Evidence Tables

Citation: 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

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).

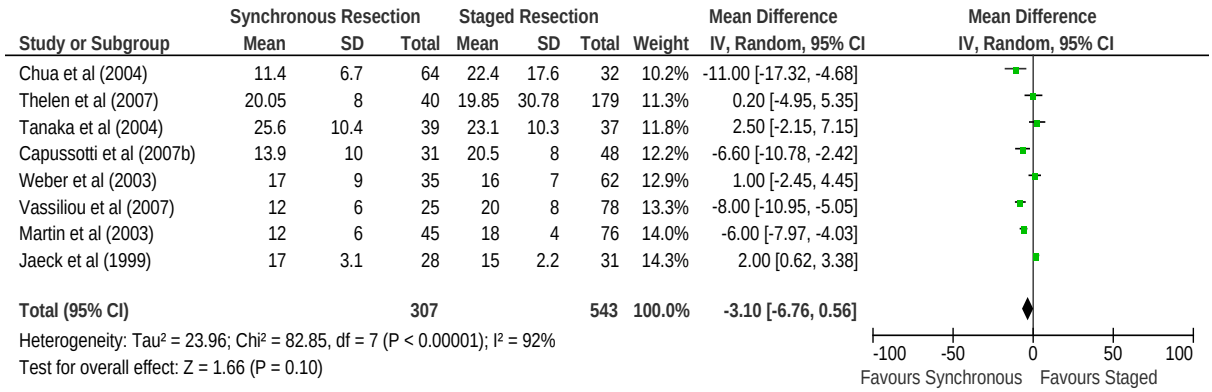
Study Duration
Literature search conducted until 5th November, 2007 (no start date was given)

Interventions
Staged or simultaneous resection of synchronous liver metastases

Outcomes
Outcome measures included:

- length of hospital stay
- surgical morbidity
- perioperative mortality
- 5 year survival

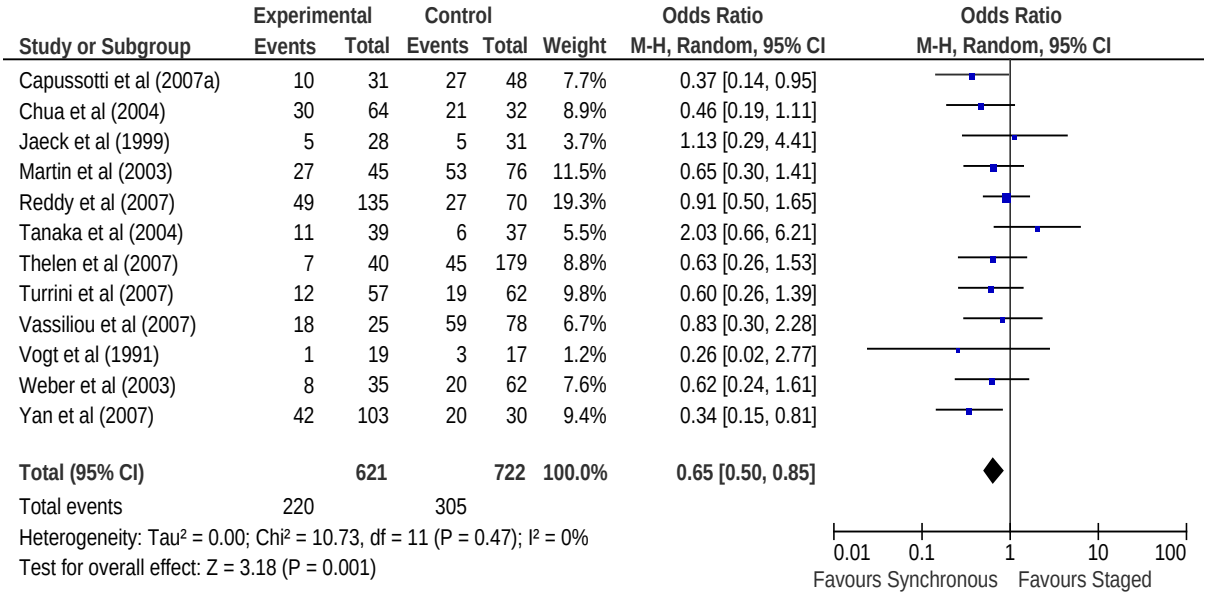
Results
Length of Hospital Stay
11 studies with a total of 850 patients (307 undergoing synchronous resection and 543 undergoing staged resection) addressed the length of hospital stay; a tendency towards shorter hospital stay was observed in the synchronous resection group.



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 (I^2=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

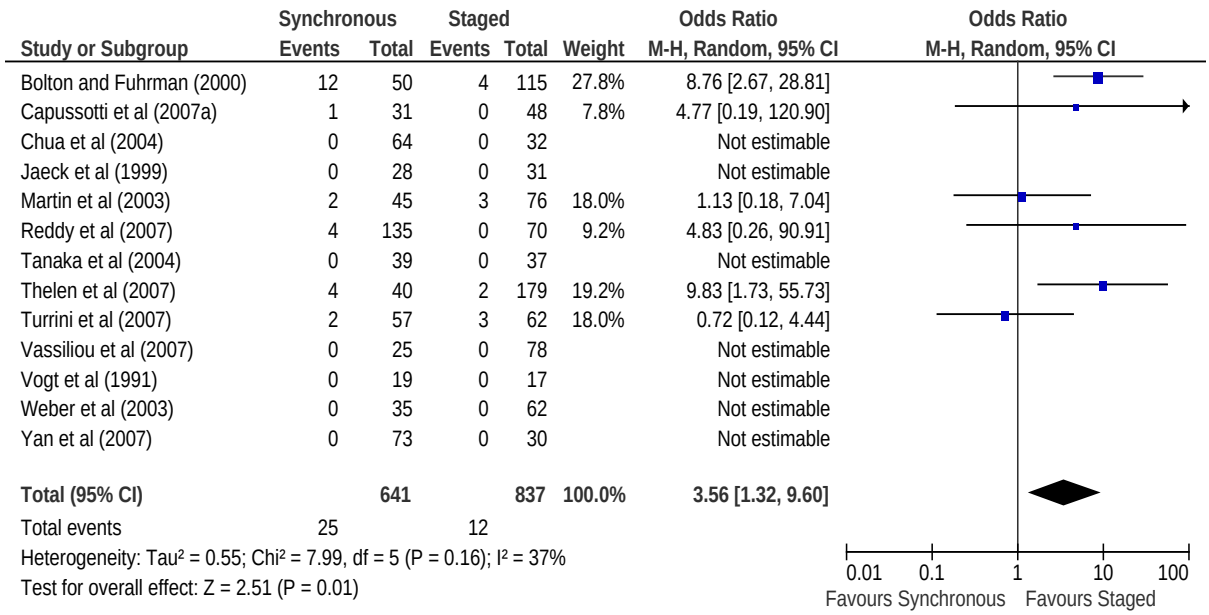
From 14 studies with a total of 1,384 patients, 224/641 (35%) of patients undergoing synchronous resection experienced complications versus 301/743 (41%) of patients undergoing staged resection.



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 I^2 is 0% and the X^2 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

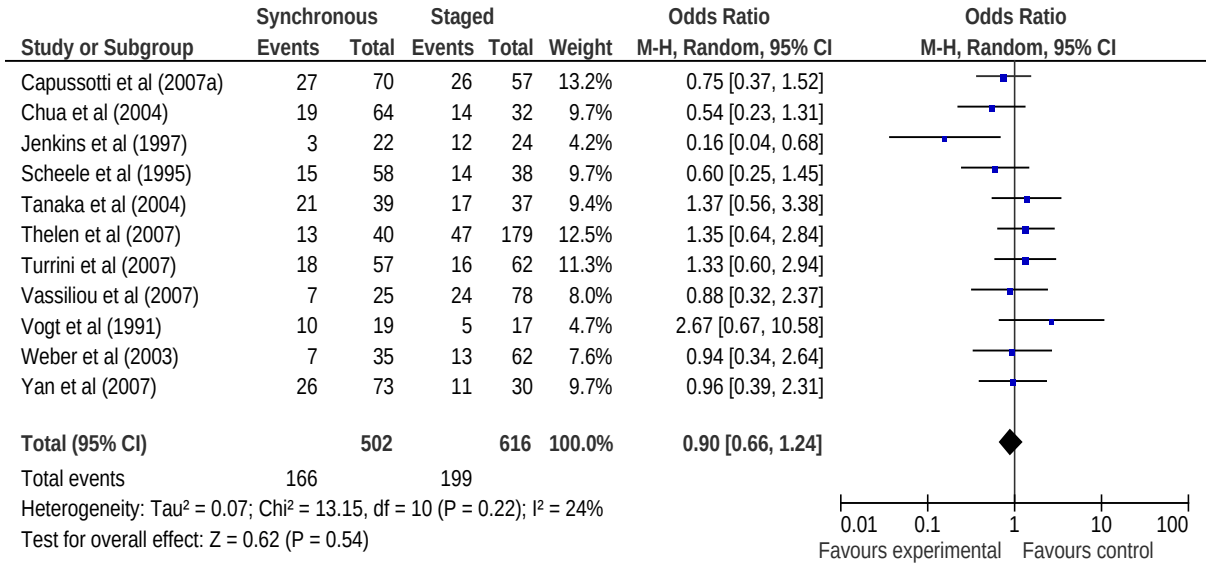
From 15 studies comparing perioperative mortality, 32/499 (6.4%) of patients undergoing synchronous resection died versus 40/1529 (2.6%) of patients undergoing staged resection showing a clear tendency towards higher mortality in the combined resection group.



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.



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 $<1.5x10^9$/L
Platelet counts $<100x10^9$/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