas the forest plot presented in the study included only 12 studies and the total number of patients on reproduction of the forest plot was actually 1,343 (220/621 patients with complications in the synchronous group versus 305/722 patients in the staged group experiencing complications). The text of the review also states that pooled analysis was not performed on the basis of significant heterogeneity, however from the reproduced forest plot above, it can be seen that the I² is 0% and the X² is statistically insignificant (p=0.47) which suggest no statistical heterogeneity. The pooled odds ratio was 0.65 (95% CI 0.5-0.85) in favour of synchronous resection.

Mortality
From 15 studies comparing perioperative mortality, 32/499 (6.4%) of patients undergoing synchronous resection died versus 40/1529 (2.6%) of patients undergoing staged resection showing a clear tendency towards higher mortality in the combined resection group.

Study or Subgroup	Synchronous Events	Synchronous Total	Staged Events	Staged Total	Weight	Odds Ratio M-H, Random, 95% CI
Bolton and Fuhrman (2000)	12	50	4	115	27.8%	8.76 [2.67, 28.81]
Capussotti et al (2007a)	1	31	0	48	7.8%	4.77 [0.19, 120.90]
Chua et al (2004)	0	64	0	32		Not estimable
Jaeck et al (1999)	0	28	0	31		Not estimable
Martin et al (2003)	2	45	3	76	18.0%	1.13 [0.18, 7.04]
Reddy et al (2007)	4	135	0	70	9.2%	4.83 [0.26, 90.91]
Tanaka et al (2004)	0	39	0	37		Not estimable
Thelen et al (2007)	4	40	2	179	19.2%	9.83 [1.73, 55.73]
Turrini et al (2007)	2	57	3	62	18.0%	0.72 [0.12, 4.44]
Vassiliou et al (2007)	0	25	0	78		Not estimable
Vogt et al (1991)	0	19	0	17		Not estimable
Weber et al (2003)	0	35	0	62		Not estimable
Yan et al (2007)	0	73	0	30		Not estimable
Total (95% CI)		**641**		**837**	**100.0%**	**3.56 [1.32, 9.60]**
Total events	25		12			

Heterogeneity: Tau² = 0.55; Chi² = 7.99, df = 5 (P = 0.16); I² = 37%
Test for overall effect: Z = 2.51 (P = 0.01)

Odds Ratio M-H, Random, 95% CI (scale 0.01 0.1 1 10 100) — Favours Synchronous / Favours Staged

The forest plot has been reproduced using the data published in the systematic review and it should be noted that there are differences between text and tables. The text states that 15 studies with a total population of 2,028 patients (499 undergoing synchronous resection and 1529 undergoing staged resection) whereas from the forest plot presented there are only 13 studies with a total population of 1,478. Again the data are not pooled in the systematic review with the authors stating that this is due to heterogeneity; on reproducing the forest plot however the I^2 is 37% and X^2 is statistically insignificant (p=0.16) indicating a lack of statistical heterogeneity. The pooled odds ratio was 3.56 (95% CI 1.32-9.6) in favour of staged resection.

Survival
11 studies reported on long term survival (5-year survival); 166/502 (33%) of patients in the synchronous resection group versus 199/616 (32%) in the staged resection group suggesting no difference in overall 5-year survival between the two groups.

Study or Subgroup	Synchronous Events	Synchronous Total	Staged Events	Staged Total	Weight	Odds Ratio M-H, Random, 95% CI
Capussotti et al (2007a)	27	70	26	57	13.2%	0.75 [0.37, 1.52]
Chua et al (2004)	19	64	14	32	9.7%	0.54 [0.23, 1.31]
Jenkins et al (1997)	3	22	12	24	4.2%	0.16 [0.04, 0.68]
Scheele et al (1995)	15	58	14	38	9.7%	0.60 [0.25, 1.45]
Tanaka et al (2004)	21	39	17	37	9.4%	1.37 [0.56, 3.38]
Thelen et al (2007)	13	40	47	179	12.5%	1.35 [0.64, 2.84]
Turrini et al (2007)	18	57	16	62	11.3%	1.33 [0.60, 2.94]
Vassiliou et al (2007)	7	25	24	78	8.0%	0.88 [0.32, 2.37]
Vogt et al (1991)	10	19	5	17	4.7%	2.67 [0.67, 10.58]
Weber et al (2003)	7	35	13	62	7.6%	0.94 [0.34, 2.64]
Yan et al (2007)	26	73	11	30	9.7%	0.96 [0.39, 2.31]
Total (95% CI)		**502**		**616**	**100.0%**	**0.90 [0.66, 1.24]**
Total events	166		199			

Heterogeneity: Tau² = 0.07; Chi² = 13.15, df = 10 (P = 0.22); I² = 24%
Test for overall effect: Z = 0.62 (P = 0.54)

Odds Ratio M-H, Random, 95% CI (scale 0.01 0.1 1 10 100) — Favours experimental / Favours control

The forest plot was again reproduced from the systematic review, in this case there were no discrepancies between text and tables. The pooled result was not reported in the systematic review though in this case no reason was provided. There was no statistical heterogeneity (I^2=24% and X^2 was not significant (p=0.22)); the pooled odds ratio was 0.9 (95% CI, 0.66-1.24) indicating that there is no difference between the two procedures (synchronous versus staged) in relation to 5-year overall survival.

Although the in some cases there does not appear to be statistical heterogeneity when pooling the results from

individual studies, the authors identify clinical heterogeneity in relation to the patients undergoing each resection procedure. For example, the review reports that the majority of included studies reported differences between the two patient groups in relation to surgery, primary cancer and metastatic disease.

In patients undergoing resection of primary colonic tumour, all included studies reported that right-sided cancer or minor curative liver resections (wedge or segmentectomies) due to fewer, smaller and uni-lobar metastases, more often resulted in a combined procedure while in patients undergoing staged resections, metastases were more often larger and more numerous.

The review also reports that from the included studies, there appeared to be a tendency towards extending the criteria for synchronous resections over time and newer studies reported a greater number of major hepatectomies in more recent years (i.e. more than three segments).

The decision not to calculate pooled estimates of the data appears to have been made on the basis that there is obvious clinical heterogeneity between the patient groups.

General comments
No pooled analyses of data were performed due to the presence of clinical heterogeneity. As part of the methodology, the authors stated that sensitivity analysis would be performed should the data show severe clinical or statistical heterogeneity; however the results of the review include neither heterogeneity scores nor sensitivity analyses where heterogeneity was deemed present.

Author Conclusions
A randomised trial would be the best way to provide strong evidence on which to base recommendations, however sample size calculations show that more than 1,000 patients would need to be treated in each group in order that a clinically relevant difference in post-operative morbidity be observed. To achieve this, a large multi-centre trial would be required and there is a possible ethical dilemma in that persuading patients, particularly those with the least disseminated disease to the staged arm would be difficult. It was therefore concluded that such a trial would never be performed.

On the basis of weak evidence (resulting from bias and apparent heterogeneity) the authors recommend that combined resection be undertaken in selected patients provided surgeons specialised in colorectal and hepatobiliary surgery are available as the data suggest that this approach leads to shorter hospital stay and less post operative morbidity but there was no difference in 5 year survival. In the early decade at least, combined resection had greater 30 day mortality.

Citation: Mentha G, Roth A, Terraz S, et al (2008) 'Liver First' Approach in the treatment of colorectal cancer with synchronous liver metastases *Digestive Surgery*25;430-435
Design: Retrospective Case Series (data were collected prospectively in the database) **Country**: Switzerland **Setting**: **Aim**: to update on an initial series and share additional experience in the management of colorectal cancer with synchronous liver metastases.
Inclusion criteria Age <70 years Performance Status <2 Nonocclusive primary tumour At least 2 liver segments without metastases no or resectable extrahepatic disease (lungs, lymph nodes)
Exclusion criteria No details
Sample Size No details
Randomisation Method N/A
Population N=35
Study Duration Data were collected between January 1998 and December 2007
Interventions 3-6 courses of chemotherapy before liver resection (chemotherapy was oxaliplatin combined with 5-fluorouracil and leucovorin). Since 2006 bevacizumab was given to 7 patients and cetuximab to 2 patients. Radiological assessments were done during the 3rd course of chemotherapy and when a patients was considered to be resectable with a decrease in CEA level, liver surgery was planned for 2-3 weeks after the 3rd course of chemotherapy and further chemotherapy was only given if it was determined that further response would confer surgical advantage.
Outcomes
Results 5/35 (14%) of patients could not complete treatment; 1 died of sepsis, 2 patients had disease progression during different surgical steps, 1 had rapid regrowth of liver metastases following the second phase of a 2 step hepatectomy to remove 18 bilobar noduls and was put on chemotherapy without rectal surgery and 1 patient had 6 small metastases deeply located in the left and right liver the metastases disappeared after chemotherapy and the patient underwent resection of the primary tumour. All 5 patients died after 2, 5, 8, 30 and 62 months, the last four due to recurrence. 30 patients, 16 males and 14 females, completed the program. The median age of patients was 52 years (32-69) and 13/30 patients had a rectal primary. Median number of metastases was 6 (mean=5.2; range=1-21) and the median size of the largest metastases was 6cm (mean=7.3cm, range=1-14). 3 patients had resectable lung metastases at the time of diagnosis, one of whom had positive lymph nodes of the hepatic pedicle. Primary tumour could be removed at the same time as the liver metastases in 7 patients (or at the same time as the first liver resection for 2-step hepatectomies).

There was no preoperative mortality and no deaths before completion of the therapeutic program apart from the single patient that died of sepsis during chemotherapy.

5 patients (17%) experienced complications of liver surgery.

Recurrences were observed in 20 patients
At the end of follow-up 14 patients had died, 6 patients were alive with disease and 10 patients were alive with no evidence of disease.

Considering all patients as intention to treat (n=35), the overall actuarial survival rates were 91% at 1 year, 82% at 2 years, 54% at 3 years, 41% at 4 years and 30% at 5 years from start of treatment.
Median survival was 44 months.
Considering only the 30 patients that completed the program, overall actuarial survival rates were 100%, 89%, 60%, 44% and 31% with a median survival of 44 months.

Citation: Moug SJ, Smith D, Leen E, Roxburgh C, and Horgan PG (2010) Evidence for a synchronous operative approach in the treatment of colorectal cancer with hepatic metastases: A case matched study *European Journal of Surgical Oncology* 36;4:365-370
Design: Retrospective Case Matched Study **Country**: UK **Setting:** Hospital **Aim**: to determine the short and long term outcomes in patients undergoing synchronous procedures compared with patients undergoing staged procedures.
Inclusion criteria Patients with colorectal cancer and hepatic metastases who underwent a synchronous operative approach
Exclusion criteria No details given
Sample Size N/A
Randomisation Method N/A
Population N=32 patients undergoing synchronous procedures matched with 32 patients undergoing staged procedure. Total N=64
Study Duration No details given
Interventions Synchronous resection
Outcomes Operative blood loss In hospital morbidity and mortality Duration of hospital stay Time to Recurrence Long Term Survival
Results The criteria for synchronous surgery included; fitness for anaesthesia, expected margin negative resection (R0) of the primary disease, no unresectable extra-hepatic disease and adequate predicted volume of hepatic remnant post resection. All patients were considered synchronous resections according to these criteria, irrespective of the type of colonic or hepatic resection that would be required. No statistical differences were observed between the synchronous and staged resection groups in relation to sex, age, ASA grade, TNM staging or clinical risk score. Similar numbers of patients in each group had received chemotherapy and or radiotherapy. 78% of patients underwent major colorectal resections and 22% underwent major hepatic resections. Radiofrequency ablation was performed in 6 (5 synchronous and 1 staged patient) patients, with 1 liver metastasis ablated in each case. *Intraoperative Blood Loss* Median operative blood loss was 475ml (range 150-850ml) in the synchronous resection group compared with 425ml (range 50-1700ml) in the staged group (p<0.050). No patient returned to theatre with postoperative bleeding. *Postoperative Outcomes* No significant difference was observed between the two groups in relation to morbidity with (34% (n=11) in the synchronous group versus 59% (n=19) in the staged group, p=0.69).

10/11 of the complications in the synchronous resection group were considered minor versus 19/19 in the staged resection group.
Median duration of hospital stay was 12 days (range, 8-21) in the synchronous resection group versus 20 days (range 7-51) in the staged resection group (p=0.008).
There was no recorded mortality for either group.

Long term outcomes
There were no statistically significant differences in either disease free survival or overall survival between the two groups.
Median time to cancer recurrence was 10 months (95% CI 5.8-13.7) in the synchronous group versus 14 months (95% CI 12.2-16.3) in the staged group (p=0.487).
Overall median survival was 39 months in the synchronous resection group versus 42 months in the staged resection group.
Overall survival rate at 5 years was 21% in the synchronous group versus 24% in the staged group (log rank p=0.838).

Citation: Nordlinger B, Sorbye H, Glimlius B, Poston G et al (2008) Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial

Design: Randomised Trial

Country: Multiple

Setting:

Aim: to compare perioperative (before and after surgery) chemotherapy with surgery alone in patients with one to four hepatic colorectal cancer metastases considered to be resectable on imaging

Inclusion criteria
Aged between 18 and 80 years
WHO performance status ≤2
1-4 liver metastases that were potentially resectable
No detectable extra-hepatic metastases
Primary tumour already resected or deemed resectable by the multidisciplinary team at the treating hospital

Exclusion criteria
Previous chemotherapy with oxaliplatin
Any history of cancer in the past 10 years apart from non-melanoma skin cancer or in-situ cervical cancer
Major hepatic insufficiency
Absolute neutrophil count $<1.5\times10^9$/L
Platelet counts $<100\times10^9$/L
Serum creatinine more than twice the upper limit of normal
Grade of common toxicity criteria more than 1 for peripheral neuropathy
Uncontrolled congestive heart failure
Angina pectoris
Hypertension
Arrythmia
History of significant neurological or psychiatric disorders
Active infection
Pregnant or lactating women

Sample Size

Randomisation Method
Minimisation technique with stratification for centre, previous adjuvant chemotherapy to primary surgery for colorectal cancer and risk score.

Population
N=364 patients enrolled (182 per arm)

Study Duration
The study was planned to detect a 40% increase in median progression free survival or an increase of 3 year progression free survival from 21% to 32.8% in all patients randomly assigned to perioperative chemotherapy (HR=0.714) with 80% power and a two-sided 5% significance level requiring 278 events.
The trial was expected to produce this number of events after 6.5 years however events did not accumulate at the anticipated rate and with pressure to have trial results disclosed, a stopping boundary for efficacy was implemented.
An interim analysis was undertaken in November, 2006 and shown to the EORTC independent data monitoring committee who recommended updated results in June 2007 as the stopping boundary had been reached. The results were updated in March 2007 and presented at the two-sided 0.0434 significance level because of interim analysis.

Interventions
Six cycles of FOLFOX 4 before and six cycles of FOLFOX 4 after surgery (given unless the tumour progressed during preoperative chemotherapy)

Surgery alone

Outcomes

Progression free survival (from randomization to the date of either progressive or recurrent disease, surgery if metastases were not deemed resectable or death of any cause).

Results

There was no significant difference in patient and tumour characteristics between the two groups at baseline.
11 patients in each arm were deemed ineligible due to reasons including; more advanced disease than was allowed by the protocol, primary liver cancer, no data, second cancer, late informed consent, high serum creatinine and resection of primary less than 14 days of randomisation.

79% (n=143) of patients in the chemotherapy arm completed the planned 6 cycles of preoperative chemotherapy and 6% (n=11) of patients did not start treatment.

No toxic deaths were recorded.
Partial or complete response (according to RECIST) was observed in 43% (n=67) of patients and total lesion diameter was reduced by about a quarter after chemotherapy.
7% (n=12) of patients progressed during preoperative chemotherapy; 8 after 3-4 cycles (3 resected) and 4 after 6 cycles (1 resected). None of these patients received post-operative chemotherapy (it is not clear whether this related to just the 8 unresected patients or the whole group of 12 patients who progressed).

In the surgery only group, one patient underwent the complete perioperative chemotherapy at his own request, no other patient in the group received chemotherapy before recurrence.

Surgery according to the protocol was performed at a median of 16.6 weeks (range 0.1-30) in the perioperative chemotherapy group and at a median of 4.1 weeks (range 2-16.4) after last administration of preoperative chemotherapy and more patients in the surgery group (93%) received the operation versus the chemotherapy group (87%).
The primary reason for non-resectability was more advanced disease than expected (7 patients in the chemotherapy arm and 18 patients in the surgery arm).
Reversible postoperative complications occurred more frequently in the chemotherapy arm compared with surgery alone (25% versus 16% p=0.04).

63% (n=115) of patients started postoperative protocol chemotherapy of whom 80 (70%) received all six cycles, reasons for not starting postoperative chemotherapy included refusals, perioperative complications, toxic effects from preoperative chemotherapy, and disease progression.

Median follow-up was 3.9 years as of March 2007 with 254 recorded events of progression free survival in all randomised patients including 240 in eligible patients.
22 patients assigned to chemotherapy and 19 patients assigned to surgery were alive without disease and had been followed up for less than three years. A total of 139 patients had died.
The hazard ratio for progression free survival was 0.79 (95.66% CI 0.62-1.02, p=0.058) in all randomly assigned patients which corresponds to a 7.3% increase in the rate of progression free survival at 3 years from 28.1% (21.3-35.3) to 35,4% (28.1-42.7) with chemotherapy and to an increase of the median progression free survival from 11.7 months to 18.7 months.

On analysing only patients eligible to enter the trial, the hazards ratio was 0.77 (0.6-1.00, p=0.041) which corresponds to an 8.1% increase in the rate of progression free survival at 3 years from 28.1% (21.2-36.6) to 36.2% (28.7-43.8) with chemotherapy.

On analysis of the 303 patients in whom resection was actually achieved, the hazard ratio was 0.73 (0.55-0.97, p=0.025) and the rate of progression free survival at 3 years was increased by 9.2% from 33.2% (25.3-41.2) to 42.4% (34-50.5).

When applying the usual definition of progression free survival (those not operated or not resected were not penalised as events until further disease progression or death), the hazards ratio was 0.76 (0.59-0.98, p=0.023) corresponding to a 7.3% increase in the rate of progression free survival at 3 years from 28.6% (21.7-35.8) to 37.9% (30.5-45.3) with chemotherapy and adjustment of primary analysis for stratification factors did not change the results.

General comments

Study treatment had to start within 3 weeks of randomization. Liver resection was performed 2-5 weeks after last administration of chemotherapy and whenever patients had recovered from the side-effects of chemotherapy with a WHO performance status of 0 or 1 and adequate liver function.

In order to address lead-time bias, the event time to have occurred at 10 weeks was assigned in both treatment groups in the following circumstances: any patient who was operated on but in whom tumour was not resectable, any patients whose tumour was resected but recurred within week 1 and 20 or those who died between week 1 and 20 of follow-up. Week 10 was chosen as being in the middle of those 20 weeks.

Citation: Scheer MG, Sloots CE, van der Wilt GJ and Ruers TJM (2008) Management of patients with asymptomatic colorectal cancer and synchronous irresectable metastases *Annals of Oncology* 19;11:1829-1835
Design: Systematic Review
Country: N/A
Setting: N/A
Aim: to compare the complication rate after resection of the primary tumour alone and resection of the primary tumour following pre-operative chemotherapy.
Inclusion criteria   Studies that reported a series of patients presenting with stage IV colorectal cancer that underwent surgery for the primary colorectal tumour or were treated with systemic chemotherapy   Studies reporting complications, response data and/or survival data
Exclusion criteria   Reasons for excluding studies (from flow-chart in paper) included: • study irrelevant on title   • study irrelevant on abstract   • study irrelevant on article   • new publications by cross reference
Sample Size   N/A
Randomisation Method   N/A
Population   N=7 studies were included
Study Duration   Searches appear to have been set to begin at January 1980 and no end date for the searches was stated.
Interventions   Surgery   Chemotherapy
Outcomes   Rate of primary tumour related complications in patients not undergoing surgery.   Complications of patients undergoing surgery of the primary tumour or patients receiving systemic chemotherapy.   Survival of all patients   Rate of curative surgery after chemotherapy
Results   No studies identified described randomisation between surgical and non surgical treatment o the primary tumour. Of the 7 included studies, 4 were retrospective case series, 2 were prospective case series and 1 described a retrospective case control study.   2 of the included studies described only the results of initial chemotherapy (i.e. no comparator) while the remaining studies all compared both treatments. *The results of the two studies which had no comparator are not relevant to the current topic as without a comparator they do not add anything to the evidence body however it may not be possible to present the results of only the 5 studies which did compare treatment strategies.*   In total 850 patients were described; 536 underwent surgery as initial treatment, and 314 patients underwent chemotherapy as initial treatment.   Median follow-up of patients initially treated with chemotherapy ranged from 18 to 26 months (reported in 4 studies) and for patients who underwent surgery ranged from 23-30 months (reported in 2 studies).

Comparison between the groups was limited due to differences in the extent of liver involvement, the presence of extra hepatic metastatic disease and the rate of left sided tumours. Larger percentages of liver involvement were reported for the group initially treated with chemotherapy in 4/5 included studies and 3/5 studies reported a higher percentage of extra hepatic disease in the group treated with chemotherapy, with one study reporting significant differences (Ruo et al, 2003). Of the included studies, 2 reported significant differences between treatment groups in relation to tumour location (Ruo et al, 2003 and Michel P et al, 2004).

Outcome measures in patients treated initially with chemotherapy
The most important tumour related complication was intestinal obstruction, details of which were reported in 6/7 studies.
The rate of intestinal obstruction ranged from 5.6%-29%; the pooled proportion of patients developing bowel obstruction was 13.9% (95% CI 9.6% - 18.8%).

Haemorrhage due to primary tumour was reported in 4/7 studies and ranged from 0%-3.7%; the pooled proportion of patients experiencing bleeding due to primary tumour was 3% (95% CI 0.95% - 6%).

2 studies reported on peritonitis and fistula due to the unresected tumour; one study (Tebbutt et al, 2003) reported that 6.1% of patients developed peritonitis or fistulae. It appears that the second study reported that no patients developed fistulae or peritonitis thought this is somewhat unclear from the text.

3/7 studies reported on patients in whom curative resection of primary tumour and metastases was attempted as a result of downstaging by chemotherapy; 1 study (Benoist et al, 2005) reported that curative resection was successful in 6/13 patients with 3 undergoing one-stage resection and 3 undergoing staged resection. The success rate for resection was not reported in the second study (Muratore et al) and in the third study only as single patient underwent curative resection (Sarela et al, 2001).

Benoist et al (2005) reported that 37% of patients initially treated with chemotherapy experienced grade 3-4 toxicities.

Outcome measures of resection of the primary tumour as initial therapy
5/7 studies described the results of primary tumour resection with postoperative morbidity described in 4 studies.
Postoperative mortality ranged from 0% to 4.6%; meta-analysis of the four studies showed a mortality of 2.7% (95% CI 1.1% - 5%).
Postoperative morbidity ranged from 18.8% to 47% though these results included complications of variable severity; major complications included obstruction, haemorrhage and sepsis and pooled analysis resulted in 11.8% (95% CI 4.4% - 22%) of patients experiencing major complications after surgery.

A total of 3 studies reported minor complications with the most common complications being wound infection (5.5%-10.6%) and urinary tract infection (2.4%-6.1%); pooled analysis resulted in an overall 20.6% (95% CI 15.6%-26%) of patients who had minor complications following surgery.

Survival
Median survival was addressed in 6/7 studies and for patients that underwent resection of the primary tumour median survival range from 14-23 months versus 8.2-22 months for patients treated with chemotherapy as first treatment.
From two studies, a statistically significant difference in survival was reported between resected and unresected patients. One study described a median survival of 8.2 months in the group initially treated by chemotherapy versus 14 months for patients treated with resection though multivariate analysis revealed that performance status and a presence of peritoneal or omental metastases were significant factors affecting survival and that resection status of the primary tumour was not significantly associated with survival.
The second study reported a median survival of 16 months for patients initially treated with resection versus 9 months for patients treated with chemotherapy, though again on univariate analysis, resection status was not significantly associated with survival while number of distant sites involved, metastatic disease confined to the liver and volume of hepatic replacement by the tumour were significant factors.

General comments
It is not entirely clear whether this study will provide anything to add to the current evidence base as it is not fully clear what the population and intervention of interest are. It appears that giving chemotherapy as initial treatment was not done with the intention of resecting the primary tumour though in some cases, curative resection was attempted if the tumour/metastases were downstaged.

References:

Scoggins CR et al (1999) Nonoperative management of primary colorectal cancer in patients with stage IV disease *Annals of Surgical Ocology* 6;651-657

Sarela AI et al (2001) Non-operative management of the primary tumour in patients with incurable stage IV colorectal cancer *British Journal of Surgery* 88;1352-1356

Tebbutt NC et al (2003) Intestinal complications after chemotherapy for patients with unresected primary colorectal cancer and synchronous metastases *Gut* 52;568-573

Ruo L et al (2003) Elective bowel resection for incurable stage IV colorectal cancer: prognostic variables for asymptomatic patients *Journal of the American College of Surgeons* 196;722-728

Michel P et al (2004) Colorectal cancer with non-resectable synchronous metastases: should primary tumour be resected? *Gastrointestinal Clinical Biology* 28;434-437

Benoist S et al (2005) Treatment strategy for patients with colorectal cancer and synchronous irresectable liver metastases *British Journal of Surgery* 92;1155-1160

Muratore A et al (2007) Asymptomatic colorectal cancer with unresectable liver metastases: immediate colorectal resection or up-front systemic chemotherapy? *Annals of Surgical Oncology* 14;766-770

4.2. Imaging Hepatic Metastases

4.2.1. In a patient with colorectal cancer metastasised to the liver which imaging modality(s) most accurately determine the number and extent of metastases pre-operatively?

Short Summary

There were two meta-analyses available comparing PET to MRI and CT (Bipat et al 2005) and PET to CT (Wiering et al 2005). In both studies per patient analysis showed that PET has higher sensitivity than MRI and CT but this was not the case on a per lesion basis with sensitivities for al modalities comparable. Gadolinium contrast-enhanced MRI and SPIO-contrast enhanced MRI were better than non-enhanced MRI and CT and this was more manifest in the subgroup analysis that looked at specific sizes of lesions which showed that MRI had a better sensitivity in detecting the micrometastases of <1cm.

Since 2005 a number of studies have been carried out continuing comparing MRI and CT. In the recent 5 years PET has been fused with CT and there are now studies looking at the performance of PET/CT and comparing it to MRI, PET alone, and CT alone.

It appears that in a per-patient analysis PET/CT has consistently higher sensitivity in all the studies compared to MRI and CT with pooled analysis showing a summary sensitivity and accuracy for PET/CT of 94% for both compared with MRI (80% and 91% respectively) and CT (87% for both).

On per lesion analysis MRI appeared to be the modality showing higher sensitivities across individual studiescompared to CT and Pooled data shows comparable results with MRI having a combined sensitivity of 88% and accuracy of 87%, CT a sensitivity of 74% and accuracy of 78% and PET/CT a sensitivity of 79% and accuracy of 97%.

A number of studies carried out subgroup analyses looking at how the modalities diagnose lesions of particular sizes. Bartolozzi et al (2004), Bhattarajha et al (2004) and Wiering et al (2007) all found MRI has better sensitivity at picking up the smaller lesions <1cm compared to PET/CT and CT. The majority of lesions missed by PET/CT were micrometastases of <1cm.

Chua et al (2007) and Liu et al (2007) reported change in management as an outcome however both studies include the diagnosis of extrahepatic in their analysis. It was not possible to extract data for this relating to hepatic metastases only.

Updated Evidence

A systematic review and meta-analysis of data comparing the diagnostic accuracy of different imaging modalities for the diagnosis of colorectal liver metastases was available (Floriani et al, 2010). Pairwise comparisons suggested that MRI performed significantly better than CT for the detection of metastatic lesions (sensitivity OR: 0.66 (95%CI: 0.55-0.80) P<0.0001) but the data were highly heterogeneous. The superiority of MRI differed between the various CT techniques in per lesion analysis which probably accounts for the observed heterogeneity. MRI was also better than CT in a per patient analysis (sensitivity OR: 0.69 (95%CI: 0.47-0.99) P=0.05) which is a more reliable indicator. FDG-PET and ultrasound performed similarly to CT although significant between studies heterogeneity may well have confounded these results.

From a prospective case series of 34 patients (Mainenti et al, 2010) comparing MRI, PET/CT and CT, ROC analysis showed no significant difference between Gd and SPIO enhanced MRI and showed that both forms of MRI performed significantly better than all other modalities (p<0.05).
For lesions ≥10mm, the performance of PET/CT was significantly better than contrast enhanced CT (p<0.05).
No significant difference was observed between the modalities when considering the groups of lesion <10mm.

Review Protocol

Population	Intervention	Comparison	Outcomes
Patients with colorectal cancer metastasised to the liver	• PET-CT • Contrast enhanced MRI • laparoscopic ultrasound	• Contrast enhanced CT • Each other	• Sensitivity • Specificity

Following a systematic search of relevant data sources (see appendix .1), the information specialist created a database of potentially relevant studies. All titles and abstracts were sifted by a single reviewer. Queries about inclusion were clarified by the GDG topic subgroup. The full studies were then obtained and reviewed and relevant studies were included in the final evidence review.

All update searches were sifted by a single reviewer and the list of potentially relevant studies was also checked for irrelevant studies by the GDG subgroup. Only studies which all subgroup members were in agreement were excluded. The remaining studies were obtained and reviewed with relevant studies included in the final evidence review.

It was felt by GDG members that high level (randomised trials) should be considered in the first instance if not available then look to lower level (case series studies).

A number of date limits for searches were provided by GDG members in order to more efficiently target searches:
PET-CT – 2000 (this is when it came into use)
Contrast enhanced CT – 1995 (the advent of helical CT)
Contrast enhanced MRI – 1997 (marked an improvement in technology and contrast agents)

Other issues considered by the GDG included whether to look at determining operability form the imaging of the metastatic disease and whether consideration needed to be given to the incidence of metastatic disease at other sites, what would be the best method of detecting this e.g. with a PET scan or whether there are certain factors which imply a worse prognosis therefore needing additional scanning?

It was felt that this topic potentially posed two quite different questions: which investigation(s) offer the most accurate depiction or the anatomical relationships of known metastases for the surgeon or interventional radiologist to debate what is technically feasible - and secondly, which investigation(s) provide the most accurate assessment of the size / number of metastases?

These sound like similar questions, but there is an important distinction, with the answer to the first question likely to be determined by the inherent spatial resolution of the imaging techniques (ability to display small abnormalities) and the tissue contrast between metastases and normal liver. The two factors are interdependent - the human eye can only detect very small objects if they are presented with high contrast, while even quite large objects can escape detection if there is very little contrast with the background.

As a rule of thumb, both CT and US tend to suffer from a lack of liver lesion contrast but have high spatial resolution (1-2mm), while MR has much higher contrast but poorer (theoretical) spatial resolution (perhaps 5mm). The topic is interested in evidence which is right at the leading edge of imaging capabilities, therefore the searches can be restricted to spiral / helical CT; MR studies after about 1995 and US studies no earlier than 1990. US scanning augmented by microbubble contrast agents may also figure, though it was felt that the evidence will be thin and it's not a widely used technique.

There was some brief discussion on intraoperative US at the last meeting (this is where the surgeon or a radiologist applies a high-frequency US probe directly to the liver during surgery to detect lesions which may not have been detected preoperatively and give details of the precise relationships of tumours to the major hepatic vessels). It was suggested that this practice is essentially obsolete, and if the thrust is to give guidance on preoperative assessment / patient selection, then clearly intraoperative US would be inappropriate to consider.

Reasons for excluding studies:
Expert Reviews
Foreign Language with no translation
Guidelines not providing evidence base
2x2 tables not presented
Data unable to be extracted
Studies not relevant to PICO
Studies published prior to 2005
Duplicate data

Quality of the included studies
Systematic review of RCTs (n =0)
Systematic review of combined study designs
(n =3)
Randomized controlled trial (n =2)
Prospective cross sectional study (n =16)
Retrospective cohort study (n=5)
Case Series Studies (n = 0)

287 (+44) possibly relevant papers identified

→

193 (+35) papers excluded based on title & abstract
2 papers could not be obtained

↓

92(+9) papers obtained for appraisal

→

68 (+7) papers excluded

↓

24 (+2) papers included in evidence table
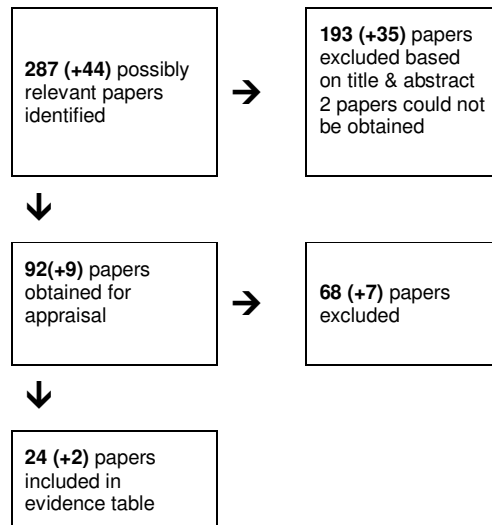
Volume of evidence

There are 2 systematic reviews of cohort studies (Bipat 2005, Wiering 2005); both studies have been well designed and conducted according to the NICE quality checklist . Bipat et al (2005) applied the QUADAS checklist to assess the quality of included studies. Wiering et al (2005) applied a weighted quality assessment checklist which had been devised by the authors. Both reviews comment on the poor quality of the reporting of diagnostic accuracy studies as well as the flaws in study design.

There are 2 randomised controlled trials in the literature (Kim 2006 and Ruers 2009) both of good quality according to the NICE quality checklist.

There are 20 cohort studies available of which15 were prospective and 5 were retrospective with population ranging from 15 patients to 467.

For the purpose of this review the QUADAS checklist was used to extract the relevant study design characteristics and to perform quality assessment of the studies included. (as appears in the NICE guidelines manual p196-266).

The main QUADAS points where many studies were found to be sub optimal are as follows:
- 64% of the included studies did not report the period between the time the reference test was performed (histology or follow up imaging for those that did not have surgery) and the index test was carried out (14/22 studies scored 'unclear' to question 4 of the QUADAS). These studies may have incorporated disease progression bias.
- 50% of included studies did not give a description of the execution of the reference standard (11/22 studies scored 'no' to question 9 of the QUADAS). There may therefore be heterogeneity that has not been accounted for.
- 77% of included studies did not report on whether the interpretation of the reference standard results was carried out without knowing the result of the index test (blinding). An additional 14% of studies reported that they did not have blinding. (17/22 studies scored 'unclear' and 3/22 studies scored 'no' in response to question 11 of the QUADAS). There may be review bias as a result.

- In 100 % of the studies there were more than 1 reference tests. The participants received one of two reference tests depending on the result of their index test (22/22 studies scored no in response to question 6 of QUADAS). Patients that proceeded with hepatic resection have the lesion verified by histology. Patients that have a lesion thought to be benign do not go to surgery but are followed up with imaging 3 or 6 months later. The reference standards differ in their definition of liver metastasis. Histopathology has a precise definition and is the gold standard compared to repeat imaging, which bases definitions on the change in size of a lesion. This may lead to differential verification bias.

It is also important to note that the analysis of the data in the studies included both 'per patient' and 'per lesion analyses'. Not all studies reported on both. Per lesion sensitivies are more impressive for MRI. Per lesion analysis on its own is potentially biased. Lesions in each patient are a cluster of observations. Each lesion is not always an independent observation from another lesion if a patient has multiple lesions. This introduces bias to the results.

Applicability
All included studies were directly applicable to the population of interest having looked at data relating to patients both females and male, with a confirmed diagnosis of colorectal cancer only, and either confirmed or lesions suspicious of liver metastases.

Studies that reported on diagnostic accuracy of the modalities of interest but did not distinguish between liver metastases from colorectal cancer and other cancers were excluded.

The age of the population, their co-morbidities, the referral patterns, the diagnostic setting are also similar between the studies and the population of interest.

None of the studies have excluded patients that have had prior chemotherapy but some have performed subgroup analysis.

Consistency
Studies which include patients who have received chemotherapy without performing subgroup analysis may introduce clinical heterogeneity and bias as lesions that are responding to chemotherapy treatment do not appear as well defined on PET scanning. The metabolism of the lesion is changed and this results in lesser or no appearance on the PET scan (Strauss 2007). This could lead to higher number of false negatives for PET-CT whereas chemotherapy does not affect CT or MRI. Some studies including patients receiving chemotherapy do subgroup analysis to investigate whether there is any effect, though this is not the case for all included studies.

The lesions patients present with are very heterogeneous; some are cystic others are solid, some are very small (micrometastases <1cm) and others are larger. Some studies report on accuracy of the modalities separately for two or three groups of different sized lesions.

The imaging modalities are heterogeneous in their technologies both in principle of how they make the diagnosis and in how they are developed over the years. Slice thickness, amount of contrast used, strength of magnetic field applied are some of the characteristics that have changes over the years. The two meta-analyses presented in the evidence have performed subgroup analyses looking at these features separately (Wiering et al, 2005 and Bipat et al, 2005).

The diagnosis is based on different radiologists across all the studies reading the images. They have different levels of experience and different abilities.

Other factors
Selection bias
For this review studies that were published prior to 2005 have been excluded as two high quality meta-analyses that summarise the data prior to 2005 were identified in the literature. This may introduce a selection bias to the review. However heterogeneity may be reduced looking at studies that compare modalities of more recent technological advancement.

Evidence Statement

Per patient analysis
12 studies reported CT data per patient, 9 studies reported MRI data per patient, 7 studies reported PET/CT data per patient.

CT data
The sensitivity of CT ranged from 47% to 100%. The PPV for CT ranged from 86%-100%. Specificity for CT ranged from 0 to 100%. The accuracy for CT ranged from 50% to 98%.

Though there has been no weighting to the following summary values the overall sensitivity and PPV for CT from the 12 studies as calculated from a summary 2x2 table is

Total TP=770
Total FP=41
Total FN=112
Total TN=266
Total = 1189
SUMMARY SENSITIVITY FOR CT = 770 / 882 = 87%
SUMMARY PPV FOR CT = 770 / 770+41 = 770 / 811 = 95%
SUMMARY ACCURACY = 770 + 266 / 1189 = 87%

MRI data
The sensitivity of MRI ranged from 50% to 100%. Specificity ranged from 0% to 100%. In a number of studies specificity estimates are not possible as there are no benign lesions identified at all in the population. PPV ranged from 91% to 100%. The accuracy for MRI ranged from 48% to 100%.
Though there has been no weighting to the following summary values the overall sensitivity and PPV for MRI from the 9 studies as calculated from a summary 2x2 table is

Total TP=336
Total FP=13
Total FN=86
Total TN=142
Total = 577

SUMMARY SENSITIVITY FOR MRI = 336 / 336 + 86 = 80%
SUMMARY PPV FOR MRI = 336 / 336 +13 = 96%
SUMMARY ACCURACY FOR MRI = 336+142 / 577 = 91%

PET/CT data
The sensitivity for PET/CT ranged from 91% to 100%. Specificity ranged from 60% to 100%. In a number of studies specificity estimates are not possible as there are no benign lesions identified at all in the population. The PPV tanged from 93% to 100%. Accuracy ranged from 91%-100%
Though there has been no weighting to the following summary values the overall sensitivity and PPV for PET/CT from the 6 studies as calculated from a summary 2x2 table is

Total TP=273
Total FP=8
Total FN=19
Total TN=153
Total = 453

SUMMARY SENSITIVITY FOR PET/CT = 273 /273+19 = 94%
SUMMARY PPV FOR PET/CT = 273 / 273+19 = 94%
SUMMARY ACCURACY FOR PET/CT = 273+153/453 = 94%

Per lesion analysis
7 studies reported CT data per lesion, 12 studies reported MRI data per lesion, 6 studies reported PET/CT data per lesion.

CT data

The sensitivity of CT ranged from 67% to 97%. The PPV for CT ranged from 63%-100%. Specificity for CT ranged from 0 to 67%. In a number of studies specificity estimates are not possible as there are no benign lesions identified at all in the population. This is a possibility in a population that is so highly selective for suspicion of malignancy. The accuracy for CT ranged from 64% to 84%.

Though there has been no weighting to the following summary values the overall sensitivity and PPV for CT from the 7 studies as calculated from a summary 2x2 table is

Total TP=704
Total FP=78
Total FN=252
Total TN=114
Total = 1048

SUMMARY SENSITIVITY FOR CT = 704 / 956 = 74%
SUMMARY PPV FOR CT = 704 / 792 = 90%
SUMMARY ACCURACY FOR CT = 704+114 / 1048 = 78%

MRI data

The sensitivity of MRI ranged from 81% to 100%. Specificity ranged from 59% to 100%. In a number of studies specificity estimates are not possible as there are no benign lesions identified at all in the population. PPV ranged from 81% to 100%. The accuracy for MRI ranged from 71% to 100%.
Though there has been no weighting to the following summary values the overall sensitivity and PPV for MRI from the 12 studies as calculated from a summary 2x2 table is

Total TP=1139
Total FP=45
Total FN=158
Total TN=229
Total = 1571

SUMMARY SENSITIVITY FOR MRI = 1139 / 158 = 88%
SUMMARY PPV FOR MRI = 704 / 792 = 96%
SUMMARY ACCURACY FOR MRI = 1139+229 / 1571 = 87%

PET/CT data

The sensitivity for PET/CT ranged from 61% to 100%. Specificity ranged from 60% to 100%. In a number of studies specificity estimates are not possible as there are no benign lesions identified at all in the population. The PPV tanged from 94% to 100%. Accuracy ranged from 61%-100%
Though there has been no weighting to the following summary values the overall sensitivity and PPV for PET/CT from the 6 studies as calculated from a summary 2x2 table is

Total TP=410
Total FP=5
Total FN=112
Total TN=96
Total = 523

SUMMARY SENSITIVITY FOR PET/CT = 410 / 522 = 79%
SUMMARY PPV FOR PET/CT = 410 / 415 = 99%
SUMMARY ACCURACY FOR PET/CT = 410+96 / 523 = 97%

Study	TP	FP	FN	TN	Sensitivity	Specificity
CT Bartolozzi	91	3	37	0	0.71 [0.62, 0.79]	0.00 [0.00, 0.71]
CT Liu	6	0	3	0	0.67 [0.30, 0.93]	Not estimable
CT Nanashima	92	18	3	15	0.97 [0.91, 0.99]	0.45 [0.28, 0.64]
CT Rappeport	43	25	28	50	0.61 [0.48, 0.72]	0.67 [0.55, 0.77]
CT Regge	137	26	54	48	0.72 [0.65, 0.78]	0.65 [0.53, 0.76]
CT Truant	78	3	21	1	0.79 [0.69, 0.86]	0.25 [0.01, 0.81]
CT Wiering	257	3	106	0	0.71 [0.66, 0.75]	0.00 [0.00, 0.71]
MRI Bartolozzi	92	2	36	0	0.72 [0.63, 0.79]	0.00 [0.00, 0.84]
MRI EPI Conegrahts	77	0	0	0	1.00 [0.95, 1.00]	Not estimable
MRI Gad Cantwell	98	0	2	10	0.98 [0.93, 1.00]	1.00 [0.69, 1.00]
MRI MnDPDP Bartolozzi	115	2	13	0	0.90 [0.83, 0.94]	0.00 [0.00, 0.84]
MRI MnDPDP Kong	163	0	2	6	0.99 [0.96, 1.00]	1.00 [0.54, 1.00]
MRI MnDPDP Regge	158	7	33	67	0.83 [0.77, 0.88]	0.91 [0.81, 0.96]
MRI MT Kim	37	2	1	0	0.97 [0.86, 1.00]	0.00 [0.00, 0.84]
MRI Regge	143	6	48	68	0.75 [0.68, 0.81]	0.92 [0.83, 0.97]
MRI SPIO Conegrahts	69	0	8	0	0.90 [0.81, 0.95]	Not estimable
MRI SPIO Kim	31	0	1	0	0.97 [0.84, 1.00]	Not estimable
MRI SPIO Nanashima	98	12	1	17	0.99 [0.95, 1.00]	0.59 [0.39, 0.76]
MRI SPIO Rappeport	58	14	13	61	0.82 [0.71, 0.90]	0.81 [0.71, 0.89]
PETCT Cantwell	85	0	15	10	0.85 [0.76, 0.91]	1.00 [0.69, 1.00]
PETCT Conegrahts	47	0	30	0	0.61 [0.49, 0.72]	Not estimable
PETCT Kong	155	0	10	6	0.94 [0.89, 0.97]	1.00 [0.54, 1.00]
PETCT Liu	9	0	0	0	1.00 [0.66, 1.00]	Not estimable
PETCT ne Cantwell	67	4	33	6	0.67 [0.57, 0.76]	0.60 [0.26, 0.88]
PETCT Rappeport	47	1	24	74	0.66 [0.54, 0.77]	0.99 [0.93, 1.00]

Figure 4.6: PER LESION SUMMARY ANALYSIS.

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
CT Akiyoshi	22	1	0	42	1.00 [0.85, 1.00]	0.98 [0.88, 1.00]		
CT Arulampalam	8	1	9	10	0.47 [0.23, 0.72]	0.91 [0.59, 1.00]		
CT Ashraf	16	2	2	32	0.89 [0.65, 0.99]	0.94 [0.80, 0.99]		
CT Bartolozzi	22	3	19	0	0.54 [0.37, 0.69]	0.00 [0.00, 0.71]		
CT Bhattarhaja	73	12	9	6	0.89 [0.80, 0.95]	0.33 [0.13, 0.59]		
CT Chua	61	6	6	2	0.91 [0.82, 0.97]	0.25 [0.03, 0.65]		
CT Liu	4	0	1	10	0.80 [0.28, 0.99]	1.00 [0.69, 1.00]		
CT Orlacchio	336	6	30	95	0.92 [0.89, 0.94]	0.94 [0.88, 0.98]		
CT Rappeport	28	2	0	1	1.00 [0.88, 1.00]	0.33 [0.01, 0.91]		
CT Regge	30	2	32	61	0.48 [0.35, 0.61]	0.97 [0.89, 1.00]		
CT Selzner	63	3	3	7	0.95 [0.87, 0.99]	0.70 [0.35, 0.93]		
CT Wiering	127	3	1	0	0.99 [0.96, 1.00]	0.00 [0.00, 0.71]		
MRI Bartolozzi	21	2	21	0	0.50 [0.34, 0.66]	0.00 [0.00, 0.84]		
MRI EPI Conegrahts	24	0	0	0	1.00 [0.86, 1.00]	Not estimable		
MRI Gad Bhattarhaja	69	7	6	13	0.92 [0.83, 0.97]	0.65 [0.41, 0.85]		
MRI MnDPDP Bartolozzi	33	2	9	0	0.79 [0.63, 0.90]	0.00 [0.00, 0.84]		
MRI MnDPDP Kong	60	0	1	4	0.98 [0.91, 1.00]	1.00 [0.40, 1.00]		
MRI MnDPDP Regge	41	1	21	62	0.66 [0.53, 0.78]	0.98 [0.91, 1.00]		
MRI Regge	36	1	26	62	0.58 [0.45, 0.70]	0.98 [0.91, 1.00]		
MRI SPIO Conegrahts	24	0	0	0	1.00 [0.86, 1.00]	Not estimable		
MRI SPIO Rappeport	28	0	2	1	0.93 [0.78, 0.99]	1.00 [0.03, 1.00]		
PETCT Chua	63	2	4	6	0.94 [0.85, 0.98]	0.75 [0.35, 0.97]		
PETCT Conegrahts	23	0	1	0	0.96 [0.79, 1.00]	Not estimable		
PETCT Kong	60	0	1	4	0.98 [0.91, 1.00]	1.00 [0.40, 1.00]		
PETCT Liu	5	0	0	10	1.00 [0.48, 1.00]	1.00 [0.69, 1.00]		
PETCT Orlacchio	336	3	7	121	0.98 [0.96, 0.99]	0.98 [0.93, 0.99]		
PETCT Rappeport	26	2	0	3	1.00 [0.87, 1.00]	0.60 [0.15, 0.95]		
PETCT Selzner	60	1	6	9	0.91 [0.81, 0.97]	0.90 [0.55, 1.00]		

Figure 4.7: PER PATIENT SUMMARY ANALYSIS

Updated Evidence

Floriani *et al* (2010) presented a systematic review and meta-analysis of data on the diagnostic accuracy of different imaging modalities for the diagnosis of colorectal liver metastases. The number of patients exceeded 1,774. The authors noted that high likelihood ratios indicated that all imaging modalities performed well. Pairwise comparisons suggested that MRI performed significantly better than CT for the detection of metastatic lesions (sensitivity OR: 0.66 (95%CI: 0.55-0.80) P<0.0001) but the data were highly heterogeneous. The superiority of MRI differed between the various CT techniques in per lesion analysis which probably accounts for the observed heterogeneity. MRI was also better than CT in a per patient analysis (sensitivity OR: 0.69 (95%CI: 0.47-0.99) P=0.05) which is a more reliable indicator. FDG-PET and ultrasound performed similarly to CT although significant between studies heterogeneity may well have confounded these results.

Mainenti et al (2010) conducted a prospective c ase series study which compared contrast enhanced ultrasound (CEUS), mulidetector CT (MDCT), 1.5T MRI with godlinium chelate and superparamagnetic iron oxide (SPIO) contrast agents and PET-CT in 34 patients.

ROC analysis showed no significant difference between Gd and SPIO enhanced MRI and showed that both forms of MRI performed significantly better than all other modalities (p<0.05).

For lesions ≥10mm, the performance of PET/CT was significantly better than contrast enhanced CT (p<0.05).

No significant difference was observed between the modalities when considering the groups of lesion <10mm.

On a per patient basis, no significant difference was observed between the modalities.

On a per patients basis, PET/CT correctly identified 100% of patients with liver metastasis as compared with 83% for all other modalities (5/6 patients).

Gd and SPIO enhanced MRI showed higher sensitivities than other modalities; both identified 81% of metastatic lesions (13/16) including all lesions ≥10mm and 5/8 lesions <10mm.

References

Akiyoshi T, Oya M, Fujimoto Y, Kuroyanagi H, Ueno M, Yamaguchi T, Koyama M, Tanaka H, Matsueda K, Muto T. Comparison of preoperative whole-body positron emission tomography with MDCT in patients with primary colorectal cancer. Colorectal Disease 2009; 11:464-469

Arulampalam THA. FDG-PET for the pre-operative evaluation of colorectal liver metastases. Eur.J.Surg.Oncol. 2004; 30:286-291

Ashraf K. Colorectal carcinoma, preoperative evaluation by spiral computed tomography. Journal of the Pakistan Medical Association 2006; 56:149-153

Bartolozzi C, Donati F, Cioni D, Procacci C, Morana G, Chiesa A, Grazioli L, Cittadini G, Cittadini G, Giovagnoni A, Gandini G, Maass J, Lencioni R. Detection of colorectal liver metastases: a prospective multicenter trial comparing unenhanced MRI, MnDPDP-enhanced MRI, and spiral CT. Eur.Radiol. 2004; 14:14-20

Bhattaharjya S. B. Prospective study of contrast-enhanced computed tomography, computed tomography during arterioportography, and magnetic resonance imaging for staging colorectal liver metastases for liver resection. Br.J.Surg. 2004; 91:1361-1369

Bipat S, van Leeuwen MS, Comans EF, Pijl ME, Bossuyt PM, Zwinderman AH, Stoker J. Colorectal liver metastases: CT, MR imaging, and PET for diagnosis. Meta-analysis (DARE structured abstract). Radiology 2005; 237:123-131

Cantwell CP, Setty BN, Holalkere N, Sahani DV, Fischman AJ, Blake MA. Liver Lesion Detection and Characterization in Patients With Colorectal Cancer: A Comparison of Low Radiation Dose Non-enhanced PET/CT, Contrast-enhanced PET/CT, and Liver MRI. J.Comput.Assist.Tomogr. 2008; 32:738-744

Chua SC, Groves AM, Kayani I, Menezes L, Gacinovic S, Du Y, Bomanji JB, Ell PJ. The impact of F-18-FDG PET/CT in patients with liver metastases. European Journal of Nuclear Medicine and Molecular Imaging 2007; 34:1906-1914

Coenegrachts K, De GF, ter BL, Walgraeve N, Bipat S, Stoker J, Rigauts H. Comparison of MRI (including SS SE-EPI and SPIO-enhanced MRI) and FDG-PET/CT for the detection of colorectal liver metastases. Eur.Radiol. 2009; 19:370-379

Floriani I, Torri V, Rulli E, Garavaglia D, Compagnoni A, Salvolini L and Giovagnoni A (2010)- Performance of imaging modalities in diagnosis of liver metastases from colorectal cancer: a systematic review and meta-analysis. *J. Magn. Res. Imaging* **31 (1):**19-31.

Kim HJ, Kim KW, Byun JH, Won HJ, Shin YM, Kim PN, Lee MS, Lee MG. Comparison of mangafodipir trisodium- and ferucarbotran-enhanced MRI for detection and characterization of hepatic metastases in colorectal cancer patients. AJR.American journal of roentgenology. 2006; 186:1059-1066

Koh DM, Brown G, Riddell AM, Scurr E, Collins DJ, Allen SD, Chau I, Cunningham D, Desouza NM, Leach MO, Husband JE. Detection of colorectal hepatic metastases using MnDPDP MR imaging and diffusion-weighted imaging (DWI) alone and in combination. Eur.Radiol. 2008; 18:903-910

Kong G, Jackson C, Koh DM, Lewington V, Sharma B, Brown G, Cunningham D, Cook GJR. The use of F-18-FDG PET/CT in colorectal liver metastases-comparison with CT and liver MRI. European Journal of Nuclear Medicine and Molecular Imaging 2008; 35:1323-1329

Liu YN, Huang MX, An Q, Wei JM. The Impact of PET/CT on Therapeutic Strategy of Patients with Colorectal Cancer Metastasis. Hepatogastroenterology. 2009; 56:968-970

Mainenti P, Mancini M, Mainolfi et al (2010) Detection of colorectal liver metastases: prospective comparison of contrast enhanced US, multidetector CT, PET/CT and 1.5 Tesla MR with extracellular and reticulo-endothelial cell specific contrast agents *Abdominal Imaging* 35(5):511-521

Nanashima A, Taheshita H, Sawai T, Sumida Y, Abo T, Tanaka K, Nonaka T, Sengyoku H, Hidaka S, Yasutake T, Nagayasu T. Preoperative Assessment of Liver Metastasis Originating from Colorectal Carcinoma: Is Super Paramagnetic Iron Oxide Particles-Magnetic Resonance Imaging (SPIO-MRI) Useful for Screening? Hepatogastroenterology. 2008; 55:1750-1753

Orlacchio A, Schillaci O, Fusco N, Broccoli P, Maurici M, Yamgoue M, Danieli R, D'Urso S, Simonetti G. Role of PET/CT in the detection of liver metastases from colorectal cancer. Radiol.Med.(Torino). 2009; 114:571-585

Rappeport ED, Loft A, Berthelsen AK, von der Recke P, Larsen PN, Mogensen AM, Wettergren A, Rasmussen A, Hillingsoe J, Kirkegaard P, Thomsen C. Contrast-enhanced FDG-PET/CT vs. SPIO-enhanced MRI vs. FDG-PET vs. CT in patients with liver metastases from colorectal cancer: A prospective study with intraoperative confirmation. Acta Radiol. 2007; 48:369-378

Regge D, Campanella D, Anselmetti GC, Cirillo S, Gallo TM, Muratore A, Capussotti L, Galatola G, Floriani I, Aglietta M. Diagnostic accuracy of portal-phase CT and MRI with mangafodipir trisodium in detecting liver metastases from colorectal carcinoma. Clin.Radiol. 2006; 61:338-347

Ruers TJM. Improved selection of patients for hepatic surgery of colorectal liver metastases with 18F-FDG PET: A randomized study. J.Nucl.Med. 2009; 50:1036-1041

Schwartz L, Brody L, Brown K, Covey A, Tuorto S, Mazumdar M, Riedel E, Jarnagin W, Getrajdman G, Fong Y. Prospective, blinded comparison of helical CT and CT arterial portography in the assessment of hepatic metastasis from colorectal carcinoma. World J.Surg. 2006; 30:1892-1901

Selzner MK, Hany TF, Wildbrett P, McCormack L, Kadry Z, Clavien PA. Does the novel PET/CT imaging modality impact on the treatment of patients with metastatic colorectal cancer of the liver? Ann.Surg. 2004; 240:1027-1036

Strauss LG, mitrakopoulou-Strauss A. Can PET-CT with FDG replace contrast enhanced CT for imaging of liver metastases? European Journal of Nuclear Medicine and Molecular Imaging 2007; 34:1902-1905

Truant S, Huglo D, Hebbar M, Ernst O, Steinling M, Pruvot FR. Prospective evaluation of the impact of 18Ffluoro 2 deoxy D glucose positron emission tomography of resectable colorectal liver metastases. The British journal of surgery 2005; 92:362-369

Vidiri A, Carpanese L, D'Annibale M, Caterino M, Cosimelli M, Zeuli M, David V, Crecco M. Evaluation of hepatic metastases from colorectal carcinoma with MR-superparamagnetic iron oxide. Journal of Experimental & Clinical Cancer Research 2004; 23:53-60

Wiering B, Ruers TJM, Krabbe PFM, Dekker HM, Oyen WJG. Comparison of multiphase CT, FDG-PET and intra-operative ultrasound in patients with colorectal liver metastases selected for surgery. Ann.Surg.Oncol. 2007; 14:818-826

Evidence Tables

Citation: Bipat S, van Leeuwen MS, Comans EF, Pijl ME, Bossuyt PM, Zwinderman AH, Stoker J. Colorectal liver metastases: CT, MR imaging, and PET for diagnosis. Meta-analysis (DARE structured abstract). Radiology 2005; 237:123-131

Design: systematic review and meta-analysis (search ended Jan 2004)
Country: the Netherlands

Aim: to perform a meta-analysis to obtain sensitivity estimates of CT, MRI, and, FDG-PET for detection of colorectal liver metastases on per-patient and per-lesion basis.

Inclusion criteria
- Articles reported in English, French or German languages
- CT, MRI, or FDG-PET were used to identify and characterise colorectal liver metastases
- Histopathological analysis (performed at surgery, biopsy, and autopsy), intra-operative observation (manual palpation or intra-operative ultrasound), and/or follow up were used as the reference standard
- Sufficient data was present to calculate the true positive and false negative valuess for imaging techniques
- When data or subsets of data were presented in more than one article, the article with the most details or the most recent article was selected.

Exclusion criteria
- If results of different imaging modalities were presented in combination and could not be differentiated for performance assessment of an individual modality.
- Review articles, letters, comments, articles that did not include raw data were not selected.

Population
61 articles fulfilled the inclusion criteria, 3187 patients in total.
Patients with colorectal cancer
Age range 12-93, age mean 61
In 57 studies the gender was reported. 1733 patients were male and 1128 were female

Interventions
CT
- Non-helical (1915 patients), helical (621 patients)
- the range of section thickness was 5-12mm, median 10mm
- the range in the amount of iodine contrast given (reported in 23 studies) was 30-60g
MRI
- 1.0T (173 patients), 1.5T (391 patients)
- the range in section thickness was 5-10mm, median 10mm
- 15 studies used gadolinium as contrast or other liver specific agents such as SPIO
FDG-PET (1058 patients)

Outcomes
Sensitivity on per patient and per lesion basis

Results

Per patient analysis	Sensitivity%	95% confidence interval	P value
Non-helical CT	60.2%	55.7%-64.6%	
Helical CT	64.7%	30.4%-88.5%	
1.5 T MRI	75.8%	55.9%-88.6%	
FDG-PET	94.6%	92.5%-96.1%	PET had highest sensitivity compared to non-helical CT P<0.001 helical CT p=0.003 1.5T MRI p<0.001

Per lesion analysis			
Non helical CT	52.3%		Nonhelical CT had lowest sensitivity compared to Helical CT p<0.017 1.0 T MRI p<0.001 1.5 T MRI p<0.001 FDG PET p<0.003
Helical CT	63.8%		
1.0 T MRI	66.1%		
1.5 T MRI	64.4%		
FDG -PET	75.9%		

Subgroup analysis 1

Helical CT	Sensitivity	
<5mm section thickness	68.2%	
>5mm section thickness	69.1%	
<45g iodine contrast	61.4%	
>45 g iodine contrast	64.0%	
One phase CT	71.4%	
two phase CT	65.7%-not significant	
1.5T MRI		
Non-enhanced	59.8%	
Gadolinium enhanced	78.2%	Higher compared to non enhanced MRI p=0.19 helical CT <45g iodine p=0.02
SPIO enhanced	73.2%	Higher compared to non enhanced MRI p<0.001 helical CT <45g iodine p<0.001

Subgroup Analysis 2

Non helical CT	sensitivity	95% confidence interval	
Lesions<1cm	25.3	15.9-37.6	
Lesions >1cm	74.3	66.5-80.9	
Helical CT			
Lesions <1cm	23.1	7.0-54.7	
Lesions >1cm	73.5	62.2-82.4	
Non enhanced MRI			
Lesions <1cm	12.6	8.0-17.5	
Lesions >1cm	65.7	56.4-73.9	
Gadolinium MRI			
Lesions <1cm	11.6	9.5-14.2	
Lesions>1cm	68.8	61.9-75.0	
SPIO MRI			
Lesions <1cm	29.3	18.2-43.6	
Lesions >1cm	90.2	87.5-92.4	Higher p<0.001

General comments

Conclusion: PET has higher sensitivity on a per patient basis but not on a per lesion basis. On a per lesion basis the modalities are comparable but all significantly more accurate than non-helical CT. Subgroup analyses showed no difference between section thickness, amount of iodine, numbers of phases for helical CT. Gadolinium and SPIO MRI however were better compared to non-enhanced MRI and helical CT with 45g or less of iodine.

References of Included Studies (For systematic reviews):

Citation: Wiering B, Krabbe PF, Jager GJ, Oyen WJ, Ruers TJ. The impact of fluor-18-deoxyglucose-positron emission tomography in the management of colorectal liver metastases: a systematic review and metaanalysis (DARE structured abstract). Cancer 2005; 104:2658-2670

Design: systematic review and meta-analysis (search ended Dec 2003)
Country: The Netherlands

Aim:
- to identify how the descriptive statistics (sensitivity and specificity) for FDG-PET compare with those for CT in the assessment of both hepatic and extra-hepatic metastases.
- To identify whether FDG-PET has a significant impact on change in management.

Inclusion criteria
- Articles that included either a description of the impact of FDG-PET on clinical management or a description of imaging results for FDG-PET.

Exclusion criteria

Population
32 articles were included

Interventions
FDG-PET
CT

Outcomes
Sensitivity and specificity of CT scanning for extra and intra hepatic disease
Sensitivity and specificity of FDG-PET for extra and intra hepatic disease
Change in management for FDG-PET.

Results

Hepatic lesions	Sensitivity and 95% CI	Specificity and 95% CI
FDG PET	88.0% (CI 88%-98%)	96.1% (CI 70.4%-?)
CT	82.7% (CI 64.2%-88.6%)	84.1% (CI 68.2%-97.0%)
Extra hepatic lesions		
FDG PET	91% (CI 84.3%-96.2%)	95% (CI 71.4%-98.4%)
CT	60.9% (CI 44.4%-68.9%)	91.1% (CI 66.0%-92.8%)

Per lesion analysis

Hepatic lesions	Sensitivity	Specificity
FDG PET	79.9%	92.3%
CT	85.8%	88.3%
Extra hepatic lesions		
FDG PET	91.2%	98.4%
CT	55.3%	95.6%

Subgroup analysis (only the 6 high quality diagnostic studies)

In this analysis it is evident that FDG PET has value in the detection of extrahepatic disease compared to CT.

On a patient basis there is a >25% change in clinical management after FDG PET. This however is attributable mostly to the detection of extra hepatic disease, which generally precludes liver resection.

General comments
Despite omissions and quality issues in the diagnostic literature the pooled sensitivity of FDG PET indicates it has added value in the workup of patients with liver metastases.

Citation: Akiyoshi T, Oya M, Fujimoto Y, Kuroyanagi H, Ueno M, Yamaguchi T, Koyama M, Tanaka H, Matsueda K, Muto T. Comparison of preoperative whole-body positron emission tomography with MDCT in patients with primary colorectal cancer. Colorectal Disease 2009; 11:464-469

Design: retrospective
Country: Japan

Aim: to evaluate the additional value of FDG PET in comparison with multidetector row CT (MDCT) in patients with primary colorectal cancer

Inclusion criteria
65 patients with histologically proven colorectal cancer
patients with suspected liver or lymph node metastases
or patients with CEA >5ng/ml
or patients with low rectal cancer awaiting pre op chemoradiotherapy to check lateral lymph node metastases.

Exclusion criteria
Not specifically mentioned.

Population
65 patients (36 men, 29 women)
characteristics as in the inclusion criteria

Interventions
MDCT
FDG PET

Outcomes
Sensitivity, specificity, PPV, NPV, Accuracy

Results

	Liver mets +	Liver mets -	total
CT +	22	1	23
CT -	0	42	42
total	22	43	65

2x2 table

Sensitivity	100% (22/22) (CI 85%-100%)
Specificity	98% (42/43) (CI 88%-100%)
PPV	96% (22/23) (CI 78%-100%)
NPV	100% (42/42) (CI 92%-100%)
Accuracy	98% (64/65) (CI 92%-100%)

	Liver mets +	Liver mets -	total
FDG PET +	20	0	20
FDG PET -	2	43	45
total	22	43	65

Sensitivity	91% (20/22) (CI 91%-99%)
Specificity	100% (43/43) (CI 92%-100%)
PPV	100% (20/20) (CI 83%-100%)
NPV	96% (43/45) (CI 85%-99%)
Accuracy	97% (63/65) (CI 89%-100%)

FDG PET failed to identify liver metatases detected by MDCT in two patients.

General comments
CT appears sufficient for detection of metastases in the liver. The strength of PET is in the ability to screen for extraheaptic metastases and this is what leads to the change in management.

Citation: Arulampalam THA. FDG-PET for the pre-operative evaluation of colorectal liver metastases. Eur.J.Surg.Oncol. 2004; 30:286-291

Design: prospective
Country: Royal Free Hospital, UK

Aim: To assess the accuracy of routine whole body FDG PET in the pre operative staging of patients with colorectal liver metastases.

Inclusion criteria
Patients referred to a single surgeon for consideration for resection of colorectal liver metastases.
Sep 1999-May 2002
Patients had both FDG PET and spiral CT.

Exclusion criteria

Population
31 patients were studied. (median age 67, range 41-82), 15 male.
28 patients had a lesion on both PET and CT. This was considered the index lesion and only these patients were considered for assessment by resection. Follow up was for 21 months (range 5-33)
No loss to follow up.

Interventions
FDG PET
CT

Outcomes

Results
Accuracy of FDG PET and CT in detecting additional metastatic lesions in 28 patients with confirmed colorectal liver metastases.

	Liver mets +	Liver mets -	total
CT +	8	1	9
CT -	9	10	19
total	17	11	28

Sensitivity	47%
Specificity	91%
PPV	89%
NPV	53%

	Liver mets +	Liver mets -	total
FDG PET +	17	1	18
FDG PET -	0	10	10
total	17	11	28

Sensitivity	100%
Specificity	91%
PPV	94%
NPV	100%

11 patients were confirmed to have solitary liver met correctly demonstrated by both modalities.
10 patients were noted to have multifocal liver mets. All were correctly diagnosed by PET. CT was only able to identify multiple lesions in the 5 patients. In 4 of these patients PET showed lesions that were not amenable to surgery. In the 5th patient laparotomy was performed. The sencond PET lesion was not found but later identified on the follow up imaging at 3 months.

There was altered patient management in 12 patients (including the extrahepatic disease results) 39%.

General comments

FDG PET greatly adds to the decision making power of the surgical oncologist.

Citation: Ashraf K. Colorectal carcinoma, preoperative evaluation by spiral computed tomography. Journal of the Pakistan Medical Association 2006; 56:149-153

Design: cross sectional prospective
Country: Pakistan

Aim: to assess the capability of spiral CT in preoperative evaluation of colorectal carcinoma. (local spread, lymph node mets and liver mets).

Inclusion criteria
Patients with biopsy proven colorectal cancer undergoing surgery
All patients must have had the CT scan within 1 month prior to surgery

Exclusion criteria
Patients that had previous treatment for colorectal cancer or had concurrent disease process which could result in false reading of the CT scan

Population
52 patients (32 male, 20 female,)
mean age was 58, range 22-87

Interventions
Spiral CT scan, 7mm, with gastrograffin
1 radiologist reading the images
not blinded to the location of the primary tumour or the biopsy result.

Outcomes

Results

	Liver mets +	Liver mets -	total
CT+	16	2	18
CT -	2	32	34
total	18	34	52

Sensitivity	89% (CI 63.9%-98.1%)
Specificity	94% (CI 78.9%-99.0%)
PPV	89% (CI 63.9%-98.1%)
NPV	94% (CI 78.9%-99.0%)
Accuracy	92%

Citation: Bartolozzi C, Donati F, Cioni D, Procacci C, Morana G, Chiesa A, Grazioli L, Cittadini G, Cittadini G, Giovagnoni A, Gandini G, Maass J, Lencioni R. Detection of colorectal liver metastases: a prospective multicenter trial comparing unenhanced MRI, MnDPDP-enhanced MRI, and spiral CT. Eur.Radiol. 2004; 14:14-20

Design: prospective, multi-institutional trial
Country: Italy

Aim: to compare unenhanced MRI, MnDPDP-enhanced MRI and spiral CT in the detection of hepatic colorectal metastases.

Inclusion criteria
Adult patient with hepatic colorectal cancer metastasis
Patient scheduled for partial hepatectomy or itra operative radio frequency thermal ablation

Exclusion criteria
Pregnant or lactating woman
Severe biliary or renal insufficiency
Severe hepatic dysfunction (Child class C)
General contraindication to MRI
Inclusion in another study 7 days prior to enrollment

Population
44 consecutive patients with colorectal hepatic metastases were examined with all 3 above modalities.
3 blinded readers interpreted the images

Interventions
- unenhanced MRI
- MnDPDP-enhanced MRI
- spiral CT

Outcomes
primary endpoint
- Sensitivity

Secondary outcome
- Lesion conspicuity
- quality of lesion delineation
- confidence in diagnosis

Results

Per patient analysis

	Liver mets +	Liver mets -	total
CT+	22	3	25
CT -	19	0	19
total	41	3	44

Sensitivity	53.6%
Specificity	NA%
PPV	88.0%
NPV	NA%
Accuracy	50.0%

	Liver mets +	Liver mets -	total
MRI +	21	2	23
MRI -	21	0	21
total	42	2	44

Sensitivity	50.0%
Specificity	NA%
PPV	91.3%
NPV	NA%

Accuracy	47.7%	

	Liver mets +	Liver mets -	total
MnDPDP MRI +	33	2	35
MnDPDP MRI -	9	0	9
total	42	2	44

Sensitivity	78.6%
Specificity	NA%
PPV	94.2%
NPV	NA%
Accuracy	75.0%

Per lesion analysis

	Liver mets +	Liver mets -	total
CT+	91	3?	94
CT -	37	0?	37
total	128	3?	141

Sensitivity	71%
Specificity	%
PPV	%
NPV	%
Accuracy	%

	Liver mets +	Liver mets -	total
MRI +	92	2?	
MRI -	36	0?	
total	128	2?	

Sensitivity	72%
Specificity	%
PPV	%
NPV	%
Accuracy	%

	Liver mets +	Liver mets -	total
MnDPDP MRI +	115	2?	
MnDPDP MRI -	13	0?	
total	128	2	

Sensitivity	90%
Specificity	%
PPV	%
NPV	%
Accuracy	%

Lesion size	IOUS	CT	MRI	MnDPDP MRI
<10mm	47	18(38%)	24(51%)	39(83%)
10-20mm	31	28 (90%)	24 (77%)	31(100%)
>20mm	45	45 (100%)	44 (98%)	45(100%)
All	128 (*)	91(71%)	92 (72%)	115 (90%)

* 47+31+45 = 123 not 128. this is in all the text and tables. ??? either the 128 is a typo and all their calculations of sensitivities are based on the wrong number or one of the sums is a typo.

- MnDPDP MRI is more sensitive than both CT (P=0.0007) and unenhanced MRI (P<0.0001) in the per lesion analysis.
- In the very small lesions the sensitivity difference is even more manifest.
- In the per patient analysis MnDPDP MRI sensitivity was higher than CT (p=0.0023) and unenhanced MRI (p=0.0013).

General comments
MnDPDP MRI is better than CT and unenhanced MRI.

Citation: Bhattacharjya S. B. Prospective study of contrast-enhanced computed tomography, computed tomography during arterioportography, and magnetic resonance imaging for staging colorectal liver metastases for liver resection. Br.J.Surg. 2004; 91:1361-1369

Design: prospective
Country: UK

Aim: To compare the value of contrast-enhanced CT, CT during arterioportography, and magnetic resonance imaging for staging patients with colorectal liver metastases.

Inclusion criteria
Consecutive patients between January 1996 – December 2001 with known or suspected colorectal liver metastases.

Exclusion criteria
- Pulmonary metastases
- Intra-abdominal extrahepatic disease

All patients without evidence of extrahepatic disease on imaging underwent laparotomy.
Diagnostic laparoscopy was performed before the laparotomy in 54 patients. Suspicious nodules were biosied and sent for frozen section.confirmation of extrahepatic disease contraindicated liver resection.
- Local recurrence or metachronous primaries (all patients had colonoscopy to exclude this)
- Medical contraindications to MRI (pacemaker, claustrophobia)
- Medical contraindication to surgery

Population
120 patients with known or suspected colorectal liver metastases.
64 men / 56 women mean age 62 (29-74)
31 synchronous metastases – 89 metachronous metastases
85 patients had all three modalities and were finally included in the study population.
120 patients referred for consideration for resection.
120 had CT chest abdo pelvis
13 excluded after CT as either unfit for surgery or have pulmonary mets
15 do not have an MRI due to contraindications
92 have MRI.
54 of the 107 patients that had a CT and were fit for surgery proceed to have laparoscopy (as part of another study being carried out in the unit)
7 are excluded because of peritoneal mets
100 patients proceed to laparotomy, bimanual palpation and IOUS.
11 were opened and closed as they either had positive lymph nodes (4 – included in the study) or additional mets or unfavourable positioned mets.
89 patients went on to have liver resection

Interventions
Spiral contrast-enhanced CT (dual phase)
Contrast-enhanced MRI (gadolinium)
CTAP
MRI and CTAP were performed within 3 weeks of CT.
Gold standard: intraoperative ultrasound IOUS, bimanual palpation, histology of resected specimen.

The films were reviewed by one of two consultant hepatobiliary radiologists. They were blinded to the clinical history, the surgical and the pathological findings. The IOUS was performed by surgeons competent in this imaging modality and they were aware of the pre-operative findings. The pathologist that performed the histology of the resected specimens was blinded

Outcomes
Per lesion basis analysis
- Sensitivity
- Specificity
- Positive predictive value
Per patient basis analysis

Results
The results for CTAP have been excluded from this summary as not relevant to our PICO.

It has also not been possible to extract all the information for the 2x2 tables but the summary diagnostic values have been presented.

Per lesion analysis

	Liver mets +	Liver mets -	total
CT+	176	20	196
CT -	65		
total	241		

Sensitivity	73%
Specificity	96.5%
PPV	89.8%
NPV	%
Accuracy	%

	Liver mets +	Liver mets -	total
GAD MRI+	154	22	176
GAD MRI-	34		
total	188		

Sensitivity	81.9%
Specificity	93.2%
PPV	87.5%
NPV	%
Accuracy	%

Lesion size	TOTAL	CT	GAD MRI
<10mm	42	22 of 42 (52%)	16 of 28 (57%)
>10mm	199	154 of 199 (77.4%)	138 of 150 (92%)
All	241	176 of 241 (73%)	154 of ? (86.3%)

Per patient analysis

	Liver mets +	Liver mets -	total
CT+		16	
CT -	21		
total			85?

Sensitivity	73.0%
Specificity	%
PPV	%
NPV	%
Accuracy	Area under ROC curve 0.73

	Liver mets +	Liver mets -	total
GAD MRI+		18	103
GAD MRI-	16		
total	101		85?

Sensitivity	82%
Specificity	%
PPV	%
NPV	%
Accuracy	Area under ROC curve 0.82

Detection of liver metastases by various imaging modalities on an individual patient basis stratified by number of lesions.

Modality	No of patients examined	No correctly identified	No understaged	No overstaged
Solitary liver met				
CT	40	35	1	4
MRI	41	28	1	2
2 liver mets				
CT	28	24	3	1

MRI	22	19	1	2
3 liver mets				
CT	16	8	4	4
MRI	16	14	1	1
4 liver mets				
CT	7	4	0	3
MRI	7	3	2	2
5 liver mets				
CT	2	1	1	0
MRI	2	1	1	0
≥ 6 liver mets				
CT	7	1	6	0
MRI	7	4	3	0

Based on these results MRI is significantly superior to spiral CT (p=0.043) in staging colorectal cancer liver metastases on an individual patient basis once the number of metastases exceeds 4.

No single modality diagnosed all hepatic metastases and a multimodal imaging approach is recommended.

General comments
The diagnostic accuracy of these modalities is similar.

Citation: Cantwell CP, Setty BN, Holalkere N, Sahani DV, Fischman AJ, Blake MA. Liver Lesion Detection and Characterization in Patients With Colorectal Cancer: A Comparison of Low Radiation Dose Non-enhanced PET/CT, Contrast-enhanced PET/CT, and Liver MRI. J.Comput.Assist.Tomogr. 2008; 32:738-744

Design: retrospective
Country: Boston,USA

Aim: To compare low-radiation dose non-enhanced FDG-PET/CT, contrast-enhanced FDG-PET/CT and gadolinium-enhanced liver MRI for the detection and characterisation of liver lesions in patients with colorectal cancer.

Inclusion criteria
Patients with colorectal cancer who had a gadolinium-enhanced MRI within 6 weeks of the PET/CT scan.
The follow up diagnosis of the liver lesion must have been established either through histology of resected specimen or through imaginf follow up of at least 6 months for lesion stability or growth.
Patient should have at least 1 but no more than 10 liver lesions

Note: previous hepatic resection and previous chemotherapy was allowed.

Exclusion criteria
More than 10 liver lesions (possibility of lesion overlap).

Population
33 non-consecutive patients (22 men, 11 women, mean age 63 years)
retrospective review of imaging database of patients with colorectal cancer with suspected liver metastases from one institution in Boston Massachusetts from Jan 2004 to Dec 2005

Interventions
low-radiation dose non-enhanced FDG-PET/CT
contrast-enhanced FDG-PET/CT
gadolinium-enhanced liver MRI

Data were analysed by 2 radiologists. Patient demographic data was blinded as was clinical data. All data was interpreted in consensus.

Outcomes
Sensitivity
Specificity
accuracy

Results

Per lesion analysis

	Liver mets +	Liver mets -	total
Gad MRI +	98	0	98
Gad MRI -	2	10	12
total	100	10	110

Sensitivity	98%
Specificity	100%
PPV	100%
NPV	83%
Accuracy	98%

	Liver mets +	Liver mets -	total
PET CT+	85	0	85
PET CT -	15	10	25
total	100	10	110

Sensitivity	85%
Specificity	100%
PPV	100%
NPV	40%
Accuracy	86%

	Liver mets +	Liver mets -	total
Ne PET CT+	67	4	71
Ne PET CT -	33	6	39
total	100	10	110

Sensitivity	67%
Specificity	60%
PPV	94%
NPV	15%
Accuracy	66%

- No statistical significant difference in lesion detection was found between enhanced PET CT and MRI.
- Both PET CT and MRI had a higher detection rate than non-enhanced PET-CT.
- For lesion characterisation MRI was significantly more accurate than PET CT enhanced and non-enhanced. In turn enhanced was better than non-enhanced PET-CT.

General comments
Contrast enhanced PET CT is better than unenhanced PET CT.
MRI and contrast enhanced PETCT are comparable in their detection rate
MRI is better than contrast enhanced PETCT with regard to lesion characterization.

Citation: Chua SC, Groves AM, Kayani I, Menezes L, Gacinovic S, Du Y, Bomanji JB, Ell PJ. The impact of F-18-FDG PET/CT in patients with liver metastases. European Journal of Nuclear Medicine and Molecular Imaging 2007; 34:1906-1914

Design: retrospective
Country: UCLH London, UK

Aim: To assess the performance of PETCT versus contrast enhanced CT in the detection of colorectal liver disease.

Inclusion criteria
All patients that presented to one institution with suspected metastatic disease who underwent both PETCT and CT within 6 weeks of each other were retrospectively analysed covering a 5 year period.

Exclusion criteria

Population
131 patients
67 men, 64 women
mean age 62 (range 30-85 years)
75 had primary CRC
56 had other malignancies
patients were either pre chemotherapy or minimum 6 weeks post chemo

Interventions
CECT (contrast enhanced CT)
FDG PET CT

Outcomes
Sensitivity, specificity, PPV, NPV
Subgroup analysis for those patients that had undergone chemotherapy (as this has the potential to alter the PET CT results

Results
Colorectal malignancy results only

Per patient analysis

	Liver mets +	Liver mets -	total
PET CT+	63	2	65
PET CT -	4	6	10
total	67	8	75

Sensitivity	94% (CI 85%-98%)
Specificity	75% (CI 34%-96%)
PPV	97% (CI 89%-99%)
NPV	60% (CI 26%-87%)
Accuracy	%

	Liver mets +	Liver mets -	total
ceCT+	61	6	67
ceCT -	6	2	8
total	67	8	75

Sensitivity	91% (CI 81%-96%)
Specificity	25% (CI 3%-65%)
PPV	91% (CI 81%-96%)
NPV	25% (CI 3%-65%)
Accuracy	%

Subgroup analysis for patients that had and didn't have chemotherapy prior to PETCT scanning.

Sensitivity -chemo	89% (CI 51%-99%)
Sensitivity – no chemo	95% (CI 85%-98%)

Specificity - chemo	100% (CI 29%-100%)
Specificity – no chemo	60% (CI 14%-94%)
PPV - chemo	100% (CI 63%-100%)
PPV – no chemo	97% (CI 87%-99%)
NPV - chemo	75% (CI 19%-99%)
NPV – no chemo	50% (CI 11%-88%)
Accuracy	%

Chemotherapy did not statistically significantly impact on the diagnostic accuracy of FDG PET CT p=0.178

General comments
 FDG PETCT is more accurate than ceCT in the detection of metastatic liver disease both from colorectal cancer and from other malignancies. (only colorectal results presented here.)
When the detection of extrahepatic disease was also taken into account there was a change in management from the use of PETCT of about 25% (33 patients).

Citation: Coenegrachts K, De GF, ter BL, Walgraeve N, Bipat S, Stoker J, Rigauts H. Comparison of MRI (including SS SE-EPI and SPIO-enhanced MRI) and FDG-PET/CT for the detection of colorectal liver metastases. Eur.Radiol. 2009; 19:370-379

Design: pprospective
Country: Belgium and the Netherlands

Aim: To prospectively compare the FDG-PET/CT and MRI in 24 consecutive patients suspected of having colorectal liver metastases.

Inclusion criteria
USS shows new non-cyctic focal lesion
And / or CEA >3.4ng/ml for non-smokers, >4.3 ng/ml for smokers
ALT>41 U/L for males, >31 U/L for females
ALP >129 u/l
And /or bilirubin >1.2mg/dl
Time interval between MRI and FDG PET/CT was at most 3 weeks.

Note: patients that had previously received chemotherapy for their colorectal malignancy were included including those in which the treatment was within a month of the PET.

Exclusion criteria
Contraindications to MRI e.g. pacemaker,metalic implants

Population
14 men, 10 women with suspected colorectal cancer liver metastases
mean age 65.3 +/- 10.8 years
consecutive presentation between Oct 2005-Jan 2008

Interventions
FDG-PET/CT
MRI
All patient data were blinded. Blinded evaluations were done by 2 radiologists independently. In case of disagreement a consensus opinion was reached.

Reference standard: for lesions that were operated on intraoperative ultrasound scan and the histology result
For lesions that were not operated on follow up was with repeat MRI.

Outcomes
Sensitivity (per lesion and per patient analysis)
Positive Predictive Value PPV (per lesion and per patient analysis)

Results

Per patient analysis

	Liver mets +	Liver mets -	total
EPI MRI+	24	0	24
EPI MRI -	0	0	0
total	24	0	24

Sensitivity	100%
Specificity	na
PPV	100%
NPV	na
Accuracy	100%

	Liver mets +	Liver mets -	total
SPIO MRI +	24	0	24
SPIO MRI -	0	0	0
total	24	0	24

Sensitivity	100%
Specificity	na
PPV	100%

	NPV	na
	Accuracy	100%

	Liver mets +	Liver mets -	total
PET CT +	23	0	23
PET CT -	1	0	1
total	24	0	24

Sensitivity	96%
Specificity	na
PPV	100%
NPV	na
Accuracy	96%

Per lesion analysis
MRI and PETCT concordant in 9 patients

MRI identified more liver mets than PETCT

	Liver mets +	Liver mets -	total
EPI MRI+	77	0	77
EPI MRI -	0	0	0
total	77	0	77

Sensitivity	100%
Specificity	na
PPV	100%
NPV	na
Accuracy	100%

	Liver mets +	Liver mets -	total
SPIO MRI +	69	0	69
SPIO MRI -	8	0	8
total	77	0	77

Sensitivity	90%
Specificity	na
PPV	100%
NPV	na
Accuracy	90%

	Liver mets +	Liver mets -	total
PET CT +	47	0	47
PET CT -	30	0	30
total	77	0	77

Sensitivity	61%
Specificity	na
PPV	100%
NPV	na
Accuracy	61%

Citation: Kim HJ, Kim KW, Byun JH, Won HJ, Shin YM, Kim PN, Lee MS, Lee MG. Comparison of mangafodipir trisodium- and ferucarbotran-enhanced MRI for detection and characterization of hepatic metastases in colorectal cancer patients. AJR.American journal of roentgenology. 2006; 186:1059-1066

Design: block randomisation trial
Country: South Korea

Aim: to evaluate the validity of mangafodipir trisodium versus ferucarbotran-enhanced MRI in the detection and characterisation of hepatic lesions in colorectal cancer patients.

Inclusion criteria
Patients known to have or suspected of having hepatic metastases form colorectal cancer on the basis of prior helical CT examinations
Patients scheduled to have laparotomy for their hepatic mets or an intervention such as ablation.

Exclusion criteria
Multiple (>5) hepatic metastases on CT
Known contraindications to MRI (pacemaker or aneurysm clip)

Population
41 patients
48 patients between June 2003 – Feb 2004 enrolled. 7 patients further excluded for multiple mets or histology confirming hepatocellular or chalangiocarcinoma.

Interventions
1.5 T MRI with either
- mangafodipir trisodium (a type of liver specific contrast like gadolinium)
- ferucarbotran (a type of SPIO MRI)

Outcomes

Results

PER LESION ANALYSIS

	Liver mets +	Liver mets -	total
MT MRI +	37	2	39
MT MRI -	1	0	1
total	38	2	40

Sensitivity	97%
Specificity	NA
PPV	95%
NPV	NA
Accuracy	37/40= 93%

	Liver mets +	Liver mets -	total
SPIO MRI+	31	0	31
SPIO MRI -	1	0	1
total	32	0	32

Sensitivity	97%
Specificity	NA
PPV	100%
NPV	NA
Accuracy	31/32= 97%

Citation: Koh DM, Brown G, Riddell AM, Scurr E, Collins DJ, Allen SD, Chau I, Cunningham D, Desouza NM, Leach MO, Husband JE. Detection of colorectal hepatic metastases using MnDPDP MR imaging and diffusion-weighted imaging (DWI) alone and in combination. Eur.Radiol. 2008; 18:903-910

Design: prospective
Country: Royal Marsden Oncology Hospital, UK

Aim: To compare the diagnostic accuracy of MnDPDP MRI and diffusion weighted MRI alone and in combination.

Inclusion criteria
Consecutive patients with suspected colorectal liver metastatic disease
Pathologically proven adenocarcinoma of the colon or rectum
At least one liver lesion detected on CT scan or ultrasound that was diagnostic or suspicious of liver metastasis
Patients candidates for liver resection (i.e disease sparing at least two contuguous liver segments)

Exclusion criteria
Contraindication to MRI
Previous history of other malignancies.

In 5 patients no metastatic disease was diagnosed on MRI nor at follow up hence these patients were excluded from the analysis.

Population
38 consecutive patients originally referred for consideration into the study
5 patients had no evidence of metastatic disease at MRI or follow up so they were excluded.
33 patients were the final study population.
23 males, 10 females.
Mean age 57 years old (range 45-67)

Interventions
- MnDPDP MRI (liver contrast MRI)

- DWI MRI (diffusion weighted imaging)
DWI is sensitive to the molecular diffusion of water in biological tissues and recent advancements have enabled high quality DWI images of the liver to be obtained. Breath-hold single shot echo planar diffusion weighted (SS-EPI-DWI) MRI has been shown to be superior to SPIO liver contrast enhanced MRI.

- The combination of both MnDPDP and DWI MRI

Outcomes
ROC curve analysis with summary sensitivity and specificity.

Results
Average sensitivity and specificity from two observers reading the images of the different modalities.

	Sensitivity	specificity
MnDPDP MRI	81.3%	93%
DWI MRI	78.3%	95%
MnDPDP + DWI MRI	92.2%	97%

	Accuracy as Area under curve from observer 1	Accuracy as Area under curve from observer 2
MnDPDP MRI	Az=0.92 (0.86-0.96)	Az=0.88 (0.82-0.93)
DWI MRI	Az=0.83 (0.76-0.89)	Az=0.90 (0.84-0.95)
MnDPDP + DWI MRI	Az 0.94 (0.89-0.98)	Az=0.96 (0.91-0.99)

There was no significant difference in the averaged sensitivities between MnDPDP and DWI
For the combined MnDPDP + DWI the sensitivity was better compared to MnDPDP (p=0.01)
And there was a trend of improved sensitivity compared to DWI (p=0.06)

Accuracy was good but significantly improved for observer 2 who was more experienced in reading DWI images.

General comments
Combination of MnDPDP and DWI improved sensitivity without loss of specificity.

Citation: Kong G, Jackson C, Koh DM, Lewington V, Sharma B, Brown G, Cunningham D, Cook GJR. The use of F-18-FDG PET/CT in colorectal liver metastases-comparison with CT and liver MRI. European Journal of Nuclear Medicine and Molecular Imaging 2008; 35:1323-1329

Design: Retrospective
Country: Royal Marsden, UK

Aim: to compare FDG-PET/CT with liver MRI (Mn-DPDP) for the presence and number of liver metastases in patients with colorectal liver metastases being considered for surgery.

Inclusion criteria
Patients that had colorectal cancer and known or suspicion of liver mets that were thought operable from 2004-2006
Had PETCT and MRI with median time between studies <1month

Exclusion criteria
Patients with chemotherapy <3months before PETCT (lesions that are responding to treatment wont be detected on PET.

Population
65 patients (42 men) median age 65 years with colorectal cancer and known or suspicion of liver metastases retrospective identification of patients from 2004-2006 that presented to the Royal Marsden Hospital

Interventions
PETCT
MRI (Mn-DPDP)
Proof of metastases in the lesions operated came from histopathology reports or for those not operated from follow up MRI.

Outcomes
Per patient and per lesion analysis
Sensitivity
Specificity
False positives

Results
Per patient analysis:

	Liver mets +	Liver mets -	total
MnDPDP MRI+	60	0	60
MnDPDP MRI -	1	4	5
total	61	4	65

	Mn-DPDP MRI
Sensitivity	98%
Specificity	100%

	Liver mets +	Liver mets -	total
PET CT+	60	0	60
PET CT -	1	4	5
total	61	4	65

	PET CT
Sensitivity	98%
Specificity	100%

Per lesion analysis

	Liver mets +	Liver mets -	total
MnDPDP MRI+	163	0	163
MnDPDP MRI -	2	6	8
total	165	6	171

	Mn-DPDP MRI
Sensitivity	99%
Specificity	100%

	Liver mets +	Liver mets -	total
PET CT+	155	0	155
PET CT -	10	6	16
total	165	6	171

	PETCT
Sensitivity	94%
Specificity	100%

MRI and PETCT Concordant 85% of lesions
MRI and PETCT Discordant 15% of lesions
MRI detected total 30 lesions / mean 3.8 per patient
PETCT detected 20 lesions / mean 2.5 per patient
The lesions not detected by PETCT were all <1cm apart from 1
PETCT correctly identified more mets than MRI in 1 case and confirmed mets in an equivocal MRI lesion.

General comments
PETCT has high sensitivity and specificity for the presence of liver metastases and should be included early in the initial pre surgical evaluation and could potentially guide the use of MRI. However MRI is superior for small liver mets and remains a prerequisite for surgical planning in patients with confined liver mets.

Citation: Liu YN, Huang MX, An Q, Wei JM. The Impact of PET/CT on Therapeutic Strategy of Patients with Colorectal Cancer Metastasis. Hepatogastroenterology. 2009; 56:968-970

Design: prosepctive
Country: China

Aim: to assess the impact of the PETCT on the therapeutic strategy of patients with colorectal cancer metastases.

Inclusion criteria
Patients that had suspicion of liver metastases on CT scan and CEA after resection for colorectal cancer.

Exclusion criteria

Population
15 patients that all had contrast enhanced CT scan and CEA and had suspicion of liver metastasis
7 men, 8 women

Interventions
Contrast enhanced CT
PET CT

Outcomes
Sensitivity
Specificity
Change in therapeutic management

Results

	Liver mets +	Liver mets -	total
PETCT+	5 patients 9 lesions	0	5 patients 9 lesions
PETCT -	0	10 patients	10 patients
total	5 patients 9 lesions	10 patients	15 patients / 9 lesions

	PETCT
Sensitivity	100%
Specificity	100%

	Liver mets +	Liver mets -	total
CT+	4 patients 6lesions	0	4 patients 6 lesions
CT -	1 patient 3 lesions	10 patients	11patients 3 lesions
total	5 patients 9 lesions	10 patients	15 patients / 9 lesions

	PETCT
Sensitivity	80%
Specificity	100%

PET CT is statistically more sensitive than CT p=0.0009 - SIGNIFICANT

General comments
 PETCT is more sensitive than contrast enhanced CT in detecting liver metastases from colorectal cancer.
Taking into account the extrahepatic disease as well the results of which are not presented in this review there is a change in therapeutic strategy in 40% of patients based on the results of the PETCT.

Citation: Nanashima A, Taheshita H, Sawai T, Sumida Y, Abo T, Tanaka K, Nonaka T, Sengyoku H, Hidaka S, Yasutake T, Nagayasu T. Preoperative Assessment of Liver Metastasis Originating from Colorectal Carcinoma: Is Super Paramagnetic Iron Oxide Particles-Magnetic Resonance Imaging (SPIO-MRI) Useful for Screening? Hepatogastroenterology. 2008; 55:1750-1753

Design: retrospective
Country: Japan

Aim: To retrospectively examine the accuracy of diagnosis for metastatic lesions per patient and per lesion by enhanced CT and SPIO-MRI in one institution in Japan over a 7 year period.

Inclusion criteria
Data of 47 consecutive patients with metastatic liver carcinoma who underwent hepatectomy between 2000 and June 2007 were collected retrospectively. During this period enhanced CT and SPIO-MRI were performed routinely 2 weeks before hepatic resection.

The reference standard was intraoperative ultrasound scan or palpation and histological findings in the resected specimen.

Exclusion criteria

Population
32 male, 15 female, mean age 61.4 years (24-85)
10 synchronous liver metastases (same time as primary colorectal tumour)
35 metachronous liver metastases

Interventions
Enhanced CT (dual phase multi detector)
SPIO-MRI

Outcomes
Accuracy
Sensitivity
Positive predictive value
Negative predictive value

Results
Per patient analysis:
40 of 47 patients with liver metastases were accurately diagnosed by both modalities.
Sensitivity 85% CT and SPIO-MRI
Positive predictive value 100% CT and SPIO-MRI
Negative predictive value 100% CT and SPIO-MRI
The 7 patients that were missed had small liver metastases 5-8mm.

Per lesion analysis
Comparison of diagnosis of liver metastases between enhanced CT and SPIO-MRI in patients with liver metastases undergoing liver resection.

		Histology Liver mets (-)	Histology Liver mets (+)
Enhanced CT	**Liver mets (-)**	15	3
Enhanced CT	**Liver mets (+)**	18	92
SPIO-MRI	**Liver mets (-)**	17	1
SPIO-MRI	**Liver mets (+)**	12	98

	Enhanced CT	**SPIO-MRI**
Sensitivity	92/110 (84%)	98/110 (89%) p=0.32
Positive predictive value PPV	92/92 (99%)	98/99 (99%)
Negative predictive value NPV	15/18 (83%)	17/18 (94%) p=0.6

Undetectable liver mets by CT in 18 lesions included 4 lesions of 5mm, 5 of 6mm, 5 of 7mm, 3 of 8mm, 1 of 9mm.
Undetectable liver mets by SPIO-MRI in 12 lesions included 4 lesions of 5mm, 4 of 6mm, 2 of 7mm, 2 of 8mm.

Conclusions
Undetectable cases had small tumours less than 8mm
In the per lesion analysis SPIO-MRI appears superior to CT but this is not statistically significant. In the per-patient analysis there was no difference between the two modalities.

General comments

Citation: Orlacchio A, Schillaci O, Fusco N, Broccoli P, Maurici M, Yamgoue M, Danieli R, D'Urso S, Simonetti G. Role of PET/CT in the detection of liver metastases from colorectal cancer. Radiol.Med.(Torino). 2009; 114:571-585

Design: prospective
Country: Italy

Aim: to compare the diagnostic accuracy of FDG PET versus CT verus PET-CT in the detection of liver metastases during tumour staging in patients suffering from colorectal cancer for the purposes of correct surgical planning and follow up.

Inclusion criteria

Exclusion criteria

Population
467 patients from April 2005 to Dec 2007.
With diagnosis of colorectal cancer and suspected liver metastases.
301 men, 166 women
mean age 64.4 +/-10.2 years

Interventions
CT
FDG PET
PET CT

Outcomes

Results
426 cases (91.2%) there was concordance among the three modalities

	Liver mets +	Liver mets -	total
CT+	336	6	342
CT -	30	95	125
total	366	101	467

Sensitivity	91.07% (CI 88.02%-94.12%)
Specificity	95.42% (CI 91.84%-99.0%)
PPV	98.08% (CI 96.55%-99.6%)
NPV	80.65% (CI 74.43%-86.86%)
Accuracy	92.29% (CI 89.87%-94.71%)

	Liver mets +	Liver mets -	total
PET+	336	11	347
PET -	20	100	120
total	356	111	467

Sensitivity	94.05% (CI 91.52%-96.58%)
Specificity	91.6% (CI 86.85%-96.35%)
PPV	96.64% (CI 94.68%-98.59%)
NPV	85.71% (CI 79.92%-91.51%)
Accuracy	93.36% (CI 91.10%-95.62%)

	Liver mets +	Liver mets -	total
PETCT+	336	3	339
PETCT -	7	121	128
total	343	124	467

Sensitivity	97.92% (CI 96.39%-99.44%)
Specificity	97.71% (CI 95.15%-100%)
PPV	99.10% (CI 98.08%-100%)

NPV	94.81% (CI 91.07%-98.56%)
Accuracy	97.86%(CI 96.55%-99.17%)

There is statistically significant difference between the sensitivity, specificity and accuracy of PET CT v PET (P<0.05). There is also statistically significant difference between the sensitivity and accuracy of PET CT v CT (P<0.05). There is no difference between PET and CT.

General comments
 PET CT offers excellent diagnostic performance. It may modify a patients treatment protocol. The all in one examination may lead to considerable cost savings.

Citation: Rappeport ED, Loft A, Berthelsen AK, von der Recke P, Larsen PN, Mogensen AM, Wettergren A, Rasmussen A, Hillingsoe J, Kirkegaard P, Thomsen C. Contrast-enhanced FDG-PET/CT vs. SPIO-enhanced MRI vs. FDG-PET vs. CT in patients with liver metastases from colorectal cancer: A prospective study with intraoperative confirmation. Acta Radiol. 2007; 48:369-378

Design: prospective
Country: Denmark

Aim: To compare PET/CT with SPIO-MRI, PET, CT in the detection of liver metastases and extrahepatic tumour from colorectal cancer.

Inclusion criteria

Exclusion criteria
Diabetes
Contraindications to MRI imaging
Timing of imaging not feasible before surgery
Extrahepatic metastases confirmed on histology

Population
35 consecutive patients with suspected liver metastases from colorectal cancer
patients referred between March 2004 and Nov 2005 for surgery for suspected or verified mets
16 men, 19 women
median age 62 (range 33-74)

Interventions
PET/CT
SPIO-MRI
PET
CT

Readers of the imaging studies were blinded to the results of other imaging studies but were informed of the date for the primary colorectal cancer surgery.

Reference standard was intraoperative ultrasound scan and histological result of the resected specimen.

Outcomes
Sensitivity (true positives/[true positives+false negatives]
Specificity (true negatives/[true negatives+false positives]
Accuracy (true positives +true negatives)/all lesions
Positive predictive value PPV(true positives/[true positives +false positives])
Negative predictive value NPV (true negatives /[true negatives+false negatives])

Results

Per patient

	Liver mets +	Liver mets -	total
CT+	28	2	30
CT -	0	1	1
total	28	3	31

Sensitivity	100% (CI %)
Specificity	33% (CI %)
PPV	93% (CI %)
NPV	100% (CI %)
Accuracy	94% (CI %)

	Liver mets +	Liver mets -	total
PET+	23	0	23

PET -	5	3	8
total	28	3	31

Sensitivity	82% (CI %)
Specificity	100% (CI %)
PPV	100% (CI %)
NPV	38% (CI %)
Accuracy	84% (CI %)

	Liver mets +	Liver mets -	total
PETCT+	26	0	28
PETCT -	2	3	3
total	28	3	31

Sensitivity	93% (CI %)
Specificity	100% (CI %)
PPV	93% (CI)
NPV	100% (CI %)
Accuracy	94%

	Liver mets +	Liver mets -	total
SPIO MRI+	28	2	30
SPIO MRI -	0	1	1
total	28	3	31

Sensitivity	100% (CI %)
Specificity	33% (CI%)
PPV	93% (CI%)
NPV	100% (CI%)
Accuracy	94

Per lesion analysis

	Liver mets +	Liver mets -	total
CT+	43	25	68
CT -	28	50	78
total	71	75	146

Sensitivity	61% (CI %)
Specificity	67% (CI %)
PPV	72% (CI %)
NPV	86% (CI %)
Accuracy	77% (CI %)

	Liver mets +	Liver mets -	total
PET+	38	1	39
PET -	33	74	107
total	71	75	146

Sensitivity	54% (CI %)
Specificity	99% (CI %)
PPV	97% (CI %)
NPV	69% (CI %)
Accuracy	77% (CI %)

	Liver mets +	Liver mets -	total
PETCT+	47	1	48
PETCT -	24	74	98
total	71	75	146

Sensitivity	66% (CI %)
Specificity	99% (CI %)
PPV	98% (CI %)
NPV	76% (CI %)

Accuracy	83% (CI %)

	Liver mets +	Liver mets -	total
SPIO MRI+	58	14	72
SPIO MRI -	13	61	74
total	71	75	146

Sensitivity	82% (CI %)
Specificity	81% (CI %)
PPV	81% (CI %)
NPV	82% (CI %)
Accuracy	82% (CI %)

Both CT and SPIO MRI were significantly more sensitive than PET alone. P<0.0001, p<0.0001 respectively and PET CT p<0.001, p<0.05 respectively.
There was no difference between SPIO MRI and CT

All modalities were more sensitive in detecting liver metastases larger than 1cm compared to liver metastases of up to 1cm. Of the 19 liver metastases that were less than 1cm in size PET diagnosed 1, PETCT 5, SPIO MRI 10 and CT 13.

There were four patients that had chemotherapy less than 1 month prior to PETCT. Even when these patients were excluded from the analysis CT and SPIO were significantly more sensitive than PET. (p=0.001)

General comments
 PET alone was significantly less sensitive than CT and SPIO MRI in the detection of LM. This is in contradiction to the conclusions from meta-analyses. Only some of the studies reported in the meta-analysis reported lesion by lesion sensitivity.
PET CT equaled MRI imaging in accuracy for liver metastasis detection.

Citation: Regge D, Campanella D, Anselmetti GC, Cirillo S, Gallo TM, Muratore A, Capussotti L, Galatola G, Floriani I, Aglietta M. Diagnostic accuracy of portal-phase CT and MRI with mangafodipir trisodium in detecting liver metastases from colorectal carcinoma. Clin.Radiol. 2006; 61:338-347

Design: prospective
Country: Italy

Aim: to compare the diagnostic accuracy of single section spiral CT and MRI with and without tissue specific contrast agent MnDPDP in the detection of colorectal liver metastases.

Inclusion criteria
Consecutive patients referred to one institution undergoing surgery for primary and / or metastatic colorectal cancer.
>18 years of age
Histologically confirmed diagnosis of CRC
Surgical indication for either resection of the primary and/or liver resection of metastases according to colonoscopy and CT chest/abdo
Life expectancy of at least 12 weeks
Normal renal function (creatinine <1.5mg/dl)

Exclusion criteria
Pregnancy or lactation
Contraindication to CT, MRI, laparoscopic surgery
CT-MRI interval > 4 weeks
CT or MRI imaging of poor quality due to movement artefact

Population
125 consecutive patients from one institution considered (Dec 2000-Mar 2003)
61 men (48.8%)
Median age 64.4 (41-86)
82/125 had resection of primary
19/82 also had synchronous metastases
43/125 had resection of metachronous metastases
19/125 had received neoadjuvant chemotherapy prior to inclusion in the study.

Interventions
Dual phase spiral single section CT with contrast. (Triple phase (delayed phase – done only when required by radiologist to differentiate between slowly filling haemangioma and metastasis.)

MRI with and without MnDPDP contrast.

Reference Standard: IOUS combined with palpation and surgical inspection together with histopathologic reliefs (intra operative frozen section histology when needed and histology on resected specimens).

2 radiologists assessed CT images and 2 the MRI images. Disagreement between readers was resolved by consensus re-evaluation. The readers were aware that the patient had CRC but were unaware of the result of other investigations and of the other readers. IOUS was performed by 1 of 2 radiologists and they were aware of the results of the CT and MRI.

Outcomes
Primary outcome

- sum of TP, sum of TN for all patients for CT, unenhanced MRI, MnDPDP MRI (per patient analysis)

TP = when the procedure detected the same metastases as the reference standard
TN = when the procedure correctly diagnosed no metastases.

Secondary outcome

- Sensitivity / specificity - per patient basis
- Sensitivity / PPV – per lesion basis

- The level of diagnostic confidence
- Inter-observer agreement

Per-patient basis analysis definitions

Sensitivity = number of TP cases / number of patients with at least one metastasis.

Specificity = number of TN cases / all cases in whom the reference standard did not detect any metastases.

Results
- MnDPDP MRI is more accurate than CT on a per patient basis. There is no difference between CT and MRI and only a trend of higher accuracy for MnDPDP MRI compared to unenhanced MRI.
- MnDPDP MRI has a significantly higher sensitivity on a per lesion basis than both CT (OR 2.6; 95% CI 1.44, 4.92) and unenhanced MRI (OR 2.1; 95% CI 1.11, 3.84). (multiple logistic model accounting for lesion dimensions and intra-patient variability)
- Kappa for inter-observer variability was 0.85 for CT, 0.77 for both enhanced and unenhanced MRI. Overall Kappa was 0.75 suggesting excellent agreement.
- Diagnostic confidence levels have not been included in this evidence table as not a relevant outcome to our PICO.
- No serious side effects were reported from any of the investigations.

	CT	MRI	MnDPDP MRI	CT v MRI	CT v MnDPDP MRI	MRI v MnDPDP MRI
Per patient analysis						
Accuracy	91/125(72.8%)	98/125(78.4%)	103/125(82.4%)	p=0.071	p=0.005	P=0.059
Sensitivity	30/62(48.4%)	36/62(58.1%)	41/62(66.1%)	p=0.083	p=0.004	p=0.059
Specificity	61/63(96.8%)	62/63(98.4%)	62/63(98.4%)			
Per lesion analysis						
Sensitivity	137/191(71.7%)	143/191(74.9%)	158/191(82.7%)			
Sensitivity per lesion size						
≤ 10mm	31/65(47.7%)	35/65(53.8%)	44/65(67.7%)			
11-20mm	39/53(73.6%)	40/53(75.5%)	46/54(86.8%)			
>20mm	67/73(91.8%)	68/73(93.2%)	68/73(93.2%)			
PPV	137/163(84%)	143/149(96%)	158/165(95.8%)			

Per patient analysis

	Liver mets +	Liver mets -	total
MnDPDP MRI+	41	1	42
MnDPDP MRI -	21	62	83
total	62	63	125

Sensitivity	66.1%
Specificity	98.4%
PPV	97.6%
NPV	74.7%
Accuracy	82.4%

	Liver mets +	Liver mets -	total
MRI+	36	1	37
MRI -	26	62	88
total	62	63	125

Sensitivity	58.1%
Specificity	98.4%
PPV	97.3%
NPV	70.5%
Accuracy	78.4%

	Liver mets +	Liver mets -	total
CT+	30	2	32
CT -	32	61	93

total	62	63	125

Sensitivity	48.4%
Specificity	96.8%
PPV	94%
NPV	66%
Accuracy	72.8%

There was no difference between CT and MRI
MnDPDP MRI was more accurate and more sensitive than CT
There was a higher accuracy and sensitivity tendency for MnDPDP MRI v unenhanced MRI but not statistically significant.

Per lesion analysis

	Liver mets +	Liver mets -	total
MnDPDP MRI+	158	7	165
MnDPDP MRI -	33	67	100
total	191	74	265

Sensitivity	82.7%
Specificity	90.5%
PPV	95.8%
NPV	67.0 %
Accuracy	84.9%

	Liver mets +	Liver mets -	total
MRI+	143	6	149
MRI -	48	68	116
total	191	74	265

Sensitivity	74.9%
Specificity	91.9%
PPV	96%
NPV	58.6%
Accuracy	79.6%

	Liver mets +	Liver mets -	total
CT+	137	26	163
CT -	54	48	102
total	191	74	265

Sensitivity	71.7%
Specificity	64.9%
PPV	84%
NPV	47.1%
Accuracy	69.8%

CT and unenhanced MRI showed no difference in sensitivity in the per lesion analysis (OR 1.3, CI 0.73-2.27)
The sensitivity of MnDPDP MRI was significantly higher than both CT (OR 2.6 CI 1.44-4.92), and unenhanced MRI (OR 2.1 CI 1.11-3.84)

General comments
 On a per patient basis MnDPDP MRI is significantly more accurate and sensitive than CT in the detection of colorectal liver metastases. Specificity was similar. However MnDPDP MRI failed to be more accurate and sensitive than unenhanced MRI for both comparisons. There was no difference between CT and unenhanced MRI.

Citation: Ruers TJM. Improved selection of patients for hepatic surgery of colorectal liver metastases with 18F-FDG PET: A randomized study. J.Nucl.Med. 2009; 50:1036-1041

Design: randomised phase III multicentre trial
Country: the Netherlands

Aim: to investigate whether the addition of FDG PET to conventional CT-based the preoperative screening of colorectal liver metastases is beneficial and reduces the number of futile laparotomies.

Inclusion criteria
Histologically documented colorectal cancer treated by R0 resection
1-4 suspected potentially resectable liver metastases
No evidence of extrahepatic metastatic disease (except up to a maximum of 2 resectable lung mets on CT)
No evidence of recurrent or second colorectal carcinoma on barium enema or colonoscopy
WHO performance status of 0-2
Age 18 - 75

Exclusion criteria
Previous malignancies (except in situ carcinoma of the cervix, non-melanoma cancer of the skin, or a cancer where there had been a disease-free interval of at least 10 years)
Liver dysfunction (bilirubin, ALP x3 times upper limit if normal)
Active infection
Poorly regulated diabetes mellitus

Population
150 patients with colorectal liver metastases selected for surgical treatment by CT
Multicentre
Between May 2002 and February 2006.

Interventions
FDG PET and CT
Versus
CT only

Outcomes
Primary
Number of futile laparotomies (defined as any laparotomy that did not result in complete tumour treatment, that revealed benign disease, or that did not result in disease-free survival period longer than 6 months.
Secondary
Disease-free survival (DFS)
Overall survival (OS)

Results

Futile laparotomies

Variable	Control arm (no PET) n=75	Experimental arm (PET) n=75
No laparotomy	0	5 (7%)
Confirmed benign disease	-	2
Confirmed extrahepatic disease	-	3
laparotomy	75 (100%)	70(93%)
Futile laparotomy	34 (45%)	21(28%)
Extra hepatic disease at laparotomy – not resectable	6	2
Too extensive liver disease at laparotomy – not resectable	8	3
Benign disease at laparotomy	3	2
Benign disease after resection	1	1
Disease recurrence in <6 months	16	13

- A significantly higher proportion of patients underwent futile laparotomies in the control-no PET arm than in the experimental arm (45% v 28%) p=0.042
- The relative risk reduction was 38% (CI 4%-60%)
- The absolute difference of 17% means that 6 patients need to undergo PET to avoid 1 futile laparotomy.
- Futile laparotomy was not found to be associated with other prognostic factors as measured by the Fong score (p=0.539)

Survival

All patients were followed up for at least 3 years after randomization. For all patients randomized

3 year survival	Control arm (no PET)	Experimental arm (PET)
Overall survival OS	65.8%	61.3%
Disease free survival DFS	29.8%	35.5%

Both OS and DFS were not significantly different between the experimental and the control groups.

General Comments:

The introduction of PET in the preoperative work up of patients with suspected liver metastases from colorectal cancer significantly reduces the number of futile laparotomies due to unexpected unresectable disease.

Citation: Schwartz L, Brody L, Brown K, Covey A, Tuorto S, Mazumdar M, Riedel E, Jarnagin W, Getrajdman G, Fong Y. Prospective, blinded comparison of helical CT and CT arterial portography in the assessment of hepatic metastasis from colorectal carcinoma. World J.Surg. 2006; 30:1892-1901

Design: prospective
Country: Memorial Sloan Kettering Cancer Centre - USA

Aim: To compare helical CT with helical CT with arterial portography aimed at detecting liver metastases from colorectal carcinoma.

Cannot obtain 2X2 table as only ROC curve presented.

Inclusion criteria

Exclusion criteria
Patients with evidence of extrahepatic disease on imaging (37 patients)

Population
87 consecutive patients between April 1999 and April 2001 with suspected colorectal liver metastases .
all imaging done at a single institution
no evidence of extrahepatic disease (final population analysed n=50)

Interventions
Helical CT
Helical CTAP – results not presented as not relevant to PICO

Outcomes
Sensitivity from ROC curve

Results
Only CT results are presented as they are relevant to the PICO.

	CT using cutt-off 1 0-1 benign 2-3-4 malignant	CT using cutt-off 2 0-1-2 benign 3-4 malignant
Sensitivity	76%	69%
Specificity	56%	82%
PPV	61%	78%
NPV	73%	75%
Accuracy	65%	76%

Citation: Selzner MK, Hany TF, Wildbrett P, McCormack L, Kadry Z, Clavien PA. Does the novel PET/CT imaging modality impact on the treatment of patients with metastatic colorectal cancer of the liver? Ann.Surg. 2004; 240:1027-1036

Design: prospective
Country: Switzerland

Aim: To compare the diagnostic value of contrast enhanced CT with that of FDG PETCT in patients with metastatic colorectal cancer to the liver.

Inclusion criteria
All patients referred for consideration for liver resection between Jan 2002 and July 2003.
CT and PETCT must have occurred within 2 weeks of each other.

Exclusion criteria
Synchronous metastatic lesions (i.e. metastatic liver disease at the same time as the primary colon cancer diagnosed)

Population
76 patients
52 men, 24 women
median age of 63 years (range 35-78)
62 patients received chemotherapy after their initial bowel resection
Median interval between chemo and PETCT = 3 months (range 7 days to 15 months)
Median follow up 16 months (range 6 months to 3 years)

Interventions
Contrast enhanced CT
FDG PET CT

Follow up was at 3 and 6 months for those patients that did not proceed to surgery.
Separate CT radiologist and PET radiologist. Both blinded to the results of other findings.

Outcomes
Primary outcome
Does PETCT alter the indications for surgery compared to CT.

Secondary outcome
True positive/negatives, false positive/negatives for PETCT
The diagnostic ability of the modality in patients with a previous hepatectomy
The influence of previous chemotherapy on the detection of tumours by PETCT

Results

Per patient analysis

	Liver mets +	Liver mets -	total
CT+	63	3	66
CT -	3	7	10
total	66	10	76

Sensitivity	95%
Specificity	70%
PPV	95%
NPV	70%
Accuracy	92%

	Liver mets +	Liver mets -	total
PETCT+	60	1	61
PETCT -	6	9	15
total	66	10	76

Sensitivity	91%
Specificity	90%

PPV	98%
NPV	60%
Accuracy	91%

No difference between CT and PETCT with regard to specificity p=0.58

General comments
 Comparable results between PETCT and CT with regard to the diagnosis of hepatic metastases.
Management is latered by PETCT but purely on the identification of extrahepatic disease.
PETCT is also better at diagnosing recurrent liver disease in patient with prior hepatectomy.

Citation: Truant S, Huglo D, Hebbar M, Ernst O, Steinling M, Pruvot FR. Prospective evaluation of the impact of 18Ffluoro 2 deoxy D glucose positron emission tomography of resectable colorectal liver metastases. The British journal of surgery 2005; 92:362-369

Design: prospective double blind
Country: France

Aim: to assess the additional value of information provided by FDG PET over that provided by CT in patients with respectable liver metastases from colorectal cancer.

Inclusion criteria
Oct 2001-Nov 2002
Those patients that on CT were thought to be eligible for liver resection
If the PET was discordant with the CT this did not alter the decision to proceed to laparotomy.

Exclusion criteria

Population
All 53 patients underwent laparotomy
40 men, 13 women
mean age 63, range 44-78
27 patients presented with synchronous liver metastases., 26 had metachronous liver metastases.

Interventions
FDG PET
Helical CT, dual phase, 5mm slices, with iodinated contrast
Mean time between PET and CT was 24 days (range 0-61 days)
All PET scan performed within 2 months of laparotomy

Outcomes

Results

Per patient analysis
Unable to extract 2x2 table from descriptive statistics of the per patient analysis.

Per lesion analysis

	Liver mets +	Liver mets -	total
CT+	78	3	81
CT -	21	1	22
total	99	4	103

Sensitivity	79%
Specificity	25%
PPV	96%
NPV	5%
Accuracy	77%

	Liver mets +	Liver mets -	total
PET+	78	1	79
PET-	21	4	25
total	99	5	104

Sensitivity	79%
Specificity	80%
PPV	99%
NPV	16%
Accuracy	79%

General comments
Comparable results between PET and CT with regard to liver mets. Any additional lesions identified are extra hepatic

Citation: Vidiri A, Carpanese L, D'Annibale M, Caterino M, Cosimelli M, Zeuli M, David V, Crecco M. Evaluation of hepatic metastases from colorectal carcinoma with MR-superparamagnetic iron oxide. Journal of Experimental & Clinical Cancer Research 2004; 23:53-60					

Design: prospective
Country: Italy

Aim: To compare the results obtained with SPIO-MRI, unenhanced MRI to that of spiral CT (does not say triple phase but I think it is) in order to select those patients suitable for liver resection.

Really difficult to make sense of their despcriptive statistics to get 2x2 table.

Inclusion criteria
Patients with known colorectal neoplasm who were candidates for liver resection

Exclusion criteria
age <18
pregnancy and or lactation
hypersensitivity to Destran's administration
stage C liver cirrhosis (Child-Pugh classification)
serious kidney insufficiency
haematological disease with splenomegaly
administration of a different contrast within 24 hours.

Population
35 patients , mean age 65, 20 men, 15 women, all potentially suitable for hepatic resection of metastatic lesions

Interventions
All patients had all the investigations.
spiral CT
SPIO-MRI (with body coil)
unenhanced MRI

All imaging was performed within 7 days
Pre and post op evaluation time period max 30 days

Gold standard:IOUS combined with palpation and surgical inspection together with histopathologic reliefs on resected specimens.

Outcomes
Sensitivity per lesion basis
Change in overall decision per patient basis

Results
Of the 35 patients included 26 went to surgery and 9 did not (unresectable). Of the 9 unresectable cases 8 had chemo and 1 had radiofrequency ablation.

Of patients submitted to surgery

dimensions	No of lesions	CT	MRI	SPIO-MRI	IOUS
	48	34	32	41	48
<1cm	13	4	2	9	13
1-2cm	14	10	10	12	14
>2cm	21	20	20	20	21

3 FP on CT
2 FP on MRI
2 FP on SPIO-MRI (same as above)
5 patients were found to have unresectable disease at operation (missed by both CT and MRIs)
2 lesions considered by CT to be mets were correctly identified by MRIs to be non-metastatic.
1 lesion identified by MRI as a met and not picked up by CT at all was not a met (angioma)

Of patients not operated

dimensions	CT	MRI	SPIO-MRI
	8	8	15
<1cm			4
1-2cm	2	2	5
>2cm	6	6	6

Per patient

In 5 cases SPIO-MRI concluded that surgery was contraindicated – the opposite to the CT conclusion
(in 4 cases SPIO-MRI showed greater number of lesions per segment, in 1 case it identified the lesion as benign not metastatic).

Statistics

Kappa CT v MRI 0.9 good agreement
Kappa CT v SPIO-MRI 0.59 mild agreement
Kappa MRI v SPIO-MRI 0.51 mild agreement

Per patient analysis

	Liver mets +	Liver mets -	total
CT+	9+	3	
CT -	5		
total			35

	Liver mets +	Liver mets -	total
MRI+	9+	2	
MRI -	5		
total			35

	Liver mets +	Liver mets -	total
SPIO MRI+	9+	2	
SPIO MRI -	5		
total			35

Per lesion analysis

	Liver mets +	Liver mets -	total
CT+	34	3	37
CT -	14		
total	48		

Sensitivity	71%
Specificity	%
PPV	%
NPV	%
Accuracy	%

	Liver mets +	Liver mets -	total
MRI+	32	2	34
MRI -	16		
total	48		

Sensitivity	66.6%
Specificity	%
PPV	%
NPV	%
Accuracy	%

	Liver mets +	Liver mets -	total
SPIO MRI+	41	2	43
SPIO MRI -	7		
total	48		

Sensitivity	85.4%

Specificity	%
PPV	%
NPV	%
Accuracy	%

McNemar test: significantly greater number lesions identified with SPIRO-MRI v MRI (p=0.008

Citation: Wiering B, Ruers TJM, Krabbe PFM, Dekker HM, Oyen WJG. Comparison of multiphase CT, FDG-PET and intra-operative ultrasound in patients with colorectal liver metastases selected for surgery. Ann.Surg.Oncol. 2007; 14:818-826

Design: prospective
Country: The Netherlands

Aim: to evaluate the predictive value of CT and FDG PET of the liver and extra hepatic findings compared to findings at laparotomy and 6 months follow up.

Inclusion criteria
Consecutive patients between Jan 1999 and Nov 2004.
Suitable for liver resection of hepatic metastases from colorectal cancer on CT imaging

Exclusion criteria
Presence of local recurrence on colonoscopy or colonography
No previous liver surgery
Poorly regulated diabetes

Population
131 consecutive patients thought suitable for liver resection of hepatic metastases on CT imaging

Interventions
CT dual phase helical with IV contrast – iodine
PET

Outcomes
Diagnostic 2x2 tables for each modality for liver metastases, extra hepatic intra abdominal and other sites.
Only liver-related results presented.

Results

Per patient analysis

	Liver mets +	Liver mets -	total
CT+	127	3	130
CT -	1	0	1
total	128	3	131

Sensitivity	99.2%
Specificity	NA%
PPV	97%
NPV	NA%
Accuracy	97%

	Liver mets +	Liver mets -	total
PET+	126	0	126
PET-	2	3	5
total	128	3	131

Sensitivity	98.4%
Specificity	100%
PPV	100%
NPV	60%
Accuracy	98.5%

Per lesion analysis

	Liver mets +	Liver mets -	total
CT+	257	3	260
CT -	106	0	106
total	363	3	366

Sensitivity	70.8%
Specificity	NA%

PPV	98.8%
NPV	NA%
Accuracy	70.2%

	Liver mets +	Liver mets -	total
PET+	260	0	260
PET-	103	3	106
total	363	3	366

Sensitivity	71.6%
Specificity	100%
PPV	100%
NPV	2.8%
Accuracy	71.8%

PET and CT both missed the majority of lesions that were smaller than 10mm. Many were only a few mm.

Detection rate of histologically proven liver metastases

Lesion size	IOUS	CT	PET	CT and/or PET
<10mm	63	10 (16%)	10 (16%)	12 (19%)
10-20mm	172	123 (72%)	129 (75%)	142 (83%)
>20mm	128	124 (97%)	121 (95%)	125 (98%)
All	363	257 (71%)	260 (72%)	279 (77%)

CT and PET may be discongruent and complementary for detection of metastases.

After 6 months follow up 42 new lesions developed in 15 patients. CT and PET had previously detected all the lesions though it had not been possible to identify them at laparotomy with palpation and IOUS.

General comments

CT and PET have similar diagnostic yield for the detection of liver metastases; both modalitiesare adequate on a patient basis but inadequate to detect the smallest of liver lesions. The significance of the latter is limited clinically.

4.3. Imaging Extra-Hepatic Metastases

4.3.1. In a patient with colorectal cancer and extrahepatic metastases (e.g. lung, brain, peritoneum), which imaging modality most accurately determines the extent of metastases?

Short Summary
The evidence base for this question comprises one systematic review of observational studies (Wiering *et al.* 2005) and nine retrospective case series (Desai *et al.,* (2003; Imdahl *et al.,* 2000; Potter *et al.,* 2009; Schmidt *et al.,* 2009; Selzner *et al.,* 2004; Squillaci *et al.,* 2008; Tanaka *et al.,* 2002; Valk *et al.,* 1999, and Votrubova *et al.,* 2006) None of the studies were designed to directly compare the effectiveness of the imaging techniques in detecting extra-hepatic metastases.

FDG-PET versus CT
Wiering *et al.* (2005) found that FDG-PET had a higher sensitivity and specificity (91.5% and 95.4%) than CT scan (60.9% and 91.1%) in detecting extra-hepatic metastases. Using only the highest weighted studies from the meta-analysis, the pooled sensitivity and specificity for FDG-PET were 91.2% and 98.4% respectively and for CT the sensitivity and specificity were 55.3% and 95.6%. Tanaka *et al.* (2002) reported that FDG-PET also had higher accuracy and sensitivity (78% and 88%) than CT (44% and 38%) in diagnosing peritoneal metastases, but the study numbers were very low (n=23). Valk *et al.* (1999) reported sensitivity and specificity for detecting extrahepatic metastases of 92% and 99% for FDG-PET compared with 61% and 96% for CT. The authors also added that FDG-PET had a significantly higher specificity than CT in detecting lung metastases.

Potter *et al.* (2009) found no significant difference in diagnostic accuracy between FDG-PET and CT/MRI but the study provided some information with regard to the role of the reader, since a significant difference in accuracy and sensitivity was found between the three individuals who interpreted the CT/MRI scans.

PET/CT versus MRI
Schmidt *et al.* (2009) found that PET/CT had higher sensitivity than whole body MRI in the detection of distant metastasis (80% versus 78%) but there was no difference in specificity (95%) and accuracy was similar (PET/CT: 87%, WB-MRI: 86%). Squillaci *et al.* (2008) did not report sensitivity or specificity but suggested that both modalities were equivalent in detecting extrahepatic metastases. Both studies concluded that PET/CT detected more lung metastases than WB-MRI.

PET/CT versus CT
Selzner *et al.* 2004 found no difference in the ability of PET/CT or ceCT to detect the presence of extrahepatic metastases but PET/CT was more sensitive than CT in the detection of lung metastases (100% versus 78%). PET/CT was also more sensitive than CT for portal and para-aortic lymph node metastasis (77% versus 46%) although these differences were not statistically significant.

Others
Votrubova *et al.* (2006) showed PET/CT was superior (sensitivity 95%, specificity 100%, accuracy 100%) to FDG uptake (sensitivity 74%, specificity 88%, diagnostic accuracy 88%) for the diagnosis of extra abdominal and/or hepatic recurrence of colorectal cancer and in the diagnosis of any form of colorectal cancer recurrence (p<0.05).

Desai *et al.* (2003) presented no data on the effect of PET on surgical decision making in patients with metastatic or recurrent colorectal cancer but observed that the information provided by PET complemented that provided by the CT scan. Imdahl *et al.* (2000) reported a higher sensitivity and specificity for PET (94% and 100%) compared with chest X-ray (64% and 98%) for the detection of pulmonary metastases.

Updated Evidence
Two studies (Metser *et al.*, 2010 and Choi *et al.*, 2010) were identified during updates as providing evidence for the topic though both studies were case series studies and neither were specifically designed to answer the question of which modality is best for identifying number and extent of extrahepatic metastases.

Choi et al (2010) evaluated the role of chest CT on preoperative staging of rectal cancer to assess the impact on treatment strategy though the study was of a low quality and it was difficult to draw any conclusions as to the effectiveness of chest CT on the preoperative staging of pulmonary metastases when compared with standard chest X-Ray.

Metser et al. (2010) compared the detection of tumour recurrence and metastases with FDG-PET/CT with contrast enhanced MDCT in patients with colorectal cancer and elevated CEA levels and reported that on event based analysis (number of lesions) PET/CT was significantly more sensitive that MDCT (p=0.002) but there was no difference in specificity (p=1.0) of the two modalities for detection or recurrence or metastases.

Tumour based analysis showed that PET/CT was significantly better than MDCT for the detection of recurrence and metastases (p<0.0001) though again there was no difference in specificity (p=0.56).

Review Protocol

Population	Intervention	Comparison	Outcome
Patients with colorectal cancer and extrahepatic metastases (e.g. lung, brain, peritoneum, adrenal/spleen)	• PET • PET-CT • MRI	• CT • Each other	• Sensitivity • Specificity

Following a systematic search of relevant data sources (see appendix .1), the information specialist created a database of potentially relevant studies. All titles and abstracts were sifted by a single reviewer. Queries about inclusion were clarified by the GDG topic subgroup. The full studies were then obtained and reviewed and relevant studies were included in the final evidence review.

All update searches were sifted by a single reviewer and the list of potentially relevant studies was also checked for irrelevant studies by the GDG subgroup. Only studies which all subgroup members were in agreement were excluded. The remaining studies were obtained and reviewed with relevant studies included in the final evidence review.

High level evidence such as randomised controlled trials do not exist for this topic, therefore the evidence level accepted included lower level studies such as retrospective case series. A single systematic review was available for this topic however the evidence quality of the studies included in the review was low as this is all that is available.

A number of date limits were set by the GDG for more efficient and targeted searches:
PET-CT: 2000 onwards
PET: 1990 onwards
CT: 1993 onwards (data from spiral/helica CT era only)
MRI: 1990 onwards
The dates were selected by the GDG subgroup on the basis of improvements in available technology and likelihood that older methods are no longer used.

Reasons for excluding studies:
Studies did not report on extrahepatic metastases
Studies were designed for follow-up rather than preoperative staging
Intervention modality not relevant to PICO
Comparison not relevant to PICO
Foreign Language (no translation available)

Quality of the included studies
Systematic review of RCTs (n = 0)
Systematic review of combined study designs (n = 1)
Randomized controlled trial (n = 0)
Prospective cross sectional study (n = 0)
Case Series Studies (n = 11)

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┌─────────────────────┐        ┌─────────────────────┐
│ 212 (+94) possibly  │   →    │ 159 (+85) papers    │
│ relevant papers     │        │ excluded based      │
│ identified          │        │ on title & abstract │
└─────────────────────┘        └─────────────────────┘
          ↓
┌─────────────────────┐        ┌─────────────────────┐
│ 53 (+9) papers      │   →    │ 43 (+7) papers      │
│ obtained for        │        │ excluded            │
│ appraisal           │        │                     │
└─────────────────────┘        └─────────────────────┘
          ↓
┌─────────────────────┐
│ 10 (+2) papers      │
│ included in         │
│ evidence table      │
└─────────────────────┘
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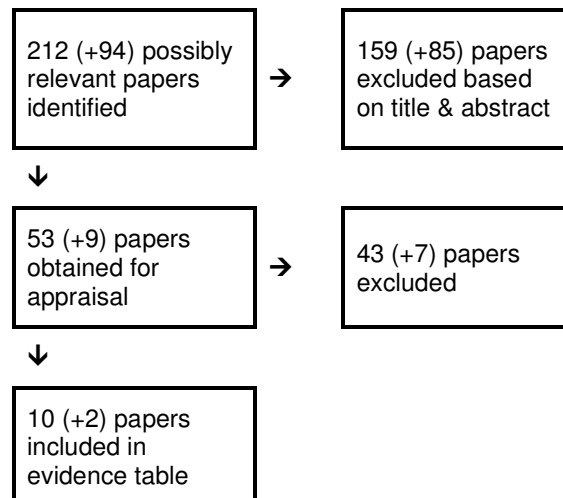
Volume of evidence

There was very little, poor quality evidence available to address this question. There was a single systematic review and meta-analysis of case-series studies, and the remainder of the evidence was drawn from retrospective case series' in which the numbers of cases available to be reviewed is small with little detail provided with regards to factors such as inclusion/exclusion criteria, co-morbidities or other factors that may impact on the outcome of imaging.

Applicability

There is little direct evidence with which to answer this question. None of the studies identified were designed to address the question of which imaging modality provided the most accurate information on number and extent of extrahepatic metastases. The majority of studies identified were concerned with how effective imaging modalities were in detecting colorectal cancer recurrence (primary or metastastic) and how the results impact on management decisions. The accuracy of detecting extrahepatic metastases was a secondary outcome in the majority of studies, in many studies detecting metastases (liver and extrahepatic) was the focus and in such studies it was not possible to elucidate the results relating specifically to extrahepatic metastases, therefore such studies were not included.

Consistency

There appears to be some degree of consistency across the evidence base in relation to the effectiveness of the different imaging modalities in detecting extrahepatic metastases. There appears to be reasonable agreement that PET and PET/CT are more sensitive and specific than CT and/or MRI in the detection of extrahepatic metastases.

Other factors

Due to the poor evidence available with which to address this question, all study types were considered for inclusion, as well as any studies which reported potentially relevant or indirect information to answer the question. The majority of the included studies had very small numbers which meant that any meaningful statistical analysis was difficult to conduct and although accuracy, sensitivity and specificity were reported in many cases, in some cases this information was not available. Due to methodological differences across the studies it was not possible to combine the results of the different case series studies, though pooled estimates of sensitivity and specificity are provided as part of a systematic review and meta-analysis (Wiering *et al.* 2005).

The PICO listed MRI, CT, PET and PET-CT to be the interventions of choice and most studies compared two or more of these interventions, however in one case CT scanning was used to confirm PET diagnosis and therefore the results should be interpreted with caution (Imdahl *et al.* 2000) as from an initial look at the results it appears that CT scanning has 100% sensitivity and specificity.

Evidence Statement

There is a lack of good quality evidence available on which to base recommendations for the optimal imaging modality for determining the extent and number of extrahepatic metastases in patients with colorectal cancer. Much of the evidence has been drawn from studies which look at the contribution of such imaging modalities to the treatment plan for patients with recurrent colorectal cancer, including hepatic metastases. In patients with resectable liver metastases imaging is done to determine the presence or absence of extrahepatic metastases as the presence of any extrahepatic metastases is likely to preclude such patients from surgery. For this reason, the ability of imaging to determine the extent and number of extrahepatic metastasis is predominantly a secondary outcome in studies looking at whether patients with recurrence of either primary tumour or metastatic liver recurrence are candidates for surgery.
For the purposes of this evidence review, it was not possible to combine data as it was presented in any of the included studies due to inconsistencies and differences in study aims.
It is unlikely that it will be possible to conduct a randomised controlled trial to determine the best imaging modality.

Sensitivity and Specificity

There is evidence from a single systematic review and meta-analysis of case series studies that FDG-PET has a higher sensitivity and specificity (91.5% and 95.4% respectively) than does CT scan (60.9% and 91.1% respectively) (Wiering *et al.* 2005) for the detection of extra-hepatic metastases. When taking only the highest weighted studies included in the meta-analysis, the pooled sensitivity and specificity for FDG-PET were 91.2% and 98.4% respectively while for CT the sensitivity and specificity were 55.3% and 95.6% respectively.

FDG-PET versus CT
Two case series studies (Tanaka *et al.* 2002, Valk *et al.* 1999) with a combined patient population of 138, compared accuracy, sensitivity and specificity of FDG-PET and CT scanning. In both studies FDG-PET showed higher sensitivity and specificity than CT. Tanaka *et al.* found that FDG-PET was more accurate and sensitive (78% and 88% respectively) than CT (44% and 38% respectively) in the diagnosis of peritoneal metastases, though the numbers in this study were small (N=23). Valk *et al.* reported an overall sensitivity and specificity for extrahepatic metastases of 92% and 99% for FDG-PET compared with 61% and 96% for CT. In looking at specific sites of metastases, Valk *et al.* reported that FDG-PET was significantly more specific than CT for lung metastases.

PET/CT versus MRI
Two studies (Schmidt *et al.* 2009, Squillaci *et al* 2008) compared PET/CT to MRI. Schmidt *et al.* reported the PET/CT was more sensitive than whole body MRI in the detection of distant metastasis (80% compared with 78%), though there was no difference in specificity for either modality (95%) and accuracy was similar for both (PET/CT - 87%, WB-MRI - 86%). Squillaci *et al.* did not report sensitivity or specificity, but reported that PET/CT similar detection rates for both modalities in relation to extrahepatic metastases. Both studies reported that PET/CT revealed more lung metastases in patients than did WB-MRI.

PET/CT versus CT
From a single study (Selzner *et al.* 2004), the presence of extrahepatic metastases identified by ceCT and PET/CT were 31% and 45% respectively, though the difference was not statistically significant (p=0.13).
PET/CT was more sensitive than CT in the detection of lung metastases (100% and 78% respectively). PET/CT was also more sensitive than CT for portal and para-aortic lymph node metastasis (77% and 46% respectively) though these differences were not statistically significant.

In a study by Desai *et al.* (2003) the effect of PET on surgical decision making in patients with metastatic or recurrent colorectal cancer was the main focus. The study did not present any sensitivities or specificities, however it observed that the information provided by PET scans complements that which if provided by the CT scan.

A study by Potter *et al.* compared sensitivity and specificity of FDG-PET CT to CT and/or MRI serial review in colorectal cancer follow-up. There was no significant difference between FDG-PET and CT/MRI in relation to accuracy, sensitivity or specificity, though this is an overall result and does not distinguish between site of recurrence, therefore it is not possible comment on the accuracy, sensitivity and specificity in relation to extrahepatic metastases. The study may however provide some important information in relation to the role of the reader, as a significant difference in accuracy and sensitivity was found between the three individual readers of the CT/MRI scans.

Imdahl *et al.* (2000) reported a sensivity and specificity for PET of 94% and 100% respectively, compared with chest X-ray (64% and 98% respectively) for the detection of pulmonary metastases. In this study, CT was performed only in patients for whom PET scan or chest X-ray was indicative of pulmonary metastases and for this reason reported a sensitivity and specificity of 100%. It would however be misleading to say that CT was the better modality in this case however, as it was used for confirmatory purposes.

Votrubova *et al.* (2006) compared FDG uptake to PET/CT and reported a sensitivity of 74% and 95% respectively, a specificity of 88% and 100% respectively and an accuracy of 85% and 99% respectively. The specificity and accuracy of PET/CT was significantly higher for the diagnosis of extra abdominal and/or hepatic recurrence of colorectal cancer and in the diagnosis of any form of colorectal cancer recurrence (p<0.05).

Updated Evidence
Update searches identified 94 new studies of which the GDG members identified 9 as being potentially relevant for full review. On obtaining the full studies it was determined that only 2 studies were of relevance to the topic (Choi et al, 2010 and Metser et al, 2010).
Choi et al (2010) evaluated the role of chest CT on preoperative staging of rectal cancer to assess the impact on treatment strategy though the study was of a low quality and it was difficult to draw any conclusions as to the effectiveness of chest CT on the preoperative staging of pulmonary metastases when compared with standard chest X-Ray. The authors however, concluded that chest CT was an acceptable approach as it picked up pulmonary metastases which were not visualised on chest X-ray. In total 9 patients with pulmonary metastases were identified on chest CT, 5/9 of whom were also identified on chest X-ray and in 3/4 patients whose metastases were missed, treatment strategy changed as a result of the findings of chest CT.

Metser et al. (2010) compared the detection of tumour recurrence and metastases with FDG-PET/CT with contrast enhanced MDCT in patients with colorectal cancer and elevated CEA levels
Event based analysis showed that for PET/CT and ceCT the sensitivities were 97.3% (95% CI, 85-99) and 70.3% (95% CI, 53-84) respectively (p=0.002) and the specificities were 94.4% (95% CI, 72-99) and 94.4% (72-99) respectively (p=1.0).
Tumour site based analysis showed that sensitivity for PET/CT and ceCT was 98.1% (95% CI, 52-78%) respectively (p<0.0001) and the specificities were 75% (95% CI, 34-96%) and 62.5% (95% CI, 24-91) respectively (p=0.56).

References

Choi D, Kwak J, Kim J et al (2010) Preoperative Chest Computerised Tomography in Patients with Locally Advance Mid or Low Rectal Cancer: Its Role in Staging and Impact on Treatment Strategy *Journal of Surgical Oncology* 102;6:588-592

Desai D, Zervos E, Arnold M, Burak W, Mantil J, Martin E (2003) Positron Emission Tomography Affects Surgical Management in Recurrent Colorectal Cancer Patients *Annals of Surgical Oncology* 10;1:59-64

Imdahl A, Reinhardt MJ, Nitzche EU, Mix M, Dingeldey A, Einert A, Baier P, Farthmann EH (2000) Imapct of ^{18}F-FDG-positron emission tomography for decision making in colorectal cancer recurrences. *Langenbeck's Archives of Surgery* 385;129-134

Metser U, You J, McSweeny S et al (2010) Assessment of Tumour Recurrence in Patients with colorectal cancer and elevated carcinoembryonic antigen level: FDG PET/CT versus contrast enhanced 64-MDCT of the chest and abdomen *AJR* 194;766-771

Potter KC, Husband JE, Houghton SL, Brown G (2009) Diagnostic accuracy of serial CT/Magnetic resonance imaging review vs. positron emission tomography/CT in colorectal cancer patients with suspected and known recurrence *Diseases of the Colon and Rectum* 52;2:253-259

Schmidt GP, Baur-Melnyk A, Haug A, Utzschneider S, Becker CR, Tiling R, Reiser MF, Hermann KA (2009) Whole-body MRI at 1.5 T and 3 T compared with FDG-PET-CT for the detection of tumour recurrence in patients with colorectal cancer.

Selzner M, Hany T, Wildbreet P, McCormack L, Zakiyah K, Clavien PA (2004) Does the novel PET/CT imaging modality impact on the treatment of patients with metstatic colorectal cancer of the liver *Annals of Surgery* 240;6:1027-1036

Squillaci E, Maneti G, Mancino S, Ciccio C, Calabria F, Danieli R, Schillaci O, Simonetti G (2008) Staging of colon cancer: whole body MRI vs. whole body PET-CT – initial clinical experience *Abdom Imaging* 33:676-688

Tanaka T, Kawai Y, Kanai M, Taki Y, Nakamoto Y, Takabayashi A (2002) Usefulness of FDG-positron emission tomography in diagnosing peritoneal recurrence of colorectal cancer. *The American Journal or Surgery* 184;433-436

Valk P, Abella-Culmna E, Haseman M, Pounds T, Tesar R, Myers R, Greiss H, Hofer G (1999) Whole-body PET Imaging with [F^{18}] Fluorodeoxyglucose in Management of Recurrent Colorectal Cancer *Arch. Surg.* 134;503-511

Votrubova J, Belohlavek O, Jaruskova M, Oliverius M, Lohynska R, Trskova K, Sedlackova E, Lipska L, Stahalova V (2006) The role of FDG-PET/CT in the detection of recurrent colorectal cancer *Eur J Nucl Med Mol Imaging* 33;779-784

Wiering B, Krabbe P, Jager G, Oyen W, Ruers T (2005) The impact of fluor-18-deoxyglucose-poitron emission tomography in the management of colorectal liver metastases; a systematic review and meta-analysis *Cancer* 104;12:2658-2670

Evidence Tables

Citation: Choi D, Kwak J, Kim J et al (2010) Preoperative Chest Computerised Tomography in Patients with Locally Advance Mid or Low Rectal Cancer: Its Role in Staging and Impact on Treatment Strategy *Journal of Surgical Oncology* 102;6:588-592
Design: Prospective Case Series **Country**: South Korea **Setting:** **Aim**: to evaluate the role of chest CT on preoperative staging in rectal cancer patients and to assess the impact on treatment strategy.
Inclusion criteria Patients with biopsy proven adenocarcinoma within 12cm of the anal verge
Exclusion criteria Patients with tumour stage T1 or T2
Sample Size N/A
Randomisation Method N/A
Population N=103
Study Duration Patients were enrolled between September 2006 and October 2008
Interventions Abdominal CT, pelvic MRI and/or ERUS Plain chest PA/lateral X-ray and chest CT to evaluate lung metastases
Outcomes The outcome for the study appears to be changes in management and/or treatment strategy based on scan results.
Results Thoracic imaging was prospectively evaluated interpreted by two radiologists who were both blinded to the local staging of rectal tumour. Radiologists were also blinded to the results of chest x ray when interpreting the CT scans The patient population differed at baseline with more males (70%), more tumours located in the lower rectum (60%), more T3 tumours (78.8%) and more moderately differentiated tumours (60.6%). No p values for the differences were provided. 5 patients showed metastases on Chest X-ray compared with 9 patients on Chest CT. Of the 73 patients with negative findings in X-ray, 2 were found to have evidence of metastases and 28 had indeterminate nodules on chest CT 22 patients had benign lesions on Chest X-ray of whom 1 had evidence of definite metastases and 10 had indeterminate nodules on Chest CT. 3 patients had indeterminate nodules on chest CT 1 of whom had evidence of definite metastases on CT.

9 patients had unequivocal metastases on chest CT of who 5 were identified by chest X-ray.

Of the 4 patients whose metastases were not identified on chest X-ray, treatment strategy changed in 3 as a result of the findings on Chest CT.

40 patients had indeterminate lesions on chest CT and follow-up scans were performed in 37/40 patients at 3 to 6 months intervals.
In 4 patients the lesion had grown and/or new lesions developed indicating the presence of lung metastases that could not initially be diagnosed.
3/4 patients showed no metastases on follow-up chest X-Ray.

Histopathological results were available for 99 patients and of these, 82 (82.2%) had the correct T stage in MRI

37 patients who had follow-up CT scan because of indeterminate nodule were analysed according to nodal status and in 4/12 patients who had positive lymph nodes, the indeterminate nodules had progressed.
No change was observed in any of the patients with N0 disease (n=25).

	CT				
CXR	Negative	Benign	Indeterminate	Metastasis	Total
Negative	40	3	28	2	73
Benign	3	8	10	1	22
Indeterminate	0	0	2	1	3
Metastasis	0	0	0	5	5
Total	43	11	40	9	103

Comparison between Chest CT and Chest X-Ray (CXR)

General comments
Chest images were graded as negative, benign, indeterminate or metastatic.
Follow up chest CT scans were performed in the indeterminate group at 3 to 6 month intervals; policy at the institute meant that locally advanced rectal cancers were selectively treated with preoperative long course chemoradiotherapy.
In the group of patients with preoperative chemoradiotherapy, follow up chest CT scans for indeterminate nodules were performed at 3 to 6 month intervals after primary tumour resection while in the patients undergoing preoperative chemoradiotherapy, follow-up scans were performed again before primary tumour resection.
For patients with no adjuvant chemotherapy, follow-up CT's were performed once while for patients receiving adjuvant chemotherapy, follow-up CT scans were performed at 3 to 6 month intervals during chemotherapy and 1-2 more follow-up scans were performed after treatment.

This is a poor quality study with no really clear aims and outcomes. It is difficult to draw any conclusions as to the appropriateness of using chest X-ray in the preoperative staging of pulmonary metastases.

Citation: Desai D, Zervos E, Arnold M, Burak W, Mantil J, Martin E (2003) Positron Emission Tomography Affects Surgical Management in Recurrent Colorectal Cancer Patients *Annals of Surgical Oncology* 10;1:59-64
Design: Case Series **Country**: USA **Aim**: To determine the effect of positron emission tomography (PET) on surgical decision making in patients with metastatic or recurrent colorectal cancer.
Inclusion criteria
Exclusion criteria Patients with underlying inflammatory bowel disease and diabetes.
Population N=114 N=89 with presumed recurrent colorectal cancer + N=25 with presumed isolated liver metastases.
Interventions CT scan of the abdomen + whole body PET scan
Outcomes
Results PET/CT Negative Correlation 42/114 patients had presumably resectable recurrences on CT scan. 17/42 patients had presumed isolated liver metastases by CT scan but had evidence of additional, extrahepatic disease rendering them unresectable on PET scan. PET scan found extrahepatic disease in the abdomen or chest in 14 patients, retroperitoneal disease in 2 as well as bilobar liver involvement in 3 patients. PET/CR Positive Correlation PET and CT were in agreement for 25 patients with no evidence of disease found in 13, 7 with isolated liver metastases and 5 with isolated foci of recurrent disease in the abdomen. Patients with isolate liver disease by CT 25 patients had presumed isolated liver metastases on CT scan. PET findings correlated with CT in 7 patients, found additional disease in 17 patients and PET was negative in 1 patient with a positive CT. Therapeutic decision making was altered in 17 of 42 potentially operable patients with information obtained from PET scans allowing surgery to be avoided in patients it could not help. Information provided by PET scans complements that which is provided by CT scan.
General comments All CT and PET scans were performed within 2 months of each other Patients were evaluated by a single surgeon and PET scans were interpreted by two nuclear radiologists with PET expertise and who knew the results of the previous CT scan.

Citation: Imdahl A, Reinhardt MJ, Nitzche EU, Mix M, Dingeldey A, Einert A, Baier P, Farthmann EH (2000) Imapct of ^{18}F-FDG-positron emission tomography for decision making in colorectal cancer recurrences. *Langenbeck's Archives of Surgery* 385;129-134

Design: Prospective Case Series

Country: Germany

Aim: to evaluate the clinical impact of whole body ^{18}F-FDG-PET for the detection and localisation of tumour recurrence and tumour spread in patients with colorectal cancer.

Inclusion criteria
Patients suspected of having a tumour recurrence or metastases either due to imaging or raised CEA levels.

Exclusion criteria
Patients with elevated fasting blood glucose level or diabetes

Population
N=71 with suspected tumour recurrence or metastases either due to raised CEA level or to imaging methods.

Interventions
All patients received ^{18}F-FDG-PET, one received three investigations and three patients received two investigations.

Outcomes
Sensitivity
Specificity
Positive predictive value (PPV)
Negative predictive value (NPV)

Results
^{18}F-FDG-PET was performed in 14 patients due to raised CEA level, for suspicion of local recurrence or metastases in 33 patients and for staging in 24 patients. Results of ^{18}F-FDG-PET resulted in a change in the treatment strategy in 16 patients. The results for each patients group are not provided therefore it is not possible to determine the sensitivity and specificity of FDG-PET in relation to those patients with suspected metastases only.

Pulmonary metastases were demonstrated in 16 of 76 investigations (21%) while chest x-ray demonstrated pulmonary metastases in 9 of 69 (13%) patients but failed in 5 of 69 patients (7.2%). FDG-PET demonstrated pulmonary metastases in 5 patients with negative chest x-rays and missed a pulmonary lesion in one patient. CT scan was performed only in patients in whom a chest x-ray or FDG-PET was indicative of pulmonary metastases.

	FDG-PET (performed in 71 patients)	Chest X-Ray (performed in 69 patients)	CT (performed in 21 patients)
Sensitivity	0.94 (94%)	0.64 (64%)	1 (100%)
Specificity	1 (100%)	0.98 (98%)	1 (100%)
PPV	1 (100%)	0.9 (90%)	1 (100%)
NPV	0.98 (98%)	0.92 (92%)	1 (100%)

Table: Comparison of FDG-PET, CT and chest X-ray for the detection of pulmonary metastases

Note: the paper reports there to be 77 investigations and 17 pulmonary metastases however the numbers do not add up.

General comments
The paper is not solely concerned with the best imaging method for the detection of extra-hepatic metastases, the result reflect only the data that are related to the PICO in some way.

Care should be taken when interpreting the results of this study as CT scan was used as a confirmation procedure for patients showing evidence of metastases on FDG-PET or chest X-ray thus giving 100% sensitivity and specificity which is misleading.

Citation: Metser U, You J, McSweeny S et al (2010) Assessment of Tumour Recurrence in Patients with colorectal cancer and elevated carcinoembryonic antigen level: FDG PET/CT versus contrast enhanced 64-MDCT of the chest and abdomen *AJR* 194;766-771

Design: Retrospective case series

Country: Canada

Setting:

Aim: to compare the detection of tumour recurrence with FDG-PET/CT with detection with contrast enhanced 64-MDCT of the chest, abdomen and pelvis in patients with colorectal cancer and elevated CEA levels.

Inclusion criteria
History of colorectal cancer
Elevated or increasing CEA levels and conventional imaging did not reveal an unequivocal explanation for the raised CEA levels.

Exclusion criteria
None given

Sample Size
N/A

Randomisation Method
N/A

Population
N= 50

Study Duration
Recruitment occurred over a 30 month period

Interventions
FDG PET/CT
ceCT
Histopathologic exam (reference)

Outcomes
Sensitivity
Specificity

Results
50 patients with 55 PET/CT scans available for review underwent CECT of the chest, abdomen and pelvis within 60 days of PET/CT (mean=22days).
In 18 cases ceCT followed PET/CT and in 37 cases the PET/CT was performed before ceCT.
All patients were followed up for at least 6 months (median 12 months, range 6-31 months)

All PET/CT images were reviewed by two expert reviewers with all sites of abnormal FDG uptake recorded and graded as definite or equivocal for tumour. Abnormalities observed in the unenhanced CT portion of the PET/CT that were consistent with or equivocal for tumour recurrence were recorded.

Reviewers were aware of the patient history of colorectal cancer and elevated CEA levels but were blinded to patients' outcome clinical outcome, results of surgery or biopsy and subsequent imaging findings.

Event based analysis

19/55 events of CEA level had not recurred by final analysis; in 6 of these events, lesions identified with at least 1 technique were benign and 13 events, both PET/CT and ceCT showed no tumour. These patients underwent follow-up (clinical and imaging) for a mean period of 18 months (average, 18.5 months, range 6-31 months) without evidence of recurrence.

36/55 events had confirmed metastatic disease or recurrence.

For PET/CT and ceCT the sensitivities were 97.3% (95% CI, 85-99) and 70.3% (95% CI, 53-84) respectively (p=0.002) and the specificities were 94.4% (95% CI, 72-99) and 94.4% (72-99) respectively (p=1.0).

Tumour Site Based Analysis
61 suspicious tumour sited were identified on either PET/CT or ceCT, 54 of which were true positive for recurrent or metastatic colorectal cancer.

All tumour sites found at PET/CT were associated with abnormal FDG uptake apart from 2 metastatic lung lesions which were identified on the CT portion and on ceCT.

Sensitivity for PET/CT and ceCT was 98.1% (95% CI, 52-78%) respectively (p<0.0001) and the specificities were 75% (95% CI, 34-96%) and 62.5% (95% CI, 24-91) respectively (p=0.56).

General comments
 This is a poor quality study with little to add to the overall body of evidence.

	Citation: Potter KC, Husband JE, Houghton SL, Brown G (2009) Diagnostic accuracy of serial CT/Magnetic resonance imaging review vs. positron emission tomography/CT in colorectal cancer patients with suspected and known recurrence *Diseases of the Colon and Rectum* 52;2:253-259

Design: Case Series

Country: UK

Aim: to examine the sensitivity and specificity of CT/magnetic resonance imaging serial review compared to FDG-PET/CT to optimise colorectal cancer follow-up

Inclusion criteria
Patients undergoing follow-up for colorectal cancer via FDG-PET/CT imaging within 40 days of CT and/or MRI. Patients referred for PET/CT to evaluate findings initially deemed to be equivocal on CT/MRI, to investigate unexplained CEA elevation or to exclude any further sites of recurrence prior to surgical resection of recurrence.

Exclusion criteria
Patients undergoing PET/CT for the evaluation of treatment
Patients whose imaging results were unavailable

Population
N=50

Interventions
FDG-PET/CT
CT/MRI

Outcomes
Accuracy
Sensitivity
Specificity

Results
FDG-PET/CT was performed in 20 patients to evaluate findings considered equivocal on CT/MRI, in 17 patients to investigate CEA levels and in 13 patients to exclude further sites of recurrence prior to potentially curative surgery.

There was no significant difference between FDG-PET/CT and CT/MRI in relation to accuracy, sensitivity or specificity (table).

	FDG-PET/CT		**CT/MRI**		
	N (%)	95% CI	N (%)	95% CI	P value
Accuracy	46/50 (92%)	81%-98%	46/50 (92%)	81%-98%	0.999
Sensitivity	20/23 (87%)	66%-97%	19/23 (83%)	61%-95%	0.999
Specificity	26/27 (96%)	81%-100%	27/27 (100%)	87%-100%	0.999

Table: Accuracy, sensitivity and specificity of FDG-PET/CT and CT/MRI

A significant difference was found in accuracy and sensitivity between the three individual readers of the CT/MRI scans, but no significant difference in specificity. Reader 1 and 2 h ad good agreement while reader 3 had poorer agreement with both reader 1 and reader 2.

	Reader 1		**Reader 2**		**Reader 3**		
	N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	P value
Accuracy	44/50 (92)	76-95	43/50 (86)	73-94	35/50 (70)	55-82	0.012
Sensitivity	19/23 (83)	61-95	19/23 (83)	61-95	13/23 (57)	34-77	0.011
Specificity	25/27 (93)	76-99	24/27 (89)	71-98	22/27 (81)	62-94	0.556

Table: Accuracy, sensitivity and specificity among independent readers for CT/MRI

37 of 50 patients underwent FDG-PET/CT for apparently unexplained elevated CEA or equivocal CT or MRI results and careful reviewing of serial images using defined protocol enabled a definitive diagnosis to be made in 24 of the 37 patients.

7 false negative diagnoses were made on consensus imaging review and comprised 3 pelvic recurrences, a peritoneal recurrence, a patient with lung, liver and retroperitoneal lymph node recurrence and a patient with lung

metastasis. 2 of the three patients with pelvic recurrence had no pelvic MRI available for review which would have provided improved soft-tissue contrast and is more sensitive in identifying pelvic pathology.
No false positives were diagnosed on consensus serial imaging review although individual readers did make false positive errors.
There were 3 false-negative diagnoses on FDG-PET/CT, a patient with small lung metastases that were visible on serial CT/MRI imaging, a patient with peritoneal disease shown on CT and a patient with a large mucinous pelvic recurrence visible on MRI that did not show any activity on FDG-PET/CT.
There was one false positive diagnosis of pelvic recurrence on FDG-PET/CT, conventional CT and MRI were negative in this patient.

Citation: Schmidt GP, Baur-Melnyk A, Haug A, Utzschneider S, Becker CR, Tiling R, Reiser MF, Hermann KA (2009) Whole-body MRI at 1.5 T and 3 T compared with FDG-PET-CT for the detection of tumour recurrence in patients with colorectal cancer.
Design: Retrospective Case Series
Country: Germany
Aim: To compare the diagnostic potential of FDG-PET-CT and WB-MRI at 1.5 T and 3 T in patients with colorectal cancer and suspected tumour recurrence.
Inclusion criteria
Exclusion criteria To avoid bias in diagnostic accuracy of PET-CT due to suppressed metabolic activity, patients receiving chemotherapy or radiotherapy immediately before or between examinations were excluded from statistical analysis.
Population N=24 patients with a history of colorectal cancer.
Interventions Whole body MRI at 1.5 T and at 3 T FDG-PET-CT
Outcomes Sensitivity Specificity Accuracy Location, extension and number of suspected malignant legions

Results

Only results relating to distant metastases are presented.

A total of 83 distant lesions were observed from PET-CT and WB-MRI, 46 malignant and 37 benign. PET-CT detected 37 of the 46 malignant lesions while WB-MRI detected 36 of 46.

	PET-CT	WB-MRI
Sensitivity	80% (37/46)	78% (36/46)
Specificity	95% (35/37)	95% (35/37)
Accuracy	87% (72/83)	86% (71/83)

Table: Diagnostic accuracy, sensitivity and specificity for PET-CT and WB-MRI for the detection of distant metastases.

PET-CT revealed more lung metastases and was more sensitive to detecting peritoneal spread. WB-MRI revealed more metastases of the bone and when considering the full field of view of WB-MRI examination (covering the body from head to calves) additional metastatic disease was found in the brain in one patient.

General comments
Two certified radiologists read the MRI examinations and a third radiologist and a nuclear medicine physician read the PET-CT images; each group was blinded to the other investigation and had no knowledge of previous or current diagnostic imaging results.

The standard of reference was the confirmation of local recurrent tumour, node involvement and distant metastatic disease using radiological follow-up within at least five months.

Citation: Selzner M, Hany T, Wildbreet P, McCormack L, Zakiyah K, Clavien PA (2004) Does the novel PET/CT imaging modality impact on the treatment of patients with metstatic colorectal cancer of the liver *Annals of Surgery* 240;6:1027-1036

Design: Prospective case series
Country: Switzerland
Aim: To compare the diagnostic value of contrast enhanced CT (ceCT) and 2-[18-F]-fluoro-2-deoxyglucose-PET/CT in patients with metastatic colorectal cancer to the liver

Inclusion criteria Patients evaluated for resection of liver metastases from colorectal cancer

Exclusion criteria Cases with synchronous metastases

Population N=76

Interventions Conventional work-up including ceCT of the chest and abdomen. PET/CT

Outcomes The primary outcome was to assess how PET/CT may change the indications for surgery compared with conventional radiology. **Secondary outcomes included the ability of ceCT and PET/CT to detect extrahepatic disease**

Results The presence of extrahepatic metastases was identified by ceCT and PET/CT in 24/76 (31%) and 34/76 (45%) patients respectively though the difference was not statistically significant (p=0.13). In 66 patients with documented liver metastases, extrahepatic metastases were present in 36; ceCT failed to diagnose extrahepatic metastases in 13/36 (36%) (sensitivity 64%) whereas PET/CT failed to diagnose extrahepatic lesions in only 4/36 (11%) sensitivity 89%; p=0.02. Lung metastases were present in 18 patients and all were correctly identified by PET/CT (sensitivity 100%) whereas ceCT detected only 14 (sensitivity 78%, p=0.1). Portal and para-aortic lymph node metastases were present in 13 patients; PET/CT detected 10 (sensitivity 77%) and ceCT failed to identify lesions in 7 patients (sensitivity 46%, p=0.4). Bone metastases were identified in 4 patients and PET/CT missed 1 while ceCT missed 2. Extrahepatic metastases were identified in 9 of 18 patients with recent chemotherapy (within 1 month prior to PET). No FDG uptake was noted in 3 of the 9 patients (sensitivity 66%). In comparison, 27 of the remaining 58 patients without recent chemotherapy were identified with extrahepatic metastases. FDG uptake was negative in 1 patient (sensitivity 96%, p=0.05).

General comments The primary focus of the study was not to compare imaging modalities in relation to their ability to detect extra-hepatic metastases; however as this was a secondary outcome the relevant data only have been presented here. Each patient was evaluated for respectability of liver metastases and received a ceCT and a PET/CT within a period of two weeks.

Citation: Squillaci E, Maneti G, Mancino S, Ciccio C, Calabria F, Danieli R, Schillaci O, Simonetti G (2008) Staging of colon cancer: whole body MRI vs. whole body PET-CT – initial clinical experience *Abdom Imaging* 33:676-688

Design: case series

Country: Italy

Aim: to define the potential role of WB-MRI in staging and follow-up of patients diagnosed with CRC compared to morphological and functional findings of PET-CT.

Inclusion criteria
Patients with previously undiagnosed colorectal cancer

Exclusion criteria
Exclusion criteria were based on contraindications to MR imaging including the presence of a pacemaker, metallic implants in critical organs, severe claustrophobia and lack of willingness or ability to sign informed consent.

Population
N=20

Interventions
WB MRI
WB PET-CT

Outcomes

Results

WB MRI detected 19 pulmonary metastases in five patients, the smallest of which was 4mm in diameter. PET-CT detected 25 pulmonary metastases in 7 patients.
Nine bone metastases were detected on WB MRI in 3 patients.
One spine lesion was missed on PET-CT while a rib lesion was missed on WB MRI.
Peritoneal metastatic involvement was detected in two patients by both PET-CT and WB MRI.
No brain metastases were detected on WB MRI or PET-CT.

	PET-CT	WB-MRI
Brain	0	0
Lung	25	19
Bone	9	9
Other	5	5

Table: Number of extrahepatic metastases by site and imaging modality

General comments
The morphological and functional results obtained by PET-CT analysis were considered as the reference standard for the correct assessment of malignancy presence in the definitive interpretation of WB-MRI and relative diagnostic value.

WB-MRI exam was performed within 10 following PET-CT.

Both imaging modalities were performed without adverse effects in all patients.

| | **Citation**: Tanaka T, Kawai Y, Kanai M, Taki Y, Nakamoto Y, Takabayashi A (2002) Usefulness of FDG-positron emission tomography in diagnosing peritoneal recurrence of colorectal cancer. *The American Journal or Surgery* 184;433-436 |

Design: Case Series

Country: Japan

Aim: To compare sensitivity and accuracy of FDG-PET and CT in the diagnosis of peritoneal metastases of colorectal cancer.

Inclusion criteria

Exclusion criteria

Population
N=23

Interventions
FDG-PET
CT

Outcomes
Sensitivity
Accuracy

Results
Overall sensitivity and accuracy of FDG-PET were 95% and 93% respectively as compared with those of CT, sensitivity 83% and accuracy 83%.

Peritoneal Metastases
Peritoneal metastases were suspected in 9 sites of six patients with 8 of the 9 suspected lesions confirmed benign in 5 patients. Sensitivity and accuracy for CT and FDG-PET for the detection of peritoneal metastases is outlined in the table below.

	True Positive	False Positive	True Negative	False Negative	Sensitivity	Specificity	Accuracy
CT	3	0	1	5	3/8 (38%)	0/1 (0%)	4/9 (44%)
FDG-PET	7	1	0	1	7/8 (88%)	1/1 (100%)	7/9 (78%)

Table: Comparison of CT and FDG-PET for the detection of peritoneal metastases

FDG PET detected lesions 15mm in diameter whereas CT did not detect anything smaller than 30mm. In all of the 5 patients proved to have peritoneal metastases, FDG-PET identified at least some of the metastases in all patients compared to CT which detected metastases in only 2 of the 5 patients.

General comments
FDG-PET scanning was performed at an interval of at least six months following first operation.
All patients underwent CT scan within a month of the PET scan.
The PET and CT images were interpreted independently by at least two experienced radiologists.

Authors Conclusion: FDG-PET may be superior to CT in the detection of peritoneal metastases.

Citation: Valk P, Abella-Culmna E, Haseman M, Pounds T, Tesar R, Myers R, Greiss H, Hofer G (1999) Whole-body PET Imaging with [F^{18}] Fluorodeoxyglucose in Management of Recurrent Colorectal Cancer *Arch. Surg.* 134;503-511

Design: Prospective Case Series

Country: USA

Aim: To demonstrate the accuracy of PET in patients with known or suspected recurrent colorectal cancer.

Inclusion criteria

Exclusion criteria
Six patients with less than 1 year of follow-up after studies with negative findings.
Six patients lost to follow-up
Five patients died without validation of sites of tumour involvement
Four patients treated by radiation or chemotherapy without further validation of findings

Population
N=115

Interventions
FDG-PET
CT

Outcomes
Sensitivity
Specificity

Results
115 patients underwent both PET and CT and validation procedures established a diagnosis of recurrent tumour at 157 sites in 101 patients and no tumour recurrence in 14 patients.
Validated recurrence was found 149 of 171 sites that were abnormal PET, CT or both and at 8 sites that were normal by both modalities.
A final diagnosis of no recurrence was established at 22 sites of image abnormality, 17 of which were abnormal by CT only, 3 abnormal by PET only and 2 abnormal by both.
5 patients without recurrence and who had a normal PET and CT scan remained clinically disease free for more than 1 year after imaging.

104 sites were true positive for both PET and CT
48 sites were false negative by CT, 42 (88%) of these were true positive by PET
11 sites were false negative by PET, 5 (45%) of these were true positive by CT

PET was more sensitive than CT at all locations apart from the lungs (and liver though liver data have not been included due to not being relevant to this particular question).
PET was more specific that CT at all sites apart from the retopritoneum, though the only statistically significant difference was in the lungs.

Site	PET Scan (%)	CT Scan (%)	Difference % (95% CI)
Pelvis	30/31 (97)	21/31 (68)	11 (-1 to 22)
Abdomen	22/28 (79)	13/28 (46)	29 (9 to 49)
Retroperitoneum	12/12 (100)	7/12 (58)	33 (11 to 54)
Lungs	16/17 (94)	16/17 (94)	42 (10 to 74)
Other	12/12 (100)	4/12 (33)	0 (-19 to 19)
Total	92/100 (92)	61/100 (61)	31 (18 to 42)

Table: Sensitivity of PET and CT by site

Site	PET Scan (%)	CT Scan (%)	Difference % (95% CI)
Pelvis	81/84 (96)	76/84 (90)	6 (-2 to 13)
Abdomen	87/87 (100)	85/87 (98)	2 (-2 to 6)
Retroperitoneum	103/103 (100)	103/103 (100)	0 (0 to 0)
Lungs	97/98 (99)	94/98 (96)	3 (1 to 5)
Other	103/104 (99)	101/104 (98)	1 (-1 to 1)
Total	471/476 (99)	459/476 (96)	3 (1 to 4)

Table: Specificity of PET and CT by site

The positive predictive value of PET was 97% on a site by site basis and 97% patient by patient basis while the positive predictive value of CT was 85% (109/128) on a site by site basis and 93% (79/85) on a patient by patient basis.
The negative predictive value of PET was 69% (11/16) on a patient by patient basis, while for CT it was 24% (7/29).

The largest number of false negative CT findings occurred in the abdomen, retroperitoneum and pelvis with 30 of 71 disease sites (42%) not detected. 21 of these missed sites were positive on PET.

General comments
The interval between CT and PET ranged from 0 to 56 days, with a median interval of 22 days.

The diagnosis was established histologically at 103 sites, surgically at 93 sites and by needle biopsy at 10 sites. Abnormal imaging findings were validated by demonstration of progression or no progression at a second CT imaging. Clinical evidence of tumour progression was accepted as positive evidence at 20 sites of imaging abnormality. Clinical evidence of absence of disease was accepted as negative evidence at 13 sites of imaging abnormality and in 5 patients with normal PET and CT findings.

Citation: Votrubova J, Belohlavek O, Jaruskova M, Oliverius M, Lohynska R, Trskova K, Sedlackova E, Lipska L, Stahalova V (2006) The role of FDG-PET/CT in the detection of recurrent colorectal cancer *Eur J Nucl Med Mol Imaging* 33;779-784

Design: Retrospective Case Series

Country: Czech Republic

Aim: To compare the value of FDG-PET and PET/CT in the detection of colorectal cancer recurrence subsequent to colonic resection or rectal amputation.

Inclusion criteria
None given

Exclusion criteria
None given

Population
N=84

Interventions
FDG-PET/CT

Outcomes
Sensitivity
Specificity

Results
Intra-abdominal extra-hepatic recurrence (including metastases to the peritoneum)
33 patients had proven intra-abdominal extra-hepatic recurrence. 27 showed focally increase FDG uptake while 6 showed no pathological FDG uptake (false negative). 4/6 false negative results showed no pathological signs on CT scan.
Of the 51 patients with no recurrence, 45 had no signs of focally increased FDG uptake.
The sensitivity, specificity and accuracy of FDG uptake were 82%, 88% and 86% respectively.
The sensitivity, specificity and accuracy of integrated FDG-PET/CT for the detection of intra-abdominal extrahepatic recurrence were 88%, 94% and 92% respectively.

Extra-abdominal and/or hepatic recurrence
Extra-abdominal and/or hepatic recurrence was detected in 19 patients, with 14/19 patients showing increased FDG uptake.
The sensitivity, specificity and accuracy of focal FDG uptake were 74%, 88% and 85% respectively.
The sensitivity, specificity and accuracy of PET/CT were 95%, 100% and 99% respectively.
Integrated FDG-PET/CT achieved significantly higher specificity and accuracy in the diagnosis of extra-abdominal and/or hepatic recurrence of colorectal cancer and in the diagnosis of any form of colorectal cancer recurrence (p<0.05).

	Intra-abdominal extrahepatic	Extra-abdominal and/or hepatic	Any recurrence
Sensitivity FDG uptake	82% (27/33)	74% (14/19)	80% (36/45)
PET/CT	88% (29/33)	95% (18/19)	89% (40/45)
Specificity FDG uptake	88% (45/51)	88% (57/65)	69% (27/39)
PET/CT	94% (48/51	100% (65/65)	92% (36/39)
Accuracy FDG uptake	86% (72/84)	85% (71/84)	75% (63/84)
PET/CT	92% (77/84)	99% (83/83)	90% (76/84)

Table: Sensitivity, specificity and accuracy of FDG uptake and combined PET/CT

General comments
All patients underwent FDG-PET/CT no earlier than 1 month following surgery.

Final diagnosis was based on histology and/or follow-up information. The histological confirmations were obtained within 4 weeks of FDG-PET/CT and patients without histological confirmation were followed-up for a mean period of 6.5 months.

The data in this study are combined and it is not possible to elucidate sensitivity and specificity for specific extra-hepatic metastases alone, therefore the evidence from this study should be interpreted with caution when discussing the benefits of FDG-PET versus FDG-PET/CT.

Citation: Wiering B, Krabbe P, Jager G, Oyen W, Ruers T (2005) The impact of fluor-18-deoxyglucose-poitron emission tomography in the management of colorectal liver metastases; a systematic review and meta-analysis *Cancer* 104;12:2658-2670

Design: Systematic Review and meta-analysis

Country: Conducted in the Netherlands, studies included from various countries

Aim: To assess the usefulness of FDG-PET for the selection of patients to undergo resection for colorectal liver metastases.

Inclusion criteria
Articles concerning recurrent liver metastases and PET imaging from Medline and EMBASE up to January 2004. Articles were included only if they provided a description of the impact of FDG-PET results in patients with recurrent colorectal carcinoma or a description of the impact on clinical management of patients.

Exclusion criteria
Systematic review articles as the individual studies were included in the review.

Population
N=32 studies included in the systematic analysis with all selected articles scored according to a weighting procedure.

Interventions
FDG-PET
CT

Outcomes
Sensitivity
Specificity

Results

	FDG-PET (95% CI)	CT (95% CI)
Pooled Sensitivity	91.5% (84.3 to 96.2)	60.9% (44.4 to 68.9)
Pooled Specificity	95.4% (71.4 to 98.4)	91.1% (66 to 92.8)

Table: pooled sensitivity and specificity for FDG-PET and CT for extra-hepatic metastases

	FDG-PET (95% CI)	CT (95% CI)
Pooled Sensitivity	91.2% *From 4 studies*	55.3% *From 3 studies*
Pooled Specificity	98.4% *From 4 studies*	95.6% *From 3 studies*

Table: pooled sensitivity and specificity for FDG-PET and CT for extra-hepatic metastases using only data from the 6 highest scoring articles to be included in the review.

General comments
The main focus of the review was to address the usefulness of FDG-PET in determining best management for patients with recurrent liver metastases, part of which addressed the effectiveness of FDG-PET in detecting extra-hepatic metastases. Only data relating to extrahepatic metastases are presented here.

The authors devised a system to compare, weight and summarise the data from different studies. This was done in a stepwise process:
1) A panel of experts consisting of a hepatic surgeon, a nuclear medicine physician, a methodologist and a radiologist constructed a concept study containing all items that should be included and weighted. The experts identified 5 different domains, each containing several items (detailed in the paper).
2) Every item in a domain was weighted (5-very significant to 1-not significant) by each individual member of the team and a consensus was achieved on the final weight factor of each item.
3) All articles were screened for the presence of the selected items. When an item was not available no points were awarded, in articles in which an item was covered partially 0.5 points were awarded and in articles where an item was present and reported 1 point was awarded.
4) The awarded points for each item were multiplied by the weight factor to achieve a final value per item and a total number of points per domain were calculated.

The scoring system was not designed to assess the quality of the individual studies, merely the contribution a given study made in addressing the usefulness of FDG-PET, that said there were no randomised trials with which to answer the question and therefore the studies included were of a generally low quality (prospective or retrospective case series) with small numbers (smallest study n=8, largest study n=115).

Several gaps in the literature were identified including a lack of randomised controlled trials. The included studies also failed to include a number of relevant items of information such as xo-morbidities, patient selection criteria and characteristics of primary tumour.

Author Conclusion: Despite apparent omissions in the literature, the pooled results indicate FDG-PET is useful in the diagnostic workup of patients with potentially resectable hepatic metastases from colorectal carcinoma, particularly in the detection of extrahepatic metastases which would preclude liver resection.

References of Included Studies (For systematic reviews):
A total of 32 studies were included in the review the citations for the six highest scoring studies (as determined by the authors) are:

Fong Y, Saldinger PF, Akhurst T, et al. (1999) Utility of 18F-FDG positron emission tomography scanning on selection of patients for resection of hepatic colorectal metastases *Am J Surg* 178;282-287

Imdahl A, Reinhardt MJ, Nitzsche EU, et al. (2000) Impact of 18F-FDG-positron emission tomography scanning for decision making in colorectal cancer recurrences. *Langenbecks Arch Surg* 385;129-134

Lai DT, Fulham M, Stephen MS, et al. (1996) The role of whole body positron emission tomography with [18F]fluorodeoxyglucose in identifying operable colorectal cancer metastases to the liver.

Langenhoff BS, Oyen WJ, Jager GJ, et al. (2002) Efficacy of fluorine-18-deoxyglucose positron emission tomography in detecting tumour recurrence after local ablative therapy for liver metastases: a prospective study *J Clin Oncol* 20;4453-4458

Ruers TJ, Langenhoff BS, Neeleman N, et al. (2002) Value of positron emission tomography with [F-18]fluorodeoxyglucose in patients with colorectal liver metastases: a prospective study *J Clin Oncol* 20;388-395

Valk P, Abella-Culmna E, Haseman M, et al (1999) Whole-body PET imaging with [F^{18}] fluorodeoxyglucose in management of recurrent colorectal cancer *Arch. Surg.* 134;503-511

4.4. Chemotherapy in Metastatic Colorectal Cancer

4.4.1. What is the effectiveness of oxaliplatin and irinotecan-based chemotherapy regimens for patients with advanced and metastatic colorectal cancer?

Short Summary

The objective of this review and analysis was to identify and synthesise the evidence on the clinical and cost effectiveness of chemotherapy regimens containing irinotecan or oxaliplatin for the treatment of advanced colorectal cancer. Evidence on the use of irinotecan or oxaliplatin for the treatment of advanced colorectal cancer has been previously reviewed and appraised within the scope of NICE Technology Appraisal Guidance 93 (TA93). The current review includes both an update to identify new evidence that has become available after TA93 was issued (August 2005) and an expansion to the scope to address the following issues that were deemed by the GDG to be relevant to recent developments in clinical practice:

- the use of irinotecan or oxaliplatin in combination with the oral fluoropyrimidine capecitabine
- sequencing of combination chemotherapy (first and second line)

The current review does not address the use of targeted agents or the use of capecitabine as monotherapy for the treatment of advanced colorectal cancer. These topics are covered elsewhere in related NICE technology appraisal guidance.

The following chemotherapy regimens were considered relevant to this review:

1. FOLFOX (oxaliplatin in combination with 5-flourouracil and folinic acid)
2. FOLFIRI (irinotecan in combination with 5-flourouracil and folinic acid)
3. XELOX (oxaliplatin in combination with capecitabine)
4. XELIRI (irinotecan in combination with capecitabine)
5. irinotecan as a single agent

The GDG identified ten sequences based on these chemotherapy regimens that were considered relevant to current clinical practice (Table 4.10). Sequences were limited to two lines of treatment.

Strategy	First line	Second line
1	FOLFOX	FOLFIRI
2	FOLFOX	XELIRI
3	FOLFOX	irinotecan
4	XELOX	FOLFIRI
5	XELOX	XELIRI
6	XELOX	irinotecan
7	FOLFIRI	FOLFOX
8	FOLFIRI	XELOX
9	XELIRI	FOLFOX
10	XELIRI	XELOX

Table 4.10 Summary of ten chemotherapy treatment sequences of interest

The search for evidence included randomised controlled trials (RCTs) that reported on response, progression-free survival and overall survival for one or more of the chemotherapy regimens of interest as first-line treatment, second-line treatment or as part of a prospectively sequenced trial. Head-to-head RCTs were not available to inform all comparisons of interest. In addition, overall survival is likely to be influenced by the sequence of chemotherapy treatments; data on overall survival that was reported from studies conducted only in first line (with limited information about subsequent treatment) or only in second line (with limited information about prior treatment) was

regarded with caution, thus further limiting the number of head-to-head comparisons available to inform this endpoint.

In order to facilitate a comparative analysis of all ten chemotherapy sequences, it was necessary to consider evidence that enabled indirect comparison of the treatments of interest. For example, if an RCT existed comparing two treatments A vs B, and another RCT existed comparing B vs C, however no RCT was identified comparing A vs C, then the evidence from the RCTs comparing A vs B and B vs C can be used to produce an indirect estimate of the relative effectiveness of A vs C. For the analysis of first-line treatment effects, both head-to-head trials (direct comparisons) as well as indirect comparisons were simultaneously considered as part of the evidence base to inform the estimate of effect size between 2 or more treatments of interest, therefore the analysis for first line is referred to as a mixed treatment comparison (MTC). To quantify second-line treatment effects and overall survival for sequences of chemotherapy, only a small number of relevant studies were identified as part of the evidence base. Each comparison was informed by using either direct evidence from a head-to-head trial or indirect evidence via a common comparator, but not by both types of evidence simultaneously. Therefore the second-line analysis is more accurately referred to as an indirect (rather than mixed) treatment comparison.

The motivations for applying mixed and indirect treatment comparison techniques to the present analysis include:

• Indirect comparisons allow estimation of treatment effects for comparisons that have not been trialled head-to-head, without breaking randomisation (Sutton et al. 2008)
• All ten treatment sequences of interest can be compared simultaneously, using one consistent evidence base (for each outcome of interest). Consideration of both direct and indirect comparisons provides an opportunity to formally assess the consistency of the evidence
• Results of the analysis are needed to inform a comparative cost-effectiveness analysis of all ten treatment sequences of interest

Mixed and indirect treatment comparisons were modelled to estimate relative effects to a common baseline for the outcomes response rate, progression-free survival and overall survival. Important assumptions and methods underpinning the analysis are described in detail below. The analysis was performed using the Bayesian WinBUGS 1.4.3 software.

Assessing each individual trial using the NICE methodology checklist for randomised trials showed that in almost all aspects the individual studies were of a high standard methodologically. The method of randomisation was adequate in most cases with only a small number of studies not providing details of the method used and in almost all cases, the groups were well balanced at baseline, primarily the result of stratification for key factors. It was not clear in any study however, whether there was adequate allocation concealment. It was therefore concluded that overall, there was a low risk of selection bias.

In all studies patients in both arms received the same care apart from the treatment of interest, however none of the patients or treatment administrators was blinded as it was not possible given the type of treatments administered and methods of administration. Despite this however, it is unlikely that there was a high risk of performance bias overall as the studies were all comparing very similar treatments in comparable patients.

In first line, there appears to be a small benefit in favour of FOLFOX with respect to response rate. XELIRI was associated with the second highest probability of being the best out of the four regimens, however as there was only one RCT to connect XELIRI to FOLFIRI in the evidence network, the estimate of effectiveness for XELIRI is associated with a high degree of uncertainty as seen by the width of the 95% credible interval.

Treatment with FOLFOX/XELOX in second line (following FOLFIRI/XELIRI in first line) was associated with significantly higher response rate than FOLFIRI/XELIRI in second line (following FOLFOX/XELOX in first line). Response rates for single agent irinotecan in second line were comparable to FOLFOX/XELOX in second line, however FOLFOX/XELOX were still the treatment options associated with the highest probability of being the most effective regimens in second line.

Review Protocol

Population	Intervention (first line, second line)	Comparison	Outcomes
Patients with advanced and metastatic colorectal cancer	FOLFOX, FOLFIRI FOLFOX, XELIRI FOLFOX, irinotecan XELOX, FOLFIRI XELOX, XELIRI XELOX, irinotecan FOLFIRI, FOLFOX FOLFIRI, XELOX XELIRI, FOLFOX XELIRI, XELOX	Each other	• Response • Progression-free survival • Overall survival • Toxicity • Quality of life

Following a systematic search of relevant data sources (see appendix .1), the information specialist created a database of potentially relevant studies. All titles and abstracts were sifted by a single reviewer. Queries about inclusion were clarified by the GDG topic subgroup. The full studies were then obtained and reviewed and relevant studies were included in the final evidence review.

All update searches were sifted by a single reviewer and the list of potentially relevant studies was also checked for irrelevant studies by the GDG subgroup. Only studies which all subgroup members were in agreement were excluded. The remaining studies were obtained and reviewed with relevant studies included in the final evidence review.

Evidence on the use of irinotecan or oxaliplatin for the treatment of advanced colorectal cancer has been previously reviewed and appraised within the scope of NICE Technology Appraisal Guidance 93 (TA93). The current review includes both an update to identify new evidence that has become available after TA93 was issued (August 2005) and an expansion to the scope to address the following issues that were deemed by the GDG to be relevant to recent developments in clinical practice:

- The use of irinotecan or oxaliplatin in combination with the oral fluoropyrimidine capecitabine
- Sequencing of combination chemotherapy (first and second line)

In this PICO, it was assumed that patients are eligible to receive either oxaliplatin or irinotecan treatment. This means separate consideration was not specifically given to patients who received oxaliplatin in the adjuvant setting (and who may therefore be less likely to benefit from further oxaliplatin as a first-line treatment for advanced disease).

The current review does not address the use of targeted agents or the use of capecitabine as monotherapy for the treatment of advanced colorectal cancer.

The following chemotherapy regimens were considered relevant to this review:

- FOLFOX (oxaliplatin in combination with 5-flourouracil and folinic acid)
- FOLFIRI (irinotecan in combination with 5-flourouracil and folinic acid)
- XELOX (oxaliplatin in combination with capecitabine)
- XELIRI (irinotecan in combination with capecitabine)
- irinotecan as a single agent

From the PICO, it is clear we are interested in looking at sequences of treatment. It is likely that some of these sequences will not have been studied prospectively in a controlled trial. In order to make use of the widest possible evidence base, it will be likely that there will be a need to apply methods to put together (synthesise) the available evidence for the analysis. The following approach is planned:
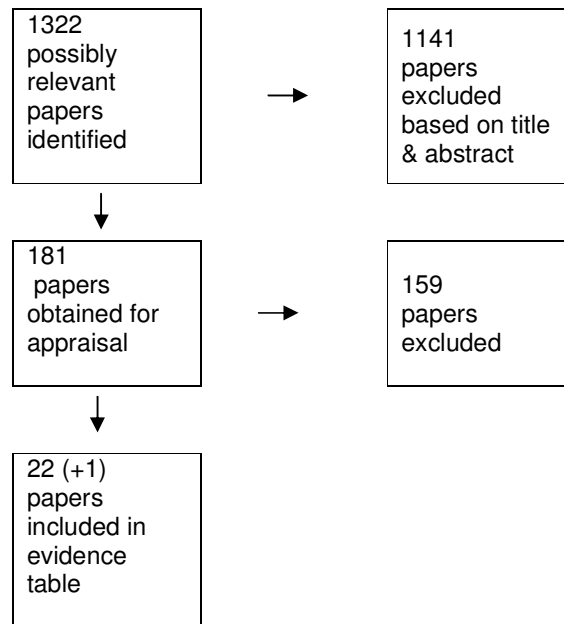
- All available evidence on any of the regimens identified in the line of treatment which have been specified will be reviewed. For those regimens that were reviewed as part of TA93, the body of evidence that was identified and included as part of TA93 will be combined with any new evidence that is identified through an updated search of the relevant literature published since TA93.
- Response/progression free survival data by line will be extracted where available
- Overall survival will be based on data available from sequenced trials
- If head-to-head evidence is not available for some regimens, there may be a need to use indirect treatment comparisons.
-

Reasons for Exclusion:

Not a relevant comparator
Population not relevant
Not a randomised trial
Foreign Language
Expert Reviews
Abstracts Only
Data not reported in a format suitable for inclusion in mixed treatment analysis

Quality of the included studies

Systematic review of RCTs (n =0)
Systematic review of combined study designs (n =0)
Randomized controlled trial (n =23)
Prospective cross sectional study (n =)
Retrospective cohort study (n=)
Case Series Studies (n = 0)

1322 possibly relevant papers identified → 1141 papers excluded based on title & abstract

↓

181 papers obtained for appraisal → 159 papers excluded

↓

22 (+1) papers included in evidence table

Head-to-head RCTs were not available to inform all comparisons of interest. In addition, overall survival is likely to be influenced by the sequence of chemotherapy treatments; data on overall survival that was reported from studies conducted only in first line (with limited information about subsequent treatment) or only in second line (with limited information about prior treatment) was regarded with caution, thus potentially further limiting the number of head-to-head comparisons available to inform this endpoint.

In order to facilitate this review, it was necessary to consider evidence that also enabled indirect comparison of the treatments of interest. For example, if an RCT existed comparing two treatments A vs B, and another RCT existed comparing B vs C, however no RCT was identified comparing A vs C, then the evidence from the RCTs comparing A vs B and B vs C can be used to produce an indirect estimate of the relative effectiveness of A vs C. For the present review, both head-to-head trials (direct comparisons) as well as indirect comparisons were considered as part of the evidence base, therefore the analysis presented here is referred to as a mixed treatment comparison (MTC).

Quality Assessment

The quality assessment for this topic cannot be produced in GRADE as the software cannot yet accommodate the issues surrounding indirect treatment comparisons. GRADE has been designed to assess the quality of the total body of evidence for a given outcome rather that the methodological quality of individual studies included in the analysis. While this is certainly a more informative and useful way in which to assess the quality of evidence, an indirect treatment comparison presents a particular problem in that the information used to inform the model includes, where possible, direct evidence, but in many cases will also include data from studies which do not directly assess the interventions of interest against each other and is so considered indirect evidence.

Assessing each individual trial using the NICE methodology checklist for randomised trials showed that in almost all aspects the individual studies were of a high standard methodologically. The method of randomisation was adequate in most cases with only a small number of studies not providing details of the method used and in almost all cases, the groups were well balanced at baseline, primarily the result of stratification for key factors. It was not clear in any study however, whether there was adequate allocation concealment. It was therefore concluded that overall, there was a low risk of selection bias.

In all studies patients in both arms received the same care apart from the treatment of interest, however none of the patients or treatment administrators was blinded as it was not possible given the type of treatments administered and methods of administration. Despite this however, it is unlikely that there was a high risk of performance bias overall as the studies were all comparing very similar treatments in comparable patients.

In the majority of studies, it was unclear how the individual arms were affected by patient drop outs or partial treatment administration. The median number of treatment cycles per arm was reported and in some studies a full study flow chart was provided which detailed the number of patients in each arm that received treatment, dropped out or were lost to follow-up. Median length (and in some cases, range) of follow up was reported in all studies and a number of studies also reported the length of time post recruitment that data were collected, however this information was for the whole patient group as opposed to each arm and it was not clear from any of the individual studies whether the length of follow-up was similar in both arms. There is a possibility that some studies might be affected by attrition bias, however, from the data that are reported, this seems unlikely.

Overall, the length of follow-up and outcomes reported were deemed to be appropriate. The primary outcomes of interest to the topic were response, progression-free survival and overall survival, with toxicity and quality of life also of interest where available.

- Response: a precise definition was provided as to what was considered a response and the data were clearly reported across the individual studies.
- Progression-free Survival: data on time to disease progression was reported as progression-free survival in most studies, however some trials reported time to progression instead
- Overall Survival
- Toxicity: toxicity was reported in some format in the majority of studies included in the review; most commonly reported were Grade 3-4 toxicities, though some studies also reported Grades 1-2 toxicities. Toxicities were reported primarily as a rate or an absolute value for each specific toxicity of interest.
- Quality of Life: the quality of reporting of quality of life was very poor across the individual studies, the majority of studies which included quality of life as an outcome did not provide any data, with only a small number of studies making any attempt to quantify the changes in QoL from baseline through the use of questionnaires.

Design
All studies included in the review were RCTs comparing treatments in first line or in a predetermined sequence of treatments and were all of high methodological quality.

Data for progression-free survival first line were taken from 22 randomised studies, including the prospectively sequenced studies; data for progression-free survival second line were taken from only prospectively sequenced studies and data to inform overall survival on second line treatment for a given sequence.

Limitations
The primary limitation was the lack of trials comparing predefined sequences of treatment with the majority of studies available comparing treatments of interest either in first line only or second line only trials. A second major limitation occurred in relation to the second line studies in that results of second line treatment, particularly overall survival, are dependent not only on second line treatment but what the patient received in the first line and this was a factor that was not adequately addressed in second line studies.

Consistency
There was a high degree of consistency across the individual trials in relation to populations included (irrespective of treatments under investigation); effect size for treatments was consistent across the individual studies. On reviewing the individual trials it appeared that there were some differences in the doses administered for some treatment regimens which may have precluded combining the data, however this did not appear to impact effect size and GDG members were satisfied that studies could be combined for meta-analysis.

Indirectness
There were three sequenced studies (Tournigand et al, 2004; Cunningham et al, 2009 and Koopman et al, 2007) one of which was directly relevant to the topic in question and two of which provided some indirect evidence for the comparisons of interest. The majority of the data were taken from studies which were not comparing treatments of interest and so under normal GRADE methodology the evidence body would be downgraded for indirectness, however this was not considered appropriate in the context of an MTC analysis.

Evidence Synthesis Methods

First-line treatment
A total of twenty-three studies reported the number of responders out of the total number of patients receiving each treatment as first-line therapy, corresponding to the network of evidence in Figure 4.8. A list of included studies is provided in Table 4.18.

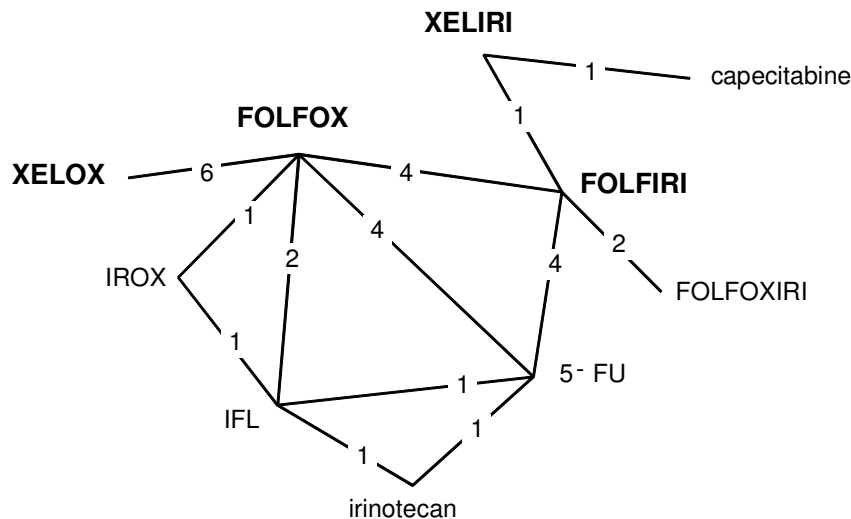

Figure 4.8 MTC network of evidence used to inform response rate and progression-free survival for first-line treatments. Treatments in bold text are of primary interest to the analysis. A line between two treatments indicates a head-to-head comparison (RCT) exists; the numbers represent the number of trials comparing two treatments.

Study first author	Year	Treatment

		Arm 1	Arm 2	Arm 3
Comella	2009	FOLFOX	XELOX	
Martoni	2006	FOLFOX	XELOX	
Diaz-Rubio	2007	FOLFOX	XELOX	
Porschen	2007	FOLFOX	XELOX	
Hochster	2008	FOLFOX	XELOX	
Ducreux	2010	FOLFOX	XELOX	
Tournigand*	2004	FOLFOX	FOLFIRI	
Comella	2005	FOLFOX	FOLFIRI	
Colucci	2005	FOLFOX	FOLFIRI	
Seymour*	2007	FOLFOX	FOLFIRI	5-FU
de Gramont	2000	FOLFOX	5-FU	
Giacchetti	2000	FOLFOX	5-FU	
Cunningham	2009	FOLFOX	5-FU	
Goldberg	2006	FOLFOX	IFL	
Goldberg	2004	FOLFOX	IFL	IROX
Kohne	2008	FOLFIRI	XELIRI	
Kohne	2005	FOLFIRI	5-FU	
Douillard	2000	FOLFIRI	5-FU	
Souglakos	2006	FOLFIRI	FOLFOXIRI	
Falcone	2007	FOLFIRI	FOLFOXIRI	
Gennatas	2006	FOLFIRI	5-FU	
Saltz	2000	5-FU	IFL	irinotecan
Koopman*	2007	XELIRI	capecitabine	

*Sequenced trial: only first-line data used

Table 4.11 – Studies that informed the MTC for response rate and progression-free survival for first-line treatments.

First-line response rate relative effects

We assumed that for each trial j, the number of events in arm k, r_{jk}, has a binomial likelihood $r_{jk} \sim \text{Bin}(p_{jk}, n_{jk})$ where p_{jk} is the probability of an event (response) in arm k of trial j and n_{jk} are the total number of patients in arm k of trial j. A random effects model for p_{jk} was fitted on the logit scale, such that for each trial $\text{logit}(p_{j1}) = \mu_j$ in the control arm ($k=1$) and $\text{logit}(p_{jk}) = \mu_j + \delta_{jk}$, for the treatment arms ($k=2$ or 3 for three arm trials) with δ_{jk} representing the trial-specific log-odds ratio of the treatment in arm k relative to the control treatment in trial j and μ_j representing the study-specific effects (baseline effects). We fit a random effects MTC model, with FOLFOX as the reference treatment, under the assumption of consistency and homogeneous variance of the random effects (Lu and Ades, 2004). Defining t_{jk} as the treatment in arm k of trial j, the trial-specific log-odds ratios, δ_{jk}, are drawn from one of the random effects distributions $\delta_{jk} \sim N(d(t_{jk}) - d(t_{j1}), \sigma^2)$ where $d(t_{jk})$ is the relative treatment effect of the treatment t_{jk} vs FOLFOX, $k=1,2,3$ and σ^2 is the between-study heterogeneity. A vague inverse-gamma prior on σ^2 was used since it resulted in faster convergence and smoother posterior densities than the alternative Uniform prior on σ. Posterior mean and median results were largely unaffected by the choice of prior distribution, but the estimates of σ^2 varied slightly.

First-line response rate baseline calculation for absolute effects

In order to obtain absolute effects, it is necessary to obtain a baseline treatment effect for the reference treatment (FOLFOX), on which the relative treatment effects are applied. Any of the four first-line treatments of interest could be used as the reference treatment, however FOLFOX was chosen as it was the most frequently studied treatment out of the twenty-three available head-to-head trials. A separate meta-analysis (on the logit scale) was performed on just the FOLFOX arms of the

fifteen trials comparing FOLFOX to any other drug (in first line). The predictive distributions of the log-odds of FOLFOX in a future trial were assumed to be normal with posterior means m_A=-0.1119 and standard deviations sd_A=0.3071. These results were then used in the MTC model to generate a baseline treatment effect for FOLFOX, A~Normal(m_A, sd_A^2) on the log-odds scale on which relative effects were added at each iteration, to deliver the posterior summaries of the absolute probability of response for each treatment.

First-line progression-free survival relative effects
All twenty-three studies listed in Table 4.18 that reported response rates also provided data on disease progression (reported as progression-free survival or time to progression). In twelve of these studies, median PFS was accompanied by a hazard ratio (HR) with associated confidence interval (CI). The HR should be preferred to the median for survival analysis as it incorporates information on censoring (Tierney et al., 2007), so when both were available, the analysis was carried out on the log-hazard ratio (LHR). The data were transformed from HR into LHR and the standard error of the LHR obtained from the transformed CI by assuming an underlying normal distribution (Parmar et al.1998).

When only the median PFS and its CI were available (five studies), these were log-transformed and the standard error of ln(median) calculated by assuming an underlying normal distribution (Parmar et al., 1998). Checks were made to ensure that the CI were symmetric on the log-median scale.

Six studies presented only the median PFS with no measure of uncertainty. In five of these studies (Colucci et al. 2005, Seymour et al. 2007, de Gramont et al. 2000, Gennatas et al. 2006, Douillard et al. 2000, Souglakos et al. 2006) a p-value for the log-rank test of a difference in the Kaplan-Meier curves was available. This was used to obtain an approximate LHR and standard error assuming the test statistic referred to a standard normal distribution and no censoring. Since no information was available on the number of observed events it was assumed that all analysed patients had progressed (Tierney et al. 2007). Saltz et al. 2000 did not present a p-value for the comparisons of interest but the number of patients at risk at different time points was available. Survival probabilities at each of the time points were read off the survival curves and a LHR and variance estimated following Williamson et al. 2002.

Let y_{jk} represent the log-hazard ratio of the treatment in arm k of study j, relative to the treatment in arm 1 of trial j, and W_{jk} represent the variance of the corresponding LHR. For the 17 trials for which the LHR and standard error were available (from the publications or imputed), the likelihood was defined as

$$y_{jk} \sim \text{Normal}(\delta_{jk}, W_{jk}) \text{ with } \delta_{jk} \sim \text{N}(d(t_{jk})-d(t_{j1}), \sigma^2) \quad j=1,\ldots,17, k=2,3$$

where δ_{jk} are the trial-specific LHR for each study, assumed to come from the random effects distribution above. A random effects mixed treatment comparisons (MTC) model was fitted, with FOLFOX as the reference treatment, under the assumption of consistency and homogeneous variance of the random effects, as above (Lu et al. 2004).

Let M_{jk} represent the median PFS in arm k of study j and V_{jk} represent the variance of ln(M_{jk}). Then, for the 5 trials where the media PFS is used, the median PFS is assumed to follow a log-normal distribution such that $M_{jk} \sim$ log-Normal(m_{jk}, V_{jk}), and

$$\ln(M_{jk}) \sim \text{Normal}(m_{jk}, V_{jk}) \quad j=1,\ldots,5, k=1,2$$

Assuming the underlying PFS in arm k of trial i has an exponential distribution with rate λ_{jk}, the expected value of the median of an exponential distribution is $\ln(2)/\lambda_{jk}$ and the HR of arm k compared to arm 1 in trial j is $\lambda_{jk}/\lambda_{j1}$. Further, the expected value from a log-normal distribution is exp($m_{jk} + V_{jk}/2$), therefore we can model the log-rates by taking

$$m_{jk}=\ln(\ln 2) - \ln(\lambda_{jk}) - V_{jk}/2$$

and $\ln(\lambda_{jk})= \mu_j+\delta_{jk}$ with $\delta_{jk} \sim \text{N}(d(t_{jk})-d(t_{j1}), \sigma^2)$, for the treatment arms (k=2 or 3 for three arm trials) with δ_{jk} representing the trial-specific log-hazard ratio of the treatment in arm k relative to the control treatment in trial j and μ_j representing the study-specific effects (baseline effects). Note that the trial-specific LHR, δ, are assumed to be coming from the same random effects distributions, whether they

refer to a study with data on the LHR directly or through the link function for studies with data given as medians with uncertainty.

First-line progression-free survival baseline calculation for absolute effects
In order to obtain absolute effects, it is necessary to obtain a baseline median PFS for FOLFOX, on which the relative treatment effects are applied. Of the fifteen studies comparing FOLFOX to any other treatment (in first line), six did not report any uncertainty measure for the median in the FOLFOX arm. We have therefore used only the nine studies for which a variance for the log-median could be extracted (Comella et al. 2009, Martoni et al. 2006, Diaz-Rubio et al. 2007, Hochster et al. 2008, Ducreuc et al. 2010, Tournigand et al. 2004, Comella et al. 2005, Giacchetti et al. 2000, Cunningham et al. 2009) to calculate the baseline PFS on FOLFOX. A separate meta-analysis was performed on the FOLFOX arms of these nine trials. The predictive distributions of the log-hazard of PFS on FOLFOX in a future trial were approximately normal with posterior means m_A= -2.467 and standard deviations sd_A= 0.1569. These results were then used in the MTC model to generate a baseline $A \sim Normal(m_A, sd_A^2)$ on the log-hazard scale on which relative effects were added at each iteration, to deliver the posterior summaries on the absolute log-hazard and hazard PFS and time to progression for each treatment.

Second-line treatment and sequences
The search for RCTs identified four studies in which two treatments of interest had been compared specifically as second-line chemotherapy (Table 4.19). However upon examination of the inclusion criteria for these studies, it was noted that all patients in these trials had received either single agent irinotecan or singe agent 5-fluorouracil as first-line treatment for advanced colorectal cancer. Therefore, these studies did not reflect the specific treatment sequences of interest to the current review and were excluded from the indirect treatment comparison analysis.

Study first author	Year	Treatment		Prior first-line treatment
		Arm 1	Arm 2	
Rothenberg	2008	FOLFOX	XELOX	irinotecan
Kim	2009	FOLFOX	irinotecan	5-FU
Rougier	1998	irinotecan	5-FU	5-FU
Haller	2008	irinotecan	IROX	5-FU or capecitabine

Table 4.12 Second-line studies that included patients who received first-line treatment outside the treatment sequences of interest and were therefore excluded from the indirect treatment comparison analysis

The only other source of data on second-line response rates and PFS for the treatment sequences of interest was from prospectively sequenced studies. Three prospectively sequenced trials were available (Tournigand et al. 2004, Koopman et al. 2007 and Seymour et al. 2007) and reported data on response rate and PFS after first and second line. However, Seymour et al. 2007 did not compare any sequences of interest or any sequences common to the other two trials, and was therefore excluded from the evidence space. The remaining trials provide evidence on only three of the ten sequences of interest and do not form a connected evidence network.

The endpoint overall survival was reported for all studies (first line, second line and prospectively sequenced). However, in the majority of the first-line studies, patients went on to receive a mix of second-line treatments. The second-line treatments offered were usually not pre-specified and rarely reported in sufficient detail. Furthermore, where some data was available on which second-line treatments were received by patients, the medians or HR for overall survival were not reported separately for the different treatments. Since we expect second-line treatment to influence overall survival (preliminary analyses, not shown, also suggested this was the case), it was not considered appropriate to use data on overall survival from first-line studies in which the patients who had second-line treatment received a mix of different chemotherapy to inform the analyses for specific treatment sequences. An exception to this was the Cunningham et al. 2009 trial that compared FOLFOX and 5-FU; although this was a first-line study, the protocol had pre-specified that patients who progressed on the first-line treatment should be offered irinotecan as second-line treatment. The trial further reported that a high proportion (over 75%) of patients received second-line irinotecan in

both arms. It was therefore decided that this trial could be considered a 'quasi-sequenced' trial comparing the sequence FOLFOX followed by irinotecan to the sequence 5-FU followed by irinotecan. One other study (Porschen et al. 2007) also fulfilled these criteria. This was a first-line study of FOLFOX vs XELOX in which a high proportion of patients went on to receive irinotecan-based second-line treatment. This study was considered a 'quasi-sequenced' trial of FOLFOX followed by irinotecan vs XELOX followed by irinotecan. No other studies fulfilled the criteria for sequences of interest.

Even after inclusion of Cunningham et al. 2009 and Porschen et al. 2007 in the evidence base (Table 4.20), the network remains disconnected and still does not provide sufficient data to compare all sequences of interest. In discussion with members of the GDG, equivalence of the effectiveness of the oral and iv fluoropyrimidine formulations (capecitabine and 5-FU) was hypothesised. If data supported the assumption that the treatment effect of FOLFOX is the same as the treatment effect of XELOX, the treatment effect of FOLFIRI is the same as the treatment effect of XELIRI, and treatment effect of capecitabine is the same as the treatment effect of 5-FU in first and second line, this would allow the ten sequences of interest to reduce to only three sequences comprised of a fluoropyrimidine backbone combined with either oxaliplatin or irinotecan and irinotecan as a single agent in second line:

1. FOLFOX or XELOX followed by FOLFIRI or XELIRI
2. FOLFIRI or XELIRI followed by FOLFOX or XELOX
3. FOLFOX or XELOX followed by single agent irinotecan

Exploratory analyses were conducted to confirm that this assumption was supported by the data on response and PFS. We checked if the 95% credible interval obtained from the first-line random effects MTC analysis for the HR of PFS included 1, which was the case for both XELOX vs FOLFOX and for XELIRI vs FOLFIRI. Similarly for response, the 95% credible interval for the OR for XELIRI vs FOLFIRI included 1, although for XELOX vs FOLFOX the upper limit did not (0.98). Although MTC analysis was not performed on studies that were only conducted in second line, data from Rothenberg et al. 2008 (comparing FOLFOX to XELOX) could still inform the equivalence of fluoropyrimidine-containing regimens. Analysis of this study showed that the 95% credible intervals for OR for response and HR for PFS both included 1.

Statistical models assuming equivalence of the effects of FOLFOX to XELOX, FOLFIRI to XELIRI and capecitabine to 5-FU were fitted for first -line response and PFS and were compared using the Deviance Information Criterion (DIC) to models that did not assume equivalence. These models were found to be similar in terms of model fit (DIC 83.2 for response and 54.4 for PFS, which were comparable to 83.6 and 56.1 respectively for the model not assuming equivalence).

Applying the above assumptions, this allowed us to form a connected evidence network shown in Figure 4.9. Since only one trial was available to inform each sequenced treatment comparison, a fixed effect model was fitted. It should be note that the assumption of equivalence in treatment effect between capecitabine and 5-FU was not extended to other aspects of treatment such as toxicity or cost. The latter parameters were not included in the indirect treatment comparison analysis and have been summarised elsewhere.
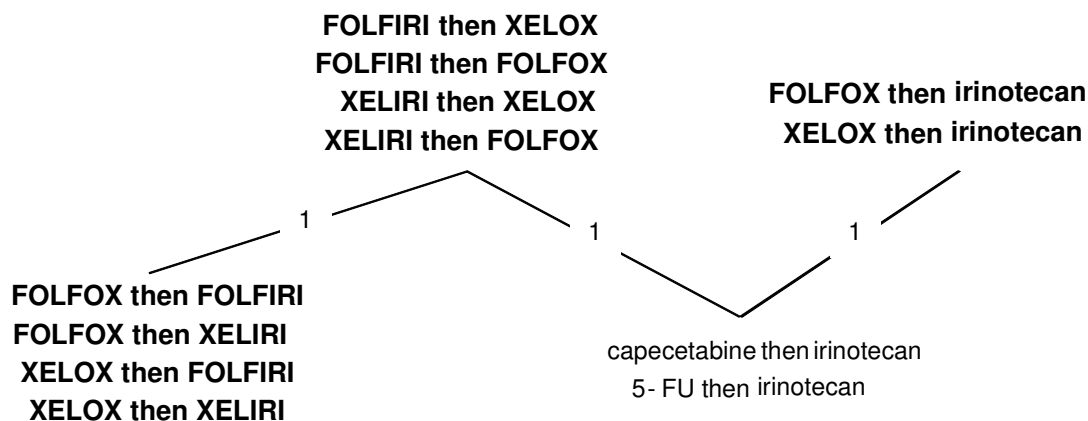
Figure 4.9 Network of sequenced studies to inform second-line response rate, progression-free survival and overall survival (assuming equivalent effect of capecitabine and 5-FU).

Study first author	Year	Treatments (sequenced)	
		Arm 1	**Arm 2**
Tournigand	2004	FOLFOX then FOLFIRI	FOLFIRI then FOLFOX
Koopman	2007	XELIRI then XELOX	capecitabine then irinotecan
Porschen* +	2007	FOLFOX then irinotecan	XELOX then irinotecan
Cunningham*	2009	FOLFOX then irinotecan	5-FU then irinotecan

*Quasi-sequenced trials: the protocol pre-specified patients should receive single agent irinotecan in second line.
+This trial informed the relationship (equivalence) between FOLFOX followed by irinotecan and XELOX followed by irinotecan

Table 4.13 Sequenced studies included in the MTC analysis to inform second-line response rate, progression-free survival and overall survival.

Second-line response rate and progression-free survival for sequences relative effects
Data on response rate and median PFS on second-line treatment for the sequences of interest were reported in Tournigand et al. 2004 and Koopman et al. 2007, but not in Cunningham et al. 2009 as the latter was a 'quasi-sequenced' study. However, Cunningham et al. 2009 did report that the median duration of second-line treatment was the same in both arms of this study. As patients usually continue treatment until disease progression (or unacceptable toxicity), we assumed that mean duration of treatment is highly correlated with PFS and imputed the HR of PFS on second-line treatment in the Cunningham et al. 2009 study as 1 (i.e. no difference in treatments). The standard error of the LHR was imputed as 0.1393 based on the relationship between the standard errors for all other LHRs and the study sample size, available from first and second- line studies both observed and imputed.

For the analysis of response rate on second-line treatment for a given sequence, rather than impute the number of patients responding to second-line treatment for the two arms of the trial, we imputed the LOR expected for this study, based on the relationship between all other observed LOR and the LHR for PFS in second line. The standard error for the LOR was imputed based on the relationship between all other available se(LHR) and the study sample size. The LOR of response on second line for the Cunningham et al. 2009 study was imputed as 0.03 with standard error=0.2492.

Overall survival for sequences relative effects
Two studies presented the HR and CI for overall survival. The analysis was carried out on the LHR for these studies with the standard error of the LHR obtained from the log-transformed CI by assuming an underlying normal distribution as above. One study reported only median overall survival and CI. These were log-transformed and the standard error of ln(median) calculated from the CI, as before.

The model used to combine the LHR and medians was the fixed effects version of the model used for first line data, so that for all trials for which the LHR and standard error were available, the likelihood was defined as

$$y_{jk} \sim \text{Normal}(d(t_{jk})-d(t_{j1}), W_{jk}) \text{ with } j=1,2,3, k=2$$

and for the trial in which median OS was reported, this was assumed to follow a log-normal distribution such that $\ln(M_{jk}) \sim \text{Normal}(m_{jk}, V_{jk})$, $j=1$, $k=1,2$, $m_{jk}=\ln(\ln2) - \ln(\lambda_{jk})- V_{jk}/2$ as before, and $\ln(\lambda_{jk})= \mu_j+d(t_{jk})-d(t_{j1})$.

Second-line response rate, progression-free survival and overall survival baseline calculation for absolute effects

Only one sequenced study provided information on the absolute effect of FOLFOX (XELOX) followed by FOLFIRI (XELIRI) (Tournigand et al. 2004). The baseline value calculated in the model for this study was taken to be the absolute effect of this sequence on second-line response rate, PFS and overall survival. A further element of uncertainty was added so that the absolute effects were calculated as the absolute effect of FOLFOX (XELOX) followed by FOLFIRI (XELIRI) plus a random term E with $E \sim N(0,s_E^2)$ where s_E was the predictive standard deviation for a future trial with FOLFOX as first-line treatment (obtained from all the first-line data, as above).

A baseline median OS for FOLFOX based on the first-line studies was obtained as follows: of the fourteen studies comparing FOLFOX to any other treatment in first line, data on OS was not extractable for the relevant comparisons for Seymour et al. 2007; Martoni at al.2006 had no data on OS and a further 5 trials did not have any measure of uncertainty around the median OS in the FOLFOX arm. We therefore used the remaining eight trials (Comella et al. 2009, Diaz-Rubio et al. 2007, Hochster et al. 2008, Ducreux et al. 2010, Comella et al. 2005, Giacchetti et al. 2000, Cunningham et al. 2009, Tournigand et al. 2004) to calculate the baseline OS when receiving FOLFOX in first line. A separate meta-analysis was performed on the FOLFOX arms of these eight trials. The predictive distributions of the log-hazard of OS of FOLFOX in a future trial were approximately normal with posterior means m_A= -3.218 and standard deviations sd_A= 0.4690. Therefore s_E=0.3071, 0.1606 and 0.4690 for response, PFS and OS respectively.

Model criticism

The posterior mean of the residual deviance (ResDev) will be used to assess whether the MTC model is satisfactory in terms of fit to the data. The residual deviance is the deviance for the fitted model minus the deviance for the saturated model. In an adequately fitting model, each data point should contribute about 1 to the posterior mean residual deviance (Spiegelhalter et al., 2002), so the posterior mean of the residual deviance will be compared to the number of data points used to inform each analysis. Inspection of each data point's contribution to the residual deviance can help identify data points contributing to the model's poor fit.

Estimation

All posterior summaries were obtained using Markov chain Monte Carlo (MCMC) simulation implemented in the WinBUGS 1.4.3 software. The study effects, μ_i, and all relative treatment effects have been given vague priors: N(0,10000). For all random effects MTC models, a vague prior is assumed for the common variances so that, $1/\sigma^2 \sim$ Gamma(0.001,0.001). Sensitivity of the results to Uniform(0,10) prior for σ was assessed and this did not change the posterior means of the treatment effects, but did make the results more unstable. Results using the Gamma priors are quoted throughout.

Three chains were run until convergence according to the Brooks-Gelman-Rubin diagnostic tool (Brooks et al. 1998) and through inspection of the history plots. These "burn-in" simulations were then discarded, and a further 100,000 iterations run for three independent chains in the models for first line data. In models for sequences 200,000 iterations were run post-convergence since there was moderate auto-correlation between the treatment effect estimates. All inference is based on the posterior summaries from these combined chains.

Mixed and Indirect Treatment Comparison Results

Results are presented below for the MTC for first-line treatment response rate and PFS and for the indirect treatment comparison for second-line sequenced treatment response rate, PFS and overall survival. Both relative effects and absolute estimates are reported for each outcome.

First-line treatment response rate

The results for first-line treatment response rate are shown in Tables 4.21 and 4.22.

Treatment	OR (95% CrI)	Prob best	
FOLFOX (reference)	1	0.63	
XELOX	0.79 (0.63, 0.98)	0.01	
FOLFIRI	0.74 (0.61, 0.91)	0.00	
XELIRI	0.80 (0.23, 2.89)	0.36	
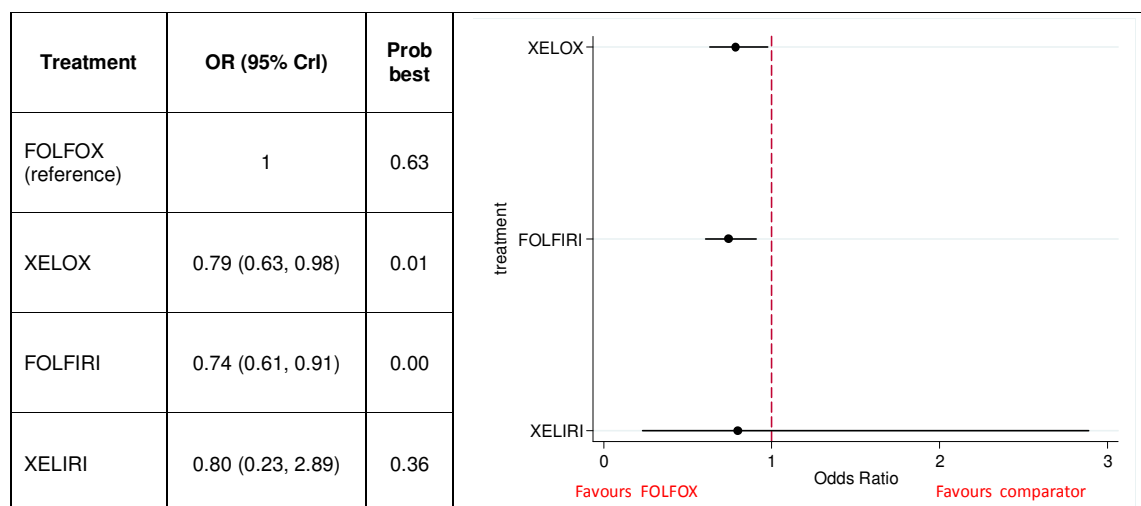
Table 4.14 Posterior median of odds ratio (OR) for response rate for first-line treatment with 95% credible interval and probability that each treatment is best out of the four treatments of interest. OR < 1 favours the reference treatment.

The residual deviance for the random effects model used for the analysis of first-line response rates was 48.7 which, compared to 49 data points, suggests a good model fit.

Treatment	Absolute response rate (95% CrI)
FOLFOX (reference)	0.47 (0.33, 0.62)
XELOX	0.41 (0.27, 0.57)
FOLFIRI	0.40 (0.26, 0.56)
XELIRI	0.42 (0.15, 0.75)

Table 4.15 Posterior summaries of the absolute response rate for first-line treatment (median with 95% credible interval).

In first line, there appears to be a small benefit in favour of FOLFOX with respect to response rate. XELIRI was associated with the second highest probability of being the best out of the four regimens, however as there was only one RCT to connect XELIRI to FOLFIRI in the evidence network, the estimate of effectiveness for XELIRI is associated with a high degree of uncertainty as seen by the width of the 95% credible interval.

First-line treatment progression-free survival

The results for first-line treatment progression-free survival are shown in Tables 4.23 and 4.24.

Treatment	HR (95% CrI)	Prob best	
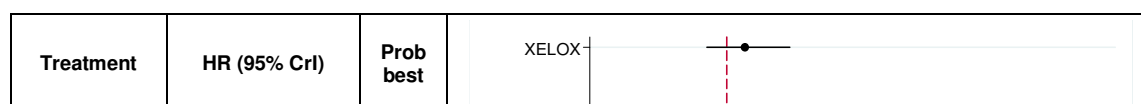
FOLFOX (reference)	1	0.66
XELOX	1.07 (0.92, 1.25)	0.15
FOLFIRI	1.09 (0.94, 1.26)	0.10
XELIRI	1.43 (0.82, 2.48)	0.09

Table 4.16 Posterior summaries (median with 95% credible interval) of hazard ratio (HR) for PFS for first-line treatment and probability that each treatment is best out of the 4 treatments of interest. HR > 1 favours the reference treatment.

The residual deviance for the random effects model used for the analysis of first-line PFS was 33.0 which, compared to 31 data points, suggests a good model fit.

Treatment	Mean PFS in months (95% CrI)	Median PFS in months (95% CrI)
FOLFOX (reference)	11.8 (8.67, 16.01)	8.2 (6.01, 11.10)
XELOX	11.0 (7.79, 15.44)	7.6 (5.40, 10.70)
FOLFIRI	10.9 (7.72, 15.25)	7.5 (5.35, 10.57)
XELIRI	8.3 (4.39, 15.49)	5.7 (3.04, 10.74)

Table 4.17 Posterior summaries (median with 95% credible interval) of mean and median PFS for first-line treatment. Baseline effects are based on all the available FOLFOX arms and assumed underlying exponential distribution.

FOLFOX was associated with a 66% probability of being the most effective of the four regimens with respect to PFS, however the 95% credible intervals for the hazard ratios of all other treatments included 1 (no difference between treatments). The uncertainty surrounding the effectiveness of XELIRI in terms of PFS is again evident by the width of the 95% credible interval. Estimates of median PFS for first-line treatment ranged from 5.7 months for XELIRI to 8,2 months for FOLFOX.

Second-line treatment response rates for sequences

The results for second-line treatment response rate are shown in Tables 4.25 and 4.26

Treatment sequence	OR (95% CrI)	Prob best	
FOLFOX/XELOX then **FOLFIRI/XELIRI** (reference)	1	0.01	
FOLFOX/XELOX then **irinotecan**	4.80 (0.75, 18.28)	0.26	
FOLFIRI/XELIRI then **FOLFOX/XELOX**	5.72 (1.21, 19.67)	0.73	

Table 4.18 Posterior median of odds ratio (OR) for response rate for second-line treatment (in bold) as part of a sequence of treatments with 95% credible interval and probability that each second-line treatment is best out of the 3 regimens of interest, assuming equivalence between the effect of capecitabine and 5-FU. OR < 1 favours the reference treatment.

The residual deviance for the fixed effects model used for the analysis of second-line response rates was 5.1 which, compared to 5 data points, suggests a good model fit.

Treatment	Absolute response rate (95% CrI)
FOLFOX/XELOX then **FOLFIRI/XELIRI** (reference)	0.04 (0.01, 0.12)
FOLFOX/XELOX then **irinotecan**	0.12 (0.04, 0.29)
FOLFIRI/XELIRI then **FOLFOX/XELOX**	0.14 (0.06, 0.28)

Table 4.19 Posterior summaries of the absolute response rate for second-line treatment (in bold) as part of a sequence of treatments (median with 95% credible interval).

Treatment with FOLFOX/XELOX in second line (following FOLFIRI/XELIRI in first line) was associated with significantly higher response rate than FOLFIRI/XELIRI in second line (following FOLFOX/XELOX in first line). Response rates for single agent irinotecan in second line were comparable to FOLFOX/XELOX in second line, however FOLFOX/XELOX were still the treatment options associated with the highest probability of being the most effective regimens in second line.

Second-line treatment progression-free survival for sequences

The results for second-line progression-free survival are shown in Tables 4.27 and 4.28.

Treatment sequence	HR (95% CrI)	Prob best	
FOLFOX/XELOX then **FOLFIRI/XELIRI** (reference)	1	0.21	
FOLFOX/XELOX then **irinotecan**	1.45 (0.94, 2.23)	0.46	
FOLFIRI/XELIRI then **FOLFOX/XELOX**	1.68 (1.26, 2.23)	0.39	

Table 4.20 Posterior summaries (median with 95% credible interval) of hazard ratio (HR) for PFS for second-line treatment (in bold) as part of a sequences of treatments and probability that each second-line treatment is best out of the 3 regimens of interest, assuming equivalence between the effect of capecitabine and 5-FU. HR > 1 favours the reference treatment.

The residual deviance for the fixed effects model used for the analysis of second-line PFS was 5.0 which, compared to 5 data points, suggests a good model fit.

Treatment	Mean PFS in months (95% CrI)	Median PFS in months (95% CrI)
FOLFOX/XELOX then **FOLFIRI/XELIRI** (reference)	6.1 (4.26, 8.71)	4.2 (2.95, 6.04)
FOLFOX/XELOX then **irinotecan**	4.2 (2.54, 6.97)	2.9 (1.76, 4.83)

| FOLFIRI/XELIRI then **FOLFOX/XELOX** | 3.6 (2.46, 5.35) | 2.5 (1.70, 3.71) |

Table 4.21 Posterior summaries (median with 95% credible interval) of mean and median PFS for second-line treatment (in bold) as part of a sequence of treatments. Baseline effects are based on FOLFOX followed by FOLFIRI data with added uncertainty and assumed underlying exponential distribution.

The reported hazard ratios favour FOLFIRI/XELIRI over FOLFOX/XELOX as a second-line treatment for the specified sequences. Estimates of median PFS for second-line treatment ranged from 2.5 months for FOLFOX/XELOX (when given after FOLFIRI/XELIRI in first line) to 4.2 months for FOLFIRI/XELIRI in second line (when given after FOLFOX/XELOX in first line).

<u>**Overall survival for sequences**</u>

The results for overall survival for sequences of treatment are shown in Tables 4.29 and 4.30.

Treatment sequence	HR (95% CrI)	Prob best	
FOLFOX/XELOX then **FOLFIRI/XELIRI** (reference)	1	0.28	
FOLFOX/XELOX then **irinotecan**	0.96 (0.68, 1.37)	0.39	
FOLFIRI/XELIRI then **FOLFOX/XELOX**	0.96 (0.74, 1.24)	0.33	

Table 4.22 Posterior summaries (median with 95% credible interval) of hazard ratio (HR) for overall survival for sequences of treatment and probability that each sequence is best out of the 3 regimens of interest, assuming equivalence between the effect of capecitabine and 5-FU. HR > 1 favours the reference treatment.

The residual deviance for the fixed effects model used for the analysis of overall survival was 4.0 which, compared to 4 data points, suggests a good model fit.

Treatment	Mean OS in months (95% CrI)	Median OS in months (95% CrI)
FOLFOX/XELOX then **FOLFIRI/XELIRI** (reference)	29.9 (11.74, 76.02)	20.7 (8.14, 52.69)
FOLFOX/XELOX then **irinotecan**	31.0 (11.78, 81.66)	21.5 (8.17, 56.60)
FOLFIRI/XELIRI then **FOLFOX/XELOX**	31.2 (12.17, 80.04)	21.6 (8.44, 55.48)

Table 4.23 Posterior summaries (median with 95% credible interval) of mean and median OS for sequences of treatment, assuming equivalence between the effect of capecitabine and 5-FU. Baseline effects are based on FOLFOX followed by FOLFIRI data with added uncertainty and assumed underlying exponential distribution.

The estimate of median overall survival for all sequences in the indirect treatment comparison is approximately 21 months. There is a high degree of uncertainty in the estimates as seen by the wide 95% credible intervals, but nonetheless the analysis suggests with respect to overall survival, the effectiveness of all treatment sequences is comparable.

Cost-effectiveness analysis methods

A review of existing literature did not identify any published cost-effectiveness analyses that addressed all chemotherapy regimens and sequences of interest in the current guideline, therefore a new decision analytic model was developed alongside the MTC analysis.

A decision tree was constructed to reflect key events in the treatment pathway for advanced colorectal cancer patients in order to compare costs and health effects for the ten sequences of chemotherapy (Figure 4.10). In first line, patients receive one of four possible irinotecan or oxaliplatin-based combination chemotherapy regimens. Following disease progression on first-line treatment, the model allows for a proportion of patients to discontinue treatment. The remaining proportion of patients went on to receive one of five possible second-line treatments.

Effectiveness was quantified in terms of quality-adjusted life years (QALYs). Survival time is partitioned in the model using the progression-free survival and overall survival results from the mixed and indirect treatment comparisons. While receiving chemotherapy, and prior to the onset of progressive disease, patients are assumed to be in a stable disease state. Following the point of progression in the model, patients are assumed to be in a progressive disease state with a lower overall quality of life. The model does not explore survival conditional on best response to treatment. This is because there was insufficient detail reported in the clinical literature to facilitate survival analysis dependent on tumour response.

Figure 4.10 Basic structure of the cost-effectiveness model. The same structure was applied to all ten treatment sequences in the analysis.
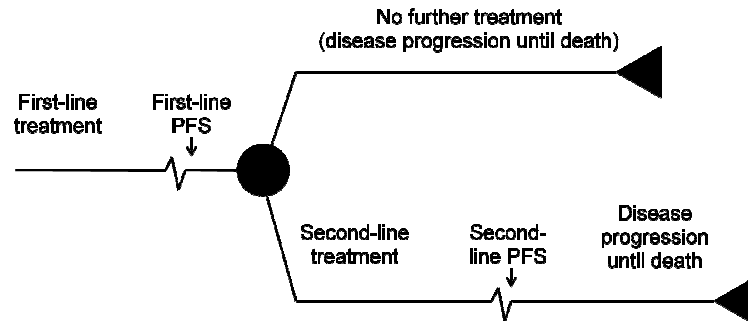
The MTC analysis produced estimates of progression-free survival for each of the first-line treatments. Some assumptions (described in detail above) were made in order to create a connected evidence network to estimate second-line progression-free survival and overall survival for the treatment sequences of interest. Survival time was quality adjusted in the cost-effectiveness analysis using utility weights obtained from published sources.

For patients who only received one line of treatment, QALYs were calculated as follows:

$$(PFS1 \times utility\_stable) + ((OS - PFS1) \times utility\_prog)$$

For patients who received two lines of treatment, QALYs were calculated as follows:

$$(PFS1 \times utility\_stable) + (PFS2 \times utility\_stable) + ((OS - PFS1 - PFS2) \times utility\_prog)$$

where PFS1 = mean progression-free survival while on first-line treatment, PFS2 = mean progression-free survival while on second-line treatment and OS = mean overall survival for a given sequence of treatments for the combined population of patients receiving either one or two lines of treatment. The proportion of patients who went on to receive second-line treatment was reported in 15 studies (Colucci et al. 2005, Comella et al. 2005, Cunningham et al. 2009, Diaz-Rubio et al. 2007, Douillard et al. 2000, Goldberg et al. 2004, Goldberg et al. 2006, de Gramont et al. 2000, Kohne et al. 2005, Koopman et al. 2007, Martoni et al. 2006, Porschen et al. 2007, Seymour et al. 2007, Souglakos et al. 2006, Tournigand et al. 2004). This proportion was found to be approximately consistent (60%) across studies and also across different first-line treatments. As it was not possible to obtain separate overall survival curves for the subgroup of patients who only received one line of treatment and the subgroup of patients who received two lines of treatment, the QALY calculations above should be viewed as a weighted average of quality-adjusted survival across the combined patient population and not as separate absolute estimates of survival for each subgroup.

QALYs were further adjusted to take into account disutility associated with treatment-related toxicities. The toxicities included in the model were those that had considerable cost implications associated with management and/or measurable impact on patient well-being that could be quantified using disutility estimates available from published sources. Estimates of the rates of febrile neutropenia, Grade 3/4 diarrhoea and Grade 3/4 hand-foot syndrome were obtained from the clinical literature. It was not possible to conduct an MTC analysis using the available toxicity data, so mean rates of toxicity for each treatment were used to inform the cost-effectiveness model.

The model was developed from an NHS cost perspective. Costs in the model included drugs and drug administration, management of adverse events and supportive care. Given the relatively short time horizon of the model, discounting was not applied to either costs or health outcomes.

The model was made probabilistic to take into account the impact of parameter uncertainty on results. Probability distributions were created to reflect imprecision and Monte Carlo simulation was used to draw samples across all distributions. The decision tree was developed in TreeAge Pro 2009 software (TreeAge Software Inc, Williamstown, MA, USA).

Cost-effectiveness model inputs
Progression-free survival and overall survival

Details of the data sources, methods and results for estimating progression-free survival and overall survival using MTC techniques are presented above. For the cost-effectiveness analysis, a random sample of 30,000 simulations for first-line progression-free survival, second-line progression-free survival and overall survival estimates was obtained from the WinBUGS output. Rather than fitting a distribution to reflect uncertainty around the mean estimates for these parameters, simulations were inputted directly as chains into the cost-effectiveness model and sampled using Monte Carlo simulation.

Toxicity rates for febrile neutropenia, Grade 3/4 diarrhoea and Grade 3/4 hand-foot syndrome were obtained from the clinical literature that was identified during the systematic review for the MTC and are shown in Tables 4.31 and 4.32. Separate estimates were obtained for first-line treatment and second-line treatment. If there was insufficient data on second-line toxicity rates from prospectively sequenced studies, then studies conducted specifically in second line were included for the purpose of informing the cost-effectiveness analysis. Uncertainty in the estimates for toxicity rates was reflected by fitting beta distributions.

First-line treatment febrile neutropenia				
Treatment	Mean (%)	Standard dev	Distribution	Sources
FOLFOX	6.2	5.6	Beta (mean, SD)	Comella et al. 2005, Comella et al. 2009, Diaz-Rubio et al. 2007,Ducreux et al. 2010, Goldberg et al. 2004, Goldberg et al. 2006, Tournigand et al. 2004
XELOX	2.4	3.2	Beta (mean, SD)	Comella et al. 2009, Diaz-Rubio et al. 2007, Ducreux et al. 2010
FOLFIRI	4.0	2.4	Beta (mean, SD)	Comella et al. 2005, Douillard et al. 2000, Falcone et al. 2007, Kohne et al. 2005, Kohne et al. 2008, Souglakos et al. 2006, Tournigand et al. 2004
XELIRI	8.3	2.5	Beta (mean, SD)	Kohne et al. 2008, Koopman et al. 2007
First-line treatment grade 3/4 diarrhoea				
Treatment	Mean (%)	Standard dev	Distribution	Sources
FOLFOX	15.7	10.7	Beta (mean, SD)	Colucci et al. 2005, Comella et al. 2005, Comella et al. 2009, Cunningham et al. 2009, Diaz-Rubio et al. 2007, Ducreux et al. 2010, Giachetti et al. 2000, Goldberg et al. 2004, Goldberg et al. 2006, de Gramont et al. 2000, Hochster et al. 2008, Martoni et al. 2006, Seymour et al. 2007, Tournigand et al. 2004
XELOX	16.6	10.0	Beta (mean, SD)	Comella et al. 2009, Diaz-Rubio et al. 2007, Ducreux et al. 2010, Hochster et al. 2008, Martoni et al. 2006
FOLFIRI	17.2	9.5	Beta (mean, SD)	Colucci et al. 2005, Comella et al. 2005, Douillard et al. 2000, Falcone et al. 2007, Gennatas et al. 2006, Seymour et al. 2007, Kohne et al. 2005, Kohne et al. 2008, Souglakos et al. 2006, Tournigand et al. 2004

XELIRI	30.3	6.6	Beta (mean, SD)	Kohne et al. 2008, Koopman et al. 2007

First-line treatment grade 3/4 hand-foot syndrome

Treatment	Mean (%)	Standard dev	Distribution	Sources
FOLFOX	2.4	2.7	Beta (mean, SD)	Comella et al. 2009, Diaz-Rubio et al. 2007, Ducreux et al. 2010, Giachetti et al. 2000, Hochster et al. 2008, Martoni et al. 2006, Porschen et al. 2007, Seymour et al. 2007
XELOX	7.0	7.6	Beta (mean, SD)	Comella et al. 2009, Diaz-Rubio et al. 2007, Ducreux et al. 2010, Martoni et al. 2006, Hochster et al. 2008, Porschen et al. 2007
FOLFIRI	0.7	0.5	Beta (mean, SD)	Douillard et al. 2000, Kohne et al. 2005, Kohne et al. 2008, Seymour et al. 2007
XELIRI	6.0	-	Beta (integers)	Kohne et al. 2008, Koopman et al. 2007

Table 4.24 First-line treatment toxicity rates used in the cost-effectiveness analysis

Second-line treatment febrile neutropenia

Treatment	Mean (%)	Standard dev	Distribution	Sources
FOLFOX	3.1	2.8	Beta (mean, SD)	Kim et al. 2009, Rothenberg et al. 2008, Tournigand et al. 2004
XELOX	1.0	-	Beta (integers)	Rothenberg et al. 2008
FOLFIRI	1.0	-	Beta (integers)	Tournigand et al. 2004
XELIRI	8.3	2.5	Beta (mean, SD)	No studies identified - assumed equivalent to first-line toxicity rate
irinotecan	10.2	0.8	Beta (mean, SD)	Haller et al. 2008, Kim et al. 2009

Second-line treatment grade 3/4 diarrhoea

Treatment	Mean (%)	Standard dev	Distribution	Sources
FOLFOX	7.2	2.8	Beta (mean, SD)	Kim et al. 2009, Rothenberg et al. 2008, Seymour et al. 2007, Tournigand et al. 2004
XELOX	19.9	-	Beta (integers)	Rothenberg et al. 2008
FOLFIRI	7.9	0.2	Beta (mean, SD)	Seymour et al. 2007, Tournigand et al. 2004
XELIRI	30.3	6.6	Beta (mean, SD)	No studies identified - assumed equivalent to first-line toxicity rate
irinotecan	23.3	6.1	Beta (mean, SD)	Haller et al. 2008, Kim et al. 2009, Rougier et al. 1998, Seymour et al. 2007

Second-line treatment grade 3/4 hand-foot syndrome

Treatment	Mean (%)	Standard dev	Distribution	Sources
FOLFOX	1.8	1.7	Beta (mean, SD)	Rothenberg et al. 2008, Seymour et al. 2007
XELOX	3.5	-	Beta (integers)	Rothenberg et al. 2008
FOLFIRI	1.1	-	Beta (integers)	Seymour et al. 2007

XELIRI	6.0	-	Beta (integers)	No studies identified - assumed equivalent to first-line toxicity rate
irinotecan	0.6	-	Beta (integers)	Seymour et al. 2007

Table 4.25 – Second-line treatment toxicity rates used in the cost-effectiveness analysis

Quality of Life

Quality of life was included as an outcome in a total of seven studies; 4 were first-line studies (Comella et al, 2009; Falcone et al, 2007; Douillard et al, 2000; DeGramont et al, 2000); 2 were second-line studies (Cunningham et al, 1999; Rougier et al, 1998) and 1 was a sequenced study (Koopman et al, 2007). Only 1 trial compared two treatments of interest and only in first line (Comella, 2009).

To compare quality of life in the FOLFOX and XELOX arms, baseline questionnaires were filled in by a total of 312 patients (97% of total patient population) and again at 8 weeks, 16 weeks and 24 weeks following treatment (Comella, 2009). The baseline single item and global health status/quality of life scores did not differ significantly between the two arms.

No significant differences in the change of single scores were observed between the two arms apart from constipation (p=0.001) and financial item score (p=0.004).

At the predetermined time point for the comparison, a preservation of the quality of life was observed in 47% of patients in either arm.

A higher proportion of patients in the XELOX arm showed a deterioration of the global health status/quality of life score after 16 weeks and 24 weeks though the differences were not statistically significant.

Arm	After 8 weeks		
	Improved[1]	Stable	Deteriorated[2]
OXXEL	24 (23%)	50 (47%)	30 (30%)
OXAFAFU	25 (22%)	56 (47%)	37 (31%)
Arm	After 16 weeks		
	Improved[1]	Stable	Deteriorated[2]
OXXEL	30 (37%)	29 (35%)	23 (28%)
OXAFAFU	17 (24%)	40 (57%)	13 (19%)
Arm	After 24 weeks		
	Improved[1]	Stable	Deteriorated[2]
OXXEL	5 (17%)	2 (7%)	47 (76%)
OXAFAFU	1 (3%)	7 (18%)	30 (79%)

[1] ≥10 pt increment of baseline score
[2] ≤10 pt decrease of baseline score

Table 4.26- Patients showing significant change in the quality of life score during treatment

Utility estimates

Utility estimates for stable (on treatment) and progressive disease were obtained from a published study of elicited preference values for health states associate with colon cancer (Best et al. 2010). The study was conducted using time trade-off techniques to elicit preferences from both patients and community members. The estimates for stable and progressive metastatic disease from the community sample only were applied in the cost-effectiveness model.

Disutility estimates to capture the impact of treatment-related toxicity on patient well-being for the specific regimens of interest in colorectal cancer were not available. Estimates obtained from a utility study conducted in metastatic breast cancer were used as a proxy (Lloyd et al. 2006). These estimates were applied in the cost-effectiveness model as utility decrements to the proportion of patients experiencing each of the toxicities.

Table 4.27 summarises the utility estimates used in the analysis.

Health state	Value	Distribution	Source
Metastatic disease, stable	0.51	Beta (assumed se = 0.1)	Best et al. 2010
Metastatic disease, progressive	0.21	Beta (assumed se = 0.1)	Best et al. 2010
Disutility febrile neutropenia	-0.15	Fixed	Lloyd et al. 2006
Disutility grade 3/4 diarrhoea	-0.103	Fixed	Lloyd et al. 2006
Disutility grade 3/4 hand foot syndrome	-0.116	Fixed	Lloyd et al. 2006

Table 4.27 Utility values used in the cost-effectiveness analysis

Drug costs

Information on drug doses for each treatment regimen was obtained from the literature. For some regimens, variations in dose or administration schedule were observed across studies. If inconsistency across studies was noted, then GDG input was obtained to confirm which doses were most reflective of current UK clinical practice (Table 4.35).

Regimen	Dose	Cycle length (weeks)
FOLFIRI	5-FU 400 mg/m2 iv bolus Day 1, 2400 mg/m2 ci, 46 hrs folinic acid 200 mg/m2 iv, 2 hrs, Day 1 irinotecan 180 mg/m2, iv 30 mins, Day 1	2
FOLFOX	5-FU 400 mg/m2 iv bolus Day 1, 2400 mg/m2 ci, 46 hrs folinic acid 200 mg/m2 iv, 2 hrs, Day 1 oxaliplatin 85 mg/m2 iv, 2 hrs, Day 1	2
XELIRI	capecitabine 1000 mg/m2 oral bid, Day 1-14 irinotecan 200 mg/m2 iv, Day 1	3
XELOX	capecitabine 1000 mg/m2 oral bid, Day 1-14 oxaliplatin 130 mg/m2 iv, 2 hrs, Day 1	3
irinotecan	irinotecan 350 mg/m2 iv 30 min, Day 1	3

Table 4.28 Drug doses and administration schedule

Drug cost per cycle
Drug cost per cycle was calculated based on cost data obtained from the British National Formulary assuming no wastage and an average body surface area of 1.75 m^2 (NICE Developing Costing Tools Methods Guide January 2008). When available, the unit cost of non-proprietary formulations was used. An estimate of the cost of administration was obtained from NHS Reference Costs. Drug costs and drug administration costs per cycle are summarised in Tables 4.36 and 4.37.

Regimen (cycle length)	oxaliplatin	irinotecan	folinic acid	5-FU	capecitabine	Total cost per cycle
FOLFOX (2 weeks)	449.50	-	90.98	62.72	-	£ 603.20
FOLFIRI (2 weeks)		388.89	90.98	62.72	-	£ 542.59
XELOX (3 weeks)	681.50	-	-	-	223.16	£ 904.66

XELIRI (3 weeks)	-	430.63	-	-	223.16	£ 653.79
irinotecan (3 weeks)	-	736.53	-	-	-	£ 736.53

Table 4.29 Drug cost per cycle

Chemotherapy delivery	Cost per cycle	Source	Comments
Deliver simple parenteral chemotherapy	£272	NHS Reference Costs 2008-2009 (SB12Z)	Applied to XELOX, XELIRI, irinotecan
Deliver more complex parenteral chemotherapy	£335	NHS Reference Costs 2008-2009 (SB13Z)	Applied to FOLFOX, FOLFIRI

Table 4.30 Drug administration cost per cycle

Number of cycles
The duration of treatment in terms of number of cycles was extracted from the clinical literature (Table 4.38). For most first-line studies, the total number of cycles was reported and used to derive the mean number of cycles per patient. For second-line treatment and for XELIRI as first-line treatment, studies typically only reported the median number of cycles. For these estimates, uncertainty was reflected assuming a uniform distribution in the cost-effectiveness model.

First line (cycle length)	Number of cycles	Standard deviation	Distribution
FOLFOX (2 weeks)	8.99	1.73	Gamma (mean, SD)
FOLFIRI (2 weeks)	7.89	0.71	Gamma (mean, SD)
XELOX (3 weeks)	5.87	0.78	Gamma (mean, SD)
XELIRI (3 weeks)	6.50	2 (assumption)	Uniform
Second line (cycle length)	**Number of cycles**	**Standard deviation**	**Distribution**
FOLFOX (2 weeks)	7.13	2 (assumption)	Uniform
FOLFIRI (2 weeks)	6.00	2 (assumption)	Uniform
XELOX (3 weeks)	5.00	2 (assumption)	Uniform
XELIRI (3 weeks)	5.53	2 (assumption)	Uniform
irinotecan (3 weeks)	5.21	2 (assumption)	Uniform

Table 4.31 Number of treatment cycles

Cost of adverse event management

Estimates of the cost of management of febrile neutropenia and severe diarrhoea were based on NHS reference costs (Table 4.39). The cost of management of hand-foot syndrome was not factored into the model as this is typically managed by interruption of treatment or dose-reduction (Gressett et al. 2006) so it was not possible to assess the impact on cost or effectiveness specifically attributable to this toxicity alone.

Toxicity	Cost	Source
Febrile neutropenia	£ 6,278	PbR Tariff 2010-2011 (PA45Z)
Diarrhoea (Grade 3/4)	£ 388	NHS Reference Costs 2008-2009 (FZ45C)

Table 4.32 Cost of management for febrile neutropenia and grade 3/4 diarrhoea

Supportive care

Healthcare resource use associated with supportive care for advanced cancer patients was obtained from a UK study of the DIN-Link database (Guest et al. 2005). Estimates of resource use for GP visits, district nurse visits, outpatient visits and hospitalisations were obtained from this study while unit costs were based on more recent sources (Table 4.40). Supportive care costs were applied throughout the model during both active treatment and progressive disease.

Supportive care	Number of units per year	Unit cost	Source for unit cost
GP visits	17.38	£40	PSSRU 2009
District nurse visits	17.38	£23	PSSRU 2009
Outpatient visits	0.617	£205	PbR Tariff 2010-2011 (WF01B)
Hospitalisations	0.717	£1,422	NHS reference costs 2008-2009 (FZ48B)

Table 4.33 Supportive care costs

<u>Sensitivity analyisis</u>

The cost-effectiveness model was analysed by performing Monte Carlo simulation, sampling 30,000 times from all available distributions and MTC chains. Mean costs and QALYs for each of the ten treatment sequences are reported, as well as the incremental cost-effectiveness ratio (ICER) for all treatment strategies that are not ruled out by dominance. Parameter uncertainty is propagated through the model using probabilistic sensitivity analysis and is reflected in the results shown in the cost-effectiveness acceptability curve (CEAC). The CEAC shows the probability that each treatment sequence is cost effective over a range of willingness to pay thresholds.

In addition to the base case analysis, a sensitivity analysis was run to assess the impact of drug discounts on the results of the cost-effectiveness model. Information on drug discounts was obtained from the NHS Commercial Medicines Unit (CMU) electronic Market Information Tool (eMIT), which provides suppliers with access pertaining to the generic pharmaceutical products that are covered within framework agreements (Table 4.41). The discounted prices are based on an estimate of NHS hospital-sector annual usage from English trusts for a given drug, the average (weighted arithmetic mean) price paid for that drug over the last four months of the period and a measure of the variance of that average (Department of Health, NHS Commercial Medicines Unit). At the time this modelling exercise was undertaken, discounted drug prices were available for all drugs included in the analysis except capecitabine.

Regimen (cycle length)	Cost per cycle list price	Cost per cycle discounted price
FOLFOX (2 weeks)	£603.20	£64.01
FOLFIRI (2 weeks)	£542.59	£131.81
XELOX (3 weeks)	£904.66	£282.31
XELIRI (3 weeks)	£653.79	£341.46
irinotecan (3 weeks)	£736.53	£207.03

Table 4.34 Comparison of list price and discounted drug cost per cycle

Cost-effectiveness analysis results

Base case analysis

The total costs and total QALYs in the base case analysis for each of the ten sequences of chemotherapy are summarised in Table 4.42. Costs ranged from £16,285 for FOLFOX - irinotecan up

to £18,568 for FOLFOX – XELIRI. Total QALYs ranged from 0.819 for XELIRI – XELOX up to 0.941 for FOLFOX – FOLFIRI.

Strategy	Cost	Effectiveness (QALYs)
FOLFOX-irinotecan	£ 16,285	0.922
XELOX-FOLFIRI	£ 16,662	0.919
XELIRI-XELOX	£ 16,798	0.819
XELOX-XELIRI	£ 16,894	0.895
XELOX-irinotecan	£ 17,328	0.900
XELIRI-FOLFOX	£ 17,334	0.826
FOLFIRI-XELOX	£ 17,400	0.903
FOLFIRI-FOLFOX	£ 17,935	0.910
FOLFOX-FOLFIRI	£ 18,336	0.941
FOLFOX-XELIRI	£ 18,568	0.917

Table 4.35 Total costs and effectiveness by treatment strategy (in order of increasing cost)

Taking FOLFOX – irinotecan as the reference (least expensive) strategy, all other strategies were shown to be less effective and also more costly (i.e. dominated) except the sequence FOLFOX – FOLFIRI (Table 4.43 and Figure 4.11). Compared to the reference strategy, the sequence FOLFOX – FOLFIRI produces 0.019 more QALYs (equivalent to approximately 7 days in 'perfect' health) and incurs £2,051 in additional costs. This yields an incremental cost-effectiveness ratio (ICER) of £109,604/QALY, suggesting that at a willingness to pay (WTP) threshold of £20,000/QALY, the sequential strategy of FOLFOX – FOLFIRI is not cost effective.

Strategy	Incremental cost	Incremental effectiveness (QALYs)	ICER
FOLFOX-irinotecan			-
XELOX-FOLFIRI	£ 377	-0.004	Dominated
XELIRI-XELOX	£ 513	-0.104	Dominated
XELOX-XELIRI	£ 609	-0.027	Dominated
XELOX-irinotecan	£ 1,043	-0.022	Dominated
XELIRI-FOLFOX	£ 1,048	-0.096	Dominated
FOLFIRI-XELOX	£ 1,115	-0.020	Dominated
FOLFIRI-FOLFOX	£ 1,650	-0.012	Dominated
FOLFOX-FOLFIRI	£ 2,051	0.019	£109,604/QALY
FOLFOX-XELIRI	£ 2,283	-0.005	Dominated

Table 4.36 Incremental cost effectiveness results
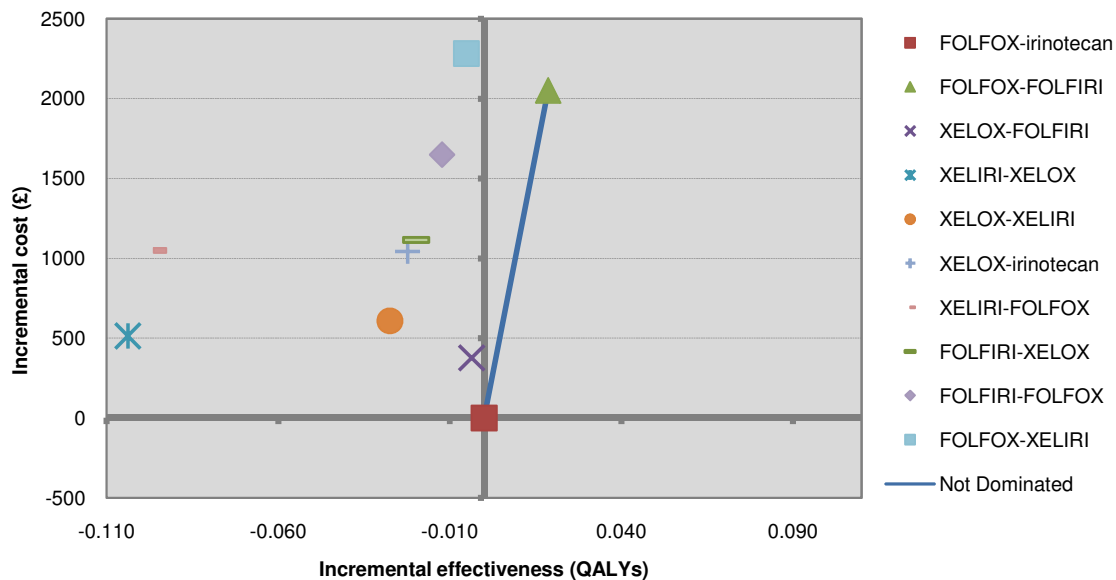
Figure 4.11 Cost-effectiveness plane showing all ten treatment sequences. The slope of the line connecting FOLFOX-irinotecan and FOLFOX-FOLFIRI indicates the incremental cost-effectiveness ratio (ICER).

Results presented above reflect the expected costs and effectiveness estimates for the treatment sequences of interest, however given uncertainty associated with many parameters in the model, we are also interested in the distribution over incremental costs, incremental effectiveness and the joint cost-effectiveness distribution (Briggs 2007). This is particularly relevant in the present analysis given that the differences in total QALYs between several strategies are small, with a number of data points lined up closely along the vertical axis of the cost-effectiveness plane which represents a difference in effectiveness of 0. Taking into account parameter uncertainty, probabilistic sensitivity analysis showed that simulation results for several sequences cross the vertical axis, suggesting there is a non-negligible probability that some sequences other than FOLFOX – FOLFIRI may also be equivalent or even more effective than the reference strategy. Cost-effectiveness acceptability curves (CEAC) can be used to show the probability of the various treatment options being cost effective over a range of WTP thresholds. The CEACs show that FOLFOX – irinotecan is consistently the strategy with the highest probability of being cost-effective, however as the WTP threshold increases, so does the probability that the sequences FOLFOX-FOLFIRI and XELOX-FOLFIRI are cost-effective (Figure 4.12).
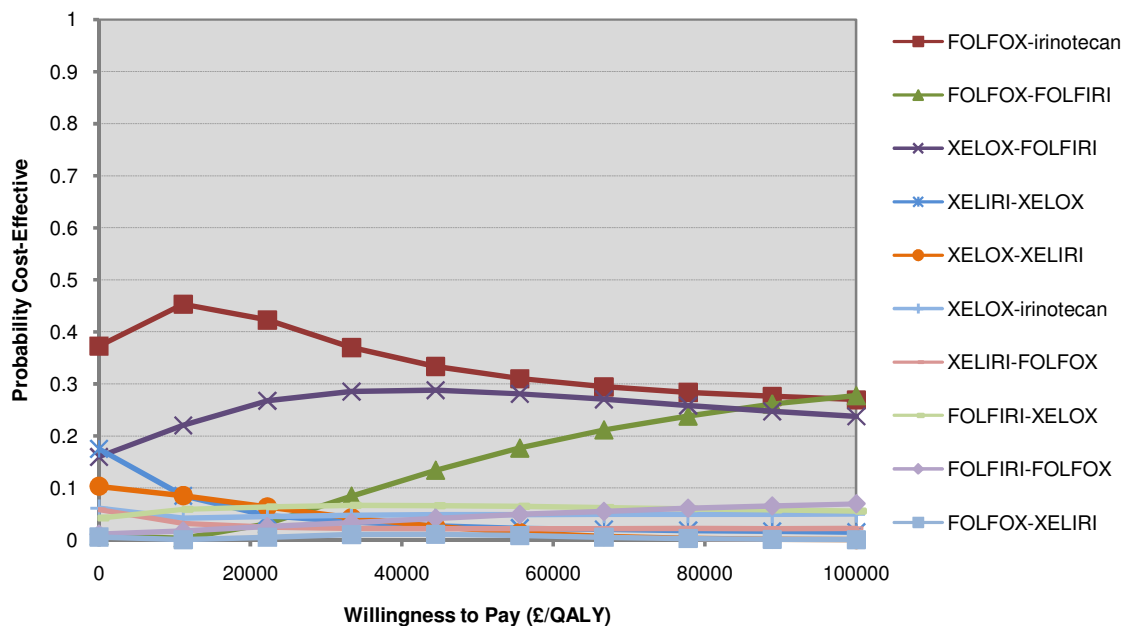
Figure 4.12 Cost-effectiveness acceptability curves for the base case analysis

Sensitivity analysis - drug discounts

If currently available data on the impact of price discounts for generic pharmaceutical products across the NHS are taken into account, FOLFOX-FOLFIRI remains the only non-dominated treatment strategy and the ICER falls to £47,801/QALY (Table 4.44).

Strategy	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER
FOLFOX-irinotecan	£ 11,136	-	0.925	-	-
FOLFOX-FOLFIRI	£ 12,029	£ 893	0.944	0.019 QALY	£47,801/QALY

Table 4.37 Cost-effectiveness results for non-dominated strategies taking into account price discounts for generic pharmaceutical products

Probabilistic sensitivity analysis using discounted drug prices showed there is greater uncertainty about which strategy has the highest probability of being cost effective, as shown by the intersecting CEACs for FOLFOX-irinotecan, FOLFOX-FOLFIRI and XELOX-FOLFIRI over the range of WTP thresholds between approximately £20,000 and £40,000/QALY (Figure 4.13).
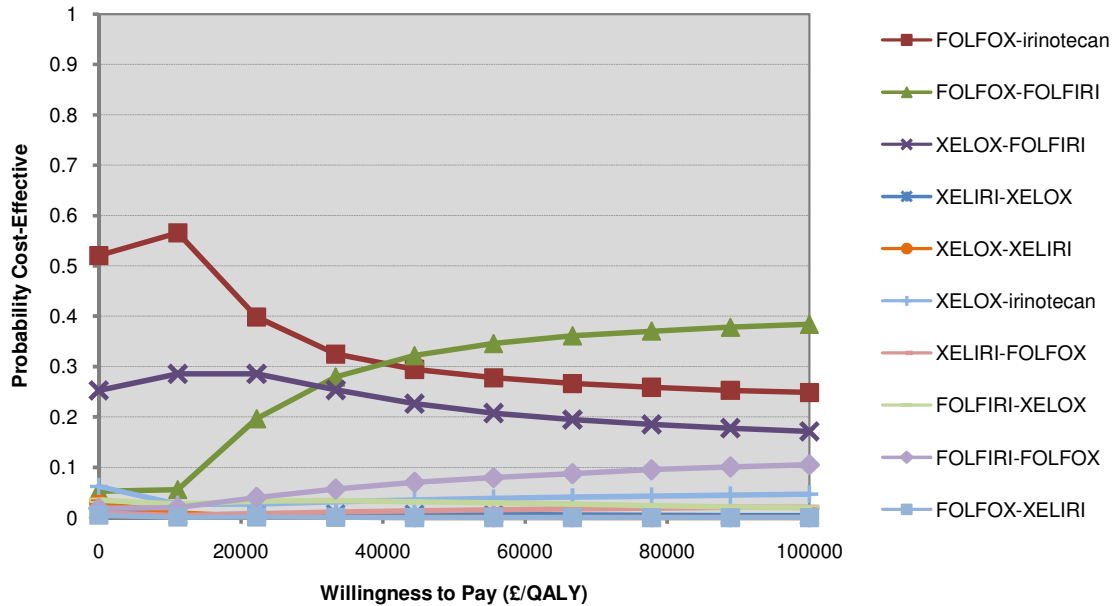
Figure 4.13 Cost-effectiveness acceptability curves using discounted drug prices

Discussion

As the number of systemic treatment options for the management of colorectal cancer increases, and with more and more patients able to receive additional lines of chemotherapy, questions about the most effective way to use combinations and sequences of treatments have become relevant to current clinical practice. A systematic review was undertaken to identify new evidence that has become available since the publication of NICE Technology Appraisal 93 in 2005 on the clinical and cost-effectiveness of oxaliplatin and irinotecan-based chemotherapy. This evidence base was then used to conduct an integrated mixed treatment comparison and cost-effectiveness analysis to inform decision-making regarding optimal combinations and sequences of chemotherapy for the management of advanced colorectal cancer. Mixed treatment comparisons that draw on both direct and indirect evidence have become an important method to address decision problems that, often for feasibility reasons, cannot be practically answered by conducting further randomised controlled trials.

As a first-line treatment option, the mixed treatment comparison results suggest that FOLFOX was associated with a higher probability of being the most effective regimen with respect to both response rate and PFS. The small benefit in favour of FOLFOX was also evident when comparing second-line response rates, however was not the case with respect to second-line PFS. Perhaps most importantly, for the endpoint overall survival, the analysis showed no differences between the treatment sequences of interest.

The high level of uncertainty surrounding some of the results of the mixed treatment comparison are evident by the width of the 95% credible intervals. This is particularly evident in the estimates of effectiveness for XELIRI in first line where there was limited data available. To address the issue of sequencing of treatments, a decision was made to exclude evidence for which we could not be confident in determining that patients had received both first and second-line treatments that were of direct relevance to this analysis. The implication was that there were fewer studies to inform the second-line analysis of response rate, PFS and of overall survival. In order to connect the evidence network for sequences of treatment, a number of assumptions were required with respect to the equivalence of the effectiveness of the oral and iv fluoropyrimidine formulations. The validity of these assumptions were explored both by statistical methods and through discussion with GDG members.

The results of the mixed and indirect treatment comparisons were used as inputs to conduct a cost-effectiveness analysis. The cost-effectiveness analysis showed that when survival was quality-adjusted (taking into account both disease status and toxicities), the difference in total QALYs

between the various sequential treatment strategies was in most cases modest. Taking FOLFOX-irinotecan as the reference (least costly) strategy, all other treatment sequences were found to be less effective (in terms of QALYs) and more costly except the sequence FOLFOX-FOLFIRI. The ICER comparing FOLFOX-FOLFIRI to FOLFOX-irinotecan was of £110K/QALY. When drug discounts were taken into account, the ICER for FOLFOX – FOLIRI vs FOLFOX-irinotecan fell to approximately £48K/QALY. Because of the small differences in total QALYs between strategies, it was important to consider how uncertainty may impact the results of the cost-effectiveness analysis. Taking parameter uncertainty and drug discounts into account, three strategies (FOLFOX-irinotecan, FOLFOX-FOLFIRI and XELOX-FOLFIRI) were associated with the highest probability of being cost effective.

References

Best JH, Garrison LP, Hollingworth W, Ramsey SD, Veenstra DL (2010) Preference values associated with stage III colon cancer and adjuvant chemotherapy *Quality of Life Research* 19:391-400

Briggs A, Claxton K, Sculpher M (2007) Decision modelling for healh economic evaluation Oxford University Press

British National Formulary (accessed 11 November 2010). http://bnf.org/bnf/index.htm

Brooks S, Gelman A (1998) General methods for monitoring convergence of iterative simulations *Journal of Computational and Graphical Statistics* 7;434-55

Colucci G, Gebbia V, Paoletti G, Giuliani F et al (2005) Phase III Randomised Trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicentre study of the Gruppo Oncologico Dell'Italia Meridonale *Journal of Clinical Oncology* 23;22:4866-4875

Comella P, Massidda B, Filipelli G, Farris A, Natale D et al (2009) Randomised trial comparing biweekly oxaliplatin plus oral capecitabine versus oxaliplatin plus iv bolus fluorouracil/leucovorin in metastatic colorectal cancer patients: results of the Southern Italy Cooperative Oncology Study 0401 Journal of Cancer Research and Clinical Oncology 135; 217-26

Comella P, Massidda B, Filippelli G, Palmeri S, Natale D (2005) Oxaliplating plus high dose folinic acid and 5 fluorouracil i.v. bolus (OXAFAFU) versus irinotecan plus high dose folinic acid and 5-fluorouracil i.v. bolus (IRIFAFU) in patients with metastatic colorectal carcinoma: a Southern Italy Cooperative Oncology Group phase III trial *Annals of Oncology* 16;6:878-886

Cunningham D, Sirohi B, Pluzanska A, et al (2009) Two different first line 5 fluorouracil regimens with or without oxaliplatin in patients with metastatic colorectal cancer *Annals of Oncology* 20;244-250

Department of Health, Confirmation of Payment by Results (PbR) arrangements for 2010-11 http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_112284

Department of Health. National Reference Costs 2008-09 http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_123459

Department of Health, NHS Commercial Medicines Unit, Generic Pharmaceuticals electronic Market Information Tool (eMIT) WEB_VERSION_20100629 (accessed 21 December 2010) http://www.cmu.nhs.uk/Medicines/Generic/Pages/eMIT.aspx

Diaz-Rubio E, Tabernero J, Gomez-Espana A et al (2007) Phase III study of Capecitabine plus oxaliplatin compared with continuous infusion fluorouracil as first line therapy in metastatic colorectal cancer: final report of the Spanish Cooperative Group for the treatment if digestive tumours trial *Journal of Clinical Oncology* 25;27:4224-4230

Douillard J, Cunnigham D, Roth A, Navarro, James R et al (2000) Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial *Lancet* 355;9209:1041-1047

Falcone A, Ricci S, Brunetti I, Pfanner E et al (2007) Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin and irinotecan (FOLFIRI) as first line treatment for metastatic colorectal cance: the GRUPPO Ocologico Nord Ovest *Journal of Clinical Oncology* 25;13

Gennatas C, Papaxoninis G, Michalaki V et al (2006) A prospective randomised study of irinotecan (CPT-11), leucovorin (LV) and 5-fluorouracil (5FU) versus leucovorin and 5-fluorouracil in patients with advanced colorectal carcinoma *Journal of Chemotherapy* 18;5:538-544

Giacchetti S, Perpoint B, Zidani R, Le B et al (2000) Phase III multicenter randomised trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first line treatment of metastatic colorectal cancer *Journal of Clinical Oncology* 18;1:136-147

Goldberg, RM, Sargent DJ, Morton RF, Fuchs CS et al (2006) Randomised controlled trial of reduced dose bolus fluorouracil plus leucovorin and irinotecan or infused fluorouracil plus leucovorin and oxaliplatin in patients with previously untreated metastatic colorectal cancer: A North American intergroup trial *Journal of Clinical Oncology* 24;21:3347-3353

Goldberg R, Sargent D, Morton R, Fuchs C et al (2004) A randomised controlled trial of fluourouracil plus leucovorin, irinotecan and oxaliplation combinations in patients with previously untreated metastatic colorectal cancer *Journal of Clinical Oncology* 22;1:23-30

de Gramont A, Figer A, Seymour M, Homerin M, et al (2000) Leucovorin and Flourouracil with or without oxaliplatin as first line treatment in advanced colorectal cancer *Journal of Clinical Oncology* 18;2938-2947

Gressett S, Stanford B, Hardwicke F. (2006) Management of hand-foot syndrome induced by capecitabine. *Journal of Oncology Pharmacy Practice* 12: 131-141

Guest J, Ruiz F, Greener M, Trotman I (2006) Palliative care treatment patterns and associated costs of healthcare resource use for specific advanced cancer patients in the UK. *European Journal of Cancer Care* 15: 65–73

Hochster HS, Hart LL, Ramanathan RK et al (2008) Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first line treatment of metastatic colorectal cancer: results of the TREE study *Journal of Clinical Oncology* 26;21: 3523-3529

Kohne CH, De Greve J, Hartmann JT, Lang I et al (2008) Irinotecan combined with infusional 5-fluorouracil/folinic acid or Capecitabine plus celecoxib or placebo in the first line treatment of patients with metastatic colorectal cancer. EORTC study 40015 *Annals of Oncology* 19;920-926

Kohne CH, van Cutsem E, Wils J, Bokemeyer C et al (2005) Phase III study of weekly high dose infusional fluorouracil plus folinic acid with or without irinotecan in patients with metastatic colorectal cancer: European organisation for research and treatment of cancer gastrointestinal group study 40986

Koopman M, Antonini NF, Douma J, Wals J et al (2007) Sequential versus combination chemotherapy with Capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial *Lancet* 370;9582:135-142

Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J (2006) Health state utilities for metastatic breast cancer *British Journal of Cancer* 95:683-90

Lu G, Ades AE (2004) Combination of direct and indirect evidence in mixed treatment comparisons. *Statistics in Medicine* 23:3105–24

Martoni AA, Pinto C, Di Fabio F Lelli G et al (2006) Capecitabine plus oxaliplatin (XELOX) versus protracted 5-fluorouracil venous infusion plus oxaliplatin (PVIFOX) as first line treatment in advanced colorectal cancer: A GOAM phase II randomised study (FOCA trial)

Parmar M, Torri V and Stewart L (1998) Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics In Medicine* 17: 2815-2834

Porschen R, Arkenau HT, Kubica S, Greil R et al (2007) Phase III study of Capecitabine plus oxaliplatin compared with fluorouracil and leucovorin plus oxaliplatin in metastatic colorectal cancer: A final report of the AIO colorectal study group *Journal of Clinical Oncology* 25;27:4217-4223

Seymour MT, Maughan TS, Ledermann JA, Topham C et al (2007) Different strategies of sequential and combination chemotherapuy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial *Lancet* 370;9582:143-152

Saltz L,Cox, J, Blanke C, Rosen L, Fehrenbacher L et al (2000) Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer *New England Journal of Medicine* 343;13:905-915

Souglakos J, Androulakis N, Sygrigos K, Polysos A (2006) FOFLFOXIRI (folinic acid, 5 fluorouracil, oxaliplatin and irinotecan) versus (folinic acid, 5 fluorouracil and irinotecan) as first line treatment in metastatic colorectal cancer (MCC): a multicentre randomised phase III trial from the Hellenic Oncology Research Group (HORG) *British Journal of Cancer* 94;6:798-805

Spiegelhalter D, Best N, Carlin B, and van der Linde A (2002) Bayesian measures of model complexity and fit. *Journal of the Royal Statistical Society (B)* 64: 583-616

Sutton A, Ades A, Cooper N, Abrams K (2008) Use of indirect and mixed treatment comparisons for technology assessment. *Pharmacoecnomics* 26: 753-767

Tierney J, Stewart L, Ghersi D, Burdett S and Sydes M (2007) Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007; 8

Tournigand C, Andre T, Achille R, Lledo G, Flesh M et al. (2004) FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomised GERCOR study *Journal of Clinical Oncology* 22;15:229-237

Unit Costs of Health and Social Care 2009
http://www.pssru.ac.uk

Williamson P, Smith C, Hutton J and Marson A (2002) Aggregate data meta-analysis with time-to-event outcomes. *Statistics In Medicine* 21: 3337-3351

Evidence Tables

Citation: Colucci G, Gebbia V, Paoletti G, Giuliani F et al (2005) Phase III Randomised Trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicentre study of the Gruppo Oncologico Dell'Italia Meridonale Journal of Clinical Oncology 23;22:4866-4875
Design: Randomised Phase III Study **Country**: Italy **Setting**: **Aim**: to compare irinotecan, leucovorin (LV) and fluorouracil (FU) regimen (FOLFIRI) versus oxaliplatin, LV and FU regimen (FOLFOX4) in previously untreated patients with colorectal cancer.
Comparison: FOLFIRI versus FOLFOX4 (first line)
Inclusion criteria ≥18 years and ≤75 years Histologically confirmed locally advanced and/or metastatic colorectal cancer with bidimensionally measurable disease Life expectancy of >3 months ECOG Performance Status of 0-2 Adequate bone marrow, renal and hepatic functions Adjuvant therapy completed at least 6 months before enrollment
Exclusion criteria Active of uncontrolled infections Known brain metastases or carcinomatous meningitis interstitial pneumonia or interstitial fibrosis History of myocardial infarction within the previous 6 months or current clinical evidence of congestive heart failure (patients taking medication for congestive heart failure and showing no clinical signs or symptoms were eligible). Symptoms of coronary artery disease History of thromboembolic disease in the past 5 years of a prior malignancy, except of adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer Any psychological or psychiatric conditions that interfere with consent and precluded treatment or adequate follow-up Pregnant or lactating women
Sample Size The expected response rates were 35% and 50% for the FOLFIRI and FOLFOX4 regimens respectively, therefore the study was designed to have the power to detect a 15% difference in objective response rate between the two arms using a two-sided log rank test with an α risk of 0.05 and a β risk of 0.02. The number of patients calculated to be included in each arm was 176.
Randomisation Method Randomisation was performed centrally with a random ratio of 1:1 Stratification factors were size of disease (limited or extensive disease; < or > 10 cm2 respectively) and liver involvement (with or without liver involvement, H+ or H- respectively).
Population N = 360 Arm A, FOLFIRI N=178 Arm B, FOLFOX N=182
Study Duration Recruitment Stage: March 199 – November 2002
Interventions Arm A, FOLFIRI: Irinotecan 180mg/m2 (150mg/m2 for patients ≥70 years and <75 years) only on day 1, with LV 100mg/m2 (L-isomer form) administered as a 2 hour infusion before FU 400mg/m2 administered as an intravenous bolus injection; FU 600mg/m2 was administered as a 22 hour infusion immediately after FU bolus injection. LV and FU were repeated on days 1 and 2 according to a previously recorded schedule.

Arm B, FOLFOX4: Oxaliplatin 85mg/m2 only on day 1, with LV 100mg/m2 (l-isomer form) administered as a 2-hour infusion before FU 400 mg/m2 administered as an intravenous bolus injection; FU 600mg/m2 was administered as a 22 hour infusion immediately after FU bolus injection. LV and FU were repeated on days 1 and 2 according to a previously recorded schedule.

Both schedules were administered at 2 week intervals

Outcomes
Response rate (evaluation of objective response)

Time to progression (determined from the date of first treatment until death or last follow-up and progression)
Overall Survival
Toxicity Profile

Results
The arms were well balanced with respect to stratification factors and baseline characteristics.

336 patients were deemed assessable for response (164 in Arm A and 172 in Arm B) Reasons for patients being unassessable included noneligibility or protocol violation (n=4, arm A, n=4 arm B), patient refusal (n=6 in arm A, n=5 in arm B), toxicity (n=1 in arm B) and early death unrelated to treatment (n=1 in arm A).

A total of 1,264 cycles of the FOLFIRI regimen were administered during the study with a median of 8 cycles per patient (range 1-22 cycles).
A total of 1,321 cycles of the FOLFOX regimen were administered with a median of 8 cycles per patient (range 1-15 cycles).
The average number of cycles (intention to treat analysis) was 7.14 and 7.26 in arms A and B respectively. More than 12 cycles were administered to 4 patients in Arm A and 2 patients in Arm B.

Response Rates
There was no significant difference in the response rates between the two arms (p=0.6 for ITT analysis and p=0.71 for assessable patients only).

Arm	FOLFIRI	FOLFOX4
	Overall response rate (95% CI)	Overall response rate (95% CI)
Assessable Patients	34% (26.9%-41.4%)	36% (28.9%-43.2%)
Intention to Treat Analysis	31% (24.6%-38.3%)	34% (27.2%-41.5%)

Median duration of response was 9 months in arm A and 10 months in arm B (p=0.06) whereas the median time to progression according to ITT analysis was 7 months in both arms.
According to ITT analysis, the median overall survival was 14 and 15 months for patients in Arms A and B respectively (p=0.28).
Median follow-up time was 31 months (range 11-56 months) and the 1 year survival rate was 55% and 62% in arms A and B respectively (p=0.16).

Second line therapy was administered to 61% of patients treated with FOLFIRI and to 58% of patients treated with FOLFOX4 and consisted primarily of oxaliplatin based therapy for patients treated with FOLFIRI and irinotecan based therapy for patients treated with FOLFOX4.
Median overall survival for patients receiving second line therapy was 17 months compared with 10 months for patients that did not receive second line therapy.

	CR + PR	SD	PD
FOLFIRI	18	15	8
FOLFOX4	20	15	9

CR=Complete Response, PR=Partial Response, SD=Stable Disease, PD=Progressive Disease
Table: Median overall survival (months) in arms A and B according to obtained objective response

No difference in response rates was observed between arms A and B for patients with hepatic metastatic disease (33% versus 34% respectively p=0.86 with ITT analysis) whereas patients with lung metastases obtained better results with FOLFOX4 (25% versus 40% for arms A and B respectively) though the difference was not statistically significant. (pp=0.11).
When analysing objective response rates according to primary tumour site response rates were 30% (18/60) in arm A versus 37% (22/59) in arm B for rectal cancer and 32% (38/118) in arm A versus 33% (40/123) in arm B for

colon cancer (ITT analysis).

Objective response was recorded in 41% (26/64) of patients in arm A in whom the liver was the only site of metastases compared with 35% (24/68) in arm B.

23% (15/64) of patients in arm A with liver plus other disease sites showed objective response compared with 32% (21/65) in arm B.

Secondary surgery to remove liver metastases was performed on 9 patients in arm A and 8 patients in arm B.

	FOLFIRI	FOLFOX	P
H+ and tumour > 10cm^2	30%	37%	0.31
H+ and tumour <10cm^2	37.5%	24%	0.25
H- and tumour > 10cm^2	25%	29%	0.76
H- and tumour <10cm^2	36%	43%	0.66

Table; Objective response by stratification group

In patients with only a single site of disease overall response rate was 38% in arm A and 34% in Arm B (p=0.13).

Multivariate analysis of prognostic factors related to response rate did not show statistically significant difference; the only factor predictive of improved overall survival was number of metastatic sites. In the four stratification groups patients with the absence of liver metastases <10cm2 had statistically better survival than patients with liver metastases >10cm2.

Toxicity

All patients were assessable for toxicity; there were 2 treatment related deaths in Arm A (febrile neutropenia), and none in Arm B, one patient in Arm A died of causes unrelated to treatment.

Overall, toxicity in the two arms was mild and grade 3/4 toxicities were uncommon.

	FOLFIRI	FOLFOX	P
Thrombocytopenia	15%	43%	<0.0001
Nausea and vomiting	72%	59%	0.009
Diarrhoea	63.5%	46%	0.007
Hair Loss	42%	19%	<0.0001
Neurologic toxicity	5%	45%	<0.0001

Table 4: Toxicities which were statistically significantly different between the two arms (all grades)

The most frequent toxicity in the FOLFIRI arm was gastrointestinal and more alopecia was observed; toxicities were primarily grade 1 to 2. In the FOLFOX4 more grade 1-2 thrombocytopenia and neurological toxicity was observed.

Hypersensitivity reactions were observed in the FOLFOX4 arm only and occurred primarily as grade 1-2 toxicity following 5 to 6 cycles of treatment.

Death rates within the first 60 days of treatment were 2.8% for patients in the FOLFIRI arm and 1.1% for patients in the FOLFOX4 arm (p=0.24).

Tables

	FOLFIRI (n=178)	FOLFOX4 (n=182)
	N (%)	N (%)
Sex		
Male	93(52)	10 (60)
Female	85 (48)	73 (40)
Age, years		
Median	62	62
Range	32-75	31-75
ECOG Performance Status		
Median	0	0
0	108 (60)	106 (58)
1	67 (38)	68 (38)
2	3 (2)	8 (4)
Previous Adjuvant Therapy		
Yes	55 (31)	52 (29)
No	123 (69)	130 (71)

Table: Patient Characteristics (other factors listed include Primary tumour location, metastatic disease, stratification groups, site of disease and no. of sites)

	FOLFIRI	FOLFOX4	P
No. of patients entered	178	182	
No. of patients assessable	164	172	
Response			
Complete Response (CR)			
No. (%)	8 (4.8)	9 (5.2)	
Partial Response (PR)			
No. (%)	48 (29.2)	53 (30.8)	
Stable Disease (SD)			
No. (%)	68 (41.6)	66 (38.3)	
Progressive Disease (PD)			
No. (%)	40 (24.4)	44 (25.7)	
CR + PR No.	56	62	
Response Rate			
Assessable Population			
%	34	36	0.71
95% CI	24.6-38.3	28.9-43.2	
Intent to Treat			
%	31	34	0.6
95% CI	24.6-38.3	27.2-41.5	
Duration, months			
Response			
Median	9	10	0.06
Range	4-47	5-27	
Time to Progression (TTP)			
Median	7	7	0.64
Range	1-47	1-32	
Survival			
Median	14	15	0.28
Range	1-48	1-43	

Table: Response rates for the treatment arms

Variable	HR	95% CI for HR	SE	P
Treatment	1.044	0.798-1.366	0.143	0.752
Age	1.009	0.993-1.024	0.007	0.255
sex	0.946	0.723-1.237	0.129	0.686
Adjuvant Therapy	1.204	0.865-1.676	0.203	0.269
Synchronous/Metachronous metastases	1.055	0.761-1.463	0.175	0.746
Single/Multiple Sites	1.348	1.024-1.774	0.188	0.033
ECOG PS 0 v 1	1.088	0.817-1.449	0.158	0.562
ECOG PS 0 v 2	1.648	0.813-3.341	0.165	0.813
H-, tumour <10cm^2 v H-, tumour >10cm^2	1.201	0.691-2.088	0.338	0.515
H-, tumour <10cm^2 v H+, tumour <10cm^2	1.082	0.616-1.901	0.311	0.782
H-, tumour <10cm^2 v H+ tumour >10cm^2	1.688	1.039-2.743	0.418	0.034

Table: Multivariate analysis of Prognostic factors

	FOLFIRI		FOLFOX	
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
	No (%)	No (%)	No (%)	No (%)
Anaemia	67 (38)	1 (1)	60 (33)	3 (2)
Leukopenia	65 (37)	5 (3)	70 (38)	5 (3)
Neutropenia	63 (35)	17 (10)	58 (32)	18 (10)
Thrombocytopenia	26 (15)	1 (1)	76 (42)	3 (3)
Nausea/vomiting	120 (67)	8 (4)	102 (56)	5 (3)
Diarrhea	95 (53)	18 (10)	74 (41)	9 (5)
Mucositis	61 (34)	2 (1)	52 (29)	2 (1)
Loss of Hair	75 (42)	-	35 (19)	-
Cholinergic Syndrome	18 (10)	-	-	-
Neurologic	9 (5)	-	74 (41)	8 (4)
Fever	26 (15)	2 (1)	37 (20)	-
Asthenia	28 (16)	-	24 (13)	-
Cardiac	2 (1)	1 (1)	3 (2)	2 (1)
Skin	6 (3)	-	7 (4)	-
Hypersensitivity	-	-	4 (2)	2 (1)

Table: Observed Toxicities for both treatment arms

General comments

Kaplan Meier curves are presented for time to progression and overall survival

Citation: Comella P, Massidda B, Filipelli G, Farris A, Natale D et al (2009) Randomised trial comparing biweekly oxaliplatin plus oral capecitabine versus oxaliplatin plus iv bolus fluorouracil/leucovorin in metastatic colorectal cancer patients: results of the Southern Italy Cooperative Oncology Study 0401

Comparison: Oxaliplatin + FU/FA versus Oxaliplatin + Capecitabine (1st Line)

Design: Randomised Trial

Country: Italy

Setting:

Aim: to compare oxaliplatin combined with either fluorouracil/leucovorin or capecitabine in terms of response rate, safety, progression free survival and quality of life.

Inclusion criteria
Histologically proven diagnosis of advanced adenocarcinoma of the colon or rectum
Age ≥18 years
Life expectancy >3 months
ECOG performance status ≤2
Adjuvant chemotherapy completed at least 6 months before commencing treatment
Presence of a bidimensionally measurable lesion
Normal renal function
Neutrophil count ≥2x10^6/L, platelet count ≥100x10^6/L, haemoglobin level ≥100g/L, serum bilirubin ≤1.25 times the normal upper limit, serum alanine aminotransferase and aspartate aminotransferase ≤2.5 times the normal upper limit in the absence of liver metastases and ≤5 times the normal upper limit in the presence of liver metastasis.

Exclusion criteria
None given

Sample Size
The study planned an 80% power to demonstrate, with an alpha error =0.05, a minimum difference in response rate between the two arms.
Planned accrual was 150 patients per arm, a sample size that also allowed the comparison of progression free survival.

Randomisation Method
Not Reported
Patients were stratified according to centre, performance status and previous exposure to adjuvant chemotherapy prior to randomisation.

Population
N=344 registered
N=322 eligible patients randomized (Arm A N=158 and Arm B N=164).

Study Duration
Recruitment Stage: May 2004 – April 2007

Interventions
Arm A - OXXEL: oxaliplatin 100mg/m^2 iv (2hours) on day 1; capecitabine 1,000mg/m^2 orally twice daily (12-hours apart) from the evening of day 1 to the morning of day 11.
Arm B - OXAFAFU: oxaliplatin 85mg/m^2 iv (2hours) on day 1; 6S-leucovorin 250mg/m^2 iv (2hours) followed by fluorouracil 850mg/m^2 iv bolus on day 2.

Cycles were repeated every 2 weeks until progression, unacceptable toxicity or patient refusal or for a maximum of 12 cycles.

Outcomes
Response Rate
Failure Free Survival
Progression Free Survival
Overall Survival

| Safety |
| Quality of Life |

Results

Patient Evaluation

Biochemistry profile, blood cell count and CEA serum level assessment were performed at baseline

Target lesions were measured by CT or MRI not more than 4 weeks before initial therapy.

Toxicity was assessed according to WHO criteria while neuropathy was assessed according to the Levi scale. Patients' worst toxicity was recorded.

Patients completed the EORTC QLQ-C30 before randomisation and every 8 weeks during treatment.

CT or MRI scan was repeated after every 4 cycles and at the end of treatment.

Response was defined according to WHO criteria and reassessed 8 weeks after the date of their first documentation with only confirmed responses were computed in the activity analysis.

Baseline characteristics were well balanced between the groups apart from more males and more patients with liver metastasis in Arm A and more patients with elevated CEA basal value in Arm B.

Delivered Treatment and Toxicity

A total of 1251 cycles of OXXEL and 1282 cycles of OXAFAFU were delivered with a median number of 8 cycles (range 1-12) in both arms.

Median duration of treatment was 17 weeks (range 1-36) in either arm.

Median cumulative dose was significantly greater for patients treated with OXXEL (739mg/m^2, range 75-1232mg/m^2) compared with OXAFAFU (659mg/m^2, range 63-1069mg/m^2) (p=0.001).

Median dose intensity of oxaliplatin was higher for OXXEL (43mg/m^2 per week, range 14-81mg/m^2 per week) than for OXAFAFU (34mg/m^2 per week, range, 13-78mg/m^2 per week) (p=0.001).

Median relative dose intensities of oxaliplatin were similar in the two arms (84% versus 80%)

Median dose intensity for capecitabine was 8046mg/m^2 per week (range; 5450-12,000mg/m^2) representing 80% of the planned dose intensity (not clear if that is what is meant from the statement made in the paper) and the median dose intensity of fluorouracil was 308m/m^2 (range; 153-406mg/m^2) representing 72% of the intended dose intensity.

Severe neutropenia (10% versus 27%; p<0.001) and febrile neutropenia (6% versus 13%; p=0.043) were significantly lower in the OXXEL arm.

Frequencies of grade ≥3 thrombocytopenia (4% versus 3% and anemia (3% versus 1%) were similar.

13% of patient in the OXXEL arm suffered severe diarrhoea compared to 8% in the OXAFAFU arm, though the difference was not significant.

Gastric intolerance was more common with oral assumption of capecitabine (8% versus 3%; p=0.028).

Other non-haematological side effects were comparable in both arms.

Overall, treatment related adverse events affected significantly fewer patients in the OXXEL arm than the OXAFAFU arm (32% versus 43%, p=0.026).

Deaths within the first 60 days of treatment commencing were similar in both arms (3% in the OXXEL arm versus 4% in the OXAFAFU arm).

There were two toxic deaths in the OXXEL arm in elderly patients, both of whom had received previous cycles of chemotherapy without experiencing severe toxicity and both of whom had normal renal functions.

Response Rates

There were 11 complete responses and 42 partial responses in the OXXEL arm for a response rate of 34%; in the OXAFAFU arm there were 6 complete responses and 48 partial responses for a response rate of 33% (OR=1.03. 95% CI, 0.63-1.68, p=0.999).

An overall disease control (response or stabilisation) was achieved in 68% of patients in the OXXEL arm and in 70% of patients in the OXAFAFU arm.

Response was slightly higher in patients with synchronous metastases (27% vs. 27%) and in patients ≤60 years (40% vs. 30%) irrespective of treatment arm. At multivariate analysis only age of patient adversely affected the probability of response (p<0.001).

Median failure free survival was 4.9 months (95% CL, 4.2-5.6 months) in the OXXEL arm and 4.7 months (95% CL, 4-5.4 months) in the OXAFAFU arm. HR=0.92, 95% CL, 0.73-1.17, p=0.555.

At Cox analysis, number of disease sites was significantly associated with a shorter failure-free survival (p=0.049).

Median progression free survival was 6.6 months (95% CL, 6.0-7.0 months) in the OXXEL arm and 6.5 months (95% CL, 5.4-7.6 months) in the OXAFAFU arm. HR=1.12, 95% CL, 0.88-1.45, p=0.354.
Number of disease sites (p=0.001) and elevated basal CEA value (p=0.036) were negative factors for progression free survival.

Overall Survival
Following a median follow-up of 24 months (range 6-42 months) 50% of patients had died (78 in the OXXEL arm and 84 in the OXAFAFU arm).
Median overall survival was 16 months (95% CL, 11.2-20.2 months) in the OXXEL arm and 17.1 months (95% CL, 13.8 – 20.4 months) in the OXAFAFU; **HR=1.01, 95% CL, 0.74-1.38, p=0.883**).
One, 2 and 3 year probabilities of survival were 59%, 36% and 31% for the OXXEL arm and 63%, 35% and 26% for the OXAFAFU arm.

Quality of Life
97% (n=312) patients, 151 in the OXXEL arm and 161 in the OXAFAFU arm, filled in a baseline questionnaire.
After 8 weeks the questionnaire was available for 78% (225/287) of patients on therapy; after 16 weeks the questionnaire was available for 81% (156/193) of patients on therapy and after 24 weeks questionnaires were available for 79% (72/91) patients on therapy.
Baseline single item and global health status/quality of life scores did not significantly differ between the two arms.
No significant differences in the change of single scores were observed between the two arms apart from constipation (p=0.001) and financial item score (p=0.004).
At the predetermined time point for the comparison , a preservation of the quality of life was observed in 47% of patients in either arm.
A higher proportion of patients in the OXXEL arm showed a deterioration of the global health status/quality of life score after 16 weeks and 24 weeks though the differences were not statistically significant.

Tables

Arm Characteristics	OXAFAFU	Fisher's Test	OXXEL	Total
	No (%)		No (%)	No (%)
Eligible Patients	164 (100)		158 (100)	322 (100)
Males	89 (54)	0.023	104 (66)	193 (58)
Females	75 (46)		54 (34)	129 (42)
Median age	65 (range: 37-79)		64 (range: 39-84)	63 (range: 37-84)
Aged ≥70 years	65 (40)		51 (32)	116 (36
ECOG Performance Status				
0	99 (60)		96 (61)	195 (61)
1	59 (36)		57 (36)	116 (36)
2	6 (4)		5(3)	87 (3)
Previous Surgery	125 (76)		114 (72)	239 (74)
Previous Adjuvant Chemotherapy	41 (25)		39 (25)	80 (25)

Table 1: Baseline characteristics (other reported factors include primary tumour location, tumour grading, no. of disease sites and metastases)

Arm Characteristics	OXAFAFU	Fisher's Test	OXXEL	Total
	No (%)		No (%)	No (%)
Eligible Patients	164 (100)		158 (100)	322 (100)
Total number of cycles	1,272		1,243	2,515
Median cycles/patient	8 (range 1-12)		8 (1-12)	8 (1-12)
Patients treated with:				
≥ 4 cycles	146 (89)		141 (89)	287 (89)
≥ 8 cycles	97 (59)		96 (61)	193 (60)
≥ 12 cycles	46 (28)		45 (28)	91 (28)
Patients still on therapy	7 (4)		7 (4)	14 (4)
Patients off treatment for:				
Protocol	110 (67)		101 (64)	210 (65)
Refusal	13 (8)		16 (10)	29 (9)
Toxicity	10 (6)	0.015	21 (13)	32 (10)
Disease Complications	14 (8)		5 (3)	19 (6)
Physicians decisions	10 (6)		8 (5)	18 (5)

Table 2: Treatment profiles

Arm	OXAFAFU		OXXEL		Fishers Test	
WHO toxicity %	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Neutropenia	49	27	15	10	0.001	0.001
Febrile Neutropenia		13		6		0.043
Anemia	30	1	23	3	N/S	N/S
Thrombocytopenia	21	3	24	4	N/S	N/S
Diarrhoea	43	8	36	13	N/S	N/S
Neuropathy	43	7	48	10	N/S	N/S
Gastric Symptoms	41	3	50	8	N/S	0.028
Stomatitis	18	2	15	2	N/S	N/S
Liver Toxicity	15	1	22	0	N/S	N/S
Hair Loss	14	0	7	0.6	N/S	N/S
Hand & Foot Syndrome	10	1	15	4	N/S	N/S
Renal Toxicity	4	0.6	8	2	N/S	N/S
Allergic Reactions	4	3	3	0.6	N/S	N/S
Fatigue	4	1	5	1	N/S	N/S

Table 3: Frequencies of main side effects

	Baseline Assessment		8 weeks		16 weeks		24 weeks	
	OXXEL	OXAFAFU	OXXEL	OXAFAFU	OXXEL	OXAFAFU	OXXEL	OXAFAFU
N	151	161	107	118	83	73	33	39
Physical	81 (1.4)	80 (1.5)	79 (2.1)	75 (1.8)	80 (2.1)	74 (2.6)	83 (4.6)	74 (2.6)
Role	76 (2.4)	75 (2.1)	76 (2.5)	68 (3.4)	79 (2.5)	76 (3.6)	77 (5.7)	85 (3.6)
Emotional	72 (1.7)	68 (1.7)	70 (2.2)	71 (2.1)	74 (2.1)	72 (2.9)	72 (3.8)	75 (3.7)
Cognitive	87 (1.7)	85 (1.5)	82 (2.7)	83 (1.8)	85 (2.3)	82 (3.0)	86 (4.2)	77 (9.0)
Social	82 (1.8)	80 (2.1)	78 (2.5)	77 (2.1)	77 (2.9)	79 (3.1)	78 (5.2)	87 (3.1)
Fatigue	28 (1.9)	30 (1.9)	31 (2.5)	37 (2.4)	30 (2.2)	38 (3.9)	34 (5.1)	28 (3.6)
Nausea/Vomiting	5 (0.9)	6 (1.3)	15 (2.3)	13 (1.6)	12 (1.7)	12 (2.4)	10 (3.8)	4 (1.5)
Pain	18 (1.9)	13 (1.5)	23 (4.1)	21 (2.2)	15 (2.5)	16 (2.9)	23 (4.8)	13 (2.9)
Dyspnoea	9 (1.4)	13 (1.6)	12 (2.3)	14 (1.6)	11 (2.2)	12 (2.5)	19 (4.7)	9 (2.9)
Insomnia	25 (2.3)	31 (2.4)	26 (2.9)	24 (2.4)	20 (2.8)	23 (3.3)	29 (5.5)	16 (3.7)
Appetite Loss	16 (2.1)	18 (1.9)	23 (2.1)	21 (1.9)	19 (2.9)	22 (3.4)	16 (4.5)	11 (3.1)
Constipation	20 (2.4)	20 (2.1)	16 (2.6)	22 (2.7)	13 (2.6)	27 (3.5)	10 (3.2)	15 (3.4)
Diarrhoea	9 (1.5)	10 (1.5)	16 (2.4)	20 (2.5)	14 (2.2)	15 (2.8)	10 (3.6)	11 (3.3)
Financial Difficulties	17 (2.2)	20 (2.1)	19 (2.8)	18 (1.8)	19 (3.0)	21 (3.9)	25 (5.5)	19 (2.9)
General Health Status	66 (1.8)	65 (1.7)	65 (2.2)	65 (1.8)	70 (2.2)	67 (2.5)	67 (5.1)	69 (2.9)

Table 4: Quality of Life (means and standard errors)

Arm	After 8 weeks		
	Improved[1]	Stable	Deteriorated[2]
OXXEL	24 (23%)	50 (47%)	30 (30%)
OXAFAFU	25 (22%)	56 (47%)	37 (31%)
Arm	After 16 weeks		
	Improved[1]	Stable	Deteriorated[2]
OXXEL	30 (37%)	29 (35%)	23 (28%)
OXAFAFU	17 (24%)	40 (57%)	13 (19%)
Arm	After 24 weeks		
	Improved[1]	Stable	Deteriorated[2]
OXXEL	5 (17%)	2 (7%)	47 (76%)
OXAFAFU	1 (3%)	7 (18%)	30 (79%)

[1] ≥10 pt increment of baseline score
[2] ≤10 pt decrease of baseline score

Table 5: Patients showing significant change in the quality of life score during treatment

General comments

After first line treatment was discontinued, patients were followed every 2 months to assess the disease status and survival.

Further treatment was not planned and the decision was left to single investigator choice.

Kaplan Meier Curves are given for progression free survival and overall survival.

Citation: Comella P, Massidda B, Filippelli G, Palmeri S, Natale D (2005) Oxaliplating plus high dose folinic acid and 5 fluorouracil i.v. bolus (OXAFAFU) versus irinotecan plus high dose folinic acid and 5-fluorouracil i.v. bolus (IRIFAFU) in patients with metastatic colorectal carcinoma: a Southern Italy Cooperative Oncology Group phase III trial *Annals of Oncology* 16;6:878-886
Comparison: Oxaliplatin + FA/FU versus Irinotecan + FA/FU (1st line)
Design: Randomised Trial **Country**: Italy **Setting:** Multicentre **Aim**: to assess the activity and toxicity of OXAFAFU compared with IRIFAFU in metastatic colorectal cancer patients
Inclusion criteria Histologically proven diagnosis of adenocarcinoma of the colon or rectum Age ≥18 years Life expectancy of >3 months ECOG performance status of ≤2 Metastatic unresectable disease At least one bideminsionally measurable lesion Normal renal function Neutrophil count ≥2,000/mm^3 Platelet count ≥100,000/mm^3, Bilirubin ≤1.25x upper normal limit Alanine aminotransferase and aspartate aminotransferase ≤5x upper normal limit
Exclusion criteria Patients with previous palliative chemotherapy Patients receiving adjuvant chemotherapy within 6 months of starting therapy Inflammatory bowel disease or significant diarrhoea Previous total colectomy or ileostomy Bowel obstruction Uncontrolled metabolic disorders or active infections Severe cardiac arrhythmia or acute myocardial infarction within 6 months of starting therapy Symptomatic cerebral metastasis Concomitant or previous malignant tumour
Sample Size It was assumed that the OXAFAFU regimen might increase by 50% (From 5-7.5 months) the median failure free survival in comparison with the IRIFAFU regimen. With 257 events on the whole series of patients there is an 80% power to demonstrate this difference with a 0.05 alpha error. A recruitment of 280 patients was planned for the comparative analysis; a number of patients may also give an 80% power to detect a 15% difference in response rates between OXAFAFU and IRIFAFU.
Randomisation Method Randomisation method not reported Patients were stratified according to centre, previous adjuvant chemotherapy and performance status
Population N=288 N=276 eligible patients randomized Arm A (IRIFAFU): 74 patients randomised prior to amendment and 62 patients randomised after Arm B (OXAFAFU): 71 patients randomised to receive high dose regimen prior to amendment and 69 patients randomised to low dose regimen
Study Duration Recruitment Stage: January 2001 – June 2003
Interventions

Arm A (IRIFAFU): Irinotecan 200mg/m^2 i.v. (90 min) on day 1, *l*-FA 250mg/m^2 i.v. (2h), 5-FU 850mg/m^2 i.v. bolus on day 2
Arm B (OXAFAFU): Oxaliplatin 100 mg/m^2 i.v. (2h) on day 1, *l*-FA 250 mg/m^2 i.v. (2h), 5-FU 1,050 mg/m^2 i.v. bolus on day 2 (OXAFAFU, high dose), later amended to Oxaliplatin 85mg/m^2 and 5-FU 850mg/m^2(OXAFAFU, low dose).

Cycles were repeated every 2 weeks in both arms

Outcomes
Not clear, reported as being activity and toxicity

Results
One patient in each arm refused the assigned regimen (does not say what happened to these patients).
The median number of cycles was 6 (range: 1-16) in the IRIFAFU arm and 8 (range 1-12) in the OXAFAFU (both high dose and low dose); patients in the IRIFAFU arm stayed on study for a median of 16 weeks (range 2-44) and in the OXAFAFU arm patients stayed on study for a median of 18 weeks (range 2-40) in the high dose group and for a median of 22 weeks (range 2-39) in the low dose group.
19% of patients treated with IRIFAFU dropped out for refusal or toxicity compared with 11% of OXAFAFU (high dose) and 12% of OXAFAFU (low dose).

Dose Intensity and OXA Cumulative Dosage

	4 Week		8 Week		12 Week	
	Irinotecan/Oxaliplatin	5-FU	Irinotecan/Oxaliplatin	5-FU	Irinotecan/Oxaliplatin	5-FU
IRIFAFU	88mg/m^2/week	372 mg/m^2/week	82 mg/m^2/week	343 mg/m^2/week	76 mg/m^2/week	346 mg/m^2/week
OXAFAFU (high dose)	41 mg/m^2/week	426 mg/m^2/week	37 mg/m^2/week	374 mg/m^2/week	39 mg/m^2/week	354 mg/m^2/week
OXAFAFU (low dose)	39 mg/m^2/week	417 mg/m^2/week	34 mg/m^2/week	344 mg/m^2/week	35 mg/m^2/week	327 mg/m^2/week

Table 1: Median dose intensity for each treatment regimen and cycle

Cumulative Oxaliplatin dosage was 705 mg/m^2 (range 100-1200) with OXAFAFU high dose and 780 mg/m^2 (range 82-1114) with OXAFAFU low dose.

Activity
There were 42 confirmed responses (16 complete responses and 26 partial responses) in the IRIFAFU group, 29 in the OXAFAFU high dose group (7 complete responses and 22 partial responses) and 32 in the OXAFAFU low dose group (13 complete responses and 19 partial responses).
12/16 complete respsonses in the IRAFAFU group were achieved in patients with only one involved organ; 6/7 complete responses in the OXAFAFU high dose group were in patients with only one site of disease and 8/13 complete responses in the OXAFAFU low dose group were in patients with a single metastatic site.

OXAFAFU yielded a significantly higher response rate (44%, 95% CI 35%-52%) compared to IRIFAFU (31%, 95% CI 23% - 40%) (p=0.029).
The proportion of patients achieving a partial response was greater among patients treated with OXAFAFU (29% versus 19%; p=0.002) and no difference was observed in complete response (14% versus 12%)
There was a significant difference in response rate between IRIFAFU and OXAFAFU low dose (p=0.032).
The rate of disease control (response or stabilisation) was greater with Oxaliplatin (66%) than with Irinotecan (58%).

Response rates were adversely affected by a number of baseline characteristics including performance status ≥1, presences of symptoms of disease, loss of body weight, CEA baseline value >100ng/ml, no primary surgery and more than one disease site.
Including these factors together with treatment type in multivariate analysis good performance status (p=0.000), the OXAFAFU regimen (p=0.011) and a low CEA baseline value (p=0.035) showed significant correlation with response rates

Time to response achievement was 2.9 months (range 1.6-9 months) for IRIFAFU and 3.2 months (range 1.7-9.3) for OXAFAFU.
Median duration of complete responses was 5.2 months (range 2-19 months) in the IRIFAFU group, 17.2 months (range 2.3-25.3 months) in the OXAFAFU high dose group and 8.5 months (range 2-16.4 months) in the

OXAFAFU low dose group.
Median duration of all responses was 7.9 months (range 1.9-20.8 months) treated with irinotecan and 8.5 months (range, 1.5-22.1 months) for patients treated with oxaliplatin (10.5 months for OXAFAFU high dose and 7.9 months for OXAFAFU low dose).

Toxicity
At interim analysis, neutropenia was more pronounced with OXAFAFU high dose than with IRIFAFU (grade ≥3 toxicity was 55% versus 39%; p=0.029) and febrile neutropenia was more frequent (19% versus 9%, p=0.041). After dosage amendment, there was no difference in sever haematological toxicity between OXAFAFU low dose and IRIFAFU.
Occurrence of diarrhoea was significantly lower among patients treated with OXAFAFU low dose and grade ≥3 was less frequent (12% versus 28%, p=0.005).
The proportion of patients complaining of severe emesis was more than halved (4% versus 10%, p=0.113) and hair loss was less pronounced with OXAFAFU based treatment.
Grade 3 neuropathy was recorded in 14% of patients treated with OXAFAFU high dose and in 3% of patients treated with OXAFAFU low dose.
Overall 44% of patients treated with OXAFAFU low dose and 53% of patients treated with IRIFAFU suffered at least one episode of grade ≥3 toxicity.

Early deaths (within 60 days of initial therapy) were 4% in both IRIFAFU and OXAFAFU groups.
5 patients died due to severe adverse events possibly related to received treatment; 3 patients died as a consequence of severe diarrhoea, 1 died of myocardial infarction following the first course of IRIFAFU and 1 patient had a gastric haemorrhage after the first course of OXAFAFU low dose.

Failure Free Survival and Overall Survival
Median follow-up was 24 months (range 10-36), 252 (91%) patients had an induction failure and 150 (54% patients died.
According to treatment, median failure free survival was 5.8 months (95% CI 4.4 - 7.2 months) for patients treated with IRIFAFU, 6 months (95% CI 5.9 – 9.3 months) for patients treated with OXAFAFU high dose and 7.6 months (95% CI 5.9-9.3) for patients treated with OXAFAFU low dose.

Median overall survival was 15.6 months (95% CI 13.5 – 17.9) for IRIFAFU and 18.9 months (95% CI 15.3 – 22.5) for OXAFAFU. Median overall survival for patients treated with OXAFAFU high dose was 17.6 months (95% CI 13.1 – 22.1) and exceeded 23 months for patients treated with OXAFAFU low dose.

Failure free survival was 8.3 months for patients with performance status 0 compared with 3.4 months for patients with performance status ≥1 and overall survival was 20.5 months compared with 11.1 months.
The difference in failure free survival for patients treated with irinotecan and oxaliplatin was statistically significant when adjusted for performance status (p=0.046).
Comparison of overall survival between irinotecan and oxaliplatin treated patients was significant when adjusted for performance status (p=0.032)

Survival probability for OXAFAFU treated patients compared to IRIFAFU treated patients was 60% versus 65% at 12 months, 42% versus 52% at 18 months and 23% versus 39% at 24 months.

Overall survival for patients treated sequentially with all three active drugs (5-FU, Irinotecan and oxaliplatin) was significantly longer than that of patients not receiving all three drugs (median 16.6 months versus 13 months, p=0.009).

Off-study treatments
9 patients with partial response were rendered disease free by surgical resection of liver metastases (3 in the IRIFAFU group and 6 in the OXAFAFU group).

At progression following 1st line IRIFAFU 57% (n=77) of patients went on to receive second line treatments, 62 of whom received Oxaliplatin associated with 5-FU or capecitabine.
Local treatment of liver metastases was performed in 5 patients.
13% (n=18) of patients received a third line treatment in the form of oral fluoropyrimidines.
Salvage treatments were delivered to 56% (n=78) of patients receiving OXAFAFU front line consisting of irinotecan alone or combined with 5-FU or mitomycin C in 52 patients, local management of liver metastases in 6 patients and third line treatment with oral fluoropyrimidines in 20 patients.

Tables

	IRIFAFU	OXAFAFU high dose	OXAFAFU low dose	OXAFAFU
	n (%)	n (%)	n (%)	n (%)
Eligible Patients	136 (100)	71 (100)	69 (100)	140 (100)
Males	72 (53)	46 (65)	35 (51)	81 (58)
Females	64 (47)	25 (35)	34 (49)	59 (42)
Median Age, years	62 (range: 38-80)	62 (range: 41-79)	63 (37-76)	62 (37-79)
Aged ≥70 years	22 (16)	16 (22)	12 (17)	28 (20)
Previous Surgery	111 (82)	49 (69)	55 (80)	104 (74)
Previous Adjuvant Chemotherapy	34 (25)	19 (27)	15 (22)	34 (24)
ECOG Performance Status				
0	82 (60)	33 (47)	42 (61)	75 (54)
1	50 (36)	35 (49)	26 (38)	61 (44)
2	4 (4)	3 (4)	1 (1)	4 (3)

Table 2: Patient Characteristics (other reported details included Primary tumour site, no. of metastatic sites, liver involvement, synchronous metastasis, symptoms of disease, CEA values and weight loss)

Treatment	IRIFAFU	OXAFAFU high dose	OXAFAFU low dose
Total number of cycles	1022	549	572
Median cycles/ patient (range)	8 (1-16)	8 (1-12)	8 1-12)
No. of patients receiving (%)			
≥4 cycles	117 (87)	63 (89)	61 (90)
≥8 cycles	77 (57)	40 (56)	46 (68)
≥12 cycles	41 (30)	18 (25)	23 (34)
No. of patients off treatment (%)			
As per protocol	96 (71)	54 (76)	50 (74)
Refusal	15 (11)	6 (8)	6 (9)
Toxicity	11 (8)	2 (3)	2 (3)
Disease Complication	3 (2)	5 (7)	5 (7)
Physician Decision	10 (7)	4 (6)	5 (7)

Table 3: Summary of treatment

	IRIFAFU	OXAFAFU high dose	OXAFAFU low dose	OXAFAFU
	n (%)	n (%)	n (%)	n (%)
Complete Response	16 (12)	7 (10)	13 (19)	20 (14)
Partial Response	26 (19)	22 (31)	19 (28)	41 (29)
Stable Disease	36 (27)	15 (21)	15 (22)	30 (22)
Progressive Disease	38 (28)	19 (27)	14 (21)	33 (24)
Not Assessed	19 (14)	8 (11)	7 (10)	15 (11)
Treated Patients	135 (100)	71 (100)	68 (100)	1139 (100)

Table 4: Activity according to treatment

	IRIFAFU n=135	OXAFAFU high dose n=71	OXAFAFU low dose n=68	OXAFAFU n=139
Grade	Any (≥3)	Any (≥3)	Any (≥3)	Any (≥3)
Neutropenia	59 (31)	78 (55)	49 (29)	65 (40)
Febrile neutropenia/infections	9 (7)	19 (13)	3 (3)	11 (7)
Anaemia	33 (1)	35 (2)	35 (1)	35 (3)
Thrombocytopenia	10 (1)	32 (4)	29 (3)	32 (4)
Emesis	62 (10)	54 (4)	53 (4)	54 (6)
Diarrhoea	66 (28)	44 (13)	32 (12)	39 (11)
Stomatitis	23 (3)	35 (6)	15 (4)	26 (4)
Fatigue	5 (2)	6 (4)	7 (3)	6 (3)
Neuropathy	5 (1)	48 (14)	47 (3)	48 (7)
Cholinergic	10 (2)	0 (0)	0 (0)	0(0)
Hair Loss	49 (23)	23 (1)	9 (2)	16 (1)
Allergic	1 (0)	4 (1)	7 (1)	5 (1)
Treatment related death	- (2)	-(1)	-(1)	-(1)

Table 5: Frequency of Toxicity

General comments

After progressive disease a crossover policy (IRIFAFU second line for the OXAFAFU arm and OXAFAFU second line for the IRIFAFU arm) was advised but not mandatory.

Kaplan Meier curves for failure free survival and overall survival are presented

There is a table comparing the efficacy and toxicity of 5-FU/FA with either oxaliplatin or irinotecan in advanced colorectal cancer with 2 other randomised trials (Tournigand, 2004 and Goldberg, 2004).

Citation: Cunningham D, Sirohi B, Pluzanska A, et al (2009) Two different first line 5 fluorouracil regimens with or without oxaliplatin in patients with metastatic colorectal cancer *Annals of Oncology* 20;244-250
Design: Open label Phase IIIb randomised trial **Country**: Multiple **Setting:** Multicentre **Aim**: to evaluate two 5-FU regimens ± Oxaliplatin followed by Irinotecan on progression
Inclusion criteria Patients with histologically proven colorectal cancer with distant metastases Age ≥18 years No prior chemotherapy for metastatic disease WHO performance status ≤2 No major biochemical/haematologic abnormalities Unidimensionally measurable lesions Prior chemotherapy to be completed ≥6 months before study entry.
Exclusion criteria Patients with resectable disease Unresolved bowel obstruction/diarrhea Peripheral neuropathy Prior malignancies History of hyper sensitivity or intolerance to previous 5-FU Pregnant/lactating females
Sample Size A sample size of 700 patients was required in order to provide ≥90% power to detect a difference between the two arms using a two-sided log-rank test at the 0.05 level on the basis of the assumption that two year survival would be 30% in arm A and 20% in arm B.
Randomisation Method Patients were randomly allocated to arm A or arm B and then further subdivided into arm A1 or A2 and Arm B1 or B2. No further details are given.
Population N=725 (Intention to Treat) N=720 (Safety) N=5 (Not Treated)
Study Duration
Interventions Arm A1: Oxaliplatin very 2 weeks (85mg/m^2 2hour i.v. infusion on D1 + 5-FU 250mg/m^2/day CIV given continuously without interruption for the two week duration of the treatment cycle). Arm A2: Oxaliplatin every 2 weeks (85mg/m^2 2hour i.v. infusion on D1 + 5-FU 400mg/m^2 bolus + 600mg/m^2 22-hour CIV on D1, 2 + LV, 200mg/m^2 2hour infusion on D1, 2) (FOLFOX4) Arm B1: 5-FU 300mg/m^2/day CIV (5-FU CIV) without interruption Arm B2: 5-FU 400mg/m^2 bolus + 600mg/m^2 22hour CIV on D1,2 + LV 200mg/m^2 2hour infusion on D1, 2)
Outcomes Survival (defined as percentage of patients still alive at 2 years) Progression free survival Time to treatment failure Safety

Results
Reasons for not treating patients included physician decision,intercurrent medical problem, voluntary withdrawal and death before treatment.

362 patients were randomised to Arm A and 363 were randomised to Arm B
Arm A1=58
Arm A2=304
Arm B1=62
Arm B2=301

A total of 7908 cycles were administered to 720 patients with a median of 10 cycles per patient
Mean planned 5-FU dose intensity was 78.3% in Arm A1, 83.6% in Arm A2, 76.7% in Arm B1 and 91% in Arm B2.
Mean planned oxaliplatin dose intensity was 77% in Arm A1 and 83% in Arm A2
5-FU dose reductions were more common with the CIV regimen (Arm A, 61%; Arm B69%) compared to the two weekly regimens (Arm A 41%; Arm B, 16%).
Oxaliplatin reductions were required in 34% of patients in Arm A1 and in 39% of patients in Arm A2.

196 in Arm A patients and 220 patients in Arm B received second line chemotherapy; 150 patients in Arm A and 177 patients in Arm B received Irinotecan. Details of second line treatment received by the remaining patients in each arm are not provided.

2 year survival rates were similar between the two arms; 27.3% in Arm A versus 24.8% in Arm B.
Median overall survival was 15.9 months (95% CI, 15.0-17.3) in Arm A and 15.2 months (95% CI, 14.0-16.1) in Arm B.
Hazard Ratio for survival: HR=0.93 (95% CI, 0.78-1.10; p=0.155)

1 year survival rates were 62.6% (95% CI, 57.6-67.7%) in Arm A and 61.5% (95% CI, 56.5-66.5%) in Arm B.
The study reported a numerically greater probability of survival in Arm A compared with Arm B at all time points (assumed that this meant that the number of patients still alive at any given time point was greater in Arm A compared with Arm B).

Survival analysis conducted 2 years after the last patient was randomised showed no significant difference between the two arms: **HR=0.92 (95% CI, 0.78-1.08, p=0.106)**.
Overall survival was higher for patients on oxaliplatin compared with 5-FU±LV alone (Relative Risk: RR=0.93; 95% CI, 0.79-1.09) and for patients who received the 5-FU CIV regimen compared with 5-FU+LV (RR=0.84; 95% CI, 0.67-1.05).
Retrospective analysis showed that median overall survival appeared to be longer in centres where >50% of patients received Irinotecan second line (19.9 months in Arm A and 16.4 months in Arm B).

Overall response rate (CR+PR) was significantly higher in Arm A (54.1%; 95% CI, 48.9-59.45%) than in Arm B (29.8%; 95% CI, 25.1-34.7%), p<0.0001.
Median progression free survival was significantly longer in Arm A compared with Arm B (7.9 months (95% CI 7.3-9.0) versus 5.9 months (95% CI 5.1-6.8). **HR=0.67 (95% CI, 0.58-0.79, p<0.0001)**.
The probability of being alive without disease progression was greatest in Arm A at all time points.
Median TTF was 5.5 months in Arm A (95% CI, 5.2-6.1) and 4.9 months in Arm B (95% CI, 4.7-5.3). **HR=0.9 (95% CI 0.77-1.04, p=0.053)**.

Oxaliplatin versus non-oxaliplatin: 77% of patients in Arm A versus 51% of patients in Arm B experienced at least one episode of grades 3-4 toxicity.
Treatment discontinuation occurred in 17% of patients in Arm A and 5% in Arm B.

CIV versus two weekly schedule: In arm A, the incidence of several grade 3-4 toxic effects differed according to the administered 5-FU schedule including diarrhoea, neutropenia, febrile neutropenia, infection without neutropenia, skin exfoliation, fatigue and vomiting.
In Arm B, the incidence of grade 3-4 toxicities was similar for both treatment regimens with the exception of skin exfoliation which was more common with the 5-FU CIV regimen (15% versus 1%).

Serious Adverse Events: The total number of serious adverse events leading to hospitalisation, prolonged hospitalisation, death or considered medically important was 424 for Arm A and 310 for Arm B.
40 patients died between date of randomisation and 30 days after completion of chemotherapy, mostly as a result

of disease progression.

The number of patients requiring hospitalisation during the study was 146 (40%) in Arm A and 125 (34%) in Arm B.

Tables

Response Category	Patients, n (%)	
	Arm A: Oxaliplatin +5-FU (n=362)	**Arm B: 5-FU (n=363)**
Complete Response	24 (6.6)	6 (1.7)
Partial Response	172 (47.5)	102 (28.1)
Stable Disease	76 (21)	128 (35.3)
Progressive Disease	46 (12.7)	89 (24.5)
Not Evaluable	8 (2.2)	4 (1.1)
Not Done/Missing Data	36 (9.9)	34 (9.4)

Toxicity	Patients, n (%)			
	Arm A: oxaliplatin + 5-FU (n=358)		**Arm B: 5-FU (n=362)**	
	Any Grade	**Any Grade 3-4**	**Any Grade**	**Any Grade 3-4**
Neutropenia	223 (62)	117 (33)	82 (23)	17 (5)
Diarrhoea	209 (58)	50 (14)	172 (48)	29 (8)
Fatigue	262 (73)	32 (9)	228 (63)	29 (8)
Pain	182 (51)	27 (8)	203 (56)	27 (7)
Infection without neutropenia	113 (32)	28 (8)	111 (31)	24 (7)
Sensory Neuropathy	267 (75)	45 (13)	69 (19)	5 (1)
Vomiting	163 (46)	22 (6)	100 (28)	11 (3)
Injection Site Reaction	77 (22)	17 (5)	74 (20)	12 (3)
Chest Pain	6 (2)	1 (<1)	6 (2)	2 (1)
Myocardial Ischaemia	1 (<1)	1 (<1)	3 (1)	2 (1)

Toxicity (Arm A)	Patients, n (%)	
	CIV	**2 weekly schedule**
	Any Grade 3-4	**Any Grade 3-4**
Neutropenia	2%	39%
Diarrhoea	28%	11%
Febrile Neutropenia	0%	3%
Infection without neutropenia	19%	6%
Skin Exfoliation	11%	1%
Vomiting	12%	5%
Fatigue	4%	10%

Citation: Diaz-Rubio E, Tabernero J, Gomez-Espana A et al (2007) Phase III study of Capecitabine plus oxaliplatin compared with continuous infusion fluorouracil as first line therapy in metastatic colorectal cancer: final report of the Spanish Cooperative Group for the treatment if digestive tumours trial *Journal of Clinical Oncology* 25;27:4224-4230
Comparison: XELOX versus FUOX (1st line)
Design: Multi-centre Open Label Randomised Trial **Country**: Spain **Setting:** Outpatients **Aim**: to compare the efficacy and safety of Capecitabine plus oxaliplatin versus Spanish-based continuous infusion high-dose fluorouracil plus oxaliplatin regimens and first line therapy for metastatic colorectal cancer
Inclusion criteria Age ≥18 years Histological confirmed MCRC Karnofsky performance status ≥70% Life expectancy >3 months At least one measurable lesion according to Response Evaluation Criteria in Solid Tumours Group criteria Chemotherapy to have been completed at least 1 year before study entry Adequate haematological, hepatic and renal function
Exclusion criteria Pregnant or breast feeding women Clinically significant cardiac disease or myocardial infarction within the 12 months prior to study inclusion Severe renal failure Lack of physical integrity of the upper GI tract Peripheral neuropathy History of other malignant disease apart from cured basal cell carcinoma or in situ cervical carcinoma or CNS metastases
Sample Size Sample size determination was based on the results of a previously published study which showed a median time to progression of approximately 7 months. A noninferiority hypothesis was considered when the median time to progression in the XELOX arm was not lower than 5.5 months (corresponding to a Hazard Ratio <1.27). The sample size estimated for noninferiority with an α=0.05 and an 80% power was 165 patients in each treatment arm. Assuming a 5% loss of patients to follow-up, the total number of patients to be enrolled needed to be 174 per treatment arm.
Randomisation Method Centrally generated computer randomisation code
Population N=348 (intention to treat population) , 174 to each arm 6 patients (3 in each arm) did not initiate study treatment leaving 342 patients (per protocol population), 171 in each arm.
Study Duration Recruitment Phase: April 2002 to August 2004 Cut-off date for analysis was June 15, 2006
Interventions Arm A, XELOX: oral Capecitabine 1,000mg/m^2 bid for 14 days plus oxaliplatin 130 mg/m^2 on day 1 every 3 weeks. Arm B, FUOX: FU 2,250 mg/m^2 diluted in saline, administered by CIV during 48 hours on days 1, 8, 15, 22, 29 and 36, plus oxaliplatin 85mg/m^2 on days 1, 15 and 29 every 6 weeks. Oxaliplatin was administered as a 120 minute intravenous infusion in 5% dextrose

Outcomes
Time to progression between groups in the per protocol (no definition)

Safety
Response Rate
Time to Treatment Failure
Overall Survival
Duration of Response

Results
 Baseline demographics and clinical characteristics were well balanced between the two arms, though significantly more patients in the XELOX arm (26%) than the FUOX arm (16%) had received previous adjuvant chemotherapy (p=0.032) which consisted of fluoropyrimidine therapy with or without leucovorin.

Efficacy
Median duration of follow-up was 17.5 months.
Median time to progression was 8.9 months (95% CI, 7.8-9.9 months) in the XELOX arm versus 9.5 months (95% CI, 7.8-9.9 months) in the FUOX arm **(Hazard Ratio, 1.18; 95% CI 0.9 to 1.5; p=0.153)**.
There were no statistically significant differences in the median time to progression whether patients received adjuvant chemotherapy or not (p=0.527).
Median overall survival was 18.1 months (95% CI, 15.5-20.4 months) in the XELOX arm versus 20.8 months (95% CI, 16.6-25 months) in the FUOX arm **(Hazard Ratio, 1.22; 95% CI 0.9 to 1.6, p=0.145)**.
One and 2 year survival rates were 66.3% (95% CI, 59%-73.6%) and 35.7% (95% CI, 28.1%-43.3%) for XELOX and 71.5% (95% CI, 64.6%-78.4%) and 44% (95% CI, 37%-51.7%) for FUOX respectively.
There was no statistically significant difference between the arms in relation to time to treatment failure; median time to treatment failure was 6 months (95% CI 5.1-6.8 months) in the XELOX arm and 6.9 months (95% CI, 6.2-7.6 months) in the FUOX arm **(Hazard Ratio, 1.15; 95% CI, 0.9 to 1.4; p=0.204)**.

Confirmed objective response rate was 37% (95% CI, 30.2-44.7%) in the XELOX arm and 46% (95% CI, 38.1%-53.1%) in the FUOX arm(Fishers exact test P=0.154).
Median duration of response was 9.2 months (95% CI, 7.6-11 months) in the XELOX arm and 9.4 months (95% CI, 7.6-11.2 months) in the FUOX arm (p=0.430).
Tumour control rate was similar in both arms: 66% (95% CI, 59-73.2%) in the XELOX arm and 71% (95% CI, 63.9-77.5%) in the FUOX arm.

22 patients in the XELOX arm and 15 patients in the FUOX arm were not assessed for response; these patients withdrew from the study before the scheduled response evaluation (established by protocol at 12 weeks after the start of treatment).
Reasons for not evaluating patients included adverse events, death as a result of different reasons, consent withdrawal or protocol violation, loss to follow-up, major surgery and patient withdrawn and discretion of investigator.

Poststudy Treatment
58.2% (n=199) of patients received second line therapy; 57.9% (n=99) in the XELOX arm and 58.5% (n=100) in the FUOX group. The most common second line treatment was irinotecan (80.4%, n=160), either in combination with FU with or without LV or with Capecitabine, cetuximab or raltitrexed (52.7%, n=105) or in monotherapy (27.6%, n=55).
There was no statistically significant difference between the two arms in the second line treatment rate (>0.999).
11.4% (39/342) of patients receiving chemotherapy underwent surgery for metastasectomy, 38 for liver metastases and 1 for lung metastasis.
10% (n=17) of the surgeries were on patients in the XELOX arm and 12.9% (n=22) on patients in the FUOX arm.
An R0 liver resection was performed in 71% (27/38) of patients: 13/16 in the XELOX group and 14/22 in the FUOX group (p=0.296).
Median time to progression in patients with R0 resections was 16.9 months in the XELOX arm and 18.8 months in the FUOX arm.
Median overall survival in patient with R0 resections was 31.1 months for patients receiving XELOX and had not been reached for patients in the FUOX arm and the time of publication.

Safety
Safety was evaluated in all patients receiving treatment and the safety profiles were generally similar.

There were significantly lower rates of grade 3/4 diarrhoea (14% v 24%, p=0.027) and grade 1/2 mucositis (28% v 43%, p=0.005) and significantly higher rates of grade 1/2 hyperbilirubinemia (37% v 21%, p=0.001) and grade 1/2 hand-foot syndrome (14% v 5%, p=0.009) in the XELOX arm compared with the FUOX arm.

There was a similar rate of venous thrombotic events (4% (n=7) in each arm). In the XELOX arm, two serious events were deemed possibly treatment related and in the FUOX arm one event was deemed treatment related but not seious.

27% of patients in each arm (n=45) discontinued treatment because of adverse events with the main reason for discontinuation including neurological toxicity, oxaliplatin intolerance, allergic reactions, pharyngolaryngeal dysesthesias or gastrointestinal disorders, haemototoxicity, diarrhoea, asthenia, hepatic toxicity and cerbrovascular events.

Deaths were considered to be treatment related in 4 patients (one receiving XELOX and 3 receiving FUOX); cause of death was febrile neutropenia, stomatitis and thrombocytopenia in the patient receiving XELOX and pneumonia (n=2) and septic shock (n=1) in the patients receiving FUOX).
60 day mortality rates were 2% (n=3) with XELOX and 3% (n=5) with FUOX).

Tables

	XELOX (n=171)	FUOX (n=171)	P
	N (%)	N (%)	
Sex			
Male	107 (63)	100 (58)	0.507
Female	64 (37)	71 (42)	
Age, years			
Median	64	65	0.485
Range	32-80	35-81	
Karnofsky Performance Status			
≤70	18 (11)	17 (10)	0.99
>70	153 (89)	154 (90)	
Previous Treatment			
Surgery	138 (81)	142 (83)	0.674
Chemotherapy	44 (26)	27 (16)	0.032
Radiotherapy	16 (9)	27 (16)	0.102

Table 1: Patient Characteristics (other factors reported include Body weight, primary tumour site, tumour stage at initial diagnosis, tumour status, metastatic site)

	XELOX (n=171)	FUOX (n=171)
	N (%)	N (%)
Objective Response (CR +PR)	64 (37)	78 (46)
Complete Response (CR)	8(5)	10 (6)
Partial Reponse (PR)	56 (32)	68 (40)
Stable Disease	49 (29)	43 (25)
Tumour Control (CR+PR+SD)	113 (66)	121(71)
Progressive Disease	36 (21)	35 (20)
Not Assessable	22 (13)	15 (9)

Table 2: Antitumour Efficacy (per protocol)

Chemotherapy	XELOX (n=99)	FUOX (n=100)
	N (%)	N (%)
FU±LV	2 (2)	1 (1)
FU±LV+Irinotecan	32 (32.3)	42 (42)
FU±LV+Oxaliplatin	1 (1)	6 (6)
Capecitabine	1 (1)	8 (8)
Capecitabine+Oxaliplatin	5 (5.1)	
Capecitabine+Irinotecan	15 (15.2)	4 (4)
Irinotecan	27 (27.3)	28 (28)
Irinotecan+Cetuximab	5 (5.1)	5 (5)
Irinotecan+Raltitrexed	2 (2)	
Oxaliplatin+Raltitrexed	3 (3)	2 (2)
Others	6 (6.1)	4 (4)

Table 3: Chemotherapy after withdrawal from study treatment

	XELOX		FUOX	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
	N (%)	N (%)	N (%)	N (%)

Haematologic				
Anaemia	114 (67)	5 (3)	131 (77)	3 (2)
Leukopenia	68 (40)	4 (2)	77 (45)	7 (4)
Thrombocytopenia	80 (47)	6 (4)	81 (47)	6 (4)
Neutropenia	78 (46)	12 (7)	80 (47)	18 (11)
Non Haematologic				
Paresthesia	108 (63)	31 (18)	113 (66)	28 (16)
Asthenia	86 (50)	21 (12)	86 (50)	29 (17)
Transaminases Increase	101 (59)	3 (2)	106 (62)	4 (2)
Diarrhoea	61 936)	24 (14)	74 (43)	41 (24)
Nausea	73 (43)	5 (3)	75 (44)	9 (5)
Vomiting	63 (37)	9 (5)	59 (35)	13 (8)
Hyperbilirubinemia	63 (37)	5 (3)	35 (21)	6 (4)
Mucositis	48 (28)	4 (2)	74 (43)	7 (4)
Anorexia	44 (26)	5 (3)	56 (33)	4 (2)
Constipation	39 (23)	1 (<1)	42 (25)	3 (2)
Abdominal Pain	36 (21)	1 (<1)	42 (25)	4 (2)
Fever	34 (20)	0 (0)	34 (20)	1 (<1)
Hand-Foot Syndrome	24 (14)	4 (2)	9 (5)	2 (1)
Increased Creatinine	16 (9)	0 (0)	20 (12)	2 (1)
Rash	13 (8)	3 (2)	16 (9)	1 (<1)
Dysgeusia	14 (8)	0 (0)	16 (9)	1 (<1)
Allergic Reaction	2 (1)	2 (1)	12 (7)	1 (<1)
Alopecia	4 (2)	0 (0)	15 (9)	0 (0)
Dyspepsia	2 (1)	0 (0)	19 (11)	1 (<1)
Epistaxis	3 (1)	0 (0)	12 (7)	0 (0)

Table 4: Most Common Adverse Events (>5% of patients)

General comments
Patients were scheduled to receive a total of 12 cycles of XELOX and 6 cycles of FUOX (36 weeks in each group) or until disease progression, intolerable adverse events or patient refusal. Patients with stable disease could continue to receive treatment after this period at the discretion of the individual investigator. Patients could also continue Capecitabine or FU single agent therapy after discontinuation of oxaliplatin due to toxicity.

Kaplan Meier curves are presented for time to progression and overall survival

Citation: Douillard J, Cunnigham D, Roth A, Navarro, James R et al (2000) Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial *Lancet* 355;9209:1041-1047
Design: Randomised Trial **Country**: **Setting:** **Aim**: to assess whether the addition of irinotecan to fluorouracil and calcium folinate would benefit patients previously untreated with chemotherapy for metastatic colorectal cancer.
Inclusion criteria Histologically proven adenocarcinoma of the colon/rectum Age 18-75 years WHO performance status 0-2 Life expectancy >3 months Previous chemotherapy to be completed more than 6 months before randomisation
Exclusion criteria Central nervous system metastasis Unresolved bowel obstruction or diarrhea Known contraindications to fluorouracil (angina pectoris, myocardial infarction)
Sample Size 338 evaluable patients were needed to show a significant difference in response rates between the two treatment groups assuming response rates of 35% in the no irinotecan group and 50% in the irinotecan group by use of two tailed X^2 tests (α=0.05, power 0.8).
Randomisation Method Central randomisation by a computer generated random scheme and stratified by centre
Population 387 patients randomised Irinotecan + FU = 199 FU = 188
Study Duration
Interventions Irinotecan 80mg/m^2 with fluorouracil 2300mg/m^2 by 24hour infusion plus calcium folinate 500mg/m^2 once weekly (n=54) or irinotecan 180mg/m^2 on day 1 with fluorouracil 400mg/m^2 bolus and 600mg/m^2 by 22 hour infusion plus calcium folinate 200mg/m^2 on day 1 and 2 every two weeks (n=145). Once weekly fluorouracil 2600mg/m^2 by 24 hour infusion plus calcium folinate 500mg/m^2 (n=43) or every two weeks, fluorouracil and calcium folinate fluorouracil 400mg/m^2 bolus and 600mg/m^2 by 22 hour infusion plus calcium folinate 200mg/m^2 on day 1 and 2 (n=143).
Outcomes Response Rate Time to Progression (defined as time from randomisation to progression) Duration of Response (time from first infusion to progression in responding patients) Time to treatment failure (time from randomization to treatment discontinuation or disease progression) Overall Survival (date of randomization to date of death)
Results Median duration of treatment was longer in the irinotecan versus no irinotecan arm irrespective of regimen (24 weeks versus 21 weeks for the weekly regimen and 24.6 weeks versus 18 weeks for the two week regimen). Relative dose intensity was 0.82 for irinotecan and 0.81 for fluorouracil in the weekly regimen and 0.93 and 0.92 respectively in the 2 weekly regimen.

39.4% of patients in the Irinotecan group and 58.3% in the no-irinotecan group received further chemotherapy with 31% of the no-irinotecan group receiving irinotecan. Similar proportions of patients in each group received further treatment with oxaliplatin (15.7 in the irinotecan arm versus 12.8% in the no irinotecan arm).

Efficacy
In the evaluable population the response rate was 49% in the irinotecan arm and 31% in the no irinotecan arm (p<0.001). Confirmed responses (after 6-7 weeks) resulted in response rates of 41% (95% CI 33.3-48.6) and 23% (17-30.2) respectively.
In the intent to treat population, response rate was significantly higher in the irinotecan group than the no-irinotecan group (34.8 [28.2-41.9] versus 21.9% [16.2-28.5], p=0.005).
Median time to onset of response was 8.9 (range: 4.7-25.4) weeks in the irinotecan group and 11.4 (5.3-29.6) in the no-irinotecan group.
Median response duration was 9.3 (2.8-13.1) months in the irinotecan group and 8.8 (3.7-11.8) months in the no-irinotecan group (p=0.08). Duration of response and stabilisation was longer in the irinotecan group than the no irinotecan group (median 6.7 [0+ to 13.8+] versus 4.4 [0+ to 11.8+] months, p<0.001. The interaction between treatment and regimen was not significant. The log rank, stratified by regimen (p<0.001) and that stratified by country (p<0.001) were significant.

Median follow-up was 23.3 (20.0-29.7) months.

Survival in the irinotecan group was significantly longer than in the no-irinotecan group (median 17.4 [0.4-28.4+] versus 14.1 [0.5-27.6+] months, p=0.031). The probability of survival in the irinotecan group was 82.1% at 9 months and 69.1% at 12 months and in the no-irinotecan group the probability of survival was 71.6% at 9 months and 59.1% at 12 months.
The interaction between treatment and regimen was not significant, supporting the hypothesis that the difference in the two regimens would be similar in both groups and therefore allow pooling of the data.
The log rank test stratified by regimen was significant (p=0.03) as was that stratified by country (p=0.04).

Intent to treat analysis showed that for the weekly regimen, the response rates in the irinotecan and no irinotecan groups did not differ significantly (39.6 [95% CI 26.5 -54] versus 25% [13.2-40.3]).
Median time to progression was 7.2 (range 0+-13.8) months and 6.5 (0+-12.3+) month.
Probability of survival in the irinotecan group was 84.9% at 9 months and 75.5% at 12 months and in the no-irinotecan group was 773% at 9 months and 62.7% at 12 months.
In the intent to treat analysis of the 2 weekly regimen, the response rate was 33.1% (95% CI 25.5-41.4) in the irinotecan group and 21% (95% CI 14.6-28.6) in the no-irinotecan group (p=0.021).
Median time to progression was 6.5 (range 0+-13.2) in the irinotecan group and 3.7 (0+-13.1+) months in the no irinotecan group (p=0.001) and median survival was 17.4 (0.4-28.3+) months in the irinotecan and 13.0 (0.5-27.6+) months in the no-irinotecan group. The log rank p was significant (p=0.0098).
The probability of survival in the irinotecan group was 81% at 9 months and 66.7% at 12 months and in the irinotecan group and 69.8% at 9 months and 54.8% at 12 months in the no-irinotecan group.

In Cox's multivariate analysis of time to progression, age and number of organs involved were significant predictors. In patients younger than 58 years, the risk of progression increased by about 28% with all other variables fixed. If 3 or more organs were involved, the risk of progression was increased by about 56%. The treatment effect was significant (p<0.001). The risk of progression for a patient in the no irinotecan group was increased by about 69% compared with that for a patient in the irinotecan group when all other variables were equal.

The median time to treatment failure was 5.3 (0.4-15.7+) months in the irinotecan group and 3.8 (0.4-11.5+) in the no-irinotecan group.
Time to definitive deterioration in performance status was significantly longer in the irinotecan group than in the no-irinotecan group (median 11.2 [0.1+-15.7+] versus 9.9 [0+-13.6+] months (p=0.046).

Safety
In the irinotecan group the most common side effects were diarrhoea and neutropenia and were significantly more frequent and severe than in the no-irinotecan group.
Doses were reduced because of toxic effects more frequently for the weekly regimen and more in the irinotecan group than the no-irinotecan group. Doses were reduced in 29.6% of patients on the weekly regimen and in 18.6% of patients on the two weekly regimen in the irinotecan and no-irinotecan groups respectively. Most dose

reductions occurred during the first two cycles in the weekly regimen. One patient treated with the irinotecan combination on the 2-weekly regimen did not receive appropriate therapy for the management of diarrhoea and died early in the first cycle.

Despite the high frequency of side-effects in the irinotecan group, the relative dose intensity was preserved compared with the no-irinotecan group.

Quality of Life
1161 questionnaires were obtained from the 385 patients in the intent to treat population and the rate of return was similar in the two treatment groups (62% in the irinotecan group and 59% in the no-irinotecan group), the two groups did not differ significantly at baseline apart from cognitive function (mean 89.9, SE, 1.1 versus 86.1, SE 1.5 (p=0.05)).

QoL did not differ significantly between groups; when missing data for death, progressive disease or grade 3-4 adverse events were taken into account with the two imputation methods, results were biased towards the no-irinotecan group. The analysis of variance on QoL showed significantly better quality of life in the irinotecan group after the first imputation method was used (p=0.03) with the same trend seen with the second imputation method. Definitive deterioration in quality of life occurred consistently later in the irinotecan for a deterioration from baseline of 5% (p=0.03), 10% (p=0.06), 20% (p=0.04) and 30% (p=0.03).

Tables

	Irinotecan (n=198)	No Irinotecan (n=187)
	N (%)	N (%)
Sex		
Male	132 (66.7)	99 (52.9)
Female	66 (33.3)	88 (47.1)
Age		
Median	62	59
Range	27-75	24-75
WHO Performance Status		
0	102 (51.5)	96 (51.3)
1	83 (41.9)	77 (41.2)
2	13 (6.6)	14 (7.5)
Synchronous Metastases	110 (55.6)	121 (64.7)
Previous Adjuvant Chemotherapy	51 (25.8)	44 (23.5)
At least one tumour related symptom at baseline	95 (48)	96 (51.3)
At least one abnormal laboratory value at baseline	177 (89.4)	157 (84)

Table 1: Patient Characteristics at baseline

	Evaluable Population (n=338)		Intent to treat population (n=385)	
	Irinotecan (n=169)	No Irinotecan (n=169)	Irinotecan (n=198)	No Irinotecan (n=187)
	N (%)	N (%)	N (%)	N (%)
Complete Response	6 (3.6)	0	6 (3)	0
Partial Response	63 (37.3)	39 (23.1)	63 (31.8)	41 (21.9)
Overall Response	69 (40.8)	39 (23.1)	69 (34.8)	41 (21.9)
Stable Disease	64 (37.9)	84 (49.7)	70 (35.4)	86 (46)
Progressive Disease	36 (21.3)	46 (27.2)	38 (19.2)	49 (26.2)
Not Evaluable	0	0	21 (10.6)	11 (5.9)

Table 2: Response Rates

Covariate	Parameter Estimate	Wald X^2	p	Hazard Ratio (95% CI)
Treatment Group				
No Irinotecan				1.00
Irinotecan	0.780	9.558	0.002	2.18 (1.33-3.58)
Weight Loss				
>5%				1.00
≤5%	0.804	6.829	0.009	2.23 (1.22-4.08)
Time between first diagnosis and first metastasis (months)				
>12				1.00
3-12	1.001	4.689	0.030	2.72 (1.10-6.73)
0-3	1.063	11.831	0.001	2.9 (1.58-5.31)

Table 3: Logistic Regression of predictive factors for response rate

Covariate	Parameter Estimate	Wald X^2	p	Hazard Ratio (95% CI)
Treatment Group				
Irinotecan				1.00
No Irinotecan	0.522	15.731	<0.001	1.69 (1.3-2.18)

Number of organs involved				
>3				1.00
≤3	0.443	5.776	0.016	1.56 (1.09-2.23)
Age (years)				
≥58				1.00
<58	0.248	3.643	0.056	1.28 (0.99-1.65)

Table 4: Cox's Model for Time to Progression

	Irinotecan group (n=54)		No Irinotecan group (n=43)		p*
	Total	Grade 3-4	Total	Grade 3-4	
	N (%)	N (%)	N (%)	N (%)	
Non Haematological toxic effects					
Diarrhoea	48 (88.9)	24 (44.4)	28 (65.1)	11 (25.6)	0.055
Nausea	39 (72.2)	4 (7.4)	25 (58.1)	2 (4.7)	0.57
Vomiting	30 (55.6)	6 (11.1)	19 (44.2)	2 (4.7)	0.25
Asthenia	23 (42.6)	4 (7.4)	6 (14)		0.068
Alopecia	20 (37)		7 (16.3)		
Anorexia	16 (29.6)	4 (7.4)	6 (14)	1 (2.3)	0.26
Mucositis	14 (25.9)		15 (34.9)	1 (2.3)	0.26
Abdominal Pain	12 (22.2)	3 (5.6)	1 (2.3)	1 (2.3)	0.47
Cholinergic Syndrome	11 (20.4)	1 (1.9)			0.37
Hand and Foot Syndrome	9 (16.7)		17 (39.5)	2 (4.7)	0.11
Fever in absence of infection without concomitant grade 3-4 neutropenia	6 (11.3)		4 (9.3)		
Cutaneous signs	4 (7.4)		4 (9.3)		
Pain	4 (7.4)	1 (1.9)	6 (14)	1 (2.3)	0.87
Weight Loss	4 (7.4)	1 (1.9)			0.37
Infection without concomitant grade 3-4 neutropenia	2 (3.7)		2 (4.7)		
Haematological Toxic Effects					
Anaemia	51 (94.4)	3 (5.6)	41 (97.6)		0.12
Neutropenia	37 (71.2)	15 (28.8)	9 (21.4)	1 (2.4)	0.001
Leukopenia	40 (74.1)	11 (20.4)	16 (38.1)	1 (2.4)	0.009
Fever in absence of infection with concomitant grade 3-4 neutropenia	5 (9.3)	5 (9.3)	1 (2.3)	1 (2.4)	0.16
Infection with concomitant grade 3-4 neutropenia	1 (1.9)	1 (1.9)			0.37

*based on comparison of frequency of grade 3 or 4 toxic effects

Table 5: Patients with any adverse event and with grade 3-4 adverse event related to study treatment (weekly regimen)

	Irinotecan group (n=145)		No Irinotecan group (n=143)		p*
	Total	Grade 3-4	Total	Grade 3-4	
	N (%)	N (%)	N (%)	N (%)	
Non Haematological toxic effects					
Diarrhoea	99 (68.3)	19 (13.1)	8 (5.6)	8 (5.6)	0.028
Nausea	85 (58.6)	3 (2.1)	2 (1.4)	2 (1.4)	0.66
Alopecia	82 (56.6)				
Asthenia	65 (44.8)	9 (6.2)	1 (0.7)	1 (0.7)	0.011
Vomiting	60 (41.4)	4 (2.8)	1 (0.7)	1 (0.7)	0.18
Mucositis	56 (38.6)	6 (4.1)	3 (2.1)	3 (2.1)	0.32
Cholinergic Syndrome	41 (28.3)	2 (1.4)			0.16
Anorexia	25 (17.2)	3 (2.1)	1 (0.7)	1 (0.7)	0.32
Cutaneous signs	16 (11)	1 (0.7)			0.32
Abdominal Pain	14 (9.7)	1 (0.7)			0.32
Hand and Foot Syndrome	13 (9)	1 (0.7)	1 (0.7)	1 (0.7)	0.99
Pain	12 (8.3)		1 (0.7)	1 (0.7)	0.31
Fever in absence of infection without concomitant grade 3-4 neutropenia	9 (6.2)		1 (0.7)	1 (0.7)	
Infection without concomitant grade 3-4 neutropenia	7 (4.8)	4 (2.8)			0.045
Weight Loss	6 (4.1)	2 (1.4)			0.16
Haematological Toxic Effects					
Anaemia	140 (97.2)	3 (2.1)	130 (90.9)	3 (2.1)	0.99
Neutropenia	118 (82.5)	66 (46.2)	68 (47.9)	19 (13.4)	0.001
Leukopenia	117 (81.3)	25 (17.4)	60 (42)	5 (3.5)	0.001
Fever in absence of infection with concomitant grade 3-4 neutropenia	5 (3.4)	5 (3.4)	1 (0.7)	1 (0.7)	0.10

Infection with concomitant grade 3-4 neutropenia	3 (2.1)	3 (2.1)			0.08

Table 6: Patients with any adverse event and with grade 3-4 adverse event related to study treatment (2 weekly regimen).

General comments

Kaplan Meier curves for time to progression, survival and time to definitive deterioration in performance status.

Citation: Ducreux M, Bennouna J, Hebbar M et al (2010) Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/leucovorin plus oxaliplatin (FOLFOX-6) as first line treatments for metastatic colorectal cancer *International Journal of Cancer* 128;3:682-690

Design: Randomised Control Trial

Country: France

Setting: Multicentre

Aim: to demonstrate non-inferiority of capecitabine plus oxaliplatin (XELOX) versus FOLFOX-6 for patients with advanced metastatic colorectal cancer

Inclusion criteria
Aged ≥18 years
Previously untreated, histologically confirmed metastatic colorectal cancer
ECOG performance status ≤2
Life expectancy ≥3 months
Normal renal function
Adequate haematological and hepatic function

Exclusion criteria
Pregnant or breast feeding women
Patients who had received (neo) adjuvant therapy <6 months previously containing oxaliplatin, 5-FU or capecitabine.
Patients with a history of neuropathy or uncontrolled congestive heart failure, angina pectoris, hypertension or myocardial infarction within the 12 months previous to study inclusion.

Sample Size
Assuming that 55% of patients in each arm would respond to treatment at 6-8 weeks and allowing for approximately 10% of patients to be excluded from the per protocol population, it was planned that 304 patients (152 per arm) would be recruited to ensure 80% power to demonstrate non-inferiority of XELOX versus FOLFOX-6 with a non-inferiority margin of 15% and a one-sided type 1 error of 5%.

Randomisation Method
Minimisation method with stratification for centre, age, Kohnes predictive risk factors (low, intermediate and high) and previous chemotherapy.

Population
N=306 patients (XELOX=156; FOLFOX-6=150)

Study Duration
Recruitment: May 16th 2003-August 31st 2004
Trial Ended: December 2006 (18 months after recruitment of the last randomised patient)

Interventions
XELOX: 2hour intravenous infusion of oxaliplatin 130mg/m^2 on day 1 plus oral capecitabine 1,000mg/m^2 twice daily on days 1-14 every 3 weeks.

FOLFOX-6: 2hour intravenous infusion of oxaliplatin 100mg/m^2 followed by a 2hour infusion of LV 400mg/m^2 followed by 5-FU 400mg/m^2 iv bolus injection then 5-FU 2,400-3,000 mg/m^2 as a 46hour continuous infusion every 2 weeks.

Outcomes
Non-inferiority in relation to tumour response
Tumour response assessed by investigators

Progression Free Survival
Overall Survival
Time to response
Duration of Response
Time to Treatment Failure

Results
The baseline characteristics for both arms were generally well balanced

Mean treatment duration was 19 weeks (±8 weeks) in the XELOX arm and 21 weeks (±8 weeks) in the FOLFOX-6 group.
Median number of cycles was 8 (range: 0-8) in the XELOX arm and 11 (range 0-12) in the FOLFOX-6 arm.
Mean cumulative dose of oxaliplatin was higher in the FOLFOX-6 group (1,508±538mg) compared with the XELOX arm (1,330±520mg).
Median relative dose intensity of oxaliplatin was 93.8% in the XELOX group and 83.3% in the FOLFOX-6 group.
Median relative dose intensity of capecitabine was 93.7% and for infusional 5-FU was 77.5%.
Dose modifications were performed in 93.5% of patients in the FOLFOX-6 group compared with 80.1% of patients in the XELOX group.

Median duration of follow-up was 18.8 months (range, 0.1-41.6) in the intention to treat population

Efficacy
The overall response rate was 42% in the XELOX group and 46% in the FOLFOX-6 group.
The difference between the groups was 4.7%, the upper limit of the unilateral 95% confidence interval (14.4%) was below the non-inferiority margin of 15%.

Independent review resulted in an overall response rate for the intention to treat population of 39% for the XELOX group and 46% for the FOLFOX-6 group. The difference between the groups was 6.9%, the upper limit of the unilateral 95% CI (16.2%) exceeded the non-inferiority margin of 15%.

According to assessment of investigators, the overall response rate in the per protocol population was 46% in the XELOX group and 45% in the FOLFOX-6 group and in the intention to treat group it was 44% in both groups.

Secondary Endpoints
Median progression free survival was 8.8 months in the XELOX group and 9.3 months in the FOLFOX group **(HR=1.00, 90% CI 0.82-1.22)** in the intention to treat population. The upper limit of the 90% CI was below the predefined non-inferiority limit of 1.75.

Median overall survival was 19.9 months in the XELOX arm and 20.5 months in the FOLFOX-6 arm **(HR=1.02, 90% CI 0.81-1.30)**. The upper limit of the 90% CI was below the predefined non-inferiority limit of 1.75.

In total, 30 patients in the XELOX arm and 34 patients in the FOLFOX-6 group underwent potentially curative resection of lung, liver or lymph node metastases.

Safety
The safety population consisted of 304 patients (XELOX n=155; FOLFOX-6 n=149).
XELOX was associated with more hand-foot syndrome (20% versus 13%) though the difference was not significant (p=0.088).
Considering all grade events, there was significantly less nausea (57% versus 70%, p=0.019), asthenia (45% versus 59%, p=0.011), alopecia (8% versus 26%, p<0.001), neutropenia (27% versus 62%; p<0.001) and thrombocytopenia (27% versus 50%, p<0.001) recorded in the XELOX group compared with the FOLFOX-6 group.

Considering only grade 3-4 adverse events, XELOX was associated with significantly less grade 3/4 neuropathly (11% versus 26%, p<0.001), neutropenia (5% versus 47%, p<0.001) and febrile neutropenia (0% versus 6%; p=0.001) compared with FOLFOX-6.

XELOX was associated with more grade 3/4 diarrhoea (14% versus 7%, p=0.034) and thrombocytopenia (12% versus 5%, p=0.052).

20% of patients in the XELOX arm and 22% of patients in the FOLFOX arm discontinued treatment due to toxicity.

There were 193 deaths in the over the course of the study (98 n the XELOX group and 95 in the FOLFOX-6 group) with the main cause of death being disease progression.

The 60 day mortality rate in the per protocol population was 4.2% (4/144 patients, 90% CI: 1.3-6.4) in the XELOX arm and 2.1% (3/140 patients; 90% CI: 0.01-3.9) in the FOLFOX-6 group.

Tables

Endpoint	Per Protocol		Intention to Treat	
	XELOX (n=144)	FOLFOX-6 (n=140)	XELOX (n=156)	FOLFOX-6 (n=150)
Primary Endpoint				
Overall Response Rate (independent review)	42	46	39	46
Difference (upper limit of unilateral 95% CI)	4.7% (14.4%)[1]		6.9% (16.2%)[1]	
Complete Response	2	<1	2	1
Partial Response	40	46	37	45
Secondary Endpoints				
Median PFS (months)	8.9	9.3	8.8	9.3
Hazard Ratio (90% CI)	0.98 (0.8-1.21)[2]		1.00 (0.82-1.22)[2]	
Median OS (months)	20.1	18.9	19.9	20.5
Hazard Ratio (90% CI)	1.02 (0.79-1.30)[2]		1.02 (0.81-1.30)[2]	
Median Time to Treatment Failure (months)	5.9	6.8	6.1	6.8
Hazard Ratio (90% CI)	1.29 (0.97-1.73)[2]		1.32 (0.97-1.78)[2]	
Median Duration of Response (months)	9.9	8.8	10.1	8.8
Hazard Ratio (90% CI)	0.91 (0.67-1.24)[2]		0.88 (0.64-1.21)[2]	

Efficacy Analyses

	XELOX (n=155)		FOLFOX (n=149)	
	All Grades	Grades 3/4	All Grades	Grades 3/4
Adverse Event	No (%)	No (%)	No (%)	No (%)
Neuropathy	139 (90)	17 (11)	141 (95)	38 (26)
Diarrhoea	95 (61)	22 (14)	85 (57)	10 (7)
Nausea	88 (57)	4 (3)	104 (70)	9 (6)
Asthenia	69 (45)	13 (8)	88 (59)	14 (9)
Vomiting	54 (35)	3 (2)	58 (39)	7 (5)
Hand-Foot Syndrome	31(20)	5 (3)	19 (13)	1 (<1)
Fever	22(14)	3 (2)	23 (15)	4 (3)
Alopecia	12 (8)	0 (0)	39 (26)	1 (<1)
Stomatitis	10(7)	0 (0)	15 (10)	1 (<1)
Neutropenia	41(27)	8 (5)	93 (62)	70 (47)
Thrombocytopenia	41(27)	18 (12)	74 (50)	8 (5)
Anaemia	23(15)	3 (2)	33 (22)	6 (4)
Febrile Neutropenia	0(0)	0(0)	9 (6)	9 (6)

Toxicities

Citation: Falcone A, Ricci S, Brunetti I, Pfanner E et al (2007) Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin and irinotecan (FOLFIRI) as first line treatment for metastatic colorectal cance: the GRUPPO Ocologico Nord Ovest *Journal of Clinical Oncology* 25;13

Design: Randomised Phase III Trial

Country: Italy

Setting: Multi-centre

Aim: to compare the simplified FOLFOXIRI regimen to a standard FOLFIRI regimen

Inclusion criteria
Adenocarcinoma of the colon or rectum
Unresectable metastatic disease
Age 18-75 years
ECOG performance status of 2 or lower if aged 70 years or younger
ECOG performance status of 0 is aged 71-75 years
Measurable disease according to WHO criteria
Adequate haematologic parameters
AST, ALT and alkaline phosphatase 2.5 x normal values or less (≤5 if liver metastases)
Previous fluoropyrimidine based chemotherapy to be completed at least 6 months before randomisation

Exclusion criteria
Previous palliative chemotherapy for metastatic disease
Previous chemotherapy including oxaliplatin or irinotecan
Symptomatic cardiac disease
Myocardial infarction in the last 24 months or uncontrolled arrhythmia
Active Infections
Inflammatory bowel disease
Total Colectomy

Sample Size
Assuming a response rate of 40% in the FOLFIRI arm, to demonstrate an improvement of 20% in with FOLFOXIRI (60%), using a two-sided X^2 test with a power of 0.8 and an alpha error of 0.05, and considering approximately 10% of patients non –assessable, the study planned to randomise a total of 240 patients.

Randomisation Method
Patients were stratified according to centre, ECOG performance status and history or adjuvant therapy and were then randomly assigned to either FOLFOXIRI or FOLFIRI (no method or randomisation reported).

Population
N=244

Study Duration
Recruitment Phase: November 2001 to April 2005

Interventions
FOLFIRI: Irinotecan 180mg/m^2, 1 hour I.V. on day 1, Leucovorin 100mg/m^2, 2hours i.v. on days 1 and 2, FU 400mg/m^2 bolus followed by FU 600mg/m^2 22 hour continuous infusion on days 1 and 2.

FOLFOXIRI: Irinotecan 165mg/m^2, 1 hour I.V. on day 1, oxaliplatin 85mg/m^2, 2 hours i.v. on day 1, Leucovorin 200mg/m^2 on day 1 and FU 3,200mg/m^2 48 hours flat continuous infusion i.v. days 1-3.

Each cycle repeated every two weeks until evidence of disease progression, unacceptable toxicity or patient refusal or for a maximum 12 cycles.

Outcomes
Response Rate

Progression Free survival (defined as the length of time from randomisation to disease progression or death resulting from any cause or to last contact)

Overall survival
Postchemotherapy R0 surgical resections
Safety
Quality of Life

Results

Treatment Administration and Safety
All patients received at least one cycle of study treatment and both treatments were relatively well tolerated and associated with manageable toxicities.

Median number of cycles administered was 10 in the FOLFIRI arm and 11 in the FOLFOXIRI arm and the relative dose intensity of administered FU, Irinotecan and Oxaliplatin ranged between 82% and 87% of planned for all agents in both arms.
Treatment interruptions for toxicity were 4% in the FOLFIRI arm and 9% in the FOLFOXIRI arm (p=0.19), there were no toxic deaths and 2 patients in each arm died within 60 days of treatment start due to rapidly progressive disease.
Grade 3/4 toxicities were incommon apart from neutropenia.

Objective Tumour Response
According to intention to treat analysis, all patients were considered assessable for response and response rate (assessed by study investigators) was 66% for FOLFOXIRI and 41% for FOLFIRI (p=0.0002). External assessment response rate was 60% for FOLFOXIRI and 34% for FOLFIRI (p<0.0001).
Rate of progression was significantly lower for patients treated with FOLFOXIRI than FOLFIRI (11% versus 24%, p=0.02).
In multivariate analysis, only treatment with FOLFOXIRI was an independent predictive factor for response: **Hazard Ratio 2.8; 95% CI 1.7 – 4.8, p<0.001**.

Secondary Surgery on Metastases
15% of patients (n=18) in the FOLFOXIRI arm underwent radical (R0) surgery of metastases compared with 6% (n=7) in the FOLFIRI arm (p=0.033).
For patients with metastases confined to the liver, the rate of secondary R0 surgery was 36% for FOLFOXIRI compared with 12% for FOLFIRI (p=0.017).
In multivariate analysis, only treatment with FOLFOXIRI was an independent predictor for achieving R0 resection: **Hazard Ratio 3.1, 95% CI, 1.2-7.9, p=0.018**.

Progression free survival and second line treatment
At the time of analysis, 104 patients in the FOLFOXIRI arm and 112 patients in the FOLFIRI arm had progressed; median progression free survival was 9.8 months for FOLFOXIRI and 6.9 months for FOLFIRI (p=0.0006), **Hazard Ratio 0.63 (95% CI, 0.47-0.81)**.
The rate of early progression (progression within 6 months from treatment onset) was significantly higher on FOLFIRI compared with FOLFOXIRI (18% vs. 45%, p<0.0001).
Independent prognostic factors for reduction of the progression risk were:
> Treatment Arm **Hazard Ratio 0.6, 95% CI, 0.46-0.79, p<0.001**
> Male Sex **Hazard Ratio 0.68, 95% CI, 0.51-0.91, p=0.01**
> Leukocyte count <8,000/mm^3 **Hazard Ratio 0.60, 95% CI, 0.45-0.81, p=0.003**

73% of patients on FOLFIRI and 76% on FOLFOXIRI received second line treatment.

Overall Survival
After median follow up of 18.4 months, 65 patients in the FOLFOXIRI arm and 81 patients in the FOLFIRI arm had died.
Median overall survival was significantly longer for FOLFOXIRI (22.6 vs. 16.7 months, p=0.032) **Hazard Ratio 0.7 (95% CI, 0.5-0.96)**.
Independent prognostic factor for reduction of death risk was liver involvement less than 25% **Hazard Ratio 0.57 (95% CI, 0.39-0.84, p=0.005)**.
Treatment with FOLFOXIRI was significantly associated with prolonged survival on univariate analysis (p=0.032) but not on multivariate analysis (p=0.054).

Quality of Life
36% of patients in the FOLFIRI arm and 37% on the FOLFOXIRI arm were assessable for quality of life and there

were no significant difference between the two arms.

Tables

	FOLFIRI	**FOLFOXIRI**
	N (%)	**N(%)**
Sex		
Male	69 (57)	75 (61)
Female	53 (43)	47 (39)
Age (years)		
Median	64	62
Range	21-75	27-75
ECOG Performance Status		
0	74 (61)	74 (61)
1	41 (34)	45 (37)
2	7 (6)	3 (2)
Previous Adjuvant Chemotherapy		
Yes	29 (24)	29 (24)
No	93 (76)	93 (76)
Time from diagnosis to random assignment (months)		
<3	76 (65)	76 (65)
≥3	43 (35)	43 (35)

Table 1: Patient characteristics

	FOLFIRI	**FOLFOXIRI**
No. of Cycles		
Total	1056	1083
Median	10	11
Range	1-16	1-16
Relative dose intensity with respect to planned		
Oxaliplatin		83
Irinotecan	87%	82
Fluorouracil	86%	82

Table 2: Number of Cycles and relative dose intensities

	FOLFIRI (n=122)	**FOLFOXIRI (n=122)**	
	N (%)	**N (%)**	**P**
Nausea			
Grade 1	48 (39)	49 (40)	NS
Grade 2	20 (16)	34 (28)	
Grade 3	1 (1)	7 (6)	
Grade 4	0 (0)	0 (0)	
Vomiting			
Grade 1	28 (23)	24 (20)	NS
Grade 2	22 (18)	31 (25)	
Grade 3	1 (1)	8 (7)	
Grade 4	1 (1)	0 (0)	
Diarrhoea			
Grade 1	30 (25)	40 (33)	NS
Grade 2	27 (22)	30 (25)	
Grade 3	13 (11)	21 (17)	
Grade 4	1 (1)	4 (3)	
Stomatitis			
Grade 1	28 (23)	32 (26)	NS
Grade 2	7 (6)	17 (14)	
Grade 3	4 (3)	5 (4)	
Grade 4	0 (0)	1 (1)	
Neurotoxicity			
Grade 1	0 (0)	45 (37)	<0.0001 (grade 2-3)
Grade 2	0 (0)	21 (17)	
Grade 3	0 (0)	3 (2)	
Grade 4	0 (0)	0 (0)	
Astenia			
Grade 1	29 (24)	27 (22)	NS
Grade 2	12 (10)	19 (16)	
Grade 3	4 (3)	7 (6)	
Grade 4	0 (0)	0 (0)	

Thrombocytopenia			
Grade 1	5 (4)	22 (18)	NS
Grade 2	3 (2)	7 (6)	
Grade 3	1 (1)	2 (2)	
Grade 4	0 (0)	0 (0)	
Anaemia			
Grade 1	50 (41)	53 (43)	NS
Grade 2	11 (9)	23 (19)	
Grade 3	1 (1)	4 (3)	
Grade 4	0 (0)	0 (0)	
Neutropenia			
Grade 1	22 (18)	16 (13)	0.0006
Grade 2	16 (13)	24 (20)	
Grade 3	21 (17)	40 (33)	
Grade 4	13 (11)	21 (17)	
Febrile Neutropenia	4 (3)	6 (5)	NS

Table 3: Maximum toxicity per patient

	FOLFIRI (n=122)	FOLFOXIRI (n=122)	
Investigators Assessment			P
Complete	6%	8%	
Partial	35%	58%	
Complete + Partial	41%	66%	0.0002
95 % CI	0.32-0.50	0.56-0.74	
Stable Disease	33%	21%	
Progression	24%	11%	0.002
Not Assessable	2%	2%	
Externally Reviewed			
Complete	6%	7%	
Partial	28%	53%	
Complete + Partial	34%	60%	<0.0001
95 % CI	0.25-0.43	0.51-0.68	
Stable Disease	34%	21%	
Progression	24%	11%	
Not Reviewed	8%	8%	

Table 4: Objective Response

General comments.
Overall the population was relatively selected to exclude elderly and frail patients expected to have and increased risk of toxicity by using combination chemotherapy.

Kaplan Meier curves presented for progression free and overall survival.

Citation: Gennatas C, Papaxoninis G, Michalaki V et al (2006) A prospective randomised study of irinotecan (CPT-11), leucovorin (LV) and 5-fluorouracil (5FU) versus leucovorin and 5-fluorouracil in patients with advanced colorectal carcinoma *Journal of Chemotherapy* 18;5:538-544

Design: Prospective Randomised Trial

Country:

Setting:

Aim: to compare the activity and toxicity of an irinotecan, leucovorin and 5-FU combination with a standard regimen of leucovorin and 5-FU.

Inclusion criteria
Histologically documented colorectal cancer
Patients ≥18 years
ECOG performance status 0-2
Measurable disease
Adequate organ function

Exclusion criteria
Prior therapy for metastatic disease
Previous adjuvant chemotherapy which contained topoisomerase I inhibitors

Sample Size
IT was estimated that 80 patients per arm was required to detect a 40% improvement in median progression free survival (7 months for the experimental group with triple drug therapy and 4.3 months for the reference group) with a power of 0.85.

Randomisation Method
Details not provided

Population
N=160

Study Duration
Recruitment Phase: January 1998-December 2001
Data were collected for an additional 24 months after accrual ended, with data on survival collected through December 2003.

Interventions

Group A	Group B
Leucovorin 20mg/m^2 iv. Bolus	Irinotecan 80 mg/m^2 iv. (over a 30-90 minute period)
5-Fluorouracil 425mg/m^2 iv. bolus	Leucovorin 20mg/m^2 iv. bolus
	5-flourouracil 425mg/m^2 iv. bolus
Given on days 1-5, every 4 weeks	Given on days 1, 8, 15, 22, 29, 36 every 8 weeks

Outcomes
Response Rates
Progression free survival (defined as the time interval from randomisation to progression or death. For patients removed from the study or who died of causes unrelated to colorectal cancer, PFS was conservatively defined as the time from randomisation to the last date on which the patient was known to be progression free)
Overall survival

Results
Median treatment duration was 4.5 months in group A and 5.8 months in group B. The median relative intensity of the dose of 5FU in group B was lower than that in group A (71% vs. 86%) possibly as a result of the weekly reductions in dose permitted in group B.

Most patients with disease progression received second line treatment; 56% of patients in group A received an irinotecan based regimen and patients in group B received an oxaliplatin based regimen (no numbers provided).

No patient received surgical treatment

Efficacy
Progression free survival was significantly higher among patients in group B compared with group A (median; 7.5 months versus 4.5 months, p=0.0335).

Group B patients showed higher response rates compared with group A (47.5% versus 30%, p=0.034). Complete response was seen in 3 (3.8%) patients in group B.
Median duration of confirmed response was approximately 3.5 months in group A and 5.5 months in group B.
Median survival of patients in group A and group B was similar (15 months versus 14 months, p=0.3531).

Adverse Events
Patients in group B had higher rates of grade 3 diarrhoea (35% versus 19%, p=0.032) and mucositis (14% versus 2%; p=0.017).
There was no difference between the groups in the incidence of grade 3 vomiting or neutropenia and there were no grade 4 toxicities or treatment related deaths in either group.

Tables

	5FU+LV (n=80)	CPT-11+5FU+LV (n=80)	P
	N (%)	N (%)	
Gender			
Male	54 (68)	56 (70)	0.733
Female	26 (32)	24 (30)	
Age, years			
Median	63	62	0.832
Range	35-78	32-78	
ECOG Performance Status			
0	23 (29)	22 (28)	0.920
1	43 (54)	42 (52)	
2	14 (17)	16 (20)	
Prior Adjuvant fluorouracil			
Yes	7 (9)	9 (11)	0.598
No	73 (91)	71 (89)	
Prior Radiotherapy			
Yes	21 (26)	16 (20)	0.348
No	59 (74)	64 (80)	

Table 1: Patient Characteristics

	5FU+LV (n=80)	CPT-11+5FU+LV (n=80)	P
Median progression free survival (months)	4.5	7.5	0.0335
Objective Response Rate (%)	30	47.5	0.034
Median duration of response (months)	3.5	5.5	
Median overall survival (months)	14	15	0.3531

Table 2: Efficacy

	5FU+LV	CPT-11+5FU+LV	
	%	%	P
Diarrhoea			
Grade 3	19	35	0.032
Grade 4	0	0	
Vomiting			
Grade 3	3	5	0.681
Grade 4	0	0	
Mucositis			
Grade 3	2	14	0.017
Grade 4	0	0	
Neutropenia			
Grade 3	20	24	0.702
Grade 4	0	0	

Table 3: Adverse Events

Citation: Giacchetti S, Perpoint B, Zidani R, Le B et al (2000) Phase III multicenter randomised trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first line treatment of metastatic colorectal cancer *Journal of Clinical Oncology* 18;1:136-147
Design: Phase III Randomised Trial **Country**: Multiple **Setting:** Multicentre (outpatient) **Aim**: To study how adding oxaliplatin
Inclusion criteria Histologically proven adenoncarcinoma Bidimensionally measurable metastatic lesions with one diameter of at least 20mm WHO performance status 0-2 Prior adjuvant chemotherapy completed at least 6 months prior to randomisation Adequate bone marrow, renal and hepatic function Clinical, biologic and radiologic assessments to be performed within 30 days of starting treatment
Exclusion criteria Brain metastases Age greater than 76 years Previous Chemotherapy or radiotherapy for metastatic disease Second malignancy (except in situ carcinoma of the cervix or basal cell skin cancer) Peripheral sensory neuropathy
Sample Size A target size of 200 patients was calculated based on the assumption that the objective tumour response would be 30% in the 5-FU-LV arm and 50% in the 5-FU-LV/l-OHP arm. This sample size would show a 20% difference in response rate with a 5% probability of a type 1 error, a power of 80% and two intermediate analyses in the first 30 and 100 patients.
Randomisation Method A prerandomised list of treatment allocation by blocks of four subjects was computer generated from a hazards table for each of the 15 participating institutions. The study coordinator held the list and assigned each registered patients to the next available study number at the centre where the patient was recruited. The inclusion forms were faxed from each centre to the coordination centre to verify the randomisation checklist before registration.
Population N=200
Study Duration
Interventions 5-FU-LV (arm A): 5 day course of chronomodulated, intravenous infusion 5-FU ($700mg/m^2/d$) and LV ($300mg/m^2/d$) simultaneously infused from 22:15-09:45 hours in an outpatients setting. 5-FU-LV/l-OHP (arm B): 5 day course of chronomodulated, intravenous infusion 5-FU ($700mg/m^2/d$) and LV ($300mg/m^2/d$) simultaneously infused from 22:15-09:45 hours in an outpatients setting and l-OHP ($125mg/m^2$) as a continuous 6-hour intravenous infusion from 10:00 to 16:00 hours on day 1.
Outcomes Maximum tumour response Toxicity Progression Free Survival (defined as time from randomisation to date of disease progression with patients who dropped out for reasons other than disease progression censored at dropout point. Patients for whom response was not evaluated were considered to have progressed on day 1) Overall Survival
Results

200 patients were enrolled, 2 patients in arm A (5-FU-LV) and 1 patient in arm B (5-FU-LV/l-OHP) were ineligible. One patient in arm B did not receive oxaliplatin.
There were some imbalances in baseline patient's characteristics between the two group; the incidence of rectal cancer was higher in arm B compared to arm A, twice as many patients in arm A had received 5FU based adjuvant chemotherapy compared to arm B (p=0.013) and twice as many patients in arm B had normal CEA levels compared to arm A (p=0.03).

A total of 728 courses were given to patients in arm A and 776 to patients in arm B; the median number of courses per patients was 6 in arm A and 8 in arm B (range 1-15 for both arms).

Follow-up ranged from 35 to 67 months (median follow-up, 47 months).

Toxicity
One patient in arm 2 was not assessed for toxicity as he did not receive oxaliplatin.
2 treatment related deaths were recorded; 1 patient in arm A died of respiratory failure after thrombosis of the central venous line and 1 patient died with grade 4 diarrhoea and sepsis.
12 patients in arm B withdrew from therapy due to toxicity including grade 4 diarrhoea and vomiting in 1 patient.

Antitumour Efficacy
Independent assessment was carried out for 91% of all registered patients; 16 patients in arm A and 53 patients in arm B achieved an objective response for an objective response rate of 16% (95% CI 9-24%) in arm A and 53% (95% CI 42%-63%) in arm B (p<0.0001).
Responses were further confirmed at 9 weeks in 12 patients in arm A and 34 patients in arm B; the objective response rate was 12% (95% CI 6-20%) in arm A and 34% (95% CI 24-44%) in arm B (p<0.001)
Median time to best response was similar in both arms at 6 months (range:4.3-7.4) in arm A and 5 months (range 4.3-5.5) in arm B.

Metastases Surgery
Surgical removal of metastases was attempted in 21 patients in arm A and in 32 patients in arm B. A complete macroscopic resection was performed in 17 patients in arm A and in 21 patients in arm B.

Progression Free Survival and Overall Survival
Median progression free survival was 6.1 months (range 4-7.4) for arm A and 8.7 months (range 7.4-9.2) for arm B (p=0.048).
When treatment failed for 57 patients in arm 1, oxaliplatin was added to the 5-FU-LV regimen.

Median overall survival was 19.9 months (range 14-25.7) in arm A and 19.4 (range 15.4-23.4) in arm B. The estimated survival rates at 2 and 3 years were 45% and 30% respectively in arm A and 37% and 23.5% respectively in arm B.

Prognostic Factors for Response and Survival
On multivariate analysis, number of involved organs was the only factor to influence both response and survival. Treatment arm and age were joint prognostic factors for response and performance status and percentage of liver involvement were jointly predictive for survival.

Tables

	Arm A: 5-FU-LV (n=100)	Arm B: l-OHP+5-FU-LV (n=100)	P
Age, years			
Median	61	61	
Range	29-74	31-75	
Sex			
Female	36	34	
Male	64	66	
WHO Performance Status			
0	66	69	
1	27	20	
2	7	11	
Previous Adjuvant Treatment			
Chemotherapy	28	10	0.013
Radiotherapy	8	12	
Previous surgery to remove metastases	8	6	

Table 1: Patient Characteristics

	Arm A: 5-FU-LV (n=100)	Arm B: I-OHP+5-FU-LV (n=100)	P
Hospital Admission for severe toxic event, (n)	3	11	<0.1
Withdrawal for toxic effects, no of patients			
Total no. of patients	1	13	0.01
Grade 4 gastrointestinal	1	1	
Senosry Neuropathy	0	10	
Other	0	2	
Grade 3-4 Diarrhoea			
% patients	5	43	0.001
No. of courses	5	73	
% of courses	0.7	10	
Grade 3-4 nausea/vomiting			
% patients	2	25	0.001
No. of courses	2	34	
% of courses	0.2	5	
Grade 3-4 mucositis			
% patients	4	10	0.09
No. of courses	6	13	
% of courses	1	2	
Grade 3-4 hand-foot syndrome			
% patients	1	0	0.319
No. of courses	2	0	
% of courses	0.2		
Grade 3-4 anaemia			
% patients	3	1	0.254
No. of courses	4	1	
% of courses	1	0.1	
Grade 3-4 Neutropenia			
% patients	1	2	0.555
No. of courses	1	2	
% of courses	0.1	0.2	
Grade 3-4 Thrombocytopenia			
% patients	0	1	0.314
No. of courses	0	1	
% of courses		0.1	

Table 2: Incidence of severe toxicity per patient and per course

	Arm A: 5-FU-LV (n=100)		Arm B: I-OHP+5-FU-LV (n=100)			
	5-FU		5-FU		I-OHP	
	Dose Intensity (mg/m^2/wk)	No. of patients	Dose Intensity (mg/m^2/wk)	No. of patients	Dose Intensity (mg/m^2/wk)	No. of patients
No. of courses given						
3	1092 ±84	97	1017±104.3	99	34.6±5	99
6	1088±66.5	62	1018±104	82	34.5±4.7	82
9	1083±61.3	39	1016±95.6	44	34.3±4.6	44

Table 3: Dose Intensities of 5-FU and I-OHP over 3, 6 and 9 courses

	Arm A: 5-FU-LV (n=100)	Arm B: I-OHP+5-FU-LV (n=100)
Total no. of patients	100	100
Not evaluated	8	12
Progressive Disease	31	11
Stable Disease	45	24
No. of Objective Responses		
Partial	16	50
Complete	0	3
Total	16	53
Objective Response Rate, %	16*	53*
95% CI	9-24	42-63
Rate of confirmed response at 9 weeks, %	12	34
95% CI	6-20	24-44

*p<0.0001

Table 4: Resposne Rates (Intent-to-treat analysis)

	Response (p)	Survival (p)
No. of organs involved	0.003	0.0017
Treatment group	0.0002	NS

Age	0.126	NS
Performance Status	NS	0.0001
Percentage of liver involved	NS	0.0013

Table 5: Results from multivariate analysis of prognostic factors for tumour response and survival

General comments
Kaplan Meier Curves for progression free survival and overall survival

Citation: Goldberg, RM, Sargent DJ, Morton RF, Fuchs CS et al (2006) Randomised controlled trial of reduced dose bolus fluorouracil plus leucovorin and irinotecan or infused fluorouracil plus leucovorin and oxaliplatin in patients with previously untreated metastatic colorectal cancer: A North American intergroup trial *Journal of Clinical Oncology* 24;21:3347-3353
Design: Randomised Trial **Country**: USA **Setting**: **Aim**:
Inclusion criteria Histologically proven unresectable adenocarcinoma Biopsy required if Dukes A or B primary or ≥5 years since surgery Age ≥18 years Life expectancy >12 weeks ECOG performance status 0-2 Effective contraception if child bearing potential Neutrophils ≥1.5x10^9/l Platelets ≥100x10^9/l Haemoglobin ≥9.0g/dl Creatinine and total bilirubin ≤1.5x institutional normal upper limit AST and alkaline phosphatase ≤5x institutional normal upper limit Signed informed consent Institutional review board approval
Exclusion criteria Adjuvant fluorouracil within the previous 12 months Prior treatment for advanced disease Prior radiation to ≥15% of bone marrow Radiotherapy of major surgery within 4 weeks Minor surgery within 2 weeks Uncontrolled infection Symptomatic peripheral neuropathy Known brain or meningeal metastases Interstitial pneumonia Grade ≥ 2 dyspnea ≥3 loose stools per day Comorbid condition that could confound outcome Active or prior malignancy in the past 3 years (exceptions: nonmelanoma skin cancer, cervical carcinoma in situ and other malignancy with <10% chance of relapse within 3 years).
Sample Size 275 patients per arm to afford 80% power to detect a hazard ratio of 1.33 between the treatment arms using a 2 sided log rank test at p=0.025. Interim analysis demonstrated that the outcomes of patients treated on FOLFOX4 were superior to the outcomes of patients treated with the full dose IFL in the earlier component of the trial with, based on the crossing of prespecified boundaries for superiority of one regimen over the other as a result the trial was closed with 305 patients enrolled.
Randomisation Method Dynamic allocation designed to balance random assignment for performance status score (0 vs. 1 or 2), prior adjuvant chemotherapy (yes vs no), prior immunotherapy (yes vs. no), age (<65 vs. ≥65) and treating location.
Population N=305
Study Duration Recruitment phase: April 25th, 2001 – April 23rd, 2002

Interventions

rIFL: Irinotecan 100mg/m^2 and bolus FU 400 mg/m^2 plus leucovorin 20mg/m^2 on days 1, 8, 15 and 22 every 6 weeks

FOLFOX4: Oxaliplatin 85mg/m^2 on day 1 and bolus FU 400mg/m^2 plus leucovorin 200mg/m^2 followed by FU 600mg/m^2 as 22 hour infusion on days 1 and 2 every 2 weeks.

Outcomes

Time to progression (calculated from study entry to disease progression regardless of patients treatment status. In post hoc sensitivity analysis, patients were censored for TTP when they discontinued initial treatment)

Response Rate
Overall Survival
Toxicity

Results
Efficacy
Median follow up time was 40 months by which time 87.5% of patients had experienced disease progression. Time to disease progression was significantly different between patients receiving rIFL and patients receiving FOLFOX4 (median 5.5 months versus 9.7 months, p<0.0001; hazard ratio=0.55; 95% CI 0.43-0.7).

In sensitivity analysis in which patients whose initial treatment ceased without progression were censored at the completion of protocol-specified therapy, these results remained significant (median time to disease progression, 5.6 and 10.1 months on rIFL and FOLFOX4 respectively; hazard ratio=0.42; p<0.0001).

Median survival time for patients receiving rIFL was 16.4 months versus 19 months for patients receiving FOLFOX4 (p=0.26 hazard ratio=0.76, 95% CI 0.6-0.97).

The response rate of patients receiving FOLFOX4 was higher than in patients receiving rIFL (48% versus 32%, p=0.006).

Time to treatment discontinuation was not significantly different between the two treatment groups though the reasons for discontinuation of treatment were different in each arm; 71.8% of patients in the rIFL group discontinued due to disease progression or death compared with 36.2% of patients receiving FOLFOX4 (p<0.0001).

Adverse Events
The death rates within the first 60 days of treatment were 3.3% (95% CI, 1.1-7.7%) in the IFL group and 2% (95% CI, 0.4-5.7%) in the FOLFOX4 group.
Rates of paresthesis and neutropenia were significantly lower in the IFL group compared with the FOLFOX4 group.

Second Line Therapy
A high proportion of patients in each arm received second line therapy (74% on rIFL and 75% on FOLFOX4). The proportion of patients receiving second line therapy before progression was 40% on IFL and 29% on FOLFOX4. 58% of patients initially treated with rIFL received an oxaliplatin based regimen second line while 55% of patients intitially treated with FOLFOX4 received an irinotecan based regimen second line.

Dose-Intensity of rIFL compared with IFL
In the prior stage of N9741, the full dose IFL regimen was used and comparing the dose intensity of irinotecan in patients treated with rIFL and patients treated with IFL showed that many patients required a dose reduction of full dose IFL with 85.5% of the intended dose delivered during the first cycle compared with 93.8% of the planned dose of rIFL (p=0.012).
The absolute doses of irinotecan also differed in cycle 2, with a median delivered dose of 375mg/m^2 of rIFL versus 425mg/m^2 of full dose IFL (p<0.001).
At cycles 3 and 6, there was no significant difference observed between the absolute doses of the drugs administered in IFL and iIFL due to the fact that the IFL dose had been reduced to a dose similar to that of the rIFL protocol.

Tables

	rIFL (N=151)	FOLFOX4 (N=154)
	N (%)	N (%)
Age, years		
Median	60	58
Range	27-83	19-83
ECOG Performance Status		
0-1	147 (97)	131 (86)
2	4 (3)	21 (14)
Sex		
female	54 (36)	64 (42)
Male	97 (64)	90 (58)
Prior Adjuvant Chemotherapy		
Yes	21 (14)	21 (14)
No	130 (86)	131 (85)
Unknown		2 (1)

Table 1: Patient Characteristics

	rIFL (n=146)	FOLFOX4 (n=146)	
	n (%)	n (%)	P
Nausea	15 (10.3)	10 (6.9)	0.296
Vomiting	12 (8.2)	9 (6.2)	0.497
Diarrhoea	24 (16.4)	18 (12.3)	0.317
Febrile Neutropenia	10 (6.9)	18 (12.3)	0.112
Dehydration	8 (5.5)	6 (4.1)	0.584
Parathesias	1 (0.7)	21 (14.4)	≤0.0001
Neutropenia	39 (26.7)	86 (58.9)	≤0.0001

Table 2: Toxicity Grade ≥3

	rIFL (n=149)	FOLFOX4 (n=149)	
	n (%)	n (%)	P
Any second line therapy			
Overall	110 (74)	112 (75)	0.79
Before Progression	44 (40)	32 (29)	0.07
Irinotecan			
Overall	37 (24.8)	82 (55)	<0.001
Before progression	15 (10)	32 (21.5)	0.71
Oxaliplatin			
Overall	86 (57.7)	31 (20.8)	<0.001
Before Progression	45 (30.2)	15 (10)	0.71
Fluorouracil			
Overall	85 (57)	69 (46.3)	0.011
Before Progression	36 (24.2)	21 (14.1)	

Table 3: Second line therapy

Cycle	No. of Patients	Absolute dose delivered of Irinotecan (mg/m^3)		% targeted dose delivered of Irinotecan	
		Median (Range)	P	Median (Range)	P
[1] iIFL	145	375 (97.8-461.2)	<0.001	93.8 (24.5-115.3)	0.12
IFL	274	427.6 (122.2-623.9)		85.5 (24.4-124.8)	
[3] rIFL	88	373.1 (148.6-500.9)	0.57	93.3 (37.1-125.2)	0.002
IFL	179	392.9 (59.9-523.4)		78.6 (12-104.7)	
[6] rIFL	35	373.1 (148.6-500.9)	0.62	100 (18.7-125.1)	0.006
IFL	86	75-520.9		76.9 (15-104.2)	

Table 4: Dose Intensity of rIFL compared with IFL

General comments
Kaplan Meier curves presented for time to tumour progression, overall survival and time to treatment discontinuation.

Citation: Goldberg R, Sargent D, Morton R, Fuchs C et al (2004) A randomised controlled trial of fluourouracil plus leucovorin, irinotecan and oxaliplation combinations in patients with previously untreated metastatic colorectal cancer *Journal of Clinical Oncology* 22;1:23-30
Design: Randomised Trial **Country**: USA **Setting**: **Aim**: to compare the activity and toxicity of three different two-drug combinations in patients with metastatic colorectal cancer who had not been previously treated for advanced disease.
Inclusion criteria Histologically proven unresectable adenocarcinoma Biopsy required if Dukes A or B primary or ≥5 years since surgery Age ≥18 years Life expectancy >12 weeks ECOG performance status 0-2 Effective contraception if child bearing potential Neutrophils ≥1.5x10^9/l Platelets ≥100x10^9/l Haemoglobin ≥9.0g/dl Creatinine and total bilirubin ≤1.5x institutional normal upper limit AST and alkaline phosphatase ≤5x institutional normal upper limit Signed informed consent Institutional review board approval
Exclusion criteria Adjuvant fluorouracil within the previous 12 months Prior treatment for advanced disease Prior radiation to ≥15% of bone marrow Radiotherapy of major surgery within 4 weeks Minor surgery within 2 weeks Uncontrolled infection Symptomatic peripheral neuropathy Known brain or meningeal metastases Interstitial pneumonia Grade ≥ 2 dyspnea ≥3 loose stools per day Comorbid condition that could confound outcome Active or prior malignancy in the past 3 years (exceptions: nonmelanoma skin cancer, cervical carcinoma in situ and other malignancy with <10% chance of relapse within 3 years).
Sample Size The protocol specified 375 patients per arm to give 90% power to detect a hazard ratio of 0.75 between each experimental regimen and control, using a two sided log-rank test at level 0.025 for each comparison.
Randomisation Method Dynamic allocation to balance random assignment for performance status, prior adjuvant chemotherapy, prior immunotherapy, age and randomising location.
Population N=795
Study Duration Enrolment and randomisation: May 1999-April 2001
Interventions IFL: Irinotecan 125 mg/m^2 and bolus FU 500mg/m^2 + LV 20 mg/m^2 on days 1, 8, 15 and 22 every 6 weeks FOLFOX: Oxaliplatin 85 mg/m^2 on day 1 and bolus FU 400 mg/m^2 plus LV 200 mg/m^2 followed by FU 600 mg/m^2

in 22 hour infusions on days 1 an 2 every 2 weeks.

IROX: Oxaliplatin 85 mg/m^2 and Irinotecan 200 mg/m^2 every 3 weeks.

Outcomes
Time to progression (calculated from study entry to disease progression regardless of treatment status. In post-hoc sensitivity analysis, patients were censored for TTP when they discontinued initial treatment and deaths occurring within 30 days of treatment discontinuation were considered progression in both analyses)

Overall Survival
Tumour response rate (complete and partial response in measurable patients, regression in evaluable patients, confirmed at second evaluation)
Time to treatment discontinuation (time from randomisation to treatment cessation on assigned treatment)

Results
Treatment continued until disease progression, unacceptable toxicity or withdrawal of consent

The arms were balanced in relation to stratification factors and other baseline characteristics.

Median follow up was 20.4 months at which point 85% of patients had disease progression.

Time to progression differed significantly between patients receiving IFL and patients receiving FOLFOX (median time to progression: 6.9 months versus 8.7 months; hazard ratio, 0.74; 95% CI 0.61 – 0.89; p=0.0014). In the sensitivity analysis, the results remained significant (median time to progression: 7 months versus 9.3 months, p=0.0015).
For patients receiving IROX, median time to progression was 6.5 months which, when compared to IFL was not significantly different (Hazard Ratio; 1.02; 95% CI, 0.85-1.23; p>0.5) and when compared to FOLFOX was significantly lower (Hazard Ratio; 0.72; 95% CI 0.6-0.87; p=0.001).

Median survival for patients receiving IFL was 15 months, 19.5 months for patients receiving FOLFOX and 17.4 months for patients receiving IROX.

Experimental	Control	Hazard Ratio (95% CI)	P
FOLFOX	IFL	0.66 (0.54-0.82)	0.0001
IROX	IFL	0.81 (0.66-1.00)	0.04
IROX	FOLFOX	0.83 (0.67-1.03)	0.09

Table: Pairwise comparison for Survival

The response rate for patients receiving FOLFOX was higher than for patients receiving IFL or IROX while response rates of patients receiving IROX and IFL did not differ significantly.

Comparison	Response Rates	P
FOLFOX versus IFL	45% versus 31%	0.002
IROX versus IFL	31% versus 35%	0.34
FOLFOX versus IROX	45% versus 35%	0.03

Table: Pairwise Comparison of response rates

Time to treatment discontinuation did not differ significantly for any pairwise comparison however reason for treatment discontinuation did differ significantly between the treatment arms.

Comparison	Rate of treatment discontinuation	P
FOLFOX versus IFL	42% versus 67%	0.0001
IROX versus IFL	55% versus 67%	0.004
FOLFOX versus IROX	42% versus 55%	

Table: Pairwise comparison for treatment discontinuation

Patients treated with IFL had significantly higher rates of diarrhoea, vomiting, nausea, febrile neutropenia and dehydration when compared with patients treated with FOLFOX. Patients in the IFL group had significantly lower rates of paresthesias and neutropenia.
Onset of grade 3 paresthesias in FOLFOX patients occurred after a median of twelve 2-week treatment cycles. The rates of grade 3 or higher toxicity for patients receiving IROX were similar to those for patients receiving IFL.

The death rates within the first 60 days of treatment were 4.5% (95% CI, 2.4% to 7.8%) for patients receiving IFL, 2.6% (95% CI, 1.1% to 5.3%) for patients receiving FOLFOX and 2.7% (95% CI, 1.1% to 5.4%) for patients receiving IROX.

The proportion of patients receiving 2nd line treatment before progression was similar across the three arms (26% to 32%).
A high proportion of patients treated with FOLFOX received second line irinotecan; fewer patients receiving IFL were treated with oxaliplatin regimens as second line therapy due the limited availability of the agent at the time the study was underway.

Toxicity Grade ≥3	IFL (n=255)	FOLFOX (n=258)	IROX (n=256)	p (IFL versus FOLFOX)	p (IFL versus IROX)	p (FOLFOX versus IROX)
	%	%	%			
Nausea	16	6	19	0.001	0.43	0.001
Vomiting	14	3	22	0.001	0.02	0.001
Diarrhoea	28	12	24	0.001	0.35	0.001
Febrile Neutropenia	15	4	11	0.001	0.23	0.002
Dehydration	9	4	6	0.03	0.17	0.41
Paresthesias	3	18	7	0.001	0.04	0.001
Neutropenia	40	50	36	0.04	0.35	0.002

Table: Toxicity Grade ≥3

Second line therapy	IFL (n=251)	FOLFOX (n=259)	IROX (n=262)
Any			
Overall	67	75	70
Before Progression	32	26	26
Irinotecan			
Overall	25	60	32
Before Progression	9	25	10
Oxaliplatin			
Overall	24	8	9
Before Progression	17	3	3
Fluorouracil			
Overall	41	40	50
Before Progression	18	14	21

Table: Second line therapy

General comments
An imbalance between the arms in the number of deaths within the first 60 days of treatment was detected; a higher number of deaths in the IFL was observed and on the recommendation of the External data monitoring committee, doses of irinotecan and FU were reduced in that arm. The results of the current study report on the comparative efficacy and toxicity for the 795 patients that were randomised to full dose IFL or to FOLFOX or IROX.

Citation: de Gramont A, Figer A, Seymour M, Homerin M, et al (2000) Leucovorin and Flourouracil with or without oxaliplatin as first line treatment in advanced colorectal cancer *Journal of Clinical Oncology* 18;2938-2947

Design: Randomised Trial

Country:

Setting: Multicentre

Aim: to investigate the effect of combining oxaliplatin with LV5FU2.

Inclusion criteria
Adenocarcinoma of the colon or rectum
Unresectable metastases
At least one bidemensionally measurable lesion of ≥ 2cm
Adequate bone marrow, liver and renal function
WHO performance status of 0-2
Age 18-75 years
Ability of complete QoL questionnaires
Previous adjuvant chemotherapy completed at least 6 months prior to inclusion

Exclusion criteria
Patients with CNS metastases, second malignancies of disease confined to previous radiation fields

Sample Size
The study was designed to have the power to detect a 3 months prolongation of progression free survival using a two sided log-rank test with an alpha risk of 0.05 and a beta risk of 0.2

Randomisation Method
Minimisation technique with stratification for performance status, number of metastatic sites and institution.

Population
N=420 (210 in each arm)

Study Duration
Recruitment Phase: August 1995 to July 1997
Cut-off date for follow-up: December 1st 1998

Interventions
LV5FU2: leucovorin 200mg/m^2, 5FU bolus 400mg/m^2, 5FU infusion 600 mg/m^2 repeated for 2 consecutive days every 2 weeks.

LV5FU2+oxaliplatin (FOLFOX4): LV 200mg/m^2, 5FU bolus 400mg/m^2, 5FU infusion 600mg/m^2 repeated for 2 consecutive days every two weeks with Oxaliplatin 85mg/m^2 given on day 1 of each cycle.

Outcomes
Progression Free Survival (defined as the time interval from randomisation to disease progression or death for patients who died without evidence of progression)

Response Rate
Overall Survival
Tolerability
Quality of Life

Results
Seven patients were unassessable for treatment efficacy; four on Arm A and three on Arm B, all 7 were retained for intent to treat analysis.

Potential median follow-up for the entire cohort was 27.7 months

Objective Tumour Response
An external panel of radiologists reviewed CT scans of 380 patients (90.5%); response rates for assessable patients were 22.3% in Arm A and 50.7% in Arm B.

The intent to treat response rates were 21.9% (95% CI 17.9-25.9%) in Arm A and 50% (95% CI, 46.1-54.9%) in Arm B (p=0.0001).
Median time to response in arm A was 12 weeks and in arm B was 9 weeks and the median duration of response was 46.1 weeks and 45.1 weeks respectively.
Secondary surgery to remove metastases could be performed in 7 patients in Arm A and in 14 patients in Arm B.

Treatment allocation to oxaliplatin and synchronous metastases were the only independent prognostic factors for response on multivariate analysis.

Progression Free Survival
On external review, median progression free survival was 6 months in arm A and 8.2 months in arm B (p=0.0003). Treatment allocation to oxaliplatin, low LDH level and good performance status were significant predictors for improved progression free survival.

Survival
Median overall survival was not significantly different between the arms 14.7 months in arm A versus 16.2 months in arm B; log rank p =0.12; Wilcoxin p=0.05). 69% of patients receiving oxaliplatin were alive at 1 year compared with 61% of patients not receiving oxaliplatin.

Post study chemotherapy was administered to 127 patients on Arm A (60.5%) and 122 patients on arm B (58.1%). Among those 78 patients on Arm A and 62 patients on Arm B received oxaliplatin post study and/or irinotecan. For patients that did not receive second line post-study oxaliplatin or irinotecan, median overall survival was 12.2 months for arm A (132 patients) and 14.8 months for arm B (148 patients); p=0.04) and median time from progression to death was 8.2 months in arm A and 7.2 months in arm B.
Independent prognostic factors for improved overall survival were allocation to oxaliplatin, low LDH level, good performance status, low alkaline phosphatase level and a limited number of involved sites.

Toxicity
Median of number of on study cycles was 11for arm A and 12 for arm B.
There was one therapy related death in arm B, resulting from gastrointestinal and haematologic toxicities. Grade 3/4 neutropenia, diarrhoea, musositis and neuropathy were more frequent on arm B than arm A.
Grade 3/4 neutropenia was more frequent in women than in men (52% versus 35%, p=0.015).
1.9% of patients on arm B had severe allergic reactions.

Dose Intensity
The 5FU dose intentsity was 92% of the scheduled dose for the first four cycles and 89% for all cycles in arm A and in arm B the 5FU dose intensity was 84% and oxaliplatin dose intensity was 86% during the first four cycles and 76% for 5FU and 73% for oxaliplatin during all cycles.

Quality of Life
83.6% of patients participated in the QoL assessment; age and sex influenced baseline QoL scores.
At cycle 4, emotional functioning improved and insomnia was attenuated on both arms, general condition improved and pain decreased on arm A and nausea and vomiting were worse on arm B.
At cycle 8, emotional functioning improved on both arms, role functioning and general condition improved and insomnia diminished on arm A and nausea and vomiting worsened on arm B.
Overall median QoL scores were comparable for the two arms and neither response to treatment nor occurrence of side effects significantly influenced the changes in patients QoL.
Time to deterioration of the global health status of 20%(p=0.0039) or 40% (p=0.0004) was significantly prolonged on arm B.
Performance status improved in 59/108 patients on arm A and in 71/119 patients on arm B.

Tables

	Arm A: LV5FU2 (n=210)	Arm B LV5FU2+Oxaliplatin (n=210)
	N (%)	N (%)
Sex		
Male	122 (58.1)	127 (60.5)
Female	88 (41.9)	83 (39.5)
Age, years		
Median	63	63

Range	22-76	20-76
WHO Performance Status		
0	102 (48.6)	91 (43.3)
1	88 (41.9)	97 (46.2)
2	20 (9.5)	22 (10.5)
Adjuvant Chemotherapy		
Yes	43 (20.5)	72 (20)
No	167 (79.5)	168 (80)

Table 1: Patient Characteristics

	Arm A: LV5FU2			Arm B: LV5FU2+Oxaliplatin		
	No. of Patients	No. of Responses	%	No. of Patients	No. of Responses	%
Overall						
Intent to Treat	210	46	21.9	210	105	50
Assessable	206	46	22.3	207	105	50
Complete Response	210	1	0.5	210	3	1.4
Partial Response	210	45	21.4	210	102	48.6
Stable Disease	210	107	51	210	67	31.9
Disease Progression	210	34	16.2	210	21	10
Not reviewed/not assessable	210	23	10.9	210	17	8.1
Response (CR/PR) by age						
≤65 years	126	28	22.2	134	67	50
>65 years	84	18	21.4	76	38	50
Response (CR/PR) by disease						
Synchronous	139	32	23	135	76	56.3
Metachronous	70	14	20	70	29	41.4
Liver only	68	16	23.6	79	43	54.4
Liver + other sites	105	23	21.9	103	54	52.4
Other sites	37	7	18.9	28	8	28.6
Response (CR/PR) by prior adjuvant chemotherapy						
Yes	43	6	14	42	16	38.1
No	167	40	23.9	168	89	53

Table 2: Objective tumour response rates after external review

	Response		Progression Free Survival		Overall Survival	
	P	Odds Ratio	P	Risk Ratio	P	Risk Ratio
WHO Performance Status	0.5938		0.0049	1.24	0.0001	1.52
Synchronous/metachronous metastases	0.0423	1.58	0.2458		0.1548	
No. of metastatic sites, continuous	0.1040		0.0008	1.21	0.0001	1.34
Alkaline Phosphatase, NCI grade	0.5887		0.0031	1.25	0.0001	1.59
LDH, ≤upper limit versus >upper limit	0.4944		0.0001	1.57	0.0001	2.17
Assigned oxaliplatin	0.0001	3.43	0.0001	0.81	0.1171	
Treatment Centre	0.504		0.6637		0.0079	
Sex	0.8903		0.793		0.4079	
Age, Continuous	0.7390		0.3976		0.5753	
Liver involved, yes versus no	0.2439		0.2773		0.8469	
Prior Chemotherapy	0.04	0.57	0.5632		0.2163	
Prior radiotherapy	0.5958		0.2253		0.0374	0.65
Primary Site, colon versus rectum	0.3026		0.6282		0.3798	
ALT, NCI grade	0.6829		0.1070		0.0012	1.38
AST, NCI grade	0.8721		0.6455		0.5086	
Creatinine, NCI grade	0.5684		0.5019		0.5960	
CEA, ≤5ng/ml, 5050ng/ml, >50ng/ml	0.5406		0.0015	1.251	0.0001	1.48

Table 3: Prognostic Factors in Univariate Analysis

	Response		Progression Free Survival		Overall Survival	
	Odds ratio	P	Risk Ratio	P	Risk Ratio	P
WHO Performance Status		NS	1.30	0.0023	1.5	0.0001
Synchronous/metachronous metastases	1.57	0.0306		NS		NS
No. of metastatic sites		NS		NS	1.17	0.0029
Alkaline phosphatase		NS		NS	1.34	0.0062
LDH		NS	1.60	0.0001	1.94	0.0001
Assigned Oxaliplatin	1.84	0.0001	1.71	0.0001	0.80	0.0001

Table 4: Prognostic Factors in Multivariate Analysis

	Arm A: LV5FU2				Arm B: LV5FU2+Oxaliplatin				
	1	2	3	4	1	2	3	4	P (grade 3/4)
Neutropenia	16.3	8.6	3.8	1.5	14.3	14.3	29.7	12.0	<0.001
Thrombocytopenia	26.5	2.4	0.5	0.0	62.2	11.5	2.0	0.5	NS

Anaemia	57.7	21.2	1.5	1.0	59.8	23.5	3.3	0.0	NS
Infection	15.9	5.8	1.0	0.5	17.7	6.7	1.5	0.0	NS
Nausea	40.4	11.1	2.0	NA	44.0	22.5	5.7	NA	0.043
Vomiting	18.3	9.1	1.5	0.5	24.0	24.4	4.3	1.5	0.043
Diarrhoea	27.9	10.6	3.8	1.5	30.6	16.3	8.6	3.3	0.015
Mucositis	25	9.1	1.5	0.0	24.9	12.9	5.3	0.5	0.019
Cutaneous	20.2	10.6	0.0	0.5	19.6	9.1	0.0	0.0	NS
Alopecia	15.4	3.4	NA	NA	15.8	1.9	NA	NA	NS
Neurological Toxicity	9.1	2.9	0.0	NA	20.6	29.2	18.2	NA	<0.001

Table 5: Maximum Toxicity per patient (%)

General comments

Kaplan-Meier Curves for Progression Free Survival, Overall Survival, Time to Global Health Status Deterioration of 40%.

Citation: Hochester HS, Hart LL, Ramanathan RK et al (2008) Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first line treatment of metastatic colorectal cancer: results of the TREE study *Journal of Clinical Oncology* 26;21: 3523-3529

Comparison: FOLFOX versus bFOL versus XELOX

Design: Open label Randomised Trial

Country: USA

Setting:

Aim: To evaluate the safety and efficacy of three oxaliplatin and fluorourpyrimidine regimens with or without bevacizumab as first line treatment for metastatic colorectal cancer.

Inclusion criteria
Histologically documented mCRC or recurrent CRC
No prior therapy for metastatic or recurrent disease
Adjuvant treatment completed ≥6 months prior to study registration
Age ≥18 years
≥1 unidimensionally measurable lesion
ECOG performance status 0-1
Adequate haematologic and hepatic parameters

Exclusion criteria
Myocardial infarction within 6 months
Current congestive heart disease
Nonstable coronary artery disease
Peripheral neuropathy
Interstitial pneumonia or extensive lung fibrosis
Uncontrolled infection
Malabsorption syndrome
Dihyropyrimidine fehydrogenase deficiency
Therapeutic warfarin
Uncontrolled hypertension

Sample Size
Accrual of 70 patients per arm was deemed to be sufficient to detect a 15% increase in the overall incidence of grade 3/4 adverse events for the experimental treatments compared with historical controls based on a one group X^2 test with a normal one sided 0.05 significance level and 80% power within the 50% t0 70% Adverse Event rate of historical controls.

Randomisation Method
Central Registry to randomly assign patients in a 1:1:1 ratio

Population
TREE 1 – 150 patients

mFOLFOX6 – 50 patients
bFOL – 50 patients
CapeOx – 50 patients

Study Duration
Recruitment Stage: November 2002 to November 2003

Interventions
mFOLFOX-6: oxaliplatin 85mg/m^2 IV with leucovorin 350mg/m^2 IV over 2 hours plus FU 400mg/m^2 IV bolus and 2,400mg/m^2 continuous infusion over 46 hours every 2 weeks

bFOL: oxaliplatin 85mg/m^2 IV on days 1 and 15 and leucovorin 20mg/m^2 IV over 10 to 20 minutes followed by FU 500mg/m^2 IV push on days 1, 8 and 15 every 4 weeks

CapeOx: oxaliplatin 130mg/m^2 IV on day 1 and caecitabine 1,000mg/m^2 orally twice daily on days 1-15 every 3

weeks		

Outcomes

Overall incidence of grade 3/4 adverse events possibly or probably related to study drug within the first 12 weeks of treatment in each of the TREE-2 groups

Adverse events in TREE-1 during the first 12 weeks of treatment
All adverse events occurring within 30 days of treatment
Overall response rate
Time to treatment failure (defined as time from randomisation to first documentation of tumour progression, discontinuation of study treatment or death from any cause)
Time to Progression (defined as time from randomisation to first documented progression or death from any cause in the absence of documented tumour progression)
Overall Survival

Results

 Baseline characteristics were similar across groups except for prior adjuvant chemotherapy, male:female ratio and primary site of diagnosis.

147/150 patients were treated (1 ineligible due to prior chemotherapy and 2 did not start treatment).

Discontinuation of treatment was primarily attributable to adverse events (mFOLFOX6 29%, bFOL 46% and CapeOx 52%) or disease progression (mFOLFOX6 43%, bFOL 42% and CapeOx 25%).

Treatment delays were most common with mFOLFOX6 (81%) although the number of cycles administered was highest in this arm. The most common cause of treatment delay was neutropenia and thrombocytopenia in the mFOLFOX6 and bFOL arms and diarrhoea, nausea and dehydration with CapeOx.
Oxaliplatin dose reductions were more common with mFOLFOX6 (50%) reflecting the longest time on study. Median dose intensity was ≥82% for all arms.

69% of patients received subsequent therapy including biologic agent (bevacizumab, n=31, cetuximab, n=28, other biologic agents, n=3) or oxaliplatin (n=36).

Safety and Tolerability
59%, 36% and 67% of patients in the mFOLFOX6, bFOL and CapeOx arms respectively had at least one grade 3/4 toxicity during the first 12 weeks of treatment.
Four patients had adverse events leading to death within 30 days of last treatment, 1 patient in the CapeOx arm died due to grade 4 dehydration and diarrhoea considered treatment related. No treatment related deaths were reported in the FOLFOX arm.
Overall 60 day mortality was 3.4%

Efficacy
The highest confirmed overall response rate occurred with mFOLFOX6 (41%) but there was no statistically significant difference between the arms.
Median time to failure was longer for mFOLFOX6 (6.5 months, 95% CI 5.4 – 8.3).
Median survival was 18.2 months (95% CI 14.5-21.6) and at the time of follow-up 70% of patients had died.

Tables

	mFOLFOX6	bFOL	CapeOx
No. of Patients	49	50	48
Age, years			
Median	62	62	62.5
Range	35-79	31-84	32-84
Sex			
Female	43%	38%	35%
Male	57%	62%	65%
ECOG Performance Status			
0	61%	58%	52%
1	39%	42%	48%
Prior Adjuvant Chemotherapy			
Primary Site	45	16	27
Colon	55	74	75

Colon/Rectum	27	14	19
Rectum	18	12	6
OTher	0	0	0

Table 1: Demographic and baseline characteristics

	mFOLFOX6	bFOL	CapeOx
No. of Patients	49	50	48
Duration of therapy (weeks)			
Median	24	22	18
Range	2-52	4-60	3-83
No. of cycles	490	275	282
Patients receiving >1 cycle (%)	98	88	83
Patients with ≥1 delay (%)	81	64	63
Patients with oxaliplatin dose reduction (%)	50	32	20
Median RDI			
Oxaliplatin	82	88	94
FU/Capecitabine	81	86	80

Table 2: Treatment Administration

	mFOLFOX6	bFOL	CapeOx
No. of Events	49	50	48
Events occurring during the first 12 weeks of treatment			
Related to treatment	55	36	67
95% CI	44-73	23-51	52-80
Regardless of casualty	76	44	73
95% CI	61-87	30-59	58-85
Selected events occurring during or within 30 days of treatment			
Anaemia	8	2	6
Leukopenia	4	2	2
Neutropenia	53	18	15
Thrombocytopenia	6	8	10
Abdominal Pain	2	4	13
Diarrhoea	31	26	31
Nausea or vomiting	31	24	38
Fatigue	8	14	6
PT	NR	NR	NR
Dehydration	8	12	27
Paresthesia	18	10	21
Hand-foot syndrome	8	2	19
Deep vein thrombosis	6	2	0
Hypertension	0	0	2

Table 3: Incidence of Grade 3 and Grade 4 Adverse Events

	mFOLFOX6	bFOL	CapeOx
No. of Patients	49	50	48
Response			
Complete Response	0	0	2
Partial Response	41	20	25
Stable Disease	24	42	40
Progressive Disease	27	26	10
Overall Response Rate	41	20	27
95% CI	27-56	10-34	15-42
Median time to treatment failure, months	6.5	4.9	4.4
95% CI	5.4-8.3	3.5-6.1	3.0-5.8
Median time to progression, months	8.7	6.9	5.9
95% CI	6.5-9.8	4.2-8	5.1-7.4
Median OS, months	19.2	17.9	17.2
95% CI	14.2-24.9	11.5-24.6	12.5-22.3
1 year survival	77.2	60	

Table 4: Efficacy

General comments

This study had two different populations with later patients randomised to receive XELOX, FOLFOX or bFOL + bevacizumab. Only the results from the population without bevacizumab are presented here as these are the only relevant comparisons for the topic.

Kaplan Meier curves presented for survival time (months).

Citation: Kohne CH, De Greve J, Hartmann JT, Lang I et al (2008) Irinotecan combined with infusional 5-fluorouracil/folinic acid or Capecitabine plus celecoxib or placebo in the first line treatment of patients with metastatic colorectal cancer. EORTC study 40015 *Annals of Oncology* 19;920-926

Comparison: CAPIRI versus FOLFIRI

Design: Prospective 2x2 factorial Phase III Randomised Trial

Country: Belgium

Setting:

Aim: to demonstrate the non-inferiority of Capecitabine to 5-fluorouracil (5-FU)/folinic acid (FA) in relation to progression free survival after first line treatment of metastatic colorectal cancer (i.e. that Capecitabine could replace 5FU/FA as the fluorourpyrimidine component of an irinotecan combination without compromising progression free survival).

Inclusion criteria
Aged ≥18 years with previously untreated metastatic, histologically verified adenocarcinoma of the colon or rectum.
WHO performance status ≤2
Measurable disease according to RECIST
Located outside the field of any radiotherapy
Radiotherapy to have been completed at least 4 weeks prior to randomisation
Prior adjuvant chemotherapy to have been completed at least 6 months prior to randomisation
Adequate renal, hepatic and haematological function

Exclusion criteria
Central Nervous system metastases
Second Malignancies
Severe Cardiac Disease
Active Crohns disease
Any uncontrolled severe medical condition

Sample Size
Unacceptable inferiority of Capecitabine over 5-FU/FA in relation to progression free survival was defined by a hazard ratio ≥1.25. Given a one sided alpha level of 2.5% it was estimated that 632 events were needed to exclude a difference of this magnitude with 80% probability. This number of events would also allow the detection of a 2 month difference between the celecoxib and placebo arms with a power of 89% and a two sided 5% significance level test. It was determined that 692 patients should be randomised (1:1).

Randomisation Method
Minimisation technique with stratification for institution, previous adjuvant therapy and risk groups (low risk: performance status of 1 or 0 and only 1 tumour site, intermediate risk: patients with performance status <1 but with more than one tumour site plus alkaline phosphatase level of <300U/l, or those with a poor PS, a low white blood cell count and only one tumour site; high risk: patients with good PS but more than one tumour site and a high ALP level, or a poor PS plus high WBC count or a poor PS, low WBC count and more than two tumour sites)

Population
N=85

Study Duration
May 2003 – January 2005

Interventions
FOLFIRI: Irinotecan 180mg/m^2 as a 30 to 90 minute i.v. infusion on days 1, 15 and 22; FA 200mg/m^2 as a 2-hr infusion on days 1, 2, 15, 16, 29 and 30 (1hour after irinotecan on days 1, 15 and 29); 5-FU as a 400mg/m^2 bolus given after FA followed by 22hour continuous infusion, 600mg/m^2 given after the bolus (days 1, 1, 15, 16, 29 and 30).

CAPIRI: Irinotecan 250mg/m^2 as a 30 to 90 minute iv infusion on days 1 and 22 and Capecitabine p.o. 1000mg/m^2, twice daily on days 1-15 and 22-36.

Within these arms patients were randomly assigned to either celecoxib or placebo (800mg as 2x200mg twice daily, before irinotecan when administered)

Outcomes

Progression free survival (calculated as time from randomisation until first report of progression or death; patients with no evidence of progression at the time of their last visit were censored at that point)

Safety
Response Rate
Time to treatment failure
Overall Survival

Results

Recruitment was suspended as a consequence of 7 deaths not due to disease progression; there was one further death following suspension (6 in CAPIRI and 2 in FOLFIRI). Following review of the individual hospital files, it was determined that 7/8 deaths were deemed to be treatment related with no underlying risk factors identified as a likely explanation.

The results are based on the data available from 85 eligible patients recruited before trial closure.

Median follow-up time was 14.6 months (95% CI 13.1-16.8)
Patient characteristics were similar in both groups
Dose reductions were more common in the CAPIRI arms and were primarily the result of gastrointestinal toxicity with 53% of CAPIRI versus 33% of FOLFIRI patients experiencing at least one cycle with dose reduction.
Treatment delays were more common in the FOLFIRI arm; 54% of patients on FOLFIRI versus 30% on CAPIRI experiencing at least one cycle with delay.
Relative dose intensity for Capecitabine and 5-FU did not differ (82.4% versus 84.8%) (placebo arms)

Adverse Events
4% (n=3) of patients were not included in the analysis as they did not receive study treatment.
62% of patients experienced at least one grade 3/4 adverse event, the most common of which were diarrhoea and WBC toxicity.

Efficacy
Response rates were 48% for CAPIRI + placebo and 46% for FOLFIRI + placebo (higher than for either treatment + celecoxib).

Tables

	CAPIRI + Placebo	FOLFIRI + Placebo
No. of patients	**21**	**22**
Sex		
Male n(%)	12 (57)	14 (64)
Female n(%)	9 (43)	8 (36)
Age, years		
Median	65	60.5
Range	43-78	45-75
≤65 years n(%)	11 (52)	14 (64)
>65 years n(%)	10 (58)	8 (36)
Risk Group		
Good n(%)	10 (48)	11 (50)
Intermediate n(%)	6 (29)	8 (36)
Poor n(%)	5 (24)	3 (14)
WHO Performance Status		
0 n(%)	12 (57)	14 (64)
1 n(%)	8 (38)	8 (36)
2 n(%)	1 (5)	0 (0)
Patients who started chemotherapy	20	21
Dose reductions in at least one cycle n(%)	10 (50)	10 (48)
Delays in at least one cycle n(%)	5 (25)	13 (62)
Median relative dose intensities % (range)		
Capecitabine	82.4 (47.5-119.6)	
5-FU		92.1 (21.2-107.4)
Irinotecan	83.6 (47.5-101.7)	88.4 (20.9-98.6)
Celecoxib/Placebo	98.3 (59.5-101.2)	96.2 (37.6-100.0)

Table 1: Patient Characteristics

Treatment	Total number of cycles	Time since last treatment (days)	Relatedness	Agreed Classification
CAPIRI + Placebo	1	6	Exacerbated	Pulmonary Embolism
CAPIRI + Placebo	1	75	Related	Diarrhoea/neutropenia/septic shock
CAPIRI + Placebo	2	9	Related	Diarrhoea/myocardial infarction
CAPIRI + Placebo	1	5	Related	Diarrhoea/suspected pulmonary embolism

Table 2: Early death and relationship to study treatment (classified by panel of experts)

	CAPIRI + Placebo	FOLFIRI + Placebo
Best overall response n(%)	21	22
Complete Response	1 (5)	0
Partial Response	9 (43)	10 (45)
Stable Disease	5 (24)	9 (41)
Progressive Disease	2 (10)	3 (14)
Early death	3 (14)	0
Not assessable	1 (5)	0
Response Rate (CR+PR)	10 (48)	10 (45)
Disease Control Rate (CR+PR+SD)	15 (71)	19 (86)
Adverse Event n(%)	n=20	n=21
Diarrhoea	7 (35)	2 (10)
Vomiting	1 (5)	1 (5)
Nausea	1 (5)	2 (10)
Gastrointestinal	0	1 (5)
Cardiovascular	1 (5)	0
Febrile Neutropenia	2 (10)	0
Hepatic Toxicity	1 (5)	1 (5)
White Blood Cells	3 (15)	4 (19)
Haemoglobin	0	0
Renal Toxicity	0	0
All grade 3/4 events	13 (65)	11 (52)

Table 3: Best overall response to treatment and grade 3/4 adverse events reported for 2 or more patients who started treatment

	CAPIRI (n=44)	FOLFIRI (n=41)
Progression Free Survival		
Median, months (95% CI)	5.9 (4.4-8.9)	9.6 (6.9-10.9)
1 year, % (95% CI)	22.6 (11.4-36.2)	29.3 (16.4-43.4)
Hazard Ratio (95% CI)	1.00	0.76 (0.48-1.21)
Overall Survival		
Median, months (95% CI)	14.75 (10.7-18.3)	19.9 (18.9-NR)
1 year, % (95% CI)	53.5 (36-68.2)	84.9 (69.4-92.9)
Hazard Ratio (95% CI)	1.00	0.31 (0.14-0.71)

Table 4: Progression Free and overall survival

General comments

The data from the arms with Celecoxib are not relevant to this topic, therefore only the data from the results of the arms with placebo are recorded here.

Kaplan Meier curves are included for available data

Citation: Kohne CH, van Cutsem E, Wils J, Bokemeyer C et al (2005) Phase III study of weekly high dose infusional fluorouracil plus folinic acid with or without irinotecan in patients with metastatic colorectal cancer: European organisation for research and treatment of cancer gastrointestinal group study 40986
Design: Randomised Phase III Trial **Country**: **Setting:** **Aim**: to demonstrate that adding irinotecan to a standard weekly schedule of high dose, infusional fluorouracil and leucovorin can prolong progression free survival
Inclusion criteria Aged >18 years Histologically verified adenocarcinoma of the colon or rectum WHO performance status 0-2 Measurable or assessable disease outside of the irradiation field in patients who had recently received radiotherapy Previous adjuvant chemotherapy that did not contain topoisomerase I inhibitors and had been completed at least 6 months prior to randomisation. Adequate haematological, renal and hepatic function
Exclusion criteria Therapeutic drugs within 4 weeks of trial entry Second malignancies except for in situ carcinoma of the cervix or nonmelanoma skin cancer Bowel obstruction or subobsruction Crohn's disease, ulcerative colitis or history of chronic diarrhea Pregnant or breast feeding women Fertile patients (male or female) not using adequate contraception
Sample Size A total of 350 progressions or deaths (events) were required to provide an at least 80% power to be able to detect a shift in the median progression free survival from 7 months to 9.5 months thus is was estimated that 430 patients were needed (215 per arm).
Randomisation Method Minimisation technique with stratification for institution, prior adjuvant treatment, WHO performance status and serum alkaline phosphatase
Population N=430 recruited
Study Duration Recruitment Phase: August 1999-July 2001
Interventions Reference Group: AIO schedule of FA 500mg/m^2 administered by intravenous infusion over 2 hours followed by FU 2.6g/m^2 administered by infusion over 24 hours. Both drugs administered on days 1, 8, 15, 22, 29 and 36 followed by a two week rest. Each treatment cycle consisted of 49 days. Experimental group: The same schedule but with FU 2.3g/m^2, subsequently reduced to 2.0g/m^2 because of toxicity. Treatment preceded by irinotecan 80mg/m^2 administered intravenously over 30 minutes.
Outcomes Progression Free survival (defined as the time interval from randomisation to progression or death. Patients were censored at date of last visit) Overall Survival Tumour Response Toxicity
Results *Toxicity and dose amendment*

Of the first 89 patients assigned to irinotecan and HDFU/FA with the FU dose of 2.3g/m^2, 18 serious adverse events were reported in 16 patients which were thought to be treatment related compared with 7 serious adverse events in 7 patients in the standard arm.
There were 3 toxic deaths in the irinotecan arm and one toxic death in the HDFU/FA arms respectively.

37% of patients in the Irinotecan arm and 18% of patients in the reference arm showed toxicity necessitating FU dose reduction. In the 2nd cycle, dose reduction was in 17% in the reference arm and 14% in the irinotecan arm and in cycle 3, dose reduction was in 6% and 7% respectively. Thereafter dose reductions occurred in no more than 2% of patients.

Of the 89 patients in the irinotecan arm that received the initial dose of FU, 40.4% needed a dose reduction during the first chemotherapy cycle compared with 33.9% of the 124 irinotecan patients exposed to the amended FU dose.

Overall, relative dose intensities for FU and FA were similar in both groups with a median of approximately 80% of the intended dose being administered.

Treatment Response
Median follow-up duration was 2.3 years (95% CI, 2.1-2.4 years).

Median progression free survival in the irinotecan group was 8.5 months (95% CI 7.6-9.9 months) versus 6.4 months (95% CI 5.3-7.2) in the reference group (p<0.0001) **Hazard Ratio 0.71 (95% CI 0.55 to 0.91)**
At 1 year, 27.6% (95% CI, 21.5%-33.7%) and 14.8% (95% CI, 10%-19.5%) of patients were free from progression in the irinotecan arm and reference arm respectively.

Improvement in progression free survival was not associated with enhanced overall survival. Median overall survival was 20.1 months (95% CI 18.0-21.9) in the irinotecan arm and 16.9 months (95% CI 15.3-19 months) in the reference group.
A transient benefit of irinotecan was observed in the short term (Wilcoxin P=0.0509) with a 1 year survival rate of 74.5% (95% CI, 69.6%-81.3%) in the irinotecan group compared with 66.4% (95% CI 60-72.8%) in the reference group.

The survival curves cross at around 24 months of the trial, reflecting a greater benefit of salvage treatment in the reference arm.

Overall the trial shows no statistically significant benefit of immediate intensive treatment in terms of overall survival (log rank p=0.2779).
The observed survival difference corresponded to a hazard rate of 0.88 (95% CI, 0.7-1.11) for the whole cohort.
For patients entering the trial after the FU dose reduction the **hazard ratio was 0.87 (95% CI 0.63-1.20)**.

The response to treatment in patients with measurable disease was 62.2% (95% CI, 55%-69.5%) in the irinotecan group and 34.4% (95% CI, 27.5%-41.3%) in the reference group (p<0.0001).
Median response duration was 10.1 months (95% CI, 8.7-11.2) in the irinotecan group and 9.2 months (95% CI, 8.2 to 10.4 months) in the reference group (log rank p=0.11).

Secondary resection of metastases was possible in 6 patients in the irinotecan group and in 14 patients in the reference group.

Treatment Discontinuation and Second line Therapy
A higher proportion of patients in the reference group discontinued treatment because of disease progression or relapse (61.5% versus 43.7% in the irinotecan group.
No difference was observed between patients receiving FU 2.3g/m^2 and patients receiving FU 2.0g/m^2.
A lower proportion of patients in the irinotecan group (55.6%) received additional second line treatment than in the reference group (65.3%).
A higher proportion of patients in the irinotecan group received oxaliplatin as second line therapy compared with reference group patients (34% versus 52% respectively).

Tables

	Reference Group	Irinotecan Group

	N (%)	N (%)
Age, years		
Range	24-80	32-78
Median	60.5	61
>70 years	(14.3)	(15.4)
Sex		
Male	(61.1)	(63.6)
Female	(38.9)	(36.4)
Performance Status		
0	126 (58.3)	120 (56.1)
1	81 (37.5)	84 (39.3)
2	9 (4.2)	10 (4.7)
Adjuvant treatment for primary disease		
No	167 (77.3)	166 (77.6)
Yes	49 (22.7)	48 (22.4)
Radiotherapy		
No	204 (94.4)	196 (91.6)
Yes	12 (5.6)	18 (8.4)

Table 1: Patient Characteristics (other factors reported include Alkaline phosphatase, primary tumour site, differentiation grade of primary tumour, adjuvant treatment for primary disease and number of disease sites)

	Reference Group	Irinotecan group		
Grade 3 and 4 Toxicity	**Total (n=213)**	**Total (n=213)**	**$2.3g/m^2$ (n=89)**	**$2.0 g/m^2$ (n=124)**
Leukopenia	3	7	8	6
Febrile Neutropenia	1	3	5	2
Diarrhoea	21	29	36	24
Stomatitis	1	3	2	3
Nausea	7	8	8	8
Vomiting	5	7	5	9
Alopecia, grade 2	2	8	12	5
Hand-foot syndrome	2	1	1	1
Cardiovascular (any grade)	9	8	11	5
Cardiovascular (grade 3/4)	4	2	3	1

Table 2: Toxic Side Effects Experienced

	Treatment Group	
Dose-Intensity	**Reference Group**	**Irinotecan Group**
No of Cycles		
Median	3	3
Range	1-9	1-9
Relative Dose Intensity, FU		
Median (%)	83.4	80.8
Range (%)	11.8-103.7	15.9-114.2
No. of patients	213	213
Relative Dose Intensity, FA		
Median (%)	80.7	80.3
Range (%)	11.8-105.6	7.9-101.0
No of Patients	213	212
Relative Dose Intensity, Irinotecan)		
Median (%)		78.7
Range (%)		15.4-104.2
No of patients		212*

*One patient received FU but did not receive FA or Irinotecan

Table 3: Relative Dose Intensities or Different Drugs for Reference and Experimental Drugs

	Reference Group (n=189)	Irinotecan Group (n=180)
Treatment Outcome	**N (%)**	**N (%)**
Complete Response	7 (3.7)	5 (2.8)
Partial Response	58 (30.7)	107 (59.4)
No Change	78 (41.3)	30 (16.7)
Progressive Disease	31 (16.4)	14 (7.8)
Early Death as a result of malignant disease	1 (0.5)	1 (0.6)
Early death as a result of toxicity	4 (2.1)	2 (1.1)
Early death as a result of other cause	3 (1.6)	0 (0)
Not Assessable	7 (3.7)	21 (11.7)
Responders, CR+PR	65 (34.4)	112 (62.9)

Table 4: Treatment Outcomes and Response Rates

	Reference Group (n=141)	Irinotecan Group (n=119)
Treatment	**N (%)**	**N (%)**
FU/FA + Irinotecan	44 (31)	23 (19.3)
Irinotecan + Oxaliplatin	16 (11.3)	7 (5.9)
Irinotecan + Other	24 (17)	12 (10)
Oxaliplatin + Other	32 (22.7)	55 (46)
Other	25 (17.7)	22 (18.5)

Table 5: First second line treatment administered

General comments

Kaplan Meier Curves for progression free survival and overall survival

Citation: Koopman M, Antonini NF, Douma J, Wals J et al (2007) Sequential versus combination chemotherapy with Capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial *Lancet* 370;9582:135-142
Design: Open Label Randomised Trial **Country**: The Netherlands **Setting:** Multicentre **Aim**: To determine whether first line combination treatment is better than sequential administration of the same drugs in terms of overall survival in patients with advanced colorectal cancer
Inclusion criteria Aged ≥18 years Histologically proven advanced colorectal cancer not amenable to curative surgery Measurable of assessable disease parameters No previous systemic treatment for advanced disease Previous adjuvant chemotherapy completed 6 months before randomisation WHO performance score 0-2 Adequate hepatic, bone marrow and renal function
Exclusion criteria Serious concomitant disease preventing the safe administration of chemotherapy or likely to interfere with the study assessments Other malignancies in the past 5 years with the exception of adequately treated carcinoma in situ of the cervix and squamous or basal cell carcinoma of the skin Pregnancy or lactation Patients with reproductive potential not implementing adequate contraceptive measures (both male and female) Central nervous system metastases Serious active infections Inflammatory bowel disease or other diseases associated with chronic diarrhea Previous extensive irradiation of the pelvis or abdomen (excluding 5x5 Gy irradiation for rectal carcinoma) Concomitant (or within 4 weeks before randomization) administration of any other experimental drug Concurrent treatment with any other anti cancer therapy
Sample Size Anticipated median overall survival sequential treatment of 14 months and assuming a median overall survival for combination treatment of 17.5 months it was calculated that to have 80% power to detect a 20% reduction in the hazard of death at a significance level of 5% a sample size of 800 patients was required.
Randomisation Method Minimisation technique with stratification according to WHO performance status (0-1 vs. 2), serum lactate dehydrogenase concentration (normal vs. abnormal), previous adjuvant treatment (yes vs. no), predominant location of metastases (liver vs. extrahepatic) and treatment centre
Population N=820 randomised (803 eligible)
Study Duration Randomisation Phase: January 2003-December 2004
Interventions Sequential treatment group: first line treatment consisted of Capecitabine, 1250mg/m^2 twice daily for 14 days; second line treatment of Irinotecan, 350mg/m^2 on day 1 and third line treatment of Capecitabine, 1000mg/m^2 twice daily for 14 days plus oxaliplatin, 130mg/m^2 on day 1. Combination treatment group: Capecitabine, 1000mg/m^2 twice daily for 14 days plus irinotecan, 250mg/m^2 on day 1 as first line treatment and Capecitabine, 1000mg/m^2 twice daily for 14 days plus oxaliplatin, 130mg/m^2 on day 1 as second line treatment.
Outcomes Overall survival (calculated as the interval from the date of randomization until death from any further cause or

until date of last follow-up)

Progression free survival*
Tumour Response
Toxicity Profile
Quality of life

*Progression free survival for first line treatment was calculated from the date of randomization to the first observation of disease progression or death from any cause and was also calculated for the first line and second line treatment (PFS2) and for first line, second line and third line treatment (PFS3).

Results
795 patients received at least one cycle of treatment; in the sequential group median number of cycles was 6 (range 1-45) in first line; 6 (range 1-35) in second line and 4 (range 1-14) in third line treatment and in combination group, the median number of cycles was 7 (range 1-42) in first line treatment and 4 (range 1-23) in second line.

Median time (interval between start of protocol treatment and a patient being off study) on treatment was 10.7 (range 0.1-45.1) months in the sequential group and 7.4 months (range 0.1-43.2) in the combination group (p=0.002).

At the time of analysis 84% (675/803) patients had died; 336 in the sequential group and 339 in the combination group. Median follow-up for the 128 patients still alive was 31.5 months (range 14-49months).

Median overall survival was 16.3 months (95% CI 14.3-18.1) for the sequential group and 17.4 months (95% CI 15.2-19.2) for the combination group.
Hazards Ratio for combination versus sequential treatment was 0.92 (95% CI 0.79-1.08) though the difference was not significant (p=0.3281). Multivariate analysis taking account of the stratification factors and age over 70 years; performance status 2 **(HR 1.44, 95% CI 1.02-2.06; p=0.04)** and abnormal serum LDH **(HR 1.9, 95% CI 1.68-2.33; p<0.0001)** were associated with worse survival.

In first line treatment, progression free survival was significantly longer in the combination treatment group than it was in the sequential treatment group (p=0.0002); **Hazard Ratio 0.77, 95% CI 0.67-0.89, p=0.0002**. Progression free survival was not affected when calculated to disease progression upon which the previous line of treatment was definitely discontinued and treatment free intervals after which the previous treatment was resumed, were ignored; 6.0, 95% CI 5.4-6.5 months in the sequential group versus 8.0, 95% CI 7.3-8.4 months in the combination group.
PFS2 was not significantly different between the two groups (p=0.15); likewise the difference between PFS3 in sequential treatment and PFS2 in combination treatment was not significant (p=0.19).

719 patients were assessable for response in first line treatment; 379 in the sequential group and 340 in the combination group.
Overall response rate in the first line was significantly better in the combination group than in the sequential group (p<0.0001).
Disease control rate was significantly better in the combination treatment group than in the sequential treatment group (p<0.001).
In second line treatment, the response rate and disease control rates were not significantly different between the two groups.

Results of the interim safety analysis in the first 400 patients that were enrolled were published separately. In the total patient cohort there was no significant difference in the frequency of grade 3-4 toxicity over all lines of treatment in either group (p=0.61).
Grade 3 hand-foot syndrome occurred more frequently with sequential treatment than with combination treatment (p=0.004). The frequency of thrombosis or embolism and of cardiac ischaemia did not differ significantly between the two treatment groups.

Grade 3-4 diarrhoea occurred significantly more frequently in the combination group than in the sequential group than in the sequential group (p<0.0001) as did grade 3-4 nausea (p=0.004), grade 3-4 vomiting (p=0.0002), febrile neutropenia (p<0.0001) and grade 3-4 neutropenia including febrile neutropenia (p<0.0001).
Grade 3 hand-foot syndrome occurred significantly more frequently in the sequential treatment group than in the combination treatment group (p=0.002).

Death, probably related to treatment, occurred in 11 patients (8 after sequential treatment and 3 after combination treatment; p=0.13). Causes of death included sepsis, diarrhoea and neutropenic fever.

Protocol violations were identified in 9/11 patients with violations including administration or irinotecan in patients with hyperbilirubinaemia, non-adherence to guidelines for dose reductions or delays of chemotherapy in case of diarrhoea.

6 patients (1 during sequential treatment and 5 during combination treatment) died suddenly (p=0.1); 4 of these patients had cardiopulmonary risk factors.

All cause 60 day mortality was not significantly different between the two groups (3% in the sequential group versus 4.5% in the combination group; p=0.27).

403 patients were assessable for quality of life (203 in the sequential treatment group and 200 in the combination treatment group). Change in financial problems and global health status were similar between the two groups.

The decrease in functioning was on average higher for combination treatment on average higher for combination treatment on all scales (cognitive, emotional, physical, role, and social).

The largest decrease was seen for role functioning, a decrease of 20 points for sequential treatment versus 24 points for combination treatment.

For symptomatic scales, changes were on average greater in the combination treatment except for pain and dyspnoea. The only significant difference in change was seen for diarrhoea: 20 points for sequential versus 28 points for combination treatment (p=0.002).

Tables

	Sequential Treatment (n=401)	Combination Treatment (n=402)	Total (n=803)
Age at randomisation (years)	64 (27-84)	63 (31-81)	63 (27-84)
>70 years	93 (23%)	81 (20%)	174 (22%)
Sex			
Male	252 (63%)	255 (63%)	507 (63%)
Female	149 (37%)	147 (37%)	296 (37%)
Performance Status			
0	257 (64%)	244 (61%)	501 (62%)
1	126 (31%)	142 (35%)	268 (33%)
2	18 (5%)	16 (4%)	34 (4%)
Previous Adjuvant Therapy			
Yes	55 (14%)	56 (14%)	111 (14%)
No	346 (86%)	346 (86%)	692 (86%)

Table 1: Patient characteristics (other factors reported include localisation of metastases, LDH at randomisation and site of primary tumour)

	Sequential Treatment (n=401)	Combination Treatment (n=402)	p value
Overall survival (months)	16.3 (14.3-18.1)	17.4 (15.2-19.2)	0.3281
1 year survival rate (%)	64% (59-69)	67% (62-72)	0.38
Progression free survival first line (months)	5.8 (5.1-6.2)	7.8 (7-8.3)	0.0002
PFS2 (months)	8.7 (8.2-9.6)	10.3 (9.3-10.8)	0.15
PFS3 (months)	10.3 (9-11.1)	NA	0.19*
Overall response rate (CR + PR)			
First line	77 (20%; 17-26%)	139 (41%; 36-46%)	<0.0001
Second line	23 (10%; 6-15%)	24 (12%, 7-17%)	0.46
Third line	5 (4%; 1-9%)		
Disease Control (CR+PR+SD)			
First line	280 (74%; 69-79%)	297 (87%; 82-90%)	<0.0001
Second line	162 (71%; 65-77%)	121 (63%; 56-70%)	0.06
Third line	72 (57%; 48-66%)		

*PFS3 in the sequential group versus PFS2 in the combination group

Table 2: Efficacy

	Sequential treatment (n=397)	Combination Treatment (n=398)	Total (n=795)	p value
Non haematological adverse events				
Overall grade 3-4 toxicity	271 (68%)	265 (67%)	536 (67%)	0.61
Hypersensitivity (total)	25 (6%)	18 (5%)	43 (5%)	0.27
Cardiac ischaemia/infarction (total)	14 (4%)	14 (4%)	28 (4%)	0.99
Thrombosis/embolism	35 (9%)	41 (10%)	76 (10%)	0.48
Grade 3 hand-foot skin	50 (13%)	26 (7%)	76 (10%)	0.004

reaction				
Diarrhoea				
Grade 3	83 (21%)	90 (23%)	173 (22%)	0.23
Grade 4	9 (2%)	17 (4%)	26 (3%)	
Nausea				
Grade 3	31 (8%)	39 (9%)	67 (8%)	0.45
Grade 4	0	1 (<1%)	1 (<1%)	
Stomatitis				
Grade 3	12 (3%)	5 (1%)	17 (2%)	0.15
Grade 4	0	1 (<1%)	1 (<1%)	
Vomiting				
Grade 3	24 (6%)	37 (9%)	61 (8%)	0.16
Grade 4	4 (1%)	2 (<1%)	6 (<1%)	
Neuropathy				
Grade 3	8 (2%)	12 (3%)	20 (3%)	0.18
Grade 4	1 (<1%)	0	1 (<1%)	
Non haematological adverse events				
Anaemia				
Grade 3	2 (<1%)	1 (<1%)	3 (<1%)	0.18
Grade 4	1 (<1%)	2 (<1%)	3 (<1%)	
Neutropenia				
Grade 3	17 (4%)	25 (6%)	42 (5%)	0.19
Grade 4	3 (1%)	4 (1%)	7 (1%)	
Febrile Neutropenia				
Grade 3	16 (4%)	24 (6%)	40 (5%)	0.18
Grade 4	3 (1%)	4 (1%)	7 (1%)	
Thrombocytopenia				
Grade 3	3 (1%)	3 (1%)	6 (1%)	0.99
Grade 4	1 (<1%)	1 (<1%)	2 (<1%)	

Table 3: Adverse events associated with sequential versus combination treatment (p values for grade 3 and 4 toxicities combined)

	Sequential Treatment (n=397)	Combination treatment (n=398)	Total (n=795)	p value
Hypersensitivity reaction (total)	7 (2%)	7 (2%)	14 (2%)	0.99
Cardiac ischaemia/infarction (total)	11 (3%)	13 (3%)	24 (3%)	0.68
Thrombosis/embolism (total)	28 (7%)	38 (10%)	66 (8%)	0.2.
Grade 3 hand-foot skin reaction	48 (12%)	23 (6%)	71 (9%)	0.002
Diarrhoea				
Grade 3	38 (10%)	87 (22%)	125 (16%)	<0.0001
Grade 4	5 (1%)	15 (4%)	20 (3%)	
Nausea				
Grade 3	14 (4%)	33 (8%)	47 (6%)	0.004
Grade 4	2 (<1%)	5 (1%)	7 (<1%)	
Stomatitis				
Grade 3	2 (<1%)	5 (1%)	7 (<1%)	0.16
Grade 4	0	1 (<1%)	1 (<1%)	
Vomiting				
Grade 3	9 (2%)	33 (8%)	42 (5%)	0.0002
Grade 4	1 (<1%)	1 (<1%)	2 (<1%)	
Haematological Adverse Events				
Anaemia				
Grade 3	1 (<1%)	0	1 (<1%)	0.56
Grade 4	1 (<1%)	1 (<1%)	2 (<1%)	
Neutropenia				
Grade 3	2 (<1%)	23 (6%)	25 (3%)	<0.0001
Grade 4	0	4 (1%)	4 (1%)	
Febrile Neutropenia				
Grade 3	2 (<1%)	22 (6%)	24 (3%)	<0.0001
Grade 4	0	4 (1%)	4 (1%)	
Thrombocytopenia				
Grade 3	0	0	0	0.32
Grade 4	0	1 (<1%)	1 (<1%)	

Table 4: Adverse events associated with sequential versus combination treatment first line (p values presented for grade 3 and 4 toxicities combined)

General comments

Kaplan Meier curve presented for overall survival by treatment arm

Citation: Martoni AA, Pinto C, Di Fabio F Lelli G et al (2006) Capecitabine plus oxaliplatin (XELOX) versus protracted 5-fluorouracil venous infusion plus oxaliplatin (PVIFOX) as first line treatment in advanced colorectal cancer: A GOAM phase II randomised study (FOCA trial)

Design: Phase II randomised trial

Country: Italy

Setting:

Aim: to compare pviFOX with XELOX in the first line treatment of advanced colorectal cancer

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Inclusion criteria
Histological diagnosis of colorectal carcinoma
Measurable tumour lesions
Karnofsky performance status ≥70
Age < 18 years
Life expectancy >3 months
No prior chemotherapy for metastatic disease
Adjuvant therapy terminated >6 months before
Haemoglobin levels >10g/dl
Neutrophil count ≥2000/mm^3
Platelet count ≥100,000/mm^3
Serum creatinine ≤1.2mg/dl
Creatinine clearance according to Cockcrof-Gault formul >55ml/min
Bilirubin and serum transaminase levels ≤3 times the normal values
Staging examinations carried out within 30 days of the beginning of treatment
Written informed consent

Exclusion criteria
Patients with potentially resectable lesions
Unresolved internal obstruction
Previous malignant neoplasia (except for non-melanoma skin carcinoma and adequately treated *in situ* carcinomas of the uterine cervix)
Dementia or alterations in mental status

Sample Size
The study was designed to test the null hypothesis that the objective remission rate was less than 0.2 a rate which would indicate insufficient benefits; the smallest response probability suggesting that one regimen warranted further studies was 0.35 with a two-sided alpha of 0.05 and a power of 80% (beta=0.2). On these grounds, the number of patients to be treated per arm was 56.

Randomisation Method
Not reported

Population
N=122 patients randomised, patients were subsequently determined ineligible.

N=118 analysed

Study Duration
Recruitment stage: December 2001 to March 2005

Interventions
Arm A: on day 1, dexamethasone 20mg in 100 cc of saline by the intravenous route in 15 min, granisetron 3mg in 100cc of saline i.v. in 15 min, Oxaliplatin 130mg/m^2 in 500cc of 5% glucose solution i.v. in 2hours and at the end 5-FU 250mg/m^2/day in c.i. from the 1st to the 21st day. Before starting therapy, a central venous catheter (CVC) implant was requested for the administration of 5-FU by elastomeric pump to allow for a protracted 7 day long infusion.

Arm B: Oxaliplatin on day 1 (as arm A) and oral Capecitabine 1000mg/sm bid from the 1st to the 14th day. Every patient in arm B was given a diary to help in the administration of Capecitabine and the monitoring of side-effects at home.

Outcomes
Tumour Response Rate

Time to Progression (defined as the time interval between start of treatment and evidence of progression independent of objective response)
Toxicity

Results
Treatment Delivery
A total of 739 therapy cycles were administered: patients in Arm A received a higher number of cycles (424 versus 315).
Median dose intensity was 100% for all three cytotoxic drugs
There was a higher rate of treatment suspension before completion of 6 cycles in Arm A (37.7%) compared with Arm B (27.8%) due to higher suspension resulting from disease progression and toxicity.

48.2% (n=27) of patients in arm A received full doses of 5-FU and OXA and 43.5% (n=27) of patients in arm B received full doses of Capecitabine and oxaliplatin.

Dose reduction was required for pviFU alone in 42.8% (n=27) in arm A, for Capecitabine in 37% (n=23) in arm B and oxaliplatin alone in 17.8% (n=10) in arm A and in 40.3% (n=25) in arm B.

Safety
There were statistically significantly higher rates of stomatitis observed in arm A compared with arm B (25.9% versus 13.1%, p=0.028).

The system of protracted venous infusion of 5-FU in arm A was generally well accepted by patients with minor limitations to daily activities and social life; 8 patients had venous line problems, including infection, thrombosis, bad compliance, dislodged, unthreading of the needle from CV port or sepsis, resulting in temporary suspension (n=6) or to stop 5-FU infusion (n=2).

Grade 3 toxicity resulted in the suspension of treatment in 5 patients (4 in arm A (diarrhoea (3) and stomatitis (1)) and 1 in arm B (diarrhoea and vomiting)).
3 patients died early on during treatment, 1 in arm A due to rapid general deterioration in conditions following the first treatment cycle and 2 in arm B, one due to G4 diarrhoea, dehydration and acute renal failure during the first cycle and one died suddenly following first cycle so no information could be collected.

Efficacy
8 patients (3 in Arm A and 5 in Arm B) were not evaluable as they had received only one cycle or had metastatic lesions documents only by PET.
Median response duration of CR+PR was 8 months (1-14 months) in Arm A and 9 months (4-25 months) in arm B and the median duration of stable disease was 8.5 months (4-13 months) in arm A and 6 months (3-13 months) in arm B.

There was no significant difference between the arms regarding the number of patients that experienced improvement in performance status or disease related symptoms.

Time to Progression
Timing of clinical and imaging test re-evaluation was equally distributed between the two arms: 68.6% of patients in arm A and 69% in arm B had a first re-evaluation before the fourth cycle.
Median time to progression was 7 months (95% CI 8-10 months): at the time of reporting 11 patients in arm A and 15 patients in arm B had not shown disease progression.
At the time of reporting, 92 patients had progressed, 45 in arm A and 47 in arm B while 60 patients had received second line chemotherapy (25 in arm A and 35 in arm B).
Second line chemotherapy consisted primarily of FOLFIRI (n=41), 6 patients received other Irinotecan based regimens and the remaining patients received other regimens (not detailed).
7.6% (n=9) patients underwent surgical resection for liver metastases after first line chemotherapy (5 in arm A and 4 in arm B).

Tables

	Arm A pviFOX	Arm B XELOX	Total
	N (%)	N (%)	N (%)
No of eligible patients	56	62	118
Gender			
M	28 (50)	33 (53.2)	61 (51.7)
F	28 (50)	29 (46.8)	57 (48.3)
Age			
Median	64	67	67
Range	41-79	25-79	25-79
Karnofsky performance status			
Median	90	90	90
Range	70-100	70-100	70-100
Adjuvant Chemotherapy			
Yes n (%)	13 (23.2)	18 (29.9)	31 (26.3)
No n (%)	43 (76.8)	44 (71)	87 (73.3)

Table 1: Patient Characteristics (other factors reported include primary tumour site, primary tumour surgical resection, stage at treatment start, matastases localisation, no. of metastatic sites, CEA plasma levels)

	pviFOX	XELOX	Total
Total no. of delivered cycles	315	424	739
Complete cycles (2 drugs)	307	363	670
Oxaliplatin only	7	5	12
5-FU only	1	-	1
Capecitabine only	-	56	56
Complete Cycles (2 drugs)			
Median (range)	6 (1-10)	6 (1-10)	6 (1-10)
Dose Intensity: Median (Range)			
Oxaliplatin	100% (82-100)	100% (15-100)	100% (15-100)
5-FU	100% (13-100)	-	100% (13-100)
Capecitabine	-	100% (14-100)	100% (14-100)

Table 2: Delivered Treatment

	pviFOX	XELOX	Total
	N (%)	N (%)	N (%)
Total No. of treatment suspension reasons	20 (38)	16 (27)	36 (32)
Progression	12 (23)	10 (17%)	22 (19%)
Refusal	1 (2)	1 (2%)	2 (2%)
Death	1 (2)	2 (3%)	3 (3%)
Toxicity	4 (7.5%)	1 (2%)	5 (4%)
Other	2 (4%)	2 (3%)	4 (3.5%)

Table 3: Treatment suspension before 6 cycles

	pviFOX N (%)				
Grade	0	1	2	3	4
No of evaluable patients	64				
Neutropenia	43 (79.6)	7 (13)	4 (7.4)		
Anaemia	29 (53.7)	20 (37)	4 (7.4)	1 (1.9)	
Thrombocytopenia	38 (70.4)	14 (25.9)	1 (1.9)	1 (1.9)	
Diarrhoea	18 (33.3)	14 (25.9)	15 (27.8)	6 (11.1)	1 (1.9)
Stomatitis	40 (74.1)	6 (11.1)	6 (11.1)	2 (3.7)	
Epigastralgia	50 (92.6)	2 (3.7)	2 (3.7)		
Hyperbilirubinemia	44 (81.5)	7 (13)	2 (3.7)	1 (1.9)	
SGOT, SGPT increase	38 (70.4)	10 (18.5)	6 (11.1)		
Hand-Foot Syndrome	51 (94.4)	2 (3.7)		1 (1.9)	
Neurotoxicity (chronic)	12 (22.2)	23 (43.6)	9 (16.7)	10 (18.5)	
Acute Neurotoxicity	**Yes**	**No**			

(pharyngo-laryngospasm)					
	13 (24.1)	41 (75.9)			

XELOX N (%)					
Grade	0	1	2	3	4
No of evaluable patients	61				
Neutropenia	46 (75.4)	9 (14.8)	6 (9.8)		
Anaemia	35 (57.4)	24 (39.3)	2 (3.3)		
Thrombocytopenia	30 (49.2)	24 (39.3)	5 (8.2)	2 (3.3)	
Diarrhoea	33 (54.1)	15 (24.6)	8 (13.1)	4 (6.6)	1 (1.6)
Stomatitis	53 (86.9)	8 (13.1)			
Epigastralgia	53 (86.9)	7 (11.5)		1 (1.6)	
Hyperbilirubinemia	45 (73.8)	9 (14.8)	6 (9.8)	1 (1.6)	
SGOT, SGPT increase	45 (73.8)	14 (23)	1 (1.6)	1(1.6)	
Hand-Foot Syndrome	57 (93.4)	1 (1.6)	3 (4.9)		
Neurotoxicity (chronic)	13 (21.3)	15 (24.6)	18 (29.5)	15 (24.6)	

Acute Neurotoxicity (pharyngo-laryngospasm)	Yes	No			
	15 (24.2)	47 (75.8)			

Total N (%)					
Grade	0	1	2	3	4
No of evaluable patients	115				
Neutropenia	89 (77.4)	16 (13.9)	10 (8.7)		
Anaemia	64 (55.7)	44 (38.3)	6 (5.2)	1 (0.9)	
Thrombocytopenia	68 (59.1)	38 (33)	6 (5.2)	3 (2.6)	
Diarrhoea	51 (44.3)	29 (25.2)	23 (20)	10 (8.7)	2 (1.7)
Stomatitis	93 (80.9)	14 (12.2)	6 (5.2)	2 (1.7)	
Epigastralgia	103 (89.6)	9 (7.8)	2 (1.7)	1 (0.9)	
Hyperbilirubinemia	89 (77.4)	16 (13.9)	8 (7)	2 (1.7)	
SGOT, SGPT increase	83 (72.2)	24 (20.9)	7 (6.1)	1 (0.9)	
Hand-Foot Syndrome	108 (93.9)	3 (2.6)	3 (2.6)	1 (0.9)	
Neurotoxicity (chronic)	25 (21.7)	38 (33)	27 (23.5)	25 (21.7)	

Acute Neurotoxicity (pharyngo-laryngospasm)	Yes	No			
	28 (24.1)	88 (75.9)			

Table 4: Side Effects

	pviFOX	XELOX	Total
	N (%)	N (%)	N (%)
Total no. of patients	56	62	118

Complete Response (CR)	1 (1.7)	3 (4.8)	4 (3.3)
Partial Response (PR)	26 (46.4)	24 (38.7)	50 (42.4)
CR +PR	27 (48.2)	27 (43.5)	54 (45.8)
95% CI	34.6 – 61.9	31 – 56.7	36 – 54.4
Stable Disease	13 (23.2)	20 (32.3)	33 (27.9)
Progressive Disease	13 (23.2)	10 (16.1)	23 (19.5)
Not evaluable	3 (5.4)	5 (8.1)	8 (6.8)

Table 5: Objective Response

	pviFOX	XELOX	Total
	N (%)	**N (%)**	**N (%)**
Asthenia	15/27 (56)	11/26 (42)	26/53 (49)
Anorexia	9/15 (60)	4/10 (40)	13/25 (52)
Pain	16/24 (67)	15/23 (65)	31/47 (66)
Karnofsky performance Status	8/16 (50)	8/17 (47)	16/33 (48)

Table 6: Symptomatic Improvement

General comments

Kaplan Meier curves for time to progression

Objective response and toxicity were evaluated according to RECIST criteria and CTC criteria respectively with the exception of neurotoxicity that was evaluated according to the LEVI scale.

Time to progression (TTP) was considered as the time interval between the start of therapy and the evidence of progression independently of the objective response.

Citation: Porschen R, Arkenau HT, Kubica S, Greil R et al (2007) Phase III study of Capecitabine plus oxaliplatin compared with fluorouracil and leucovorin plus oxaliplatin in metastatic colorectal cancer: A final report of the AIO colorectal study group *Journal of Clinical Oncology* 25;27:4217-4223
Comparison: CAPOX versus FUFOX (1st line)
Design: Phase III randomised Trial **Country**: Germany (68 institutes) and Austria (1 institute) **Setting:** **Aim**: To evaluate the efficacy and toxicity of CAPOX compared with infusional FU/FA plus oxaliplatin (FUFOX)
Inclusion criteria ≥18 years ECOG performace status ≤2 Life expectancy of >3 months Histologically confirmed colorectal cancer Adjuvant/neoadjuvant treatment completed more than 6 months prior to the start of treatment Measurable tumlur parameters according to the Response Evaluation Criteria in Solid Tumours
Exclusion criteria Prior treatment for metastatic colorectal cancer Previous malignancy within 5 years (apart from basal cell skin cancer or in situ carcinoma of the cervix) Central nervous system metastasis Heart disease grade New York Heart Association classification III/IV Myocardial infarction within 6 months Renal Impairment Abnormal liver function tests White blood cell count <3000/µl or platelets <100000/µl Pregnant or lactating women
Sample Size The study was designed to show non-inferiority of the Capecitabine based arm with respect to progression free survival. The sample size was based on the assumption of equal efficacy of both arms, a hypothetical inferiority of CAPOX in median progression free survival of two months or more (7 vs. 9 months, corresponding to a hazard ration of 1.29 or an absolute different of 9% in the progression free survival rate after 9 months) had to be excluded with a 95% CI and a power of 80%.
Randomisation Method Computer based randomisation performed centrally by fax with stratification for ECOG performance status (0-1 vs. 2), WBC count (<8,000 Vs. ≥8,000/µl, alkaline phosphatase (AP <300 vs. ≥300/µl) and number of metastatic sites (1 vs. >1 site).
Population N=476 randomised, 2 patients excluded (one due to double randomisation and one due to neuroendocrine tumour histology. CAPOX N=241 FUFOX N=233
Study Duration Recruitment Phase: August 2002 to August 2004 Cut off date for analysis was January 31st, 2007.
Interventions Arm A: Oxaliplatin 50mg/m^2 2-hour infusion; Folinic acid 500mg/m^2 2-hour infusion and FU 2,000 mg/m^2 22-hour infusion on days 1, 8, 15 and 22. After the 4th cycles, oxaliplatin was administered only on days 1 and 15 of each cycles to reduce the risk of oxaliplatin related cumulative peripherally neuropathy. Arm B: Oxaliplatin 70mg/m^2 2-hour infusion days 1 and 8 every 3 weeks; Capecitabine 1,000mg/m^2 bid orally days 1-14 every three weeks. After the 6th cycle, oxaliplatin was administered only on day 1 of each cycle to reduce the

risk of oxaliplatin related cumulative peripheral neuropathy.

Outcomes
Progression free survival (defined as the interval between random assignment and first recording of progression or death)

Response Rates
Overall Toxicity
Time to Treatment failure

Results
Patient and tumour characteristics were well balanced between the arms with respect to stratification factors and baseline characteristics.

Toxicity
A total of 235 patients in the CAPOX arm received a total of 1,562 cycles (median, 6 cycles/patient; range 1-28 cycles) and 231 patients in the FUFOX arm received a total of 1,073 cycles (median 5 cycles/patient, range 1-17 cycles).
Mean treatment duration in the CAPOX arm was 20.6 weeks (SD ±13.5) and in the FUFOX arm was 21.7 weeks (SD±13.2)

The most frequent nonhaematologic grade 3/4 toxicity was neuropathy (25% in the CAPOX arm verus 27% in the FUFOX arm) while grade 3/4 haematologic toxicities were infrequent and manageable in both arms. Other grade 3/4 toxicities (e.g. nausea, vomiting and diarrhoea) were similar in both arms.
Grade 2/3 hand-foot syndrome occurred more often in the CAPOX arm (10% versus 4%; p=0.028).
Dose reductions due to toxicity were necessary in 39% of patients in the CAPOX arm and in 45% of patients in the FUFOX arm.
The oxaliplatin dose intensity was 94.2% (SD±24.8%) in the CAPOX arm and 95% (SD±38.3% in the FUFOX arm. The calculated mean dose per cycle for FU was 7,127.2mg (SD±1,237.2) and for Capecitabine 26.801.5mg (SD±3232.2).
Reasons for discontinuation of treatment included tumour progression (46% in CAPOX versus 37% in FUFOX), death as a result of tumour (7% in CAPOX versus 5% in FUFOX), death from other causes (in both arms), severe adverse events (21% in CAPOX versus 24% in FUFOX), patient refusal (8% in CAPOX versus 14% in FUFOX), protocol violation (1% in CAPOX versus 3% in FUFOX) and other reasons (14% in both arms).

Objective Tumour Response and Progression Free Survival
Median follow-up was 17.3 months in both arms.
A total of 395 patients showed sign of tumour progression and objective tumour response rates were as follows: CAPOX 48% (95% CI, 41% to 54%; complete response, 2%, partial response 46%, stable disease 28%) and FUFOX, 54% (95% CI, 47% to 60%; complete response 6%, partial response 48%, stable disease 23%) (p=0.7). Secondary surgery was performed in 4 patients in the CAPOX arm and in 10 patients in the FUFOX arm.

Median progression free survival was 7.6 months (CAPOX, 7.1 months, FUFOX 8 months) **Hazard Ratio 1.17, 95% CI 0.96 to 1.43, p=0.117)**.
On multivariate analysis more than one metastatic site, higher WBC count and increase AP levels were the only independent prognostic factors.

Time to treatment failure was 5.1 months in the CAPOX arm and 6 months in the FUFOX arm; **Hazard Ratio 1.14; 95% CI 0.94 to 1.39, p=0.19)**.

Overall Survival
At the time of publication, there were 370 deaths of 470 assessable patients and median overall survival was 17.3 months (16.8 months in the CAPOX arm and 18.8 months in the FUFOX arm); **Hazard Ratio 1.12, 95% CI 0.92 to 1.38; p=0.26)**.
Independent prognostic factors for improved overall survival were age <70 years, performance status 0-1, WBC less than 8,000/µl and AP levels less than 300 U/L.

The 60 day mortality was 4.1% in the CAPOX arm and 4.3% in the FUFOX arm.

Second line therapy
66% of patients in both arms went on to receive second line therapy with the majority receiving Irinotecan based

chemotherapy (81% in both arms).
Additional treatments included reintroduction with oxaliplatin (CAPOX 13%; FUFOX 21%), cetuximab (CAPOX 22%; FUFOX 21%) or mitomycin (CAPOX 9%; FUFOX 9%).
On subsequent treatment lines, patients in the CAPOX arm 43% changed to FU and 29% continued with Capecitabine. In the FUFOX arm, 56% continued with FU and 30% received Capecitabine.
56% of the study population received all three drugs; FU, oxaliplatin and irinotecan (CAPOX 57% andFUFOX 55%).

Tables

	CAPOX (n=241)	FUFOX (n=233)
	N (%)	N (%)
Sex		
Male	150 (62)	146 (63)
Female	91 (38	87 (37)
Age, years		
Median	66	64
Range	32-81	34-86
Previous Adjuvant Treatment		
Chemotherapy	75 (31)	67 (29)
No Chemotherapy	164 (69)	164 (71)
Radiotherapy	35 (15)	30 (13)
No Radiotherapy	205 (85)	201(87)
ECOG Performance Status		
0-1	219 (91)	216 (93)
2	22 (9)	17 (7)

Table 1: Patient Characteristics (other factors reported include Alkaline phosphatase levels, WBC counts and number of metastatic sites)

General comments
Progression free survival was defined as the interval between random assignment and the first recording of disease progression or death.

Efficacy analysis was based on the intent to treat population

Kaplan Meier curves are presented for progression free survival and overall survival

Citation: Seymour MT, Maughan TS, Ledermann JA, Topham C et al (2007) Different strategies of sequential and combination chemotherapuy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial *Lancet* 370;9582:143-152
Comparison: FOLFOX versus FOLFIRI versus Irinotecan (1st and 2nd line)
Design: Randomised phase III trial **Country**: UK (59 centres), Cyprus (1 centre) **Setting:** **Aim**: To establish the best sequence of the first two cytotoxic drugs, fluorouacil and either irinotecan or oxaliplatin when treating patients with poor prognosis advanced colorectal cancer
Inclusion criteria Histologically confirmed colorectal adenocarcinoma with inoperable metastatic or locoregional disease. Disease measurable by RECIST WHO performance status 0-2 No previous chemotherapy for metastatic disease White blood count >4x10^9/L Platelet count >150x10^9/L Serum bilirubin concentration <1.25xupper limit of normal Alkaline phosphatase concentration <5xupper limit of normal Calculated glomerular filtration rate or ADTA clearance of >50ml/mon Older than 18 years
Exclusion criteria Uncontrolled medical co-morbidity likely to compromise treatment
Sample Size The planned sample size was 2100 patients; 700 in each treatment arm (A, B and C) with 350 in each subgroup of arms B and C. An anticipated 2-year survival of 15% in the control group would detect an improvement of 7.5% (to 22.5%) in any pair wise comparison of control versus an individual novel group (1050 patients, one-sided log rank, 80% power, 1% significance to correct for multiple comparisons).
Randomisation Method Minimisation procedure with stratification for clinician, performance status, primary tumour resected or in situ and distant metastases (present or absent)
Population N=2135 patients randomised Arm A N=710 Arm B$_{IR}$ N=356 and Arm B$_{OX}$ N=356 Arm C$_{IR}$ N=356 and Arm C$_{OX}$ N=357
Study Duration Recruitment Phase: May 1st 200-December 31st 2003
Interventions Arm A (FU regimen 1st line and Ir regimen 2nd line)): First line treatment with fluorouracil, continuing until treatment failure and in patients fit enough for second line, single agent Irinotecan was given. Arm B (FU regimen 1st line and either IrFU or OxFU 2nd line): Deferred combination chemotherapy, fluorouracil first line and combination chemotherapy second line in patients that were fit enough. Arm B was subdivided into two groups in a 1:1 ratio at randomisation. B$_{ir}$ received irinotecan + fluorouracil second line and B$_{ox}$ received oxaliplatin + fluorouracil second line. Arm C (IrFU or OxFU 1st line): First line combination treatment which continued until treatment failure. Arm C was also subdivided in a 1:1 ratio with patients in C$_{ir}$ receiving irinotecan + fluorouracil first line and C$_{ox}$ receiving oxaliplatin + fluorouracil first line.

	Fluorouracil	**Irinotecan**	**Irinotecan/Fluorouracil**	**Oxaliplatin/Fluorouracil**

Regimen	FU	Ir	IrFU	OxFU
Intravenous drug schedules	Levofolinate 175mg (2h) then FU 400mg/m^2 (bolus) FU 2800mg/m^2 (46hr)	Irinotecan 350mg/m^2 (30-90 mins) (300mg/m^2 if aged >70 years or performance status 2)	Irinotecan 180mg/m^2 (30 mins) then levofolinate 175mg (2hr) then FU 400 mg/m^2 (bolus) FU 2400mg/m^2 (46hr)	Oxaliplatin 85mg/m^2 plus levofolinate 175mg (concurrent, 2hr) then FU 400 mg/m^2 (46hr)
Dexamethasone	8 mg intravenously bolus day 1 Oral days 2-4 (decreasing course)	8mg intravenously bolus day 1 Oral days 2-4 (decreasing course	8mg intravenously bolus day 1 Oral days 2-4 (decreasing course	8mg intravenously bolus day 1 Oral days 2-4 (decreasing course)
Cycle Repeat	14 days	21 days	14 days	14 days

Table 1: Treatment Regimens

Outcomes

Unclear what the primary outcome of the study is

Outcomes appear to include response rates, progression free survival, overall survival and quality of life.

Results

Treatment began as soon as possible after randomisation and breaks in treatment (e.g. for holidays) were not allowed within the first 3 months and were restricted to 4 weeks during the second 3 months. Thereafter patients with responding or stable disease were allowed to pause treatment, resuming the same treatment provided progression did not take place within 12 weeks of last treatment.

Second line treatment in Arm A and B were started provided the patient met the fitness criteria of the regimen, at the first evidence of progression during – or within 12 weeks if pausing – first line fluorouracil.

Patients in Arm A and B received a median of 11 cycles (range 1-51) of the allocated 1st line fluorouracil regimen and patients in arm C received a median of 12 cycles (1-36). Patients in Arm C$_{OX}$ received a median of 12 cycles (1-58) of which oxaliplatin was included for 94% of cycles (3506/3740), median 11 cycles (1-58) per patient) the remainder were given FU alone after persistent neuropathy.

Of the 1348 patients in whom FU treatment failed at the time of analysis, 56% (n=750) had received the planned 2nd line regimen and 10% (n=131) received an alternative 2nd line regimen; 35% of patients had moved to terminal care or died without receiving further treatment.

Median amount of time spent on 2nd line combination therapy was similar in all groups. Patients in arm A received a median of 4 cycles (1-24) of irinotecan every 3 weeks, patients in group B$_{IR}$ received a median of 6 cycles (1-23) of irinotecan + fluorouracil every 2 weeks and patients in group B$_{OX}$ received a median of 6 cycles (1-24) of which oxaliplatin was included fro 1582/1688 (94%) of cycles (median 6 (1-21) per patient).

49% of patients (669/1368) in who allocated treatment failed had received salvage chemotherapy at the time of publishing. The proportion was higher for those in arm C (358/649, 55%) for whom treatment comprised a single line of treatment compared with arms A and B (311/719, 43%) who had already received two lines of therapy at the time of failure.

Changes to salvage chemotherapy recommendations in December 2002 meant that patients could receive all three drugs at some point, however at the time of analysis only 23% (n=482) of patients had done so with the proportion who had received all three higher in arm C (33%) than in arms A (16%) or arm B (19%). The proportions were similar for patients allocated to irinotecan in arms B and C (25%) and patients allocated to oxaliplatin (27%).

All regimens were well tolerated and sage with treatment delays or modification in less than 40% of patients at any point for all treatment regimens with one exception; 1st line oxaliplatin was delayed or modified in 50% of patients, usually for neurosensory of haematological toxic effects after several cycles.

29% (n=610) of patients had serious adverse events likely caused by the trial drugs and a further 12% (n=262) had serious adverse events related to venous access.

24 deaths were reported as definitely or probably precipitated by trial treatment with no significant difference between the regimens.

18/2093 patients receiving first line treatment and 6/755 patients receiving second line treatment died. Death occurred within 30 days of the final dose of the first line treatment in a further 130 patients and within 30 days of last second line chemotherapy in a further 42 patients. There was no imbalance in all cause mortality at day 60.

At the time of publication, 86% (n=1839) of patients had died and median follow up was 26.5 months for survivors. Survival in arms A and B was similar and was slightly better compared with arm A.

2-year survival was 22% in arm A, 25% in arm B and 28% in arm C. In pairwise log rank tests overall comparison of arm C with control (Arm A) reached p=0.02 but did not satisfy the level of p<0.01 required to confirm superiority in the context of multiple setting.

Survival was better in all subgroups of arms B and C when compared with that of arm A but only irinotecan used in first line combination was significantly better.
There was no significant difference between irinotecan and oxaliplatin whether used in the first line combination setting, second line combination or at any time.

An additional non-inferiority analysis was added to compare deferred combination treatment (arm B) with first line combination (arm C) as a result of changes to standard practice. **Hazards Ratio, 1.06 (90% CI 0.97-1.17)**. These data exclude and inferiority margin of HR 1.18 or more, corresponding to a reduction of more than 5% in 2 year survival or a difference in median survival of more than 2.3 months.
Results for the individual drugs are similar but the individual comparisons are not sufficiently powered to conclude non-inferiority.

Response rates and progression free survival for first line IrFU and OxFU regimens were significantly better than for fluorouracil alone. For patients in arm A or B that went on to receive their allotted second line treatment, the combination therapies gave higher response rates than Irinotecan alone though the rates of progression free survival were not significantly improved.

During the first 18 months from randomisation, the WHO performance status fell from 0.7 to 1.1 but no differences were observed between the groups. Mean overall quality of life score varied very little over time or across regimens with no advantage or disadvantage detected at 3 and 6 months associated with first line combination treatment (arm C).

There was no evidence that the effect of treatment on survival was different in any of the subgroups of patients defined by baseline characteristics.

Tables

	Arm A	Arm B		Arm C	
	FU followed by Irinotecan single agent	FU followed by Irinotecan combination	FU followed by Oxaliplatin combination	Irinotecan combination	Oxaliplatin Combination
Total	710	356	356	356	357
Male	494 (70%)	244 (69%)	235 (66%)	240 (67%)	247 (69%)
Age (years)	63 (56-69)	64 (57-70)	64 (56-69)	64 (57-69)	64 (56-69)
Prior Adjuvant Chemotherapy	163 (23%)	96 (27%)	89 (25%)	94 (26%)	94 (26%)
WHO performance status					
0	294 (41%)	147 (41%)	147 (41%)	147 (41%)	148 (41%)
1	355 (50%)	181 (51%)	178 (50%)	179 (50%)	179 (50%)
2	61 (9%)	28 (8%)	31 (9%)	30 (8%)	30 (8%)

Table 2: Patient Characteristics (other factors reported include primary tumour site, baseline WBC count, distant metastases, number of disease sites, disease sites)

	First line treatment			Second line treatment		
	FU	IrFU	OxFU	Ir	IrFU	OxFU
Study groups	A, B$_{IR}$, B$_{OX}$	C$_{IR}$	C$_{ox}$	A	B$_{IR}$	B$_{ox}$
Patients Assessed	1305	337	339	349	180	199
Neutropenia	118 (9%)	65 (19%)	94 (28%)	43 (12%)	32 (18%)	50 (25%)
Nausea or vomiting	55 (4%)	32 (10%)	31 (9%)	31 (9%)	9 (5%)	14 (7%)
Stomatitis	25 (2%)	6 (2%)	6 (2%)	3 (1%)	2 (1%)	6 (3%)
Diarrhoea	74 (6%)	38 (12%)	34 (10%)	58 (17%)	14 (8%)	16 (8%)
Hand/Foot Syndrome	22 (2%)	4 (1%)	4 (1%)	2 (1%)	2 (1%)	6 (1%)
Sensory Neuropathy	11 (1%)	5 (2%)	34 (10%)	3 (1%)	2 (1%)	6 (3%)
Alopecia	3 (<1%)	8 (2%)	3 (1%)	34 (10%)	5(3%)	0 (0%)
Lethargy	174 (13%)	66 (20%)	73 (21%)	59 (17%)	37 (21%)	41 (20%)
Pain	176 (14%)	73 (22%)	60 (18%)	79 (23%)	26 (14%)	39 (20%)
Treatment related death	11 (1%)	3 (1%)	4 (1%)	3 (1%)	1 (1%)	2 (1%)
60 day all cause mortality	52 (4%)	17 (5%)	14 (4%)	31 (9%)	13 (7%)	12 (6%)

Table 3: Grade 3 or 4 adverse events reported

Log Rank test Comparison	Hazard Ratio (95% CI)	p-value (two-sided test)	Median Survival in Reference Group (group A)[1]	Difference (95% CI) between reference group and comparator[2]
Are any of the novel plans better than the control				
A vs. B	0.94 (0.84-1.05)	0.24	13.9	0.9 (-0.7-2.6)
A vs. B_{IR}	0.91 (0.79-1.03)	0.16	13.9	1.4 (-0.4-3.7)
A vs. B_{OX}	0.97 (0.85-1.11)	0.65	13.9	0.4 (-1.4-2.5)
A vs. C	0.88 (0.79-0.98)	0.02	13.9	1.9 (0.3-3.7)
A vs. C_{IR}	0.84 (0.73-0.96)	0.01	13.9	2.6 (0.6-5.1)
A vs. C_{OX}	0.93 (0.81-1.06)	0.26	13.9	1.1 (0.8-3.3)
Does the choice of Irinotecan or Oxaliplatin affect survival				
[B_{IR} + C_{IR}] vs. [B_{OX} + C_{OX}]	1.09 (0.97-1.21)	0.14	15.8	-1.3 (-2.7-0.5)
B_{IR} vs. B_{OX}	1.06 (0.91-1.24)	0.46	15	-0.8 (-2.9-1.5)
C_{IR} vs. C_{OX}	1.12 (0.95-1.31)	0.18	16.7	-1.8 (-4.0-0.9)

[1]Group A is the reference group for whether any of the novel plans are better than control and irinotecan is the reference group for whether the choice of irinotecan or oxaliplatin should affect survival
[2]Difference calculated by application of log rank HR to median survival in control group

Table 4: Overall survival log rank comparison

Log Rank test comparison	HR (90% CI)	Median survival (months)		Confidently excludes detriment with strategy B larger than:[1]
		Arm C (reference)	Arm B	
C vs. B	1.06 (0.97-1.17)	15.9	15.1	2.3 months
C_{IR} vs. B_{IR}	1.08 (0.94-1.24)	16.7	15	3.2 months
C_{OX} vs. B_{OX}	1.04 (0.92-1.19)	15.4	15.2	2.5 months

[1]Estimation of the largest detriment to the comparator group that cannot be reliably excluded. It is calculated by u sing the upper end of the 90% CI in the following way: comparator median-([1/upper end of 90% CI]xcomparator median)

Table 5: Is deferred combination (arm B) non-inferior to first line combination (arm C)

	First line treatment			Second line treatment		
	Fluorouracil	Irinotecan + Fluorouracil	Oxaliplatin + Fluorouracil	Irinotecan	Irinotecan + Fluorouracil	Oxapliplatin + Fluorouracil
Study Groups	A, B_{IR}, B_{OX}	C_{IR}	C_{OX}	A	B_{IR}	B_{OX}
Total Number Treated (receiving ≥1 dose)	1393	342	344	364	185	201
Complete Response	57	19	29	8	1	3
Partial Reponse	335	147	166	31	29	43
Stable Disease (≥12 weeks)	487	89	72	107	68	74
Progressive Disease	249	40	40	149	52	50
Not Assessed[1]	265	47	37	69	35	31
Response Rate (CR+PR)[2]	28%	49% (p<0.001)[3]	57% (p<0.001)[3]	11%	16% (p=0.07)[4]	23% (p<0.001)[4]
Disease Control ≥12 weeks (CR+PR+SD)[2]	63%	75% (p<0.001)[3]	78% (p<0.001)[3]	40%	53% p=0.004)[4]	60% (p<0.001)[4]
Median Progression Free Survival (months)	6.3	8.5 (p<0.001)[3]	8.7 (p<0.001)[3]	4.3	4.4 (p=0.75)[4]	4.8 (p=0.74)[4]

[1]Includes any reason for failure to assess radiologically
[2]Denominator includes all patients who received one or more dose, whether or not subsequently assessed
[3]Compared with fluorouracil (X^2 test for response rate and disease control; log rank test for PFS
[4] Compared with Irinotecan (X^2 test for response rates and disease control; log rank test for PFS
[5]Responses did not need to be confirmed by a second scan

Table 6: RECIST[5] response and progression free survival

	Arm B	Arm C	O-E	Variance	Hazard Ratio (95% CI)
	No. events/No. entered	No. events/No.entered			
Sex					
Male	405/480	423/488	3.11	206.14	1.02 (0.89-1.16), p=0.828)
Female	211/231	183/225	16.54	97.89	1.18 (0.97-1.44), p=0.095)
					Interaction p=0.21
Age (Years)					
<60	203/230	201/252	19.07	99.65	1.21 (1.00-1.47), p=0.056)
60-69	258/304	257/290	-9.48	127.99	0.93 (0.78-1.10), p=0.402)
70+	155/178	148/171	8.64	74.94	1.12 (0.89-1.41), p=0.318)
					Interaction p=0.51

Primary Site					
Colon	412/467	392/452	3.27	200.09	1.02 (0.88-1.17), p=0.817
Rectum	200/237	206/253	14.21	100	1.15 (0.95-1.40), p=0.155
					Interaction p=0.31
Prior Adjuvant Fluorouracil					
Yes	155/185	159/189	-1.61	77.97	0.98 (0.78-1.22), p=0.855
No	460/523	447/523	20.51	225.33	1.10 (0.96-1.25) p=0.172
					Interaction p=0.40
WHO Performance Status					
0	243/293	240/295	7.34	120.3	1.06 (0.89-1.27), p=0.503
1	318/358	310/358	5.93	156.18	1.04 (0.89-1.22), p=0.635
2	55/59	56/60	9.52	26.13	1.44 (0.98-2.11), p=0.063
					Interaction p=0.38
WBC					
<10x10^9/L	444/526	438/526	4.48	219.78	1.02 (0.89-1.16), p=0.763
≥10x10^9/L	169/181	166/184	19.16	80.84	1.27 (1.02-1.58), p=0.033
					Interaction p=0.1
Number of Disease Sites					
1	195/242	157/205	5.84	86.91	1.07 (0.87-1.32), p=0.14
2	252/285	281/322	18.66	130.36	1.15 (0.97-1.37) p=0.102
>2	169/185	168/186	6.03	83.69	1.07 (0.87-1.33) p=0.51
					Interaction p=0.97
Type of Disease					
Measurable	594/684	583/687	25.26	292.98	1.09 (0.97-1.22), p=0.14
Unmeasurable	21/25	20/22	-3.46	9.81	0.7 (0.38-1.31), p=0.27
					Interaction p=0.18
Total	616/709	606/711	19.68	304.32	1.07 (0.95-1.19), p=0.259

Table 7: Overall Survival arm B or Arm C according to subgroups (forest plot is presented in the article)

General comments

Kaplan-Meier curves were produced for overall survival

Citation: Saltz L,Cox, J, Blanke C, Rosen L, Fehrenbacher L et al (2000) Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer *New England Journal of Medicine* 343;13:905-915
Design: Randomised Trial **Country**: Multiple **Setting:** Multicentre **Aim**: to compare a combination of irinotecan, fluorouracil and leucovorin with bolus doses of fluorouracil and leucovorin as first line therapy for metastatic colorectal cancer.
Inclusion criteria Histologically documented colorectal cancer and measurable metastatic disease ECOG performance status 0-2 Adequate organ function Patients receiving adjuvant fluorouracil based therapy if they remained free of disease for at least one year after completion of therapy
Exclusion criteria Prior therapy for metastatic disease Pelvic irradiation
Sample Size Based on a median progression free survival with fluorouracil and leucovorin of 5 months, it was estimated that 220 patients would be needed in each group in order to detect a 40% improvement in median progression free survival, to seven months with triple drug therapy with a power of 0.85.
Randomisation Method Patients were stratified according to age (<65 years versus ≥65 years), ECOG performance status (0 versus 1-2), interval from diagnosis to enrolment (<6 months versus ≥6 months) and history of adjuvant therapy with fluorouracil (yes versus no) and then randomly assigned to one of three treatment arms.
Population N=683 Intent to treat population: Arm A (Irinotecan+5FU+LV): 231 Arm B (5FU+LV): 226 Arm C (Irinotecan): 226 Treated Population Arm A (Irinotecan+5FU+LV): 225 Arm B (5FU+LV): 219 Arm C (Irinotecan): 223
Study Duration Recruitment Phase: May 1996-May 1998 Data were collected for 19 months after accrual ended, with survival data collected through December 199
Interventions Arm A: Irinotecan 125mg/m^2 of body surface area intravenously over 90 minutes, leucovorin 20mg/m^2 as an IV bolus and fluorouracil 500mg/m^2 as an IV bolus; each given weekly for 4 weeks every 6 weeks. Arm B: leucovorin 20mg/m^2 as an IV bolus and fluorouracil 425mg/m^2 as an IV bolus; each given daily for 5 days (on days 1-5) every 4 weeks. Arm C: Irinotecan 125mg/m^2 intravenously over 90 minutes; given weekly for 4 weeks every 6 weeks
Outcomes Progression free survival (defined as length of time from randomization to disease progression or to death from disease progression or unknown causes).

Results
The arms were balanced for all baseline characteristics apart from the proportion of men which was greater in arm A compared with arm B (65% versus 54%, p=0.02).

Median duration of treatment was 5.5 months in arm A, 4.1 months in arm B and 3.9 months in arm C.
Median relative dose intensity of irinotecan was 72% in arm A and 75% in arm C; median relative dose intensity of fluorouracil was 71% in arm A and 86% in arm B.

Efficacy
Progression free survival was significantly longer in arm A compared to arm B (median 7.0 versus 4.3 months, p=0.004); median progression free survival in arm C was 4.2 months.

Objective response rate was 50% in arm A and 28% in arm B (p<0.001); the rates of objective response that were confirmed by imaging 4-6 weeks later were also significantly higher among patients in arm A compared with arm B (39 versus 21%, p<0.001).
The rates of objective and confirmed response in arm C were 29% and 18% respectively.
A complete response was seen in 6 patients in arm A, 2 patients in arm B and 4 patients in arm C.
Median duration of confirmed response was approximately 9 months for all arms.

The median survival of patients in arm A was 14.8 months as compared with 12.6 months among patients in arm B (p=0.04); median survival of patients in arm C was 12 months.

Mutiple regression modelling of the rates of objective response revealed no interactions between treatment and the stratification factors or other potentially prognostic factors.

Factors predictive of improved progression free survival and overall survival were a normal lactate dehydrogenase level and a performance status of 0.
Haemoglobin levels of at least 11g/dL and a normal white cell count were predictive of better progression free survival and overall survival respectively.
An age of 65 years or older was associated with better progression free survival.
Treatment with Irinotecan, fluorouracil and leucovorin was a significant independent predictor of longer progression free survival (p<0.001) and overall survival (p=0.03) when other significant baseline characteristics were taken into account.
Treatment with irinotecan, fluorouracil and leucovorin was associated with a 36% reduction in the risk of progression and a 22% reduction in the risk of death relative to treatment with fluorouracil an leucovorin alone.
In the comparison of irinotecan, fluorouracil and leucovorin with fluorouracil and leucovorin, the reduction in the risk of death among patients with a normal lactate dehydrogenase level was 43% as compared with a reduction of 12% among those with elevated levels, suggesting a possible interaction of the lactate dehydrogenase level with treatment with respect to survival (p=0.07).

Adverse Effects
22.7% of patients in arm A hadgrade 3/4 diarrhoea as compared with 13.2% of patients in arm A and 31% of patients in arm C.

Quality of Life
No significant differences between arm A and arm B were observed in relation to quality of life. In univariate analysis comparing the greatest worsening in the QoL from base line, the mean increases in the severity of symptoms were smaller in arm A compared with arm B in respect to fatigue, anorexia and pain.
As indicated by the measurement of the greatest declies from base line in role functioning (the ability to perform the activities of daily living), arm A had a smaller decrease in function compared with arm B.

Tables

	Irinotecan, fluorouracil and leucovorin (n=231)	Fluorouracil and leucovorin (n=226)	Irinotecan Alone (n=226)
	N (%)	N (%)	N (%)
Sex			
Male	151 (65)	123 (54)	145 (64)
Female	79 (34)	101 (45)	80 (35)
Not Available	1 (<1)	2 (1)	1 (<1)

Age, years			
Median	62	61	61
Range	25-85	19-85	30-87
<65	139 (60)	136 (60)	135 (60)
≥65	91 (39)	88 (39)2 (1)	90 (40)
not available	1 (<1)		1 (<1)
ECOG Performance Status			
0	89 (39)	93 (41)	104 (46)
1	106 (46)	102 (45)	103 (46)
2	35 (15)	29 (13)	18 (8)
Not available	1 (<1)	2 (1)	1 (<1)
Time from Diagnosis to randomisation, months			
Median	1.9	1.7	1.8
Range	0.1-161	0.1-203	0.1-185
Prior adjuvant fluorouracil			
Yes	25 (11)	18 (8)	23 (10)
No	206 (89)	208 (92)	203 (90)
Prior radiotherapy			
Any	7 (3)	5 (2)	3 (1)
Pelvis or abdomen	4 (2)	2 (1)	3 (1)
Other sites	3 (1)	3 (1)	0

Table 1: Baseline patient characteristics

	Irinotecan, fluorouracil and leucovorin (n=231)	Fluorouracil and leucovorin (n=226)	p	Irinotecan Alone (n=226)
Median Progression Free Survival	7.0	4.3	0.004	4.2
Objective Response Rate	50	28	<0.001	29
Confirned Objective Response Rate	39	21	<0.001	18
Median Duration of Confirmed Response	9.2	8.7	0.37	9.0
Median Overall Survival	14.8	12.6	0.04	12.0

Table 2: Intention to treat analysis of efficacy

	Progression Free Survival		Overall Survival	
	Hazard Ratio (95% CI)	P	Hazard Ratio (95% CI)	P
Serum lactate dehydrogenase (≤UNL vs. >UNL)	0.60 (0.47-0.76)	<0.001	0.47 (0.36-0.60)	<0.001
No. of involved organs (1 vs. ≥2)	0.63 (0.50-0.80)	<0.001	0.67 (0.54-0.83)	<0.001
Performance Status (0 vs. 1 or 2)	0.74 (0.59-0.93)	0.009	0.56 (0.44-0.70)	<0.001
Bilirubin Level (≤UNL vs. >UNL)	0.56 (0.35-0.89)	0.01	0.53 (0.33-0.83)	0.005
White Blood Cell count (<8x10^3/mm^3 vs. 8x10^3/mm^3)			0.65 (0.52-0.82)	<0.001
Haemoglobin level (≥11g/dl vs. <11g/dl)	0.74 (0.58-0.95)	0.02		
Age (≥65 yr vs. <65 yr)	0.78 (0.63-0.98)	0.03	0.82 (0.65-1.02)	0.08
Treatment (Irinotecan+FU+ LV vs. FU+LV)	0.64 (0.51-0.79)	<0.001	0.78 (0.63-0.97)	0.03

Table 3: Results of Cox regression Analysis

	Irinotecan, fluorouracil and leucovorin (n=225)	Fluorouracil and leucovorin (n=219)	Irinotecan Alone (n=223)
Diarrhoea			
Grade 3 or 4	22.7	13.2	31
Grade 3	15.1	5.9	18.4
Grade 4	7.6	7.3	12.6
Vomiting			
Grade 3 or 4	9.7	4.1	12.1
Grade 3	5.3	2.7	5.8
Grade 4	4.4	1.4	6.3
Mucositis			
Grade 3 or 4	2.2	16.9	2.2
Grade 3	2.2	14.6	1.8
Grade 4	0	2.3	0.4
Neutropenia			
Grade 3 or 4	53.8	66.2	31.4
Grade 3	29.8	23.7	19.3
Grade 4	24	42.5	12.1
Neutropenic Complications			

Fever	7.1	14.6	5.8
Infection	1.8	0.0	2.2
Discontinuation due to adverse events	7.6	6.4	11.7
Drug related deaths	0.9	1.4	0.9

Table 5: Adverse Events

General comments
Kaplan Meier Curves for Progression free survival and overall survival

Citation: Souglakos J, Androulakis N, Sygrigos K, Polysos A (2006) FOFLFOXIRI (folinic acid, 5 fluorouracil, oxaliplatin and irinotecan) versus (folinic acid, 5 fluorouracil and irinotecan) as first line treatment in metastatic colorectal cancer (MCC): a multicentre randomised phase III trial from the Hellenic Oncology Research Group (HORG) *British Journal of Cancer* 94;6:798-805

Design: Randomised Trial

Country:

Setting:

Aim: to evaluate the efficacy and safety of the FOLFOXIRI regimen in comparison with the standard combination of FOLFIRI regimen as first line treatment in patients with advanced colorectal cancer.

Inclusion criteria
Histologically documented and measurable adenocarcinoma of the colon or rectum
Prior adjuvant chemotherapy if patients had remained disease free for at least 6 months after completion
ECOG performance status 0-2
At least one bidemensionally measurable lesion of ≥2cm
Life expectancy of at least 3 months
Adequate haematological parameters
Creatinine and total bilirubin ≤1.25 times the upper limit of normal
Aspartate and alanine aminotransferases ≤3.0 times the upper limit of normal
Measurable metastatic disease outside of irradiation fields for patients receiving palliative radiotherapy

Exclusion criteria
Previous chemotherapy for metastatic disease
Patients with operable metastatic disease
Active infection of malnutrition (loss of more than 10% of body weight)
Severe cardiac dysfunction
Liver metastases involving more than 50% of the liver parenchyma
Chronic diarrhea
Prior radiation affecting more than 30% of the active bone marrow

Sample Size
Using Freedman's formula, 136 patients per arm were required with the assumption that the accrual period would last 48 months. The study was designed to detect a 25% improvement in survival for the experimental arm, based on the assumption that overall survival would be 17 months in the standard arm (FOLFIRI) and 22.5 months for the experimental arm (FOLFOXIRI) (type 1 error 5%, type II error 20%).

Randomisation Method
Minimisation method with stratification for centre, prior adjuvant chemotherapy (yes or no), and ECOG performance status (0-1 vs. 2)

Population
N=285 (147 in Arm A and 138 in Arm B)

Study Duration
Recruitment Phase: October 2000 – December 2004

Interventions
FOLFIRI: Irinotecan 180mg/m^2 as a 30 minute i.v. infusion on day 1, LV 200mg/m^2 as a 2hour i.v. infusion followed by 5-FU 400mg/m^2 as i.v. bolus and then 600mg/m^2 as a 22hour continuous i.v. infusion on days 1 and 2.

FOLFOXIRI: Irinotecan 150mg/m^2 as a 30 min infusion on day 1, LV 200mg/m^2 as a 2 hour i.v. infusion, followed by 5-FU 400mg/m^2 as i.v. bolus and then 600mg/m^2 as a 22 hour continuous i.v. infusion on days 2 and 3. Oxaliplatin 65mg/m^2 on day 2 as 2 hour i.v. infusion in parallel with LV but using different lines.

Treatment was administered every two weeks until disease progression or unacceptable toxicity or until patient declined further treatment.

Outcomes
Overall Survival

Time to progression (defined as the interval between start of treatment and date of first documented progression or death from any cause)
Response Rate
Tolerance

Results

Efficacy
Median follow up was 26 months (range 1-62 months) after which 85% of patients had disease progression and 62% of patients had died.

Overall survival was not significantly different between the two arms; 19.5 months (range 1-55.7) in the FOLFIRI arm and 21.5 months (range 1-62.3) in the FOLFOXIRI arm.
The probability of 1 and 2 year survival was 64% and 34% in the FOLFIRI arm and 67% and 43% in the FOLFOXIRI arm.
Independent prognostic factors for decreased survival were performance status of 2 and non response to treatment with **Hazard Ratio 2.5 (95% CI; 1.701-3.703, p=0.0001)** and **2.102 (95% CI; 1.598-2.765, p=0.0001)** respectively.
Age, treatment arm and prior adjuvant chemotherapy were not significant factors for patient outcome.

Overall survival in the FOLFIRI group was 20 months for patients with performance status 0-1 and 6.4 months for patients with performance status 2 (p=0.03) and in the FOLFOXIRI group overall survival was 24 months for patients with performance status 0-1 and 6.6 months for patients with performance status 2 (p=0.0001). There was no statistical difference in terms of overall survival in the young or aged patients irrespective of the treatment regimen:
FOLFIRI: <65 years overall survival = 19.9 months and ≥65 years overall survival = 16.9 months (p=0.452)
FOLFOXIRI: <65 years overall survival = 22.1 months and ≥65 years overall survival = 19.9 months (p=0.263)

Patients in the FOLFIRI arm that went on to receive second line treatment had a significantly better overall survival when compared with patients that did not (median overall survival 21 months (range: 15.9-55.7) versus 12.2 months (range; 7.82-16.64); p=0.016).

Median time to disease progression was 6.9 months (95% CI 6.0-7.7 months; range 1.0-39.3) for patients receiving FOLFIRI and 8.4 months (95% CI 7-1.02 months; range 1.0-32.3) for patients receiving FOLFOXIRI; **Hazard Ratio=0.83 (95% CI; 0.64-1.08; p=0.17)**.

In the FOLFIRI arm, time to progression was 7.1 months (range 1-39.3) for patients with performance status of 0-1 and 2 months (range 1-10.7) for patients with performance status of 2 (p=0.0001).
In the FOLFOXIRI arm, time to progression was 9.7 months (range 1-32.3) and 4.1 months (range 1-15.9) for patients with performance status 0-1 and 2 respectively (p=0.0047).
On Cox multivariate analysis performance status of 2, **(Hazard Ratio 1.857, 95% CI; 1.217-2.834, p=0.004)** and no response to treatment **(Hazard Ratio 2.166, 95% CI; 1.553-3.020, p=0.0001)** were independent prognostic factors for time to progression.

Response to Treatment
In the FOLFIRI arm there were 5 (3.4%) complete response and 9 (6.5%) in the FOLFOXIRI arm; in addition 44 (30.2%) and 50 (36.5%) patients in the enrolled in the FOLFIRI and FOLFOXIRI arm respectively experienced a partial response for an overall response rate of 33.6% for FOLFIRI and 43% for FOLFOXIRI (p=0.168).
39 (26.7%) patients treated with FOLFIRI and 43 (31.3%) patients treated with FOLFOXIRI had disease stabilisation while 58 (39.7%) and 35 (25.5%) respectively patients progressed under treatment.
Median time of response duration was 9 months (range: 1-27) in the FOLFIRI arm and 9.7 months (range: 1-34.6) in the FOLFOXIRI arm (p=0.44).

Secondary metastasectomy was performed in six (4%) patients in the FOLFIRI arm and 14 (10%) patients in the FOLFOXIRI arm (p=0.08). 6 patients (3 in each arm) underwent resection of lung metastases and 14 patients (3 in FOLFIRI and 11 in FOLFOXIRI) underwent resection of liver metastases.
R0 resection could be achieved in all patients with lung lesions and 11 patients with liver metastases.

Compliance with treatment

A total of 1212 treatment cycles were administered in the FOLFIRI arm and 1179 in the FOLFOXIRI arm; median number of cycles was 9 (range 1-22) and 10 (range 1-20) per patient treated with FOLFIRI and FOLFOXIRI respectively.

A total of 101 (8.3%) chemotherapy courses in the FOLFIRI and 166 (14%) in the FOLFOXIRI arm were delayed (p=0.04); median duration of the delay was 4 days (range 1-14) in each arm.
Reasons for delay included haematologic and/or nonhaematologic toxicity and 54 (4%) courses in the FOLFIRI arm and 55 (5%) in the FOLFOXIRI arm were delayed for reasons unrelated to disease or treatment.
Median interval between cycles was 16 days in both treatment arms.
Dose reduction was required in 40 (3%) cycles in the FOLFIRI arm and in 87 (7%) cycles in the FOLFOXIRI arm (p=0.001).
In the FOLFIRI arm 10 (7%) patients discontinued treatment while 16 (12%) discontinued treatment in the the FOLFOXIRI arm (p=0.296); reasons included haemotologic and non haematologic toxicity.
Delivered relative dose intensity was 85% for Irinotecan, 84% for oxaliplatin and 88% for 5FU/LV of the protocol planned dose for FOLFOXIRI and 90% for Irinotecan and 92% for 5FU/LV in the FOLFIRI arm.

Toxicity
There was significantly higher incidence of severe alopecia (p=0.0001), diarrhoea (p=0.001) and neurosensory disorders (p=0.001) in the FOLFOXIRI arm compared with the FOLFIRI arm.
There was no significant difference in the incidence of severe (grade 3/4) haematological toxicity.
There were 2 treatment related deaths in each arm, all related to febrile neutropenia and diarrhoea.
Death rates within the first 60 days of treatment were 2.7% (95% CI, 1.1-4.6%) for patients treated with FOLFIRI and 2.9% (95% CI, 1.3-5.3%) for patients treated with FOLFOXIRI.
Patients with performance status of 2 had significantly higher incidence of grade 3/4 diarrhoea (p=0.001), neutropenia (p=0.001), fatigue (p=0.0001) and febrile neutropenia (p=0.02) when compared to patients with performance status of 0-1 in both treatment arms.
Patients older than 65 years showed significantly higher incidence of grade 3/4 diarrhoea when compared with younger patients in both treatment groups (p=0.005 for FOLFIRI and p=0.017 for FOLFOXIRI).
There was no difference in toxicity for patients who had previously received adjuvant chemotherapy or radiotherapy.

Second line treatment
Second line treatments were not protocol specified though there was a requirement to report them. A higher proportion of patients treated with FOLFIRI received second line treatment (70%), the majority of whom were treated with oxaliplatin based therapy (XELOX or FOLFOX).
58% of patients in the FOLFOXIRI arm received second line treatment compared with the 70% in the FOLFIRI arm (p=0.041) with a small proportion receiving Irinotecan and cetuximab.

Tables

	FOLFIRI (n=146)	FOLFOXIRI (n=137)
	N (%)	N (%)
Age		
Median (range	66 (39-84)	66 (25-82)
≥65 years	82 (56)	75 (55)
Sex		
Male	82 (58)	76 (55)
Female	61 (42)	61 (45)
ECOG Performance Status		
0	55 (38)	49 (36)
1	74 (51)	73 (53)
2	17 (11)	15 (11)
Kohne Prognostic Index		
Low Risk	54 (37)	44 (32)
Intermediate Risk	57 (39)	56 (41)
High Risk	35 (24)	37 (27)
Prior Therapy		
Adjuvant Chemotherapy	48 (33)	49 (36)
Adjuvant Chemoradiotherapy	18 (12)	17 (12)

Table 1: Patient Characteristics (other reported factors include location, number of metastatic sites, metastases)

	FOLFIRI (146)	FOLFOXIRI (130)		FOLFIRI (146)	FOLFOXIRI (130)	

	Any (%)		P	Grade 3/4 (%)		P
Neutropenia	60	73	NS	28	35	0.192
Febrile Neutropenia	6	9	NS	4	7	0.186
Thrombocytopenia	20	31	NS	4	2	0.4
Anaemia	59	60	NS	1	4	0.072
Nausea/Vomiting	45	52	NS	4.8	4.6	0.944
Diarrhoea	51	69	NS	10.9	27.7	0.0001
Mucositis	18	21	NS	4	5	0.748
Neurological	11	59	0.001	0	5.8	0.001
Cutaneous	15	21	NS	3	4	0.133
Alopecia	56	74	NS	12	32	0.0001
Fatigue	36	41	NS	5	5.6	0.944

Table 2: Incidence of common toxicities

	FOLFIRI	FOLFOXIRI	
Second line treatment	N (%)	N (%)	P
Any	102 (70)	80 (58)	0.041
Oxaliplatin Based	92 (63)	39 (28)	0.029
Irinotecan Based	10 (6)	14 (10)	NS
Fluoropyrimidines	44 (30)	29 (21)	NS
Cetuximab	10 (7)	7 (5)	NS

Table 3: Second Line Therapies

General comments

Kaplan Meier Curves presented for overall survival and time to tumour progression.

Citation: Tournigand C, Andre T, Achille R, Lledo G, Flesh M et al. (2004) FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomised GERCOR study *Journal of Clinical Oncology* 22;15:229-237

Comparison FOLFIRI → FOLFOX versus FOLFOX → FOLFIRI (Sequence)

Design: Randomised Trial

Country: France

Setting: Hospital Outpatients

Aim: To evaluate FOLFIRI and FOLFOX6 and determine the best sequence to treat patients with metastatic colorectal cancer

Inclusion criteria
Adenocarcinoma of the colon or rectum
Unresectable metastases
At least one bidimensionally measurable lesion of ≥2cm or a residual non measurable lesion
Adequate bone marrow, liver and renal function
WHO Performance Status of 0-2
Age 18-75 years
Previous chemotherapy to be completed at least 6 months prior to inclusion

Exclusion criteria
Patients with CNS metastases
Patients with second malignancies
Patients with bowel obstruction
Current diarrhea ≥ grade 2
Symptomatic angina pectoris
Disease confined to previous radiation fields

Sample Size
The study was designed for the two-sided log rank test to have 80% power to detect a 20% difference in the proportion of patients without progression at 15 months (60% in Arm A, 40% in Arm B, type I error of 5%, type II error of 20%).
Using Freedmans formulas, 109 patients and 49 events per arm were required.

Randomisation Method
Minimisation technique, stratifying patients by centre and by presence or absence of measurable disease

Population
N=226 randomly assigned with 6 patients ineligible (4 in Arm A and 2 in Arm B)

N=220 analysed

Study Duration
Recruitment Stage: Dec 1997-Sept 1999

Cutoff date for progression free survival was March 31st 2001 and for overall survival was August 30, 2002 with a median potential follow up for the entire cohort of 43.9 months.

Interventions
FOLFIRI consisted of *l*-LV 200mg/m^2 or *dl*-LV 400mg/m^2 as a 2 hour infusion and irinotecan given as a 90 minute infusion in 500ml dextrose 5% via a Y connector, followed by bolus FU 400mg/m^2 and a 46 hour infusion FU 2,400mg/m^2 for two cycles increased to 3,000mg/m^2 from cycle 3 in case of no toxicity > grade 1 during the first two cycles, repeated every 2 weeks.
FOLFOX6 consisted of the same LV+FU regimen with the addition of oxaliplatin 100mg/m^2 on day 1, given as a 2 hour infusion in 500ml dextrose 5%, concurrent with LV.
Antiemetic prophylaxis with a 5HT$_3$-receptor antagonist was administered.

Arm A: FOLFIRI until progression or unacceptable toxicity then FOLFOX6
Arm B: FOLFOX6 until progression or unacceptable toxicity then FOLFIRI

In case of toxicity imputed to oxaliplatin or irinotecan during first line therapy and no progressive disease patients could receive LV+FU alone until progression and then the second regimen.

Treatment continued until disease progression, unacceptable toxicity or patient choice.

Outcomes
Primary Outcome: second progression free survival (time duration from randomisation to progression after 2nd line chemotherapy). If a patient could not receive 2nd line treatment or refused 2nd line, progression free survival on the first line was used instead.

Secondary outcomes: Progression free survival (no details), overall survival, response rates and safety

Results
Characteristics of the patients were well balanced between the groups apart from sex ratio with the percentage of males in Arm A lower than in Arm B (57% versus 72%) and age >65 with a slightly lower percentage in Arm A.

Progression Free Survival
First line therapy
According to external review, median progression free survival was 8.5months (95% CI, 7-9.5) for Arm A and 8 months (95% CI, 6.2-9.4) for Arm B (p=0.26). Note: these are the figures used in the Kaplan Meier plots.

Second line therapy
According to external review, median progression free survival was 4.2 months (95% CI, 3.7 to 5.2) for Arm A versus 2.5 months (95% CI, 2.1-3.3) for Arm B (p=0.003). Note: these are the figures used in the Kaplan Meier plots.

Median delay between progression on first line and first cycle of second line was 21 days in Arm A versus 15 days in Arm B (p=0.27).

As of March 31, 2001, 74% (n=81) of patients had received per protocol FOLFOX6, second line therapy in Arm A and 62% (n=69) of patients had received FOLFIRI second line in Arm B, including one patient who received FOLFOX6 instead on FOLFIRI.
Eight patients in both arms received a second line of treatment out of study; 3 in Arm A and 5 in Arm B received the second line after the cut-off date.

Five patients in Arm A and 8 in Arm B had no tumour progression after first line treatment.
11% (n=12) of patients in arm A and 15% (n=17) of patients in Arm B could not receive second line treatment due to death, poor performance status or refusal.

Second progression free survival: According to external review, median second progression free survival was 14.2 months (95% CI12-16.9) for Arm A and 10.9 months (95% CI, 9-14.6) for Arm B (p=0.64).
At 15 months, progression free survival was 47.2% in Arm A and 37.3% in Arm B.

Independent prognostic factors for improved second progression free survival were: good performance status (p=0.001), low lactate dehydrogenase (p=0.011), no prior adjuvant chemotherapy (p=0.001) and female sex (p=0.043).

Overall Survival
Median overall survival was 21.5 months (range, 16.9 – 25.2) for Arm A versus 20.6 months for Arm B (range 17.7 to 24.6 months) (p=0.99).
Independent prognostic factors for improved OS were: good performance status (p<0.0001), low lactate dehydrogenase (p<0.001), no prior adjuvant chemotherapy (p=0.001), low alkaline phosphatise (p=0.012), metastasis confined to the liver (p=0.016), carcinoembryonic antigen (p=0.016) and female sex (p=0.048).

Objective Tumour Responses
First line Therapy
Three (2.8%) complete responses were observed with FOLFIRI versus 5 (4.5%) with FOLFOX6.
The response rates were 56% (95% CI, 47% - 65%) with FOLFIRI and 54% (95% CI, 45%-63%) with FOLFOX6.
Median time to response in Arm A was 2.1 months and in Arm B was 1.8 months (p=0.02). Response lasted a median of 11 months for Arm A and 10.6 months for Arm B.

Good performance status (p=0.001) and liver only metastasis (p=0.004) were significant independent prognostic factors.

9% (n=10) of patients in Arm A and 22% (n=24) underwent secondary surgery to remove metastases (p=0.02); 30 patients had a single metastatic site, 3 had two sites and 1 had three sites.
The mean number of cycles given before surgery was 12 cycles of FOLFIRI and 10 cycles of FOLFOX6.
According to expert review, 7% (n=8) of patients in Arm A and 13% (n=14) of patients in Arm B had a R0 resection (p=.26). In addition, 2 patients underwent a second or third surgical resection.

Median overall survival in patients who had surgery was 47 months in Arm A and was not reached in Arm B (p=0.96).

Second line therapy
The response rates were 15% (95% CI, 7% - 23%) with FOLFOX6 second line and 4% (95% CI, 0% - 9%) with FOLFIRI second line (p=0.05).
In second line therapy, the investigators assessments of objective response were 21% and 6% respectively.
Secondary surgery to remove metastases after second line therapy could be performed in two patients in Arm A and one in Arm B.

Toxicity
First line therapy
Patients in Arm A received a median of 13 cycles (1-43) of FOLFIRI and patients in Arm B received a median of 12 cycles (range 1-38) of FOLFOX6.
There was one therapy related death in Arm B as a result of haematological toxicity.
Grade 3 sensory neurotoxicity, grade 3/4 neutropenial and thrombocytopenia were significantly more frequent with FOLFOX6 than with FOLFIRI.
Grade 3/4 febrile neutropenia, nausea/vomiting, mucositis and fatigue were significantly more frequent with FOLFIRI than with FOLFOX6.
More grade 2 alopecia was observed with FOLFIRI than with FOLFOX6.

34% of patients in Arm B developed grade 3 sensory neurotoxicity , 13% (n=5) recovered within 1 month and 31% (n=12) recovered within 3 months.

More patients experienced grade 3/4 toxicities with FOLOX6 than with FOLFIRI (74% versus 53%, p=0.001) but more patients had serious adverse events with FOLFIRI than with FOLFOX6 (14% versus 5%, p=0.03).

6% (n=6) patients had to stop FOLFIRI first line as a result of toxicity compared with 11% (n=12) patients on FOLFOX first line. 4% (n=4) of patients in Arm A and 3% (n=3) patients in Arm B died during the first 60 days in first line therapy.

Elderly patients (>65 years; n=90) did not experience increased toxicity in the first line therapy as compared with younger subjects.

Second line therapy
Patients in Arm A received a median of 8 cycles (range, 2-23) of FOLFOX6 and patients in Arm B received a median of 6 cycles (range, 1-33) of FOLFIRI.
There were no therapy related deaths and the toxicity profile in each regimen showed minor differences compared with first line therapy.
Grade 3/4 neutropenia and thrombocytopenia and neurotoxicity were more frequent with FOLFIRI while gastrointestinal toxicities were more frequent with FOLFOX6.
19% of patients that developed Grade 3 neurotoxicity on first line oxaliplatin still had grade 3 neurotoxicity when starting second line FOLFIRI.

49% of patients in Arm A and 44% of patients in Arm B experienced grade 3/4 toxicities. Serious adverse events occurred in 4% of patients in Arm B and in 6% of patients in Arm A.
12% (n=10) of patients in Arm A and 1% (n=1) of patients in Arm B had to stop treatment due to toxicity.
Elderly patients (>65 years; n=59) did not experience increased toxicity as compared with younger subjects.
4% (n=3) of patients in Arm A and 3% (n=3) of patients in Arm B died during the first 60 days in second line therapy.

Vascular events were reported in 3 cases; pulmonary embolism in one FOLFIRI first line patient and one FOLFOX6 second line patient and a third patient who developed congestive heart failure on first line FOLFOX6.

Dose Intensity
On FOLFIRI first line, the FU dose could be increased for 615 cycles (39%) versus 406 cycles (29%) on FOLFOX6.
22% of patients in FOLFIRI first line and 34% of patients on FOLFOX6 first line received FU 3,000mg/m^2 for at least one cycle.
In second line, 11% of patients in FOLFIRI first line and 10% of patients in FOLFOX6 first line received FU 3,000mg/m^2 for at least one cycle.
Relative dose intensity for Irinotecan was 85.9% in first line and 87.3% in second line and for oxaliplatin relative dose intensity was 84.7% in first line and 90.1% in second line.

Weight and Performance Status
35% (n=38) of patients in Arm A and 23% (n=25) in Arm B recorded a weight increase of at least 5% (p=0.05).
Performance status (PS) improved with 18/52 assessable patients with PS>0 (35%) on FOLFIRI and 19/57 assessable patients with PS>0 (33%) on FOLFOX6 (p=0.99).
6% (n=4) of patients receiving second line FOLFIRI and 9% (n=7) of patients on FOLFOX6 recorded a weight increase of at least 5% (p=0.55).
Performance status improved with 12/24 assessable patients with PS>0 (35%) on FOLFIRI and 9/35 assessable patients with PS>0 (26%) on FOLFOX6 (p=0.44).

Tables

Parameter	Arm A: FOLFIRI/FOLFOX6	Arm B: FOLFOX6/FOLFIRI
	No. of Patients (%)	No. of Patients (%)
Demographic Characteristics		
No. of Patients	109 (100)	111 (100)
Male	62 (57)	80 (72)
Female	47 (43)	31 (28)
Age, years		
Median	61	65
Range	29-75	40-75
WHO Performance Status		
0	48 (45	52 (47)
1	42 (39)	52 (47)
2	18 (17)	7 (6)
Adjuvant Chemotherapy		
Yes	19 (17)	23 (21)
No	90 (83)	88 (79)

Table 1: Patient Characteristics (other details recorded in the study include primary tumour site, metastases, metastatic site, no. of sites, CEA and alkaline phosphatise)

	First Line		Second Line	
	Arm A: FOLFIRI/FOLFOX6 (n=109)	Arm B: FOLFOX/FOLFIRI (n=111)	Arm A: FOLFIRI/FOLFOX6 (n=81)	Arm B: FOLFOX/FOLFIRI (n=69)
Event Rate	No. of patients (%)	No. of patients (%)	No. of patients (%)	No. of patients (%)
Overall Response Rate	61 (56)	59 (54)	12 (15)	3 (4)
Complete Response	3 (3)	5 (5)	0 (0)	0 (0)
Partial Response	58 (53)	54 (49)	12 (15)	3 (4)
Stable Disease	25 (23)	30 (27)	39 (48)	21 (30)
Progression	15 (14)	14 (13)	15 (19)	35 (51)
Not Assessable	8 (7)	8 (7)	15 (19)	10 (14)

Table 2: Objective Tumour Response after external review

	First Line									Second Line								
	Arm A: FOLFIRI (n=110)[1]				Arm B: FOLFOX6 (n=110)[1]					Arm A: FOLFOX6 (n=82)				Arm B FOLFIRI (n=68)				
Toxicity	1	2	3	4	1	2	3	4	P (Grade 3/4)	1	2	3	4	1	2	3	4	P (Grade 3/4)
Neutropenia	19	33	15	9	18	20	31	13	0.003	17	24	15	2	21	18	21	0	NS
Thrombocytopenia	15	1	0	0	57	21	5	0	0.01	59	9	0	1	34	4	0	0	NS

Anemia	27	12	2	1	39	12	3	0	NS	35	9	2	1	49	13	3	0	NS
Febrile Neutropenia		0	4	3		1	0	0	0.007	0	0	0	0	0	0	1	0	NS
Nausea	29	30	13	0	39	25	3	0	0.005	37	21	6	0	26	21	0	0	0.03
Vomiting	17	23	8	2	22	17	3	0	0.027	17	17	4	1	16	16	3	0	NS
Diarrhoea	26	23	9	5	28	13	9	2	NS	22	7	4	1	29	16	7	1	NS
Mucositis	26	15	10	0	35	10	1	0	0.003	24	10	4	0	15	7	3	0	NS
Cutaneous	18	5	2	0	17	5	2	0	NS	21	2	1	0	12	1	0	0	NS
Alopecia	36	24	N/A	N/A	19	9	N/A	N/A	0.003[2]	13	9	N/A	N/A	26	13	N/A	N/A	NS
Neurological	10	0	0	N/A	26	37	34	N/A	<0.001	45	29	20	0	1	0	1	0	<0.001
Fatigue	15	27	4	0	17	15	3	0	0.028[3]	9	22	5	0	12	21	1	0	NS

[1] One patient randomised in Arm B received FOLFIRI as first line
[2] Comparison grade 2
[3] Comparison grade 2-3

Table 3: Percentage frequency of Common Toxicities

General comments

Kaplan-Meier curves for progression free survival in first line and second line therapy, time to second progression and overall survival are presented.

4.4.2. What is the most effective treatment for advanced colorectal cancer patients when 5FU/FA based regimens are not tolerated or inappropriate?

Short Summary

There is no good quality evidence with which to address this question with the body of evidence comprising one randomised trial comparing raltitrexed to 5FU/LV from which the results of the raltitrexed arm will provide indirect evidence (Popov et al (2008)), one randomised phase II trial (Feliu et al (2005)) comparing raltitrexed + oxaliplatin with raltitrexed + irinotecan and a small number of non-randomised phase II trial (Aparicio et al (2005), Chiara et al (2005), Cortinovis et al (2004), Feliu et al (2004), Laudani et al (2004), Maroun et al (2006), Santini et al (2004), Vyzula et al (2006)). For patients receiving treatment with raltitrexed, serious adverse events were reported in 16.3% of patients, deaths related to treatment were reported for 2.2% (n=20). The 5-year recurrence free survival rate was 47.8% (95% CI, 42.3% – 53%) for patients receiving raltitrexed. In the intention to treat population, the 5-year survival rate was 61.9% (95% CI 55.4% – 66.1%) (Popov, 2008).

Review Protocol

Population	Intervention	Comparison	Outcomes
Patients with advanced or metastatic colorectal cancer	Raltitrexed (single agent or in combination with oxaliplatin or irinotecan)	No further Chemotherapy Irinotecan (single agent)	Response Progression Free survival Overall Survival Toxicity Quality of Life

Following a systematic search of relevant data sources (see appendix .1), the information specialist created a database of potentially relevant studies. All titles and abstracts were sifted by a single reviewer. Queries about inclusion were clarified by the GDG topic subgroup. The full studies were then obtained and reviewed and relevant studies were included in the final evidence review.

All update searches were sifted by a single reviewer and the list of potentially relevant studies was also checked for irrelevant studies by the GDG subgroup. Only studies which all subgroup members were in agreement were excluded. The remaining studies were obtained and reviewed with relevant studies included in the final evidence review.

Include only studies published since 2004 as TA93 searches up to 2004
Include indirect evidence if necessary – studies comparing Raltitrexed to 5FU/FA based regimens are not directly applicable as they cannot randomise only patients intolerant to 5FU/FA, however the efficacy and toxicity of raltitrexed based treatments will not differ based on tolerability to 5FU/FA and therefore the raltitrexed arms of such trials will provide relevant but indirect evidence.

Reasons for excluding studies:
Expert Reviews
Population not relevant to PICO
Foreign language studies with no translations
Comparison not relevant to PICO
Did not look at 5-FU intolerant patients

Quality of the included studies
Systematic review of RCTs (n = 0)
Systematic review of combined study designs (n =0)
Randomized controlled trial (n = 1)
Non-randomised phase II trials (n=9)
Prospective cross sectional study (n = 0)
Case Series Studies (n = 0)

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116
possibly relevant
papers identified

                    96
                    papers excluded
                    based on title &
                    abstract

20
papers obtained
for appraisal

                    10
                    papers excluded

10
papers included
in evidence table
```
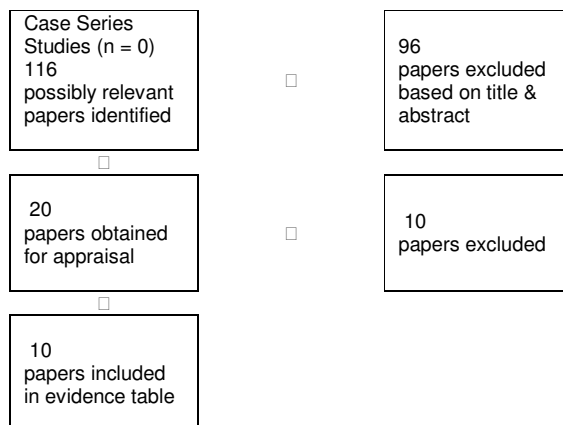
Volume of evidence

There was very little evidence available with which to address this topic, consisting primarily of single arm, non-comparator phase II studies. There was a single randomised trial comparing raltitrexed with 5FU/LV from which the data from the raltitrexed arm was deemed to provide indirect evidence.

Applicability

There are no studies which compare raltitrexed (single agent or in combination) to irinotecan (single agent) or to no further chemotherapy in patients that prove to be intolerant to 5FU/FA as such patients cannot currently be identified until they start 5FU/FA based treatment.

There are no studies comparing raltitrexed (single agent or in combination) to irinotecan (single agent) or to no further chemotherapy in any population.

There are a number of single arm, non-randomised, phase II trials which examine the efficacy and toxicities of raltitrexed in combination with oxaliplatin or irinotecan which provide indirect evidence.

There is a single randomised trial comparing raltitrexed to 5FU/LV from which the results of the raltitrexed arm will provide indirect evidence.

Evidence Statement

Raltitrexed Alone

From one randomised trial in which the risk of bias is not accurately assessable due to poor reporting (Popov, 2008), comparing raltitrexed with 5FU/LV, there is indirect evidence regarding the efficacy and toxicity of raltitrexed. The trial aimed to recruit a total of 2765 patients however early analysis of the first 647 patients showed a greater treatment completion rate in the 5FU/LV arm and more withdrawals due to serious adverse effects in the raltitrexed arm resulting in early closure of the trial with a total of 1921 patients recruited.

952 patients were randomised to the raltitrexed arm and received a median of 6 cycles of chemotherapy; the planned number of cycles was received by 42.4% (n=389) patients on the raltitrexed arm and when the study closed prematurely 28.5% (n=271) patients discontinued with raltitrexed treatment.

The median relative dose intensity of raltitrexed was 104% (range: 9-150%).

Adverse Events
From the raltitrexed arm of one randomised trial (Popov, 2008) serious adverse events were reported in 16.3% of patients, deaths related to treatment were reported for 2.2% (n=20) patients receiving raltitrexed of which 11 deaths were associated with a major protocol deviation and the majority of toxic deaths were reported from one cooperative group.

Recurrence
In the intention to treat population 38.9% of patients in the raltitrexed group relapsed or died while in the per protocol population, 43.1% of patients in the raltitrexed group relapsed or died. The 5-year recurrence free survival rate was 47.8% (95% CI, 42.3% – 53%) for patients receiving raltitrexed (Popov, 2008).

Survival
In the intention to treat population, 26.5% of patients in the raltitrexed group died during follow-up (median 49 months) and the 5-year survival rate was 61.9% (95% CI 55.4% – 66.1%).
In the per protocol population 29.5% of patients in the raltitrexed group and the 5-year survival rate was 62.6% (95% CI, 57.1% - 67.7%) in the raltitrexed group.

Raltitrexed plus Oxaliplatin

From a single phase II randomised trial comparing raltitrexed plus oxaliplatin to raltitrexed plus irinotecan (Feliu et al, 2005), overall response rate in the raltitrexed plus oxaliplatin arm was 46% (95% CI 29.5%-57.7%). Control of disease (CR, PR and SD) was achieved in 69% of patients and median time to progression was 8.2 months.

65% of patients experienced toxicity and there was one toxic death.

From three studies (Cortinovis et al (2004), Santini et al (2004), and Laudani et al (2004)) reported overall response rates ranging from 29%-45.5%.

From four studies (Cortinovis et al (2004), Vyzula et al (2006), Santini et al (2004), and Laudani et al (2004)) reported median time to progression ranged from 18 weeks – 7 months and reported median overall survival ranged from 54.4 weeks – 15 months.

Raltitrexed plus Irinotecan

From a single phase II randomised trial comparing raltitrexed plus oxaliplatin to raltitrexed plus irinotecan (Feliu et al, 2005), overall response rate in the raltitrexed plus irinotecan arm was 34%

(95% CI 19.8%-48.4%). Control of disease (CR, PR, and SD) was achieved in 67% of patients median time to progression was 8.8 months.
70% of patients experienced toxicity and there were 3 toxic deaths.

From three studies (Feliu et al, 2004; Chiara et al, 2005 and Aparicio et al, 2005) the range of complete response was 27%-34%.
Feliu et al (2004) reported progression free survival of 11.1 months, Chiara et al (2005) reported a median progression free survival of 5 months and Aparicio et al (2005) reported a median time to progression of 6.3 months (95% CI 4-8.6 months).

Raltitrexed plus Oxaliplatin and Irinotecan
Maroun et al (2006), reported an overall response rate of 45% (95% CI, 31% – 68%), median time to progression of 7.3 months (95% CI 6.51-9.2 months) and median overall survival of 16.6 months (95% CI, 13.5 – 21.3).

References

Aparicio J, Vincent JM, Maestu I, Bosch C, Galan A (2005) First line treatment with Irinotecan and raltitrexed in metastatic colorectal cancer. Mature results of a multicentre phase II study. *Oncology* 68;1:58-63

Chiara S, Nobile MT, Tomasello L, Acquati M (2005) Phase II trial of irinotecan and raltitrexed in chemotherapy-naive advanced colorectal cancer *Anticancer Research* 25;2B:1391-1396

Cortinovis D, Bajetta E, Di Bartolomeo M, Dogini G (2004) Raltitrexed plus oxaliplatin in the treatment of metastatic colorectal cancer *Tumori* 90;2:186-191

Feliu J, Salud A, Escudero P, Lopez-Gomez L (2004) Irinotecan plus raltitrexed as first-line treatment in advanced colorectal cancer: a phase II study *British Journal of Cancer* 90;8:1502-1507

Feliu J, Castanon C, Salud A, Mel JR, Escudero P, Pelegrin A, Lopez-Gomez L, Ruiz M, Gonzalez E, Juarez F, Lizon J, Castro J,, Gonzalez-Baron M (2005) Phase II randomised trial of raltitrexed-oxaliplatin versus raltitrexed-irinotecan as first line treatment in advanced colorectal cancer *British Journal of Cancer* 2005;93:1230–1235.

Laudani A, Gebbia V, Leonardi V, Savio G (2004) Activity and Toxicity of oxaliplatin plus raltitrexed in 5 fluorouracil refractory metastatic colorectal adenocarcinoma *Anti-Cancer Research* 24;2C:1139-1142

Maroun JA, Jonker D, Seymour L, Goel R, Vincent (2006) Phase I/II study of irinotecan (camptosar), oxaliplatin and raltitrexed (tomudex) (COT) in patients with advanced colorectal cancer

Popov I, Carrato A, Sobrero A, Vincent M, Kerr D (2008) Raltitrexed (Tomudex) versus standard leucovorin modulated bolus 5-fluorouracil: Results from the randomised phase III Pan-European Trial in adjuvant colon cancer 01 (PETACC-1) *European Journal of Cancer* 44;15:2204-2211

Santini D, Massacesi C, D'Angelillo RM, Marcucci M (2004) Raltitrexed plus weekly oxaliplation as first line chemotherapy in metastatic colorectal cancer: a multi centre non-randomised phase II study *Medical Oncology* 21;1:59-66

Vyzula R, Kocakova I, Demlova R, Kiss I (2006) Raltitrexed plus oxaliplatin in the second line treatment of metastatic colorectal cancer *Neoplasma* 53;2:119-127

Evidence Tables

Citation: Aparicio J, Vincent JM, Maestu I, Bosch C, Galan A (2005) First line treatment with Irinotecan and raltitrexed in metastatic colorectal cancer. Mature results of a multicentre phase II study. *Oncology* 68;1:58-63
Design: Multicentre phase II non-randomised study **Country**: Spain **Setting**: **Aim**: to assess the efficacy and toxicity of irinotecan and raltitrexed as first line treatment
Inclusion criteria Histological confirmation of colorectal cancer with metastatic disease not amenable for curative surgical resection No previous chemotherapy for advanced disease Adjuvant 5FU based chemotherapy and/or pelvic radiotherapy to be completed more than 6 months before study entry WHO performance status of 0-2 Life expectancy of at least 3 months Age more than 18 years At least one bidimensionally measurable lesion Satisfactory bone marrow, renal and liver functions
Exclusion criteria Prior exposure to irinotecan or raltitrexed Metastatic involvement of >50% of the liver Chronic enterpathy or unresolved bowel obstruction Breast feeding or pregnancy Previous malignant disease other than carcinoma *in situ* of the cervix or basal cell skin carcinoma Cerebral metastases or leptomeningeal carcinomatosis Severe or uncompensated concomitant medical conditions.
Sample Size 60 evaluable patients to better estimate efficacy (standard error of 5% for an expected 35-40% overall response rate).
Randomisation Method N/A
Population N=62
Study Duration 12 month recruitment period Median potential follow up was 37 months
Interventions Irinotecan plus raltitrexed Irinotecan 350mg/m^2 was given as a 60 min infusion followed 1 hour later by raltitrexed 3mg/m^2 administered as a 15 min infusion, both in a thrice weekly schedule. Salvage treatment was given at disease progression according to the investigator centres guidelines, but oxaliplatin based chemotherapy was recommended.
Outcomes Analysis of tumour response Toxicity Time to disease progression Overall survival
Results

331 courses of irinotecan plus raltitrexed were delivered (median: 5/patient; range 1-16); 6 patients received only 1 cycle and 9 patients received only 2 cycles.
Reasons for early discontinuation were treatment related toxicities in 5 patients, patients refusal in 4 cases, need for urgent surgery in 4 cases and disease progression in 2 cases.
32% (n=20) of patients needed dose reduction and 14% of cycles (n=48) were delayed
The main adverse events were diarrhoea, asthenia and emesis
5% (n=3) of patients died as a result of treatment related toxicities (grade III-IV diarrhoea and concomitant neutropenia leading to sepsis and hydroelectrolyte imbalance).

Response was assessed in 56 patients with measurable disease who received at least 2 cycles of treatment.
27% (n=17) achieved partial response and 3% (n=2) achieved a complete response for an overall intention to treat response rate of 30% (95% CI, 18-44%) in all 62 enrolled patients.
37% of patients showed stable disease and 23% did not respond at all (unclear but presume this relates to progressive disease).

66% of patients received any one form of therapy after first line treatment failure, primarily oxaliplatin based chemotherapy.
37 cases received a second line, 18 a third line and 4 a fourth line treatment.
7 patients were treated with salvage surgery at any time point and 3 patients were treated with palliative irradiation.

As of November 2003, 84% of patients (n=52) had died and the median potential follow-up was 37 months (31-42).
Actuarial median survival was 12.2 months (95% CI, 9.2-15.1) and median time to disease progression was 6.3 (95% CI, 4.0-8.6).

Citation: Chiara S, Nobile MT, Tomasello L, Acquati M (2005) Phase II trial of irinotecan and raltitrexed in chemotherapy-naive advanced colorectal cancer *Anticancer Research* 25;2B:1391-1396

Design: Phase II non-randomised trial

Country: Italy

Setting: Hospital

Aim: To assess the activity and tolerability of combined raltitrexed and irinotecan in patients with advanced colorectal cancer

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Inclusion criteria
Patients with histologically confirmed metastatic colorectal cancer, untreated with chemotherapy for advanced disease.
Previous adjuvant chemotherapy completed 12 months prior to study
ECOG performance status ≤2
Age ≥18 years
Life expectancy of at least three months
Measurable metastatic lesions that had not been previously irradiated and adequate bone marrow, renal and hepatic function

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Exclusion criteria
History of serious concomitant disease, prior malignancy apart from adequately treated basal cell skin cancer or *in situ* cervical carcinoma.
Presence of central nervous system metastases
Pregnancy, breast feeding or inadequate contraceptive precautions

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Sample Size
A sample of 24 patients was required in the first stage; if 6/24 patients experienced a clinical response, a further 21 patients were enrolled in the second stage and up to three more patients could be accrued to correct for attrition.
The treatment under investigation could be deemed interesting for further trials if more than 14 clinical responses were observed out of the total number of enrolled patients.

Randomisation Method

Population
N=48

Study Duration

Interventions
Irinotecan plus Raltitrexed

Irinotecan 350mg/m^2 was administered intravenously over 30 minutes on day 1
Raltitrexed was administered 24 hours later at a dose of 3mg/m^2 in a 15 minute intravenous infusion
Courses were repeated every 21 days until disease progression, patient refusal or unacceptable toxicity.

Outcomes
Toxicity
Activity
Survival

Results
Median Age was 63 years (range 46-77) and median ECOG performance status was 0 (range 0-2)
46% (n=22) of patients had synchronous metastatic disease, 26 patients had metastatic disease and 4 patients presented local relapse associated with distant metastases.
30 patients had a single involved site and 18 patients had multiple metastatic sites.
41.6% (n=20) of patients had undergone prior adjuvant chemotherapy consisting of 5-FU/FA combination regimens in 17 cases and methotrexate/5FU/FA regimens in 3 cases.

After recruitment of the first 16 patient, grade III-IV toxicity was observed in 6 patients resulting in a reduction of the total dose of both drugs by 15% for subsequent patients entering the trial (Irinotecan 300mg/m^2 and raltitrexed 2.6 mg/m^2).

290 cycles of irinotecan and raltitrexed were administered; the median number of treatment courses per patients was 6 (range 1-18).
23 patients required a dose reduction of 20% and in 2 patients a 50% dose reduction was necessary
4.5% of cycles were delayed by 1 week and 2% of cycles were delayed by 2 weeks to allow recovery from toxicity.
Median dose intensity was 0.90(0.58-1.00) for irinotecan and 0.91 (0.54-1.00) for raltitrexed.
21 patients received combination chemotherapy including oxaliplatin + 5FU/FA and 4 patients received 5-FU/FA schedules.

Toxicity
For the first group of patients recruited, 6/16 patients experienced severe toxicity; Grade III Diarrhoea in 2 patients (3rd and 7th cycles respectively), grade III diarrhoa and neutropenic fever in 1 patient (7th cycle), grade IV diarrhoea and neutropenia in one patient (4th cycle).
3/6 patients required hospitalisation due to diarrhoea and/or neutropenia.

17/32 patients treated with the initial dose of irinotecan 300mg/m^2 and raltitrexed 2.6mg/m^2 experienced grade III and grade IV toxicities.
Toxicities consisted mainly of diarrhoea, nausea/vomiting, neutropenia, transaminase elevation, asthenia and stomatitis.
Hospitalisation of 3 patients was required due to grade III hepatic toxicity, grade III diarrhoea and grade IV mucositis
One patients required 50% dose reduction for grade IV mucositis and grade III neutropenia
Two toxic deaths occurred; one due to dehydration from grade IV diarrhoea associated with grade III emesis and one related to grade III diarrhoea and grade II emesis after the 2nd course of chemotherapy (at 20% dose reduction).
Five patients interrupted chemotherapy due to combined grade III-IV toxicity after a median of 3 courses (range 1-6) and one patient refused therapy after the 6th course of chemotherapy not associated with toxicity.

Activity and Survival
43/48 patients were evaluable for response; 2 patients discontinued chemotherapy after the 1st course and 3 patients discontinued after the 2nd course due to grade III-IV toxicities (including toxic deaths).

According to intention to treat analysis, overall response rate was 27% (95% CI 16%-42%) including complete response in 6.3% and partial response in 20.8%. 29.2% of patients had stable disease and 33.3% of patients had disease progression.
31% of patients (5/16) receiving the initial dose of oxaliplatin/raltitrexed achieved objective response and 25% of patients (8/32) receiving the lower dose achieved objective response.

Median progression free survival was 5 months and overall survival was 14 months
Median duration of response was 11 months for patients in complete response (range 4-23+) and 10 months for patients in partial response (range 3-24).

Citation: Cortinovis D, Bajetta E, Di Bartolomeo M, Dogini G (2004) Raltitrexed plus oxaliplatin in the treatment of metastatic colorectal cancer *Tumori* 90;2:186-191

Design: Single Arm Phase II Study **Country**: Italy **Setting**: **Aim**: To study the antitumoral activity and safety of the combined use of raltitrexed and oxaliplatin in patients with advanced colorectal cancer.
Inclusion criteria Patients with cyto-histologically confirmed metastatic colorectal cancer and bidimensionally measured disease defined as the presence of at least one lesion with the longest diameter of ≥15mm with no radiotherapy allowed in the case of a single lesion. Prior chemotherapy must have been completed at least four weeks prior to study entry Age ≥18 years ECOG performance status of 0-1 Life expectancy of >3 months Adequate bone marrow reserve Normal liver and renal function tests
Exclusion criteria Brain metastases History of other malignancies with the exception of excised cervical cancer and basal skin/squamous cell carcinoma.
Sample Size Planned sample size of 33 patients, subsequently increased to 51 patients as interim analysis revealed the feasibility and activity of the regimen and because of the absence of any other chemotherapy program for this subset of patients available at the Institute.
Randomisation Method N/A
Population N=51
Study Duration Median Follow up was 16 months (range: 8-24 months)
Interventions Raltitrexed (TOM) + Oxaliplatin (L-OHP) 15 min iv infusion of TOM ($2.5mg/m^2$) followed by a 3 hour infusion of L-OHP ($100mg/m^2$) both administered on day 1 every 3 weeks for a maximum of six cycles.
Outcomes *Primary* Response rate (complete response (CR) defined as complete disappearance of all objective signs of disease on two occasions separated by at least 4 weeks; partial response (PR) was defined as a ≥50% reduction in the sum of the products of the greatest perpendicular dimensions of measurable bidimensional lesions without a CR and the absence of a >25% increase in any lesion without the appearance of any new lesion, confirmed on two occasions separated by at least 4 weeks; progressive disease (PD) was defined as the growth of any existing measurable lesion by at least 25% or the appearance of any new lesion; stable disease (SD) was defined as any measurement not fulfilling the criteria for CR, PR or PD) Treatment safety and toxicity *Secondary* Time to progression (measured and date of start of chemotherapy to date of documented progressive disease) Overall Survival (measured from the beginning of treatment to date of death from any cause)

Results
51 patients were enrolled in the study, of which 28 were considered 'elderly' (≥65 years).
25 patients had metastatic disease at the time of diagnosis; 33 patients had one metastatic site
20 patients had previously received chemotherapy for advanced disease with bolus FU plus leucovorin or infusional FU and 22 patients were chemotherapy naive.

A total of 215 courses of chemotherapy were administered for a median of 6 cycles per patient (range: 1-6.
24 patients completed the treatment plan and only 5 patients received less than three cycles; one patient received 3 cycles but was not re-evaluated due to sudden death for an unknown cause.

Safety Analysis
The most frequent, non-haematological toxicity was transient transaminitis: Grade I-II in 28% of patients and Grade III-IV in 31% of patients.
Grade III diarrhoea occurred in 12% of patients, nausea/vomiting in 6% and asthenia in 2% of patients
Grade IV nausea/vomiting occurred in one patient
Grade I neurotoxicity occurred in 51% of patients and Grade II in 2% of patients
Grade III neutropenia was observed in 2% of patients.
Chemotherapy was discontinued because of toxicity in 6% (n=3) of patients
15 patients required per protocol 25% reductions of L-OHP and/or TOM dose

Analysis of the 28 elderly patients showed that the adverse event profile was similar to that observed in patients aged <65 years. The main toxicities were diarrhoea (grade III in 18%) and transaminitis (grade III-IV in 21%).

Efficacy Analysis
The overall response rate in the 45 assessable patients was 31% (PR in 12 patients and CR in 2 patients).
Median time to response was 3.5 months (range: 2-6 months).
51% of patients had SD and 18% had PD.
The activity of the regimen was similar in the subset of elderly patients (n=24) with a 25% response rate and 58% of patients with AD.

After median follow-up the median time to progression was 7 months (range 6-9 months)
24/51 (47%) eligible patients were still alive at last follow-up contact, with a median overall survival of 15 months (range 8-28 months).

Citation: Feliu J, Castanon C, Salud A, Mel JR, Escudero P, Pelegrin A, Lopez-Gomez L, Ruiz M, Gonzalez E, Juarez F, Lizon J, Castro J,, Gonzalez-Baron M (2005) Phase II randomised trial of raltitrexed-oxaliplatin versus raltitrexed-irinotecan as first line treatment in advanced colorectal cancer
Design: Phase II Randomised Trial **Country**: Spain **Setting**: **Aim**: To determine which of the two schemes offered better activity and less toxicity in patients with advanced colorectal cancer
Inclusion criteria Patients with at least one histologically confirmed adenocarcinoma Patients who had received prior adjuvant 5FU-based chemotherapy if they had remained disease free for at 6 months after completion ECOG Performance status ≤2 Life expectancy of at least 3 months Adequate bone marrow function Peripheral neuropathy ≤1 Adequate hepatic and renal function
Exclusion criteria Patients with operable metastatic disease Patients with prior chemotherapy for advanced disease, brain or meningeal metastases History of malignancy apart from basal cell carcinoma or in-situ cervical carcinoma
Sample Size An accrual of 38 patients per arm was deemed to give a 90% chance of selecting the better treatment schedule if the difference in response rate is at least 15% and the smaller response rate is assumed to be 35%. 10% was added to the figures to allow for losses.
Randomisation Method Not specified
Population N=94 patients with recurrent or metastatic colorectal cancer 48 randomised to raltitrexed + oxaliplatin and 46 randomised to raltitrexed + irinotecan
Study Duration
Interventions Ralitrexed + Oxaliplatin: Median dose intensity was 41mg/m^2/week for oxaliplatin and 0.95mg/m^2 for raltitrexed representing 95% of the scheduled doses for both oxaliplatin and raltitrexed. Raltitrexed + Irinotecan: Median dose intensity was 114mg/m^2/week for irinotecan and 0.97mg/m^2/week for raltitrexed representing 98% of the scheduled irinotecan dose and 97% of the scheduled raltitrexed dose
Outcomes Response Rate Time to Progression Toxicity
Results *Tumour Response and Survival* According to intention to treat analysis there was no significant difference in overall response rate for either treatment (p>0.05); the overall response rate was 46% (95% CI 29.5%-57.7%) for raltitrexed+oxaliplatin and 34% (95% CI 19.8%-48.4%) for raltitrexed+irinotecan. In per protocol analysis the overall response rate was 49% (95% CI 33.3%-62.9%) in the raltitrexed+oxaliplatin group and 37% (95% CI 21.2%-51.3%) in the raltitrexed+irinotecan group.

Median duration of response was 7.9 months in the raltitrexed+oxaliplatin group and 9.2 months in the raltitrexed+irinotecan group (log rank p=0.696).

Control of disease (CR, PR and SD) was achieved in 69% of patients receiving raltitrexed+oxaliplatin and in 67% of patients receiving raltitrexed+irinotecan.

At the time of analysis, 77% of patients receiving raltitrexed+oxaliplatin and 74% of patients receiving raltitrexed+irinotecan had progressed.
Median time to progression (TTP) was 8.2 months for patients in the raltitrexed+oxaliplatin arm and 8.8 months for patients in the raltitrexed+irinotecan arm (log rank p=0.656).

After median follow-up of 14 months, 69% of patients in the raltitrexed+oxaliplatin group were still alive and 59% of patients in the raltitrexed+irinotecan arm were still alive

Second line chemotherapy was administered to 65% of patients who progressed in the raltitrexed+oxaliplatin arm and in 68% of patients who progressed in the raltitrexed+irinotecan arm.

Toxicity
65% of patients receiving raltitrexed+oxaliplatin and 70% of patients receiving raltitrexed+irinotecan experienced some toxicity.
The main toxicities were gastrointestinal and haematologic and in general both regimens were well tolerated.
The most common toxicity was hepatic: transaminase elevation was detected in 60% of patients receiving raltitrexed+oxaliplatin and in 62% of patients receiving raltitrexed+irinotecan, with 4 patients in each group experiencing grades 3-4 toxicity.
Significantly more diarrhoea was observed in the raltitrexed+irinotecan arm (52%) compared with the raltitrexed+oxaliplatin arm (31%); p<0.05. The difference is due to the higher rates of grade 1-2 diarrhoea in the raltitrexed+irinotecan arm (39%) and the percentage of patients with grade 3-4 diarrhoea was similar in both groups.

Asthenia was detected in 35% of patients in the raltitrexed+oxaliplatin group and in 52% of patients in the raltitrexed+irinotecan group.
Neurological toxicity was observed was observed in 64% of patients in the raltitrexed+oxaliplatin group, of which 10% was grade 3-4.
Cholinergic syndrome was detected in 19% of patients in the raltitrexed+irinotecan group.
One toxic death occurred in the raltitrexed+oxaliplatin group and 3 in the raltitrexed+irinotecan group.

Citation: Feliu J, Salud A, Escudero P, Lopez-Gomez L (2004) Irinotecan plus raltitrexed as first-line treatment in advanced colorectal cancer: a phase II study *British Journal of Cancer* 90;8:1502-1507
Design: Phase II (single arm) **Country**: Spain **Setting**: **Aim**: To evaluate the efficacy and toxicity of irinotecan (CPT-11) in combination with raltitrexed as first line treatment of advanced colorectal cancer
Inclusion criteria Patients with recurrent or metastatic colorectal cancer with at least one legion histologically confirmed as adenocarcinoma Patients that had received prior 5-FU based chemotherapy were eligible if they had remained disease free for at least six months after completion of adjuvant chemotherapy ECOG performance status ≤2 Life expectancy of at least 3 months Adequate haematological parameters Adequate hepatic function Adequate renal function
Exclusion criteria Patients with operable metastatic disease Patients with any prior chemotherapy for advanced disease, brain or meningeal metastases or a history of any other malignancy except cases of basal cell carcinoma or in situ cervical carcinoma adequately treated.
Sample Size A planned sample of 90 patients was chosen to better estimate efficacy; 20% maximum width of the 95% confidence interval for an expected 35% overall response rate.
Randomisation Method N/A
Population N=91
Study Duration
Interventions CPT-11 350mg/m^2 in a 30 minute infusion on day 1 followed after 30 minutes by a 15-minute infusion of raltitrexed 3mg/m^2
Outcomes Response Rate Clinical Benefit Survival Time to Progression
Results *Patient Characteristics* A total of 487 cycles were given with a median of five cycles per patient (range 1-14). 16 patients (18%) received less than 3 cycles, eight due to disease progression, four due to patient refusal, two moved to a different city and two due to death. *Tumour Response and Survival* Complete response was observed in 5 patients and partial response in 23 for an overall response rate of 34% (95% CI, 25.9-46.5%). 36 patients remained with a stable disease and 19 patients showed a progression Progression free survival was 11.1 months Median survival was 15.6 months

Actuarial 1 year survival was 58%
No relationship was observed between response rate and site of metastases, number of metastatic sites, previous adjuvant chemotherapy, ECOG performance, age or sex.
Progression free survival was longer in patients with ECOG 0 compared with patients with ECOG 1-2 status (13.3 vs. 7.9 months; p<0.002).
Overall survival was longer in patients with ECOG 0 compared with patients with ECOG 1-2 status (21.4 months vs. 8.3 months; p<0.0001).

Toxicity
70% of patients (n=64) suffered some toxicity, usually grade 1-2 though 18% (n=16) of patients developed grade 3-4 side effects
Primary reported toxicities were gastrointestinal and haematological
13 patients developed diarrhoea, 4 had nausea and vomiting, 2 had stomatitis, 3 febrile neutropenia, 5 anaemia, and 3 asthenia.
One patient suffered an episode of atrial fibrillation during the fourth cycle which was terminated using medical treatment.
There were 4 treatment related hospital admissions reported
No toxic deaths occurred
No relationship was observed between the occurrence of grade 3-4 toxicity and patients ECOG status, age or sex.

Citation: Laudani A, Gebbia V, Leonardi V, Savio G (2004) Activity and Toxicity of oxaliplatin plus raltitrexed in 5 fluorouracil refractory metastatic colorectal adenocarcinoma *Anti-Cancer Research* 24;2C:1139-1142
Design: Randomised Phase II Trial **Country**: Italy **Setting**: **Aim**: to evaluate the anti tumour efficacy and safety of a novel oxaliplatin/raltitrexed combination in pretreated advanced colorectal cancer patients.
Inclusion criteria Patients with histologically proven metastatic or locally recurrent colorectal adenocarcinoma and bidimensionally measurable disease according to the WHO criteria. Patients that developed progressive disease after palliative fluorouropyrimidine based chemotherapy or within 3 months of adjuvant chemotherapy completion Age 19-75 years ECOG performance status 0-2 Life expectancy of at least 3 months Adequate bone marrow function, renal function and hepatic functions Geographic accessibility to ensure close follow-up
Exclusion criteria Patients with central nervous system metastases Serious or uncontrolled concurrent medical illness Peripheral neuropathy History of other tumours with the exception of adequately excised uterine cervical of basal skin carcinomas
Sample Size No details given
Randomisation Method N/A
Population N=45
Study Duration Recruitment was between February 2000 and May 2002 No details were given on follow-up
Interventions Raltitrexed plus Oxaliplatin Raltitrexed 30mg/m^2 as a 15 minute intravenous infusion followed 45 minutes later by Oxaliplatin 130 mg/m^2 intravenous infusion as a 2 hour venous infusion on day 1 every three weeks
Outcomes Response Rate (according to WHO criteria and analysis of side effects recorded according to the NCI Common Toxicity Criteria) Duration of Response (measured from onset of the best response to date of disease progression) Progression Free Survival (calculated from the starting date of treatment to the time of progression or relapse) Overall Survival
Results All patients had previous surgery for primary disease and 5 patients also had liver surgery for metastatic disease. Previous treatments included adjuvant radiotherapy (29%) and adjuvant chemotherapy (40%) 93% of patients had received previous front line 5FU based chemotherapy and 18% (n=8) also had second line chemotherapeutic treatment. 31/45 patients had multiple metastases involving 2 or more organ systems; sites of metastases included liver, ling, pelvic region, node, pleura, peritoneum, bone, and adrenals.

A total of 178 courses of chemotherapy were administered to the 40 patients with a median number of 4 cycles/patient (range 1-10).

Response
93% (n=42) patients had adequate follow-up and were fully assessable for response and toxicity.
Overall response rate was 29% (95% CI 16-44%) including one complete response and 12 partial responses.
16% (n=6) patients showed stable disease.

Median time to progression was 4 months (range 1-12+)
Median overall survival was 9 months (range 1-29+)

Toxicity
Haematological toxicity was generally mild to moderate and fully reversible within one week in all patients.
Grade III anaemia occurred in one patient and grade I leukopenia occurred in 2 patients.
Grade III nausea/vomiting was observed in 3 patients and grade II in 10 patients
Grade III diarrhoea was observed in 3 patients and grade II in 3 patients
Transient grade I-II transaminitis occurred in 5 patients
Asthenia was severe in 5 patients
Oxaliplatin induced peripheral neurosensory toxicity in 5 patients but only two experienced moderate to severe neuropathy.
Minor side effects included fever, abdominal pain, renal toxicity, hypotension and stomatitis.

Citation: Maroun JA, Jonker D, Seymour L, Goel R, Vincent (2006) Phase I/II study of irinotecan (camptosar), oxaliplatin and raltitrexed (tomudex) (COT) in patients with advanced colorectal cancer

Design: Non-randomised Phase I/II study

Country: Canada

Setting: Academic Cancer Centres (Canada)

Aim: to determine the recommended doses of irinotecan followed by raltitrexed then oxaliplatin.

Inclusion criteria
Histologically proven advanced or metastatic carcinoma of the colon or rectum with measurable lesions
Age ≥18 years
ECOG performance status ≤2
No prior chemotherapy for metastatic disease
Adequate haematological and biochemical functions
Prior adjuvant chemotherapy with or without radiotherapy
Prior radiation completed >4 weeks prior to enrolment and affecting ≤ of marrow reserve

Exclusion criteria
Prior adjuvant irinotecan or oxaliplatin
Patients receiving concurrent treatment with other experimental drugs or anti-cancer agents
Patients with documented brain metastases or neuropathy ≥2 and serious medical conditions

Sample Size
Three cohorts of 3 patients accrued at each dose level with dose escalation between cohorts.

Randomisation Method
N/A

Population
N=31 in 5 cohorts

Study Duration

Interventions
Irinotecan + Raltitrexed + Oxaliplatin

Outcomes
Complete Response
Partial Response
Response Duration
Stable Disease
Stable Disease Duration
Progressive Disease

Results
 A total of 257 cycles were administered with a range of 1-18 cycles.
Actual dose intensity of each drug per cohort varied between 78% and 100% of the planned dose.
15 patients discontinued the protocol therapy due to progressive disease, two patients with symptomatic disease progression and four patients were taken off the study due to toxicity. Two patients were censored and removed from the study due to becoming eligible for surgery. Five patients refused further treatment further therapy after prolonged treatment. One patient was taken off the study

Toxicity
- 30 patients were evaluable for haematological toxicity.
- Grade IV granulocytopenia occurred in 50% of patients in cohort 4 and 13% of patients in cohort 5.
- Grade 3 thrombocytopenia occurred in 25% of patients in cohort 3 and 13% of patients in cohort 5 (overall incidence = 10%).
- Febrile neutropenia occurred in one patient.
- Although significant incidence and severity of haematological toxicity were reported, it was not considered to

be dose-limiting as per protocol.
- Due to neutropenia in cohorts 2-6 there were delays in dose administration and some dose reductions.
- The magnitude of dose-adjustments seemed related mostly to the dose level of irinotecan

Non-haematologic toxicity
Non-haematologic toxicity was common and dose-limiting, with the most common reported toxicities being gastro-intestinal (diarrhoea, nausea, vomiting and anorexia).
42% (n=13) patients reported grade I-II early onset diarrhoea
Late onset diarrhoea occurred in 93% of patients and was dose limiting; 78% reported grade I-II and 16% reported grade III diarrhoea.
Grade I-II nausea was reported in 80% of patients and grade III in 19% nausea of patients; grade I-II vomiting occurred in 61% of patients and grade III in 26% of patients.
Grade I-II anorexia was reported in 68% of patients and grade III anorexia was reported in 16%.
Stomatitis was infrequent (grade I-II in 16%).
Fatigue was a common side effect and contributed in some cases to patients declining further protocol treatment.
One patient on dose level 3 died following the first dose of treatment though it was concluded that the main cause of death was due to complications from disease progression and bowel obstruction.
Sensory neurotoxicity was common with oxaliplatin; neuromotor symptoms occurred in 33% of patients (n=10), neurosensory symptoms Neurosensory symptoms occurred in 81% of patients (n=25) and were grades I-II in severity. Typically these symptoms are worse on cold exposure and increased in severity and duration in subsequent cycles.

Dose limiting toxicity and maximum tolerated dose
There were no DLT's in the first two dose levels; at the third dose level 2 patients experienced dose limiting gastro-intestinal toxicity; there were no DLT's at the fourth dose level; there were 2 DLT's in the fifth cohort.

Efficacy
30 patients were evaluable for response and objective responses were documented at each dose level.
Partial remissions were recorded in 15 patients for an overall response rate of 45% (95% CI: 31-68%).
Nine patients had stable disease as best response.
Median time to progression was 7.3 months (95% CI 6.51-9.2) and overall median survival was 16.6 months (95% CI: 13.5-21.3)
6/16 patients treated at the recommend phase II dose (220 CPT-11, 2.75 tomudex and 100 oxaliplatin) had a partial response for a response rate of 56.3% (95% CI: 29.9-80.2).

General comments
Magnitude of escalation of each drug was dependent on the analysis of toxicity occurring during the previous cohort of patients and on a decision of which drug to escalate and to what extent.
If one of three patients exhibited dose limiting toxicity (DLT), three more patients were entered into the cohort. If less than 2/6 patients experienced DLT, accrual was initiated at the next dose level. If 2 or more patients exhibited DLT, the dose level was declared to be the maximum tolerated dose (MTD).

Citation: Popov I, Carrato A, Sobrero A, Vincent M, Kerr D (2008) Raltitrexed (Tomudex) versus standard leucovorin modulated bolus 5-fluorouracil: Results from the randomised phase III Pan-European Trial in adjuvant colon cancer 01 (PETACC-1) *European Journal of Cancer* 44;15:2204-2211

Design: Randomised Trial

Country: Multiple

Setting: Unclear

Aim: to assess if raltitrexed (tomudex) is non-inferior to 5FU/LV for relapse free survival (RFS) and overall survival (OS) in adjuvant stage III colon cancer

Inclusion criteria
Patients with stage III (T1-4, N1-2, M0) colon cancer and had previously undergone potentially curative surgical resection with no evidence of residual disease within 56 days before ramdomisation.
Age ≥18
WHO performance status 0-1

Exclusion criteria
None given

Sample Size
The non-inferiority hypothesis required that the HR for raltitrexed versus 5FU/LV be significantly less than 1.25 at the one-sided 0.05 significance level for both RFS and OS.

For 90% power, assuming two years of recruitment and three more years of follow-up and 10% loss on follow-up the study was estimated to require 2765 patients (703 events).

Randomisation Method
Randomisation was done at national data centres and was stratified by institution.
Patients were randomised in a 1:1 ratio
No details were given on method of randomisation

Population
N=1921 (after study recruitment was stopped by the sponsors)

Study Duration

Interventions
Ratlitrexed versus 5FU/LV

Raltitrexed 3mg/m^2 administered as a 15 min infusion on day 1, repeated on day 22 and so on for eight cycles (i.e. every three weeks for a total of 24 weeks).
Leucovorin (LV) 20mg/m^2 administered as an iv bolus followed by a 370-425mg/m^2 iv bolus of 5-fluorouracil (5FU).
Both drugs given on days 1-5, repeated on days 29-33 and so on for six cycles (i.e. every four weeks for a total of 24 weeks).

Outcomes
Primary
Relapse free survival (RFS) (counted from randomisation to the date of either radiologically proven recurrence or death, whichever occurred first).
Overall survival (OS) (counted from randomisation to the date of death from any cause)

Secondary
To compare safety profiles of raltitrexed and 5FU/LV using the NCIC-CTC scoring scales.

Results
An unscheduled analysis of the first 647 patients showed a greater treatment completion rate in the control arm and more withdrawals due to serious adverse events in the raltitrexed arm, this resulted in the sponsor deciding to stop patient inclusion.

The intention to treat population included all patients treated according to the regimen to which they were randomised (n=1921).
The per protocol population included all patients who were eligible, randomised before Jan 16, 1999 and had received at least one dose of study drug (n=993).

A total of 1921 patients were randomised prior to trial closure (969 to 5FU/LV and 952 to raltitrexed); 34 patients were not eligible, 25 patients received non-protocol treatments and treatment data were unavailable for 40. All the patients were kept in the ITT population.

Median follow-up was 49 months

Both groups received a median of 6 cycles of chemotherapy; the planned number of cycles was received by 83.9% (n=786) of patients on the 5FU/LV arm and by 42.4% (n=389) of patients on the raltitrexed arm.
When the study closed prematurely, 28.5% (n=271) patients discontinued raltitrexed treatment while almost all patients continued with 5FU/LV treatment.

Median relative dose intensity of 5-FU was 97% (0.1-134%), whilst the median relative dose intensity of raltitrexed was 104% (9-150%).

Neutropenia, diarrhoea and stomatitis were the most commonly reported grade III-IV adverse effects for patients treated with 5FU/LV.

Adverse Effect	5FU/LV	Raltitrexed
Grade III-IV Neutropenia*	27%	7.9%
Grade III-IV Diarrhoea	14.9% (n=139)	5.4% (n=49)
Grade III-IV Stomatitis	12.4% (n=116)	0.9% (n=8)
Alopecia	13.6% (n=127)	4.9% (n=45)
Grade III-IV transaminase elevation	0.6% (n=6)	20.5% (n=188)

*Grade III-IV neutropenia and was complicated by fever or infection in 4% of cases in the 5FU/LV group and in 2.2% of cases in the raltitrexed group.

Serious adverse events were reported for 18.3% (n=177) of patients in the 5FU/LV group and for 16.3% (n=155) of patients in the raltitrexed group.
Death related to treatment was reported for 0.9% (n=8) patients in the 5FU/LV group and for 2.2% (n=20) of patients in the raltitrexed group.
Overall 60 day mortality was not significantly different between the two arms, with a substantial number of the deaths in the raltitrexed arm occurring after 60 days.
Of the deaths attributed to raltitrexed, 11 were associated with major protocol deviation and the majority of toxic deaths were reported from one Cooperative Group.

Survival
In the intention to treat population, 26.1% of patients had died in the 5FU/LV group compared with 26.5% in the raltitrexed group (HR: 1.04; 90% CI 0.9-1.21)
5-year survival rate was 62.3% (95% CI 58.4-66.1) in the 5FU/LV group and 61.9% (95% CI 55.4-66.1) in the raltitrexed group.

In the per protocol population, 30% of patients in the 5FU group died compared with 29.4% in the raltitrexed group (HR 1.01; 90% CI 0.84-1.23).
5-year survival rate was 60.9% (95% CI 55.5%-65.8%) in the 5FU/LV group and 62.6% (95% CI 57.1-67.7) in the raltitrexed group.

Recurrence
In the intention to treat population 35.8% of patients in the 5FU/LV group had relapsed or dies compared with 38.9% of patients in the raltitrexed group (HR 1.14, 90% CI 1.01-1.29).
5-year recurrence free survival rate was 50.9% (95% CI, 46.6-54.9) on 5FU/LV and 46.7% (95% CI, 42.2-51) on raltitrexed.

In the per protocol population, 39.6% of patients had relapsed or died in the 5FU/LV group compared with 43.1% in the raltitrexed group.
5-year recurrence free survival rate was 50.3% (95% CI 44.8-55.6) in the 5FU/LV group and 47.8% (95% CI 42.3-

53) in the raltitrexed group.
General comments The study's independent data monitoring committee reviewed all trial data accumulated as of June 30, 1999 (1838/2765 patients had been recruited) and recommended suspension of recruitment for 2 months because of the number of drug related deaths in the raltitrexed arm was 17 (1.9%) of 911 patients which was considered unacceptable in the adjuvant setting.

Citation: Santini D, Massacesi C, D'Angelillo RM, Marcucci M (2004) Raltitrexed plus weekly oxaliplation as first line chemotherapy in metastatic colorectal cancer: a multi centre non-randomised phase II study *Medical Oncology* 21;1:59-66

Design: Phase II Trial (non-randomised)

Country: Italy

Setting: Multi-centre

Aim: to evaluate the activity and toxicity of a new raltitrexed and oxaliplatin based regimen as a first line chemotherapy in patients with metastatic colorectal cancer

Inclusion criteria
Patients with pathologically confirmed, metastatic or locally recurrent colorectal cancer
ECOG performance status 0-1
Age 18-75 years
No pulmonary or cardiovascular contraindications
Adequate haematological, hepatic and renal functions
Prior adjuvant chemotherapy completed for at least 6 months

Exclusion criteria
Serum creatinine concentration >1.5mg/dl and creatinine clearance <50ml/min

Sample Size
A planned sample size of 55 patients was chosen to better estimate efficacy; 25% maximum width of the 95% confidence interval for an expected overall 40% response rate.

Randomisation Method
N/A

Population
N=44

Study Duration
Median follow-up was 14 months (range 6-18 months)

Interventions
Raltitrexed plus oxaliplatin

Raltitrexed 3mg/m^2 given as 15 min intravenous infusion on day 1
Oxaliplatin 70mg/m^2 given as 2 hour infusion on day 1 and day 8
The cycle was repeated every 21 days.

Outcomes
Analysis of tumour response and feasibility

Time to disease progression (TTP) (Measured from the date of registration to the date of documented progressive disease or death)
Overall Survival (OS) (measured from time of registration to the date of death from any cause)
Median time to response (calculated from the date of response registration to the date of disease progression or death).

Results
 8/44 patients had previously received 5-FU-based adjuvant chemotherapy
In this study, 241 chemotherapy courses were administered; 5 patients received less than three cycles, 19 patients six to eight cycles and 5 patients received nine cycles.

Response
In 5 patients persistent toxicity resulted in early discontinuation of treatment before first evaluation.

For intention to treat analysis 44 patients were evaluated for efficacy; 4 complete responses, 16 partial responses, 18 stable disease and 6 failures.

Overall response rate was 45.5% (95% CI: 30.1-54.1%)
Tumour control rate (response + stable) was 86.4% (95% CI 45.1-91.1%
Median time of response duration was 4.8 months (range: 1.4-16)
Of the four patients who achieved complete response one had liver and bladders metastases 5 months after chemotherapy discontinuation, two had peritoneal metastases 9 and 8 months after chemotherapy discontinuation and one had abdominal lymph node metastases 4 months after chemotherapy discontinuation.

Follow-up and Survival
Median overall survival for eligible patients was more than 14.8 months (not reached the time of analysis; range 3-23 months) (95% CI; 11.2-18.4)
72.7% (32/44) of patients were still alive and 12 patients died of for progressive disease.
Median time to disease progression was 6 months (95% CI; 4.4-7.6 months)
Second line chemotherapy was performed in 27 patients (CPT-II + 5FU in 15 patients and prolonged infusional 5FU in 8 patients and oxaliplatin plus 5FU in 4 patients)
Two patients with partial response and metastatic disease confined to the lung and spleen, respectively, were submitted to radical surgery of the residual disease after discontinuation of first line chemotherapy and then treated with second line anticancer treatments.

Toxicity
Neutropenia was the most common haematological side effect: Grade III in 15.9% of patients.
Grade IV thrombocytopenia requiring hospitalisation was required in 2 patients
Transient transaminitis, neurotoxicity, asthenia and diarrhoea were the most common non-haematological side effects.
Grade III transaminitis was reported in 36.4% (n=16), neurotoxicity in 9.1% (n=4) and asthensia 9.1% (n=4) patients.
Severity of neurotoxicity was appeared related to the cumulative dose of oxaliplatin: patients with grade 0 neurotoxicity received a mean cumulative dose of 560 mg/m^2; patients with grade I received a mean cumulative dose of 723 mg/m^2; patients with grade II and III received a mean cumulative dose of 900 mg/m^2. No patients developed grade III neurotoxicity before a total cumulative dose of 530mg/m^2.
6.8% (n=3) patients experienced a grade IV non-haematological toxicity (diarrhoea).
Treatment was discontinued in 29.5% (n=13) patients due to toxicity; treatment was discontinued in 5 patients before the third cycle, before the sixth cycle in 6 patients and before the 9th cycle in 2 patients
According to the treatment plan, 4 patients had a 25% dose reduction of both cytotoxic agents due to grade III transaminitis, diarrhoea or thrombocytopenia.
In 7 patients raltitrexed dosage was modified due to a declining creatinine clearance.
Treatment was delayed at least once for 27 patients due to liver toxicity, thrombocytopenia, neutropenia, fever, anaemia, and atrial fibrillation.

Citation: Vyzula R, Kocakova I, Demlova R, Kiss I (2006) Raltitrexed plus oxaliplatin in the second line treatment of metastatic colorectal cancer *Neoplasma* 53;2:119-127
Design: Phase II study **Country**: Czech Republic **Setting:** Hospital **Aim**: to evaluate the efficacy of combined chemotherapy with raltitrexed plus oxaliplatin (TOMOX) as second line treatment in patients with metastatic colorectal cancer.
Inclusion criteria Patients aged between 18 and 70 years with histologically confirmed metastatic, non-resectable colorectal adenocarcinoma, progressing after first line palliative chemotherapy with the last chemotherapy treatment to have been ≥4 weeks prior to study entry. Performance status 0-2 Life expectancy of ≥3 months At least one measurable metastatic lesion by CT Adequate haematological parameters, liver function and renal function
Exclusion criteria Patients who had received >1 line of chemotherapy Patients with symptomatic central nervous system metastases, bone metastases alone, carcinomatous leptomeninigitis, infection or previous cancer history apart from resolved cervical cancer or basal cutaneous carcinoma Pregnant or lactating women Patients with paraesthesia greater than NCI-CTC grade 1 Patients in whom raltitrexed or oxaliplatin were contraindicated.
Sample Size
Randomisation Method N/A
Population N=51
Study Duration Median follow-up time was 48.9 weeks (range 16.7-128 weeks)
Interventions Raltitrexed plus Oxaliplatin Raltitrexed 3mg/m^2 given as a 15 minute intravenous (IV) infusion followed 45 minutes later by oxaliplatin 130mg/m^2 IV as 2 hour infusion on day 1, repeated every 3 weeks until disease progression.
Outcomes *Primary* Efficacy (Objective Response Rate) *Secondary* Overall Survival Time to Progression Toxicity
Results 17 patients had received prior adjuvant chemotherapy Most patients (78.3%) had received irinotecan as first line, either as monotherapy or in combination with an IV bolus or continuous 5FU/FA regimen. The most common site of metastases was the liver (76.5%) 47.1% of patients had more than one site of metastatic disease

Patients received a median of 6 cycles of TOMOX (range 1-11 cycles) with a total of 260 cycles administered. Median duration of TOMOX treatment was 18 weeks (range 3.3-35 weeks).
Reasons for discontinuing treatment included progressive disease in 35 patients (68.6%), toxicity in 8 patients (15.7%) and a combination of both in one patient (2%).

Efficacy, time to progression and survival
47/51 patients were evaluable.
17% (n=8) experienced partial response, 59.6% (n=28) experienced stable disease and 23.4% (n=11) experienced progressive disease after 3 cycles of chemotherapy, there were no complete responses observed.
In the 29 patients that had received six cycles of chemotherapy at the time of analysis, 3.5% (n=1) experienced a partial response, 44.8% (n=13) experienced stable disease and 51.7% (n=15) experienced progressive disease.
Median time to progression was 18 weeks (range 4-37 weeks)
Median overall survival was 54.4 weeks with 25 percentage overall survival 90.5 weeks and 75 percentage overall survival 34.2.

Toxicity
No grade 4 toxicity was observed and the only grade 3 toxicities were leukopenia and diarrhoea

General comments
First line treatment included:
FOLFIRI or weekly modifications of FOLFIRI in patients with good performance status and no contraindications to Irinotecan.
In patients whose PS deteriorated following surgery and/or patients at risk of obstructive ileus, 5FU/FA Mayo or deGramont regimens were administered.
Monotherapy with irinotecan was administered to patients with disseminated disease and to patients with possible resistance to 5FU and to patients experiencing 5FU intolerance.

4.5. Adjuncts to Chemotherapy in Unresectable Metastatic Disease

4.5.1. What is the most effective additional treatment to systemic chemotherapy to achieve cure or long-term survival in patients with apparently unresectable metastatic disease?

Short Summary

This topic aimed to determine whether patients originally identified as being incurable and with poor long term prognosis due to the presence of unresectable metastatic disease can achieve cure or long-term survival through treatment with systemic chemotherapy with or without additional treatments. There was no comparative evidence with which to address this topic.

A systematic review of the literature identified no studies comparing any combination of the interventions of interest for this topic and although a small number of non comparative studies, investigating individual interventions were identified, it was considered that the evidenciary benefits of including such studies was low and would not inform any recommendations regarding the best form of treatment for this patient group.

Review Protocol

Population	Intervention	Comparison	Outcomes
Colorectal cancer patients with unresectable metastatic disease who have had systemic chemotherapy	Any combination of treatments including: • Ablation (Covered by IP92 – special arrangements) • Surgery • Loco regional therapy - Hepatic Artery infusional and Trans arterial chemoembolisationFurther systemic chemotherapy • Best Supportive care	• Each other	• Survival • Quality of life • Complications • Risks/Safety

Following a systematic search of relevant data sources (see appendix .1), the information specialist created a database of potentially relevant studies. All titles and abstracts were sifted by a single reviewer. Queries about inclusion were clarified by the GDG topic subgroup. The full studies were then obtained and reviewed and relevant studies were included in the final evidence review.

All update searches were sifted by a single reviewer and the list of potentially relevant studies was also checked for irrelevant studies by the GDG subgroup. Only studies which all subgroup members were in agreement were excluded. The remaining studies were obtained and reviewed with relevant studies included in the final evidence review.

The GDG felt that with the number of interventions of interest, only high level should be reviewed in the first instance (randomised trials) and only if such evidence was not available should the searches be extended to include lower level studies (case series/observational studies).

Date limits set by the GDG were from 1996 onwards as this was when oxaliplatin and irinotecan became available for use and so anything prior to this would not be relevant to current UK practice.

Some other issues that were to be considered when reviewing the evidence included; surgical techniques (two-stage operations, portal vein embolisation), the addition of targeted therapies to chemotherapy, ablative techniques, and selective radiotherapy (Sirtex spheres and IMRT)
There was a need to consider sites of extrahepatic disease eg lung, nodal peritoneal and whether some have a better prognosis than others.

When reviewing evidence from clinical trials, specific issues to consider include:
• Level of staging at which treatment(s) applied
• Completion of planned care without alteration
• Patient response
• Symptom control and delay
• Adverse incidents
• Patient experience and quality of life
• Overall survival rate(s)

Reasons for Exclusion of Individual Studies:
Study population not applicable to PICO
Interventions of interest not investigated
Outcomes of interest not investigated/reported
Foreign Language studies
No comparator to allow judgement on relative
efficacy of treatments
Quality of the included studies
Systematic review of RCTs (n = 0)
Systematic review of combined study designs (n
=0)
Randomized controlled trial (n = 0)
Prospective cross sectional study (n=0)
Case Series Studies (n=0)

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┌─────────────────────┐          ┌─────────────────────┐
│ 660 (+33)           │          │ 562 (+25)           │
│ possibly relevant   │    →     │ papers excluded     │
│ papers identified   │          │ based on title &    │
│                     │          │ abstract            │
└─────────────────────┘          └─────────────────────┘
           ↓
┌─────────────────────┐          ┌─────────────────────┐
│ 98 (+8)             │          │ 98 (+)              │
│  papers obtained    │    →     │ papers excluded     │
│ for appraisal       │          │                     │
└─────────────────────┘          └─────────────────────┘
           ↓
┌─────────────────────┐
│ 0                   │
│  papers included    │
│ in evidence table   │
└─────────────────────┘
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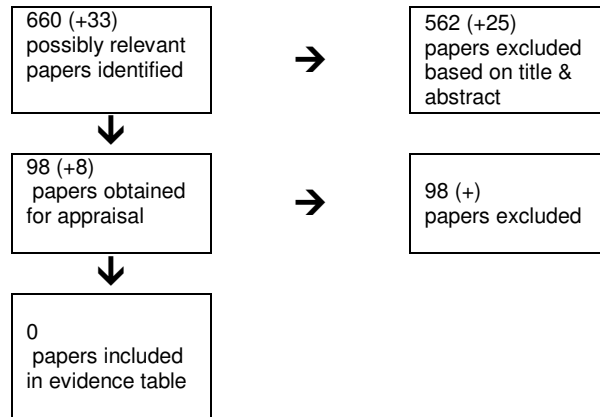
Volume of evidence
There was no evidence from randomised trials for any of the interventions under investigation and therefore the searches were extended to investigate whether there was any evidence from large cross sectional studies or case series. No comparative evidence relating to this topic could be found.

Applicability
There were no comparative studies identified as being relevant to the topic of interest and only a small number of non-comparative single arms studies which were considered to be of little use in the development of recommendations; the lack of a comparative study meant that there was no evidence available on which to base a decision on the relative efficacy and appropriateness of one intervention over another in this group of patients.

Consistency
It is not possible to comment on the consistency of the evidence as there are not enough data to compare.

Evidence Statement
There is topic represents a very specific, minority population of colorectal cancer patients. All patients in the population will be identified as having unresectable liver metastases and therefore there is little chance of curative surgery; however a small minority of patients will have their unresectable liver metastases converted to resectable liver metastases through the course of their treatment which, may lead to the patient undergoing curative surgery where it was initially deemed not to be a possible approach. There is no way to identify the patients who will 'convert to being resectable' and therefore there is a need to address whether it is appropriate to treat all initially unresectable metastasis as though they can be converted to being resectable through the course of normal treatment and whether any particular treatment approaches increase the chances of metastases becoming resectable.
A systematic review of the literature identified no studies comparing any combination of the interventions of interest for this topic and although a small number of non comparative studies, investigating individual interventions were identified, it was considered that the evidentiary benefits of including such studies was low and would not inform any recommendations regarding the best form of treatment for this patient group.

Updated Evidence
Update searches found a small number of low quality studies which were again non-comparative and investigating only single interventions.

5. Ongoing Care and Support

5.1.   Follow-up after Apparently Curative Resection

5.1.1. In asymptomatic patients who have undergone treatment with curative intent for colorectal cancer, what is the optimal method(s), frequency and duration of follow-up?

Short Summary
There is moderate quality evidence of significant overall survival benefit at 5 years with intensive follow up. (Tjandra et al, 2007 and Jeffery et al, 2007).

Low quality evidence suggests that there is uncertainty as to whether more intensive follow up confers a disease specific survival benefit when compared with less follow up (Jeffery et al 2007).

There is moderate quality evidence that the number of all recurrences detected is similar with both intensive and minimal follow up. (Jeffery et al, 2007 and Tjandra et al, 2007).

There is low quality evidence that significantly more asymptomatic recurrences are detected in the intensively followed up group.

The time to recurrence is significantly less with intensive follow up but the evidence is of low quality (Jeffery et al, 2007 and Tjandra et al, 2007)

There is low quality evidence that the number of curative procedures attempted for recurrence is significantly more with intensive follow up. (Jeffery et al, 2007 and Tjandra et al, 2007)

Intensive versus less intensive follow-up
From two systematic reviews and meta-analysis (Jeffery et al, 2007 and Tjandra and Chan, 2007) more intensive follow up was associated with improved 5 year overall survival.

Jeffery et al (2007) recorded and odds ratio of 0.73 (95% CI 0.59-0.91) in favour of more intensive follow-up which translated into a risk difference of -0.06 (95% -0.11 to -0.73). Tjandra and Chan et al (2007) reported improved overall survival at 5 years for intensive follow-up versus less intensive follow-up (OR 0.74 (95% CI, 0.59-0.93).

No significant difference in the number of recurrences detected was observed when comparing more intensive and less intensive follow-up though Tjandra and Chan (2007) reported that more intensive follow up detected significantly more asymptomatic recurrences than less intensive follow-up; odds ratio 3.42 (95% CI, 2.17-5.41).

Specific tests
There very little evidence with which to support the use of any specific tests in follow-up; a single study reported on the use of colocoscopy as part of follow-up.

In examining the intensity of colonoscopy (i.e. more versus less colonoscopy) there is low quality evidence that intensive colonoscopic surveillance does not offer any advantage in overall survival versus less intensive colonoscopic surveillance, nor was there evidence that it increases the number of recurrences detected ((Wang et al, 2009Wang et al, 2009).

Complications
1 study reported adverse events from follow up. 2 perforations and 2 GI bleeds from a total of 731 colonoscopies.

Quality of life
1 study (597 patients) reported a small but significant increase in the quality of life of patients associated with more frequent follow up visits.(Kjeldsen et al,1997)

A second study (203 patients) reported no difference in quality of life, anxiety, depression, and patient satisfaction in patients followed up in different settings; GP / hospital. (Wattchow et al, 2006)

Updated Evidence
A single prospective comparative cohort study was identified during update searchs (Laubert et al, 2010) which reported that 5 year overall survival was significantly better in the more intensively followed group versus the

minimally followed group and the no follow-up group (p<0.001) though no statistically significant difference was observed in the rates of R0 resection of recurrent disease between the groups.

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	intensive follow up	less intensive or no follow up	Odds Ratio (95% CI)	Quality	Importance
					**Quality assessment**			**Summary of findings**			
								No of patients	**Effect**		

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	intensive follow up	less intensive or no follow up	Odds Ratio (95% CI)	Quality	Importance
Overall survival at 5 years Jeffery et al 2007 (follow-up mean 5 years)											
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	218/793 (27.5%)	274/808 (33.9%) / 33.9%	OR 0.73 (0.59 to 0.91)	⬜⬜⬜⬜ MODERATE	CRITICAL
overall survival at 5 years Tjandra 2007 (follow-up mean 5 years)											
8	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	321/1474 (21.8%)	373/1449 (25.7%) / 25.7%	OR 0.74 (0.59 to 0.93)	⬜⬜⬜⬜ MODERATE	CRITICAL
no of recurrences Jeffery 2007 (follow-up mean 5 years)											
7	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	354/985 (35.9%)	351/953 (36.8%) / 36.8%	OR 0.91 (0.75 to 1.1)	⬜⬜⬜⬜ MODERATE	CRITICAL
no of recurrences (all site) Tjandra 2007 (follow-up mean 5 years)											
8	randomised trials	serious[1]	no serious inconsistency[2]	no serious indirectness	no serious imprecision	none	429/1474 (29.1%)	417/1449 (28.8%) / 28.8%	OR 0.97 (0.82 to 1.14)	⬜⬜⬜⬜ MODERATE	CRITICAL
no of asymptomatic recurrences Tjandra 2007 (follow-up mean 5 years)											
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	162/858 (18.9%)	52/821 (6.3%) / 6.3%	OR 3.42 (2.17 to 5.41)	⬜⬜⬜⬜ LOW	CRITICAL
curative surgery attempted for recurrence Jeffery 2007 (follow-up mean 5 years)											
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	95/818 (11.6%)	40/795 (5%) / 5%	OR 2.41 (1.63 to 3.54)	⬜⬜⬜⬜ LOW	CRITICAL
curative surgery attempted for recurrence Tjandra 2007 (follow-up mean 5 years)											
7	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	86/354 (24.3%)	35/353 (9.9%) / 9.9%	OR 2.81 (1.65 to 4.79)	⬜⬜⬜⬜ LOW	CRITICAL
disease specific survival Jeffery 2007 (follow-up mean 5 years)											
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3,6]	none	73/343 (21.3%)	82/361 (22.7%) / 22.7%	OR 0.92 (0.64 to 1.31)	⬜⬜⬜⬜ LOW	CRITICAL

[1] the majority of studies in this comparison had unclear reporting of allocation concealment. This could introduce significant bias to the randomisation process and the results overall.
[2] heterogeneity not reported
[3] The total number of event is low (less than the 300 rule of thumb). This can introduce imprecision to the result.
[4] heterogeneity: p=0.00002, I squared=91%, all 3 studies favour intensive follow up.
[5] heterogeneity: p<0.00001, I squared not given, 4 out of 5 studies favour intensive follow up.
[6] The CI includes 1 and the lower limit is <than 0.75 and the upper limit is > 1.25

Table 1: Intensive Follow up versus less intensive or no follow up

Review Protocol

Population	Intervention	Comparison	Outcomes
In asymptomatic patients who have undergone treatment with curative intent for colorectal cancer, including patients treated for metastatic cancer	Intensive packages including: • Colonoscopy • Imaging • Clinical Exams • CEA Tumour Marker tests • Timing and duration	• Do nothing • Less intensive packages	• Survival • Recurrence • Quality of life • Metachronous primaries • Late effects

Evidence Level to consider:
High level in the first instance if not available then look to lower level.

Date limits:
CEA -1990 onwards
CT -1995 onwards – helical thing
Colonoscopy -1990 onwards – video scopes
Look at Cochrane review

Other issues to consider:
Need to consider:
- What are the best tests to do (examination, tumour marker blood tests, U/S, CT scans for chest/abdo/pelvis)
- Frequency of tests
- Who/where should tests be performed
- Whether follow-up influences survival
- Time to discharge patients

Should follow-up be different for different stage at presentation? Or if metastatic disease has been resected?

Reasons for excluding papers
Reports of experimental tests for follow up.
Guidelines which were out of date or their grading of evidence was unclear.
Non randomised studies
Older systematic reviews
Reviews of non-randomised studies

Quality of the included studies
Systematic review of RCTs (n = 2)
Systematic review of combined study designs (n = 0)
Randomized controlled trial (n = 1)
Prospective cross sectional study (n = 0)
Case Series Studies (n = 1)

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188 (131)
possibly relevant          128 (+112)
papers identified          papers excluded
                           based on title &
                           abstract

60 (+19)
papers obtained            57 (+18)
for appraisal              papers excluded

3 (+1)
papers included
in evidence table
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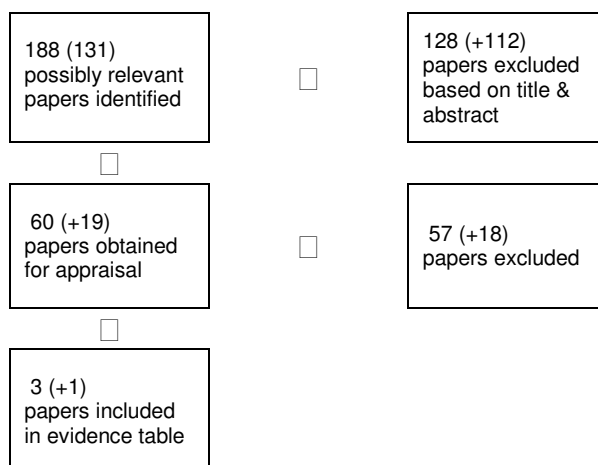
Volume of evidence

There is a wealth of studies carried out over the last 20 years on this topic. Including 7 non-randomised studies and 10 randomised controlled trials.

The studies vary greatly in methodology as well as in the follow up regimens they studied. Individually some of the studies are in favour and some are not in favour of intensive follow up for colorectal cancer, however there have also been a number of meta-analyses that have pooled the results of these studies. All meta-analyses whether of randomised or non-randomised studies conclude that there is a survival advantage with intensive follow up.

For the purposes of this systematic review the two most recent meta-analyses (Jeffery et al, 2007, and Tjandra et al, 2007) as well as the only RCT that has been published following the publication of these two systematic reviews (Wang et al, 2009) have been appraised.

In terms of their methodological quality as systematic reviews both reviews addressed a focused question that is directly relevant to the PICO.
The literature searches were appropriate and rigorous and the methodology was clearly stated and appropriate. Each review included 8 RCTs in total; they had 7 in common and 1 different.

Jeffery et al (2007) included an RCT that had quality of life as its primary outcome (Wattchow et al 2006) but excluded the GILDA trial as published results (Grossman et al, 2004) were on less patients than what they initially set out to recruit (1240 patients rather than target of 2920) and follow up is short (recruitment started in 1998 and the trial is still ongoing).

Tjandra et al, (2007) did not include the trial by Wattchow et al, 2006 but included the preliminary results of the Gilda trial (Grossman et al, 2004). However they have done a sub group analysis excluding the GILDA results and found that the trial exclusion did not alter the overall result of their meta analysis.

Both reviews assessed the quality of each individual study they included. 7 of the 8 RCTs in Jeffery et al (2007) and all of the RCTs in Tjandra et al (2007) had unclear reporting of their allocation concealment relevant to their randomisation process.

Both reviews in addition to 5 year survival have carried out a number of comparisons addressing different outcomes. Some of these are reported to be statistically significant and in others the pooled groups are either too small or too heterogeneous.

The RCT by Wang et al 2009 is looking specifically at colonoscopic surveillance in an intense and non-intense pattern of follow up. The main criticism of this trials relates to the methodology;it was unclear whether there was appropriate blinding and if this were not the case then this could introduce significant bias.

Applicability

Both systematic reviews and the RCT referred to populations similar to that of the guideline PICO. That is asymptomatic patients with non-metastatic colorectal cancer that has been treated with curative intent. Patients may or may not have had adjuvant treatment. Males and females with histologically proven adenocarcinoma of colon or rectum, staged as T1,2,3,4; N0,1,2; M0; Duke's A,B,C

Consistency

There is clinical heterogeneity of the follow up regimen used by the different trials. Some of the trials compared intensive follow up with less intensive follow up and some with no follow up at all. In addition the intensity of the intensive follow up regimen was variable and indeed the intensive regimen of one study was equal to the less intensive regimen of another study.
The individual trials have been conducted over a considerable time span.
In some studies patients were receiving adjuvant chemotherapy and radiotherapy and in others not.
All of these factors contribute towards clinical heterogeneity.
Heterogeneity has been addressed for each pooled comparison and is included in the detailed GRADE appraisal of the evidence.

Evidence statement

Intensive versus less intensive follow-up
From two systematic reviews and meta-analysis (Jeffery et al, 2007 and Tjandra and Chan, 2007) more intensive follow up was associated with improved 5 year overall survival.
Jeffery et al (2007) recorded and odds ratio of 0.73 (95% CI 0.59-0.91) in favour of more intensive follow-up which translated into a risk difference of -0.06 (95% -0.11 to -0.73). Tjandra and Chan et al (2007) reported improved overall survival at 5 years for intensive follow-up versus less intensive follow-up (OR 0.74 (95% CI, 0.59-0.93).

Jeffery et al (2007) reported no significant difference between intensive follow-up ane less intenstive follow up for the number of recurrences with an odds ratio of 0.91 (95% CI, 0.75-1.10) and a risk difference between the groups of -0.02 (95% CI, -0.08 to 0.05). Tjandra and Chan (2007) also reported no significant difference between the groups for number of recurrences (all site) with an odds ration of 0.97 (95% CI, 0.82-1.14).
Tjandra and Chan (2007) reported that more intensive follow up detected significantly more asymptomatic recurrences than less intensive follow-up; odds ratio 3.42 (95% CI, 2.17-5.41).

Specific tests
There very little evidence with which to support the use of any specific tests in follow-up; a single study reported on the use of colocoscopy as part of follow-up.
In examining the intensity of colonoscopy (i.e. more versus less colonoscopy) there is low quality evidence that intensive colonoscopic surveillance does not offer any advantage in overall survival versus less intensive colonoscopic surveillance. (Wang et al, 2009). The evidence is again low quality that frequent colonoscopic surveillance increases the number of recurrences detected (Wang et al, 2009). Equally low quality evidence suggests frequent colonoscopy does increase the number of curative operations attempted for recurrence (Wang et al, 2009). There is also low quality evidence that the time to the diagnosis of a recurrence is reduced and the time of survival after recurrence is diagnosed is increased (Wang et al, 2009).

Complications
1 study reported adverse events from follow up. 2 perforations and 2 GI bleeds from a total of 731 colonoscopies.

Quality of life
1 study (597 patients) reported a small but significant increase in the quality of life of patients associated with more frequent follow up visits.(Kjeldsen et al,1997)
A second study (203 patients) reported no difference in quality of life, anxiety, depression, and patient satisfaction in patients followed up in different settings; GP / hospital. (Wattchow et al, 2006)

Updated Evidence:
Update searches found a single prospective cohort study (Laubert et al. 2010) comparing different surveillance strategies in patients who had undergone potentially curable resection of colorectal cancer and the impact on long term outcomes. The study compared the impact of intensive follow-up (meeting more than 70% of scheduled follow-up appointments) versus minimal follow-up (meeting <70% of scheduled appointments) and no follow-up (no surveillance at all).
Results of from the study reported overall 5-year survival of 79% in the intensive group, 76% in the minimal group and 54% in the no follow-up group (p<0.0001 in favour of more intensive surveillance). Ten year overall survival was 65% in the intensive group, 50% in the minimal group and 31% in the no follow-up group (p<0.0001 in favour of more intensive follow-up).
For intensive versus minimal surveillance, 5 year survival was significantly better in the intensive group (OR 1.48; 95% CI, 1.135-1.929) and for intensive versus no surveillance 5 year survival was also significantly better in the intensive group (OR 2.606; 95% CI, 1.983-3.425).
Median 5 year survival was significantly better in the intensively followed group when compared with the minimally followed group (p<0.034) and in the intensively followed group compared with no follow-up (p<0.0001). There was no significant difference in the rate of possible R0 resections between the intensively followed group and either other group; though significantly more R0 resections of distant metastases were possible in the intensively followed group compared with the no surveillance group (p=0.002).

Question: Should intensive follow up vs less intensive or no follow up be used for non metastatic colorectal cancer?

Bibliography:
1.Jeffery M, Hickey BE, Hider PN. Follow-up strategies for patients treated for non-metastatic colorectal cancer. Cochrane Database of Systematic Reviews. 2007. Issue 1. 2007
2. Tjandra JJ, Chan MK. Follow up after curative resection of colorectal cancer: A meta-analysis. Diseases Colon & Rectum 2007;50(11):1783-1799

		Quality assessment					Summary of findings				Importance
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	intensive follow up	less intensive or no follow up	Odds Ratio (95% CI)	Quality	
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overall survival at 5 years Tjandra 2007 (follow-up mean 5 years)											
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curative surgery attempted for recurrence Jeffery 2007 (follow-up mean 5 years)											
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	95/818 (11.6%)	40/795 (5%) 5%	OR 2.41 (1.63 to 3.54)	☐☐☐☐ LOW	CRITICAL
curative surgery attempted for recurrence Tjandra 2007 (follow-up mean 5 years)											
7	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	86/354 (24.3%)	35/353 (9.9%) 9.9%	OR 2.81 (1.65 to 4.79)	☐☐☐☐ LOW	CRITICAL
disease specific survival Jeffery 2007 (follow-up mean 5 years)											
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3,6]	none	73/343 (21.3%)	82/361 (22.7%) 22.7%	OR 0.92 (0.64 to 1.31)	☐☐☐☐ LOW	CRITICAL

[1] the majority of studies in this comparison had unclear reporting of allocation concealment. This could introduce significant bias to the randomisation process and the results overall.
[2] heterogeneity not reported
[3] The total number of event is low (less than the 300 rule of thumb). This can introduce imprecision to the result.
[4] heterogeneity: p=0.00002, I squared=91%, all 3 studies favour intensive follow up.
[5] heterogeneity: p<0.00001, I squared not given, 4 out of 5 studies favour intensive follow up.
[6] The CI includes 1 and the lower limit is <than 0.75 and the upper limit is > 1.25

Table 1: Intensive Follow up versus less intensive or no follow up

Question: Should more tests vs fewer tests be used for non metastatic colorectal cancer follow up?

Bibliography:
Wang T, Cui Y, Huang WS, Deng YH, Gong W, Li CJ, Wang JP. The role of postoperative colonoscopic surveillance after radical surgery for colorectal cancer: a prospective randomised clinical study. Gastrointestinal endoscopy2009;69(3):609-615.

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	more tests	fewer tests	Effect (95% CI)	Quality	Importance
								16.1%			
more v less colonoscopy for overall survival (Wang 2009) (follow-up mean 5 years)											
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	Serious[2]	none	42/165 (25.5%)	50/161 (31.1%) / 31.1% / 3.4%	HR 1.41 (0.92 to 2.14)	⊕⊕⊕⊕ LOW	CRITICAL
more v less colonoscopy for recurrence (anastomotic and metachronous) Wang 2009 (follow-up mean 5 years)											
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	Serious[2]	none	13/165 (7.9%)	18/161 (11.2%) / 11.2%	OR 1.35 (0.64-2.83)	⊕⊕⊕⊕ LOW	CRITICAL
more v less colonoscopy for anastomotic recurrence Wang 2009 (follow-up mean 5 years)											
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	Serious[2]	none	10/13 (76.9%)	7/18 (38.9%) / 38.9%	OR 5.24 (1.06 to 26)	⊕⊕⊕⊕ LOW	CRITICAL
more v less colonoscopy for curative surgery attempted for recurrence (Wang 2009) (follow-up mean 5)											
1	randomised trials	Serious[1]	no serious inconsistency	no serious indirectness	Serious[2]	none	9/13 (69.2%)	8/18 (44.4%) / 44.4%	OR 0.12 (0.02 to 0.91)	⊕⊕⊕⊕ LOW	CRITICAL

[1] there was no blinding in the study introducing high risk of performance and detection bias.
[2] the total number of events is very low (less than 300 rule of thumb).

References

Jeffery M, Hickey BE, Hider PN. Follow-up strategies for patients treated for non-metastatic colorectal cancer. Cochrane Database of Systematic Reviews. 2007. Issue 1. 2007

Tjandra JJ, Chan MKY. Follow-up after curative resection of colorectal cancer: a meta-analysis. Diseases Colon & Rectum. 2007 50(11):1783-1799

Wang T, Cui Y, Huang WS, Deng YH, Gong W, Li CJ, Wang JP. The role of postoperative colonoscopic surveillance after radical surgery for colorectal cancer: a prospective randomised clinical study. *Gastrointestinal endoscopy* 2009;69(3):609-615.

Laubert T, Bader FG, Oevermann E, Jungbluth T, Unger L, Roblick UJ *et al.*(2010) Intensified surveillance after surgery for colorectal cancer significantly improves survival. *Eur J Med Res* **15(1):**25-30.

Kjeldsen BJ, Thorsen H, Whalley D *et al* (1997) A prospective randomised study of follow-up after radical surgery for colorectal cancer *The British Journal of Surgery* 85;5:666-669
Wattchow DA, Weller DP, Esterman A et al (2006) General practice versus surgical based follow-up for patients with colon cancer: randomised controlled trial *British Journal of Cancer* 94;8:1116-1121

Citation: Jeffery M, Hickey BE, Hider PN. Follow-up strategies for patients treated for non-metastatic colorectal cancer. Cochrane Database of Systematic Reviews. 2007. Issue 1. 2007

Design: Systematic Review and Meta-analysis **Country**: New Zealand **Aim**: To review the available evidence concerning the benefits of intensive follow-up of colorectal cancer patients with respect to survival. Secondary endpoints included: time to diagnosis of recurrence, quality of life (QoL) and the harms and costs of surveillance and investigations.

Inclusion criteria: Only randomised controlled trials comparing different follow up strategies for patients with non-matastatic colorectal cancer (CRC) treated with curative intent were included.

Exclusion criteria Non-randomised studies Ongoing randomised trials (COLFOL, FACS, GILDA)

Population: Patients with non-matastatic colorectal cancer (CRC) treated with curative intent +/- adjuvant treatment. Males and females of any age with histologically proven adenocarcinoma of the colon or rectum staged as T1,2,3,4; N0,1,2; M0. Duke's stage A, B and C.

Interventions: Strategies of follow-up.
This included comparisons of
        follow-up versus no follow up
        follow-up strategies of varying intensity
        follow-up in different healthcare settings.
 	
Follow up visits with health professionals included:
        symptom enquiry
        clinical examination
        procedures (e.g. colonoscopy)
        blood tests
        faecal analysis
        radiological examinations.

Outcomes
Primary: Overall Survival (OS)
Secondary:
        Disease specific survival
        Time to diagnosis of recurrence
        Incidence of surgery(with curative intent) for recurrence
        Interval recurrences (between planned visits)
        Quality of life
        Harms
        Cost of surveillance and investigations

Results Eight studies were included (2141 patients in total): • Overall survival benefit at five years exists for patients undergoing more intensive follow up • The absolute number of recurrences was similar • For disease free survival there is no significant survival benefit between intensive follow up and less intensive. • There is a mortality benefit for performing more tests versus fewer tests • There is a mortality benefit for performing liver imaging versus no liver imaging • The weighted mean difference for the time to recurrence was significantly reduced but there was significant heterogeneity amongst the studies.

- There was significantly more curative surgical procedures in the intensively followed arm
- No useful data on quality of life, harms or cost-effectiveness were available.

Comparison	Studies included	No of patients	Overall survival at 5 years expressed as odds ratio (OR) and risk difference (RD) S = significant NS = not significant	No of recurrences expressed as odds ratio (OR) and risk difference (RD) S = significant NS = not significant
Intensive FU v minimalist FU	6 of 8	1601	OR 0.73 (CI 0.59, 0.91) **S** RD -0.06 (CI -0.11, -0.02) **S**	
	7 of 8	1938		OR 0.91 (CI 0.71, 1.1) NS RD -0.02 (CI -0.06, 0.02) NS
Clinic visit v No clinic visit	1 of 8	107	OR 0.57 (CI 0.26, 1.29) NS RD -0.12 (CI -0.3, 0.05) NS	
	2 of 8	444		OR 0.85 (CI 0.58, 1.25) NS RD -0.04 (CI -0.13, 0.05) NS
More clinic visits v Fewer clinic visits	2 of 8	804	OR 0.78 (CI 0.58, 1.05) NS RD -0.05 (CI -012 , 0.01) NS	OR 0.93 (CI 0.69, 1.26) NS RD -0.02 (CI -0.08, 0.05) NS
More tests v Fewer tests	5 of 8	1004	OR 0.64 (CI 0.49, 0.85) **S** RD -0.09 (CI -0.14, 0.03) **S**	OR 0.90 (CI 0.69, 1.16) NS RD -0.02 (CI -0.08, 0.03) NS
CEA v No CEA	1 of 8	107	OR 0.57 (CI 0.26, 1.29) NS RD -0.12 (CI -0.3, 0.05) NS	
	2 of 8	444		OR 0.85 (CI 0.58, 1.25) NS RD -0.04 (CI -0.13, 0.05) NS
Liver imaging V No liver imaging	5 of 8	1004	OR 0.64 (CI 0.49, 0.85) **S** RD -0.09 (CI -0.14, 0.03) **S**	
	6 of 8	1341		OR 0.88 (CI 0.70, 1.10) NS RD -0.03 (CI -0.08, 0.02) NS

Comparison	Studies included	No of patients	Time to recurrence Expressed as odds ratio (OR) in months	Curative surgery at recurrence Expressed as odds ratio (OR)
Intensive FU v minimalist FU	3 of 8	420	OR -6.75 (-11.06, -2.44) **S** But significant heterogeneity	
	6 of 8	1613		OR 2.41 (1.62, 3.53) **S** RD 0.06 (0.04, 0.09) **S**

Disease-free survival (DFS):
2 studies reported on DFS and their pooled result shows no significant difference in survival benefit between intensive follow up and less intensive. OR 0.92, CI (0.64, 1.31), RD-0.01 CI (-0.08, 0.05) NS.
Metachronous tumours:
7 studies reported a total of 15 metachronous tumours in the experimental arms and 9 in the control arms of the studies. 1 study reported interval tumours and noted 8 in the control and 2 in the experimental arm.

Complications:
1 study reported adverse events from follow up. 2 perforations and 2 GI bleeds from a total of 731 colonoscopies.

Quality of life:
1 study (597 patients) reported a small but significant increase in the quality of life of patients associated with more frequent follow up visits.(Kjeldsen 1997 – separate publication 1999)
A different study (203 patients) reported no difference in quality of life, anxiety, depression, and patient satisfaction in

patients followed up in different settings; GP / hospital. (Wattchow 2006)

General comments

- This meta-analysis supports the general principle of follow up for patients with CRC after curative treatment. There is also a clear message that the use of liver imaging is associated with improved survival and this should be included in any follow up programme.
- However there is the limitation that the combined studies span a long time-frame during which clinical care and surgical technique have changed considerably. These factors may have an effect on survival and question the validity of applying the results of earlier studies to modern practice.
- Although there was no statistical heterogeneity amongst the studies the intensity of follow up was varied. For example the follow up intensity in the experimental arm of one study was the same as the intensity of follow up in the control arm of another study. Therefore a precise indication of frequency, type or setting of follow up cannot be extracted from the data.
- Time to recurrence was significantly less and significantly more surgical procedures were carried out in the intensively followed arms of the studies. Although this suggests that recurrences were detected earlier leading to salvage surgery that lead to the improved survival this result is subject to intervention bias. The decision for salvage surgery in these studies was made by clinicians that were not blinded. In addition there was significant heterogeneity amongst the studies that reported on time to recurrence and this result is not reliable.
- No useful data on quality of life, harms or cost-effectiveness were available.

References of Included Studies (For systematic reviews):

1. Kjeldsen BJ, Kronborg O, Fenger C, Jorgensen OD. A prospective randomised study of follow up after radical surgery for colorectal cancer. *British Journal of Surgery* 1997;84:666-669
2. Makela JT, Seppo OL, Kairaluoma MI. Five year follow up after radical surgery for colorectal cancer. *Archives of Surgery* 1995;130:1062-1067
3. Ohlsson B, Breland U, Ekberg H, Graffner H, Tranberg K. Follow up after curative surgery for colorectal carcinoma. *Diseases of colon and rectum* 1995;38(6):619-626
4. Pietra N, Sarli L, Costi R, Ouchemi C, Grattarola M, Peracchia A. Role of follow-up in management of local recurrences of colorectal cancer. *Diseases of colon and rectum* 1998;41:1127-1133
5. Rodriguez-Moranta F, Salo J, Arcusa A, Boadas J, Pinol V, Bessa X *et al*. Postoperative surveillance in patients with colorectal cancer who have undergone curative resection: A prospective, multicentre, randomised, controlled trial. *Journal of clinical oncology* 2005;24(3):1-8
6. Schoemaker D, Black R, Giles L, Toouli J. Yearly colonoscopy, liver CT and chest radiography do not influence 5-year survival of colorectal cancer patients. *Gastroenterology* 1998;114:7-14
7. Secco GB, Fardelli R, Gianquinto D, Bonfante P, Baldi E, Ravera G, *et al*. Efficacy and cost of risk adapted follow up in patients after colorectal cancer surgery: a prospective, randomised and controlled trial. *European Journal of Surgical Oncology* 2002;28:418-423
8. Wattchow DA, Weller DP, Esterman A, Pilotto LS, McGorm K, Hammett Z, *et al*. General practice versus surgical-based follow-up for patients with colon cancer: randomised controlled trial. *British Journal of Cancer* 2006;94:1116-1121

Citation: Laubert T, Bader FG, Oevermann E, Jungbluth T, Unger L, Roblick UJ *et al*.(2010) Intensified surveillance after surgery for colorectal cancer significantly improves survival. *Eur J Med Res* **15(1):**25-30.

Design: Prospective cohort study

Country: Germany

Aim: To compare different surveillance strategies regarding their effect on long term outcomes.

Inclusion criteria: Patients having had potentially curable (R0) resection of colorectal cancer

Exclusion criteria Patients having had R1 or R2 resections of colorectal cancer and patients with synchronous, non-resectable distant metastases. Also excluded: local excisions; patients with an inability to cooperate; patients with ulcerative colitis, Crohn's disease associated cancer or hereditary cancer syndromes.

Population:
1,469 patients having received surgery with curative intent for colorectal cancer (n=779 males).

Intensive follow-up: n=858; median age: 64.5 years (± 10.9 years).

Interventions:
- Intensive follow-up: Defined as meeting more than 70% of scheduled follow-up appointments.
  Stage I (293) stage II (266) stage III (273) stage IV (26)

- Minimal follow-up: n=297; median age: 67.3 years (± 11.5 years). Defined as meeting less than 70% of scheduled follow-up appointments.
  Stage I (104) stage II (95) stage III (92) stage IV (6)

- No follow-up: n=314; median age: 73.7 years (± 11.6 years). Defined as 'no surveillance at all.' It was noted that people in this older group were in a poorer general condition than patients in the other two groups.
  Stage I (102) stage II (116) stage III (92) stage IV (4)

Outcomes:
- Overall survival at 5 years and 10 years

- Survival after local and distant recurrence

- R0 resectability of local recurrence or distant metastases

Results

- **Overall survival – 5 years:**
Intensive: 79%
Minimal: 76%
None: 54%
All comparisons: P<0.0001 in favour of the greater amount of surveillance.

- **Overall survival – 10 years**:
Intensive: 65%
Minimal: 50%
None: 31%
All comparisons: P<0.0001 in favour of the greater amount of surveillance.

- **Median overall survival:**
Intensive: 191 months
Minimal: 116 months
None: 66 months

All comparisons: P<0.0001 in favour of the greater amount of surveillance.

- **5 year survival, intensive vs. minimal surveillance**:
OR = 1.480 (95%CI: 1.135-1.929)
5 year survival, intensive vs. no surveillance:
OR = 2.606 (95%CI: 1.983-3.425)

- **3 year survival after recurrence, intensive vs. minimal surveillance**:
OR = 1.917 (95%CI: 1.007-3.651)
3 year survival after recurrence, intensive vs. no surveillance:
OR = 2.434 (95%CI: 1.088-5.448)

- **5 year survival rates after recurrence**:
Intensive: 32%
Minimal: 13%
None: 19%
Intensive vs. minimal (P=0.034) intensive vs. none (P<0.0001) minimal vs. none (P=0.614)

- **Median overall survival after recurrence:**
Intensive: 31 months
Minimal: 21 months
None: 16 months
All comparisons: P<0.0001 in favour of the greater amount of surveillance.

- **R0 resection of recurrent disease possible:**
Intensive: 28% (14/50 patients)
Minimal: 8% (1/13 patients)
None: 25% (3/12 patients)
Intensive vs. minimal (P=0.126) intensive vs. none (P=0.238) minimal vs. none (P=0.834)

- **R0 resection of distant metastases possible:**
Intensive: 31.1% (50/161 patients)
Minimal: 19.4% (7/36 patients)
None: 6.8% (3/44 patients)
Intensive vs. minimal (P=0.165) intensive vs. none (P=0.002) minimal vs. none (P=0.215)

General comments
This paper describes the results of a prospective cohort study following patients who had been surgically treated for colorectal cancer at a single hospital between January 1990 and December 2006. Surveillance was conducted according to the ASCO 2000 guidelines (updated 2005). No patients were lost to follow-up.

The authors concluded that patients who received >70% of scheduled follow-up surveillance (termed 'intensive') according to the ASCO guidelines, had a significant improvement in overall survival compared with patients who received <70 of scheduled surveillance (termed 'minimal') or none at all. The survival after recurrence was also significantly higher for the 'intensive' group even though R0 resectability of recurrent or distant disease did not differ significantly between groups.

Although the data collection was prospective, this was not a randomised trial and therefore there may be confounders and bias unaccounted for which could over- or under-estimate the value of intensive surveillance. The authors did not list the surveillance schedules applied to their patients and so the reader is directed to the ASCO Practice Guideline Recommendations for Colorectal Cancer Surveillance 2005: http://jop.ascopubs.org/content/1/4/137.full

Citation: Tjandra JJ, Chan MKY. Follow-up after curative resection of colorectal cancer: a meta-analysis. Diseases Colon & Rectum. 2007 50(11):1783-1799
Design: Systematic review and meta-analysis **Country**: Australia **Aim**: To evaluate the impact of various follow-up intensities and strategies on the outcome of patients after curative surgery for colorectal cancer.
Inclusion criteria All RCT that randomised at or shortly after surgery and comparing different intensities of surveillance on colorectal cancer after curative resection.
Exclusion criteria Studies considered to have bias (studies that did not report on their randomization, inclusion and exclusion criteria, patient selection, allocation, study design)
Population Patients with colorectal cancers that were treated surgically with curative intent. Local excision, distant metastases, inflammatory bowel disease and polyposis were excluded. Patients with co-morbidities that could not comply with follow up or in whom treatment of recurrent disease would be contraindicated were also excluded.
Interventions Intensive follow-up strategies as defined by the different trials. The clinical assessment, the investigations as well as who delivered the follow up were to be clearly stated.

Outcomes

Mortality	Number of Asymptomatic recurrences
Cancer-related mortality	Time to recurrence
Other cause of death	Method of detection of recurrence
Total recurrence rate	Reoperation rate
Local recurrence rate (all and isolated)	Curative reoperation rate
hepatic recurrence rate (all and isolated)	Setting of follow up
lung recurrence rate	Compliance to protocol
Number of Intramural recurrence	Complications from follow-up investigations
Number of Metachronous recurrences	

Results

A total of 2,923 patients were pooled from 8 RCTs

- Overall survival benefit at five years exists for patients undergoing more intensive follow up OR 0.74 (CI 0.59, 0.93) P value = 0.01
- Cancer related mortality did not show any significant difference between intensive and non-intensive follow up arms. (11.5% v 12.5%; OR 0.91; P=0.52) – grade not done.
- The number of all site recurrences was similar between the two groups. OR 0.97 (CI 0.82, 1.14)p=0.68
- However there is a significantly higher number of asymptomatic recurrences being picked up in the intensively followed up group. OR 3.42 (CI 2.17,5.41)
- There was no difference between the two groups with regard to different types of recurrence being diagnosed i.e. local, distant, intramural, metachronous, hepatic.(p>0.05)
- The weighted mean time to recurrence detection was reduced by 6 months with intensive follow up but there was significant heterogeneity among the studies pooled.
- The number of curative operations done for recurrence was significantly higher with intensive follow up. OR 2.81 (CI 1.65, 4.75)
- There was a significant survival benefit with CEA and colonoscopy. Liver USS had a significant survival benefit but CT was not found to make a significant difference to survival. Neither made a difference to recurrence detection.
- Although the number of recurrences was not significantly different more curative operations were performed for recurrence and this was the case whichever test was used for follow up.
- As far as frequency of the testing is concerned, more frequently done CEA levels was the only test associated with

an improvement in overall mortality.

Comparison	Studies included	No of patients	Overall survival at 5 years expressed as odds ratio (OR) S = significant NS = not significant	No of recurrences expressed as odds ratio (OR) S = significant NS = not significant
Intensive FU v minimalist FU	8 of 8	2,923	OR 0.74 (CI 0.59, 0.93) **S** P value = 0.01	
	all site 8 of 8 Asymptomatic 6 of 8	2,923 1,679		All site OR 0.97 (CI 0.82, 1.14) NS P value=0.68 Asymptomatic OR 3.42 (CI 2.17,5.41) **S** P value<0.00001
CEA v No CEA	2 of 8	444	OR 0.57* forest plot CI **S** P value= 0.003 *OR calculation end of table	
	2 of 8	444		OR 0.85 (CI 0.58, 1.25) NS
More CEA v Less CEA	1 of 8	207	OR 0.51* forest plot CI **S** P value=0.03	
	1 of 8	207		OR 0.83 (CI 0.61, 1.13) NS
Overall CEA V No/less CEA	3	651	OR* 0.56 forest plot CI **S** P value= 0.0002	
	3	651		0.83 (CI 0.61, 1.13) NS
Colonoscopy v no colonoscopy	4 of 8	875	OR 0.63* forest plot CI **S** P value=0.0006	
	?	538		OR 0.94 (0.39, 2.27) NS
More colonoscopy V Less colonoscopy	3of 8	1841	OR 0.96* forest plot CI NS P value 0.86	
	3 of 8	1841		OR 1.22 (0.45, 3.29) NS
Overall colonoscopy V No/less colonoscopy	7 of 8	2716	OR*0.84 forest plot CI **S** P value=0.04	
	?	432		0.87 (CI 0.37, 2.04)
USS Liver imaging V No USS liver imaging	3 of 8	702	OR 0.70* forest plot CI **S** P value=0.008	
	1 of 8	107		OR 2.77 (CI 0.51, 14.94) NS
More USS liver V Less USS liver	2 of 8	1192	OR* 0.90 forest plot CI NS P value 0.73	
	2 of 8	1192		OR 0.69 (0.44, 1.09) NS
Overall USS liver V No/less USS liver	5 of 8	1894	OR*0.84 forest plot CI NS P value 0.11	
	?	1298		0.81 (0.44, 1.5)
CT liver imaging V No CT liver imaging	6 of 8	1989	OR*0.79 forest plot CI NS P value= 0.06	
	6 of 8	1989		OR 0.99 (0.8, 1.22) NS

Comparison	Studies included	No of patients	Time to recurrence Expressed as odds ratio (OR) in months	Curative surgery at recurrence Expressed as odds ratio (OR)
Intensive FU v minimalist FU	5 of 8	1276	OR -5.91 (-8.74, -3.09) **S** But significant heterogeneity P<0.00001	
	7 of 8	707		OR 2.81 (1.65, 4.79) **S**
CEA	2 of 8	444		OR* 2.06 forest plot CI **S**

v No CEA				P value=0.02
More CEA v Less CEA	1 of 8	207		OR*9.86 forest plot CI **S** P value=0.0006
Overall CEA V No/less CEA	3 of 8	651		OR*2.99 forest plot CI **S** P value=0.03
Colonoscopy V No colonoscopy	4 of 8	875		OR* 1.85 forest plot CI **S** P value=0.01
More colonoscopy V Less colonoscopy	2 of 8	856		OR* 2.48 forest plot CI **S** P value=0.01
Overall colonoscopy V No/less colonoscopy	6 of 8	1731		OR*2.10 forest plot CI **S** P value=0.0006
USS Liver imaging V No USS liver imaging	3 of 8	702		OR* 1.99 forest plot CI **S** P value=0.002
More USS liver V Less USS liver	1 of 8	207		OR*9.87 forest plot CI **S** P value=0.0006
Overall USS liver V No/less USS liver	4 of 8	909		OR*2.54 forest plot CI **S** P=0.002
CT liver imaging V No CT liver imaging	5 of 8	1004		OR*2.03 forest plot CI **S** P=0.01

Complication:
1 study (Schoemaker 1998) reported complications. 4 patients (1.23%) had complications as a result of colonoscopy (2 perforations – 1 requiring laparotomy, 2 haemorrhages)

General comments
- This meta-analysis supports the general principle of follow up for patients with CRC after curative treatment.
- However there is the limitation that the combined studies span a long time-frame during which clinical care and surgical technique have changed considerably. These factors may have an effect on survival and question the validity of applying the results of earlier studies to modern practice.
- Although there was no statistical heterogeneity amongst the studies the intensity of follow up was varied. For example the follow up intensity in the experimental arm of one study was the same as the intensity of follow up in the control arm of another study. Therefore a precise indication of frequency, type or setting of follow up cannot be extracted from the data.
- Time to recurrence was significantly less and significantly more surgical procedures were carried out in the intensively followed arms of the studies. Although this suggests that recurrences were detected earlier leading to salvage surgery that lead to the improved survival this result is subject to intervention bias. The decision for salvage surgery in these studies was made by clinicians that were not blinded. In addition there was significant heterogeneity amongst the studies that reported on time to recurrence and this result is not reliable.
- When looking at particular test used for follow up CEA levels and colonoscopy are the only ones that offer a significant survival benefit. The use of liver USS significantly reduced overall mortality but CT had an insignificant effect. Increasing the frequency did not improve survival or recurrence detection for any of the tests apart from CEA
- However because the contribution of individual surveillance tests varied considerably among studies and no study directly compared specific tests the optimal investigation strategy remains unclear.

References of Included Studies (For systematic reviews):
1. Kjeldsen BJ, Kronborg O, Fenger C, Jorgensen OD. A prospective randomised study of follow up after radical surgery for colorectal cancer. *British Journal of Surgery* 1997;84:666-669
2. Makela JT, Seppo OL, Kairaluoma MI. Five year follow up after radical surgery for colorectal cancer. *Archives of Surgery* 1995;130:1062-1067
3. Ohlsson B, Breland U, Ekberg H, Graffner H, Tranberg K. Follow up after curative surgery for colorectal carcinoma. *Diseases of colon and rectum* 1995;38(6):619-626

4. Pietra N, Sarli L, Costi R, Ouchemi C, Grattarola M, Peracchia A. Role of follow-up in management of local recurrences of colorectal cancer. *Diseases of colon and rectum* 1998;41:1127-1133

5. Rodriguez-Moranta F, Salo J, Arcusa A, Boadas J, Pinol V, Bessa X *et al*. Postoperative surveillance in patients with colorectal cancer who have undergone curative resection: A prospective, multicentre, randomised, controlled trial. *Journal of clinical oncology* 2005;24(3):1-8

6. Schoemaker D, Black R, Giles L, Toouli J. Yearly colonoscopy, liver CT and chest radiography do not influence 5-year survival of colorectal cancer patients. *Gastroenterology* 1998;114:7-14

7. Secco GB, Fardelli R, Gianquinto D, Bonfante P, Baldi E, Ravera G, *et al*. Efficacy and cost of risk adapted follow up in patients after colorectal cancer surgery: a prospective, randomised and controlled trial. *European Journal of Surgical Oncology* 2002;28:418-423

8. Grossmann EM, Johnson FE, Virgo KS, Longo WE, Fossati R. Follow-up of colorectal cancer patients after resection with curative intent: the GILDA trial. Surg Oncol 2004;13:119-24

Citation: Wang T, Cui Y, Huang WS, Deng YH, Gong W, Li CJ, Wang JP. The role of postoperative colonoscopic surveillance after radical surgery for colorectal cancer: a prospective randomised clinical study. *Gastrointestinal endoscopy* 2009;69(3):609-615.

Design: Randomised controlled trial

Country: China

Aim: To compare the efficacy of 2 different colonoscopic surveillance strategies in terms of survival and recurrence resectability.

Inclusion criteria
All patients undergoing curative resection for newly diagnosed colorectal cancer between January 1995 and March 2001. (curative resection was defined as one in which no macroscopic tumour remained at the end of the operation and histology of the specimen confirmed no tumour at the margins of resection)

Exclusion criteria
Duke's stage D, inflammatory bowel disease, familial adenomatous polyposis, hereditary non-polyposis colorectal cancer, patients over the age of 80, medical co-morbidity(making follow up difficult or 5 year survival unlikely), residence in remote area, refusal of consent.

Population
326 consecutive patients under the age of 80, undergoing curative resection for newly diagnosed colorectal cancer between Jan 1995 and Mar 2001 at a teaching hospital in China who consented to the trial, did not live in a remote area and did not have co-morbidities that made follow up difficult or 5 year survival unlikely.
7 patients were lost to follow up so there were 319 patients in the final statistical analysis.

Interventions
Colonoscopic strategy of follow up. Intensive colonoscopic surveillance (ICS) versus routine colonoscopic surveillance (RCS).

The intensive colonoscopy surveillance group (n=165)had colonoscopy at every follow-up visit i.e. 3 monthly for the first year, 6 monthly for the next 2 years and annually for the next two years.

The routine colonoscopy surveillance group (n=161) had colonoscopy performed at 6, 30 and 60 months. If colonoscopy had been preformed pre-operatively then it was not done at 6 months.

All patients were seen 3 monthly for the first year, 6 monthly for the next 2 years and annually for the next two years. At each visit they all had
Medical history
Clinical examination
CEA levels
CXR
Liver imaging (CT or USS)

Outcomes
5 year survival rate
Numbers of post operative colorectal cancer (anastomotic recurrence and metachronous tumours)
Time to recurrence
Curative surgery for recurrence
Complications

Results
Overall survival was no different between the ICS and the RCS groups.
Patients in the ICS group had more curative operations for postoperative colorectal cancer and survived significantly longer following the detection of the postoperative colorectal cancer.
76.9% of postoperative colorectal cancers (anastomotic and metachronous) occurred within the first 2 pos-op years.
Survival
- 42 patients (26.1%) in the ICS v 50 patients (31.6%) in the RCS group died.

- No significant difference in survival seen between the two groups P=0.27
- No difference in stage or location distribution seen.

	5 year survival (%)	5 year survival (%)	P	HR (95% CI)
	ICS	RCS		
All patients	77	73	0.25	1.41 (0.92, 2.14)
Colon cancer	81	76	0.31	1.52 (0.80, 2.87)
Rectal cancer	72	70	0.49	1.32 (0.75, 2.34)
Duke's A	91	86	0.29	1.84 (0.58, 5.84)
Duke's B	76	75	0.40	1.19 (0.62,2.27)
Duke's C	63	54	0.51	1.35 (0.70, 2.59)

Postoperative colorectal cancer
- 13 patients (8.1%) in the ICS group and 18 patients (11.4%) in the RCS group had postoperative colorectal cancer detected. No significant difference between the two groups.p=0.32
- Anastomotic recurrence was diagnosed in 10 patients (6.2%) of the ICS group and 12 patients (7.6%) of the RCS group
- Metachronous tumours were diagnosed in 3 patients (1.9%) of the ICS group and 6 patients (3.8%) of the RCS group.
- 76.9% of postoperative colorectal cancers occurred within the first 2 years.

Postoperative colorectal cancer	Year 1 No / %	Year 2 No / %	Year 3 No / %	Year 4 No / %	Year 5 No / %	Later No / %
ICS (n=13)	5 (38.5%) anastomotic	5 (38.5%) 4 anastomotic 1metachronous	1 (7.7%) Anastomotic	1(7.7%) Metachronous	0	1(7.7%) Metachronous
RCS (n=18)	-	-	14 (77.8%) 10anastomotic 1metachronous	-	3 (16.7%) 2anastomotic 1metachronous	1 (5.6%) metachronous

- Significantly more patients in the ICS group were asymptomatic at the time of detection of their postoperative colorectal cancer. (OR 5.24 (1.06, 26.0) p=0.43)
- Significantly more patients in the ICS group had curative surgery for their postoperative cancer. (OR 0.12 (0.02, 0.91) p=0.31)
- Survival after recurrence was detected was significantly longer in the ICS group compared to the RCS group. (HR 2.97 (1.05,8.44) p=0.41)
- More patients that were asymptomatic were able to have curative surgery for their recurrence. 76.5% v 35.7%
- Patients with asymptomatic recurrence survived significantly longer than those who were symptomatic.p=0.005
-

Outcome of postoperative colorectal cancer	ICS No	ICS %	RCS No	RCS %	P value
Time to recurrence(months)	Mean 22 SD 17.6		Mean 35 SD 23.9		0.49
No of asymptomatic	10	76.9%	7	38.9%	0.04
Curative surgery for tumour recurrence	9	69.2%	6	33.3%	0.48
Survival after recurrence(months)	Mean 69.1 SD 12.3		Mean 24.4 SD 5.7		

Complications.
- 3 complications occurred in the ICS group (2 bleeds, 1 perforation)
- None in the RCS group.

General comments
- Well conducted, reasonable size RCT.
- Supports the view that intensive colonoscopic surveillance does not improve overall survival even though meta-analysis have shown that intensive follow up in general does improve survival.
- Shows that what intensive colonoscopic surveillance does achieve is earlier detection of postoperative colorectal cancer, more curative surgery for this and a longer survival following its detection.

> - The study also reported a large number of postoperative cancers detected in the first 2 years post op and suggests based on this finding that colonoscopy should be undertaken annually in the first two years following colorectal cancer resection.

Evidence Tables

Citation: Jeffery M, Hickey BE, Hider PN. Follow-up strategies for patients treated for non-metastatic colorectal cancer. Cochrane Database of Systematic Reviews. 2007. Issue 1. 2007
Design: Systematic Review and Meta-analysis **Country**: New Zealand **Aim**: To review the available evidence concerning the benefits of intensive follow-up of colorectal cancer patients with respect to survival. Secondary endpoints included: time to diagnosis of recurrence, quality of life (QoL) and the harms and costs of surveillance and investigations.
Inclusion criteria: Only randomised controlled trials comparing different follow up strategies for patients with non-matastatic colorectal cancer (CRC) treated with curative intent were included.
Exclusion criteria Non-randomised studies Ongoing randomised trials (COLFOL, FACS, GILDA)
Population: Patients with non-matastatic colorectal cancer (CRC) treated with curative intent +/- adjuvant treatment. Males and females of any age with histologically proven adenocarcinoma of the colon or rectum staged as T1,2,3,4; N0,1,2; M0. Duke's stage A, B and C.

Interventions: Strategies of follow-up.
This included comparisons of
       follow-up versus no follow up
       follow-up strategies of varying intensity
       follow-up in different healthcare settings.
 	
Follow up visits with health professionals included:
       symptom enquiry
       clinical examination
       procedures (e.g. colonoscopy)
       blood tests
       faecal analysis
       radiological examinations.

Outcomes
Primary: Overall Survival (OS)
Secondary:
       Disease specific survival
       Time to diagnosis of recurrence
       Incidence of surgery(with curative intent) for recurrence
       Interval recurrences (between planned visits)
       Quality of life
       Harms
       Cost of surveillance and investigations

Results Eight studies were included (2141 patients in total): - Overall survival benefit at five years exists for patients undergoing more intensive follow up - The absolute number of recurrences was similar - For disease free survival there is no significant survival benefit between intensive follow up and less intensive. - There is a mortality benefit for performing more tests versus fewer tests

- There is a mortality benefit for performing liver imaging versus no liver imaging
- The weighted mean difference for the time to recurrence was significantly reduced but there was significant heterogeneity amongst the studies.
- There was significantly more curative surgical procedures in the intensively followed arm
- No useful data on quality of life, harms or cost-effectiveness were available.

Comparison	Studies included	No of patients	Overall survival at 5 years expressed as odds ratio (OR) and risk difference (RD) S = significant NS = not significant	No of recurrences expressed as odds ratio (OR) and risk difference (RD) S = significant NS = not significant
Intensive FU v minimalist FU	6 of 8	1601	OR 0.73 (CI 0.59, 0.91) **S** RD -0.06 (CI -0.11, -0.02) **S**	
	7 of 8	1938		OR 0.91 (CI 0.71, 1.1) NS RD -0.02 (CI -0.06, 0.02) NS
Clinic visit v No clinic visit	1 of 8	107	OR 0.57 (CI 0.26, 1.29) NS RD -0.12 (CI -0.3, 0.05) NS	
	2 of 8	444		OR 0.85 (CI 0.58, 1.25) NS RD -0.04 (CI -0.13, 0.05) NS
More clinic visits v Fewer clinic visits	2 of 8	804	OR 0.78 (CI 0.58, 1.05) NS RD -0.05 (CI -012 , 0.01) NS	OR 0.93 (CI 0.69, 1.26) NS RD -0.02 (CI -0.08, 0.05) NS
More tests v Fewer tests	5 of 8	1004	OR 0.64 (CI 0.49, 0.85) **S** RD -0.09 (CI -0.14, 0.03) **S**	OR 0.90 (CI 0.69, 1.16) NS RD -0.02 (CI -0.08, 0.03) NS
CEA v No CEA	1 of 8	107	OR 0.57 (CI 0.26, 1.29) NS RD -0.12 (CI -0.3, 0.05) NS	
	2 of 8	444		OR 0.85 (CI 0.58, 1.25) NS RD -0.04 (CI -0.13, 0.05) NS
Liver imaging V No liver imaging	5 of 8	1004	OR 0.64 (CI 0.49, 0.85) **S** RD -0.09 (CI -0.14, 0.03) **S**	
	6 of 8	1341		OR 0.88 (CI 0.70, 1.10) NS RD -0.03 (CI -0.08, 0.02) NS

Comparison	Studies included	No of patients	Time to recurrence Expressed as odds ratio (OR) in months	Curative surgery at recurrence Expressed as odds ratio (OR)
Intensive FU v minimalist FU	3 of 8	420	OR -6.75 (-11.06, -2.44) **S** But significant heterogeneity	
	6 of 8	1613		OR 2.41 (1.62, 3.53) **S** RD 0.06 (0.04, 0.09) **S**

Disease-free survival (DFS):
2 studies reported on DFS and their pooled result shows no significant difference in survival benefit between intensive follow up and less intensive. OR 0.92, CI (0.64, 1.31), RD-0.01 CI (-0.08, 0.05) NS.
Metachronous tumours:
7 studies reported a total of 15 metachronous tumours in the experimental arms and 9 in the control arms of the studies. 1 study reported interval tumours and noted 8 in the control and 2 in the experimental arm.

Complications:
1 study reported adverse events from follow up. 2 perforations and 2 GI bleeds from a total of 731 colonoscopies.

Quality of life:
1 study (597 patients) reported a small but significant increase in the quality of life of patients associated with more frequent follow up visits.(Kjeldsen 1997 – separate publication 1999)
A different study (203 patients) reported no difference in quality of life, anxiety, depression, and patient satisfaction

in patients followed up in different settings; GP / hospital. (Wattchow 2006)

General comments
- This meta-analysis supports the general principle of follow up for patients with CRC after curative treatment. There is also a clear message that the use of liver imaging is associated with improved survival and this should be included in any follow up programme.
- However there is the limitation that the combined studies span a long time-frame during which clinical care and surgical technique have changed considerably. These factors may have an effect on survival and question the validity of applying the results of earlier studies to modern practice.
- Although there was no statistical heterogeneity amongst the studies the intensity of follow up was varied. For example the follow up intensity in the experimental arm of one study was the same as the intensity of follow up in the control arm of another study. Therefore a precise indication of frequency, type or setting of follow up cannot be extracted from the data.
- Time to recurrence was significantly less and significantly more surgical procedures were carried out in the intensively followed arms of the studies. Although this suggests that recurrences were detected earlier leading to salvage surgery that lead to the improved survival this result is subject to intervention bias. The decision for salvage surgery in these studies was made by clinicians that were not blinded. In addition there was significant heterogeneity amongst the studies that reported on time to recurrence and this result is not reliable.
- No useful data on quality of life, harms or cost-effectiveness were available.

References of Included Studies (For systematic reviews):
9. Kjeldsen BJ, Kronborg O, Fenger C, Jorgensen OD. A prospective randomised study of follow up after radical surgery for colorectal cancer. *British Journal of Surgery* 1997;84:666-669
10. Makela JT, Seppo OL, Kairaluoma MI. Five year follow up after radical surgery for colorectal cancer. *Archives of Surgery* 1995;130:1062-1067
11. Ohlsson B, Breland U, Ekberg H, Graffner H, Tranberg K. Follow up after curative surgery for colorectal carcinoma. *Diseases of colon and rectum* 1995;38(6):619-626
12. Pietra N, Sarli L, Costi R, Ouchemi C, Grattarola M, Peracchia A. Role of follow-up in management of local recurrences of colorectal cancer. *Diseases of colon and rectum* 1998;41:1127-1133
13. Rodriguez-Moranta F, Salo J, Arcusa A, Boadas J, Pinol V, Bessa X *et al*. Postoperative surveillance in patients with colorectal cancer who have undergone curative resection: A prospective, multicentre, randomised, controlled trial. *Journal of clinical oncology* 2005;24(3):1-8
14. Schoemaker D, Black R, Giles L, Toouli J. Yearly colonoscopy, liver CT and chest radiography do not influence 5-year survival of colorectal cancer patients. *Gastroenterology* 1998;114:7-14
15. Secco GB, Fardelli R, Gianquinto D, Bonfante P, Baldi E, Ravera G, *et al*. Efficacy and cost of risk adapted follow up in patients after colorectal cancer surgery: a prospective, randomised and controlled trial. *European Journal of Surgical Oncology* 2002;28:418-423
16. Wattchow DA, Weller DP, Esterman A, Pilotto LS, McGorm K, Hammett Z, *et al*. General practice versus surgical-based follow-up for patients with colon cancer: randomised controlled trial. *British Journal of Cancer* 2006;94:1116-1121

Citation: Laubert T, Bader FG, Oevermann E, Jungbluth T, Unger L, Roblick UJ *et al.*(2010) Intensified surveillance after surgery for colorectal cancer significantly improves survival. *Eur J Med Res* **15(1):**25-30.

Design: Prospective cohort study

Country: Germany

Aim: To compare different surveillance strategies regarding their effect on long term outcomes.

Inclusion criteria: Patients having had potentially curable (R0) resection of colorectal cancer

Exclusion criteria Patients having had R1 or R2 resections of colorectal cancer and patients with synchronous, non-resectable distant metastases. Also excluded: local excisions; patients with an inability to cooperate; patients with ulcerative colitis, Crohn's disease associated cancer or hereditary cancer syndromes.

Population:
1,469 patients having received surgery with curative intent for colorectal cancer (n=779 males).

Intensive follow-up: n=858; median age: 64.5 years (± 10.9 years).

Interventions:
- Intensive follow-up: Defined as meeting more than 70% of scheduled follow-up appointments.
Stage I (293) stage II (266) stage III (273) stage IV (26)

- Minimal follow-up: n=297; median age: 67.3 years (± 11.5 years). Defined as meeting less than 70% of scheduled follow-up appointments.
Stage I (104) stage II (95) stage III (92) stage IV (6)

- No follow-up: n=314; median age: 73.7 years (± 11.6 years). Defined as 'no surveillance at all.' It was noted that people in this older group were in a poorer general condition than patients in the other two groups.
Stage I (102) stage II (116) stage III (92) stage IV (4)

Outcomes:
- Overall survival at 5 years and 10 years

- Survival after local and distant recurrence

- R0 resectability of local recurrence or distant metastases

Results

- **Overall survival – 5 years:**
Intensive: 79%
Minimal: 76%
None: 54%
All comparisons: P<0.0001 in favour of the greater amount of surveillance.

- **Overall survival – 10 years**:
Intensive: 65%
Minimal: 50%
None: 31%
All comparisons: P<0.0001 in favour of the greater amount of surveillance.

- **Median overall survival:**
Intensive: 191 months
Minimal: 116 months
None: 66 months
All comparisons: P<0.0001 in favour of the greater amount of surveillance.

- **5 year survival, intensive vs. minimal surveillance**:
OR = 1.480 (95%CI: 1.135-1.929)
5 year survival, intensive vs. no surveillance:
OR = 2.606 (95%CI: 1.983-3.425)

- **3 year survival after recurrence, intensive vs. minimal surveillance**:
OR = 1.917 (95%CI: 1.007-3.651)
3 year survival after recurrence, intensive vs. no surveillance:
OR = 2.434 (95%CI: 1.088-5.448)

- **5 year survival rates after recurrence**:
Intensive: 32%
Minimal: 13%
None: 19%
Intensive vs. minimal (P=0.034) intensive vs. none (P<0.0001) minimal vs. none (P=0.614)

- **Median overall survival after recurrence:**
Intensive: 31 months
Minimal: 21 months
None: 16 months
All comparisons: P<0.0001 in favour of the greater amount of surveillance.

- **R0 resection of recurrent disease possible:**
Intensive: 28% (14/50 patients)
Minimal: 8% (1/13 patients)
None: 25% (3/12 patients)
Intensive vs. minimal (P=0.126) intensive vs. none (P=0.238) minimal vs. none (P=0.834)

- **R0 resection of distant metastases possible:**
Intensive: 31.1% (50/161 patients)
Minimal: 19.4% (7/36 patients)
None: 6.8% (3/44 patients)
Intensive vs. minimal (P=0.165) intensive vs. none (P=0.002) minimal vs. none (P=0.215)

General comments
This paper describes the results of a prospective cohort study following patients who had been surgically treated for colorectal cancer at a single hospital between January 1990 and December 2006. Surveillance was conducted according to the ASCO 2000 guidelines (updated 2005). No patients were lost to follow-up.

The authors concluded that patients who received >70% of scheduled follow-up surveillance (termed 'intensive') according to the ASCO guidelines, had a significant improvement in overall survival compared with patients who received <70 of scheduled surveillance (termed 'minimal') or none at all. The survival after recurrence was also significantly higher for the 'intensive' group even though R0 resectability of recurrent or distant disease did not differ significantly between groups.

Although the data collection was prospective, this was not a randomised trial and therefore there may be confounders and bias unaccounted for which could over- or under-estimate the value of intensive surveillance. The authors did not list the surveillance schedules applied to their patients and so the reader is directed to the ASCO Practice Guideline Recommendations for Colorectal Cancer Surveillance 2005:
http://jop.ascopubs.org/content/1/4/137.full

Citation: Tjandra JJ, Chan MKY. Follow-up after curative resection of colorectal cancer: a meta-analysis. Diseases Colon & Rectum. 2007 50(11):1783-1799

Design: Systematic review and meta-analysis **Country**: Australia **Aim**: To evaluate the impact of various follow-up intensities and strategies on the outcome of patients after curative surgery for colorectal cancer.

Inclusion criteria All RCT that randomised at or shortly after surgery and comparing different intensities of surveillance on colorectal cancer after curative resection.

Exclusion criteria Studies considered to have bias (studies that did not report on their randomization, inclusion and exclusion criteria, patient selection, allocation, study design)

Population Patients with colorectal cancers that were treated surgically with curative intent. Local excision, distant metastases, inflammatory bowel disease and polyposis were excluded. Patients with co-morbidities that could not comply with follow up or in whom treatment of recurrent disease would be contraindicated were also excluded.

Interventions Intensive follow-up strategies as defined by the different trials. The clinical assessment, the investigations as well as who delivered the follow up were to be clearly stated.

Outcomes Mortality Number of Asymptomatic recurrences Cancer-related mortality Time to recurrence Other cause of death Method of detection of recurrence Total recurrence rate Reoperation rate Local recurrence rate (all and isolated) Curative reoperation rate hepatic recurrence rate (all and isolated) Setting of follow up lung recurrence rate Compliance to protocol Number of Intramural recurrence Complications from follow-up investigations Number of Metachronous recurrences

Results A total of 2,923 patients were pooled from 8 RCTs • Overall survival benefit at five years exists for patients undergoing more intensive follow up OR 0.74 (CI 0.59, 0.93) P value = 0.01 • Cancer related mortality did not show any significant difference between intensive and non-intensive follow up arms. (11.5% v 12.5%; OR 0.91; P=0.52) – grade not done. • The number of all site recurrences was similar between the two groups. OR 0.97 (CI 0.82, 1.14)p=0.68 • However there is a significantly higher number of asymptomatic recurrences being picked up in the intensively followed up group. OR 3.42 (CI 2.17,5.41) • There was no difference between the two groups with regard to different types of recurrence being diagnosed i.e. local, distant, intramural, metachronous, hepatic.(p>0.05) • The weighted mean time to recurrence detection was reduced by 6 months with intensive follow up but there was significant heterogeneity among the studies pooled. • The number of curative operations done for recurrence was significantly higher with intensive follow up. OR 2.81 (CI 1.65, 4.75) • There was a significant survival benefit with CEA and colonoscopy. Liver USS had a significant survival benefit but CT was not found to make a significant difference to survival. Neither made a difference to recurrence detection. • Although the number of recurrences was not significantly different more curative operations were performed for recurrence and this was the case whichever test was used for follow up. • As far as frequency of the testing is concerned, more frequently done CEA levels was the only test associated with an improvement in overall mortality.

Comparison	Studies included	No of patients	Overall survival at 5 years expressed as odds ratio (OR) S = significant NS = not significant	No of recurrences expressed as odds ratio (OR) S = significant NS = not significant
Intensive FU v minimalist FU	8 of 8	2,923	OR 0.74 (CI 0.59, 0.93) **S** P value = 0.01	
	all site 8 of 8 Asymptomatic 6 of 8	2,923 1,679		All site OR 0.97 (CI 0.82, 1.14) NS P value=0.68 Asymptomatic OR 3.42 (CI 2.17,5.41) **S** P value<0.00001
CEA v No CEA	2 of 8	444	OR 0.57* forest plot CI **S** P value= 0.003 *OR calculation end of table	
	2 of 8	444		OR 0.85 (CI 0.58, 1.25) NS
More CEA v Less CEA	1 of 8	207	OR 0.51* forest plot CI **S** P value=0.03	
	1 of 8	207		OR 0.83 (CI 0.61, 1.13) NS
Overall CEA V No/less CEA	3	651	OR* 0.56 forest plot CI **S** P value= 0.0002	
	3	651		0.83 (CI 0.61, 1.13) NS
Colonoscopy v no colonoscopy	4 of 8	875	OR 0.63* forest plot CI **S** P value=0.0006	
	?	538		OR 0.94 (0.39, 2.27) NS
More colonoscopy V Less colonoscopy	3of 8	1841	OR 0.96* forest plot CI NS P value 0.86	
	3 of 8	1841		OR 1.22 (0.45, 3.29) NS
Overall colonoscopy V No/less colonoscopy	7 of 8	2716	OR*0.84 forest plot CI **S** P value=0.04	
	?	432		0.87 (CI 0.37, 2.04)
USS Liver imaging V No USS liver imaging	3 of 8	702	OR 0.70* forest plot CI **S** P value=0.008	
	1 of 8	107		OR 2.77 (CI 0.51, 14.94) NS
More USS liver V Less USS liver	2 of 8	1192	OR* 0.90 forest plot CI NS P value 0.73	
	2 of 8	1192		OR 0.69 (0.44, 1.09) NS
Overall USS liver V No/less USS liver	5 of 8	1894	OR*0.84 forest plot CI NS P value 0.11	
	?	1298		0.81 (0.44, 1.5)
CT liver imaging V No CT liver imaging	6 of 8	1989	OR*0.79 forest plot CI NS P value= 0.06	
	6 of 8	1989		OR 0.99 (0.8, 1.22) NS

Comparison	Studies included	No of patients	Time to recurrence Expressed as odds ratio (OR) in months	Curative surgery at recurrence Expressed as odds ratio (OR)
Intensive FU v minimalist FU	5 of 8	1276	OR -5.91 (-8.74, -3.09) **S** But significant heterogeneity P<0.00001	
	7 of 8	707		OR 2.81 (1.65, 4.79) **S**
CEA v No CEA	2 of 8	444		OR* 2.06 forest plot CI **S** P value=0.02
More CEA v Less CEA	1 of 8	207		OR*9.86 forest plot CI **S** P value=0.0006

Overall CEA V No/less CEA	3 of 8	651		OR*2.99 forest plot CI **S** P value=0.03
Colonoscopy V No colonoscopy	4 of 8	875		OR* 1.85 forest plot CI **S** P value=0.01
More colonoscopy V Less colonoscopy	2 of 8	856		OR* 2.48 forest plot CI **S** P value=0.01
Overall colonoscopy V No/less colonoscopy	6 of 8	1731		OR*2.10 forest plot CI **S** P value=0.0006
USS Liver imaging V No USS liver imaging	3 of 8	702		OR* 1.99 forest plot CI **S** P value=0.002
More USS liver V Less USS liver	1 of 8	207		OR*9.87 forest plot CI **S** P value=0.0006
Overall USS liver V No/less USS liver	4 of 8	909		OR*2.54 forest plot CI **S** P=0.002
CT liver imaging V No CT liver imaging	5 of 8	1004		OR*2.03 forest plot CI **S** P=0.01

Complication:
1 study (Schoemaker 1998) reported complications. 4 patients (1.23%) had complications as a result of colonoscopy (2 perforations – 1 requiring laparotomy, 2 haemorrhages)

General comments
- This meta-analysis supports the general principle of follow up for patients with CRC after curative treatment.
- However there is the limitation that the combined studies span a long time-frame during which clinical care and surgical technique have changed considerably. These factors may have an effect on survival and question the validity of applying the results of earlier studies to modern practice.
- Although there was no statistical heterogeneity amongst the studies the intensity of follow up was varied. For example the follow up intensity in the experimental arm of one study was the same as the intensity of follow up in the control arm of another study. Therefore a precise indication of frequency, type or setting of follow up cannot be extracted from the data.
- Time to recurrence was significantly less and significantly more surgical procedures were carried out in the intensively followed arms of the studies. Although this suggests that recurrences were detected earlier leading to salvage surgery that lead to the improved survival this result is subject to intervention bias. The decision for salvage surgery in these studies was made by clinicians that were not blinded. In addition there was significant heterogeneity amongst the studies that reported on time to recurrence and this result is not reliable.
- When looking at particular test used for follow up CEA levels and colonoscopy are the only ones that offer a significant survival benefit. The use of liver USS significantly reduced overall mortality but CT had an insignificant effect. Increasing the frequency did not improve survival or recurrence detection for any of the tests apart from CEA
- However because the contribution of individual surveillance tests varied considerably among studies and no study directly compared specific tests the optimal investigation strategy remains unclear.

References of Included Studies (For systematic reviews):
9. Kjeldsen BJ, Kronborg O, Fenger C, Jorgensen OD. A prospective randomised study of follow up after radical surgery for colorectal cancer. *British Journal of Surgery* 1997;84:666-669
10. Makela JT, Seppo OL, Kairaluoma MI. Five year follow up after radical surgery for colorectal cancer. *Archives of Surgery* 1995;130:1062-1067
11. Ohlsson B, Breland U, Ekberg H, Graffner H, Tranberg K. Follow up after curative surgery for colorectal carcinoma. *Diseases of colon and rectum* 1995;38(6):619-626
12. Pietra N, Sarli L, Costi R, Ouchemi C, Grattarola M, Peracchia A. Role of follow-up in management of local recurrences of colorectal cancer. *Diseases of colon and rectum* 1998;41:1127-1133
13. Rodriguez-Moranta F, Salo J, Arcusa A, Boadas J, Pinol V, Bessa X *et al*. Postoperative surveillance in patients with colorectal cancer who have undergone curative resection: A prospective, multicentre, randomised, controlled trial. *Journal of clinical oncology* 2005;24(3):1-8
14. Schoemaker D, Black R, Giles L, Toouli J. Yearly colonoscopy, liver CT and chest radiography do not

influence 5-year survival of colorectal cancer patients. *Gastroenterology* 1998;114:7-14
15. Secco GB, Fardelli R, Gianquinto D, Bonfante P, Baldi E, Ravera G, *et al*. Efficacy and cost of risk adapted follow up in patients after colorectal cancer surgery: a prospective, randomised and controlled trial. *European Journal of Surgical Oncology* 2002;28:418-423
16. Grossmann EM, Johnson FE, Virgo KS, Longo WE, Fossati R. Follow-up of colorectal cancer patients after resection with curative intent: the GILDA trial. Surg Oncol 2004;13:119-24

Citation: Wang T, Cui Y, Huang WS, Deng YH, Gong W, Li CJ, Wang JP. The role of postoperative colonoscopic surveillance after radical surgery for colorectal cancer: a prospective randomised clinical study. *Gastrointestinal endoscopy* 2009;69(3):609-615.
Design: Randomised controlled trial **Country**: China **Aim**: To compare the efficacy of 2 different colonoscopic surveillance strategies in terms of survival and recurrence resectability.
Inclusion criteria All patients undergoing curative resection for newly diagnosed colorectal cancer between January 1995 and March 2001. (curative resection was defined as one in which no macroscopic tumour remained at the end of the operation and histology of the specimen confirmed no tumour at the margins of resection)
Exclusion criteria Duke's stage D, inflammatory bowel disease, familial adenomatous polyposis, hereditary non-polyposis colorectal cancer, patients over the age of 80, medical co-morbidity(making follow up difficult or 5 year survival unlikely), residence in remote area, refusal of consent.
Population 326 consecutive patients under the age of 80, undergoing curative resection for newly diagnosed colorectal cancer between Jan 1995 and Mar 2001 at a teaching hospital in China who consented to the trial, did not live in a remote area and did not have co-morbidities that made follow up difficult or 5 year survival unlikely. 7 patients were lost to follow up so there were 319 patients in the final statistical analysis.
Interventions Colonoscopic strategy of follow up. Intensive colonoscopic surveillance (ICS) versus routine colonoscopic surveillance (RCS). The intensive colonoscopy surveillance group (n=165)had colonoscopy at every follow-up visit i.e. 3 monthly for the first year, 6 monthly for the next 2 years and annually for the next two years. The routine colonoscopy surveillance group (n=161) had colonoscopy performed at 6, 30 and 60 months. If colonoscopy had been preformed pre-operatively then it was not done at 6 months. All patients were seen 3 monthly for the first year, 6 monthly for the next 2 years and annually for the next two years. At each visit they all had Medical history Clinical examination CEA levels CXR Liver imaging (CT or USS)
Outcomes 5 year survival rate Numbers of post operative colorectal cancer (anastomotic recurrence and metachronous tumours) Time to recurrence Curative surgery for recurrence Complications
Results Overall survival was no different between the ICS and the RCS groups. Patients in the ICS group had more curative operations for postoperative colorectal cancer and survived significantly longer following the detection of the postoperative colorectal cancer. 76.9% of postoperative colorectal cancers (anastomotic and metachronous) occurred within the first 2 pos-op years. Survival • 42 patients (26.1%) in the ICS v 50 patients (31.6%) in the RCS group died. • No significant difference in survival seen between the two groups P=0.27 • No difference in stage or location distribution seen.

	5 year survival (%)	5 year survival (%)	P	HR (95% CI)
	ICS	RCS		
All patients	77	73	0.25	1.41 (0.92, 2.14)
Colon cancer	81	76	0.31	1.52 (0.80, 2.87)
Rectal cancer	72	70	0.49	1.32 (0.75, 2.34)
Duke's A	91	86	0.29	1.84 (0.58, 5.84)
Duke's B	76	75	0.40	1.19 (0.62,2.27)
Duke's C	63	54	0.51	1.35 (0.70, 2.59)

Postoperative colorectal cancer
- 13 patients (8.1%) in the ICS group and 18 patients (11.4%) in the RCS group had postoperative colorectal cancer detected. No significant difference between the two groups.p=0.32
- Anastomotic recurrence was diagnosed in 10 patients (6.2%) of the ICS group and 12 patients (7.6%) of the RCS group
- Metachronous tumours were diagnosed in 3 patients (1.9%) of the ICS group and 6 patients (3.8%) of the RCS group.
- 76.9% of postoperative colorectal cancers occurred within the first 2 years.

Postoperative colorectal cancer	Year 1 No / %	Year 2 No / %	Year 3 No / %	Year 4 No / %	Year 5 No / %	Later No / %
ICS (n=13)	5 (38.5%) anastomotic	5 (38.5%) 4 anastomotic 1metachronous	1 (7.7%) Anastomotic	1(7.7%) Metachronous	0	1(7.7%) Metachronous
RCS (n=18)	-	-	14 (77.8%) 10anastomotic 1metachronous	-	3 (16.7%) 2anastomotic 1metachronous	1 (5.6%) metachronous

- Significantly more patients in the ICS group were asymptomatic at the time of detection of their postoperative colorectal cancer. (OR 5.24 (1.06, 26.0) p=0.43)
- Significantly more patients in the ICS group had curative surgery for their postoperative cancer. (OR 0.12 (0.02, 0.91) p=0.31)
- Survival after recurrence was detected was significantly longer in the ICS group compared to the RCS group. (HR 2.97 (1.05,8.44) p=0.41)
- More patients that were asymptomatic were able to have curative surgery for their recurrence. 76.5% v 35.7%
- Patients with asymptomatic recurrence survived significantly longer than those who were symptomatic.p=0.005
-

Outcome of postoperative colorectal cancer	ICS No	ICS %	RCS No	RCS %	P value
Time to recurrence(months)	Mean 22 SD 17.6		Mean 35 SD 23.9		0.49
No of asymptomatic	10	76.9%	7	38.9%	0.04
Curative surgery for tumour recurrence	9	69.2%	6	33.3%	0.48
Survival after recurrence(months)	Mean 69.1 SD 12.3		Mean 24.4 SD 5.7		

Complications.
- 3 complications occurred in the ICS group (2 bleeds, 1 perforation)
- None in the RCS group.

General comments
- Well conducted, reasonable size RCT.
- Supports the view that intensive colonoscopic surveillance does not improve overall survival even though meta-analysis have shown that intensive follow up in general does improve survival.
- Shows that what intensive colonoscopic surveillance does achieve is earlier detection of postoperative colorectal cancer, more curative surgery for this and a longer survival following its detection.
- The study also reported a large number of postoperative cancers detected in the first 2 years post op and suggests based on this finding that colonoscopy should be undertaken annually in the first two years following colorectal cancer resection.

Health economic evaluation

Short summary

A systematic search of published cost-effectiveness studies was undertaken to inform this topic about follow up of patients with colorectal cancer who have undergone treatment with curative intent. Studies published prior to 1995 were excluded as they are unlikely to have relevance to current NHS practice and costs. The review identified six potentially relevant published economic evaluations (Borie et al (2004), Hassan et al (2010), Macafee et al (2008), Michel et al (1999), Norum et al (1997), Renehan et al (2004)). Following quality assessment, two of these studies (Borie et al (2004), Michel et al (1999)) were deemed to have very serious limitations and were therefore excluded from further consideration. Two other studies (Norum et al (1997), Hassan et al (2010)) were also excluded as they were conducted in Norway and the USA respectively and were considered by the GDG to be less relevant for informing the cost effectiveness of follow up in the UK because of possible differences in clinical practice, costs and healthcare provision between countries. Therefore two studies (Macafee et al (2008), Renehan et al (2004)) were included in the review of economic evidence. Both of the included studies were conducted from the perspective of the UK NHS, but differed in most other respects.

In Renehan et al (2004), five randomised trials, each comparing a form of intensive follow up to conventional follow up, were meta-analysed to obtain estimates of health effects expressed in terms of life years gained. Details of the various follow up strategies and the frequency and type of surveillance tests from each trial were not reported in full. Costs of both follow up and treatment of recurrences were included in the analysis. Cost of chemotherapy was not included. Across the five trials, the mean per patient cost of follow up in the intensive arm ranged from £3,388 to £6,509.

Macafee et al (2008) compared an intensive follow-up regimen (based on one arm of the Follow Up after Colorectal Surgery [FACS] trial) with standard follow up (based on the principles of the British Society of Gastroenterology). Only hospital-based costs during follow up and the cost of surgically treating resectable recurrences were included in the analysis; costs of further elective operations for bowel continuity, chemo/radiotherapy and costs to primary care were not considered. The time horizon for the analysis was limited to 5 years and results were reported in terms of cost per additional resectable recurrence identified.

One additional relevant paper (Tappenden et al (2009)) was identified during the search. This paper was itself a systematic review of UK economic evaluations of colorectal cancer interventions and identified the same individual studies (Macafee et al (2008), Renehan et al (2004)) related to the topic of follow up that have been included in the current review.

DE profiles for included economic studies (to be presented alongside clinical GRADE tables)

Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Li
atients eated for olorectal ancer	Conventional follow up (based on 5 trials)	£2279	5.69 life years lost	Reference			Various scenarios were run assuming different cost, effect and discount rate assumptions. For the analysis based on 5 trials, the ICER ranged from £3,285/LYG to £10,757/LYG.	Directly applicable	M lim
	Intensive follow up (based on 5 trials)	£4758	4.97 life years lost	£2479	0.73 life years gained	£3402 / LYG			

omments: Incremental health outcomes were measured in terms of life years gained. There is some uncertainty about the impact that qual djusting survival would have on the ICER, but this is unlikely to change the conclusion of the study.

atients who ve dergone section for lorectal ncer	Standard follow up (BSG)	£53.2 mi	559 resectable recurrences	Reference			Cost per additional resectable recurrence varied from £16,134 to £25,705.	Partially applicable	Po se lim
	Intensive follow up (FACS)	£68.6 mi	1412 resectable recurrences	£15.4 mi	853 resectable recurrences	£18,077 / additional resectable recurrence			

omments: Effects were measured in terms of the number of resectable recurrences identified. The time horizon was limited to 5 years. An propriate willingness to pay threshold for interpreting the ICER results is not known.

Interpretation of economic evidence

Neither of the cost-effectiveness studies included in the economic evidence review reported an incremental cost-effectiveness ratio (ICER) in terms of cost per QALY. In the absence of information about what represents a reasonable cost per additional resectable case identified, it is difficult to interpret the results of the Macafee et al (2008) analysis and therefore this study has limited relevance for informing the current Guideline topic. The results of Renehan et al (2004), although expressed in terms of cost per life year gained, suggest that intensive follow up is cost effective when compared to conventional follow up. There is some uncertainty about the impact that quality adjustment of survival would have on the ICER reported in Renehan et al (2004), but it is unlikely to change the main conclusion of the paper.

The review of clinical and cost-effectiveness literature shows that there is no consistent definition of what constitutes intensive follow up for colorectal cancer patients. The various studies included in this review differ in terms of the types of tests and interventions included and the frequency of surveillance, therefore no single recommendation for a specific protocol for intensive follow up can be recommended. Caution should therefore also be exercised when pooling studies or making generalisations about both the effectiveness and cost effectiveness of different protocols for intensive follow up over conventional (or less intensive) follow up.

References

Borie F, Combescure C, Daurès JP, Trétarre B, Millat B.Cost-effectiveness of two follow-up strategies for curative resection of colorectal cancer: comparative study using a Markov model. World Journal of Surgery 2004; 28 (6): 563-569

Hassan C, Pickhardt PJ,, Zullo A, Di, Giulio E, Laghi A, Kim DH, Iafrate F. Cost-effectiveness of early colonoscopy surveillance after cancer resection. Digestive and Liver Disease 2009; 41; 881-885

Macafee DAL, Whynes DK, Scholefield JH. Risk-stratified intensive follow up for treated colorectal cancer – realistic and cost saving? Colorectal Disease 2008;10 (3): 222-230

Michel P, Merle V, Chiron A, Ducrotte P, Paillot B, Hecketsweiler P, Czernichow P, Colin R. Postoperative management of stage II/III colon cancer: a decision analysis. Gastroenterology 1999; 117:784-793

Norum J, Olsen JA. A cost-effectiveness approach to the Norwegian follow-up programme in colorectal cancer. Annals of Oncology 1997; 8: 1081-1087

Renehan AG, O'Dowyer ST, Whynes DK. Cost effectiveness analysis of intensive versus conventional follow up after curative resection for colorectal cancer. British Medical Journal 2004; 328 (7431): 81-84

Tappenden P, Chilcott J, Brennan A, Pilgrim H. Systematic review of economic evidence for the detection, diagnosis, treatment, and follow-up of colorectal cancer in the United Kingdom. International Journal of Technology Assessment in Health Care 2009; 25: 470-478

Evidence Tables

COLORECTAL CANCER GUIDELINE	Economic evidence summary (v4.0)

Key question: In asymptomatic patients who have undergone treatment with curative intent for colorectal cancer, what is the optimal method(s), frequency and duration of follow up?

Intervention: intensive packages of follow up
Comparator: less intensive packages or no follow up
Outcomes: survival, recurrence, metachronous primaries, quality of life, late effects, QALYs

Created by: Bernadette Li

Summary (date: 23 February, 2011 including update search)

- The following databases were searched for economic evidence relevant to the PICO: MEDLINE, EMBASE, COCHRANE, NHS EED. The SIGN economic studies filter was applied. Studies published prior to 1995 were excluded as they are unlikely to have relevance to current practice and costs. Studies conducted in OECD countries other than the UK were considered (Guidelines Manual 2009).

- 507 possibly relevant papers were identified. Of these, 23 full papers were obtained for appraisal. A further 18 papers were excluded as they were not applicable to the PICO or did not include an incremental analysis of both costs and health effects. Therefore 5 papers were appraised in the current review of published economic evidence for this topic. During the update search at the end of the guideline development process, 2 additional papers were identified. Of these, 1 additional paper was included in the updated assessment of published economic evidence. The other paper (Tappenden 2009) was systematic review and therefore could not be appraised using the same methodology as the other papers.

- In all 6 included papers, the patient population was defined as colorectal cancer patients who had undergone surgery. In Michel 1999, the patient population was further specified as patients with stage II or III colon cancer. In Borie 2004, the patient population was further defined as having Dukes A, B or C disease.

- The 6 papers reflected different strategies for follow up, often based on local guidelines, hence there is uncertainty about the appropriateness of comparing studies and uncertainty about the generalisability of findings. Norum 1997 compared follow up with no follow up. Michel 1999 compared 7 different strategies involving different combinations of follow up and adjuvant chemotherapy depending on patients' stage of disease. Borie 2004, Renehan 2004 and Macafee 2008 all compared some form of more intensive follow up with less intensive follow up. Hassan 2010 compared early to late colonoscopic surveillance following resection.

- Two papers (Norum 1997, Borie 2004) quantified health effects in terms of QALYs. The other studies reported health effects in terms of number of additional patients alive at 5 years (Borie 2004), life years gained (Renehan 2004, Hassan 2010) and additional resectable recurrences identified (Macafee 2008).

- Information on the source of effectiveness data in the 6 papers varied and was generally poorly reported. In 4 of the studies (Norum 1997, Michel 1999, Macafee 2008, Hassan 2010), effectiveness appeared to be based on a combination of epidemiological data (e.g. national statistics or databases) and published literature, but it was not specified if the reviews of the literature were conducted in a systematic manner. Data on patient outcomes from a regional tumour registry was used in 1 paper (Borie 2004). Data from a previously published meta-analysis was used in 1 paper (Renehan 2004).

- Of the 6 papers included in the review, 5 studies (Norum 1997, Michel 1999, Borie 2004, Macafee 2008, Hassan 2010) were deemed partially applicable to the guideline. The most common reasons for

partial applicability were that the analyses were conducted in countries other than the UK or did not conform to one or more aspects of the NICE reference case. Of the 5 partially applicable studies, 3 were deemed to have potentially serious limitations (Norum 1997, Macafee 2008, Hassan 2010) and 2 were deemed to have very serious limitations (Michel 1999, Borie 2004).

- One study (Renehan 2004) was deemed directly applicable to the current review. The quality of this study was graded as having minor limitations. This study suggests intensive follow up is cost effective, however incremental results were only presented as cost/life year gained. There is some uncertainty about the impact that quality adjustment of survival would have, but it is unlikely to change the conclusion of the paper.

- Following discussion with the full GDG, it was decided that for this particular topic, because of the likely differences in clinical practice and healthcare provision for follow up of colorectal cancer, economic evaluations conducted in countries other than the UK should be excluded from further consideration. Therefore only 2 papers (Renehan 2004 and Macafee 2008) were considered for the purposes of informing recommendations for this topic.

Volume of evidence

- 507 possibly relevant papers were identified. Of these, 23 full papers were obtained for appraisal. A further 18 papers were excluded as they were not applicable to the PICO or did not include an incremental analysis of both costs and health effects. One additional paper was identified during the update search. Therefore a total of 6 papers were included in the appraisal of published economic evidence for this topic.

- Of the 6 papers, 2 were conducted from a UK perspective (Renehan 2004, Macafee 2007), 2 were conducted in France (Michel 1999, Borie 2004), 1 was conducted in Norway (Norum 1997) and 1 was conducted from a US perspective (Hassan 2010).

- Four of the papers (Michel 1999, Renehan 2004, Macafee 2008, Hassan 2010) were classified as cost-effectiveness analyses. The other 2 papers quantified health effects in terms of QALYs and were therefore considered cost-utility analyses (Norum 1997, Borie 2004).

- Following discussion with the full GDG, it was decided that for this particular topic, because of the likely differences in clinical practice and healthcare provision for follow up of colorectal cancer, economic evaluations conducted in countries other than the UK should be excluded from further consideration. Therefore only 2 papers (Renehan 2004 and Macafee 2008) were considered for the purposes of informing recommendations for this topic.

Selection criteria for included evidence:

507 possibly relevant papers identified		**484** papers excluded based on title & abstract

- Studies that compare both costs and health consequences of different strategies were included (from 1995 to current)
- Studies that were conducted in OECD countries (other than the UK) were initially included

23 full text papers obtained		**18** papers excluded based on full text

- Studies that presented incremental results or allowed for incremental results to be derived

| | | 6 papers assessed for applicability and quality | | 4 papers excluded | • Studies that met applicability and quality criteria, including relevance to NICE reference case and UK NHS |

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│ **6**   │   □   │ **4**   │   • Studies that met applicability and quality criteria,
│ papers   │   │ papers   │   including relevance to NICE reference case and UK
│ assessed for │   │ excluded   │   NHS
│ applicability│   │   │
│ and quality │   └──────────────┘
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│ **2**   │
│ papers   │
│ included in │
│ full evidence│
│ review   │
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Quality and applicability of the included studies

		Applicability	
		Directly applicable	Partially applicable
Methodological quality	Minor limitations	Renehan 2004	
	Potentially serious limitations		Norum 1997 Macafee 2008 Hassan 2010
	Very serious limitations		Michel 1999 Borie 2004

- Of the 6 papers included in the review, 5 (Norum 1997, Michel 1999, Borie 2004, Macafee 2008, Hassan 2010) were deemed partially applicable to the guideline. The most common reasons for partial applicability were because the analyses were conducted in countries other than the UK or did not conform to the NICE reference case.

- Of the 5 partially applicable studies, 3 were deemed to have potentially serious limitations (Norum 1997, Macafee 2008, Hassan 2010) and 2 were deemed to have very serious limitations (Michel 1999, Borie 2004).

- One study (Renehan 2004) was deemed directly applicable to the current review. The quality of this study was assessed as having minor limitations.

References

1. Norum J, Olsen JA. A cost-effectiveness approach to the Norwegian follow-up programme in colorectal cancer. Annals of Oncology 1997; 8: 1081-1087
2. Michel P, Merle V, Chiron A, Ducrotte P, Paillot B, Hecketsweiler P, Czernichow P, Colin R. Postoperative management of stage II/III colon cancer: a decision analysis. Gastroenterology 1999; 117:784-793

3. Borie F, Combescure C, Daurès JP, Trétarre B, Millat B. Cost-effectiveness of two follow-up strategies for curative resection of colorectal cancer: comparative study using a Markov model. World Journal of Surgery 2004; 28 (6): 563-569
4. Renehan AG, O'Dowyer ST, Whynes DK. Cost effectiveness analysis of intensive versus conventional follow up after curative resection for colorectal cancer. British Medical Journal 2004; 328 (7431): 81-84
5. Macafee DAL, Whynes DK, Scholefield JH. Risk-stratified intensive follow up for treated colorectal cancer – realistic and cost saving? Colorectal Disease 2008;10 (3): 222-230
6. Tappenden P, Chilcott J, Brennan A, Pilgrim H. Systematic review of economic evidence for the detection, diagnosis, treatment, and follow-up of colorectal cancer in the United Kingdom. International Journal of Technology Assessment in Health Care 2009; 25: 470-478
7. Hassan C, Pickhardt PJ,, Zullo A, Di, Giulio E, Laghi A, Kim DH, Iafrate F. Cost-effectiveness of early colonoscopy surveillance after cancer resection. Digestive and Liver Disease 2009; 41; 881-885

Citation: Renehan AG, O'Dowyer ST, Whynes DK. Cost effectiveness analysis of intensive versus conventional follow up after curative resection for colorectal cancer. British Medical Journal 2004; 328 (7431): 81-84

Design: Cost-effectiveness analysis

Country: UK

Perspective: UK national health service

Population: Patients treated for colorectal cancer

Interventions or strategies compared: Intensive follow up vs conventional follow up

- Follow up regimens and surveillance tests varied between the trials that were considered in this analysis and were not reported in full within the paper.

Time horizon: Lifetime

Discount rate: Health effects 1.5%, costs 6%

Utilities (quality of life): Not considered

Costs: Costs of follow up and treatment of recurrences were included. Cost of chemotherapy was not included. Mean cost per patient from each of the included trials were:

	Intensive follow up (£)	Control (£)
Makela 1995	5283	3347
Ohlsson 1995	5098	1421
Schoemaker 1998	3508	2223
Pietra 1998	6509	3290
Kjeldsen 1997	3388	1113

Outcomes:

Effectiveness of intensive follow up was estimated from a pooled analysis. Results were presented as life years lost per patient.

	Intensive follow up	Control
Makela 1995	7.51	6.25
Ohlsson 1995	4.28	6.16
Schoemaker 1998	3.50	4.25
Pietra 1998	4.71	6.64
Kjeldsen 1997	4.83	5.82

Pooled difference (intensive vs control) for 5 trials: 0.82
Pooled difference (intensive vs control) for 4 trials: 0.73

Results:

Cost per LYG (5 trials): £3402 / LYG
Cost per LYG (4 trials): £3077 / LYG

At a threshold of £20000 - £30000 / LYG, the authors considered follow up to be cost effective.

Results were only presented as cost per LYG and not cost per QALY hence there is some uncertainty over the interpretation of results, but it is unlikely that quality adjusting survival would change the conclusion about the cost effectiveness of follow up.

Sensitivity analysis: A series of sensitivity analyses were undertaken varying parameters such as discount rate, distribution of deaths, false positive test rates and costs. Incremental cost per LYG estimates ranged from £3285/LYG to £10757/LYG for the 5-trial analysis and from £3077/LYG to £9825/LYG for the 4-trial analysis.

General comments:

Applicability: directly applicable

- The analysis does not meet one or more aspects of the NICE reference case but this is unlikely to change the conclusions about cost effectiveness.

Limitations: minor limitations

- Impact on quality of life was not considered in the analysis. Outcomes were measured in terms of LYG and not QALYs.

Citation: Macafee DAL, Whynes DK, Scholefield JH. Risk-stratified intensive follow up for treated colorectal cancer – realistic and cost saving? Colorectal Disease 2008;10 (3): 222-230
Design: Cost-effectiveness analysis
Country: UK
Perspective: UK national health service
Population: Patients treated for colorectal cancer
Interventions or strategies compared: Intensive follow up (FACS) vs standard follow up (BSG) FACS intensive protocol includes outpatient visits (2 in years 1 and 2, 1 in years 3 and 5); chest and liver imaging (2 in years 1 and 2, 1 in years 3 and 5); CEA (4 in years 1 and 2, 2 in years 3-5). BSG standard follow up includes outpatient visits (3 in year 1, 2 in years 2 and 3, 1 in year 4, none in year 5); colonoscopy pre and post resection and once more within 5 years; liver imaging with ultrasound or CT scan once during first 2 years.
Time horizon: 5 years
Discount rate: 3.5%
Utilities (quality of life): Not considered
Costs: Only hospital-based costs during follow up were included and the cost of surgically treating resectable recurrences; costs of further elective operations for bowel continuity, chemo/radiotherapy and costs to primary care not considered.

Intensive follow up:	£68.6 mi
Standard follow up:	£53.2 mi

Outcomes:

Effectiveness data was based on a mixture of published literature, national statistics and epidemiological data. It was not clear if these inputs were identified through a systematic review. The main outcome of interest was the number of resectable cases detected at 5 years.

	Number of patients alive	Number of recurrences detected	Number of resectable recurrences
Intensive follow up	10118	5649	1412
Standard follow up	9246	5591	559

Results:

The ICER reported was £18077 / additional resected recurrence

If follow up was conducted only in Dukes stage B and C patients, the ICER was estimated at £15956 / additional resected recurrence.

Intensive follow up will detect more resectable recurrences but the financial cost and resource requirements are considerable. The authors suggested that given a resource-constrained environment, consideration should be given to risk stratifying follow up.

Sensitivity analysis: The assumptions for incidence, survival rates, discount rates and certain costs were varied. The cost per additional resectable recurrence ranged from £16134 to £25705.

General comments:

Applicability: partially applicable

- The analysis does not meet one or more aspects of the NICE reference case.

Limitations: potentially serious limitations

- Impact on quality of life not considered in the analysis.
- Time horizon limited to 5 years.
- The relevance of these results for informing the current guideline is limited (in the absence of an appropriate willingness to pay threshold).

5.2. Information Needs Associated with Bowel Function

5.2.1. For patients with colorectal cancer, what are the information needs associated with bowel function?

Short Summary

There was a small number of studies which directly investigating the information needs of patients with colorectal cancer (Nikoletti et al, 2008, Lynch et al, 2008, Persson et al, 2005, Broughton et al (2004), Kerr et al, 2003, Sahay et al, 2000). All included studies employed qualitative methodology to assess and investigate patient information needs and included studies investigated the population of interest (colorectal cancer patients); few included studies identified specific inclusion or exclusion criteria with the majority specifying only that patients were colorectal cancer patients with the ability to understand/read the language in which the study was being conducted.

There was one study conducted in the UK which included not only colorectal cancer patients but their carers too (Broughton et al, 2004).

The number of patients in each study ranged from 20 (Sahay et al, 2000) to 1,966 (Lynch et al, 2008) and all studies included patients treated for colorectal cancer with few specific restrictions to inclusion. The included studies may be at risk from recall error due to the differing points in the treatment pathway at which each participant took part in a study. Studies may also be at risk from selection bias with response rates from 5 studies ranging from 32%-86% (Nikoletti et al, 2008, Lynch et al, 2008, Persson et al, 2005, Broughton et al (2004), Kerr et al, 2003).

Included studies addressed factors such as the specific information requirements of participants, the source of information and modes of delivery, the timing of information provision and the impact of information provision on wellbeing and quality of life.

There appeared to be a high degree of dissatisfaction with information provided on specific areas across the studies, particularly related to bowel function; in one study more than 50% of patients were not happy with the information provided in relation to bloating, wind/gas, difficulties emptying bowels, medication, the use of pads and other unspecified bowel problems (Nikoletti et al, 2008), in one study 59% of responders reported not being instructed in stoma irrigation techniques and more than 80% of respondants were dissatisfied with information received during chemotherapy and radiotherapy (Kerr et al, 2003).

The desired source of information and modes of deliveries varied across studies although common themes did appear with doctors, specialist incontinence advisors, nurses, surgeons and relatives all identified as possible sources of information. Modes of delivery included one to one teaching by a health professional, leaflets, pamphlets/booklets, discussion groups, and internet.

The timing of information provision was addressed in two studies (Broughton et al, 2008) with the best time for the provision of information considered to b either before surgery (32.9%) or after surgery while still in hospital (37.2%) (Nikoletti et al, 2008). Carers appreciated the time spent when specialist nurses provided information and several patients and carers would have appreciated more information when being discharged, in particular relating to what symptoms were considered normal after bowel surgery (Broughton et al, 2004).

From one study, bivariate analysis indicated a poorer quality of life was associated with communication problems for men and younger patients, though on multivariate analysis, controlled for clinical and demographic differences, no interaction was observed between communication and gender or age. For patients that completed the questionnaire over 3 years, differences in quality of life between clear and unclear communications groups remained. The difference was statistically significant for emotional (p<0.02) and social functioning (p<0.05) and for sleep problems (p<0.02) (Kerr et al, 2003).

Updated Evidence

Two studies which considered patient perspective were identified on updated searches (Beaver et al, 2010 and O'Connor et al, 2010).

From Beaver et al (2010) is was reported that although patients saw a nurse specialist while they were a hospital inpatient, they were unsure of what to expect once the returned home; this was particularly true of patients without a stoma as they did not usually receive a visit from the nurse

specialist once discharged home. Patients also reported that doctors did not address their concerns or provide information at follow-up appointments and this left them feeling uncertain about their condition and what to expect. This was again particularly true of patients without a stoma.

Patients without a stoma reported more feelings of isolation, though was not limited to solely to this group of participants.
There appeared to be an expectation from patients that the nurse specialist would visit them at home following discharge and a feeling of disappointment when this was not the case.
Patients with a stoma frequently commented that they learned about stoma care through 'trial and error' as they felt that follow-up care did not provide sufficient information on provision of stoma bags and care (Beaver et al, 2010).

Patients experiencing nurse led follow-up reported favourably on their outpatient experience in terms of information, support, knowing what to expect and what was 'normal' in their situation.
Written information was considered beneficial, particularly diagrams nurses drew for each patient, tailored to their own surgical procedure and pitched at their own level of understanding.
Leaflets were perceived to be helpful, providing useful future points of referral.

O'Connor et al (2010) reported that males felt that is was more important to know where their family could go to get help with dealing with their illness and also reported statistically significantly higher satisfaction levels with information on wherefamily could get help dealing with the patient's illness, whether they could wear normal clothing, how treatment works against cancer, if they were going to need help taking care of themselves and how to prepare for the investigative tests.

Younger patients expressed significantly higher information needs regarding the changed in the things they can do with and for their family, who to talk to about alternative therapies, where the family could go to get help dealing with the patient's illness, if treatment would alter the way they looked, what type treatments are available, how to prepare for the tests, what to do if they felt uncomfortable in social situations, if the illness was hereditary, if treatment would affect their relationship or sex life and if they could continue with their job after surgery and treatment.
Older patients expressed higher information needs only in knowing who to call if they had questions while still undergoing treatment.

No significant difference in information needs or how these needs were met were observed in relation to length of time since diagnosis, type of treatment and whether or not a patient had a stoma showed. Comparison of perceptions of the importance of items of information with perceptions of how these needs were met showed a statistically significant difference, indicating that patients felt that information needs with ratings of a high level of importance were not adequately addressed (O'Connor et al, 2010).

Stoma Care Nurse Specialists were reported to be the most common source of information, with other healthcare professionals such as ward nurses, chemotherapy nurses, colorectal consultant and GP mentioned.
One patient cited the internet as the preferred source of information.
Interpersonal communication with a healthcare provider was cited as the most common and preferred source of information (O'Connor et al, 2010).

Review Protocol

Population	Situation	Timing	Outcomes
Patients with colorectal cancer	Information needs associated with bowel function issues – specifically e.g.: Stoma care; Nutrition, body image, sexual function, self esteem and more, (possibly diarrhoea, bloating/wind, pain and problems with emptying bowel after stoma reversal, appropriate dietary advice after a stent has been inserted)	At the time of diagnosis and dependent of stage of disease and management options	• This question will hopefully reveal evidence about information needs (specifically related to bowel function) for patients with colorectal cancer. • Where possible the following detail will be reported: a)Content, format and context of information that patients with colorectal cancer describe, request, need b) NOTE this question will focus on what patients describe, request, and need and NOT what health professionals report that patients describe, request, need.

Following a systematic search of relevant data sources (see appendix .1), the information specialist created a database of potentially relevant studies. All titles and abstracts were sifted by a single reviewer. Queries about inclusion were clarified by the GDG topic subgroup. The full studies were then obtained and reviewed and relevant studies were included in the final evidence review.

All update searches were sifted by a single reviewer and the list of potentially relevant studies was also checked for irrelevant studies by the GDG subgroup. Only studies which all subgroup members were in agreement were excluded. The remaining studies were obtained and reviewed with relevant studies included in the final evidence review.

Evidence from all study types should be considered as it is unlikely that evidence will exist in randomised trials.

The GDG felt that searching for evidence from1995 onwards was appropriate for this topic

Reasons for excluding studies:
Did not address/discuss information needs of patients with colorectal cancer.

Quality of the included studies
Systematic review of RCTs (n = 0)
Systematic review of combined study designs (n =0)
Randomized controlled trial (n =0)
Prospective cross sectional study (n =0)
Case Series Studies (n = 0)
Qualitative Observational study (n=6)

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┌─────────────────────┐        ┌─────────────────────┐
│ 244 (+15)           │   →    │ 206 (+8)            │
│ possibly relevant   │        │ papers excluded     │
│ papers identified   │        │ based on title &    │
│                     │        │ abstract            │
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┌─────────────────────┐        ┌─────────────────────┐
│ 38 (+7)             │   →    │  32 (+5)            │
│ papers obtained     │        │ papers excluded     │
│ for appraisal       │        │                     │
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┌─────────────────────┐
│ 6 (+2)              │
│ papers included     │
│ in evidence table   │
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Volume of evidence
There were a small number of studies in which the information needs of patients with colorectal cancer were assessed in some form (Nikoletti et al, 2008, Lynch et al, 2008, Persson et al, 2005, Broughton et al (2004), Kerr et al, 2003, Sahay et al, 2000). There were no systematic reviews or randomised trials available to address this topic; all studies identified employed qualitative methodology such as telephone interviews, questionnaires and focus groups as this was the most appropriate way to investigate the feelings and perceptions of the patients in relation to their information needs.

Applicability
All included studies investigated the population of interest (colorectal cancer patients) and few included studies had specific inclusion or exclusion criteria with the majority specifying only that patients were colorectal cancer patients with the ability to understand/read the language in which the study was being conducted.
One study was conducted in the UK, with a UK population, 2 studies were conducted in Australia, and 1 each in Canada, Sweden and Germany.

Consistency
In each study, participants were at different stages in their disease (treatment and follow-up); all included studies recruited patients treated for colorectal cancer, though the patients groups differed in terms of the treatment received and many of these differences were not clarified in each of the studies (e.g. patients that underwent chemotherapy or radiotherapy). In one study, in addition to assessing patients, carers were also included (Broughton et al, 2004).
Methodology in each study was broadly similar, employing questionnaires, interviews and focus groups though each study differed in relation to factors such as specific data collection, participant numbers, included patients, timing of study in relation to patient's treatment and outcomes reported. The majority of studies interviewed/questioned participants only once, though one study required participants to complete a questionnaire at three different time points (Lynch et al, 2008) and one study interviewed participants on a one to one basis and also required that they took part in focus groups (Broughton et al, 2004).

Evidence Statement
A total of 6 studies investigating patient information needs were identified (Nikoletti et al, 2008, Lynch et al, 2008, Persson et al, 2005, Broughton et al (2004), Kerr et al, 2003, Sahay et al, 2000). All 6 studies employed qualitative methodologies such as postal questionnaires, telephone interviews or focus groups to assess patient's perceptions on information provision however each study differed in relation to factors such as data collection, participant number, included patients, timing of study in relation to patient's treatment and outcomes.

The number of patients in each study ranged from 20 (Sahay et al, 2000) to 1,966 (Lynch et al, 2008) and all studies included patients treated for colorectal cancer with few specific restrictions to inclusion. One study included only patients that underwent sphincter sparing surgery (Nikoletti et al, 2008),one included patients who had a colostomy for colorectal cancer (Persson et al, 2005), one study specified patients must be at least 6 months post diagnosis (Sahay et al, 2000) and one study included both patients and patients carers (Broughton et al, 2004), in all other studies there were no specific inclusion or exclusion criteria detailed.

In the main, the included studies assessed patients only once, however one study required participants to complete a questionnaire at three different time points, with items in the first interview specifically aimed towards elucidating the level of information provided preoperatively and items in the second and third interviews directed more towards post-operative information provision such as diet, physical activity and counselling (Lynch et al, 2008) and one study interviewed patients on a one to one basis and also required that they took part in focus groups (Broughton et al, 2004).

Risk of Bias
All qualitative studies are subject to bias, specifically selection bias and/or recall bias and this may well be the case for the included studies though it is difficult to assess the degree to which the outcomes have been affected by bias. The differing points in the treatment pathways at which

participants across the different studies were included may lead to questions over the accuracy of the responses of participants, for example, in studies where participants were well into the follow-up period the risk of recall error may be higher than in studies where patients were still undergoing treatment or had very recently undergone surgery. From the included studies, one study specified the postsurgical period for participants where they were required to be in the 6-24 months postsurgical period (Nikoletti et al, 2008), a second study interviewed patients at three time points between 5 and 25 months post diagnosis (Lynch et al, 2008), one study included patients 89 patients, 35 of whom completed the questionnaire more than a year after surgery though no details were provided as to specific times (Persson et al, 2005), one study reported that 76% participants were seen within 3 months of diagnosis (Broughton et al, 2004), one study recruited participants while they were undergoing primary treatment and followed them up for four years to assess the impact of communication on quality of life and the remaining study included participants for whom the interval since diagnosis ranged from 6 months to 7 years (Sahay et al, 2000).

Selection bias may be a particular problem for the current evidence base; volunteer bias may result in a group of participants that is not representative of the true population. Selection bias can also be caused by non-responders, with certain types of people likely to respond to such studies. In the current evidence base, response rates from 5 studies ranged from 32%-86% (Nikoletti et al, 2008, Lynch et al, 2008, Persson et al, 2005, Broughton et al (2004), Kerr et al, 2003) and could not be calculated for one study (Sahay et al, 2000). Only one study addressed the likely limitations of the study, identifying the low response rate (57.4%) as a potential for bias and highlighting that patients with rectal cancer, patients with advanced disease and older patients were under-represented in their sample (Lynch et al, 2008).

Specific Information Needs
From one study, a variety of specific information needs were reported including needs for information on diet, managing diarrhoea, bloating and emptying of bowel and a number of patients reported that they were not satisfied with the information provided with more than 50% of patients not happy with information provided in relation to bloating, wind/gas (55.2%), difficulties emptying bowels (55.6%), medications (57.1%), the use of pads (52.6%), other unspecified bowel problems (57.1%) and other therapies (80%) (Nikoletti, 2008).

From Lynch et al (2008), 89.2% of patients who underwent ostomy surgery reported having been given information about the likelihood of having an ostomy after surgery and only 6 patients (1.8%) indicated dissatisfaction at the information provided. 92.5% of patients reported that they were provided with information regarding the length of time they would need to have the ostomy and only 5 (1.6%) reported being dissatisfied with the information provided. (99.4%) of patients reported being provided with information on caring for the ostomy with only 5 patients (1.5%) dissatisfied with the information provided.

In relation to the provision of information on diet, exercise and counselling availability, the proportion of patients reporting that they received information dropped from the first interview to the third. At the first interview 88% of patients reported being provided with information on how to manage their diet compared with 20% at third interview, 67.8% of patients reported being provided with information on type and amount of exercise compared with 16% at third interview and 77.4% reported receiving information on the availability of counselling at first interview compared with 20% at third interview (Lynch et al, 2008).

A third study (Persson et al, 2005) reported that patients felt that specific information needs such as information on surgical procedure, medical exam and test results, surgical procedure results, the responsible doctor and ET nurse and dietary information were important and 15- 45% of patients were not satisfied with the information provided for certain aspects.

Significant differences between patients with and without complications regarding information about surgical procedure were reported; 3/21 (14%) of patients with complications were dissatisfied versus 12/27 patients (44%) without complications (p=0.03) (Persson et al, 2005).

Patients considered attitudes and treatment to be important (Persson et al, 2005) and with two exceptions; 54% of patients were dissatisfied with ET nurses interest in their home situations and 35% were dissatisfied with ET nurses' interest in their happiness.

88% of patients considered it important to communicate with the ET nurse in relation to health/life situation and 25% reported that they were not satisfied with said communication (Persson et al 2005).

In relation to sex life, 51% of patients considered the ability to talk to ET nurses to be important and 74% reported being dissatisfied with provisions (Persson et al 2005).

Participants in a UK study (Broughton et al, 2004) reported being confused about the process and findings following investigations when more information could have contributed to lessening anxiety.

From one study (Kerr et al, 2003), 8 factors were combined to create a single communication variable and if any patient negatively experienced any of the 8 elements then communication was considered by investigators to be unclear. In this study, 39% of patients responding to the communication questions and in total 39% of patients were thought by investigators to consider communication to have been unclear.

From Kerr et al, 2003; in relation to stoma irrigation specifically, 59% of responders reported that they were not instructed in the technique of stoma irrigation; men felt significantly less informed about this (34% versus 58%, p<0.05).
More than 80% of patients were dissatisfied with the information they received during chemotherapy and radiotherapy (Kerr et al, 2003).
90% of respondents felt that help concerning lifestyle management was important, particularly younger patients (93% versus 85%, p<0.05) though it was unclear what ages defined younger patients; only 20% of patients reported having contact with a social worker, self help group or psychologist (Kerr et al, 2003).
60% of patients would have preferred more opportunity to speak to their physician (Kerr et al, 2003).

In one study of 20 patients (Sahay et al, 2000) the majority of patients felt they had been adequately informed about their treatment and its consequences with some areas for possible improvement. Patients felt they had the opportunity to ask questions when the need arose and that they received well explained answers about their treatment. Some patients reported concerns with the lack of information about the long-term management of the illness including diet and nutrition related alternative therapies, post-operative complications, stoma care and location of colostomy supply outlets.

"I think that there's not enough emphasis made on what the outcome might be. When I was operated on back in 1993, it would have been useful to be counselled about lifestyle, diet, any kinds of supplements and alternative treatment. Give the person as many tools as she can get so that she can be fighting! Maybe the patient should be trusted more with all the available information."

Source of Information and Mode of Delivery
In one study, 46.2% of respondents (n=72) considered doctors to be the most appropriate source of information for bowel management while 21.8% considered specialist incontinence advisors to be most appropriate, followed by nurses (21.22%), physiotherapists (5.8%), dieticians (2.6%), complementary therapists (1.3%) and other unspecified sources (1.3%) (Nikoletti, 2008).

From Lynch et al, 2008, 69% of patients reported that they spoke to an ostomy nurse prior to surgery and only 1 patient indicated that they were dissatisfied with the experience.

From one UK study (Broughton et al, 2004), the main sources of information reported were from somebody they knew (n=18), reading (n=7) or from the media (n=7). Patients and carers reported on their ignorance as well as the lack of information available in surgeries and public places.

"leaflets at the surgery would have alerted me in hindsight"

"provide information in more common fashion or language then the medical profession words which they used and she does not understand"

"the cancer BACUP literature, particularly one of them...where they give a lot of information...I found that very helpful and in fact put it (the surgery) in perspective...I knew (then) what the parameters were"

The preferred mode of delivery of information was one to one teaching by a health professional (26.8%), pamphlets or booklets (21.5%), talking to someone recovering from a similar condition

(16.2%), telephone helplines (10.1%), attending support sessions (6.6%), attending education sessions given by health professionals in groups of 20-40 people (5.7%), internet (3.1%) and audiotape (2.6%) (Nikoletti, 2008).

Following diagnosis, participants in a UK study (Broughton et al, 2004) received written literature (n=14) and were given verbal information relating to their surgery (n=40). Patients reported being able to discuss matters with a health professional (n=23), usually the surgeon or specialist nurse and information for stoma patients was provided primarily by stoma nurses.

Patients looked to cancer specialist as their main source of information, particularly in relation to details of their prognosis and most patients emphasised the need for straightforward facts. Other sources of information included written material provided by cancer clinics, resources offered by friends and relatives and to a lesser extent, the internet and support groups. The family physician was considered to be someone to fill the gaps in understanding and to answer questions not addressed by the oncology team (Sahay et al, 2000).

Timing of Information Provision
In relation to the timing of information provision the majority of patients indicated that the best time for receiving information was either before surgery (32.9%) or after surgery while in hospital (37.3%), the remaining participants indicated that 1-2 weeks after surgery (14.3%) and 2-4 weeks after surgery (11.8%) were the best times (Nikoletti, 2008).
Carers appreciated the time spent when specialist nurses provided information and several patients and carers would have appreciated more information when being discharged, in particular relating to what symptoms were considered normal after bowel surgery (Broughton et al, 2004).

"about the bowels, how they react afterwards because (thought) the cancer was coming back"

Impact of information provision on wellbeing and quality of life
Patients appeared to equate involvement in their care with information and reported satisfaction with their level of involvement because they were kept informed. Patients did not feel there were too many decision points in the treatment of colorectal cancer apart from deciding to proceed with chemotherapy or radiotherapy and having input into the adjustment of chemotherapy regimens provided great satisfaction to patients for whom toxicity was a problem. Patients felt comforted to know that they had the final decision regarding course of treatment, yet relied heavily on specialists for making many treatment related decisions, with many patients feeling they would be "stupid not to" One patient reported that more information may have enabled her to play a larger role in decision making about her care. A few patients reported having false impressions about the nature of their illness initially with 1 patient reporting that she was *"astounded"* when tod her cancer had recurred as she felt that having gone through the treatment she would be cured. It is unclear whether the patient had received the information or had misunderstood what she had been told about possible recurrence.
A 2nd patient was shocked when he heard the word cancer as he had been under the impression that he was being treated for a tumour but did not realise it was cancerous. The same patient did not understand the terms oncologist or lymph node and it is therefore possible that he was told the tumour was malignant but did not understand what this meant for him.
A 3rd patient reported that he initially felt that he had not been given enough information but that with hindsight felt that perhaps he was given information but the shock of being told he had cancer made him unreceptive to the information provided.
From discussions with patients, several ways in which a patients' involvement in their care may be limited were identified including the shock of diagnosis limiting the patients' ability to formulate questions and hear what the doctor is saying. Patients also reported feeling that doctors were too busy to discuss their case in detail and did not know what type of questions to ask and with the short time between initial diagnosis and beginning treatment meant there was little time to learn the right questions to ask (Sahay et al, 2000).

"Sometimes you think there could be more (information), but then you go into the clinic and see all the people, you realise they haven't got much time for everyone"

"You don't always know what kinds of questions to ask. I'm a fairly well-educated person and fairly able to understand things, but receiving a diagnosis of cancer is such a shock in itself that is doesn't

always occur to you that maybe you should ask more questions. The suggestion was that they were going to operate, and everything was all done within 2 weeks."

Role, emotional and social functioning scores were lower in patents reporting unclear communication; these patients also experienced sleeping problems, poorer body image and more financial worries and have a worse future perspective. The trend continued into the fourth year though it was unclear whether patient numbers prevented more significant findings (Kerr et al, 2003).

Bivariate analysis indicated a poorer quality of life was associated with communication problems for men and younger patients, though on multivariate analysis, controlled for clinical and demographic differences, no interaction was observed between communication and gender or age. For patients that completed the questionnaire over 3 years (data from year 4 not used due to patient numbers), differences in quality of life between clear and unclear communications groups remained. The difference was statistically significant for emotional ($p<0.02$) and social functioning ($p<0.05$) and for sleep problems ($p<0.02$) (Kerr et al, 2003).

Updated Evidence

On update searches, a further two studies were identified as providing information relevant to this topic (Beaver et al, 2010 and O'Connor et al, 2010).

Beaver et al (2010) aimed to explore patient perceptions of their experiences of follow-up care after treatment for colorectal cancer with a series of open-ended questions. The main sections of the interview guide were as follows: Organisation of follow-up care; satisfaction with follow-up care; personal experience of care; information and advice provided during follow-up care; demographic and disease/treatment details.

One dominant theme and several subthemes were identified with the dominant theme labelled 'knowing what to expect' after bowel surgery and the subthemes relating to 'living with altered bowel function', patients gathering information about their condition through 'trial and error' and 'information and support from specialist nurses'.

Knowing what to expect
Patients reported that although they saw a nurse specialist while they were a hospital inpatient, they were unsure of what to expect once the returned home; this was particularly true of patients without a stoma as they did not usually receive a visit from the nurse specialist once discharged home

"The first few days I wasn't warned about this, that my bowels would be all haywire and I'd be going to the toilet all the time and making a mess of myself. I wasn't warned about this".

Patients reported that doctors did not address their concerns or provide information at follow-up appointments and this left them feeling uncertain about their condition and what to expect. This was again particularly true of patients without a stoma.

"I feel as if the doctors coma and they examine you like, well you're just a, you're just a number and they have a look at yer and that's it".

Patients reported not understanding whether their physical symptoms were normal for patients who had undergone colorectal cancer surgery and would have appreciated more information to alleviate concerns and anxiety.

"Because when I got these peculiar things (sensations) I would have thought, oh it's normal. Whereas not knowing that it is normal, is there something wrong".

Trial and Error
Patients reported learning about their condition through the self-accumulation of information and knowedge.
Patients reported feeling supported by a nurse specialist while in hospital but feeling left to cope alone on discharge.
Patients without a stoma reported more feelings of isolation, though was not limited to solely to this group of participants.
There appeared to be an expectation from patients that the nurse specialist would visit them at home following discharge and a feeling of disappointment when this was not the case.

Patients with a stoma frequently commented that they learned about stoma care through 'trial and error' as they felt that follow-up care did not provide sufficient information on provision of stoma bags and care. Relative, friends and the patients themselves would search the internet for more information on stoma care.

"I curse at times, but you seem to be left to battle your way throughout yourself. But then once you come home, then it's like you're left on your own. Well knowledge of these services (stoma care), I found out through my daughter going on the internet".

Concern about diet and what specific type of diet was appropriate following removal of part of the bowel was a commonly expressed theme. Patients felt that specific dietary advice was important and should be provided. Some participants reported being given a leaflet while others reported being given limited information.
It was felt that information on diet should be provided prior to discharge and patients perceived a strong link between diet and bowel function.
A fear of accidents and a hyper-awareness of altered bowel habits resulted in patients adopting practical strategies of learning which type of foods would or would not disturb their bowel function. Some patients reported contacting a nurse specialist by telephone to seek dietary advice.:

"Sometimes all she'd say was 'If you are gonna go out tomorrow whatever, to a do, leave your brussel sprouts alone. Leave your peas alone. Wait til you are stopping in you know'. I've learned myself really, trial and error".

Living with Altered Bowel Function
Approximately 50% of patients interviewed had a permanent stoma and 3 patients had experienced a temporary stoma. Daily life with a stoma had both physical and psychological consequences for patients:

"Well of course the biggest side effect, sadly, is the psychological one. The psychological impact of having a colostomy to me is dreadful"

Patients reported practical problems associated with a stoma along with a potential lack of independence. Concerns were also raised about the appearance and visibility of the stoma bag.

"You've got to watch how you dress at times. You can't swim naturally. I mean it shows when you put thin clothes on you know. It's a nuisance, a bit of tape around the edges and it doesn't show then".

For patients without a stoma, concern was expressed over uncontrollable bowel movements that were extremely distressing, with the unpredictability of movements causing a sense of insecurity, particularly in a public environment. Participants without a stoma were well able to recall a moment when their pride and dignity had been adversely affected:

"Last week I was in town and for no reason whatsosever, I'd been to the building society etc, I suddenly got a bout of diarrhoea in the middle of walking back to the carpark".

Information and support from specialist nurses
All patients had experienced doctor led hospital follow-up, while a minority had experienced a nurse led clinic, led by a colorectal nurse practitioner.
Patients experiencing nurse led follow-up reported favourably on their outpatient experience in terms of information, support, knowing what to expect and what was 'normal' in their situation.
Written information was considered beneficial, particularly diagrams nurses drew for each patient, tailored to their own surgical procedure and pitched at their own level of understanding.
Leaflets were perceived to be helpful, providing useful future points of referral:

"When I did come back for my check-up then XXX was lovely. She drew me a diagram and told me everything and there's so much I didn't know about and she was really good. She was really very good. She showed me where the lymph nodes were like, she did little dots and everything and that they've taken part of my, part of my rectum away which I didn't realise he'd done that part. I mean it's best to know, isn't it".

Support and advice was provided by the hospital based colorectal nurse specialist long after completion of treatment. Nurses were contacted by telephone for advice and information on various problems and colorectal nurse specialists were perceived to be helpful for both practical and emotional support.

"Any time I've had a problem I think oh dear, I'll phone then and that's not a problem. They're on the phone, 'wait and we'll phone you back' or I've just left a message and she will definitely phone me back. They're very good, within half an hour usually".

This was not the experience for all participants however; although they had been given contact details for the colorectal nurse specialist, many patients reported not contacting the service if they experienced difficulties or had tried to contact the service and received an answerphone with calls not always responded to promptly.

Patients without a stoma commented that they were unsure whether it was appropriate for them to contact the colorectal nurse specialist as they did not have a stoma.
On patients reported that when he contacted the service, an answerphone message mentioned stoma care and this indicated to him that the service was only for patients with a stoma.

Patients reported feeling reluctant to contact the colorectal nurse specialist after discharge:

"Alright, I had a number to ring the hospital up, but you feel as though you're.. They're always busy aren't they, the stoma nurses".

O'Connor et al (2010) adapted an instrument to measure the information needs of patients with cancer of the rectum and determined how these information needs were met using an adapted form of the Toronto Information Needs Questionnaire (TINQ).
Internal consistency of the questionnaire and subscales was measured using Cronbach's alpha testing; reliability testing of the scale indicated a Cronbach's coefficient of 0.95 for the information needs assessment and 0.97 for the questions on how information needs were met.

Information needs were high with means from each item ranging from 2.8-4.88 (1=not important to 5=extremely important).

Examination of the relationship between gender and age for different items on the scale showed some gender differences with males showing a statistically significantly higher mean score than females in some areas.
In relation to the information needs assessment only one question showed a statistically significant gender difference with males feeling that is was more important to know where their family could go to get help with dealing with their illness.

Males reported statistically significantly higher satisfaction levels with information on where family could get help dealing with the patient's illness, whether they could wear normal clothing, how treatment works against cancer, if they were going to need help taking care of themselves and how to prepare for the investigative tests.

Younger patients expressed significantly higher information needs regarding the changed in the things they can do with and for their family, who to talk to about alternative therapies, where the family could go to get help dealing with the patient's illness, if treatment would alter the way they looked, what type treatments are available, how to prepare for the tests, what to do if they felt uncomfortable in social situations, if the illness was hereditary, if treatment would affect their relationship or sex life and if they could continue with their job after surgery and treatment.
Older patients expressed higher information needs only in knowing who to call if they had questions while still undergoing treatment.

In relation to how information needs were perceived to be addressed, few age differences were observed. Younger patients expressed higher satisfaction with information on being able to continue with their job following treatment while older patients expressed higher satisfaction with information on whether there was cancer elsewhere in the body.

ANOVA for length of time since diagnosis, type of treatment and whether or not a patient had a stoma showed no significant difference in information needs or how these needs were met (no p values were reported).

A Wilcoxon Signed Rank Test compared perceptions of the importance of items of information with perceptions of how these needs were met and showed a statistically significant difference, indicating that patients felt that information needs with ratings of a high level of importance were not adequately addressed (no p values were reported).

Stoma Care Nurse Specialists were reported to be the most common source of information, with other healthcare professionals such as ward nurses, chemotherapy nurses, colorectal consultant and GP mentioned.
One patient cited the internet as the preferred source of information.
Interpersonal communication with a healthcare provider was cited as the most common and preferred source of information.

References

Beaver, K, Latif S, Williamson S et al (2010) An exploratory study of the follow-up care needs of patients treated for colorectal cancer *Journal of Clinical Nursing* 19;3291-3300

Broughton M, Bailey J, and Linney J (2004) How can experiences of patients and carers influence the clinical care of large bowel cancer? *European Journal of Cancer Care* 13;4:318-327

Kerr J, Engel J, Schlesinger-Raab A, Sauer H and Holzel D (2003) Doctor-Patient Communication Results of a four year prospective study in rectal cancer patients *Disease of the Colon and Rectum* 46;8:1038-1046

Lynch B, Hawkes A, Steginga S, Legget B and Aitken J (2008) Stoma surgery for colorectal cancer – a population based study of patient concerns *Journal of Wound Ostomy and Continence Nursing* 35;4:424-428

Nikoletti S, Young J, Levitt M, King M et al (2008) Bowel problems, self care practices and information needs of colorectal cancer survivors at 6 to 24 months after sphincter saving surgery *Cancer Nursing* 31;5:389-398

O'Connor G, Coates V and O'Neil S (2010) Exploring the information needs of patients with cancer of the rectum *European Journal of Oncology Nursing* 14;271-277

Persson E, Gustavsson B, Hellstrom A, Lappas G and Hulten L (2005) Ostomy patients perceptions of quality of care *Journal of advanced nursing* 49;1:51-58

Sahay T, Gray R, and Fitch M (2000) A Qualitative study of patient perspectives on colorectal cancer *Cancer Practice* 8;1:38-44

Evidence Tables

Citation: Beaver, K, Latif S, Williamson S et al (2010) An exploratory study of the follow-up care needs of patients treated for colorectal cancer *Journal of Clinical Nursing* 19;3291-3300
Design: Exploratory Qualitative Study **Country**: UK **Setting:** Outpatients **Aim**: to explore patient perceptions of their experiences of follow-up care after treatment for colorectal cancer
Inclusion criteria Patients who had completed treatment for colorectal cancer
Exclusion criteria Patients that had not completed treatment or demonstrated signs of recurrent disease
Sample Size A purposive sample of 27 patients comprised the study population (purposive sampling is used when the aim of the research requires a particular group of people with similar characteristics to be recruited).
Randomisation Method N/A
Population N=27
Study Duration Patients were seen for follow up at durations of 6-12 months over five years. It is not clear whether the questionnaire was administered at a specific point in follow-up or whether patients were included as any point in their follow-up.
Interventions Interviews with audio-recording
Outcomes Identifying themes from the data collected
Results The interview guide was sub-divided into several sections and designed to facilitate the exploration of general topic areas. Questions were open-ended and related to the aims of the study A series of closed questions was also administered to collect demographic details. The main sections of the interview guide were as follows: Organisation of follow-up care Satisfaction with follow-up care Personal Experience of care Information and advice provided during follow-up care Demographic and disease/treatment details There was an equal distribution of men and women in the sample with a mean age of 72 years (range: 59-86). Mean time to diagnosis was 26 months (range: 4-67 months). One dominant theme and several subthemes were identified with the dominant theme labelled 'knowing what to expect' after bowel surgery and the subthemes relating to 'living with altered bowel function', patients gathering information about their condition through 'trial and error' and 'information and support from specialist nurses'. *Knowing what to expect* Patients reported that although they saw a nurse specialist while they were a hospital inpatient, they were unsure of what to expect once the returned home; this was particularly true of patients without a stoma as they did not usually receive a visit from the nurse specialist once discharged home

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"Alright, I had a number to ring the hospital up, but you feel as though you're.. They're always busy aren't they, the stoma nurses".

General comments
 A list of the questions administered was not provided as part of the paper.

Citation: Broughton M, Bailey J, and Linney J (2004) How can experiences of patients and carers influence the clinical care of large bowel cancer? *European Journal of Cancer Care* 13;4:318-327
Design: Qualitative Study
Country: UK
Setting: Home based interview and centrally based focus groups
Aim: to investigate the care of large bowel cancer from patients' and carers perspectives' to identify recurrent themes.
Inclusion criteria No details given
Exclusion criteria No details given
Sample Size No details given
Randomisation Method N/A
Population N=57 patients invited to participate
Study Duration
Interventions Patients were interviewed using a semi-structured in depth and tape recorded technique each lasting between 30 and 90 minutes. Recordings were transcribed by an individual not associated with the research and analysed according the methods of framework analysis The data were analysed by a research nurse and checked by the health promotion specialist. Focus group discussions were guided using the same semi-structured interview questions and analysed in a similar way.
Outcomes Recurrent themes in patient and carers experiences
Results 49/57 patients were interviewed for a response rate of 86% (mean age 69 years, range 37-92). 37 (76%) of participants were seen within 3 months of diagnosis. 16 patients did not have a specific carer or declined consent for the research nurse to contact them; of the 33 carers that received information, 11 did not respond, 10 were unable to attend and 4 were not interested. 8 carers, all relatives, participated in focus groups. The main source of information about bowel cancer was from somebody the patient knew (n=18), reading (n=7) or from the media (n=7). Patients and carers commented on the their ignorance and the lack of information available in surgeries and public places. 'Leaflets at the surgery would have alerted me in hindsight' Some participants said people felt embarrassed to *'discuss their bowels'*. No-one mentioned receiving information about what to expect when attending outpatients. 18/36 patients had verbal explanations about their colonoscopy and/or barium enema; 9 received written information and were satisfied with the amount and content. Several patients reported being confused about the process and findings following investigations when more information could have contributed to lessening anxiety.

Following diagnosis, 14 patients received written literature and 40 patients were given verbal information relating to their surgery.

23 patients were able to discuss matters with a health professional, usually the surgeon or specialist nurse and information for stoma patients was provided primarily from stoma nurses.

Carers appreciated the time spent when specialist nurses provided information.

Several patients and carers would have appreciated more information when being discharged, in particular relating to what symptoms were considered normal after bowel surgery.

Quotes relating to information needs
- 'I would liked to have talked to someone, when I left hospital there was no written information'
- 'Everybody explained everything from the beginning to end right the way through'
- 'The cancer BACUP literature, particularly one of them, where they give a lot of information, I found that very helpful and in fact put it (the surgery) in perspective. I knew then what the parameters were'
- 'about the bowels, how they react afterwards because (thought) the cancer was coming back'
- 'need more information if going back to work'
- 'provide information in more common fashion or language than the medical profession words which they used and she does not understand'

Citation: Kerr J, Engel J, Schlesinger-Raab A, Sauer H and Holzel D (2003) Doctor-Patient Communication Results of a four year prospective study in rectal cancer patients *Disease of the Colon and Rectum* 46;8:1038-1046
Design: Prospective Case Series
Country: Germany
Setting:
Aim: To examine the effect of communication on rectal cancer patients quality of life over four years
Inclusion criteria See Comments
Exclusion criteria See Comments
Sample Size No details
Randomisation Method N/A
Population N=1,038 patients diagnosed with rectal cancer N=443 patients gave informed consent
Study Duration Recruitment Phase – 2 years Follow-up Phase – 4 years
Interventions Quality of life survey: Part 1 established details of treatment, medicines being taken and after care as well as questions concerning stoma care. Part 2 contained the EORTC questionnaires. In the QLQ-C30, 30 questions combine to make five functional scale, a global quality of life measure, and symptom assessment including pain fatigue, diarrhoea and constipation. In the CR38, 38 questions combine to make 8 overall scales including body image, sexual function, future perspective, and bowel problems. The scores were converted to a 0-100 scale as recommended and high scores represented positive outcomes. Part 3 obtained demographic details including marital status, education, medical insurance and employment. Part 4 assessed patients' satisfaction with hospital stay, physician communication and after care.
Outcomes Quality of Life related to communication
Results Patients giving their consent were more likely to be from clinics treating more than 13 patients a year (p<0.001), younger than 70 years (p<0.001) and male (p<0.01). 329/443 patients returned at least one questionnaire and non-responders were more likely to be older than 70 years (p<0.001) and have disease progression (p<0.01). In year 1, 83 patients had disease progression, in year 2, 106, year 3, 118 and by year 4 129 patients were excluded due to disease progression. 322 (97.9%) of responders completed the questions related to communication and 39% reported that the information they received was unclear. 8 factors were combined to create a single communication variable and if a patient negatively experienced and of the 8 elements, then communication for them was deemed to be unclear. Of the patients with a stoma, 59% were not instructed in the technique of stoma irrigation; men felt significantly less informed about this (34% versus 58%, p<0.05).

More than 80% of patients were dissatisfied with the information they received during chemotherapy and radiotherapy.

90% of responders felt that help concerning lifestyle management was important, particularly younger patients (93% versus 85%, p<0.05) however only 20% of patients had contact with a social worker, self help group or psychologist.

60% of patients would have preferred more opportunity to speak to their physician.

Role, emotional and social functioning scores were lower in patients reporting unclear communication; these patients also experienced sleeping problems, poorer body image and more financial worries and had a worse future perspective.
The trend persisted into the fourth year though it is unclear whether patient numbers prevented more significant findings.

Bivariate analysis indicated that poorer quality of life was particularly associated with communication problems for men and younger patients though on multivariate analysis, controlled for clinical and demographic differences, no interaction was observed between communication and gender or age.

For patients that completed the questionnaires repeatedly over 3 years (data from year 4 not used due to reduced patient numbers), differences in quality of life between clear and unclear communication groups remained. The difference was statistically significant for emotional (pp<0.02) and social functioning (p<0.05) and sleep problems (p<0.02).

	N (%)	N (%)
Questionnaire Variables		
Communication		
	Very well, well, average	**Badly, very badly**
How were examinations, treatment, operation and complications explained?	308 (96)	14 (4)
Were you satisfied with the explanation of your illness?	311 (97)	11 (3)
	Clear and understandable	**Incomprehensible, too little**
How did you find the information concerning the following points:		
Daignosis	283 (88)	39 (12)
Disease Process	234 (73)	88 (27)
Nature of the illness	236 (73)	86 (27)
Recovery	255 (79)	67 (21)
Treatment Choice	266 (83)	56 (17)
Other Factors	309 (96)	13 (4)
	Clear	**Unclear**
Main communication variable (if any of above unsatisfactory)	197 (61)	125 (39)
Other Variables	**Clear and Understandable**	**Incomprehensible, too little**
How were you instructed in the technique of stoma irrigation	37 (41)	53 (59)
	Very well, well, average	**Badly, very badly**
Were you satisfied with the explanations during and after chemotherapy?	95 (87)	14 (13)
Were you satisfied with the explanations during and after radiotherapy?	83 (86)	13 (14)
	Very important, important, average	**Unimportant, totally unimportant**
Do you think help concerning work, family and care issues is important?	297 (90)	32 (10)
	Yes	**No**
Do you have contact with a self-help group, psychologist or social worker?	63 (20)	259 (80)
Would you have liked more time to speak to a doctor	196 (61)	126 (39)

Table: Key communication and care variables

General comments
 No selection criteria were set other than the ability of the patient to read German though the study takes only

patients with rectal cancer from the Munich Cancer Registry which in itself is a selection criterion.

Citation: Lynch B, Hawkes A, Steginga S, Legget B and Aitken J (2008) Stoma surgery for colorectal cancer – a population based study of patient concerns *Journal of Wound Ostomy and Continence Nursing* 35;4:424-428
Design: Retrospective, Qualitative study **Country**: Australia **Setting:** **Aim**: to describe difficulties experienced by Australian colorectal cancer patients with a temporary or permanent ostomy over the initial 2 year period following diagnosis and treatment and to assess patients satisfaction with information provided by their healthcare providers over the same period.
Inclusion criteria Participants were part of the colorectal cancer and quality of life (CRCQOL) study and the inclusion criteria for that study were reported elsewhere. Criteria briefly reported in the current publication study participants had a first, primary diagnosis of colorectal cancer between January 1, 2003 and December 31, 2004 and were between the ages of 20 and 80 years at the time of diagnosis.
Exclusion criteria No details provided – will have been reported elsewhere as part of the CRCQOL study
Sample Size No details
Randomisation Method N/A
Population N=1,966 colorectal cancer patients completed Time 1 N=1,657 completed Time 2 interview N=1,488 completed Time 3 interview
Study Duration
Interventions Computer Assisted Telephone Interview

Outcomes
Preoperative Information Provision (based on recommendations in Australian guidelines for the management of colorectal cancer)
    • the likelihood of needing an ostomy
    • how long the ostomy would be needed
    • how to look after the ostomy
    • whether the participant had been visited by a stomal therapy nurse before surgery
 	
Information provision related to follow-up about (asked during time 2 and time 3 interviews)
    • diet
    • physical activity
    • availability of counseling
 	
If the answer to the information provision questions was yes, then patients were asked to rate their satisfaction with the information provided on a scale of 1 (very satisfied) to 5 (very dissatisfied).
 	
Chi squared tests were used to investigate whether there was a difference in the number and severity of symptoms depending on whether a patient was satisfied with the information provisions.

Limitations The findings came from a large population sample of Australian colorectal cancer survivors however the response rate was only 57.4% and older patients, patients with rectal cancer and patients with advanced disease were underrepresented in the sample.

Self-reported data is likely to be limited by selection bias, recall error, social desirability and other biases.

Results
1,9666/3,182 eligible patients completed the Time 1 interview for an overall response rate of 57.4%.
Time 1 interview conducted at approximately 5 months, time 2 at approximately 12 months and time 3 at approximately 24 months.

Mean time between diagnosis and time 1 interview was 4.8±1.9months
Mean time between diagnosis and time 2 interview was 12.2±0.6months
Mean time between diagnosis and time 3 interview was 24.4±0.8months

332/1966 patients completing the time 1 interview underwent ostomy surgery (218 temporary and 114 permanent). At time 2 interviews, 160/1657 patients had had ostomy surgery (48 temporary and 112 permanent) and at time 3 interviews 125/1488 participants had had ostomy surgery (16 temporary and 109 permanent).

During the first interview, patients were asked a series of questions relating to preoperative information provision.

296/332 (89.2%) patients reported having been given information about the likelihood of having an ostomy after surgery with 6 patients (1.8%) indicating dissatisfaction at the information provided.

307/332 (92.5%) of patients reported being provided information regarding the length of time they would need to have the ostomy and 5 (1.6%) reported being dissatisfied with information provided.

330/332 (99.4%) patients reported being provided with information on caring for the ostomy with 5 (1.5%) reported dissatisfaction with the information provided.

219/332 patients spoke to an ostomy nurse prior to surgery and only one patient indicated that they were dissatisfied with the experience.

Were you given information on	Time 1 (n=332)	Time 2 (N=160)	Time 3 (N=125)
	N (%)	N (%)	N (%)
How to manage your diet	292 (88)	43 (26.9)	25 (20)
Type and amount of exercise	225 (67.8)	37 (23.1)	20 (16)
Availability of counseling	257 (77.4)	25 (15.6)	25 (20)

Table 1: Provision of information on diet, exercise and counselling availability

There was no difference in the number or severity of symptoms depending on whether patients were satisfied with the information provided or whether they had seen an ostomy nurse.

General comments
This study also investigated a number of other issues relating to stoma not related to the information needs or patients and are therefore not reported here.

Citation: Nikoletti S, Young J, Levitt M, King M et al (2008) Bowel problems, self care practices and information needs of colorectal cancer survivors at 6 to 24 months after sphincter saving surgery *Cancer Nursing* 31;5:389-398

Design: Qualitative Study

Country: Australia

Setting:

Aim: To determine (a) the prevalence and type of bowel problems within a 6-24 month period after colorectal surgery (or closure of defunctioning stoma), (b) impact of bowel problems on activities of daily living and lifestyle, (c) types of self care practices undertaken by participants to manage bowel problems and their appraisal of such practices and (d) information needs of participants in relation to bowel management.

Inclusion criteria Patients who had undergone sphincter saving surgery for colorectal cancer
Exclusion criteria None given
Sample Size No details given
Randomisation Method N/A
Population N=101
Study Duration Patients were treated between 2000 and 2002 and were in the 6 to 24 month postsurgical period
Interventions A structured interview guide was developed by the research team based on information from clinical observation and literature which included both fixed response and open ended questions. There were 68 questions and the majority of the fixed response questions were rated on a Likert-type scale ranging from 4-6points and sought information on the type and frequency of problems experienced in the past 2 months. The extent to which these problems were considered to be troublesome was rated on a 4 point subscale (bother subscale) with response options as follows: not at all, a little, quite a bit and very much.
Outcomes The following areas were addressed: Medical history Appetite Digestion and bowel function Daily activities Social Interactions Self Care Practices Information needs after bowel surgery Demographic characteristics
Results Participants were recruited through hospital databases of 2 tertiary metropolitan teaching hospitals and through the private rooms of 2 colorectal surgeons. Response rates were calculated where possible and these ranged from 56% to 86%, though it was not possible to calculate the response rate from one hospital (n=14) and one of the colorectal surgeons (n=10). Participants reported a range of preference for timing and delivery of information on bowel management. There were 161 responses from 97 participants.

Timing of Information Provision
37.3% of responses indicated that the best time for receiving information was after surgery while in the hospital, 32.9% indicated that the best time was before surgery, 14.3% indicated 1-2 weeks after surgery as being the best time and 11.8% indicated 2-4 weeks as being the best time for receiving information.
Other responses specified 6 months after reversal of ileostomy (n=3), upon discharge (n=1), not while under the influence of drugs (n=1) and not needed unless requested (n=1).

Source of Information
46.2% (n=72) considered doctors to be the most appropriate source of information for bowel management, 21.8% (n=34) considered specialist continence advisors most appropriate, followed by nurses (21.2%, n=33), physiotherapists (5.8%, n=9), dieticians (2.6%, n=4), complementary therapists (1.3%, n=2) and other unspecified sources (1.3%, n=2).

Mode of Delivery
The preferred mode of delivery (228 responses from 97 participants) was one to one teaching by a health professional (26.8%), pamphlets of booklets (21.5%), talking to someone recovering from a similar condition (16.2%), telephone helpline (10.1%), attending support sessions (6.6%), attending education sessions given by health professionals in groups of 20-40 people (5.7%), video (5.7%), internet (3.1%) and audiotape (2.6%). Other suggestions included the Ostomy Association and herbalists.

There were a variety of information needs reported including needs for information on diet, managing diarrhoea, bloating and emptying the bowel.

The number of patients reporting unmet needs on unspecified topics was very small.

Type of Information Needed		Importance of Information[1]	Adequacy of Information Received	
	n(%)	Mean (SD)	n	Not enough n (%)
Diet	53 (52.5)	2.4 (0.85)	515	24 (47.1)
Diarrhoea	32 (31.7)	2.4 (0.71)	32	13 (40.6)
Bloating, wind/gas	29 (28.7)	2.3 (0.71)	29	16 (55.2)
Difficulty in emptying bowels	26 (25.7)	2.4 (0.88)	27	15 (55.6)
Pain	24 (23.8)	2.3 (0.93)	22	8 (36.4)
Nausea/Vomiting	22 (21.8)	1.9 (0.99)	20	5 (25)
Medications	20 (19.8)	2.4 (0.85)	21	12 (57.1)
Use of Pads	20 (19.8)	2.3 (1.00)	19	10 (52.6)
Other bowel problems	6 (5.9)	2.1(0.69)	7	4 (57.1)
Other therapies	4 (4.0)	2.2 (0.84)	5	4 (80)

[1]Scores were rated on a scale of 0-3 where 0= not at all, 1=somewhat important, 2=quite important, 3=very important
[2]Missing data from each item vary from n=2 (2%) to n=3 (3%)
Table: Information Needs Since Surgery[2]

Citation: O'Connor G, Coates V and O'Neil S (2010) Exploring the information needs of patients with cancer of the rectum European Journal of Oncology Nursing 14;271-277
Design: Qualitative study (questionnaire) with statistical analysis Country: UK Setting: Patients own home Aim: to adapt an instrument to measure the information needs of patients with cancer of the rectum and determine how these information needs were met using an adapted form of the Toronto Information Needs Questionnaire (TINQ).
Inclusion criteria Patients treated for rectal cancer in the previous 18 months
Exclusion criteria Patients that were at a very advanced stage of their illness
Sample Size N/A
Randomisation Method N/A
Population N=40
Study Duration
Interventions Administration of a questionnaire in a semi-structured interview
Outcomes
Results A pilot study of 5 patients was used to assess the time taken to complete the questionnaire and it was agreed that no changes were required and that these 5 questionnaires should be included in the main study. The questionnaire was administered in the patient's own home in the presence of a researcher. Many participants expressed concern about their treatment and ongoing problems related to their diagnosis and treatment during the course of the interview. These concerns were noted and necessary steps taken to deal with them including referral to participants GP, colorectal consultant and to the community stoma nurse. The age range was 44-86 years (mean=66.6, SD=11.49years) and the population was 60% male and 40% female. Internal consistency of the questionnaire and subscales was measured using Cronbach's alpha testing; reliability testing of the scale indicated a Cronbach's coefficient of 0.95 for the information needs assessment and 0.97 for the questions on how information needs were met. Information needs were high with means from each item ranging from 2.8-4.88 (1=not important to 5=extremely important). Examination of the relationship between gender and age for different items on the scale showed some gender differences with males showing a statistically significantly higher mean score than females in some areas. In relation to the information needs assessment only one question showed a statistically significant gender difference with males feeling that is was more important to know where their family could go to get help with dealing with their illness. Males reported statistically significantly higher satisfaction levels with information on where family could get help dealing with the patient's illness, whether they could wear normal clothing, how treatment works against cancer, if they were going to need help taking care of themselves and how to prepare for the investigative tests.

Younger patients expressed significantly higher information needs regarding the changed in the things they can do with and for their family, who to talk to about alternative therapies, where the family could go to get help dealing with the patient's illness, if treatment would alter the way they looked, what type treatments are available, how to prepare for the tests, what to do if they felt uncomfortable in social situations, if the illness was hereditary, if treatment would affect their relationship or sex life and if they could continue with their job after surgery and treatment.

Older patients expressed higher information needs only in knowing who to call if they had questions while still undergoing treatment.

In relation to how information needs were perceived to be addressed, few age differences were observed. Younger patients expressed higher satisfaction with information on being able to continue with their job following treatment while older patients expressed higher satisfaction with information on whether there was cancer elsewhere in the body.

ANOVA for length of time since diagnosis, type of treatment and whether or not a patient had a stoma showed no significant difference in information needs or how these needs were met.

A Wilcoxon Signed Rank Test compared perceptions of the importance of items of information with perceptions of how these needs were met and showed a statistically significant difference, indicating that patients felt that information needs with ratings of a high level of importance were not adequately addressed.

Stoma Care Nurse Specialists were reported to be the most common source of information, with other healthcare professionals such as ward nurses, chemotherapy nurses, colorectal consultant and GP mentioned.

One patient cited the internet as the preferred source of information.

Interpersonal communication with a healthcare provider was cited as the most common and preferred source of information.

General comments

The TINQ was developed to assess the information needs of patients with breast cancer and has been adapted to successfully assess the needs of men with prostate cancer. In adapting the questionnaire for this study, irrelevant items were removed and new items added.

Items added included:

If my illness/surgery/treatment will affect my relationship or sex life

If I will be able to continue with my job after surgery/treatment

If there is any financial support available to me during and after my illness/treatment

The process of adapting the questionnaire resulted in a 53 item questionnaire and patients perceptions of how their information needs had been met for each item were assessed using a 5 point Likert scale ranging from 1=poorly to 5=excellently.

A final open-ended question was asked to elucidate the main source of information during illness or treatment.

Citation: Persson E, Gustavsson B, Hellstrom A, Lappas G and Hulten L (2005) Ostomy patients perceptions of quality of care *Journal of advanced nursing* 49;1:51-58

Design: Qualitative Study (Cross sectional postal survey)

Country: Sweden

Setting:

Aim: to assess the quality of care in ostomy patients as seen from a patient perspective

Inclusion criteria
Patients who attended stoma outpatients clinic in Gothenberg, Sweden and had been operated for ulcerative colitis resulting in conventional ileostomy and patients who had a colostomy for colorectal cancer

Exclusion criteria
No details given

Sample Size
No details

Randomisation Method
N/A

Population
N=89

Study Duration
Patients treated between January 1996 and May 1999

Interventions
Postal Questionnaire

Outcomes
Data on patient's perceptions of information, participation and attitudes and treatment.

Results
49/89 patients completed the questionnaire for a response rate of 55%. 6 patients completed the questionnaire 6 months or less after surgery, 8 patients completed it between 6 months and 1 year and 35 patients completed it more than a year after surgery.

The average age of colorectal patients was 69 years (SD=11; range 42-87) with 26 females and 23 males. No significant difference was observed between responders or non-responders in relation to age or sex.

The majority of patients considered all questions on information to be of great importance and while on the whole colorectal patients were satisfied with the quality of care in general, they were less satisfied with certain aspects.

Item	Subjective Importance of Information	Satisfaction with Information
	Important	Not Satisfactory
Patient Perceptions of Information About	**N (%)**	**N(%)**
The surgical procedure	44/45 (98)	15/47 (32)
The medical exam and test results	42/44 (96)	14/47 (30)
The surgical procedure results	44/45 (98)	15/48 (31)
The responsible doctors	42/45 (93)	21/47 (45)
The responsible ET nurse	44/46 (96)	7/47 (15)
The special diet	44/45 (98)	11/45 (24)

Table 1: Perceptions of the importance of and satisfaction with information

Significant differences were between colorectal patients with and without complications regarding information about surgical procedure; 3/21 (14%) of patients with complications were dissatisfied versus 12/27 (44%) without complications (p=0.03).

Most patients considered the items on attitudes and treatment as important and were satisfied with actual attitudes and treatment, with two exceptions: 20/37 (54%) of colorectal patients were dissatisfied with ET nurses' interest in their home situation and 11/31 (35%) were dissatisfied with ET nurses' interest in their happiness.

Item	Subjective Importance of attitudes and treatment	Satisfaction with attitudes and treatments
	Important	Not Satisfactory
Patient perceptions of ET- in full nurses' attitudes toward the patient	**n (%)**	**n (%)**
Treated the patient with respect	45/46 (98)	2/47 (4)
Treated the patient in a positive manner	44/46 (96)	4/49 (8)
Gave sincere answers to questions	42/45 (93)	2/45 (4)
Fully understood the patients situation	44/46 (96)	9/48 (19)
Were interested in the patients home situation	24/42 (57)	20/37 (54)
Were interested in the patients happiness	26/40 (65)	11/31 (35)

Table 2: Perceptions of the importance of and satisfaction with attitudes and treatments

17/35 colorectal patients considered psychosocial issues to be important with 37/42 (88%) of patients considering it important to communicate with the ET nurse in relation to health/life situation and 11/44 (25%) reporting that they were not satisfied with the communication. In relation to sex life, 18/35 (51%) of colorectal patients considered the ability to talk to ET nurses to be important and 23/31 (74%) of patients reported being dissatisfied with provisions.

General comments
The study population consisted of patients who had undergone a colostomy for rectal cancer or patients who had undergone an ileostomy for ulcerative colitis, Only the experiences of the rectal cancer patients are relevant to this topic and where possible only those results are recorded.

Citation: Sahay T, Gray R, and Fitch M (2000) A Qualitative study of patient perspectives on colorectal cancer *Cancer Practice* 8;1:38-44

Design: Qualitative descriptive study

Country: Canada

Setting:

Aim: to use qualitative methods to contribute to a complete patient perspective on the psychosocial impact of colorectal cancer

Inclusion criteria
At least 6 months postdiagnosis
English speaking

Exclusion criteria
No details given

Sample Size
The decision to end accrual at 20 patients was based on the theoretical criterion that no new themes were emerging in later interviews.

Randomisation Method
N/A

Population
N=20

Study Duration

Interventions
Telephone interviews consisting of open-ended questions which were recorded and lasted less than 1 hour

Outcomes

Results
 All members of the research team discussed appropriate coding categories and a single researcher coded the transcripts with periodic double coding to ensure consistency.

The mean age of participating patients was 65 years (range 48-87) and the majority of respondants were white (n=17).
18/20 participants were married with children, 9 were retired and four were unable to work due to illness, 5 participants were actively employed at the time of the study.

17/20 patients received a diagnosis after a symptom was evident (usually rectal bleeding) and in all cases the family physician responded with either a digital rectal exam or a stool test.

At the time of interviews, the interval since diagnosis ranged from 6 months to 7 years.

All patients had surgery to remove a portion of the bowel and 11 patients had construction of a permanent (n=9) or temporary (n=2) colostomy. Surgery was typically followed by chemotherapy, radiation treatment or both.

4/20 patients were undergoing treatment for colorectal cancer at the time they were approached to participate the remaining patients were undergoing follow-up at the time.

Recurrence or relapse was reported by half of responders.

Information and Communication
The majority of patients felt that they had been adequately informed about their treatment and its consequences with some areas for possible improvement.
Patients felt they had the opportunity to ask questions when the need arose and that they received well explained

answers about their treatment.
Patients were particularly statisfied with the information provided about their prognosis, treatment options and side effects of treatments.

Patients looked to cancer specialists as their main source of information, particularly in relation to details of their prognosis and most patients placed emphasis on the importance of straightforward facts.
Other sources of information included written material provided by cancer clinics, resources offered by friends and relative and to a lesser extent, the internet and support groups. The family physician was considered to be someone to fill the gaps in understanding and to answer questions not addressed by the oncology team.

Some patients reported concerns with the lack of information about the long-term management of the illness including diet and nutrition related alternative therapies, post-operative complications, stoma care and the location of colostomy supply outlets.

1 patient reported that more information may have enabled her to play a larger role in decision making about her care.
A few patients reported having false impressions about the nature of their illness initially with 1 patient reporting that she was "astounded" when tod her cancer had recurred as she felt that having gone through the treatment she would be cured. It is unclear whether the patient had received the information or had misunderstood what she had been told about possible recurrence.
A 2nd patient was shocked when he heard the word cancer as he had been under the impression that he was being treated for a tumour but did not realise it was cancerous. The same patient did not understand the terms oncologist or lymh node and it is therefore possible that he was told the tumour was malignant but did not understand what this meant for him.
A 3rd patient reported that he initially felt that he had not been given enough information but that with hindsight felt that perhaps he was given information but the shock of being told he had cancer made him unreceptive to the information provided.
From discussions with patients, several ways in which a patients' involvement in their care may be limited were identified including the shock of diagnosis limiting the patients' ability to formulate questions and hear what the doctor is saying. Patients also reported feeling that doctors were too busy to discuss their case in detail and did not know what type of questions to ask and with the short time between initial diagnosis and beginning treatment meant there was little time to learn the right questions to ask.

Patients appeared to equate involvement in their care with information and reported satisfaction with their level of involvement because they were kept informed. Patients did not feel that there were too many decision points in the treatment of colorectal cancer apart from deciding to proceed with chemotherapy or radiotherapy and having input into the adjustment of chemotherapy regimens provided great satisfaction to patients for whom toxicity was a problem.
Patients were comforted to know that they had the final decision regarding course of treatment yet relied heavily on specialists for many making treatment related decisions with many patients feeling they would be "stupid not to".

Role of family physician
The family physician played little or no role in directly treating the cancer with the exception of management related to pain and postoperative complications.
Despite relying on specialists, a substantial number of patients (n=15) considered their family physician to be an important member of their healthcare team, serving as a sounding board for ideas, opinions and concerns and as a supporter who kept informed of patients progress, showed concern and tried to answer questions.
A few patients felt that family physicians should become more knowledgeable about colorectal cancer treatments and side effects to enable them to function readily as a source of information.

Sources of Support
In the majority of cases, the primary source of emotional and instrumental support was family and friends; a few patients had family members that were healthcare professionals and thus an additional source of information support.

Appendix 1 – Search strategies

2 Investigation, diagnosis and staging

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Colorectal Cancer	Literature search summary

Question title: What is the most effective diagnostic intervention(s) for patients with suspected colorectal cancer to establish a diagnosis?

Question no: A

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-6/2010	1174	238	06/07/2010
Premedline	All-6/2010	8	3	06/07/2010
Embase	All-6/2010	1524	228	07/07/2010
Cochrane Library	All-6/2010	695	206	23/06/2010
Cinahl	All-6/2010	109	17	08/07/2010
BNI	All-6/2010	23	2	07/07/2010
Psychinfo	All-6/2010	3	0	07/07/2010
Web of Science (SCI & SSCI) and ISI Proceedings	All-6/2010	451	78	08/07/2010
Biomed Central	All-6/2010	37	0	08/07/2010

Total References retrieved (after de-duplication): 599

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	6/2010-25/2/11	105	4	25/02/2011
Premedline	6/2010-25/2/11	4	1	25/02/2011
Embase	6/2010-25/2/11	226	13	25/02/2011
Cochrane Library	6/2010-25/2/11	44	2	25/02/2011
Cinahl	6/2010-25/2/11	31	4	25/02/2011
BNI	6/2010-25/2/11	0	0	25/02/2011
Psychinfo	6/2010-25/2/11	0	0	25/02/2011
Web of Science (SCI & SSCI) and ISI Proceedings	6/2010-25/2/11	54	1	25/02/2011
Biomed Central	6/2010-25/2/11	273	0	25/02/2011

Total References retrieved (after de-duplication): 16

Medline search strategy *(This search strategy is adapted to each database.)*
Colorectal Cancer AND Diagnostic Procedures
1. exp colorectal neoplasms/
2. ((colorect$ or colo rect$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
3. ((colon or colonic) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
4. ((rectal$ or rectum$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
5. 1 or 2 or 3 or 4
6. suspect* colorect*.tw.
7. 5 or 6

8. exp Colonoscopy/
9. colonoscop*.tw.
10. exp Colonography, Computed Tomographic/
11. CT colonograph*.tw.
12. exp Diagnostic Techniques, Digestive System/
13. diagnostic procedure*.tw.
14. Barium enema.mp.
15. (plain adj vanilla*).tw.
16. abdominal CT*.tw.
17. helical CT*.tw.
18. pneumocolon*.tw.
19. virtual*.tw.
20. exp Sigmoidoscopy/
21. Sigmoidoscop*.tw.
22. video scope*.tw.
23. or/8-22
24. 7 and 23
An RCT filter was applied to the search strategy

A Health Economics Literature search was not required for this topic.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Colorectal Cancer   **Literature search summary**

Question title: For patients diagnosed with primary colorectal cancer, what is the most effective technique(s) in order to accurately stage the disease?

Question no: Topic B

2.   Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-6/2009	294	120	16/06/09
Premedline	All-6/2009	20	10	22/06/09
Embase	All-6/2009	301	82	19/06/09
Cochrane Library	All-6/2009	81	12	22/06/09
Cinahl	All-6/2009	79	35	22/06/09
BNI	All-6/2009	0	0	22/06/09
Psychinfo	All-6/2009	0	0	22/06/09
Web of Science (SCI & SSCI) and ISI Proceedings	All-6/2009	2167	204	25/06/09
Biomed Central	All-6/2009	742	0	25/06/09

Total References retrieved (after de-duplication): 415

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2009-25/2/2011	179	75	25/2/2011
Premedline	2009-25/2/2011	23	13	25/2/2011
Embase	2009-25/2/2011	447	109	25/2/2011
Cochrane Library	2009-25/2/2011	44	1	25/2/2011
Cinahl	2009-25/2/2011	60	14	25/2/2011
BNI	2009-25/2/2011	0	0	25/2/2011

Psychinfo	2009-25/2/2011	1	0		25/2/2011
Web of Science (SCI & SSCI) and ISI Proceedings	2009-25/2/2011	333	32		25/2/2011
Biomed Central	2009-25/2/2011	205	0		25/2/2011

Total References retrieved (after de-duplication): 133

Medline search strategy *(This search strategy is adapted to each database.)*
Colorectal cancer AND Imaging AND Staging
1. exp colorectal neoplasms/
2. ((colorect$ or colo rect$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
3. ((colon or colonic) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
4. ((rectal$ or rectum$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
5. 1 or 2 or 3 or 4
6. exp Magnetic Resonance Imaging/
7. (nuclear magnetic resonance imag$ or NMRI).tw.
8. exp Magnetic Resonance Spectroscopy/
9. (MRI or MRS).tw.
10. MR imaging.tw.
11. MR scan$.tw.
12. MR spectroscop$.tw.
13. (magnet$ adj3 (scan$ or imaging)).tw.
14. exp Whole Body Imaging/mt [Methods]
15. exp Image Processing, Computer-Assisted/mt [Methods]
16. exp Positron-Emission Tomography/
17. ((positron emission tomography or PET) adj1 CT).tw.
18. (PET-CT or CT-PET).tw.
19. exp Fluorodeoxyglucose F18/du [Diagnostic Use]
20. exp Tomography, Emission-Computed/
21. comput$ emission.tw.
22. (single photon emission computed tomography or SPECT).tw.
23. exp Tomography, X-Ray Computed/
24. (comput$ adj1 tomograph$).tw.
25. electron beam computed tomography$.tw.
26. ((spiral or helical) adj CT).tw.
27. ((multi-slice or multi-detector-row) adj CT).tw.
28. exp Digital Rectal Examination/
29. (digit$ rect$ exam$ or DRE).tw.
30. per rectum$.tw.
31. endoan$ ultrasound$.tw.
32. or/6-31
33. exp Neoplasm Staging/
34. (cancer$ adj3 (stage or stages or staged or staging or classif$)).tw.
35. (neoplas$ adj3 (stage or stages or staged or staging or classif$)).tw.
36. (diagnostic$ adj3 (stage or stages or staged or staging or classif$)).tw.
37. (malignan$ adj3 (stage or stages or staged or staging or classif$)).tw.
38. (rapid adj3 (stage or stages or staged or staging or classif$)).tw.
39. (radiologic$ adj3 (stage or stages or staged or staging or classif$)).tw.
40. (immunologic$ adj3 (stage or stages or staged or staging or classif$)).tw.
41. (clinical$ adj3 (stage or stages or staged or staging or classif$)).tw.
42. (Dukes or Duke$).tw.
43. (TNM adj3 (stage or stages or staged or staging or classif$)).tw.
44. (TNM adj3 (category or system or criteria or measure$)).tw.
45. (Tumo?r node$ metastasis adj3 (stage or stages or staged or staging or classif$)).tw.
46. (Tumo?r node$ metastasis adj3 (category or system or criteria or measure$)).tw.
47. or/46-59
48. 47 and 32 and 5
RCT and SR filters were applied to the search strategy.

A Health Economics Literature search was not required for this topic.

3 Management of local disease

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Colorectal Cancer   **Literature search summary**

Question title: For patients with operable rectal cancer, what is the effectiveness of preoperative short course radiotherapy or chemoradiotherapy?

Question no: Topic G

3.   Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1990-2/2010	2475	420	25/02/2010
Premedline	1990-4/2010	35	16	16/04/2010
Embase	1990-4/2009	2234	298	12/04/2010
Cochrane Library	1990-4/2010	82	23	16/04/2010
Cinahl	1995-4/2010	69	43	16/04/2010
BNI	1990-4/2010	6	1	16/04/2010
Psychinfo	1990-4/2010	13	0	16/04/2010
Web of Science (SCI & SSCI) and ISI Proceedings	1990-4/2010	1051	264	16/04/2010
Biomed Central	1990-4/2010	126	5	16/04/2010

Total References retrieved (after de-duplication): 813

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	4/2010-25/2/11	205	36	25/02/2011
Premedline	4/2010-25/2/11	29	4	25/02/2011
Embase	4/2010-25/2/11	338	29	25/02/2011
Cochrane Library	4/2010-25/2/11	19	6	25/02/2011
Cinahl	4/2010-25/2/11	24	7	25/02/2011
BNI	4/2010-25/2/11	2	0	25/02/2011
Psychinfo	4/2010-25/2/11	3	0	25/02/2011
Web of Science (SCI & SSCI) and ISI Proceedings	4/2010-25/2/11	190	17	25/02/2011
Biomed Central	4/2010-25/2/11	25	0	25/02/2011

Total References retrieved (after de-duplication): 68

Medline search strategy *(This search strategy is adapted to each database.)*
Rectal Cancer AND Preoperative Therapy

1. ((rectal$ or rectum$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
2. exp Rectal Neoplasms/
3. operable rectal cancer*.tw.
4. 1 or 2 or 3
5. exp Drug Therapy/
6. exp Antineoplastic Agents/

7. exp Neoadjuvant Therapy/
8. exp Antineoplastic Combined Chemotherapy Protocols/
9. neoadjuvant chemotherap*.tw.
10. exp Radiotherapy/
11. (radiotherap* adj (pre operative* or pre-operative* or preoperative* or perioperative*)).tw.
12. neoadjuvant radiotherap*.tw.
13. chemoradiotherapy.mp.
14. (chemoradiotherap* adj (pre operative* or pre-operative* or preoperative* or perioperative*)).tw.
15. neoadjuvant chemoradiotherap*.tw.
16. (short course radiotherap* or short term radiotherap*).tw.
17. hyperfraction* radiotherap*.tw.
18. exp Combined Modality Therapy/
19. exp Dose Fractionation/
20. exp Radiotherapy Dosage/
21. exp Preoperative Care/
22. (care adj (pre operative* or pre-operative* or preoperative* or perioperative*)).tw.
23. exp Treatment Outcome/
24. exp Comparative Effectiveness Research/
25. exp Postoperative Complications/
26. exp Risk Factors/
27. exp Prospective Studies/
28. exp Follow-Up Studies/
29. Or/5-28
30. 4 and 29
RCT and SR filters were applied to the search strategy.
A Health Economics Literature search was not required for this topic.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Colorectal Cancer	Literature search summary

Question title:

For patients presenting with
   a) non metastatic locally advanced colon cancer is pre operative chemotherapy followed by surgery more effective than immediate surgery
   b) and for patients presenting with locally advanced rectal cancer is pre-operative radiotherapy, pre-operative chemotherapy or pre-operative chemoradiotherapy more effective than immediate surgery?.

Question no: E

4.   Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1997-9/2009	(a) 476 (b) 388	(a) 3 (b) 207	(a) 10/09/09 (b) 14/09/09
Premedline	1997-9/2009	(a) 72 (b) 24	(a) 1 (b) 12	(a) 10/09/09 (b) 16/09/09
Embase	1997-9/2009	(a) 215 (b) 339	(a) 9 (b) 156	(a) 10/09/09 (b) 15/09/09
Cochrane Library	1997-9/2009	(a) 381 (b) 137	(a) 6 (b) 77	(a) 08/09/09 (b) 16/09/09
Cinahl	1997-9/2009	(a) 11 (b) 188	(a) 2 (b) 66	(a) 10/09/09 (b) 16/09/09
BNI	1997-9/2009	(a) 23 (b) 24	(a) 0 (b) 0	(a) 10/09/09 (b) 16/09/09
Psychinfo	1997-9/2009	(a) 135	(a) 0	(a) 10/09/09

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
		(b) 0	(b) 0	(b) 16/09/09
Web of Science (SCI & SSCI) and ISI Proceedings	1997-9/2009	(a) 355 (b) 739	(a) 13 (b) 226	(a) 09/09/09 (b) 18/09/09
Biomed Central	1997-9/2009	(a) 181 (b) 71	(a) 0 (b) 2	(a) 11/09/09 (b) 18/09/09

Total References retrieved (after de-duplication): 471

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	9/2009-25/2/11	(a) 89 (b) 541	(a) 5 (b) 54	(a) 25/02/011 (b) 25/02/011
Premedline	9/2009-25/2/11	(a) 125 (b) 14	(a) 1 (b) 4	(a) 25/02/011 (b) 25/02/011
Embase	9/2009-25/2/11	(a) 645 (b) 433	(a) 9 (b) 62	(a) 25/02/011 (b) 25/02/011
Cochrane Library	9/2009-25/2/11	(a) 106 (b) 39	(a) 2 (b) 13	(a) 25/02/011 (b) 25/02/011
Cinahl	9/2009-25/2/11	(a) 224 (b) 200	(a) 0 (b) 24	(a) 25/02/011 (b) 25/02/011
BNI	9/2009-25/2/11	(a) 5 (b) 7	(a) 0 (b) 0	(a) 25/02/011 (b) 25/02/011
Psychinfo	9/2009-25/2/11	(a) 42 (b) 0	(a) 0 (b) 0	(a) 25/02/011 (b) 25/02/011
Web of Science (SCI & SSCI) and ISI Proceedings	9/2009-25/2/11	(a) 161 (b) 240	(a) 0 (b) 30	(a) 25/02/011 (b) 25/02/011
Biomed Central	9/2009-25/2/11	(a) 60 (b) 47	(a) 0 (b) 0	(a) 25/02/011 (b) 25/02/011

Total References retrieved (after de-duplication): a) 15   b) 126

Medline search strategy *(This search strategy is adapted to each database.)*
(a) Locally advanced Colon Cancer AND Neoadjuvant Chemotherapy
1. exp Colonic Neoplasms/
2. ((colon or colonic) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
3. 1 or 2
4. locally advanced.mp.
5. non metastatic.mp.
6. 5 or 4
7. 3 and 6
8. exp Drug Therapy/
9. exp Antineoplastic Agents/
10. exp Angiogenesis Inhibitors/
11. exp Neoadjuvant Therapy/
12. exp Antineoplastic Combined Chemotherapy Protocols/
13. neoadjuvant chemotherapy*.tw.
14. exp Leucovorin/
15. leucovorin*.tw.
16. Bevacizumab*.tw.
17. oxaliplatin*.tw.
18. exp Fluorouracil/
19. (Fluorouracil* or 5-FU*).tw.
20. folinic acid*.tw.
21. 11 or 9 or 17 or 12 or 20 or 15 or 14 or 8 or 18 or 19 or 16 or 10 or 13
22. 21 and 7
23. limit 22 to yr="1997 - 2011"
No filters were applied to this search strategy.

(b) Locally advanced Rectal Cancer AND (Preoperative Radiotherapy OR Preoperative Chemotherapy OR Preoperative Chemoradiotherapy)
1. ((rectal$ or rectum$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
2. exp Rectal Neoplasms/
3. 1 or 2
4. locally advanced.mp.
5. non metastatic.mp.
6. 5 or 4
7. exp Drug Therapy/
8. exp Antineoplastic Agents/
9. exp Angiogenesis Inhibitors/
10. exp Neoadjuvant Therapy/
11. exp Antineoplastic Combined Chemotherapy Protocols/
12. neoadjuvant chemotherapy*.tw.
13. exp Leucovorin/
14. leucovorin*.tw.
15. Bevacizumab*.tw.
16. oxaliplatin*.tw.
17. exp Fluorouracil/
18. (Fluorouracil* or 5-FU*).tw.
19. folinic acid*.tw.
20. 10 or 8 or 16 or 11 or 19 or 14 or 13 or 7 or 17 or 18 or 15 or 9 or 12
21. exp Radiotherapy/
22. (radiotherap* adj (pre operative* or pre-operative* or preoperative* or perioperative*)).tw.
23. neoadjuvant radiotherap*.tw.
24. chemoradiotherapy.mp.
25. (chemoradiotherap* adj (pre operative* or pre-operative* or preoperative* or perioperative*)).tw.
26. neoadjuvant chemoradiotherap*.tw.
27. 25 or 22 or 21 or 24 or 26 or 23
28. 27 or 20
29. 6 and 3
30. 28 and 29
31. limit 30 to yr="1997 - 2011"
RCT, SR and OS filters were applied to this search strategy.
A Health Economics Literature search was not required for this topic.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Colorectal Cancer	Literature search summary

Question title: **a)** For patients presenting with acute large bowel obstruction as a first presentation of colorectal cancer, what are the indications for stenting as a bridge to elective surgery?

NOTES: There are two key areas in this topic where guidance is required and as such this question will comprise two parts:
   a) Should all patients presenting with obstruction as a symptom of colorectal cancer have a CT scan to confirm diagnosis and provide evidence of metastases?
   b) What are the indications for stenting patients and the optimal timing for stenting to occur?

Question no: topic D

5. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1995-10/2009	(a) 351 (b) 428	(a) 31 (b) 162	20/10/09 02/11/09
Premedline	1995-10/2009	(a) 6 (b) 14	(a) 1 (b) 1	20/10/09 04/11/09
Embase	1995-10/2009	(a) 457 (b) 345	(a) 23 (b) 103	20/10/09 04/11/09
Cochrane Library	1995-10/2009	(a) 4 (b) 19	(a) 0 (b) 10	20/10/09 02/11/09
Cinahl	1995-10/2009	(a) 14 (b) 44	(a) 0 (b) 6	02/11/09 04/11/09
BNI	1995-10/2009	(a) 0 (b) 0	(a) 0 (b) 0	20/10/09 04/11/09
Psychinfo	1995-10/2009	(a) 0 (b) 1	(a) 0 (b) 0	20/10/09 04/11/09
Web of Science (SCI & SSCI) and ISI Proceedings	1995-10/2009	(a) 302 (b) 465	(a) 8 (b) 107	23/10/09 02/11/09
Biomed Central	1995-10/2009	(a) 78 (b) 15	(a) 0 (b) 0	23/10/09 04/11/09

Total References retrieved (after de-duplication): 294

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	11/2009-25/2/11	(a) 49 (b) 60	(a) 3 (b) 27	25/02/2011
Premedline	11/2009-25/2/11	(a) 0 (b) 2	(a) 0 (b) 2	25/02/2011
Embase	11/2009-25/2/11	(a) 143 (b) 74	(a) 4 (b) 32	25/02/2011
Cochrane Library	11/2009-25/2/11	(a) 1 (b) 7	(a) 0 (b) 1	25/02/2011
Cinahl	11/2009-25/2/11	(a) 11 (b) 33	(a) 0 (b) 5	25/02/2011
BNI	11/2009-25/2/11	(a) 0 (b) 0	(a) 0 (b) 0	25/02/2011
Psychinfo	11/2009-25/2/11	(a) 0 (b) 0	(a) 0 (b) 0	25/02/2011
Web of Science (SCI & SSCI) and ISI Proceedings	11/2009-25/2/11	(a) 69 (b) 128	(a) 1 (b) 13	25/02/2011
Biomed Central	11/2009-25/2/11	(a) 0 (b) 53	(a) 0 (b) 0	25/02/2011

Total References retrieved (after de-duplication): 53

Medline search strategy *(This search strategy is adapted to each database.)*
(a) – CT Scan AND Acute Bowel Obstruction
1. exp colorectal neoplasms/
2. ((colorect$ or colo rect$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
3. ((colon or colonic) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
4. ((rectal$ or rectum$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
5. 1 or 2 or 3 or 4
6. exp Intestinal Obstruction/

7. bowel obstruct*.tw.
8. exp Acute Disease/
9. exp Emergencies/
10. exp Emergency Treatment/
11. 8 or 6 or 7 or 10 or 9
12. 11 and 5
13. exp Tomography, X-Ray Computed/ or exp Tomography, X-Ray/
14. CT scan*.tw.
15. exp Diagnostic Imaging/
16. (diagnos* adj5 CT*).tw.
17. exp Colonography, Computed Tomographic/
18. exp Neoplasm Staging/
19. 18 or 16 or 13 or 17 or 15 or 14
20. 19 and 12
No filters were applied to this search strategy.
 (b) – Stenting AND acute bowel obstruction
1. exp colorectal neoplasms/
2. ((colorect$ or colo rect$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
3. ((colon or colonic) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
4. ((rectal$ or rectum$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
5. 1 or 2 or 3 or 4
6. exp Intestinal Obstruction/
7. bowel obstruct*.tw.
8. exp Acute Disease/
9. exp Emergencies/
10. exp Emergency Treatment/
11. (colon*obstruct* or colon* block*).tw.
12. 8 or 6 or 11 or 7 or 10 or 9
13. exp Stents/
14. colon* stent*.tw.
15. exp Colostomy/
16. emergency surger*.tw.
17. bridg*.tw.
18. (stent* adj10 tim*).tw.
19. 18 or 16 or 13 or 17 or 15 or 14
20. 19 and 12
21. 20 and 5
22. limit 21 to yr="1995 - 2011"
No filters were applied to this search strategy.
A Health Economics Literature search was not required for this topic.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Colorectal Cancer	Literature search summary

Question title: For patients diagnosed with stage I colorectal cancer, including/or polyp cancer, what are the prognostic factors for determining the most effective curative treatment?

Question no: C

6. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-2009	4024	342	18/01/10
Premedline	All-2009	14	1	26/01/10
Embase	All-2009	3081	279	26/01/10
Cochrane Library	All-2009	604	4	01/02/10
Cinahl	All-2009	50	8	01/02/10
BNI	All-2009	0	0	26/01/10
Psychinfo	All-2009	0	0	26/01/10
Web of Science (SCI & SSCI) and ISI Proceedings	All-2009	1063	74	27/01/10
Biomed Central	All-2009	1238	0	01/02/10

Total References retrieved (after de-duplication): 601

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2010-25/2/11	395	33	25/02/2011
Premedline	2010-25/2/11	25	2	25/02/2011
Embase	2010-25/2/11	729	39	25/02/2011
Cochrane Library	2010-25/2/11	85	0	25/02/2011
Cinahl	2010-25/2/11	16	0	25/02/2011
BNI	2010-25/2/11	1	0	25/02/2011
Psychinfo	2010-25/2/11	0	0	25/02/2011
Web of Science (SCI & SSCI) and ISI Proceedings	2010-25/2/11	127	30	25/02/2011
Biomed Central	2010-25/2/11	232		25/02/2011

Total References retrieved (after de-duplication): 66

Medline search strategy *(This search strategy is adapted to each database.)*
((Colorectal Cancer OR Polyp Cancer) AND Local Excision) AND Prognostic Factors
1. exp colorectal neoplasms/
2. ((colorect$ or colo rect$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
3. ((colon or colonic) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
4. ((rectal$ or rectum$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
5. 1 or 2 or 3 or 4
6. T1.tw.
7. pT1.tw.
8. ((grade or stage) adj5 (colorectal neoplasms or early)).tw.
9. (Early adj3 (invasive or colorectal or rectal or rectum or colon$)).tw.
10. exp Neoplasm Staging/
11. Duke*.tw.
12. 6 or 7 or 8 or 9 or 10 or 11
13. Resect$.tw.
14. Excision.tw.
15. exp colorectal neoplasms/su
16. Su.fs.
17. local* excision*.tw.
18. (surger* or operat* or remov*).tw.

19. Transanal endoscopic microsurgery.mp.
20. TEMS*.tw.
21. exp Lymph Node Excision/
22. Lymphovascular invasion.mp.
23. budding*.tw.
24. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. exp neoplasm invasiveness/
26. exp Prognosis/
27. prognostic factor*.tw.
28. curative treatment*.tw.
29. exp Neoplasm Recurrence, Local/
30. local control*.tw.
31. margin*.tw.
32. recurren*.tw.
33. exp Follow-Up Studies/
34. (follow-up* or follow up*).tw.
35. (Metasta$ adj5 (risk$ or potential)).tw.
36. or/25-35
37. exp Intestinal Polyps/
38. exp Colonic Polyps/
39. rectal polyp*.tw.
40. colon* polyp*.tw.
44. 37 or 38 or 39 or 40
45. 5 and 12
46. 24 and 45
47. 44 or 46
No filters were applied to this search strategy.

A Health Economics Literature search was not required for this topic.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Colorectal Cancer	Literature search summary

Question title: In patients with clinical or pathological stage II and III rectal cancer what is the effectiveness of adjuvant chemotherapy following surgery?

Question no: Topic H

7. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-11/2009	638	196	26/11/09
Premedline	All-11/2009	4	2	08/12/09
Embase	All-11/2009	777	232	08/12/09
Cochrane Library	All-11/2009	86	53	10/11/09
Cinahl	All-11/2009	80	28	08/12/09
BNI	All-11/2009	0	0	08/12/09
Psychinfo	All-11/2009	0	0	08/12/09
Web of Science (SCI & SSCI) and ISI Proceedings	All-11/2009	661	124	08/12/09
Biomed Central	All-11/2009	285	2	08/12/09

Total References retrieved (after de-duplication): 471

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	12/2009-25/2/11	62	10	25/02/2011
Premedline	12/2009-25/2/11	0	0	25/02/2011
Embase	12/2009-25/2/11	105	17	25/02/2011
Cochrane Library	12/2009-25/2/11			25/02/2011
Cinahl	12/2009-25/2/11	26	5	25/02/2011
BNI	12/2009-25/2/11	0	0	25/02/2011
Psychinfo	12/2009-25/2/11	0	0	25/02/2011
Web of Science (SCI & SSCI) and ISI Proceedings	12/2009-25/2/11	97	10	25/02/2011
Biomed Central	12/2009-25/2/11	100	1	25/02/2011

Total References retrieved (after de-duplication): 33

Medline search strategy *(This search strategy is adapted to each database.)*
Stage II and III Rectal Neoplasm AND (Primary Surgery OR Preop Radiotherapy OR Preop Chemoradiotherapy) AND Adjuvant Chemotherapy
1. exp colorectal neoplasms/
2. ((rectal$ or rectum$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
3. exp Rectal Neoplasms/
4. exp Rectum/
5. 1 or 3 or 2 or 4
6. exp colorectal neoplasms/
7. ((rectal$ or rectum$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
8. exp Rectal Neoplasms/
9. exp Rectum/
10. 6 or 8 or 7 or 9
11. (stage 2* or stage 3*).tw.
12. exp Neoplasm Staging/
13. (rectal adj5 stag*).tw.
14. 12 or 13 or 11
15. 14 and 10
16. exp Rectal Neoplasms/su [Surgery]
17. primary surger*.tw.
18. exp Surgical Procedures, Operative/
19. 16 or 18 or 17
20. exp Neoadjuvant Therapy/
21. exp Radiotherapy/
22. (preoperative radiotherap* or pre operative radiotherap* or neoadjuvant radiotherap*).tw.
23. short course radiotherap*.tw.
24. 23 or 21 or 22 or 20
25. exp Neoadjuvant Therapy/
26. exp Combined Modality Therapy/
27. (preoperative chemoradiotherap* or pre operative chemoradiotherap* or neoadjuvant chemoradiotherap*).tw.
28. 27 or 26 or 25
29. 28 or 24 or 19
30. 29 and 15
31. exp Chemotherapy, Adjuvant/
32. exp Antineoplastic Agents/ or exp Antineoplastic Protocols/
33. exp Antineoplastic Combined Chemotherapy Protocols/
34. adjuvant chemotherap*.tw.
35. exp Tegafur/ or exp Uracil/
36. exp Levamisole/
37. exp Leucovorin/
38. exp Fluorouracil/
39. (tegafur* or uracil* or levamisole* or 5-fluorouracil* or 5-FU*).tw.
40. 35 or 33 or 32 or 39 or 36 or 38 or 34 or 37 or 31

41. 40 and 30
RCT and SR filters were applied to this search strategy.
A Health Economics Literature search was not required for this topic.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Colorectal Cancer   **Literature search summary**

Question title: In patients with high risk stage II colon cancer what is the effectiveness of adjuvant chemotherapy after surgery?

Question no: Topic I

8.   Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1990-7/2009	1068	275	23/07/09
Premedline	1990-7/2009	127	12	24/07/09
Embase	1990-7/2009	1864	287	24/07/09
Cochrane Library	1990-7/2009	117	35	15/07/09
Cinahl	1990-8/2009	288	41	14/08/09
BNI	1990-7/2009	5	0	24/07/09
Psychinfo	1990-7/2009	26	0	24/07/09
Web of Science (SCI & SSCI) and ISI Proceedings	1990-8/2009	267	49	14/08/09
Biomed Central	1990-8/2009	89	0	14/08/09

Total References retrieved (after de-duplication): 466

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	7/2009-25/2/11	101	19	25/02/11
Premedline	7/2009-25/2/11	15	4	25/02/11
Embase	7/2009-25/2/11	366	43	25/02/11
Cochrane Library	7/2009-25/2/11	40	0	25/02/11
Cinahl	7/2009-25/2/11	30	4	25/02/11
BNI	7/2009-25/2/11	0	0	25/02/11
Psychinfo	7/2009-25/2/11	1	0	25/02/11
Web of Science (SCI & SSCI) and ISI Proceedings	7/2009-25/2/11	76	4	25/02/11
Biomed Central	7/2009-25/2/11	41	0	25/02/11

Total References retrieved (after de-duplication): 43

Medline search strategy *(This search strategy is adapted to each database.)*
(Colon Cancer AND Stage II) OR (Colon Cancer AND Surgery) AND Adjuvant Chemotherapy
1. ((colorect$ or colo rect$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
2. ((colon or colonic) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
3. exp Colonic Neoplasms/
4. 1 or 3 or 2
5. (high risk$ or high-risk$).tw.
6. (stage 2$ or stage II$).tw.

7. 5 or 6
8. 7 and 4
9. exp Antineoplastic Combined Chemotherapy Protocols/
10. systemic treatment.mp.
11. exp Chemotherapy, Adjuvant/
12. adjuvant$ chemotherap$.tw.
13. exp Fluorouracil/
14. (5-fluorouracil$ or 5-FU$).tw.
15. exp Leucovorin/
16. (leucovorin$ or LV$).tw.
17. exp Levamisole/
18. levamisol$.tw.
19. exp Cytotoxins/
20. cytotoxic drug$.tw.
21. oxaliplatin.mp.
22. bevacizumab.mp.
23. cetuximab.mp.
24. capecitabine.mp.
25. panitumumab.mp.
26. exp Antineoplastic Agents/
27. or/9-26
28. exp Colon/su [Surgery]
29. surgical resection$.tw.
30. (resect$ adj5 colon$).tw.
31. (post-operativ$ or post operativ$).tw.
32. 28 or 29 or 30 or 31
33. 4 and 32
34. 33 and 27
35. 34 or 8

RCT and SR filters were applied to this search strategy.

Health Economics Literature search details

SIGN Health Economics and SCHARR Quality of Life filter filter added to search

Database name	No of references found	Finish date of search
Medline	192	05/11/09
Premedline	0	05/11/09
Embase	39	05/11/09
Cochrane Library (except NHSEED)	30	05/11/09
NHSEED	6	05/11/09
Cinahl	48	05/11/09
Psycinfo	0	05/11/09
BNI	0	05/11/09
EconLit	0	05/11/09
Web of Science (SCI & SSCI) and ISI Proceedings	9	05/11/09

4   Management of metastatic disease

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Colorectal Cancer	Literature search summary

Question title: In a patient with colorectal cancer and extrahepatic metastases (e.g. lung, brain, peritoneum), which imaging modality most accurately determines the extent of metastases?

Question no: Topic L

9.   Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1990-6/2009	193	94	03/06/09
Premedline	1990-6/2009	18	6	04/06/09
Embase	1990-6/2009	589	80	04/06/09
Cochrane Library	1990-6/2009	88	38	08/06/09
Cinahl	1990-6/2009	29	6	09/06/09
BNI	1990-6/2009	1	0	08/06/09
Psychinfo	1990-6/2009	42	0	08/06/09
Web of Science (SCI & SSCI)	1990-6/2009	1032	136	08/06/09
Biomed Central	1997-6/2009	631	4	09/06/09

Total References retrieved (after de-duplication): 212

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	6/2009-25/2/11	141	43	25/02/2011
Premedline	6/2009-25/2/11	11	4	25/02/2011
Embase	6/2009-25/2/11	164	44	25/02/2011
Cochrane Library	6/2009-25/2/11	27	1	25/02/2011
Cinahl	6/2009-25/2/11	19	5	25/02/2011
BNI	6/2009-25/2/11	0	0	25/02/2011
Psychinfo	6/2009-25/2/11	4	0	25/02/2011
Web of Science (SCI & SSCI) and ISI Proceedings	6/2009-25/2/11	211	17	25/02/2011
Biomed Central	6/2009-25/2/11	283	0	25/02/2011

Total References retrieved (after de-duplication): 92

Medline search strategy *(This search strategy is adapted to each database.)*
Colorectal Cancer AND Cancer Recurrence OR Metastasis AND Imaging
1. exp colorectal neoplasms/
2. ((colorect$ or colo rect$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
3. ((colon or colonic) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
4. ((rectal$ or rectum$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
5. 1 or 2 or 3 or 4
6. exp Neoplasm Metastasis/
7. (metastas$ adj3 (brain$ or lung$ or periton$ or adren$ or spleen$ or bone$ or lymph$)).tw.
8. exp Neoplasm Staging/mt [Methods]
9. cancer recurrence.tw.
10. exp Follow-Up Studies/tu, mt [Therapeutic Use, Methods]

11. or/6-10
12. 11 and 5
13. exp Magnetic Resonance Imaging/
14. (nuclear magnetic resonance imag$ or NMRI).tw.
15. exp Magnetic Resonance Spectroscopy/
16. (MRI or MRS).tw.
17. MR imaging.tw.
18. MR scan$.tw.
19. MR spectroscop$.tw.
20. (magnet$ adj3 (scan$ or imaging)).tw.
21. exp Whole Body Imaging/mt [Methods]
22. exp Image Processing, Computer-Assisted/mt [Methods]
23. exp Positron-Emission Tomography/
24. ((positron emission tomography or PET) adj1 CT).tw.
25. (PET-CT or CT-PET).tw.
26. exp Fluorodeoxyglucose F18/du [Diagnostic Use]
27. exp Tomography, Emission-Computed/
28. comput$ emission.tw.
29. (single photon emission computed tomography or SPECT).tw.
30. exp Tomography, X-Ray Computed/
31. (comput$ adj1 tomograph$).tw.
32. electron beam computed tomography$.tw.
33. ((spiral or helical) adj CT).tw.
34. ((multi-slice or multi-detector-row) adj CT).tw.
35. or/13-34
36. 12 and 35
RCT and SR review filters were applied to this search strategy.
A Health Economics Literature search was not required for this topic.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Colorectal Cancer   **Literature search summary**

Question title: In a patient with colorectal cancer metastasised to the liver which imaging modality(s) most accurately determine the number and extent of metastases pre-operatively?

Question no: K

10. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1995-9/2009	1041	108	01/10/09
Premedline	1995-9/2009	49	21	01/10/09
Embase	1995-9/2009	1013	95	07/10/09
Cochrane Library	1995-9/2009	59	23	21/09/09
Cinahl	1995-9/2009	35	1	13/10/09
BNI	1995-9/2009	0	0	01/10/09
Psychinfo	1995-9/2009	0	0	01/10/09
Web of Science (SCI & SSCI) and ISI Proceedings	1995-9/2009	1231	128	13/10/09
Biomed Central	1995-9/2009	313	1	07/10/09

Total References retrieved (after de-duplication): 287

UPDATE SEARCH

Database name	Dates Covered	No of references	No of references	Finish date of

		found	retrieved	search
Medline	9/2009-25/2/11	185	11	25/02/11
Premedline	9/2009-25/2/11	28	6	25/02/11
Embase	9/2009-25/2/11	297	15	25/02/11
Cochrane Library	9/2009-25/2/11	12	2	25/02/11
Cinahl	9/2009-25/2/11	20	3	25/02/11
BNI	9/2009-25/2//11	0	0	25/02/11
Psychinfo	9/2009-25/2/11	0	0	25/02/11
Web of Science (SCI & SSCI) and ISI Proceedings	9/2009-25/2/11	231	27	25/02/11
Biomed Central	9/2009-25/2/11	53	0	25/02/11

Total References retrieved (after de-duplication): 44

Medline search strategy *(This search strategy is adapted to each database.)*
Colorectal Cancer AND Liver Metastasis AND Imaging
1. exp colorectal neoplasms/
2. ((colorect$ or colo rect$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
3. ((colon or colonic) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
4. ((rectal$ or rectum$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
5. 1 or 2 or 3 or 4
6. exp Liver Neoplasms/
7. (liver adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
8. exp Neoplasm Metastasis/
9. liver metastas*.tw.
10. hepatic metastas*.tw.
11. hepatic lesion*.tw.
12. exp Neoplasm Recurrence, Local/
13. 8 or 6 or 11 or 7 or 10 or 9 or 12
14. 13 and 5
15. exp Diagnostic Imaging/
16. exp Tomography, X-Ray Computed/
17. exp Magnetic Resonance Imaging/
18. exp Ultrasonography/
19. imaging modalit*.tw.
20. (contrast enhanced CT* or CT*).tw.
21. exp Positron-Emission Tomography/
22. PET*.tw.
23. contrast enhanced MR*.tw.
24. (CT adj (helic* or spiral*)).tw.
25. PET-CT*.tw.
26. exp Neoplasm Staging/
27. exp "Sensitivity and Specificity"/
28. 27 or 25 or 21 or 26 or 17 or 20 or 15 or 22 or 18 or 24 or 16 or 19 or 23
29. 28 and 14
RCT and SR filters were applied to this search strategy.

Health Economics Literature search details

SIGN Health Economics filter and SCHARR Quality of Life filter added to search

Database name	No of references found	Finish date of search
Medline	109	21/03/2010
Premedline	2	21/03/2010
Embase	165	21/03/2010
Cochrane Library (except NHSEED)	11	21/03/2010
NHSEED	13	21/03/2010

Cinahl	0	21/03/2010	
Psycinfo	0	21/03/2010	
BNI	0	21/03/2010	
EconLit	0	21/03/2010	
Web of Science (SCI & SSCI) and ISI Proceedings	39	21/03/2010	

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Colorectal Cancer   **Literature search summary**

Question title: In patients with colorectal cancer presenting with overt synchronous metastatic disease, what is the effectiveness of treating metastatic disease before, after or at the same time as treating the primary tumour?

Question no: F

11. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-6/2010	1455	321	08/06/2010
Premedline	All-6/2010	49	7	08/06/2010
Embase	All-6/2010	1853	285	15/06/2010
Cochrane Library	All-6/2010	395	48	08/06/2010
Cinahl	All-6/2010	62	15	15/06/2010
BNI	All-6/2010	0	0	15/06/2010
Psychinfo	All-6/2010	0	0	15/06/2010
Web of Science (SCI & SSCI) and ISI Proceedings	All-6/2010	166	65	15/06/2010
Biomed Central	All-6/2010	6	1	15/06/2010

Total References retrieved (after de-duplication): 548

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	6/2010-25/2/11	164	10	25/02/2011
Premedline	6/2010-25/2/11	23	4	25/02/2011
Embase	6/2010-25/2/11	399	11	25/02/2011
Cochrane Library	6/2010-25/2/11	36	0	25/02/2011
Cinahl	6/2010-25/2/11	0	0	25/02/2011
BNI	6/2010-25/2/11	0	0	25/02/2011
Psychinfo	6/2010-25/2/11	0	0	25/02/2011
Web of Science (SCI & SSCI) and ISI Proceedings	6/2010-25/2/11	43	1	25/02/2011
Biomed Central	6/2010-25/2/11	6	1	25/02/2011

Total References retrieved (after de-duplication): 20

Medline search strategy *(This search strategy is adapted to each database.)*
Colorectal Cancer AND (Liver) Metastasis AND Combined Modality Therapy
1. exp colorectal neoplasms/
2. ((colorect$ or colo rect$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.

3. ((colon or colonic) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
4. ((rectal$ or rectum$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
5. 1 or 2 or 3 or 4
6. exp Liver Neoplasms/dt, sc, su [Drug Therapy, Secondary, Surgery]
7. exp Neoplasm Metastasis/
8. liver metastas*.tw.
9. metasta* colorectal* cancer*.tw.
10. (hepatic$ adj (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
11. synchronous metasta*.tw.
12. 6 or 7 or 8 or 9 or 10 or 11
13. 5 and 12
14. exp Combined Modality Therapy/
15. exp Antineoplastic Combined Chemotherapy Protocols/tu [Therapeutic Use]
16. exp Neoadjuvant Therapy/
17. ((resectable* or resection* or irresectable*) adj3 metasta*).tw.
18. ((operable* or inoperable* or surgical* or surgery*) adj3 metasta*).tw.
19. exp Hepatectomy/
20. systemic chemotherapy*.tw.
21. 14 or 15 or 16 or 17 or 18 or 19 or 20
22. 13 and 21
23. limit 22 to yr="1999 -Current"
RCT and SR filters were applied to this search strategy.
A Health Economics Literature search was not required for this topic.

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Colorectal Cancer   **Literature search summary**

Question title:
  (a) What is the effectiveness of oxaliplatin and irinotecan-based chemotherapy regimens for patients with advanced colorectal cancer?
  (b) What is the most effective treatment for advanced or metastatic colorectal cancer patients who are   experiencing coronary artery spasm after starting treatment with 5-FU or capecitabine?

Question no: Topic M

12. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	(a) All-/3/2010	2882	1064	18/03/2010
	(b) 2004-3/10	693	204	26/02/2010
Premedline	(a) All-3/2010	148	36	26/03/2010
	(b) 2004-3/10	3	1	02/03/2010
Embase	(a) All-3/2010	1948	707	22/03/2010
	(b) 2004-3/10	1629	173	02/03/2010
Cochrane Library	(a) All-3/2010	374	188	26/03/2010
	(b) 2004-3/10	238	38	02/03/2010
Cinahl	(a) All-3/2010	130	33	26/03/2010
	(b) 2004-3/10	17	16	02/03/2010
BNI	(a) All-3/2010	8	5	26/03/2010
	(b) 20043/-10	1	1	03/03/2010
Psychinfo	(a) All-3/2010	13	7	26/03/2010
	(b) 2004-3/10	3	1	02/03/2010
Web of Science (SCI & SSCI) and ISI Proceedings	(a) All-3/2010	119	19	26/03/2010
	(b) 2004-3/10	314	168	03/03/2010

Biomed Central	(a) All-3/2010	71	1	26/03/2010
	(b) 2004-3/10	31	1	03/03/2010

Total References retrieved (after de-duplication): a) 1322   b) 338

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	(a)2010-25/2/11	311	67	25/02/2011
	(b) 2010-25/2/11	227	1	25/02/2011
Premedline	(a) 2010-25/2/11	138	30	25/02/2011
	(b) 2010-25/2/11	0	0	25/02/2011
Embase	(a) 2010-25/2/11	757	138	25/02/2011
	(b) 2010-25/2/11	138	4	25/02/2011
Cochrane Library	(a) 2010-25/2/11	44	17	25/02/2011
	(b) 2010-25/2/11	7	0	25/02/2011
Cinahl	(a) 2010-25/2/11	52	14	25/02/2011
	(b) 2010-25/2/11	0	0	25/02/2011
BNI	(a) 2010-25/2/11	3	0	25/02/2011
	(b) 2010-25/2/11	0	0	25/02/2011
Psychinfo	(a) 2010-25/2/11	3	0	25/02/2011
	(b) 2010-25/2/11	0	0	25/02/2011
Web of Science (SCI & SSCI) and ISI Proceedings	(a) 2010-25/2/11	30	6	25/02/2011
	(b) 2010-25/2/11	5	3	25/02/2011
Biomed Central	(a) 2010-25/2/11	20	1	25/02/2011
	(b) 2010-25/2/11	27	0	25/02/2011

Total References retrieved (after de-duplication): a) 168   b) 6

Medline search strategy *(This search strategy is adapted to each database.)*
(a) *Colorectal Cancer AND (Irinotecan OR Oxaliplatin OR Capcitabine)*
1. exp colorectal neoplasms/
2. ((colorect$ or colo rect$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
3. ((colon or colonic) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
4. ((rectal$ or rectum$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
5. or/1-4
6. irinotecan.mp.
7. oxaliplatin.mp.
8. FOLFOX.mp.
9. FOLFIRI.mp.
10. XELOX.mp.
11. XELIRI.mp.
12. capecitabine.mp.
13. 6 or 7 or 8 or 9
14. limit 13 to yr="2004 - 2010"
15. 10 or 11 or 12
16. 5 and 14
17. 5 and 15
18. 16 or 17

No filters were applied to this search strategy.

(b) *Colorectal Cancer AND Raltitrexed AND Coronary Artery Spasm*
1. exp colorectal neoplasms/
2. ((colorect$ or colo rect$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
3. ((colon or colonic) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
4. ((rectal$ or rectum$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
5. or/1-4
6. raltitrexed.mp. or tomudex.mp.
7. 5 and 6

8. exp Coronary Disease/ or exp Coronary Vasospasm/ or exp Myocardial Infarction/ or coronary artery spasm.mp.
9. 5 and 8
10. 7 or 9

No filters were applied to this search strategy.

Health Economics Literature search details

(SIGN Health Economics filter added to search)

Database name	No of references found	Finish date of search
Medline	(a) 94 (b) 55	(a) 31/03/2010 (b) 11/03/2010
Premedline	(a) 7 (b) 0	(a) 31/03/2010 (b) 11/03/2010
Embase	(a) 129 (b) 107	(a) 31/03/2010 (b) 11/03/2010
Cochrane Library (except NHSEED)	(a) 29 (b) 4	(a) 31/03/2010 (b) 11/03/2010
NHSEED	(a) 29 (b) 4	(a) 31/03/2010 (b) 11/03/2010
Cinahl	(a) 11 (b) 3	(a) 31/03/2010 (b) 11/03/2010
Psycinfo	(a) 2 (b) 0	(a) 31/03/2010 (b) 11/03/2010
BNI	(a) 0 (b) 0	(a) 31/03/2010 (b) 11/03/2010
EconLit	(a) 1 (b) 1	(a) 31/03/2010 (b) 11/03/2010
Web of Science (SCI & SSCI) and ISI Proceedings	(a)53 (b) 5	(a) 31/03/2010 (b) 11/03/2010

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Colorectal Cancer   **Literature search summary**

Question title: What is the most effective additional treatment to systemic chemotherapy to achieve cure or long term survival in patients with apparently unresectable metastatic disease?

Question no: J

13. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-5/2010	3472	338	25/10/2010
Premedline	All-5/2010	11	2	25/05/2010
Embase	All-5/2010	5574	298	25/10/2010
Cochrane Library	All-5/2010	141	37	25/05/2010
Cinahl	All-5/2010	497	0	25/05/2010
BNI	All-5/2010	0	0	25/05/2010
Psychinfo	All-5/2010	0	0	25/05/2010
Web of Science (SCI & SSCI)	All-5/2010	598	139	25/05/2010

and ISI Proceedings				
Biomed Central	All-5/2010	145	3	25/05/2010

Total References retrieved (after de-duplication): 649

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	5/2010-25/2/11	162	15	25/02/2011
Premedline	5/2010-25/2/11	5	0	25/02/2011
Embase	5/2010-25/2/11	827	19	25/02/2011
Cochrane Library	5/2010-25/2/11	26	0	25/02/2011
Cinahl	5/2010-25/2/11	29	5	25/02/2011
BNI	5/2010-25/2/11	0	0	25/02/2011
Psychinfo	5/2010-25/2/11	0	0	25/02/2011
Web of Science (SCI & SSCI) and ISI Proceedings	5/2010-25/2/11	81	7	25/02/2011
Biomed Central	5/2010-25/2/11	26	0	25/02/2011

Total References retrieved (after de-duplication): 29

Medline search strategy *(This search strategy is adapted to each database.)*
Colorectal Cancer AND Chemotherapy AND Additional Therapy
1. exp colorectal neoplasms/
2. ((colorect$ or colo rect$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
3. ((colon or colonic) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
4. ((rectal$ or rectum$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
5. 1 or 2 or 3 or 4
6. exp Antineoplastic Combined Chemotherapy Protocols/ or exp Antineoplastic Agents/
7. systemic chemotherap*.mp.
8. 6 or 7
9. 5 and 8
10. combin* treatment*.tw.
11. ablation*.tw.
12. loco regional therap*.tw.
13. surgery.mp.
14. chemoembolisation.mp. or exp Chemoembolization, Therapeutic/
15. hepatic arter* infusion*.tw.
16. trans arterial*.tw.
17. best supportive care.mp.
18. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 9 and 18
The search on 24 May 2010 was conducted with RCT and SR filters added to the search strategy. It was later decided to repeat the search without filters, as not sufficient evidence was found within the search result.
A Health Economics Literature search was not required for this topic.

5   Ongoing care and support

NATIONAL COLLABORATING CENTRE FOR CANCER	
Clinical Guideline Colorectal Cancer	**Literature search summary**

Question title: In asymptomatic patients who have undergone treatment with curative intent for colorectal cancer, what is the optimal method(s), frequency and duration of follow-up?

Question no: Topic N

14. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2005-2009	1351	79	18/08/09
Premedline	2005-2009	302	18	19/08/09
Embase	2005-2009	1140	68	19/08/09
Cochrane Library	1990-2009	749	76	17/08/09
Cinahl	All-2009	140	5	19/08/09
BNI	2005-2009	14	9	19/08/09
Psychinfo	2005-2009	99	2	19/08/09
Web of Science (SCI & SSCI) and ISI Proceedings	2005-2009	4424	14	19/08/09
Biomed Central	2005-2009	925	2	19/08/09

Total References retrieved (after de-duplication): 190

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	8/2009-25/2/2011	1645	71	25/2/2011
Premedline	8/2009-25/2/2011	347	24	25/2/2011
Embase	8/2009-25/2/2011	1618	29	25/2/2011
Cochrane Library	8/2009-25/2/2011	223	6	25/2/2011
Cinahl	8/2009-25/2/2011	50	5	25/2/2011
BNI	8/2009-25/2/2011	7	3	25/2/2011
Psychinfo	8/2009-25/2/2011	76	6	25/2/2011
Web of Science (SCI & SSCI) and ISI Proceedings	8/2009-25/2/2011	1193	53	25/2/2011
Biomed Central	8/2009-25/2/2011	464	0	25/2/2011

Total References retrieved (after de-duplication): 131

Medline search strategy *(This search strategy is adapted to each database.)*
Colorectal Cancer And Follow UP

1. exp colorectal neoplasms/
2. ((colorect$ or colo rect$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
3. ((colon or colonic) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
4. ((rectal$ or rectum$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
5. 1 or 2 or 3 or 4
6. exp Follow-Up Studies/
7. (follow up$ or follow-up$).tw.
8. surveillance*.tw.
9. monitor*.tw.
10. 6 or 7 or 8 or 9

11. 10 and 5

No filters were applied to this search strategy.

Health Economics Literature search details

SIGN Health Economics filter and SCHARR Quality of Life filter added to search

Database name	No of references found	Finish date of search
Medline	580	09/11/2009
Premedline	19	09/11/2009
Embase	894	09/11/2009
Cochrane Library (except NHSEED)	209	09/11/2009
NHSEED	59	09/11/2009
Cinahl	6	11/11/2009
Psycinfo	23	09/11/2009
BNI	7	09/11/2009
EconLit	0	09/11/2009
Web of Science (SCI & SSCI) and ISI Proceedings	257	09/11/2009

NATIONAL COLLABORATING CENTRE FOR CANCER

Clinical Guideline Colorectal Cancer   Literature search summary

Question title: For patients with colorectal cancer, what are the information needs associated with bowel function?

Question no: O

15. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	All-6/2010	1239	138	16/06/2010
Premedline	All-6/2010	39	3	18/06/2010
Embase	All-6/2010	1930	115	18/06/2010
Cochrane Library	All-6/2010	78	3	18/06/2010
Cinahl	All-6/2010	147	43	21/06/2010
BNI	All-6/2010	6	6	18/06/2010
Psychinfo	All-6/2010	22	4	18/06/2010
Web of Science (SCI & SSCI) and ISI Proceedings	All-6/2010	415	16	21/06/2010
Biomed Central	All-6/2010	30	1	21/06/2010

Total References retrieved (after de-duplication): 242

UPDATE SEARCH

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	6/2010-25/2/11	91	1	25/02/2011
Premedline	6/2010-25/2/11	24	3	25/02/2011
Embase	6/2010-25/2/11	317	9	25/02/2011
Cochrane Library	6/2010-25/2/11	5	0	25/02/2011
Cinahl	6/2010-25/2/11	17	3	25/02/2011

BNI	6/2010-25/2/11	0	0	25/02/2011
Psychinfo	6/2010-25/2/11	4	1	25/02/2011
Web of Science (SCI & SSCI) and ISI Proceedings	6/2010-25/2/11	59	3	25/02/2011
Biomed Central	6/2010-25/2/11	8	0	25/02/2011

Total References retrieved (after de-duplication): 15

Medline search strategy *(This search strategy is adapted to each database.)*
Colorectal Cancer AND Bowel function AND Information needs
1. exp colorectal neoplasms/
2. ((colorect$ or colo rect$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
3. ((colon or colonic) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
4. ((rectal$ or rectum$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw.
5. 1 or 2 or 3 or 4
6. bowel function.mp.
7. stoma care.mp.
8. exp Body Image/
9. body image*.tw.
10. exp Sexual Dysfunction, Physiological/ or exp Sexual Dysfunctions, Psychological/
11. sexual function*.tw.
12. exp Self Concept/
13. (self esteem* or self-esteem*).tw.
14. exp Diarrhea/pc [Prevention & Control]
15. (diarrhea* or diarrhoea*).tw.
16. (bloat* or wind*).tw.
17. ((nutrition* adj advi?e*) or (diet* adj advi?e*)).tw.
18. exp Postoperative Complications/pc [Prevention & Control]
19. (stoma* adj (reversal* or removal*)).tw.
20. exp Stents/ae [Adverse Effects]
21. (stent* adj insert*).tw.
22. temporar* ileostomy*.tw.
23. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24. 5 and 23
25. exp Choice Behavior/
26. exp Decision Making/
27. exp decision support techniques/
28. decision$.tw.
29. (choic$ or preference$).tw.
30. (decision$ adj3 (aid$ or support$)).tw.
31. exp Patient Compliance/
32. exp Patient Participation/
33. ((patient$ or consumer$) adj1 (decision$ or choice$ or prefer$ or participat$)).tw.
34. ((personal or interpersonal or individual) adj (decision$ or choice$ or prefer$ or participat$)).tw.
35. Pamphlets/
36. Pamphlet*.tw.
37. (leaflet$ or diary or diaries or booklet$ or guidebook$ or sheet$).tw.
38. (prompt$ or coach$).tw.
39. (checklist$ or check list$).tw.
40. (written or write).tw.
41. question$.tw.
42. (card$ or helpcard$).tw.
43. (video$ or tape$ or cd$ or film$ or dvd$ or telephone$ or phone$ or computer$ or internet or electronic).tw.
44. exp Audiovisual Aids/
45. (video$ or cd* or dvd$).tw.
46. exp Internet/
47. communication/
48. communicat$.tw.
49. exp patient education/

50. ((patient$ or consumer$) adj3 (educat$ or skill$ or teach$ or train$ or coach$)).tw.
51. consult$.tw.
52. (information adj3 need$).tw.
53. information material$.tw.
54. (patient$ adj3 information).tw.
55. (information adj3 web$1).tw.
56. (information adj3 print$).tw.
57. (information adj3 electronic$).tw.
58. ((inform$ or support$) adj2 (tool$ or method$ or group$)).tw.
59. exp Self-Help Groups/
60. (support$ adj2 (group$ or meet$)).tw.
61. exp Patient Education as Topic/
62. ((patient* or care*) adj pathway*).tw.
63. information deliver*.tw.
64. interactive session*.tw.
65. (face* adj face*).tw.
66. (time* or timing*).tw.
67. or/25-66
68. 5 and 67
69. 24 and 68
70. limit 69 to yr="1995 -Current"
No filters were applied to this search strategy.

A Health Economics Literature search was not required for this topic.

Appendix 2 – Economic Plan

This document identifies the priorities for economic analysis and the proposed methods for addressing these questions as described in section 8.1.3.1 of the Guidelines Manual (2006).

Guideline

Title of guideline: Colorectal cancer - diagnosis and management of colorectal cancer

Process for agreement

The economic plan was prepared by the guideline economist in consultation with the rest of the NCC technical team and GDG. It was discussed and agreed on   by the following people [1]:

For the NCC and GDG:

NCC economist: Bernadette Li
NCC representative(s) [2]: Angela Bennett
GDG representative(s) [3]:Graeme Poston, Dianna Tait

For NICE:

CCP lead [4]:
Commissioning manager: Claire Turner
Economic lead [5]:   Francis Ruiz, Stefanie Reken
Costing lead:
Proposals for any substantive changes will be circulated by email to this group. If revisions are agreed, they will be listed as addenda to this document (section 5 below).

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[1] This may be done by face-to-face meeting, teleconference, or email as convenient.

[2] May be the project manager, a systematic reviewer or research fellow and/or the centre director or manager, as appropriate for the NCC and guideline.

[3] May be GDG chair, clinical lead and/or other members as appropriate.

[4] CCP Director or Associate Director who is taking the lead for the guideline.

[5] One of the CCP health economic Technical Advisors.

al Question (in PICO format if possible)	Requires analysis? [†]	Comment and explanation
TOPIC A: What is the most effective initial diagnostic intervention(s) in patients with suspected colorectal cancer to establish a diagnosis?	4. Medium priority for a	A cursory search of the economic literature d any existing published economic studies that interventions and comparators of interest (flex sigmoidoscopy + barium enema, CT colonogr sigmoidoscopy + colonoscopy compared to c biopsy). The feasibility of undertaking a cost-e modelling exercise for this topic would be con (i) agreeing a model structure that appropriate account downstream events beyond test accu identifying appropriate data sources that can to estimate both costs and effects associated downstream events. Prior to the 2[nd] GDG mee highlighted that results of a prospective trial c the UK (SIGGAR1) are anticipated to report in study was designed to compare colonography enema and CT colonography vs colonoscopy for the SIGGAR1 study includes collection of subsequent tests and healthcare resource us planned cost-utility analysis. Given the overla objectives of the planned economic analysis t the SIGGAR1 study with any potential modell this topic within the guideline, it was felt that r economic modelling should be directed towar priority topics (agreed at 3[rd] GDG meeting).
TOPIC B: For patients with primary colorectal cancer, what is the most effective technique(s) in order to accurately stage the disease (excluding pathology)?	5. Low priority for analy	The focus of this question is on accuracy of s interventions under consideration include CT, endoanal ultrasound and digital rectal examin

1 '**Not relevant**': questions where economic analysis is not appropriate (e.g. about definitions, prognosis or information needs for patient);

2 '**In literature**': questions where high-quality, recent and relevant economic evaluations are already available;

3 '**High priority for analysis**': questions where an economic analysis is planned (important implications and analysis is thought to be feasible);

4 '**Medium priority for analysis**' questions where an economic analysis may be done (less important implications or questions over feasibility);

5 '**Low priority for analysis**': questions where economic analysis could be done, but the expected impact on outcomes and NHS resources is low.

al Question (in PICO format if possible)	Requires analysis? [1]	Comment and explanation
		economic analysis of this topic should take in downstream consequences of staging accura review of the clinical evidence identified most case studies with a large degree of variation b studies in terms of interventions, outcomes re inclusion/exclusion criteria. No studies reporte reclassification. This topic was considered a l for economic modelling partly due to the comp would be involved in downstream decisions th according to the different diagnostic interventi (i.e. different interventions may provide differe information to inform treatment decisions) and the poor quality of available data to inform an analysis.
TOPIC C: For patients diagnosed with stage I colorectal cancer, including/or polyp cancer, what are the prognostic factors for determining the most effective curative treatment?	1. Not relevant	The focus of this question is on prognostic fac determine treatment rather than a comparativ effectiveness, therefore economic modelling i help inform this topic.
TOPIC D: For patients presenting with acute large bowel obstruction as a first presentation of colorectal cancer, what is the optimal course of treatment? a) should all patients presenting with obstruction as a symptom of colorectal cancer have a CT scan to confirm diagnosis to provide evidence of metastases? b) what are the indications for stenting patients and what is the optimal timing for this to occur?	5. Low priority for analy	For part a) high quality data on the many poss downstream outcomes of a CT scan in this se patient population is unlikely to be available a available, are likely to extend beyond the issu interest to this PICO (metastases). If appropri budget impact of this could be assessed throu exercise based on the recommendation(s) at guideline process. Part b) focuses on clinical timing of stenting. This does not involve a con costs and consequences and therefore does to economic modelling.
TOPIC E: For patients presenting with a) non-metastatic locally advanced colon cancer, is pre-operative chemotherapy followed by surgery more effective than immediate surgery and for patients presenting with b) locally advanced rectal cancer is pre-operative	5. Low priority for analy	The search for clinical evidence will focus on trials that specifically address the issue of sec combinations of treatment modalities. A priori of treatment combinations or specific regimen planned. It is anticipated that the evidence ba

al Question (in PICO format if possible)	Requires analysis?[1]	Comment and explanation
adiotherapy, pre-operative chemotherapy or pre-operative chemoradiotherapy more effective than immediate surgery?		clinically heterogeneous. This would limit the appropriateness of combining or comparing d studies using quantitative methods and theref feasibility of undertaking de novo economic m would help inform this topic in a comprehensi meaningful manner.
TOPIC F: In patients with colorectal cancer presenting with overt synchronous metastatic disease, what is the effectiveness of treating metastatic disease before, after or at the same time as treating the primary tumour?	5. Low priority for analy	Similar to Topic E, the search for clinical evide on identifying trials that specifically address th sequencing of treatment. It is anticipated that base may be clinically heterogeneous. This w appropriateness of combining or comparing d studies using quantitative methods and theref feasibility of undertaking de novo economic m would help inform this topic. In addition, differ resource implications and expected health ga different sequences under comparision are ex modest.
TOPIC G: For patients with operable rectal cancer, what s the effectiveness of pre-operative short course adiotherapy or chemoradiotherapy?	4. Medium priority for a	The addition of radiotherapy or chemoradiothe surgery for rectal cancer may reduce occurrer malignancies or improve survival, but may be with additional morbidity and cost. This is a po for economic analysis, but the size of the pop patients eligible for pre-operative intervention: cancer is small compared to other topics in th and is considered a lower priority for economi
TOPIC H: In patients with clinical or pathological stage II and III rectal cancer, what is the effectiveness of adjuvant chemotherapy following surgery?	4. Medium priority for a	The patient population for this topic has been three subgroups (i) those who have had prima those who have had short-course radiotherap surgery and (iii) those who have had chemora prior to surgery. The feasibility of conducting a analysis depends on the availability of clinical to each of the subgroups. However, this topic lower priority than other topics (e.g. Topic I) b estimated impact in terms of the size of the ta

al Question (in PICO format if possible)	Requires analysis?[1]	Comment and explanation
		population and the level of uncertainty/controv regarding current practice are considered to b
TOPIC I: In patients with high-risk stage II colon cancer, what is the effectiveness of adjuvant chemotherapy after surgery?	3. High priority for anal	The clinical and cost effectiveness of adjvuan chemotherapy in Stage III colon cancer has b demonstrated, however controversy remains benefit of adjuvant chemotherapy in high-risk patients. This topic was therefore considered for cost-effectiveness modelling. However, th of the clinical literature revealed that there is a effectiveness data on adjuvant chemotherapy population of interest. There is no consistent high-risk patients in the literature and outcome generally not reported separately for this spec population. In the absence of reliable data to effectiveness parameters in the cost effective decision was reached at the 4th GDG meeting development of the economic analysis for this
TOPIC J: What is the most effective additional treatment o systemic chemotherapy to achieve cure or long term survival in patients with apparently unresectable metastatic disease?	4. Medium priority for a	The interventions/comparators that have been this topic include treatment modalities (ablatic regional therapy, systemic therapy, best supp combinations of treatment modalities rather th interventions. If sufficient high quality data co specific treatments or treatment sequences is economic modelling could be considered, but considered unlikely that direct evidence will e all comparators of interest.
TOPIC K: In a patient with colorectal cancer metastasised to the liver, which imaging modality(s) most accurately determines the number and extent of metastases pre-operatively?	3. High priority for anal	The focus of this question is on the use of ima modalities (CT, PET-CT, MRI or ultrasound) f detection of liver metastases to inform a decis resectability. An economic analysis of this top into account not only accuracy of the imaging detecting metastases, but also downstream c on treatment decisions and patient outcomes. search of the clinical literature revealed that n

al Question (in PICO format if possible)	Requires analysis? [1]	Comment and explanation
		relevant studies identified do not report inform resectability or change in patient managemen the information obtained by the imaging test. decision to resect is based on a number of dif considerations, there is insufficient information link between the imaging results and the treat Therefore the feasibility of conducting a comp cost-effectiveness analysis based on currently data is limited. These limitations were discuss GDG and at the 7[th] GDG meeting, agreement not to continue development of the economic topic.
TOPIC L: In a patient with colorectal cancer and extrahepatic metastases (e.g. lung, brain, peritoneum), which imaging modality most accurately determines the extent of metastases?	5. Low priority for analy	The focus of this question is on the use of ima modalities for the detection of extrahepatic me economic analysis of this topic should take in only accuracy of the imaging modality in dete metastases, but any downstream consequenc treatment decisions and patient outcomes. Th of patient pathways in this context is complica that different imaging modalities may provide of information beyond just presence or absen metastases (including location, size etc) and t may also have multiple sites of metastases th treatment options and may require considerat treatment decisions that fall outside the scope the current guideline (e.g.specific issues relat management of brain metastases). The feasib modelling this topic within the time and resou is limited, therefore this topic is considered a l
TOPIC M: What is the effectiveness of chemotherapy for patients with advanced and metastatic colorectal cancer?	3. High priority for anal	Update of TA93 (irinotecan, oxaliplatin and ra treatment of advanced colorectal cancer). Fur provided in Section 3.2.
TOPIC N: In asymptomatic patients who have undergone treatment with curative intent for colorectal cancer, what	2. In literature	A cursory search of the literature suggests the number of published economic studies that m

al Question (in PICO format if possible)	Requires analysis? [1]	Comment and explanation
s the optimal method(s), frequency and duration of ollow-up?		this topic. De novo economic modelling is unli existing evidence if high quality data on costs effectiveness of alternate follow-up strategies available. Therefore a systematic review of th literature will be undertaken to inform for this t
TOPIC O: What colorectal specific support should be offered to patients diagnosed with colorectal cancer?	1. Not relevant	This topic is unlikely to lend itself to economic (not comparative analysis of cost and outcom

For each question where economic analysis is proposed:

Question number(s) [g]	Outline proposed method of analysis [h]
13 (Topic M)	Update of TA93 (irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer). Two separate PICOs were developed for this topic. It was acknowledged that clinical practice has moved on since TA93. In consultation with the GDG and NICE, the areas of most importance and current relevance with respect to the use of irinotecan, oxaliplatin and raltitrexed for the treatment to of advanced colorectal cancer were identified as: A. The effectiveness of oxaliplatin and irinotecan-based chemotherapy regimens for patients with advanced and metastatic colorectal cancer (sequences up to 2 lines of treatment)

Population	Intervention (1st line, 2nd line)	Comparison	Outcomes
Patients with advanced and metatstatic colorectal cancer	FOLFOX, FOLFIRI FOLFOX, XELIRI FOLFOX, irinotecan XELOX, FOLFIRI XELOX, XELIRI XELOX, irinotecan FOLFIRI, FOLFOX FOLFIRI, XELOX XELIRI, FOLFOX XELIRI, XELOX	Each other	Response Progression-free survival Overall survival Toxicity Quality of life

B. The most effective treatment for advanced colorectal cancer patients when 5-FU /FA based regimens are not tolerated or inappropriate

Population	Intervention	Comparison	Outcomes
Patients with advanced or metastatic colorectal cancer who are not able to tolerate 5FU/FA based regimens, or for whom 5FU/FA based regimens are inappropriate	Raltitrexed (single agent or in combination with oxaliplatin or irinotecan)	No further chemotherapy	Response Progression-free survival Overall survival Toxicity Quality of life

Part A economic evaluation methods:

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[g] Two or more questions may be addressed by a single analysis if appropriate.

[h] Give a brief description of the type of analysis that is proposed, as far as is known at this stage. Consider the type of economic evaluation (CEA, CUA, CCA,…); how outcomes will be measured (QALYs, LYS,…); the type of modelling (decision tree, Markov, simulation…); proposed comparators and population subgroups to be considered; potential sources of information and assumptions; and whether analysis could be based on an existing model. Follow methods advised in the Guidelines Manual whenever possible. Note that this is not expected to be a full project protocol, and that the methods of analysis may change.

The proposed economic evaluation will be a cost-utility analysis based on a decision tree structure. Effectiveness data will be based on a mixed treatment meta-analysis that will drawn upon data from RCTs for the interventions in question by line of treatment. Cost data will be based on NHS reference costs and British National Formulary for drug costs.

Part B economic evaluation methods:

An economic model to address the use of raltitrexed was not produced for either TA33 or TA93. As it is anticipated there will be no new appropriate clinical data to inform this question, a full cost-effectiveness model is currently not being proposed to address Part B.

Key references

Figueredo A, Coombes ME, Mukherjee S. Adjuvant therapy for completely resected stage II colon cancer. Cochrane Database of Systematic Reviews 2008: 3

Halligan S, Lilford RJ, Wardle J, Morton D, Rogers P, Wooldrage K, Edwards R, Kanini R, Shah U, Atkins W. Design of a multicentre randomized trial to evaluate CT colonography versus colonoscopy or barium enema for diagnosis of colonic cancer in older symptomatic patients: The SIGGAR study. *Trials* 2007, 8:32

Hind D, Tappenden P, Tumur I, Eggington S, Sutcliffe P, Ryan A. The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation. Health Technol Assess 2008; 12 (15): 1-182

Sutton A, Ades AE, Cooper N, Abrams K. Use of indirect and mixed treatment comparisons in technology assessment. Pharmacoeconomics 2008: 26 (9): 753-767

Addenda to economic plan

The following substantive revisions to the plans set out in section 3 above have been agreed.

Date	Question number(s)	Agreed change to number or type of analyses
May 2010	Topic I and K	Due to issues with feasibility and lack of directly relevant effectiveness data, it was agreed that development of new economic models will not be pursued any further for high priority Topics I and K.
May 2010	Topic M	Information on PICOs and clarification of methods for Topic M added.