Clinical Guideline

Colorectal cancer: the diagnosis and management of colorectal cancer

Full Guideline

Contents

Key priorities for implementation

Diagnostic investigations
1. Offer colonoscopy to patients without major comorbidity, to confirm a diagnosis of colorectal cancer. If a lesion suspicious of cancer is detected, perform a biopsy to obtain histological proof of diagnosis, unless it is contraindicated (for example, patients with a blood clotting disorder).

Staging of colorectal cancer
2. Offer contrast-enhanced computed tomography (CT) of the chest, abdomen and pelvis, to estimate the stage of disease, to all patients diagnosed with colorectal cancer unless it is contraindicated. No further routine imaging is needed for patients with colon cancer.

3. Offer magnetic resonance imaging (MRI) to assess the risk of local recurrence, determined by anticipated resection margin, tumour and lymph node staging, to all patients with rectal cancer unless it is contraindicated.

Preoperative management of the primary tumour
4. Do not offer short-course preoperative radiotherapy (SCPRT) or chemoradiotherapy to patients with low-risk operable rectal cancer, unless as part of a clinical trial.

Colonic stents in acute large bowel obstruction
5. If considering the use of a colonic stent in patients presenting with acute large bowel obstruction, offer a CT of the chest, abdomen and pelvis to confirm the diagnosis of mechanical obstruction, and to determine whether the patient has metastatic disease or colonic perforation.

Stage I colorectal cancer
6. The colorectal multidisciplinary team (MDT) should consider further treatment for patients with locally excised, pathologically confirmed stage I cancer, taking into account pathological characteristics of the lesion, imaging results and any previous treatments.

Imaging hepatic metastases
7. If the CT scan shows metastatic disease only in the liver and the patient has no contraindications to further treatment, a specialist hepatobiliary MDT should decide if further imaging to confirm surgery is suitable for the patient - or potentially suitable after further treatment - is needed.

Chemotherapy for advanced and metastatic colorectal cancer
8. When offering multiple chemotherapy drugs to patients with advanced and metastatic colorectal cancer, consider one of the following sequences of chemotherapy unless they are contraindicated:
   - FOLFOX (folinic acid plus fluorouracil plus oxaliplatin) as first-line treatment then single agent irinotecan as second-line treatment **or**
   - FOLFOX as first-line treatment then FOLFIRI (folinic acid plus fluorouracil plus irinotecan[1]) as second-line treatment **or**
   - XELOX (capecitabine plus oxaliplatin) as first-line treatment then FOLFIRI (folinic acid plus fluorouracil plus irinotecan[1]) as second-line treatment.

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[1] At the time of publication (November 2011), irinotecan did not have UK marketing authorisation for second-line combination therapy. Informed consent should be obtained and documented.

Follow-up after apparently curative resection

9. Offer patients regular surveillance with:
   - a minimum of two CTs of the chest, abdomen and pelvis in the first 3 years and
   - regular serum carcinoembryonic antigen tests (at least every 6 months in the first 3 years).

Information about bowel function

10. Before starting treatment, offer all patients information on all treatment options available to them (including no treatment) and the potential benefits and risks of these treatments, including the effect on bowel function.

Key research recommendations

- **The effectiveness of preoperative chemotherapy should be compared with short-course preoperative radiotherapy (SCPRT), chemoradiotherapy or surgery alone in patients with moderate-risk locally advanced rectal cancer. Outcomes of interest are local control, toxicity, overall survival, quality of life and cost effectiveness.**

  Variation exists as to whether or not patients with moderate-risk locally advanced rectal cancer are offered a preoperative treatment or not. If they are offered treatment variation also exists as to whether it is with SCPRT or chemoradiotherapy. At present, preoperative chemotherapy, without radiotherapy, is limited to use in clinical trials. Patients with moderate-risk locally advanced rectal cancer are at risk of both local recurrence and systemic relapse, but the use of either form of radiotherapy carries the risk of significant morbidity, which may affect quality of life. It is therefore important to establish whether better outcomes can be achieved with preoperative chemotherapy or surgery alone, and whether there are groups of patients whose benefit from either SCPRT or chemoradiotherapy is greater than the risk of late effects.

- **An observational study should be conducted, incorporating standardised assessment of pathological prognostic factors, to assess the value of the proposed prognostic factors in guiding optimal management in patients with locally excised, pathological stage I cancer. Outcomes of interest are disease-free survival, overall survival, local and regional control, toxicity, cost-effectiveness and quality of life.**

  The NHS bowel cancer screening programme is detecting increasing numbers of stage I cancers, but the optimum management for these very early tumours is far from clear. The available studies looking at pathological risk factors have not used standardised features, either in terms of the factors included or the methods of assessment. Furthermore, although some consensus can be reached on the pathological risk factors that lead to poorer outcomes, there is no evidence about how these risk factors might be used to guide subsequent clinical management, particularly when the resection margins are considered to be clear. The therapeutic options are varied and there is no realistic prospect for a successful randomised control trial. Therefore, careful follow-up of patients whose tumours have been analysed in a standardised way to define specified pathological risk factors and who have been treated with one of the possible options, could form the basis of an observational study.

- **A prospective trial should be conducted to investigate the most clinically effective and cost-effective sequence in which to perform MRI and PET-CT, after an initial CT scan, in patients with colorectal cancer that has metastasised to the liver, to determine whether the metastasis is resectable. The outcomes of interest are reduction in inappropriate laparotomies and improvement in overall survival.**

  Nearly 7% of all patients with liver metastases from colorectal cancer are now being considered for liver resection with curative intent. These operations are costly and have their own inherent risks, including futile laparotomy which can be psychologically devastating for patients and carers. After the initial diagnosis of suspected liver metastases on diagnostic or follow up CT scan, it is clear that PET-CT (which is patient-specific to detect incurable extra-hepatic disease) and MRI (which is liver-specific to accurately characterise detected liver lesions) both play roles in the decision

algorithm when considering surgery. Both of these investigations are expensive and can lead to delays in starting appropriate treatment. Research is needed to determine the correct sequence of these investigations to reduce the rate of futile laparotomy, improve cost effectiveness of treatment, and ultimately improve overall survival.

- **Strategies to integrate oncological surveillance with optimising quality of life, reducing late effects, and detecting second cancers in survivors of colorectal cancer should be developed and explored.**

  Traditionally, oncological surveillance has focused on the early detection of either local recurrence or distant metastases. Although there is increasing evidence that the early detection of such recurrences is worthwhile in terms of subsequent oncological outcomes there are other issues, which are particularly important to patients, that can be detected and managed by appropriate follow-up. The detection of late effects and impact on quality of life are particularly important and research into reducing the likelihood and managing the consequences of such effects makes this all the more relevant to patients. There are numerous different models of surveillance and research should aim to establish strategies that address patient concerns.

- **Colorectal cancer-specific patient-reported outcome measures (PROMs) should be developed for use in disease management and to inform outcome measures in future clinical trials.**

  Quality of life and PROMs are now frequently being used as secondary end-points in clinical trials of cancer management. However, some investigators continue to use non-disease-specific generic methodology for this purpose. The treatment of colorectal cancer leads to very specific side effects relating to bowel function and activities of daily living. The Guideline Development Group (GDG) therefore believes that colorectal cancer-specific patient-reported outcome measures should be developed to standardise the interpretation of quality-of-life reporting as a secondary end-point in future clinical trials in colorectal cancer.

List of all recommendations

Chapter 2 Investigation, diagnosis and staging

Diagnostic investigations
- Advise the patient that more than one investigation may be necessary to confirm or exclude a diagnosis of colorectal cancer.
- Offer colonoscopy to patients without major comorbidity, to confirm a diagnosis of colorectal cancer. If a lesion suspicious of cancer is detected, perform a biopsy to obtain histological proof of diagnosis, unless it is contraindicated (for example, patients with a blood clotting disorder).
- Offer flexible sigmoidoscopy then barium enema for patients with major comorbidity. If a lesion suspicious of cancer is detected perform a biopsy unless it is contraindicated.
- Consider computed tomographic (CT) colonography as an alternative to colonoscopy or flexible sigmoidoscopy then barium enema, if the local radiology service can demonstrate competency in this technique. If a lesion suspicious of cancer is detected on CT colonography, offer a colonoscopy with biopsy to confirm the diagnosis, unless it is contraindicated.
- Offer patients who have had an incomplete colonoscopy:
  - repeat colonoscopy **or**
  - CT colonography, if the local radiology service can demonstrate competency in this technique **or**
  - barium enema.

Staging of colorectal cancer
- Offer contrast-enhanced CT of the chest, abdomen and pelvis, to estimate the stage of disease, to all patients diagnosed with colorectal cancer unless it is contraindicated. No further routine imaging is needed for patients with colon cancer.
- Offer magnetic resonance imaging (MRI) to assess the risk of local recurrence, as determined by anticipated resection margin, tumour and lymph node staging, to all patients with rectal cancer unless it is contraindicated.
- Offer endorectal ultrasound to patients with rectal cancer if MRI shows disease amenable to local excision or if MRI is contraindicated.
- Do not use the findings of a digital rectal examination as part of the staging assessment.

Chapter 3 Management of local disease

Preoperative management of the primary tumour
Patients whose primary rectal tumour appears resectable at presentation
- Discuss the risk of local recurrence, short-term and long-term morbidity and late effects with the patient after discussion in the multidisciplinary team (MDT).
- Do not offer short-course preoperative radiotherapy (SCPRT) or chemoradiotherapy to patients with low-risk operable rectal cancer (see table 3.1 for risk groups), unless as part of a clinical trial.
- Consider SCPRT then immediate surgery for patients with moderate-risk operable rectal cancer (see table 3.1 for risk groups). Consider preoperative chemoradiotherapy with an interval to allow tumour response and shrinkage before surgery for patients with tumours that are borderline between moderate and high risk.

- Offer preoperative chemoradiotherapy with an interval before surgery to allow tumour response and shrinkage (rather than SCPRT), to patients with high-risk operable rectal cancer (see table 3.1 for risk groups).

Patients whose primary colon or rectal tumour appears unresectable or borderline resectable
- Discuss the risk of local recurrence and late toxicity with patients with rectal cancer after discussion in the MDT.
- Offer preoperative chemoradiotherapy with an interval before surgery, to allow tumour response and shrinkage, to patients with high-risk locally advanced rectal cancer.
- Do not offer preoperative chemoradiotherapy solely to facilitate sphincter-sparing surgery to patients with rectal cancer.
- Do not routinely offer preoperative chemotherapy alone for patients with locally advanced colon or rectal cancer unless as part of a clinical trial.

Colonic stents in acute large bowel obstruction
- If considering the use of a colonic stent in patients presenting with acute large bowel obstruction, offer CT of the chest, abdomen and pelvis to confirm the diagnosis of mechanical obstruction, and to determine whether the patient has metastatic disease or colonic perforation.
- Do not use contrast enema studies as the only imaging modality in patients presenting with acute large bowel obstruction.
- A consultant colorectal surgeon should consider inserting a colonic stent in patients presenting with acute large bowel obstruction. They should do this together with an endoscopist or a radiologist (or both) who is experienced in using colonic stents.
- Resuscitate patients with acute large bowel obstruction, then consider placing a self-expanding metallic stent to initially manage a left-sided complete or near-complete colonic obstruction.
- Do not place self-expanding metallic stents:
  o in low rectal lesions or
  o to relieve right-sided colonic obstruction or
  o if there is clinical or radiological evidence of colonic perforation or peritonitis.
- Do not dilate the tumour before inserting the self-expanding metallic stent.
- Only a healthcare professional experienced in placing colonic stents who has access to fluoroscopic equipment and trained support staff should insert colonic stents.
- If a self-expanding metallic stent is suitable, attempt insertion urgently and no longer than 24 hours after patients present with colonic obstruction.

Stage I colorectal cancer
- The colorectal MDT should consider further treatment for patients with locally excised, pathologically confirmed stage I cancer, taking into account pathological characteristics of the lesion, imaging results and previous treatments.
- Offer further treatment to patients whose tumour had involved resection margins (less than 1 mm).
- Discuss the risks and benefits of all treatment options with the patient after discussion in the MDT.
- An early rectal cancer MDT[2] should decide which treatment to offer to patients with stage I rectal cancer, taking into account previous treatments, such as radiotherapy.

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[2] Improving outcomes in colorectal cancer (2004). NICE cancer service guidance CSGCC. Available from www.nice.org.uk/CSGCC

Laparoscopic surgery[3]

- Laparoscopic (including laparoscopically assisted) resection is recommended as an alternative to open resection for individuals with colorectal cancer in whom both laparoscopic and open surgery are considered suitable.
- Laparoscopic colorectal surgery should be performed only by surgeons who have completed appropriate training in the technique and who perform this procedure often enough to maintain competence. The exact criteria to be used should be determined by the relevant national professional bodies. Cancer networks and constituent trusts should ensure that any local laparoscopic colorectal surgical practice meets these criteria as part of their clinical governance arrangements.
- The decision about which of the procedures (open or laparoscopic) is undertaken should be made after informed discussion between the patient and the surgeon. In particular, they should consider:
  o the suitability of the lesion for laparoscopic resection
  o the risks and benefits of the two procedures
  o the experience of the surgeon in both procedures.

Adjuvant chemotherapy in rectal cancer

- Assess pathological staging after surgery, before deciding whether to offer adjuvant chemotherapy.
- Consider adjuvant chemotherapy for patients with high-risk stage II and all stage III rectal cancer to reduce the risk of local and systemic recurrence.

Adjuvant chemotherapy for high-risk stage II colon cancer

- Consider adjuvant chemotherapy after surgery for patients with high-risk stage II colon cancer. Fully discuss the risks and benefits with the patient.

Adjuvant chemotherapy for stage III colon cancer[4]

- The following are recommended as options for the adjuvant treatment of patients with stage III (Dukes' C) colon cancer following surgery for the condition:
  o capecitabine as monotherapy
  o oxaliplatin in combination with 5-fluorouracil and folinic acid.
- The choice of adjuvant treatment should be made jointly by the individual and the clinicians responsible for treatment. The decision should be made after an informed discussion between the clinicians and the patient; this discussion should take into account contraindications and the side-effect profile of the agent(s) and the method of administration as well as the clinical condition and preferences of the individual.

Chapter 4 Management of metastatic disease

Patients presenting with stage IV colorectal cancer

- Prioritise treatment to control symptoms if at any point the patient has symptoms from the primary tumour.
- If both primary and metastatic tumours are considered resectable, anatomical site-specific MDTs should consider initial systemic treatment followed by surgery, after full discussion with the patient. The decision on whether the operations are done at the same time or separately should be made by the anatomical site-specific MDTs in consultation with the patient.

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[3] The recommendations in this section are from 'Laparoscopic surgery for colorectal cancer' (NICE technology appraisal guidance 105).
[4] The recommendations in this section are from 'Capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes' C) colon cancer.' NICE technology appraisal guidance 100.

Imaging hepatic metastases

- If the CT scan shows metastatic disease only in the liver and the patient has no contraindications to further treatment, a specialist hepatobiliary MDT should decide if further imaging to confirm surgery is suitable for the patient - or potentially suitable after further treatment – is needed.

Imaging extra-hepatic metastases

- Offer contrast-enhanced CT of the chest, abdomen and pelvis to patients being assessed for metastatic colorectal cancer.
- If intracranial disease is suspected, offer contrast-enhanced MRI of the brain. Do not offer imaging of the head, neck and limbs unless involvement of these sites is suspected clinically.
- Discuss all imaging with the patient following review by the appropriate anatomical site-specific MDT.
- If the CT scan shows the patient may have extra-hepatic metastases that could be amenable to further radical surgery, an anatomical site-specific MDT should decide whether a positron emission tomography-CT (PET-CT) scan of the whole body is appropriate.
- If contrast-enhanced CT suggests disease in the pelvis, offer an MRI of the pelvis and discuss in the colorectal cancer MDT.
- If the diagnosis of extra-hepatic recurrence remains uncertain, keep the patient under clinical review and offer repeat imaging at intervals agreed between the healthcare professional and the patient.

Chemotherapy for advanced and metastatic colorectal cancer

Oxaliplatin and irinotecan in combination with fluoropyrimidines

- When offering multiple chemotherapy drugs to patients with advanced and metastatic colorectal cancer, consider one of the following sequences of chemotherapy unless they are contraindicated:
  - FOLFOX (folinic acid plus fluorouracil plus oxaliplatin) as first-line treatment then single agent irinotecan as second-line treatment **or**
  - FOLFOX as first-line treatment then FOLFIRI (folinic acid plus fluorouracil plus irinotecan[5]) as second-line treatment **or**
  - XELOX (capecitabine plus oxaliplatin) as first-line treatment then FOLFIRI (folinic acid plus fluorouracil plus irinotecan[5]) as second-line treatment.
- Decide which combination and sequence of chemotherapy to use after full discussion of the side effects and the patient's preferences.

Raltitrexed

- Consider raltitrexed only for patients with advanced colorectal cancer who are intolerant to 5-fluorouracil and folinic acid, or for whom these drugs are not suitable (for example, patients who develop cardiotoxicity). Fully discuss the risks and benefits of raltitrexed with the patient.
- Prospectively collect data on quality of life, toxicity, response rate, progression-free survival, and overall survival for all patients taking raltitrexed.

Capecitabine and tegafur with uracil[6]

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[5] At the time of publication (November 2011), irinotecan did not have UK marketing authorisation for second-line combination therapy. Informed consent should be obtained and documented.

[6] The recommendations in this section are from 'Guidance on the use of capecitabine and tegafur uracil for metastatic colorectal cancer.' NICE technology appraisal guidance 61.

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- Oral therapy with either capecitabine or tegafur with uracil (in combination with folinic acid) is recommended as an option for the first-line treatment of metastatic colorectal cancer.
- The choice of regimen (intravenous 5-fluorouracil and folinic acid or one of the oral therapies) should be made jointly by the individual and the clinician(s) responsible for treatment. The decision should be made after an informed discussion between the clinician(s) and the patient; this discussion should take into account contraindications and the side-effect profile of the agents as well as the clinical condition and preferences of the individual.
- The use of capecitabine or tegafur with uracil to treat metastatic colorectal cancer should be supervised by oncologists who specialise in colorectal cancer.

Biological agents in metastatic colorectal cancer
- Refer to 'Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer'. NICE technology appraisal guidance 212 (2010). Available from www.nice.org.uk/guidance/TA212.
- Refer to 'Cetuximab for the first-line treatment of metastatic colorectal cancer'. NICE technology appraisal guidance 176 (2009). Available from www.nice.org.uk/guidance/TA176
- Refer to 'Cetuximab for the treatment of metastatic colorectal cancer following failure of oxaliplatin-containing chemotherapy (terminated appraisal)'. NICE technology appraisal 150 (2008). Available from www.nice.org.uk/guidance/TA150
- Refer to 'Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer'. NICE technology appraisal guidance 118 (2007). Available from www.nice.org.uk/guidance/TA118

Chapter 5 Ongoing care and support

Follow-up after apparently curative resection
- Offer follow-up to all patients with primary colorectal cancer undergoing treatment with curative intent. Start follow-up at a clinic visit 4–6 weeks after potentially curative treatment.
- Offer patients regular surveillance with:
  o a minimum of two CTs of the chest, abdomen, and pelvis in the first 3 years and
  o regular serum carcinoembryonic antigen tests (at least every 6 months in the first 3 years).
- Offer a surveillance colonoscopy at 1 year after initial treatment. If this investigation is normal consider further colonoscopic follow-up after 5 years, and thereafter as determined by cancer networks. The timing of surveillance for patients with subsequent adenomas should be determined by the risk status of the adenoma.
- Start reinvestigation if there is any clinical, radiological or biochemical suspicion of recurrent disease.
- Stop regular follow-up:
  o when the patient and the healthcare professional have discussed and agreed that the likely benefits no longer outweigh the risks of further tests or
  o when the patient cannot tolerate further treatments.

Information about bowel function
- Before starting treatment, offer all patients information on all treatment options available to them (including no treatment) and the potential benefits and risks of these treatments, including the effect on bowel function.

- Before surgery, offer all patients information about the likelihood of having a stoma, why it might be necessary, and how long it might be needed for.
- Ensure a trained stoma professional gives specific information on the care and management of stomas to all patients considering surgery that might result in a stoma.
- After any treatment, offer all patients specific information on managing the effects of the treatment on their bowel function. This could include information on incontinence, diarrhoea, difficulty emptying bowels, bloating, excess flatus and diet, and where to go for help in the event of symptoms.
- Offer verbal and written information in a way that is clearly understood by patients and free from jargon. Include information about support organisations or internet resources recommended by the clinical team.

Methodology

Introduction

What is a Clinical Guideline?

Guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances – from prevention and self-care through to primary and secondary care and on to more specialised services. NICE clinical guidelines are based on the best available evidence of clinical and cost effectiveness, and are produced to help healthcare professionals and patients make informed choices about appropriate healthcare. While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

Clinical guidelines for the NHS in England, Wales and Northern Ireland are produced as a response to a request from the Department of Health (DH). They approve topics for guideline development. Before deciding whether to refer a particular topic to the National Institute for Health and Clinical Excellence (NICE) they consult with the relevant patient bodies, professional organisations and companies. Once a topic is referred, NICE then commissions one of four National Collaborating Centres (NCCs) to produce a guideline. The Collaborating Centres are independent of government and comprise partnerships between a variety of academic institutions, health profession bodies and patient groups. The National Collaborating Centre for Cancer (NCC-C) was referred the topic of the diagnosis and management of colorectal cancer in October 2007 as part of NICE's sixteenth wave work programme. However, the guideline development process began officially in February 2009 when sufficient capacity became available at the NCC-C.

Who is the Guideline Intended For?

This guideline does not include recommendations covering every detail of the diagnosis and management of colorectal cancer. Instead this guideline has tried to focus on those areas of clinical practice (i) that are known to be controversial or uncertain; (ii) where there is identifiable practice variation; (iii) where there is a lack of high quality evidence; or (iv) where NICE guidelines are likely to have most impact. More detail on how this was achieved is presented later in the section on 'Developing Clinical Evidence Based Questions'.

This guideline is relevant to all healthcare professionals who come into contact with patients with colorectal cancer or suspected of having colorectal cancer, as well as to the patients themselves and their carers. It is also expected that the guideline will be of value to those involved in clinical governance in both primary and secondary care to help ensure that arrangements are in place to deliver appropriate care for the population covered by this guideline.

The Remit of the Guideline

Guideline topics selected by the DH identify the main areas to be covered by the guideline in a specific remit. The following remit for this guideline was received as part of NICE's sixteenth wave programme of work:

> *'To prepare a clinical guideline on the diagnosis and management of patients with all stages of primary colorectal cancer. This excludes any population screening and surveillance of high-risk groups, including patients with a family history and patients with inflammatory bowel disease.'*

Involvement of Stakeholders

Key to the development of all NICE guidance is the involvement of relevant professional and patient/carer organisations that register as stakeholders. Details of this process can be found

on the NICE website or in the 'NICE guidelines manual' (NICE 2009). In brief, their contribution involves commenting on the draft scope, submitting relevant evidence and commenting on the draft version of the guideline during the end consultation period. A full list of all stakeholder organisations who registered for the diagnosis and management of colorectal cancer guideline can be found in Appendix 6.2.

The Process of Guideline Development – Who Develops the Guideline?

Overview

The development of this guideline was based upon methods outlined in the 'NICE guidelines manual' (NICE 2009). A team of health professionals, lay representatives and technical experts known as the Guideline Development Group (GDG) (see Appendix 6.1), with support from the NCC-C staff, undertook the development of this clinical guideline. The basic steps in the process of developing a guideline are listed and discussed below:

- using the remit, define the scope which sets the inclusion/exclusion criteria of the guideline
- forming the GDG
- developing clinical questions
- developing the review protocol
- systematically searching for the evidence
- critically appraising the evidence
- incorporating health economic evidence
- distilling and synthesising the evidence and writing recommendations
- agreeing the recommendations
- structuring and writing the guideline
- updating the guideline.

The Scope

The remit was translated into a scope document by the Guideline Development Group (GDG) Chair and Lead Clinician and staff at the NCC-C in accordance with processes established by NICE (NICE 2009). The purpose of the scope was to:

- set the boundaries of the development work and provide a clear framework to enable work to stay within the priorities agreed by NICE and the NCC-C and the remit set by the DH
- inform professionals and the public about the expected content of the guideline.
- provide an overview of the population and healthcare settings the guideline would include and exclude
- specify the key clinical issues that will be covered by the guideline
- inform the development of the clinical questions and search strategy

Before the guideline development process started, the draft scope was presented and discussed at a stakeholder workshop. The list of key clinical issues were discussed and revised before the formal consultation process. Further details of the discussion at the stakeholder workshop can be found on the NICE website (www.nice.org.uk).

The scope was subject to a four week stakeholder consultation in accordance with processes established by NICE in the 'NICE guidelines manual' (NICE 2009). The full scope is shown in Appendix 5. During the consultation period, the scope was posted on the NICE website (www.nice.org.uk). Comments were invited from registered stakeholder organisations and the NICE Guideline Review Panel (GRP). Further information about the GRP can also be found on the NICE website. The NCC-C and NICE reviewed the scope in

light of comments received, and the revised scope was reviewed by the GRP, signed off by NICE and posted on the NICE website.

The Guideline Development Group (GDG)

The colorectal cancer GDG was recruited in line with the 'NICE guidelines manual' (NICE 2009). The first step was to appoint a Chair and a Lead Clinician. Advertisements were placed for both posts and candidates were interviewed before being offered the role. The NCC-C Director, GDG Chair and Lead Clinician identified a list of specialties that needed to be represented on the GDG. Details of the adverts were sent to the main stakeholder organisations, cancer networks and patient organisations/charities (see Appendix 6.2). Individual GDG members were selected by the NCC-C Director, GDG Chair and Lead Clinician, based on their application forms. The guideline development process was supported by staff from the NCC-C, who undertook the clinical and health economics literature searches, reviewed and presented the evidence to the GDG, managed the process and contributed to drafting the guideline. At the start of the guideline development process all GDG members' interests were recorded on a standard declaration form that covered consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared new, arising conflicts of interest which were always recorded (see Appendix 6.1).

Guideline Development Group Meetings

Twelve GDG meetings were held between 19 May April 2009 and 2 February 2011. During each GDG meeting (either held over one or two days) clinical questions and clinical and economic evidence were reviewed, assessed and recommendations formulated. At each meeting patient/carer and service-user concerns were routinely discussed as part of a standing agenda item.

NCC-C project managers divided the GDG workload by allocating specific clinical questions, relevant to their area of clinical practice, to small sub-groups of the GDG in order to simplify and speed up the guideline development process. These groups considered the evidence, as reviewed by the researcher, and synthesised it into draft recommendations before presenting it to the GDG as a whole. Each clinical question was led by a GDG member with expert knowledge of the clinical area (usually one of the healthcare professionals). The GDG subgroups often helped refine the clinical questions and the clinical definitions of treatments. They also assisted the NCC-C team in drafting the section of the guideline relevant to their specific topic.

Patient/Carer Members

Individuals with direct experience of colorectal cancer gave an important user focus to the GDG and the guideline development process. The GDG included three patient/carer members. They contributed as full GDG members to writing the clinical questions, helping to ensure that the evidence addressed their views and preferences, highlighting sensitive issues and terminology relevant to the guideline and bringing service-user research to the attention of the GDG.

Developing Clinical Evidence-Based Questions

Background

Clinical guidelines should be aimed at improving clinical practice and should avoid ending up as 'evidence-based textbooks' or making recommendations on topics where there is already agreed clinical practice. Therefore the list of key clinical issues listed in the scope were developed in areas that were known to be controversial or uncertain, where there was identifiable practice variation, or where NICE guidelines were likely to have most impact.

Method

From each of the key clinical issues identified in the scope the GDG formulated a clinical question. For clinical questions about interventions, the PICO framework was used. This structured approach divides each question into four components: the population (the population under study – P), the interventions (what is being done - I), the comparisons (other main treatment options – C) and the outcomes (the measures of how effective the interventions have been – O). Where appropriate, the clinical questions were refined once the evidence had been searched and, where necessary, sub-questions were generated.

The final list of clinical questions can be found in the scope (see Appendix 5).

Review of Clinical Literature

Scoping search
An initial scoping search for published guidelines, systematic reviews, economic evaluations and ongoing research was carried out on the following databases or websites: National Library for Health (NLH) Guidelines Finder (now NHS Evidence), National Guidelines Clearinghouse, Cochrane Database of Systematic Reviews (CDSR), Heath Technology Assessment Database (HTA), NHS Economic Evaluations Database (NHSEED), DH Data, Medline and Embase.

At the beginning of the development phase, initial scoping searches were carried out to identify any relevant guidelines (local, national or international) produced by other groups or institutions.

Developing the review protocol
For each clinical question, the information specialist and researcher (with input from other technical team and GDG members) prepared a review protocol. This protocol explains how the review was to be carried out (see Table A) in order to develop a plan of how to review the evidence, limit the introduction of bias and for the purposes of reproducibility. All review protocols can be found in the full evidence review.

Table A Components of the review protocol

Component	Description
Clinical question	The clinical question as agreed by the GDG.
Objectives	Short description; for example 'To estimate the effects and cost effectiveness of…' or 'To estimate the diagnostic accuracy of…'.
Criteria for considering studies for the review	Using the PICO (population, intervention, comparison and outcome) framework. Including the study designs selected.
How the information will be searched	The sources to be searched and any limits that will be applied to the search strategies; for example, publication date, study design, language. (Searches should not necessarily be restricted to RCTs.)
The review strategy	The methods that will be used to review the evidence, outlining exceptions and subgroups. Indicate if meta-analysis will be used.

Searching for the evidence
In order to answer each question the NCC-C information specialist developed a search strategy to identify relevant published evidence for both clinical and cost effectiveness. Key

words and terms for the search were agreed in collaboration with the GDG. When required, the health economist searched for supplementary papers to inform detailed health economic work (see section on 'Incorporating Health Economic Evidence').

Search filters, such as those to identify systematic reviews (SRs) and randomised controlled trials (RCTs) were applied to the search strategies when there was a wealth of these types of studies. No language restrictions were applied to the search; however, foreign language papers were not requested or reviewed (unless of particular importance to that question).

The following databases were included in the literature search:
- The Cochrane Library
- Medline and Premedline 1950 onwards
- Excerpta Medica (Embase) 1980 onwards
- Cumulative Index to Nursing and Allied Health Literature (Cinahl) 1982 onwards
- Allied & Complementary Medicine (AMED) 1985 onwards
- British Nursing Index (BNI) 1985 onwards
- Psychinfo 1806 onwards
- Web of Science [specifically Science Citation Index Expanded]
- (SCI-EXPANDED) 1899 onwards and Social Sciences Citation Index (SSCI) 1956 onwards]
- Biomed Central 1997 onwards

From this list the information specialist sifted and removed any irrelevant material based on the title or abstract before passing to the researcher. All the remaining articles were then stored in a Reference Manager electronic library.

Searches were updated and re-run 6–8 weeks before the stakeholder consultation, thereby ensuring that the latest relevant published evidence was included in the database. Any evidence published after this date was not included. For the purposes of updating this guideline, 25 February 2011 should be considered the starting point for searching for new evidence.

Further details of the search strategies, including the methodological filters used, are provided in the evidence review.

Critical Appraisal
From the literature search results database, one researcher scanned the titles and abstracts of every article for each question and full publications were ordered for any studies considered relevant or if there was insufficient information from the title and abstract to inform a decision. When the papers were obtained the researcher applied inclusion/exclusion criteria to select appropriate studies, which were then critically appraised. For each question, data on the type of population, intervention, comparator and outcomes (PICO) were extracted and recorded in evidence tables and an accompanying evidence summary prepared for the GDG (see evidence review). All evidence was considered carefully by the GDG for accuracy and completeness.

GRADE (Grading of Recommendations, Assessment, Development and Evaluation)
For interventional questions, studies which matched the inclusion criteria were evaluated and presented using a modification of GRADE (NICE 2009; http://gradeworking group.org/). Where possible this included meta-analysis and synthesis of data into a GRADE 'evidence profile'. The evidence profile shows, for each outcome, an overall assessment of both the quality of the evidence as a whole (low, moderate or high) as well as an estimate of the size of effect. A narrative summary (evidence statement) was also prepared.

Each topic outcome was examined for the quality elements defined in table B and subsequently graded using the quality levels listed in table C. The reasons for downgrading or upgrading specific outcomes were explained in footnotes.

Table B Descriptions of quality elements of GRADE

Quality element	Description
Limitations	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results.
Indirectness	Indirectness refers to differences in study population, intervention, comparator or outcomes between the available evidence and the clinical question.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect relative to the minimal important difference.
Publication bias	Publication bias is a systematic underestimate or overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

Table C Overall quality of outcome evidence in GRADE

Quality element	Description
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

All procedures were fully compliant with NICE methodology as detailed in the 'NICE guidelines manual' (NICE 2009). In general, no formal contact was made with authors; however, there were ad hoc occasions when this was required in order to clarify specific details.

Needs Assessment

As part of the guideline development process the NCC-C invited a specialist registrar, with the support of the GDG, to undertake a needs assessment (see Appendix 6.3). The needs assessment aims to describe the burden of disease and current service provision for patients with colorectal cancer in England and Wales, which informed the development of the guideline.

Assessment of the effectiveness of interventions is not included in the needs assessment, and was undertaken separately by researchers in the NCC-C as part of the guideline development process.

The information included in the needs assessment document was presented to the GDG. Most of the information was presented in the early stages of guideline development, and other information was included to meet the evolving information needs of the GDG during the course of guideline development.

Incorporating Health Economics Evidence

The aim of providing economic input into the development of the guideline was to inform the GDG of potential economic issues relating to the diagnosis and management of colorectal cancer. Health economics is about improving the health of the population through the efficient use of resources. In addition to assessing clinical effectiveness, it is important to investigate whether health services are being used in a cost effective manner in order to maximise health gain from available resources.

Prioritising topics for economic analysis

After the clinical questions had been defined, and with the help of the health economist, the GDG discussed and agreed which of the clinical questions were potential priorities for economic analysis. These economic priorities were chosen on the basis of the following criteria, in broad accordance with the NICE guidelines manual (NICE 2009):

- The overall importance of the recommendation, which may be a function of the number of patients affected and the potential impact on costs and health outcomes per patient
- The current extent of uncertainty over cost effectiveness, and the likelihood that economic analysis will reduce this uncertainty

In addition, for clinical questions in the guideline that related to updates of technology appraisals, an evaluation of cost effectiveness was required if significant new clinical evidence had become available or if costs had changed since the original technology appraisal was published.

For each topic that was considered a high priority for economic analysis, a review of the economic literature was conducted. Where published economic evaluation studies were identified that addressed the economic issues for a clinical question, these are presented alongside the clinical evidence wherever possible. For those clinical areas reviewed, the information specialists used a similar search strategy as used for the review of clinical evidence but with the inclusion of a health economics filter.

For systematic searches of published economic evidence, the following databases were included:
- Medline
- Embase
- Cochrane
- NHS Economic Evaluation Database (NHS EED)

Methods for reviewing and appraising economic evidence

The aim of reviewing and appraising the existing economic literature is to identify relevant economic evaluations that compare both costs and health consequences of alternative interventions and that are applicable to NHS practice. Thus studies that only report costs, non-comparative studies or 'cost of illness' studies are generally excluded from the reviews (NICE, 2009).

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE, 2009, Appendix H). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the GDG for a specific topic within the Guideline. There are two parts to the appraisal process; the first step is to assess applicability (i.e. the relevance of the study to the specific guideline topic and the NICE reference case) (Table D).

Table D: Applicability criteria

Directly applicable	The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness.
Partially applicable	The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness.
Not applicable	The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration.

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (i.e. the methodological quality, Table D).

Table E: Methodological quality

Minor limitations	Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness.
Potentially serious limitations	Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness.
Very serious limitations	Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration.

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the GRADE table for clinical evidence.

For priority topics, if high-quality published economic evidence relevant to current NHS practice was identified through the search, the existing literature was reviewed and appraised as described above. However, it is often the case that published economic studies may not be directly relevant to the specific clinical question as defined in the guideline or may not be comprehensive or conclusive enough to inform UK practice. In such cases, consideration was given to undertaking a new economic analysis as part of this guideline.

Economic modelling

Once the need for a new economic analysis for high priority topics had been agreed by the GDG, the health economist investigated the feasibility of developing an economic model. Following this assessment, a decision was made to develop an integrated mixed treatment comparison and economic model to address the topic oxaliplatin and irinotecan-based chemotherapy in metastatic colorectal cancer. Full details of this analysis are presented in Appendix 2. In the development of the analysis, the following general principles were adhered to:

- the GDG subgroup was consulted during the construction and interpretation of the analysis
- the analysis was based on the best available clinical evidence from the systematic review
- assumptions were reported fully and transparently
- uncertainty was explored through sensitivity analysis

- costs were calculated from a health services perspective
- outcomes were reported in terms of quality-adjusted life years

Linking to NICE technology appraisals

There are several published technology appraisals (TA) which are relevant to this guideline (TA61, TA105, TA100, TA118, TA150, TA176 and TA212 - see www.nice.org.uk/TA/published). In line with NICE methodology, the recommendations from these TAs have either been reproduced verbatim in the colorectal cancer guideline or cross referenced.

Published TAs are periodically reviewed to determine if they need to be updated, particularly if any new evidence becomes available since the publication of the appraisal which means the original recommendations needed to be changed. In 2008, NICE consulted with stakeholders to assess whether TA93 should be updated within the guideline. The outcome was that TA93 should be updated within the colorectal cancer guideline.

Agreeing the Recommendations

For each clinical question the GDG were presented with a summary of the clinical evidence, and, where appropriate, economic evidence, derived from the studies reviewed and appraised. From this information the GDG were able to derive the guideline recommendations. The link between the evidence and the view of the GDG in making each recommendation is made explicit in the accompanying LETR statement.

LETR (Linking Evidence to Recommendations) statements

As clinical guidelines were previously formatted, there was limited scope for expressing how and why a GDG made a particular recommendation from the evidence of clinical and cost effectiveness. To make this process more transparent to the reader, NICE have introduced an explicit, easily understood and consistent way of expressing the reasons for making each recommendation. This is known as the 'LETR statement' and will usually cover the following key points:
- the relative value placed on the outcomes considered
- the strength of evidence about benefits and harms for the intervention being considered
- the costs and cost-effectiveness of an intervention (if formally assessed by the health economics team)
- the quality of the evidence (see GRADE)
- the degree of consensus within the GDG
- other considerations – for example equalities issues

Where evidence was weak or lacking the GDG agreed the final recommendations through informal consensus. Shortly before the consultation period, ten key priorities and five key research recommendations were selected by the GDG for implementation and the patient algorithms were agreed. To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations.

Consultation and Validation of the Guideline

The draft of the guideline was prepared by NCC-C staff in partnership with the GDG Chair and Lead Clinician. This was then discussed and agreed with the GDG and subsequently forwarded to NICE for consultation with stakeholders.

Registered stakeholders (see Appendix 6.2) had one opportunity to comment on the draft guideline which was posted on the NICE website between 29 March 2011 and 24 May 2011 in line with NICE methodology (NICE 2009). The Guideline Review Panel also reviewed the guideline and checked that stakeholder comments had been addressed.

The pre-publication check process

Following stakeholder consultation and subsequent revision, the draft guideline was then subject to a pre-publication check (NICE 2009). The pre-publication check provides registered stakeholders with the opportunity to raise any concerns about factual errors and inaccuracies that may exist in the revised guideline after consultation.

During the pre-publication check the full guideline was posted on the NICE website for 15 working days, together with the guideline consultation table that listed comments received during consultation from stakeholders and responses from the NCC-C and GDG.

All stakeholders were invited to report factual errors using a standard proforma. NICE, the NCC and the GDG Chair and Lead Clinician considered the reported errors and responded only to those related to factual errors. A list of all corrected errors and the revised guideline were submitted to NICE, and the revised guideline was then signed off by Guidance Executive. The list of reported errors from the pre-publication check and the responses from the NCC-C were subsequently published on the NICE website.

The final document was then submitted to NICE for publication on their website. The other versions of the guideline (see below) were also discussed and approved by the GDG and published at the same time.

Other Versions of the Guideline

This full version of the guideline is available to download free of charge from the NICE website (www.nice.org.uk) and the NCC-C website (www.wales.nhs.uk/nccc).

NICE also produces two other versions of the colorectal cancer guideline which are available from the NICE website:
- the NICE guideline, which is a shorter version of this guideline, containing the key priorities, key research recommendations and all other recommendations
- 'Understanding NICE Guidance' ('UNG'), which describes the guideline using non-technical language. It is written chiefly for people suspected of, or diagnosed with, colorectal cancer but may also be useful for family members, advocates or those who care for patients with colorectal cancer. For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk

The recommendations from this guideline have been incorporated into a NICE pathway, which is available from http://pathways.nice.org.uk/

Updating the Guideline

Literature searches were repeated for all of the clinical questions at the end of the GDG development process, allowing any relevant papers published before 25 February 2011 to be considered. Future guideline updates will consider evidence published after this cut-off date.

Three years after publication of the guideline, NICE will commission a review to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an early update.

Funding

The National Collaborating Centre for Cancer was commissioned by NICE to develop this guideline. Health economic analysis for this guideline was provided by the London School of Hygiene and Tropical Medicine and funded by the National Collaborating Centre for Cancer.

Disclaimer

The GDG assumes that healthcare professionals will use clinical judgment, knowledge and expertise when deciding whether it is appropriate to apply these guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient and clinical expertise.

The NCC-C disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

References

Briggs A, Claxton K, Sculpher M (2006) Decision Modelling for Health Economic Evaluation. Oxford: Oxford University Press.

National Institute for Health and Clinical Excellence (2009) The guidelines manual. London: National Institute for Health and Clinical Excellence. Available from www.nice.org.uk/guidelinesmanual

Algorithms

Overview of pathway

Patient with suspected colorectal cancer

NON-EMERGENCY PRESENTATION

Patient with major co-morbidity?

— No → Colonoscopy (with biopsy if needed) **or** CT colonography[1]

— Yes → Flexible sigmoidoscopy (with biopsy if needed) then barium enema **or** CT colonography[1]

Patient diagnosed with colorectal cancer

Contrast enhanced CT of chest, abdomen and pelvis to estimate stage of disease

Metastases?

— Yes → See "Management of metastatic disease" algorithm

— No →

Patient with rectal cancer

MRI to assess local recurrence determined by anticipated resection margin, tumour and lymph node staging, unless contraindicated

Offer endorectal ultrasound if MRI shows disease amenable to local excision or is contraindicated

Patient with operable rectal cancer

Patient with locally advanced rectal cancer

Patient with colon cancer

No further routine imaging required

Patient with operable colon cancer

Patient with locally advanced colon cancer

Appropriate treatment (see algorithms on "Management of local disease" and "Post-operative care")

Regular surveillance:
- a **minimum** of 2 CT scans of chest, abdomen and pelvis within the first 3 years
- regular serum CEA tests (at least every 6 months in the first 3 years)
- surveillance colonoscopy at 1 year after initial treatment

EMERGENCY PRESENTATION

Patient presenting with acute large bowel obstruction

CT of chest, abdomen and pelvis

Left sided obstruction → Insert SEMS if appropriate

Other sites of obstruction → Operate[2]. Do not insert SEMS

Patient information and support

[1] If the local radiology service can demonstrate competency in this technique
[2] This guideline does not make recommendations on what surgery is appropriate for this group of patients or when it is appropriate

The diagnosis and management of colorectal cancer: full guideline (November 2011)

Management of local disease – patients with rectal cancer

```
                          ┌──────────────────┐
                          │   Patient with   │
                          │   rectal cancer  │
                          └────────┬─────────┘
                                   │
                  ┌────────────────▼─────────────────┐
                  │  MRI to assess local recurrence  │
                  │ determined by anticipated resection│
                  │ margin, tumour and lymph node staging,│
                  │       unless contraindicated     │
                  └──────┬────────────────────┬──────┘
```

Patient information and support

```
         ┌──────────────────────────────────────────────────┐
         │              Risk of local recurrence            │
         ├──────────────┬──────────────┬────────────────────┤
         │   Low risk   │ Moderate risk│  High risk (locally│
         │              │              │     advanced)¹     │
         └──────┬───────┴──────┬───────┴─────────┬──────────┘
                │        Consider│  Consider──►   │
                │              ▼                  ▼
                │        ┌───────────┐      ┌─────────────┐
                │        │           │      │ Chemoradio- │
                │        │   SCPRT   │      │  therapy²   │
                │        └─────┬─────┘      └──────┬──────┘
                │   Proceed immediately to   Interval before surgery to allow
                │              │              shrinkage and response
         ┌──────▼──────────────▼──────────────────▼──────────┐
         │                     Surgery                        │
         └─────────────────────┬──────────────────────────────┘
                               │
         ┌─────────────────────▼──────────────────────────────┐
         │        See algorithm on "Post-operative care"      │
         └────────────────────────────────────────────────────┘
```
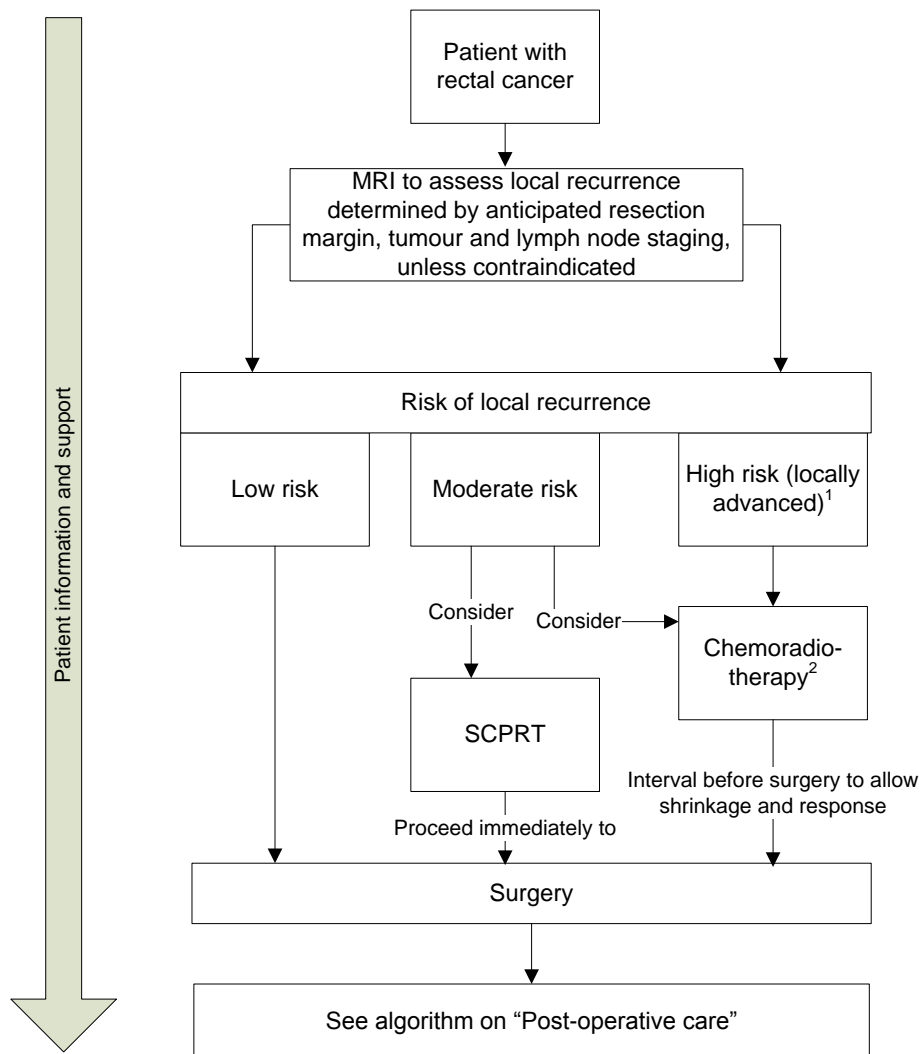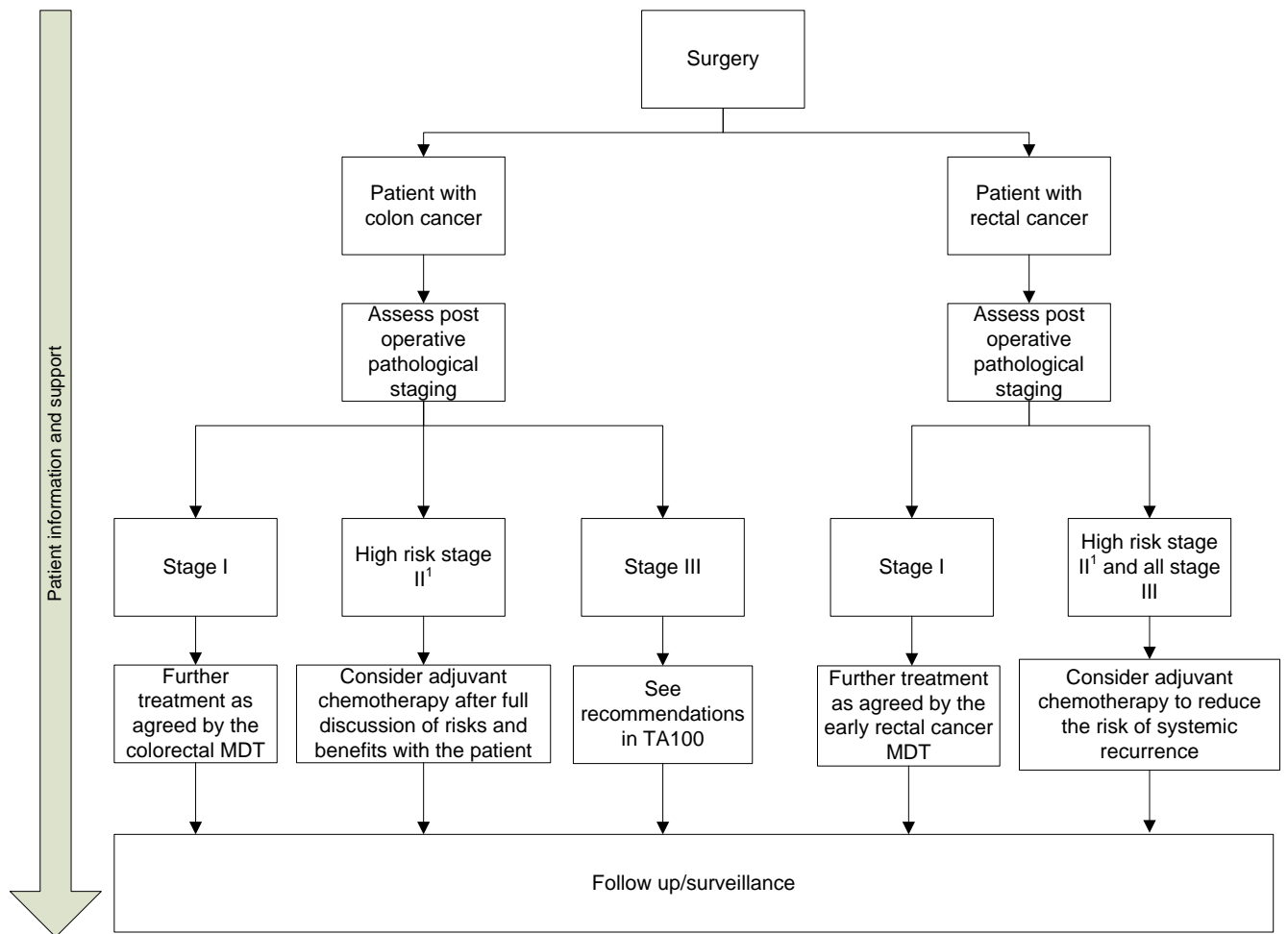
[1] Do not routinely offer preoperative chemotherapy alone to patients with locally advanced rectal cancer unless as part of a clinical trial
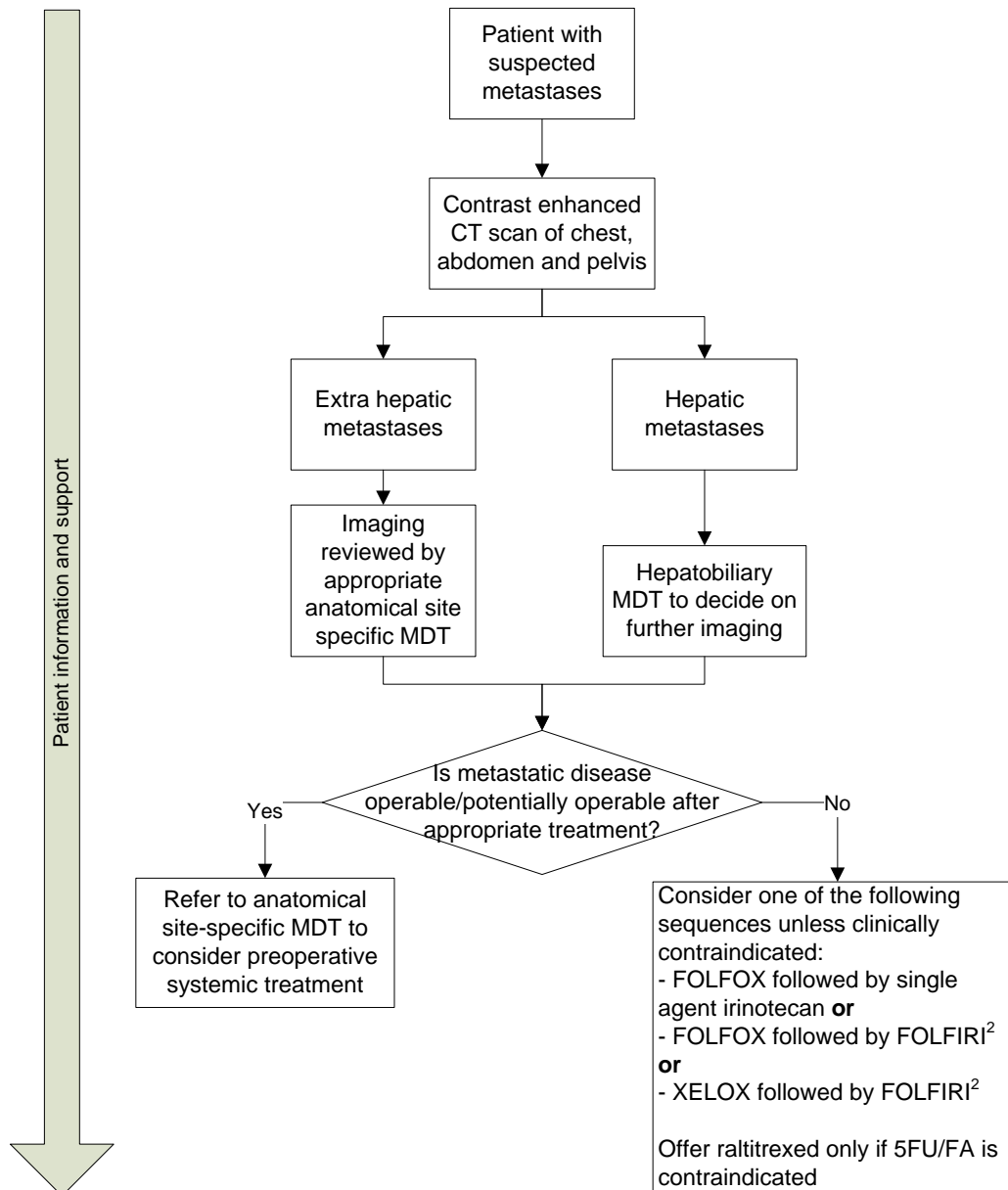[2] Do not offer preoperative chemoradiotherapy solely to facilitate sphincter sparing surgery

The diagnosis and management of colorectal cancer: full guideline (November 2011)

Post-operative care

```
                                    ┌──────────────┐
                                    │   Surgery    │
                                    └──────┬───────┘
                         ┌─────────────────┴─────────────────┐
                         ▼                                   ▼
                 ┌──────────────┐                    ┌──────────────┐
                 │ Patient with │                    │ Patient with │
                 │ colon cancer │                    │ rectal cancer│
                 └──────┬───────┘                    └──────┬───────┘
                        ▼                                   ▼
                 ┌──────────────┐                    ┌──────────────┐
                 │ Assess post  │                    │ Assess post  │
                 │ operative    │                    │ operative    │
                 │ pathological │                    │ pathological │
                 │ staging      │                    │ staging      │
                 └──────────────┘                    └──────────────┘
```

Patient information and support

Stage I	High risk stage II[1]	Stage III	Stage I	High risk stage II[1] and all stage III
Further treatment as agreed by the colorectal MDT	Consider adjuvant chemotherapy after full discussion of risks and benefits with the patient	See recommendations in TA100	Further treatment as agreed by the early rectal cancer MDT	Consider adjuvant chemotherapy to reduce the risk of systemic recurrence

Follow up/surveillance

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[1] Postoperative care of patients with stage II colorectal cancer was not included in the scope of this guideline, therefore no recommendations have been made in this area.

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Management of metastatic disease[1]

```
                        ┌─────────────────┐
                        │  Patient with   │
                        │   suspected     │
                        │   metastases    │
                        └────────┬────────┘
                                 │
                                 ▼
                        ┌─────────────────┐
                        │ Contrast enhanced│
                        │  CT scan of chest,│
                        │ abdomen and pelvis│
                        └────────┬────────┘
                   ┌─────────────┴─────────────┐
                   ▼                           ▼
          ┌────────────────┐          ┌────────────────┐
          │  Extra hepatic │          │    Hepatic     │
          │   metastases   │          │   metastases   │
          └───────┬────────┘          └───────┬────────┘
                  ▼                            ▼
          ┌────────────────┐          ┌────────────────┐
          │    Imaging     │          │  Hepatobiliary │
          │  reviewed by   │          │  MDT to decide │
          │  appropriate   │          │  on further    │
          │ anatomical site│          │    imaging     │
          │  specific MDT  │          └───────┬────────┘
          └───────┬────────┘                  │
                  └──────────────┬────────────┘
                                 ▼
```

Patient information and support

```
                      ◇ Is metastatic disease ◇
         Yes ────────◇ operable/potentially   ◇──────── No
                      ◇ operable after         ◇
                      ◇ appropriate treatment? ◇
          │                                           │
          ▼                                           ▼
┌────────────────────┐              ┌──────────────────────────────┐
│ Refer to anatomical│              │ Consider one of the following│
│ site-specific MDT  │              │ sequences unless clinically  │
│ to consider        │              │ contraindicated:             │
│ preoperative       │              │ - FOLFOX followed by single  │
│ systemic treatment │              │   agent irinotecan **or**    │
└────────────────────┘              │ - FOLFOX followed by FOLFIRI[2]│
                                    │ **or**                       │
                                    │ - XELOX followed by FOLFIRI[2]│
                                    │                              │
                                    │ Offer raltitrexed only if    │
                                    │ 5FU/FA is contraindicated    │
                                    └──────────────────────────────┘
```

[1] Recommendations from TA61, TA118, TA176 and TA212 are also relevant to this group of patients
[2] At the time of publication (November 2011), irinotecan did not have UK marketing authorisation for second-line combination therapy. Informed consent should be obtained and documented.

1 Epidemiology

1.1 Introduction

The following chapter provides a summary of the full needs assessment that was carried out as part of the evidence review for this guideline. It includes information regarding the epidemiology of colorectal cancer regionally, nationally and internationally. This guideline is not a comprehensive review of all aspects of colorectal cancer management but is limited to priority areas that were identified before and during the scoping exercise that were thought to be key topics that might help improve the overall standard and equity of care provided geographically. The purpose of this chapter therefore is to provide the context for the guideline, to describe the burden of disease and to assess whether variation exists in the treatment and outcome for individuals with colorectal cancer in England and Wales.

Health needs assessment is a systematic method for reviewing the health issues facing a population, leading to agreed priorities and resource allocation that will improve health and reduce inequalities. It is recommended in various policy documents to inform and aid their better development as well as aid future strategic planning and implementation (Hooper and Longworth, 2006).

A baseline need assessment should include information on: 1) the epidemiology of the disease and 2) current UK practice. The aim is to identify any concerning variability that exists in the management of the disease in order to help the guideline development group (GDG) members shape the guidance and identify recommendations that are likely to have the greatest impact on clinical outcomes (NICE, 2009).

1.2 Risk factors for colorectal cancer

Cancer is a major cause of morbidity in the UK. One in three people will develop some form of cancer during their lifetime. It can develop at any age but is most common in older people. Around three-quarters of cases occur in people aged 60 and over (74%) and more than a third of cases in people aged 75 and over. Life expectancy in the UK is increasing, with more elderly people alive today than ever before. In 2002, a woman aged 65 could expect to live to the age of 84, while a man could expect to live to 82 (Office for National Statistics (ONS), 2005; Welsh Cancer Intelligence and Surveillance Unit (WCISU), 2002; Information and Statistics Division (ISD) online, 2008a; Fitzpatrick, 2004; Quinn, 2000).

Colorectal cancer includes cancerous growths in the colon, rectum and appendix. Most colorectal cancers arise from adenomatous polyps. These neoplasms are usually benign, but some develop into cancer over time. The occurrence of large bowel cancer is strongly related to age, with 83% of cases arising in people who are 60 years or older. It is a common form of malignancy in developed countries but occurs much less frequently in the developing world (ONS, 2008a; WCISU, 2008; Northern Ireland Cancer Registry, 2008).

An individual's risk of developing cancer depends on many factors, including smoking, diet and genetic inheritance. It is also dependent on increasing age (ONS, 2005; WCISU, 2002; ISD online, 2008a; Fitzpatrick, 2004; Quinn, 2000; ONS, 2004). A diet with a high intake of red and processed meat, inactivity, as well as a high alcohol intake increases the chances of developing colorectal cancer. Other known risk factors are obesity with at least 10% of colon cancers in the UK related to obesity. In addition people with a first degree relative with bowel cancer are at twice the average risk of developing it themselves. In contrast, high fibre content in the diet has been shown to reduce the risk of colorectal cancer and a protective

effect is also seen with regular use of non-steroidal anti-inflammatory drugs where more than 10 years regular use reduces the risk of colorectal cancer (Boyle and Langham 2000).

1.3 Incidence

The incidence of cancer for the UK population refers to the number of new cancer cases arising in a specified period of time. Each year around 289,000 people are newly diagnosed with cancer and breast, lung, colorectal and prostate cancer account for over half of all the new cases (Figure 1.1) (ONS, 2008a; ISD online, 2008a, WCISU, 2008; Northern Ireland Cancer Registry, 2008). The ten most common cancers in males and females diagnosed in the UK in 2005 are presented in Figures 1.2 and 1.3. If current cancer incidence rates remain the same, by 2025 there will be an additional 100,000 cases of cancer diagnosed each year as a result of the ageing population (Cancer Research UK Statistical Information, 2008).

Figure 1.1 The 20 most commonly diagnosed cancers (ex non melanoma skin cancer)
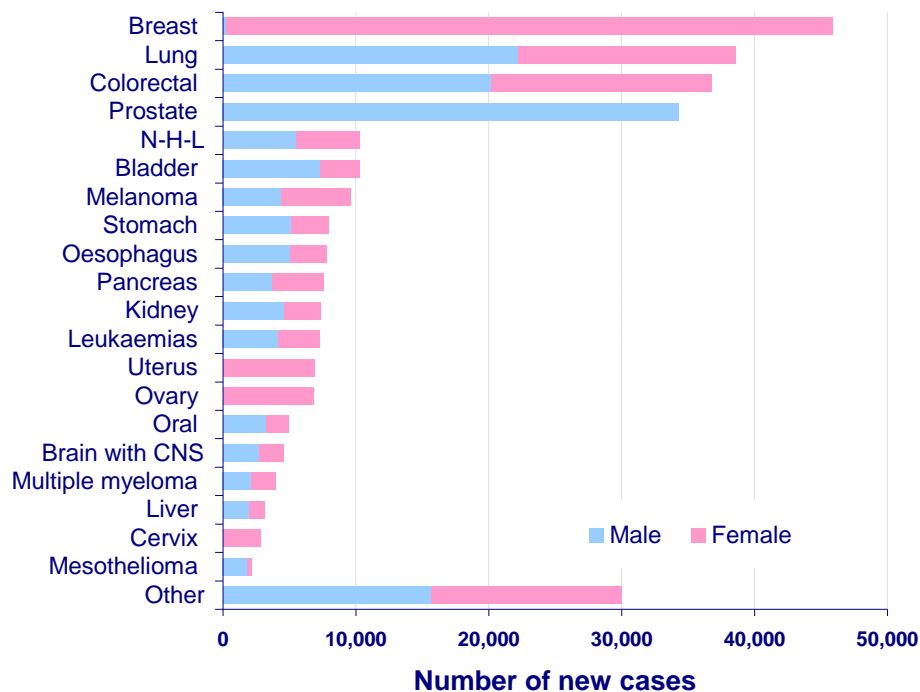
Figure 1.2 The ten most common cancers, females, UK, 2005

Other 22%
Breast 32%
Bladder 2%
Leukaemias 2%
Pancreas 3%
N-H-L 3%
Melanoma 4%
Ovary 5%
Uterus 5%
Colorectal 11%
Lung 11%

All female cancers (exc NMSC): 144,756
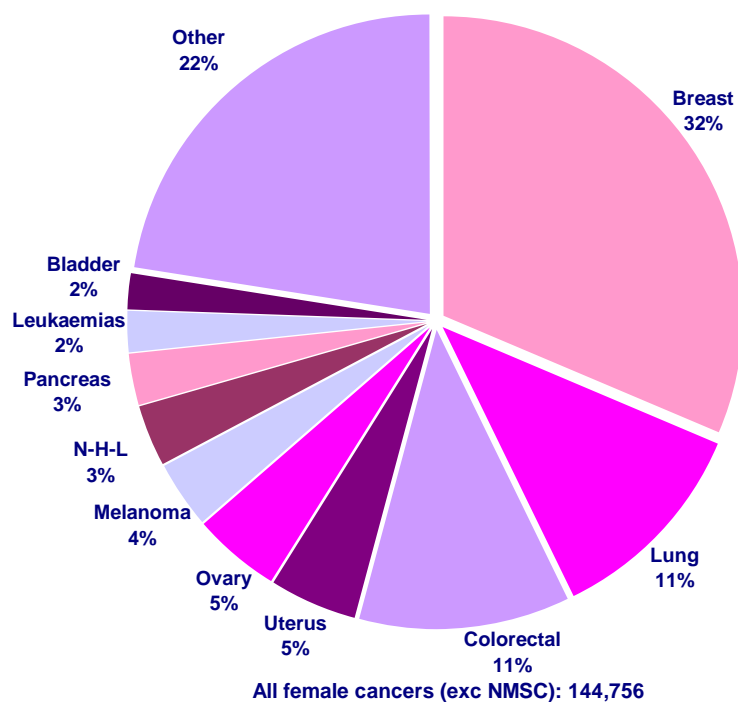
Figure 1.3 The ten most common cancers, males, UK, 2005

Other 22%
Prostate 24%
Melanoma 3%
Leukaemias 3%
Kidney 3%
Oesophagus 3%
Stomach 4%
N-H-L 4%
Bladder 5%
Colorectal 14%
Lung 15%

All male cancers (exc NMSC): 144,351

The diagnosis and management of colorectal cancer: full guideline (November 2011)
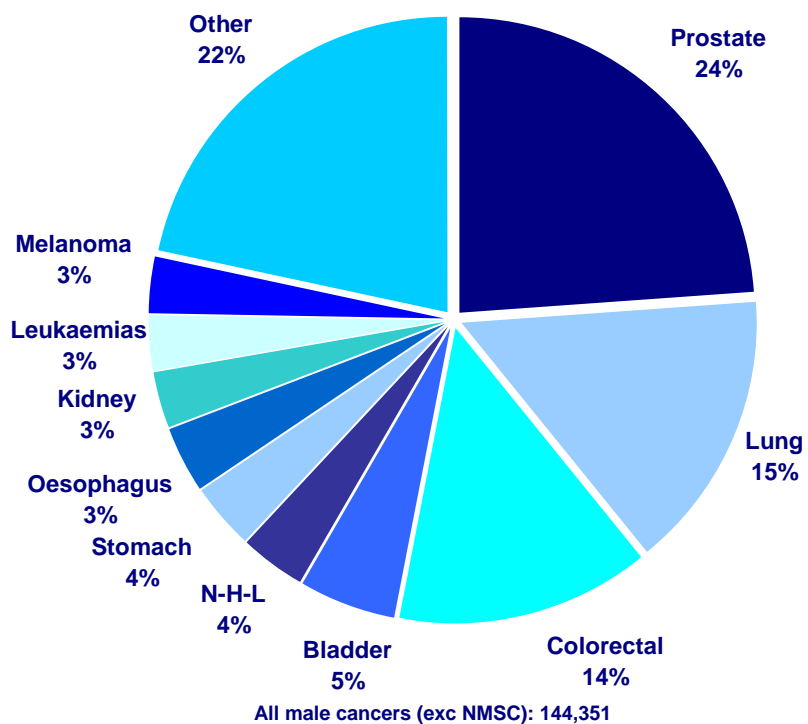
Colorectal cancer is the third most common cancer in the UK after breast and lung. Around 100 new cases of colorectal cancer are diagnosed each day in the UK. In 2005 there were 36,766 new cases of large bowel cancer registered in the UK; around two-thirds (22,748) in the colon and one-third (14,018) in the rectum. The left side of the bowel is affected by cancer more often than the right. Tumours in the sigmoid colon, rectosigmoid junction and in the rectum (Figure 1.4) together account for over half of all cases (ONS, 2008a; WCISU, 2008; Northern Ireland Cancer Registry, 2008).

Figure 1.4 Percentage distribution of cases by site within the large bowel, England, 1997-2000
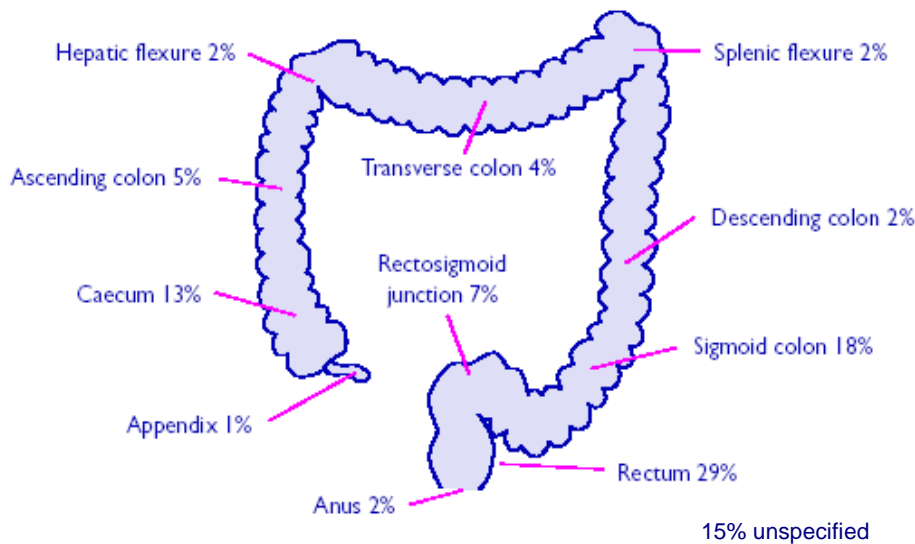
Colorectal cancer is the second most common cancer in women after breast cancer (see Figure 1.2), with around 16,500 new cases diagnosed each year. More than 20,000 men are diagnosed with bowel cancer in the UK each year making it the third most common cancer in men after prostate and lung cancer (see Figure 1.3).

Almost three-quarters of colorectal cancer cases occur in people aged 65 and over (Figure 1.5). Until age 50, men and women have similar rates for colorectal cancer, but in later life male rates predominate. In numerical terms, there are more male cases of bowel cancer up to the age of 80, after which female cases are in the majority, even though their rates are lower, as women make up a larger proportion of the elderly population. Overall the male: female ratio is 1.2:1.0.

Using England and Wales data, the lifetime risk for men of being diagnosed with colorectal cancer is estimated to be 1 in 18 and for women 1 in 20.6

Figure 1.5 Number of new cases and age-specific incidence rates by sex, colorectal cancer, UK, 2005
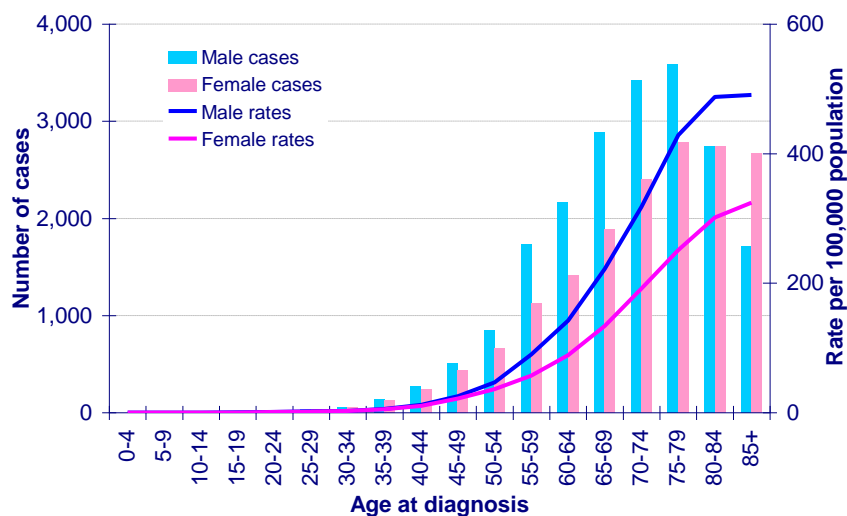
Colorectal cancer incidence rates have remained relatively stable for over a decade. A recent geographical analysis of cancer incidence in the UK and Ireland (Figure 1.6), showed that the geographical distribution was similar for colon and rectal cancer and that on the whole the variation was relatively small (National Statistics Online, 2004). The comparison across England, Wales, Scotland and Northern Ireland shows no obvious difference in incidence for colorectal cancer (ONS, 2008a; WCISU, 2008; Northern Ireland Cancer Registry, 2008).

Figure 1.6 Age standardised incidence rates by sex, colorectal cancer, regions of England, Wales, Scotland, Northern Ireland and Ireland, 1991-1999
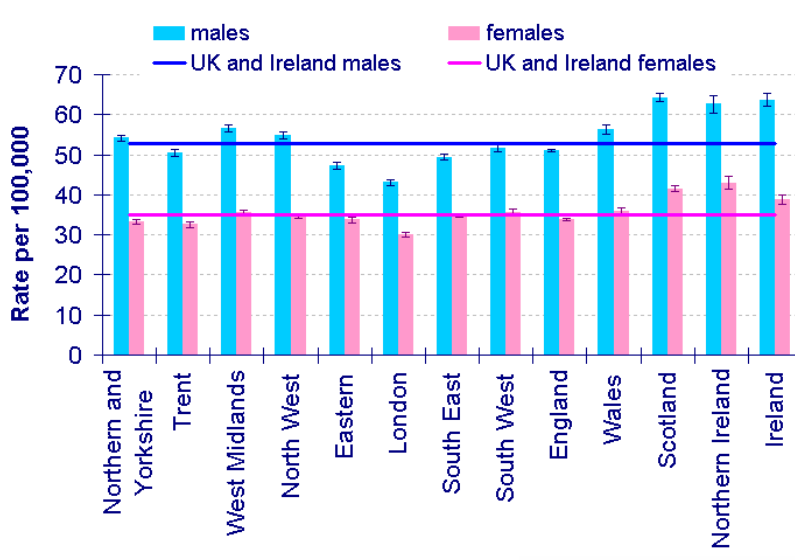
Worldwide there were around 11 million new cases of cancer in 2002 and a quarter of these were in Europe. Over a million of all new cases were colorectal cancers (9% of all new cancer cases). The lowest incidence rates of colorectal cancer are seen in South Central Asia, and Eastern, Western, Northern and Middle African countries. The highest rates are in Europe, North America and Australasia (International Agency for Research on Cancer, 2002).

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In general there are no strong socio-economic deprivation gradients reported for colorectal cancer incidence. However, data for England and Wales patients diagnosed in 1992 and 1993 did show a deprivation gradient for male rectal cancer patients with incidence rates 25% higher in the most deprived groups than in the affluent groups (Quinn *et al.*, 2001).

1.4   Mortality

In the UK in 2006, there were 154,162 deaths from cancer which represented approximately one in four (27%) of all deaths in the UK (Figure 1.7). Deaths from cancers of the lung, bowel, breast and prostate together account for 47% of all cancer deaths (ONS, 2006; General Register Office for Scorland, 2007; Northern Ireland Cancer Registry, 2008). The ten most common causes of cancer deaths in males and females in the UK in 2006 are presented in Figures 1.8 and 1.9.

Figure 1.7 The 20 most common causes of death from cancer, UK, 2006
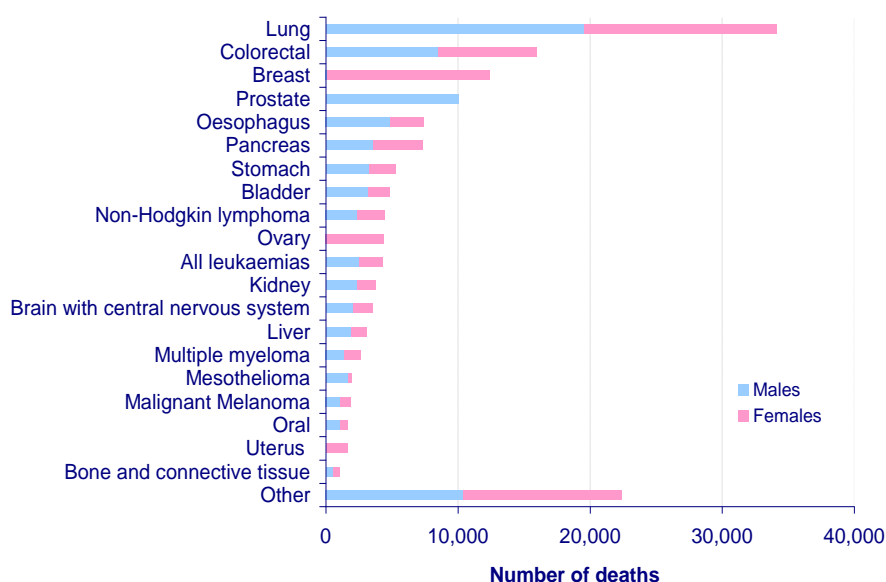
Figure 1.8 The 10 most common causes of cancer death, males, UK, 2006

All malignant neoplasms - 80,541

The diagnosis ar
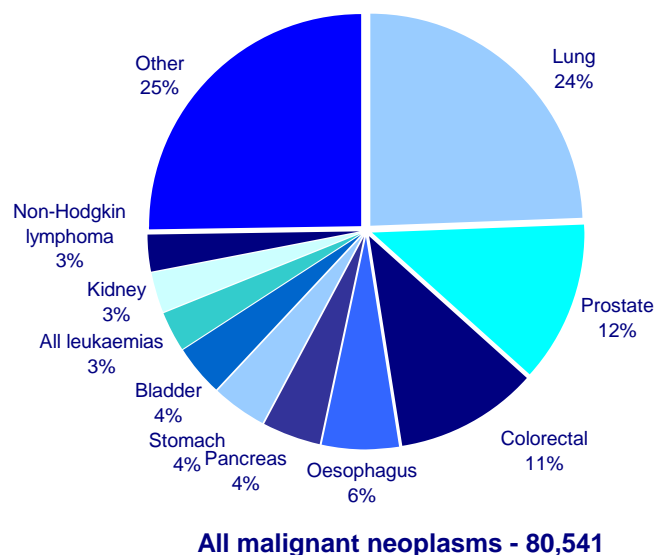
Figure 1.9 The 10 most common causes of cancer death, females, UK, 2006

All malignant neoplasms - 73,621
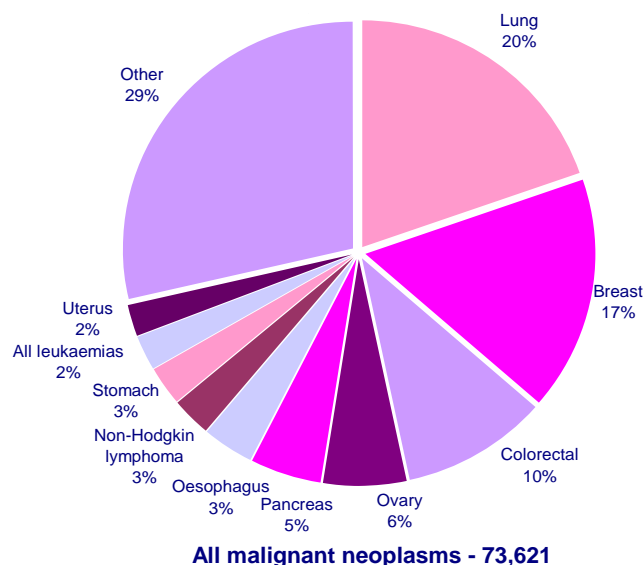
Colorectal cancer was the second most common cause of cancer death (10%) after lung cancer in the UK in 2006 (see Figure 1.7). In total there were 15,957 deaths from colorectal cancer comprising 10,119 from colon and 5,838 from rectal cancer. Colorectal cancer caused 8,511 deaths in men in 2006, accounting for 11% of all male cancer mortality. Colorectal cancer was responsible for 7,446 deaths and 10% of all cancer deaths in females (ONS 2008b; Northern Ireland Cancer Registry, 2008; ISD online, 2008) (see Figure 1.8 and 1.9).

The majority of deaths from cancer occur in the elderly. More than three quarters of cancer deaths (76%) occur in people aged 65 years and over.

The cancer death rates rise with increasing age. Although there is a higher number of cancer deaths in the over 65s, cancer causes a greater proportion of deaths in younger people. Cancer caused a quarter of deaths in the over 65s in the UK in 2006, whereas cancer was responsible for more than a third (36%) of all deaths in the under 65s. In females under the age of 65 cancer causes 45% of deaths, while in males it is only 30%.

In people under the age of 75 years in the UK in 2006, deaths from cancer continued to outnumber deaths from diseases of the circulatory system (which includes heart disease and stroke) and diseases of the respiratory system. The overall cancer death rate has fallen by 10% over the last decade around 12% for men and 9% for women (ONS, 2006; General Register Office for Scotland, 2007; Northern Ireland Cancer Registry, 2008).

Similar to the overall cancer trend, 80% of colorectal cancer deaths occurred in people aged 65 and over and almost two-fifths in the over 80s (Figure 1.10). In contrast to incidence trends, colorectal cancer mortality has been falling fairly continuously since the early 1990s (Figure 1.11).

Colorectal cancer mortality rates are substantially higher in men than in women – 23 per 100,000 males compared with 14 per 100,000 females in 2006.

Figure 1.10 Number of deaths and age-specific mortality rates, colorectal cancer, by sex, UK, 2006
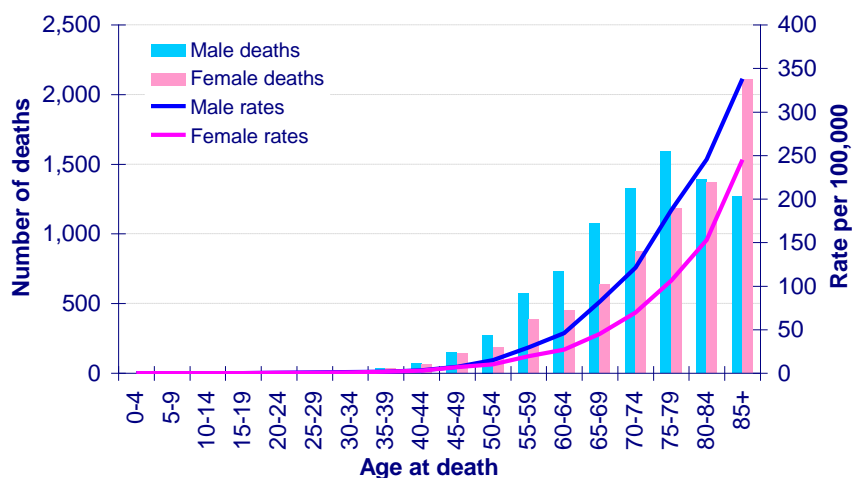
Figure 1.11 Age standardised incidence and mortality rates by sex, colorectal cancer, UK, 1975-2005
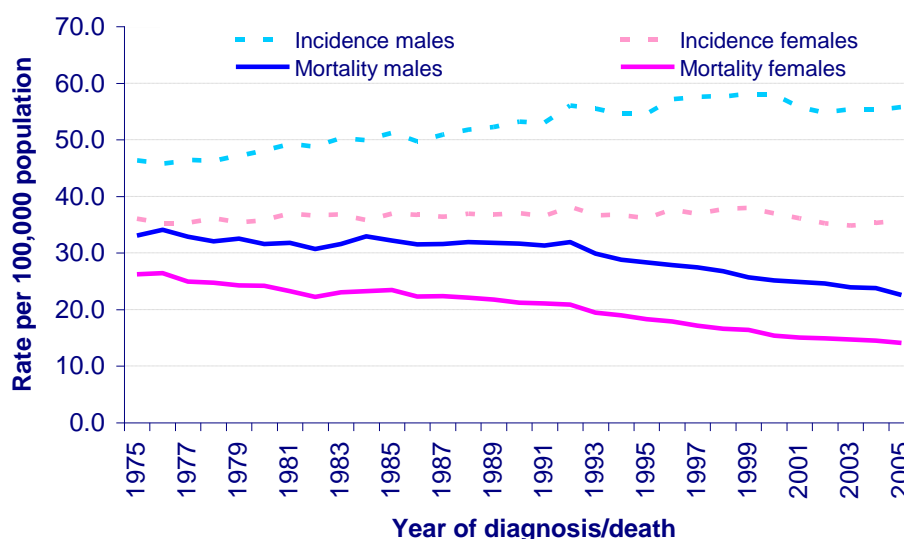
In the ten years between 1997 and 2006 (Figure 1.12), the colorectal cancer age-standardised mortality rates in the UK fell by 17%. This fall in mortality affected all age groups with the largest fall in the 40–69 age groups for men and the 55-79 age groups for women. Colorectal cancer mortality rates started to decrease in 1988 and since then the male rate has fallen by 30% and the female rate by more than a third (36%) (ONS, 2008b; Northern Ireland Cancer Registry, 2008; ISD online, 2008a).

Figure 1.12 percentage decrease in mortality rates, colorectal cancer, by age and sex, UK, 1997-2006
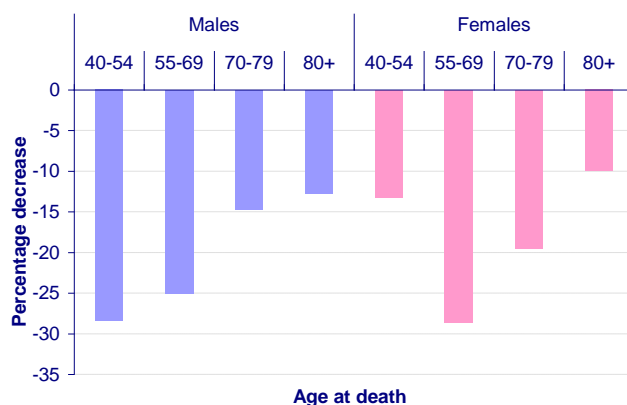
Within England, bowel cancer mortality rates are generally higher in the north of the country (Quinn *et al.*, 2005).

Worldwide colorectal cancer kills around half a million people each year. Two-thirds of these deaths are in the more developed regions. Colorectal mortality rates have been declining in most European countries from the 1990s onwards and further falls are expected (Fernandez *et al.*, 2005).

1.5   Survival

Survival is stage dependant (Table 1.1) and has improved for most cancers in both sexes during the1990s (ONS, 2003; ISD, 2008; WCISU, 2003; Northern Ireland Cancer Registry, 2008). There have been similar and significant improvements in survival for both colon and rectal cancer over the last 25 years (Coleman *et al.*, 2004). The five-year relative survival rates (Figure 1.13) for both male and female colon and rectal cancer have doubled between the early 1970s and early 2000 (Coleman *et al.*, 1999; Coleman *et al.*, 2000; Cancer Research UK, 2009).

Table 1.1 Approximate frequency and five year relative survival (%) by TNM stage (5th Edition)

TNM Stage	Approximate frequency at diagnosis	Approximate five-year survival
I	11%	83%
II	35%	64%
III	26%	38%
IV	28%	3%

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Figure 1.13 Five year survival (%) of patients diagnosed with colorectal cancer, 1996-1999, England and Wales.
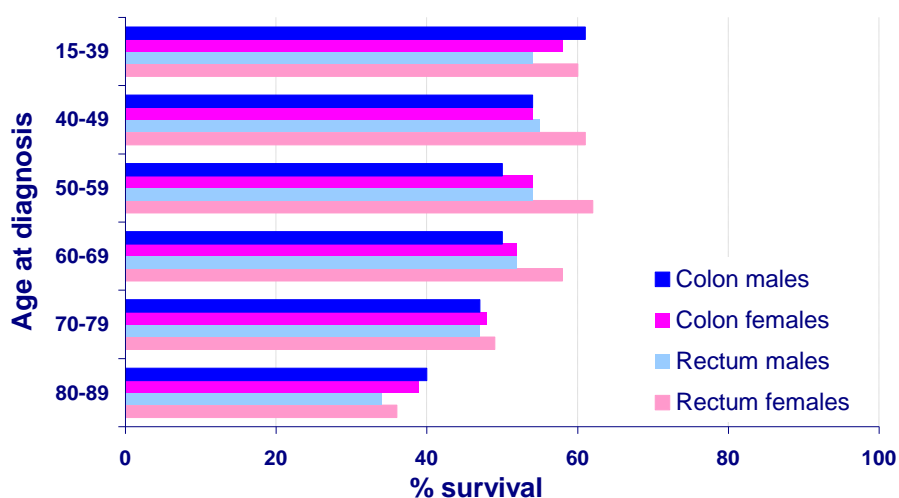
Five-year relative survival for male colon cancer rose from 22% in the early 1970s to 52% in early 2000 (Figure 1.14) for females it rose from 23% to 53% (Figure 1.15). Five-year survival rates for male rectal cancer rose from 25% in the early 1970s to 50% in early 2000 (Figure 1.16) and from 27% to 52% for female rectal cancer (Figure 1.17). On average, increases in five-year survival of around 4% every five years for colon cancer and around 5-6% for cancer of the rectum occurred in both men and women. Ten-year survival rates are only a little lower than those at five-years indicating that most patients who survive for five years are cured from this disease (Cancer Research UK, 2009). These improvements are a result of earlier diagnosis and better treatment but there is still much scope for further progress. Younger bowel cancer patients have a better prognosis than older patients (Coleman *et al*., 1999; Coleman *et al*., 2000; Cancer Research UK, 2009).

Figure 1.14 Age standardised relative survival in men diagnosed with colon cancer, England and Wales, 1986-1999

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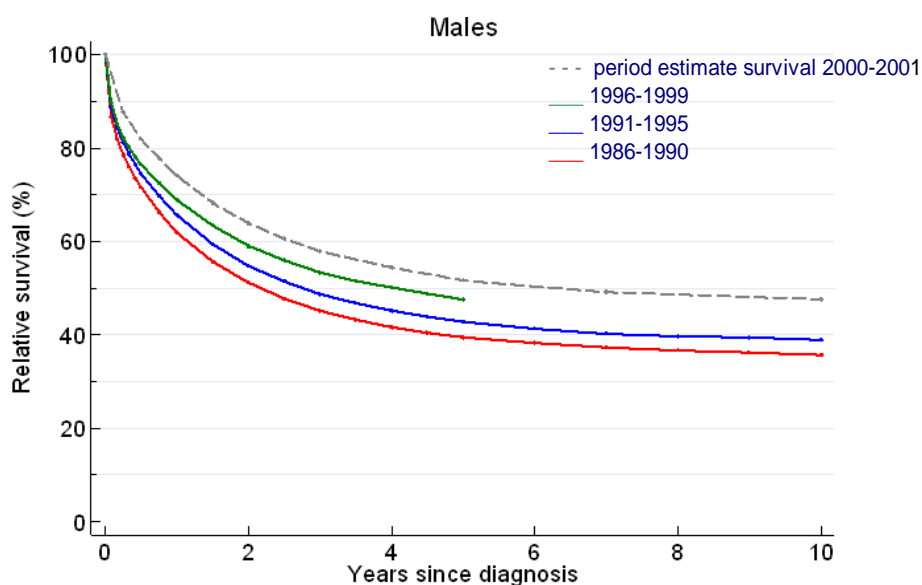
Figure 1.15 Age standardised relative survival in women diagnosed with colon cancer, England and Wales, 1986-1999
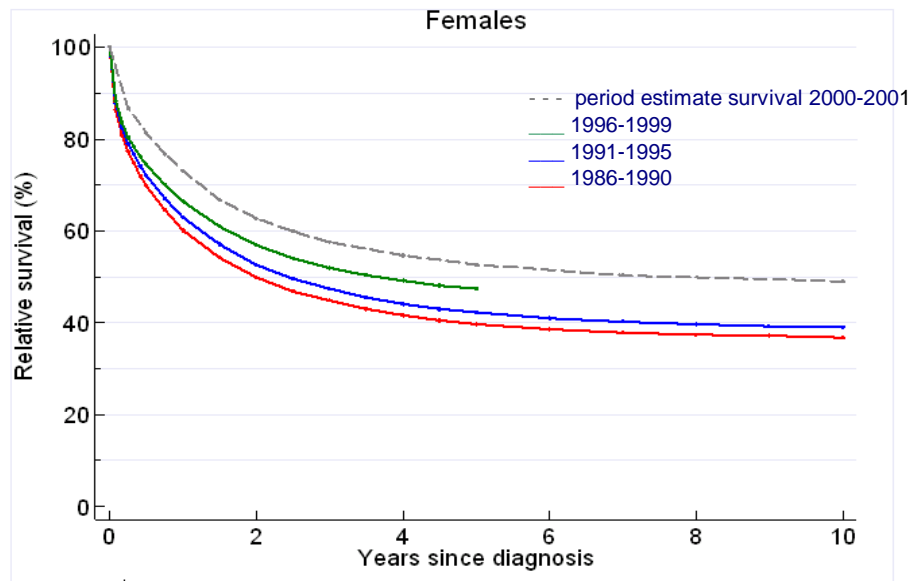
Figure 1.16 Age standardised relative survival in men diagnosed with rectal cancer, England and Wales, 1986-1999
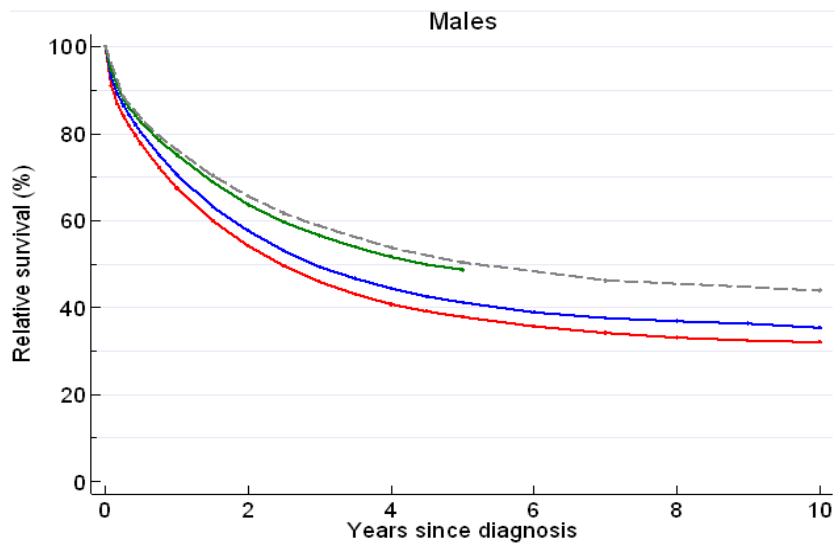
Figure 1.17 Age standardised relative survival in women diagnosed with rectal cancer, England and Wales, 1986-1999
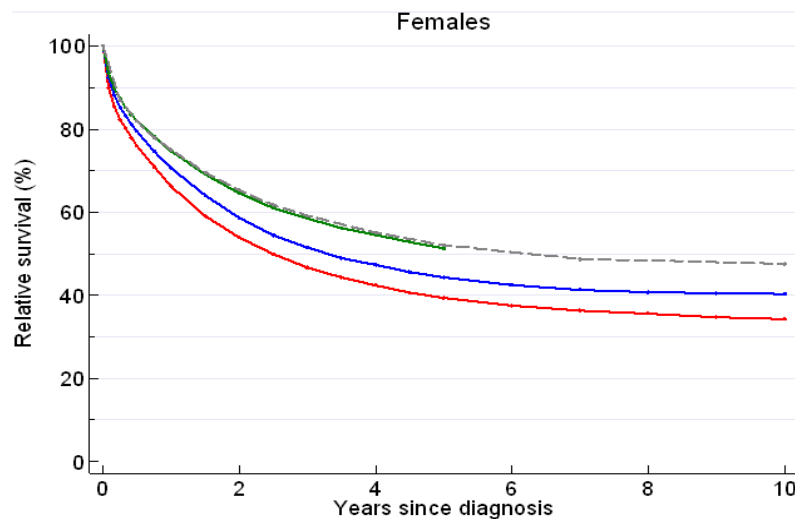
There is also an advantage of between 5% and 9% in five-year relative survival for the most affluent patients compared with the most deprived groups (Coleman *et al.*, 2004). If this deprivation difference was removed so that all groups had the highest survival, then over 2,000 deaths would be avoided in the five years following diagnosis (Coleman *et al.*, 1999)

1.6   Prevalence

Cancer prevalence refers to the total number of people in the population who have previously received a diagnosis of cancer and who are still alive at a given time point. Some of these patients will have been cured and others will not. Therefore prevalence reflects both the incidence of cancer and its associated survival pattern.

Overall, it is estimated that there are now 2 million cancer survivors in the UK, or approximately 3.3% of the population of the UK (Table 1.2) (Maddams *et al.*, 2008). This figure is rising at an estimated 3.2% per year. Overall, 10% of the total UK population over the age of 65 years is now a cancer survivor.

These latest estimates are much higher than previous forecasts of cancer prevalence (Forman *et al.*, 2003). This is mainly because incidence has been rising whilst better survival rates have contributed to falling death rates. This trend is expected to continue over the coming years as a result of a number of factors, including an ageing population, earlier detection of cancer and continued improvements in treatment.

Table 1.2 UK estimates of total cancer prevalence

	UK 2008 estimates (based on diagnoses 1971-2004 applied to 2008 population; Thames Cancer Registry, 2008)
Breast (female)	550,000
Large bowel	250,000
Prostate	215,000
Lung	65,000
Other	920,000
All cancers	2,000,000

As the incidence of bowel cancer is high and survival rates have doubled over the last 30 years there are many people alive today who have been diagnosed with bowel cancer. An estimated 250,000 people are alive in the UK having received a diagnosis of bowel cancer. The NHS Bowel Screening Programme which has now been rolled out nationally will dramatically influence the epidemiology of the disease and it will increase prevalence with more patients being diagnosed earlier and at an earlier stage giving them better prognosis and therefore increasing the prevalence of the disease. There could be up to 20,000 fewer deaths from bowel cancer over the next 20 years if just 60% of those eligible take up the invitation for bowel screening (Maddams *et al.*, 2008).

All graphs were produced by the Cancer Research UK statistical information team with data from the Office of National Statistics'

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2   Investigation, diagnosis and staging

The objectives of this chapter were to determine:
- the most effective diagnostic intervention(s) for patients with suspected colorectal cancer to establish a diagnosis
- the most effective technique(s) to accurately stage disease in patients diagnosed with primary colorectal cancer.

2.1   Diagnostic investigations

Fewer than 10% of patients referred to NHS out-patient clinics on suspicion of symptomatic colorectal cancer are diagnosed with the condition. Patients are typically aged >55 years, with a high prevalence of co-morbidities which may increase the risk of complications and influence patients' and clinicians' choice of diagnostic intervention.

This section deals with patients whose condition is being managed in secondary care. It does not deal with triage systems for referrals directly from primary care that may include flexible sigmoidoscopy as the first test. Some of the patients discussed below may already have undergone investigations initiated by their general practitioner. Recommendations for urgent referral from primary care for patients with suspected colorectal cancer can be found in 'Referral guidelines for suspected cancer' NICE clinical guideline 27[7].

The aim of investigation is to achieve adequate examination of the entire colon and rectum. Effective diagnostic interventions in symptomatic patients suspected of having colorectal cancer need to have very high sensitivity (Box 2.1) for the detection of cancers and acceptable sensitivity for detection of adenomas with significant potential for malignant transformation. They must also have high specificity, be as safe as possible and be acceptable to patients, as all these investigations are unpleasant and invasive.

Box 2.1 Definitions of sensitivity and specificity

> *Sensitivity:* a diagnostic intervention with very high sensitivity will detect the vast majority of patients with colorectal cancer and very few patients with the disease will be missed.
>
> *Specificity:* a diagnostic intervention with very high specificity will identify only those patients who truly have colorectal cancer and it will not falsely identify as positive, those patients who do not have the disease.

Historically, a number of different diagnostic interventions have been used to detect colorectal cancer, often guided by local expertise and preference. These interventions are colonoscopy, barium enema/flexible sigmoidoscopy and CT colonography. However the optimum diagnostic strategy for colorectal cancer has not yet been defined.

All initial diagnostic investigations require rigorous bowel cleansing preparation. Colonoscopy has for many years been regarded as the reference standard for diagnosing colonic pathology. Colonoscopy is known to have high sensitivity and specificity for detection of cancer, pre-malignant adenomas and other symptomatic colonic diseases. Colonoscopy also has the facility to take a biopsy from any suspected lesion (thereby increasing diagnostic accuracy and also permits complete removal of most benign lesions during the same procedure. However, it may not be possible to perform complete colonoscopy in a proportion of patients due to inadequate bowel preparation, poor tolerance of the procedure, inter-operator variation in terms of completion rate or the presence of an obstructing lesion in

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[7] www.nice.org.uk/guidance/CG27

the distal colon. Patients with serious cardiorespiratory or neurological co-morbidity may be at high risk from potential complications of colonoscopy (for example colonic perforation, effects of sedation). Such patients might be better served by alternative investigations.

Barium enema is a long-established radiological investigation of the colon and rectum offering completion rates higher than those historically recorded for colonoscopy, without the need for patient sedation and with a lower incidence of serious complications. However, there is limited published evidence of the diagnostic accuracy of barium enema and there is concern that it is less sensitive than colonoscopy. This has led many centres to offer patients a combined investigative pathway of flexible sigmoidoscopy (endoscopic examination of the distal large bowel) followed by barium enema. There is a perception that this combination has comparable sensitivity to colonoscopy for detection of cancer. This investigative route also allows biopsy of lesions detected during flexible sigmoidoscopy.

Computerised tomography colonography (CT colonography) is a more recent radiological investigation in which cross-sectional images of the abdomen and pelvis are obtained following laxative preparation and insufflation of the large bowel with air or carbon dioxide. The images are then analysed using 2-D and 3-D image reconstruction techniques. Colonoscopy can be performed at a later date to obtain biopsy confirmation of suspected tumours. It is thought that CT colonography may approach the sensitivity of colonoscopy for detection of larger polyps (>1cm). By inference, CT colonography may therefore have high sensitivity for cancer detection, but no study of sufficient statistical power has been published that supports this inference. Some studies of CT colonography suggest large variations in performance between individual operators and different centres. Reported complication and completion rates for CT colonography compare favourably with those for colonoscopy. The technique is substantially less invasive than colonoscopy and does not require patient sedation. In addition to allowing interrogation of the large bowel, CT colonography produces images of all the abdominal and pelvic organs, and this can result in clinically important chance findings of abnormalities at other sites.

When a patient is referred for investigation of symptoms suspicious of colorectal cancer, to maximise the benefit of the diagnostic intervention it is essential that the initial clinical consultation includes:
- accurate recording of the nature and duration of symptoms
- with the patient's consent, thorough digital examination of the rectum and palpation of the abdomen
- accurate recording of significant comorbidities which may increase the risks arising from investigative procedures
- explanation of the investigations which may be offered, including the morbidity, risks and benefits
- discussion of the patient's preferences.

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

Clinical evidence
The volume of evidence 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 sigmoidoscopy plus barium enema. No evidence was available for flexible sigmoidoscopy plus colonoscopy.

From two systematic reviews and meta-analysis (Chaparro *et al.*, 2009; 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 *et al.* (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: 53-87%]. 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 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 flexible sigmoidoscopy plus air contrast barium enema 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. Flexible sigmoidoscopy plus air contrast barium enema 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 (Rex *et al.*, 1990) 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 flexible sigmoidoscopy plus air contrast barium enema 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]).

Recommendations

- Advise the patient that more than one investigation may be necessary to confirm or exclude a diagnosis of colorectal cancer.
- Offer colonoscopy to patients without major comorbidity, to confirm a diagnosis of colorectal cancer. If a lesion suspicious of cancer is detected, perform a biopsy to obtain histological proof of diagnosis, unless it is contraindicated (for example, patients with a blood clotting disorder).
- Offer flexible sigmoidoscopy then barium enema for patients with major comorbidity. If a lesion suspicious of cancer is detected, perform a biopsy unless it is contraindicated.
- Consider computed tomographic (CT) colonography as an alternative to colonoscopy or flexible sigmoidoscopy then barium enema, if the local radiology service can demonstrate competency in this technique. If a lesion suspicious of cancer is detected on CT colonography, offer a colonoscopy with biopsy to confirm the diagnosis, unless it is contraindicated.
- Offer patients who have had an incomplete colonoscopy:
  o repeat colonoscopy **or**
  o CT colonography, if the local radiology service can demonstrate competency in this technique **or**
  o barium enema.

Linking evidence to recommendations

The GDG considered true positive or true negative diagnoses of colorectal cancer to be the most important outcomes for this question. True negative results were also considered important because the large majority of patients referred will not have colorectal cancer. Avoidance of false negative results was also important, but in a population with low incidence of colorectal cancer, the absolute risk of a false-negative diagnosis of colorectal cancer will be small.

The GDG noted that investigation (particularly with CT colonography) may result in diagnoses of conditions other than colorectal cancer. The GDG was unable to find sufficient evidence of benefit or harm to attach a relative significance to this outcome.

There were few studies of high quality that directly compared two or more of the investigations of interest. Many of the studies of CT colonography were performed on asymptomatic patients or used detection of polyps, rather than colorectal cancer, as the primary end-point.

The GDG concluded that colonoscopy has the highest clinical efficacy for diagnosis of colorectal tumours, but is generally considered more invasive and has higher morbidity than CT colonography or barium enema. Completion rates may vary considerably due to patient factors and operator expertise. Colonoscopy permits immediate biopsy confirmation of colorectal cancer; adenomas may also be removed during the same procedure. Therefore the GDG recommended colonoscopy as the first investigation for the diagnosis of colorectal tumours. The GDG recognised that diagnostic colonoscopy might fail because of a variety of reasons for example poor bowel preparation and felt that in certain circumstances a repeat procedure might be appropriate.

The GDG noted that several studies suggest that CT colonography is as sensitive as colonoscopy for detection of polyps >9mm in diameter. However they noted that there was no evidence of equivalent sensitivity between CT colonography and colonoscopy for the detection of colorectal cancer. The GDG was also concerned by variability in diagnostic performance between operators and institutions. The GDG were aware that CT colonography appears at face value to carry a higher risk of colonic perforation than colonoscopy, however the GDG considered that this observation may be explained by its

superior ability to detect small, clinically inconsequential perforations which cannot be seen on colonoscopy. The GDG therefore recommended CT colonography as an alternative to colonoscopy.

The GDG recognised that published studies indicate that flexible sigmoidoscopy combined with barium enema is almost as sensitive as colonoscopy for detection of colorectal cancer. However the GDG noted that this combination has much poorer specificity. Morbidity is lower than for colonoscopy but involves multiple investigations in sequence. Both barium enema and CT colonography entail exposure to ionising radiation. This is potentially harmful, particularly to young patients. However, as the majority of patients undergoing investigation are aged over 55 and ongoing technical developments are enabling substantial reduction in dose, the GDG saw this as a relatively minor concern.

The GDG agreed that colonoscopy and the package of flexible sigmoidoscopy then barium enema were widely available, and that CT colonography was becoming increasingly available as more practitioners gain expertise in its use. They therefore decided that availability was not a significant factor in what modality should be recommended.

No existing published economic studies that included all the interventions and comparators of interest were identified. The GDG considered undertaking a cost-effectiveness modelling exercise for this topic but agreed that it would be difficult to construct a model structure that appropriately took into account all downstream events beyond test accuracy. In addition it was noted that results of a prospective trial conducted in the UK (SIGGAR1) were anticipated. This study was designed to compare colonography vs barium enema and CT colonography versus colonoscopy. The protocol for the SIGGAR1 study includes collection of data on subsequent tests and healthcare resource use as well as a planned cost-utility analysis. Given the overlap in timing and objectives of the planned economic analysis that is part of the SIGGAR1 study with any potential modelling efforts for this topic within the guideline, it was agreed that resources for economic modelling should be directed towards other higher priority topics.

2.2   Staging of colorectal cancer

Initial staging of newly diagnosed colorectal cancer involves an assessment of local spread and detection of the presence or absence of distant metastases. Historically, staging relied on contrast-enhanced CT, with the addition of digital rectal examination (DRE) for low rectal tumours. The introduction of new imaging modalities (particularly endorectal ultrasound (EUS), MRI and PET-CT) and variation in their uptake, quality and availability has meant there is no standard approach to staging colorectal cancer.

For the purpose of this guideline the GDG has adopted TNM5 to be in line with the Royal College of Pathologists (see Appendix 1).

In patients diagnosed with rectal cancer, local recurrence is a particular problem. Accurate pre-treatment staging for rectal cancer can both identify characteristics that predict for local recurrence and determine the appropriate treatment strategy to minimise local recurrence. The most important characteristic in determining the likelihood of local recurrence is the circumferential resection margin, which can be predicted by imaging. EUS and MRI have been used pre-treatment to assess encroachment on the circumferential resection margin (CRM) but there is uncertainty over which imaging modality is most effective and it is possible that the optimal modality may vary with the clinical situation.

Therefore the issues to be addressed are:
*   which modality(s) demonstrates distant metastases most accurately

- which modality is best for assessing T stage in rectal cancer
- which modality best defines the mesorectal fascia and predicts its anatomical relationship to the invading tumour in rectal cancer i.e. the CRM.

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

Clinical evidence

There were three systematic reviews of case series studies (Kwok *et al.*, 2000; Bipat *et al.*, 2004; Dighe *et al.*, 2010) and a large volume of low quality case series studies with which to address this topic (Akin *et al.*, 2004; Beets-Tan *et al.*, 2001; Beynon *et al.*, 1986; Bianchi *et al.*, 2005; Brown *et al.*, 2004; Brown *et al.*, 2003; Brown *et al.*, 1999; Chun *et al.*, 2006; Dirisamer *et al.*, 2010; Fillipone *et al.*, 2004; Fuchsjager *et al.*, 2003; Halefoglu *et al.*, 2008; Kantorova *et al.*, 2003; Kim *et al.*, 2007; Kim *et al.*, 2006; Kulinna *et al.*, 2004a; Kulinna *et al.*, 2004b; Llamas-Elvira *et al.*, 2007; Low *et al.*, 2003; Mainenti *et al.*, 2006; Mercury Study Group, 2007; Mercury Study Group, 2006; Nicholls *et al.*, 1982; Rafaelsen *et al.*, 1994; Rao *et al.*, 2007; Salerno *et al.*, 2009; Tatli *et al.*, 2006; Tateishi *et al.*, 2007).

The evidence body relating specifically to colon cancer was poor, with only a single systematic review available (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.

Colon cancer

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%].

Rectal cancer

For digital rectal exam, a total of 4 studies reported results (Beynon *et al.*, 1986; Mercury Study Group, 2006; Brown *et al.*, 2004; Rafaelson *et al.*, 1994). 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 endorectal sonography/endorectal ultrasound had the highest sensitivity, specificity and accuracy of the modalities investigated (CT, endorectal sonography/endorectal ultrasound and MRI). Kwok *et al.* (2000) reported a pooled sensitivity, specificity and accuracy for endorectal sonography 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 endorectal ultrasound of 94% and 86% respectively for muscularispropria invasion, 90% and 75% respectively for peri-rectal 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 peri-rectal tissue invasion and 66% and 76% respectively for lymph node involvement. For muscularispropria invasion, endorectal sonography specificity was significantly higher than that of MRI (p=0.02); for peri-rectal

tissue invasion, endorectal 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 (2006, 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 preoperative 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 preoperative 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 preoperative 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; 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.

Recommendations
- Offer contrast enhanced CT of the chest, abdomen and pelvis, to estimate the stage of disease, to all patients diagnosed with colorectal cancer unless it is contraindicated. No further routine imaging is needed for patients with colon cancer.
- Offer magnetic resonance imaging (MRI) to assess the risk of local recurrence, determined by anticipated resection margin, tumour and lymph node staging, to all patients with rectal cancer unless it is contraindicated.
- Offer endorectal ultrasound to patients with rectal cancer if MRI shows disease amenable to local excision or if MRI is contraindicated.
- Do not use the findings of a digital rectal examination as part of the staging assessment.

Linking evidence to recommendations

The GDG placed a high value on accurate staging at presentation because this information informs the optimum treatment strategy for patients with colorectal cancer. The evidence consisted of two good quality systematic reviews and several low-quality case series studies. The GDG noted that no study specifically addressed patients with colon cancer.

The GDG considered the imaging interventions themselves to have minimal side effects. However, they were aware that there were potential harms for patients who were incorrectly staged and therefore received sub-optimal treatment, possibly resulting in a higher risk of subsequent local recurrence or future morbidity associated with inappropriate treatment.

The GDG noted that there was no evidence that any of the imaging modalities investigated was superior at local staging for patients with colon cancer. The GDG decided not to make a specific recommendation regarding further imaging, as they agreed that all the relevant staging information would be provided by the initial CT scan

In patients with rectal cancer, the GDG were aware that the available evidence had shown EUS to have higher sensitivity, specificity and accuracy compared to MRI or CT for identifying those patients whose tumours are suitable for local resection. The GDG noted

that EUS is not appropriate in bulky, obstructing tumours and does not visualise the total extent of nodal disease in the pelvis. It was also noted that the evidence may reflect non-UK practice because EUS is not widely used in the UK. There was also significant inter-observer variation in the performance of EUS. The GDG therefore recommended MRI be used for the initial assessment of patients with rectal cancer and that EUS be considered if the MRI suggested disease which was amenable to local resection.

The GDG recognised that although DRE has a role in diagnosis and assessment of rectal cancer, evidence showed it is less sensitive and specific than the other modalities for staging rectal cancer. Therefore they recommended it was not used for staging.

This clinical question was considered a low priority for economic analysis because of the complexity that would be involved in downstream decisions which could vary according to the diagnostic interventions of interest (i.e. different interventions may provide different kinds of information to inform treatment decisions) and also because of the poor quality of available data to inform an economic analysis.

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3 Management of local disease

The objectives of this chapter were to determine:
- the effectiveness of short course preoperative radiotherapy or chemoradiotherapy in patients with operable rectal cancer
- whether preoperative chemotherapy followed by surgery was more effective than immediate surgery in patients presenting with non-metastatic locally advanced colon cancer
- whether preoperative radiotherapy, preoperative chemotherapy or preoperative chemoradiotherapy was more effective than immediate surgery in patients presenting with locally advanced rectal cancer
- whether all patients presenting with obstruction as a first symptom of colorectal cancer should have a CT scan to confirm diagnosis and provide evidence of metastases and to identify the indications for stenting these patients and the optimal timing for stenting to occur
- whether the use of prognostic factors can determine the most effective curative treatment in patients who have undergone local excision (with/without neoadjuvant treatment for low rectal tumours) and been diagnosed with stage I colorectal cancer (including/or polyp cancer)
- the effectiveness of adjuvant chemotherapy following surgery in patients with clinical or pathological stage II and III rectal cancer
- the effectiveness of adjuvant chemotherapy after surgery on patients with high risk stage II colon cancer.

3.1 Preoperative management of the patient's primary tumour

3.1.1 Patients whose primary rectal tumour appears resectable at presentation
The National Bowel Cancer Audit Programme (NBOCAP, 2005)[8] report recognised that the positive circumferential resection margin rates for anterior resection by total mesorectal excision (TME) and abdomino-perineal resection (APR) were 6.5% and 15.6%, respectively (assuming all missing values were negative). The inference from these results is that many patients with rectal cancer are understaged prior to surgery and/or the chosen treatment strategy was either inappropriate or suboptimal.

The effectiveness of any form of preoperative therapy is dependent on the subsequent quality of surgery. TME is the accepted standard resection for most rectal cancers. Low rectal tumours may require an APR. The value of neoadjuvant therapy for low rectal tumours is debatable at present and requires further evaluation.

The gains in local control from preoperative radiotherapy are well established but they need to be balanced against the significant late effects in terms of sexual, urinary and bowel dysfunction and the potential risk of second malignancies. Although preoperative chemoradiotherapy and short-course preoperative radiotherapy (SCPRT) are widely used to reduce the risks of local recurrence over surgery alone, and have similar biological equivalent radiation dose, there is uncertainty over which schedule to use in which particular clinical setting. SCPRT is a brief (typically 5 days) treatment with high dose per fraction radiotherapy. Short term side effects are minimal though there is some risk from long-term morbidity. Chemoradiotherapy involves a protracted (minimum of 5 weeks) course of radiotherapy with concomitant chemotherapy. Short term side effects are more marked and although long-term effects do occur there are less published data to establish their extent.

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[8] www.nbocap.org.uk

Since this topic only addressed preoperative and not postoperative therapy, the results of the large MRC CR07/NCIC-CTG C016 trial of preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer were not considered in the evidence review.

The findings of the initial pelvic imaging are key determinants of the rationale and type of preoperative radiotherapy or chemoradiotherapy administered. This is particularly important for low rectal cancers where T-staging may not be clear even with high-quality imaging. These details inform both the type of surgery and the type of preoperative strategy.

For the purposes of this guideline we have defined three different risk groups of patients with rectal cancer, according to the risk of local recurrence. These groups are defined in Table 3.1.

Table 3.1 Risk of local recurrence for rectal tumours as predicted by MRI

Risk of local recurrence	Characteristics of rectal tumours predicted by MRI
High	- a threatened (<1 mm) or breached resection margin **or** - low tumours encroaching onto the inter-sphincteric plane or with levator involvement
Moderate	- any cT3b or greater, in which the potential surgical margin is not threatened **or** - any suspicious lymph node not threatening the surgical resection margin **or** - the presence of extramural vascular invasion*
Low	- cT1 or cT2 or cT3a **and** - no lymph node involvement

* This feature is also associated with high risk of systemic recurrence

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Clinical question: For patients with operable rectal cancer, what is the effectiveness of short course preoperative radiotherapy or chemoradiotherapy?

Clinical evidence

Short-course 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; Birgisson *et al.*, 2005). In addition there was a systematic review (Birgisson *et al.*, 2007) which addressed the late adverse effects of preoperative (and postoperative) radiotherapy in patients treated for rectal cancer. The evidence was considered to be moderate to high quality on GRADE assessment (Table 3.2).

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 short-course preoperative radiotherapy 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 short course preoperative radiotherapy 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 short-course preoperative radiotherapy in improving disease-free survival (HR: 0.87 [95%CI: 0.78-0.98] (p=0.02)) but there was high heterogeneity between studies 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 short course preoperative radiotherapy (HR: 0.89 [95%CI: 0.82-

0.97] (p<0.001)). The most common side effect of short-course preoperative radiotherapy was diarrhoea. Patients in the surgery only group experienced less 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 short-course preoperative radiotherapy 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.

Stephens *et al.* (2010) conducted a quality of life study within a randomised controlled trial that had compared short-course preoperative radiotherapy then surgery with surgery and postoperative chemotherapy (if tumour was within 1mm of resection margin). 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 quality of life was sexual dysfunction (p<0.001 for men, regardless of group, between baseline and 3 months) caused primarily by surgery but exacerbated by radiotherapy (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 short-course preoperative radiotherapy then surgery 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 quality of life. Although the quality of the trial from which these data were derived may have been good, the lack of sensitivity of quality of life instruments in the questionnaires applied may have rendered them less sensitive to detecting differences in outcomes.

Preoperative chemoradiotherapy versus short course preoperative 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 preoperative chemoradiotherapy with short course preoperative radiotherapy. The evidence was considered to be high quality on GRADE assessment (Table 3.3).

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 preoperative chemoradiotherapy compared with short course preoperative radiotherapy. 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 short-course preoperative radiotherapy and those having had preoperative chemoradiotherapy (61% versus 58%). Bujko *et al.* (2006) found no significant difference in the rate of postoperative 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 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 preoperative chemoradiotherapy or short-course preoperative radiotherapy. 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 preoperative radiotherapy group and by 37% of patients in the preoperative 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).

Table 3.2 GRADE profile: For patients with operable rectal cancer is short-course preoperative radiotherapy more effective than surgery

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Preoperative radiotherapy no. of patients	Surgery alone no. of patients	Relative Effect (95% CI)	Absolute Effect	Quality
		Quality Assessment				Summary of Findings				
						No. of patients		Effect		
Overall survival (Wong _et al.,_ 2007) (p=0.15)										
14	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	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
5 year overall survival rate (Peeters _et al.,_ 2007) (p=0.39)										
1	randomised trial	serious[2]	N/A	N/A	N/A	64.2%	63.5%	N/A	N/A	MODERATE
Cause specific mortality (Wong _et al.,_ 2007) (p=0.016)										
4	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	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)	HIGH
5 year cancer-specific survival rate (Peeters _et al.,_ 2007) (p=0.26)										
1	randomised trial	serious[2]	N/A	N/A	N/A	75.4%	72.4%	N/A	N/A	MODERATE
Any recurrence (Wong _et al.,_ 2007) (p=0.0056)										
8	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	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)	HIGH
5 year distant disease recurrence rate (Peeters _et al.,_ 2007) (p=0.39)										
1	randomised trial	serious[2]	N/A	N/A	N/A	25.8%	28.3%	N/A	N/A	MODERATE
Local recurrence (Wong _et al.,_ 2007) (p<0.00001)										
13	randomised trials	no serious limitations	serious[3]	no serious indirectness	no serious imprecision	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)	MODERATE
5 year local recurrence rate (Peeters _et al.,_ 2007) (p<0.001)										

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Preoperative radiotherapy no. of patients	Surgery alone no. of patients	Relative Effect (95% CI)	Absolute Effect	Quality
Quality Assessment						**Summary of Findings**				
						No. of patients		**Effect**		
1	randomised trial	serious[2]	N/A	N/A	N/A	5.6%	10.9%	N/A	N/A	MODERATE
Curative resectability (Wong et al., 2007) (p=0.059)										
15	randomised trials	no serious limitations	serious	no serious indirectness	no serious imprecision	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)	HIGH
Sphincter sparing surgery (Wong et al., 2007)										
15	randomised trials	no serious limitations	serious[4]	no serious indirectness	no serious imprecision	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)	MODERATE
Acute post surgery toxicity (Wong et al., 2007) (p=0.00015)										
6	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	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
Adverse events – risk of infection within 6 months of surgery (Birgisson et al., 2005) (p<0.01)										
1	randomised trial	no serious limitations	N/A	N/A	N/A	-	-	RR 7.67 (1.76 to 33.39)	-	HIGH
Adverse events – risk of gastrointestinal diagnosis (Birgisson et al., 2005) (p<0.01)										
1	randomised trial	no serious limitations	N/A	N/A	N/A	-	-	RR 2.57 (1.55 to 4.26)	-	HIGH
Adverse events – risk of hospital admission, all admissions (Birgisson et al., 2005) (NSD)										
1	randomised trial	no serious limitations	N/A	N/A	N/A	-	-	RR 1.07 (0.91 to 1.26)	-	HIGH
Adverse events – risk of hospital admission, early admissions (Birgisson et al., 2005) (p<0.05)										
1	randomised trial	no serious limitations	N/A	N/A	N/A	-	-	RR 1.64 (1.21 to 2.22)	-	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 3.3 GRADE profile: For patients with operable rectal cancer is preoperative chemoradiotherapy more effective than short course preoperative radiotherapy

Quality Assessment						Summary of Findings				
						No. of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Preoperative chemoRT no. of patients	Preoperative radiotherapy no. of patients	Relative effect (95% CI)	Absolute Effect	Quality
Sphincter preservation rate (Bujko *et al.,* 2004) (p=0.57)[1]										
1	randomised trial	no serious limitations	N/A	N/A	N/A	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)	HIGH
Acute post RT grade III-IV toxicity (Bujko *et al.,* 2004) (p<0.001)[1]										
1	randomised trial	no serious limitations	N/A	N/A	N/A	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)	HIGH
Post-operative morbidity (Bujko *et al.,* 2005) (p=0.27)[1]										
1	randomised trial	no serious limitations	N/A	N/A	N/A	31/157 (21%)	39/155 (27%)	OR 0.73 (0.43 to 1.25)	61 fewer per 1000 (from 134 fewer to 52 more)	HIGH
4 year risk of death (Bujko *et al.,* 2006) (NSD)										
1	randomised trial	no serious limitations	N/A	N/A	N/A	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)	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	44.4%	41.6%	HR 1.12 (0.64 to 1.96)[2]	4 more per 1000 (from 91 fewer to 202 more)	HIGH
4 year risk of local recurrence (Bujko *et al.,* 2006) (NSD)										
1	randomised trial	no serious limitations	N/A	N/A	N/A	15.6%	10.6%	HR 1.56 (0.68 to 3.60)[2]	53 more per 1000 (from 32 fewer to 221 more)	HIGH

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Preoperative chemoRT no. of patients	Preoperative radiotherapy no. of patients	Relative effect (95% CI)	Absolute Effect	Quality
Quality Assessment						**Summary of Findings**				
						No. of patients		**Effect**		
Rate of distant metastases (Bujko _et al.,_ 2006) (NSD)										
1	randomised trial	no serious limitations	N/A	N/A	N/A	34.6%	31.4%	-	-	HIGH
Rate of late toxicity (Bujko _et al.,_ 2006) (NSD)										
1	randomised trial	no serious limitations	N/A	N/A	N/A	27%	28.3%	RR 0.94 (0.66 to 1.35)[2]	17 fewer per 1000 (from 97 fewer to 99 more)	HIGH
Rate of severe late toxicity (Bujko _et al.,_ 2006) (NSD)										
1	randomised trial	no serious limitations	N/A	N/A	N/A	7.1%	10.1%	RR 0.68 (0.33 to 1.41)[2]	33 fewer (from 69 fewer to 42 more)	HIGH
Risk of permanent stoma (Bujko _et al.,_ 2006) (NSD)										
1	randomised trial	no serious limitations	N/A	N/A	N/A	51.6%	56.9%	RR 0.91 (0.74 to 1.12)[2]	52 fewer (from 149 fewer to 69 more)	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, male sexual dysfunction, bowel function etc (Stephens _et al.,_ 2010)[4]										
1	randomised trial	no serious limitations	N/A	N/A	N/A	-	-	-	-	HIGH

Footnotes

[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] No data suitable to put into GRADE.

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Recommendations

- Discuss the risk of local recurrence, short-term and long-term morbidity and late effects with the patient after discussion in the multidisciplinary team (MDT).
- Do not offer short-course preoperative radiotherapy (SCPRT) or chemoradiotherapy to patients with low-risk operable rectal cancer (see Table 3.1 for risk groups), unless as part of a clinical trial.
- Consider SCPRT then immediate surgery for patients with moderate-risk operable rectal cancer (see Table 3.1 for risk groups). Consider preoperative chemoradiotherapy with an interval to allow tumour response and shrinkage before surgery for patients with tumours that are borderline between moderate and high risk.
- Offer preoperative chemoradiotherapy with an interval before surgery to allow tumour response and shrinkage, (rather than SCPRT) to patients with high-risk operable rectal cancer (see Table 3.1 for risk groups).

Linking evidence to recommendations

The GDG considered the outcomes of local control and both short and long term toxicity to be the most important as these are clearly defined outcomes and have the highest impact on patients' quality of life. The GDG agreed that the potential development of a second malignancy was important but there were insufficient data to inform the recommendations.

The overall quality of the evidence was moderate to high, as assessed by GRADE. The evidence looked at historical use of radiotherapy, surgery and imaging.

The GDG were aware that pelvic radiotherapy is associated with significant long-term morbidity and the likelihood of morbidity is independent of a patient's risk of local recurrence. However the potential benefits of radiotherapy do depend on a patient's risk of local recurrence and therefore the clinical benefits and harms need to be considered for each of the three risk groups in making recommendations.

The GDG noted that for patients at low-risk for local recurrence, the incidence of long term morbidity from radiotherapy outweighs the potential benefit. Therefore they decided not to recommend radiotherapy for this group of patients.

For those patients at moderate-risk for local recurrence, the GDG concluded from the evidence that both types of radiotherapy treatment offer equivalent benefit in reduction in local recurrence and similar risks of morbidity. The GDG noted that whilst SCPRT was less expensive and more convenient for patients, there will be individuals whose tumour characteristics on MRI (for example cT3d in a narrow male pelvis, concern about extent of lymph node involvement) raise concern that the tumour may be borderline between moderate and high risk of local recurrence. The opinion of the GDG based on clinical experience was that these patients would be better treated by chemoradiotherapy followed by delayed surgery. Therefore they agreed it was inappropriate to only recommend SCPRT for this group of patients. The GDG also acknowledged that there may be patients in the moderate risk group who may choose, following discussion of risks, not to have preoperative treatment but proceed directly to surgery. They therefore recommended that both treatment options be considered.

For patients at high-risk for local recurrence, the GDG noted that there were no direct data on the effectiveness of SCPRT. They were also aware that the reduction in the risk of a positive margin would be facilitated by tumour shrinkage during an appropriate interval before surgery. Since there was evidence for the effectiveness of chemoradiotherapy in this setting, and a lack of evidence for the use of SCPRT, the GDG decided to recommend the use of chemoradiotherapy.

The size of the population of patients eligible for preoperative interventions for rectal cancer is small compared with other topics in the guideline and hence this topic was considered a lower priority for economic modelling.

3.1.2 Patients whose primary colon or rectal tumour appears unresectable or borderline resectable at presentation

In contrast to rectal cancer, colon cancer occurs at several different sites along the remainder of the large bowel with variation in the anatomy affected. However, for most of these sites, the main risk is peritoneal involvement which when it occurs is usually wide-spread. Any strategy to reduce the risk of recurrence needs to have a systemic approach. However it is not known whether preoperative chemotherapy is able to reduce the risk of this type of recurrence.

Preoperative chemoradiotherapy is given to patients with locally advanced rectal cancer, with the intention of reducing tumour size to facilitate potentially curative surgery. There is concern that for a small proportion of patients their tumour may progress while on such therapy, thereby losing the window of opportunity for surgical resection. There is also concern that preoperative chemoradiotherapy is being used for the treatment of very low rectal tumours to facilitate sphincter saving surgery.

> **Clinical question: For patients presenting with a) non metastatic locally advanced colon cancer is preoperative 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 preoperative chemoradiotherapy more effective than immediate surgery?**

Clinical evidence
There was no evidence with which to address the issue of preoperative 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 preoperative treatment in patients with locally advanced rectal cancer (radiotherapy, chemoradiotherapy or chemotherapy) versus immediate surgery, though the volume and quality of evidence was dependent on the particular comparison under investigation (Tables 3.4 – 3.6).

In relation to preoperative chemoradiotherapy versus preoperative 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 preoperative radiotherapy versus surgery alone.

There was no evidence available to address the issue of preoperative chemotherapy versus surgery alone in patients with locally advanced rectal cancer. Nor were there any studies comparing preoperative chemotherapy with preoperative radiotherapy for patients with locally advanced rectal cancer.

Preoperative chemotherapy versus surgery alone in patients with non-metastatic locally advanced colon cancer
There was no evidence with which to determine the benefits, if any, of preoperative chemotherapy versus surgery alone in patients with locally advanced colon cancer.

Preoperative chemoradiotherapy versus preoperative radiotherapy alone in patients with locally advanced rectal cancer (see Table 3.4)
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]). 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). From Broendengen 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). 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).

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). 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 in patients with locally advanced rectal cancer (see Table 3.5)
There was little evidence available and all 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. 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).

Chessin et al. (2005) did not report a significant difference in relapse free survival between patients experiencing major postoperative complications and patients not experiencing major postoperative 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).

In a retrospective review (Klos et al., 2010) patients (n=390) 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).

Preoperative radiotherapy versus surgery alone in patients with locally advanced rectal cancer (see Table 3.6)
Wong et al. (2007) reported a pooled hazards ratio (from 14 studies) for overall mortality of 0.93 [95% CI: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 biological effective dose and treatment fields focused to the posterior pelvis showed significant benefit.

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 [95% CI: 0.64-0.78].

From 15 studies, Wong et al. (2007) reported a pooled risk ratio (RR) for curative resectability of 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%).

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).

The proportion of patients with no toxicities postoperatively favoured the surgery alone group; from 6 studies the risk ratio was 0.88 [95% CI: 0.82-0.94] (Wong et al., 2007).

Stephens et al. (2010) conducted a quality of life study within a randomised controlled trial that had compared short-course preoperative radiotherapy then surgery with surgery and post-operative chemotherapy (if tumour was within 1mm of resection margin). 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 radiotherapy (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 short-course preoperative radiotherapy then surgery 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.

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 8 studies grade III/IV toxicity was reported in 13.2% (62/470) of patients (range 1-43%) (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). One study (De Paoli et al., 2006) reported no grade III/IV toxicity. 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).

Table 3.4 GRADE profile: For patients presenting with locally advanced rectal cancer is preoperative chemoradiotherapy more effective than preoperative radiotherapy alone

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

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	preoperative chemotherapy, radiotherapy and chemoradiotherapy	immediate surgery	Relative (95% CI)	Absolute	Quality
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)	MODERATE
								64.1%		5 more per 1000 (from 72 fewer to 87 more)	
Local Recurrence (follow-up 5-7 years)											
4	randomised trials	Serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision[7]	none	76/839 (9.1%)	130/821 (15.8%)	OR 0.53 (0.39 to 0.72)[8]	69 fewer per 1000 (from 40 fewer to 92 fewer)	MODERATE
								15.8%		69 fewer per 1000 (from 40 fewer to 92 fewer)	
Cancer Specific Survival at 5 years (follow-up median 61 months)											
1	randomised trials	Serious[9]	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)[10, 11]	359 more per 1000 (from 77 more to 661 more)	MODERATE
								55%		359 more per 1000 (from 77 more to 661 more)	
Disease Free Survival at 5 years (follow-up 5-7 years)											
2	randomised trials	serious[12]	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)	MODERATE
								54.9%		43 more per 1000 (from 33 fewer to 127 more)	
Pathologic Complete Response (follow-up 5-7 years)											
4	randomised trials	serious[13]	no serious inconsistency	no serious indirectness	no serious imprecision[14]	none	145/1194 (12.1%)	47/1214 (3.9%)	OR 3.46 (2.46 to 4.86)[15]	84 more per 1000 (from 52 more to 127 more)	MODERATE
								3.9%		85 more per 1000 (from 52 more to 127 more)	
Toxicity (Grade III/IV (follow-up 5-7 years)											
4	randomised trials	serious[16]	Serious[17]	no serious indirectness	no serious imprecision[18]	none	178/1113 (16%)	58/1126 (5.2%)	RR 4.51 (2.15 to 9.49)[19]	181 more per 1000 (from 59 more to 437 more)	LOW
								5.2%		183 more per 1000 (from 60 more to 441 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 I^2 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 *et al.*, 1984) and a benefit for chemoradiotherapy

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(Braendengen *et al.*, 2008) 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

[6] None of the studies were described as being double blinded or using blinded outcome assessment.

[7] Pooled Estimate: 95% CI do not cross the line of no effect

[8] p<0.0001

[9] None of the studies were described as being double blinded or using blinded outcome assessment.

[10] Braendengen *et al* (2008) did not report odds ratios, however to remain consistent with the results for the rest of this section, the odds ratio was calculated using RevMan.

[11] p=0.01

[12] None of the studies were described as being double blinded or using blinded outcome assessment.

[13] None of the studies were described as being double blinded or using blinded outcome assessment.

[14] Pooled Estimate: 95% CI do not cross the line of no effect

[15] p<0.00001

[16] None of the studies were described as being double blinded or using blinded outcome assessment.

[17] Significant Heterogeneity between studies (p=0.005)

[18] Pooled Estimate: 95% CI do not cross the line of no effect

[19] p<0.0001

Table 3.5 GRADE profile: For patients presenting with locally advanced rectal cancer is preoperative chemoradiotherapy more effective than immediate surgery

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
			Quality assessment			Other considerations	Quality

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
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	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	VERY LOW
Overall Survival (Memershtain _et al._, 2005)							
1	observational studies	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	VERY LOW
Overall Survival (Twu _et al._, 2009) (follow-up median 1.5 years[10])							
1	observational studies	very serious[7]	no serious inconsistency	no serious indirectness	Serious[8]	none	VERY LOW
Relapse and Disease Free Survival (Chessin _et al._, 2005) (follow-up median 43.9 months)							
1	observational studies	very serious[6]	no serious inconsistency	no serious indirectness	Serious[7]	none	VERY LOW
Relapse and Disease Free Survival (Twu _et al._, 2009) (follow-up median 1.5 years[9])							
1	observational studies	very serious[6]	no serious inconsistency	no serious indirectness	Serious[7]	none	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.
[6] Not a randomised trial
[7] Imprecision cannot be assessed
[8] Relapse free survival did not differ significantly between patients with major postoperative complications and those without (p=0.1)
[9] Median follow-up time was longer than 1.5 years, but the study does not report actual median follow-up time.
[10] Disease free survival was higher in the patients responding to preoperative chemoradiotherapy than in patients not responding (p=0.06)

Table 3.6 GRADE profile: For patients presenting with locally advanced rectal cancer is preoperative radiotherapy more effective than surgery alone

	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
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)	
Local Recurrence											
13	randomised trials	no serious limitations	Serious[2]	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)	MODERATE
								27.5%		71 fewer per 1000 (from 53 fewer to 89 fewer)	
Curative and Overall Resectability											
15	randomised trials	no serious limitations	Serious[3]	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)	MODERATE
								75.3%		15 more per 1000 (from 0 more to 38 more)	
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)	

[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.
[2] Differences in recurrence rates ranged from 11% to 54%
[3] Data were heterogeneous across the studies for overall resectability which precluded pooling.

Recommendations
- Discuss the risk of local recurrence and late toxicity with patients with rectal cancer after discussion in the MDT.
- Offer preoperative chemoradiotherapy with an interval before surgery, to allow tumour response and shrinkage, to patients with high-risk locally advanced rectal cancer.
- Do not offer preoperative chemoradiotherapy solely to facilitate sphincter-sparing surgery to patients with rectal cancer.
- Do not routinely offer preoperative chemotherapy alone for patients with locally advanced colon or rectal cancer unless as part of a clinical trial.

Linking evidence to recommendations

The GDG considered local recurrence and toxicity to be important outcomes due to the long term impact on patient wellbeing. There is evidence that small improvements in local control are gained at the expense of significant late morbidity. The gains in local control from radiotherapy are proportional to the risk of local recurrence and should be balanced against the significant late effects in terms of sexual, urinary and bowel dysfunction. The GDG therefore agreed it was important for these issues to be discussed with the patient prior to treatment.

There was no evidence that chemoradiotherapy facilitates an increased opportunity for sphincter sparing surgery, therefore the GDG agreed to recommend that preoperative chemoradiotherapy was not given for this intention.

Data on preoperative chemotherapy alone in patients with either colon cancer or rectal cancer were not robust and the GDG did not feel able to make a recommendation regarding the value of preoperative chemotherapy alone separate from preoperative chemotherapy concurrent with radiotherapy. However, in view of the high risk of metastatic disease in patients with locally advanced colon and rectal cancer, the GDG recommended that research should be undertaken to address this problem for both colon and rectal cancer in the preoperative setting.

This clinical question was considered a low priority for economic analysis because it focused on identifying evidence that specifically addressed the issue of sequencing / combinations of treatment modalities. Identification of treatment combinations or specific regimens were not planned. It was anticipated that the evidence base may be clinically heterogeneous. This would limit the appropriateness of combining or comparing data across studies using quantitative methods and therefore impact on the feasibility of undertaking de novo economic modelling that would help inform this topic in a comprehensive and meaningful manner.

Research recommendations
- The effectiveness of preoperative chemotherapy should be compared with short-course preoperative radiotherapy (SCPRT), chemoradiotherapy or surgery alone in patients with moderate-risk locally advanced rectal cancer. Outcomes of interest are local control, toxicity, overall survival, quality of life and cost effectiveness.
- Consider patients with rectal cancer for entry into current and upcoming NCRN trials of chemoradiotherapy, timing of surgery and deferment of surgery (in patients with a complete clinical response).

3.2   Colonic stents in acute large bowel obstruction

In the absence of population screening, up to 30% of colorectal cancer cases initially present in the emergency setting. Emergency surgery performed for obstructing lesions is associated

with a high morbidity and cited peri-operative mortalities ranging from 10-20%, compared with rates less than 5% in cases of elective surgery. In addition, emergency surgery results in a high rate of stoma formation, high utilisation of intensive care and prolonged hospital stays.

The introduction of self-expanding metal stents (SEMS) has provided the opportunity for endoscopic decompression of these patients in an attempt to reduce the risks of surgery. Following decompression there is an opportunity to correct electrolyte imbalance, evaluate the extent of disease, determine the presence of synchronous lesions and evaluate comorbidities, thus enabling the planning of the most appropriate elective surgery. The placement of SEMS, however, is not without adverse effects including colonic perforation, stent migration, malposition or if the procedure is unsuccessful a delay in emergency surgery. The incidence of stent-related complications significantly increases the longer the stent remains in situ.

It has been suggested that the success rate for stent insertion is lower for tumours proximal to the sigmoid colon, but with the advent of newer devices, able to pass through the endoscopic therapy channel, the success of stent placement in the right colon is likely to increase. The potential hazards of SEMS placement in this context, however, must be balanced against the lower surgical mortality in cases of emergency surgery for right-sided colonic obstruction, when compared with left-sided lesions.

There are currently ongoing trials evaluating the efficacy of SEMS placement as a bridge to surgery, which in turn will assess long term oncological outcome.

Clinical question: 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? 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?

Clinical evidence

There is 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). Multi-detector CT colonography gave 1 false positive result in a population of 44 patients with obstruction. Overall multi-detector CT colonography 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; Repici *et al.*, 2008).

Technical Failure
From one pooled analysis with a total of 1,198 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% (1,061/1,198) 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).

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 postoperative complication; 1 pulmonary embolism and 1 wound infection (Repici *et al.*, 2008).

On update searches, a further two studies were found to be relevant to the current topic (Iverson *et al.*, 2011; 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% versus 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% versus 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 (range 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% (range 72-97%) and 77% (range 54-89%).

Recommendations

- If considering the use of a colonic stent in patients presenting with acute large bowel obstruction offer CT of the chest, abdomen and pelvis to confirm the diagnosis of mechanical obstruction, and to determine whether the patient has metastatic disease or colonic perforation.
- Do not use contrast enema studies as the only imaging modality, in patients presenting with acute large bowel obstruction.
- A consultant colorectal surgeon should consider inserting a colonic stent in patients presenting with acute large bowel obstruction. They should do this together with an endoscopist or a radiologist (or both) who is experienced in using colonic stents.
- Resuscitate patients with acute large bowel obstruction, then consider placing a self-expanding metallic stent to initially manage a left-sided complete or near-complete colonic obstruction.
- Do not place self-expanding metallic stents:
  o in low rectal lesions **or**
  o to relieve right-sided colonic obstruction **or**
  o if there is clinical or radiological evidence of colonic perforation or peritonitis.
- Do not dilate the tumour before inserting the self-expanding metallic stent.
- Only a healthcare professional experienced in placing colonic stents who has access to fluoroscopic equipment and trained support staff should insert colonic stents.
- If a self-expanding metallic is suitable, attempt insertion urgently and no longer than 24 hours after patients present with colonic obstruction.

Linking evidence to recommendations
The GDG noted that there were no studies which were directly applicable to this topic and so consideration was given to studies which compared stenting as a bridge to surgery, stenting for palliative purposes or immediate emergency surgery. Despite the paucity of evidence, the GDG agreed that recommendations on stenting were required because of the high mortality associated with emergency surgery.

The GDG placed a high value on the outcomes of sensitivity and specificity of CT scanning in the emergency presentation of large bowel obstruction. The GDG noted that a CT scan is the most sensitive way of confirming that the obstruction is due to colonic tumour, identifying

colonic perforation and imaging the extent of disease that may impact on future management. They therefore decided to recommend its use.

The GDG agreed that contrast enema studies, used on their own, do not demonstrate the longitudinal and radial extent of the tumour, are less sensitive than CT for identifying bowel perforation and give no information on metastatic status. The GDG therefore decided to recommend that they are not used in isolation but may be used to facilitate stent placement.

The GDG recognised the significant mortality/morbidity associated with operating on patients in the emergency setting. Relieving large bowel obstruction by stenting could allow patient stabilisation leading to planned elective surgery by the appropriate surgeon. Such a treatment strategy could also reduce the incidence of stomas. The GDG were interested whether stenting affected quality of subsequent surgery but no evidence was found.

The GDG believed that the decision to stent should involve a consultant colorectal surgeon in consultation with an endoscopist/radiologist experienced in the management of these cases since this decision must balance the risks between stent insertion and emergency surgery.

The GDG concluded that SEMS were most effective in left-sided complete colonic obstruction because they have a lower complication rate and higher success rate. The GDG agreed that SEMS were not appropriate in patients with low rectal lesions (because of intractable symptoms of tenesmus) or right-sided colonic obstructions (because of high complication rates, low success rate and more complicated stent insertion). Lastly, the GDG decided that SEMS are contraindicated where there is evidence of perforation or peritonitis because these patients need immediate surgery.

The GDG concluded that tumours should not be pre-dilated prior to SEMS insertion because of the high risk of tumour perforation. While there is no evidence with which to recommend a maximum delay between diagnosis of large bowel obstruction and SEMS insertion, the GDG believe strongly that delaying more than 24 hours is potentially harmful to the patient (for example increased risk of perforation and metabolic deterioration).

This topic was considered a low priority for economic analysis because high quality data on the many possible downstream outcomes of a CT scan in this setting and patient population were unlikely to be available. In addition, the second part of the topic focuses on the clinical indications and timing of stenting. Since this did not involve a comparison of costs and consequences, it did not lend itself to economic modelling.

3.3   Stage I colorectal cancer

Stage I colorectal cancer encompasses tumours which have extended either into the submucosa (T1) or into, but not beyond, the muscularis propria (T2) and in which there is no evidence of spread into the lymph nodes (N0). In patients found to have stage I colorectal cancer a five year cancer specific survival of >95% can be expected following segmental resection with clear surgical margins (where there is removal of a segment of large bowel including its associated mesentery) and in these cases, surgery is essentially a curative procedure. Stage I colorectal cancer may be identified following histopathological assessment of an endoscopically resected polyp (malignant polyp), usually unsuspected at the time of polypectomy. Alternatively, and less commonly, it may be suspected in a polypoid lesion (usually laterally spreading) that appears amenable to local resection. In these cases, specialised techniques such as endoscopic submucosal dissection (ESD) or transanal endoscopic micro surgery (TEMS) may be used to perform complete 'en bloc' resection of the lesion, particularly if it is situated in the left colon or rectum.

Following the introduction of the NHS bowel cancer screening programme in England and Wales, malignant colonic polyps are being detected with increasing frequency. Almost all locally removed malignant polyps are stage I cancers and would therefore be expected to have a very good prognosis. Endoscopic resection of malignant polyps may be sufficient as the only management but there is a risk of local recurrence or metastatic spread, particularly to local lymph nodes, since the mesentery, which contains the local lymph nodes, is not resected. It is uncertain, therefore, whether the same prognostic outcome can be expected as that seen in stage I tumours following segmental resection. These risks may be reduced by subsequent surgery, but the associated potential complications such as bleeding, infection or peri-operative death, and the effects on quality of life, need to be balanced against the potential benefits.

A number of retrospective studies have attempted to identify risk factors associated with recurrent malignancy in local resections, although none of these data have proven conclusive. The completeness of the endoscopic excision appears to be the most reliable predictor of tumour recurrence and, although publications vary, it can be assumed that a distance of less than 1mm from the tumour to the margin of excision is associated with a high risk of cancer recurrence. Studies have tried to refine further the prognostic features in polyp cancers that have clear margins and are thus deemed to have been completely excised. The risk of recurrence appears to correlate with degree of local advancement. Thus, in the Haggitt classification (applicable only to polyp cancers with long stalks), it is only the most advanced lesions, where there is extension of the tumour beyond the polyp stalk, (Haggitt level 4), which is suggested to be associated with a poor outcome. The Kikuchi classification (for sessile polyps) suggests that lesions extending into the lower third of the submucosa are of the highest risk (Kikuchi level SM 3). The Ueno classification suggests that the tumour volume is directly correlated with risk of recurrence. These systems are, however, not easy to apply due to the nature of the polypectomy specimens, making assessment and subsequent decision-making problematic. Furthermore, the depth of invasion, or proximity of the tumour to the resection margin, may not be possible to assess when the lesion has been resected piecemeal and thus these lesion are best regarded as high risk. Other factors that have been suggested to predict poor outcome include tumour differentiation, (with poorly differentiated tumours conferring the highest risk), the presence of venous or lymphatic invasion and tumour budding. Uncertainty exists about the benefit to patient outcome of using these prognostic factors to guide subsequent management.

Clinical question: 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, can the use of prognostic factors determine the most effective curative treatment?

Clinical evidence
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 I colorectal cancer (including polyps) and subsequently found to have unfavourable prognostic features. If possible, the topic aimed to identify whether treatment efficacy was impacted by specific prognostic features.

There was no evidence with which to answer this question as much of the literature concentrated 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.

Recommendations
- The colorectal MDT should consider further treatment for patients with locally excised, pathologically confirmed stage I cancer taking into account pathological characteristics of the lesion, imaging results and any previous treatments.
- Offer further treatment to patients whose tumour had involved resection margins (less than 1 mm).
- Discuss the risks and benefits of all treatment options with the patient after discussion in the MDT.
- An early rectal cancer MDT[9] should decide which treatment to offer to patients with stage I rectal cancer, taking into account previous treatments, such as radiotherapy.

Linking evidence to recommendations

The GDG acknowledged that there was no evidence that specifically addressed this question. As a consequence of the impact of the NHS bowel cancer screening programme, there has been a significant increase in the number of patients with stage I cancers being detected. Furthermore the GDG is aware of wide variation in practice and patient experiences. Therefore the GDG considered it to be extremely important for this question to be addressed.

The GDG strongly believed that when patients had an involved resection margin (incompletely excised cancer) then further treatment was important. However, given the lack of evidence, the GDG did not feel able to make specific recommendations for the type of treatment that should be given.

The GDG also agreed that it was important for all patients with locally excised, pathological stage I cancer to be discussed at the appropriate MDT, where specialist pathological expertise is available, in order to determine future management. The GDG also agreed that it was important that full discussion of the risks and benefits of all treatment options should take place with the patient.

The GDG acknowledged that patients whose rectal cancer has been downstaged to stage I by prior treatment, are a specific group in whom treatment may/may not have altered the biology of the tumour and the information provided by the prognostic factors may not be relevant.

Research recommendation
- An observational study should be conducted, incorporating standardised assessment of pathological prognostic factors, to assess the value of the proposed prognostic factors in guiding optimal management in patients with locally excised, pathological stage I cancer. Outcomes of interest are disease-free survival, overall survival, local and regional control, toxicity, cost-effectiveness and quality of life.

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[9] Improving outcomes in colorectal cancer (2004). NICE cancer service guidance CSGCC. Available from www.nice.org.uk/CSGCC

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3.4   Laparoscopic surgery

The recommendations in this section are from 'Laparoscopic surgery for colorectal cancer', NICE technology appraisal guidance 105 (NICE 2006).

Recommendations
- Laparoscopic (including laparoscopically assisted) resection is recommended as an alternative to open resection for individuals with colorectal cancer in whom both laparoscopic and open surgery are considered suitable.
- Laparoscopic colorectal surgery should be performed only by surgeons who have completed appropriate training in the technique and who perform this procedure often enough to maintain competence. The exact criteria to be used should be determined by the relevant national professional bodies. Cancer networks and constituent trusts should ensure that any local laparoscopic colorectal surgical practice meets these criteria as part of their clinical governance arrangements.
- The decision about which of the procedures (open or laparoscopic) is undertaken should be made after informed discussion between the patient and the surgeon. In particular, they should consider:
  o   the suitability of the lesion for laparoscopic resection
  o   the risks and benefits of the two procedures
  o   the experience of the surgeon in both procedures.

Linking evidence to recommendations
These recommendations are from 'Laparoscopic surgery for colorectal cancer', NICE technology appraisal guidance 105 (NICE 2006). They were formulated by the technology appraisal and not by the guideline developers. They have been incorporated into this guideline in line with NICE procedures for developing clinical guidelines, and the evidence to support these recommendations can be found at www.nice.org.uk/TA105.

3.5   Adjuvant chemotherapy in rectal cancer

Colonic and rectal tumours occur anatomically in continuity, and have similar histopathological features. They might therefore be expected to respond similarly to chemotherapy.

Although it is established that patients with stage III (and possibly high-risk stage II) colon cancer will benefit from adjuvant chemotherapy, uncertainty remains around the benefits of such chemotherapy for patients with stage II and III rectal cancer.

Clinical question: In patients with clinical or pathological stage II and III rectal cancer what is the effectiveness of adjuvant chemotherapy following surgery?

Clinical evidence
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 *et al.*, 2006; Cionini *et al.*, 2001; Fisher *et al.*, 1988; Akasu *et al.*, 2006; Sakamoto *et al.*, 2004; Sakamoto *et al.*, 1999; Glimelius *et al.*, 2005).

There was one systematic review (Germond *et al.*, 1998) which was conducted as part of a Canadian guideline programme, 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 analysis. A Cochrane review protocol (Kirkeby *et al.*, 2002), and a second trial protocol (Glynne-Jones *et al.*, 2007) which

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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 currently clinically relevant. 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 Collaborative Group, 2007). The quality of the studies included in the pooled analysis was considered to be moderate according to GRADE assessment (Table 3.7) 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 0.8 [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 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 (for example 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.

Table 3.7 GRADE profile: In patients with clinical or pathological stage II and III rectal cancer, what is the effectiveness of adjuvant chemotherapy following surgery

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Adjuvant Chemotherapy	control	Relative (95% CI)	Absolute	Quality
			Quality assessment				No of patients		Effect		
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)	
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.

Recommendations
- Assess pathological staging after surgery before deciding whether to offer adjuvant chemotherapy.
- Consider adjuvant chemotherapy for patients with high-risk stage II and all stage III rectal cancer to reduce the risk of systemic recurrence.

Linking evidence to recommendations

The GDG were aware that preoperative treatment is widely used in current practice and may affect post-operative pathological staging. However, the evidence did not include studies where patients had received preoperative chemoradiotherapy and therefore the role of clinical staging in the decision around adjuvant chemotherapy is not known. The GDG decided that post-operative pathological staging took precedence over preoperative clinical staging when considering the benefit of adjuvant treatment.

The GDG placed a high value on the outcomes of survival, local recurrence, metastatic disease, complication rates and quality of life. They noted that there were limitations to the evidence. Few studies had examined 5FU alone as adjuvant treatment outside the combination with radiotherapy, and there were no completed studies that had been specifically designed to look at the effectiveness of oxaliplatin containing regimens in patients with rectal cancer. Recent randomised studies designed to evaluate the benefit of adjuvant chemotherapy, where preoperative chemoradiotherapy had been delivered, failed to recruit. The published randomised studies were underpowered; the compliance to post-operative treatment was poor; the clinical staging was variable, making classification of rectal cancer difficult; the treatments given were poorly documented; and quality of life was either doctor reported or not reported at all.

The GDG were aware of the established benefits of adjuvant chemotherapy in colon cancer. The GDG also noted that the evidence showed a survival benefit from post-operative adjuvant chemotherapy for patients with involved lymph nodes on surgical histopathology who had not received preoperative treatment. They were also aware that there were additional considerations regarding toxicity for patients who have had short course preoperative radiotherapy or chemoradiotherapy.

The GDG agreed that the gains in local control and survival from adjuvant chemotherapy were proportional to the risk of local and distant recurrence and balanced against the temporary deterioration in quality of life resulting from acute side-effects of chemotherapy, and the small risk of dying (as a result of toxicity from chemotherapy).

The GDG therefore recommended adjuvant chemotherapy should be offered to patients who had received either surgery with no preoperative treatment or short course preoperative radiotherapy followed by immediate surgery. For patients who had received preoperative chemoradiotherapy, the GDG were unable to make a recommendation.

The GDG noted that the evidence for the effectiveness of adjuvant chemotherapy in patients with rectal cancer only related to 5FU-based chemotherapy. Because of the lack of data from completed phase III trials, the GDG was unable to recommend which specific combination chemotherapy regimen should be used (oxaliplatin or irinotecan).

This clinical question was considered a medium priority for economic analysis because the estimated impact in terms of the size of the target patient population and the level of uncertainty and controversy regarding current practice were considered to be lower than for other questions.

3.6   Adjuvant chemotherapy for high-risk stage II colon cancer

A benefit from adjuvant chemotherapy in colorectal cancer was first demonstrated in 1990 in patients with stage III disease. The benefit for stage III patients has been confirmed and treatment schedules refined in the intervening years.

Some of these studies of stage III disease included a proportion of patients with stage II disease. As the risk of recurrence is less with stage II disease the absolute benefit of adjuvant chemotherapy will be less than for stage III disease (assuming the relative risk reduction is the same for adjuvant chemotherapy in both stage II and stage III disease).

It is recognised that overall patients with stage II disease have a better prognosis than those with stage III disease, but that outcomes for patients within stage II vary and that there is a spectrum of risk for recurrence.

There are several pathological features which have been shown to be associated with poor prognosis in stage II disease such as extramural vascular invasion, pT4 disease (serosal breach or perforation), poorly differentiated tumours, obstructed tumours, perineural invasion and low lymph node recovery from the resection specimen. These features have been used to identify "high-risk" patients and have become, de-facto, criteria for adjuvant chemotherapy in stage II disease but their value to predict for treatment outcome has not been established.

Other tumour features, such as microsatellite instability may have both prognostic and predictive characteristics, but their exact role in the selection for adjuvant chemotherapy in patients with colon cancer is not clear.

Clinical question: In patients with high-risk stage II colon cancer what is the effectiveness of adjuvant chemotherapy after surgery?

Clinical 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 (Erlichman *et al.*, 1999; Labianca *et al.*, 1995; Mamounas *et al.*, 1999), a single randomised trial (O'Connell *et al.*, 1997) and two case-series studies (one prospective and one retrospective) which added limited, poor quality and indirect evidence (Lin *et al.*, 2009; Yoshimatsu *et al.*, 2006). All of the available evidence was considered to be low to moderate quality for all outcomes on GRADE assessment (Table 3.8), 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 extramural vascular invasion, grade 3/poor differentiation, T4 stage/perforation, peri-neural invasion, obstructive tumours, mucinous tumours, micro-satellite instability and 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 *et al.*, 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% versus 84.7%, p=0.045) and 5-year overall survival benefit (100% versus 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 as 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 *et al.*, 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 confers 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.

Table 3.8 GRADE profile: In patients with high-risk stage II colon cancer what is the effectiveness of adjuvant chemotherapy after surgery?

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Adjuvant Chemotherapy	Surgery Alone	Relative (95% CI)	Quality
			Quality assessment				No of patients		Effect	
Overall Survival (Erlichman *et al.*, 1999) (follow-up median 5.75 years)										
5	randomised trials	no serious limitations[1]	no serious inconsistency[2]	serious[3]	serious[4]	none	98/507 (19.3%)	120/509 (23.6%) / 23.6%	HR 0.81 (0.64 to 1.01)[5]	LOW
Overall Survival (Mamounas *et al.*, 1999)										
1	randomised trials	no serious limitations[1]	serious[6]	serious[3]	serious[4]	none	116/351 (33%)	150/375 (40%)[7] / 40%	not pooled	VERY LOW
Overall Survival (Mamounas *et al.*, 1999)										
1	randomised trials	no serious limitations[1]	serious[6]	serious[3]	serious[4]	none	89/340 (26.2%)	113/343 (32.9%)[8] / 32.9%	not pooled	VERY LOW
Overall Survival (Labianca *et al.*, 1995) (follow-up median 37 months[9])										
3	randomised trials	no serious limitations[1]	no serious inconsistency[10]	serious[3]	very serious[4]	none	0/0 (0%)	0/0 (0%) / 0%	HR 0.91 (0.63 to 1.34)[11]	VERY LOW
Event Free Survival (Erlichman *et al.*, 1999) (follow-up median 5.75 years)										
5	randomised trials	no serious limitations[1]	no serious inconsistency[2]	serious[3]	serious[4]	none	101/507 (19.9%)	110/509 (21.6%) / 21.6%	HR 0.83 (0.68 to 1.01)	LOW
Event Free Survival (Labianca *et al.*, 1995) (follow-up median 37 months[9])										
3	randomised trials	no serious limitations[1]	no serious inconsistency[10]	serious[3]	no serious imprecision	none	193/754 (25.6%)	262/736 (35.6%) / 35.6%	HR 0.84 (0.62 to 1.12)[12]	MODERATE

[1] Details from the individual trial methodologies were not given in the paper.
[2] It appears to be an updated version of Labianca *et al.*, 1995 with more trials added and using individual patient data for analysis.
[3] The study did not look at the high-risk population specifically
[4] Less than 300 events
[5] The HR presented is the unadjusted HR; the adjusted HR was 0.86, 90% CI; 0.68-1.07 (adjusted for age and tumour grade).
[6] Individual trials included had different treatment regimens and comparators. No other information is given.
[7] p=0.07
[8] p=0.08
[9] Median follow-up for the treatment group was 40 months and for the intervention group was 37 months.
[10] It appears 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 collaborative analysis.
[11] HR is the 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.
[12] The HR presented 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

Recommendations

- Consider adjuvant chemotherapy after surgery for patients with high-risk stage II colon cancer. Fully discuss the risks and benefits with the patient.

Linking evidence to recommendations

The GDG considered overall survival was the most important outcome, as this was the primary endpoint of adjuvant studies comparing treatment to no treatment.

The overall quality of the evidence was poor. No prospective randomised studies have been performed comparing adjuvant chemotherapy to no treatment in patients deemed to have high-risk stage II colon cancer.

Despite the poor evidence, the GDG believed it was likely that patients with high-risk stage II colon cancer would benefit from chemotherapy.

The GDG was concerned that a large number of patients with (all) stage II colon cancer would need to be treated with adjuvant chemotherapy to confer a survival benefit for the few patients with high-risk stage II disease. Adjuvant chemotherapy carries significant toxicities and a small mortality rate, so a large number of patients would be treated without benefit and be exposed to potential harms, with significant costs to the health service. Therefore the GDG recommended that adjuvant chemotherapy should be considered for patients with high-risk stage II colon cancer, but only after full discussion of the risks and benefits with the patient.

The GDG considered making a research recommendation in this area but concluded that it would not be practical to conduct a randomised study as it would not be possible to recruit the large number of patients needed to show a statistically significant benefit.

3.7 Adjuvant chemotherapy for stage III colon cancer

The recommendations in this section are from 'Capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes' C) colon cancer', NICE technology appraisal guidance 100 (NICE 2006).

Recommendations

- The following are recommended as options for the adjuvant treatment of patients with stage III (Dukes' C) colon cancer following surgery for the condition:
  - capecitabine[10] as monotherapy
  - oxaliplatin in combination with 5-fluorouracil and folinic acid.
- The choice of adjuvant treatment should be made jointly by the individual and the clinicians responsible for treatment. The decision should be made after an informed discussion between the clinicians and the patient; this discussion should take into account contraindications and the side-effect profile of the agent(s) and the method of administration as well as the clinical condition and preferences of the individual.

Linking evidence to recommendations

These recommendations are from 'Capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes' C) colon cancer', NICE technology appraisal guidance 100 (NICE 2006). They were formulated by the technology appraisal and not by the guideline developers. They have been incorporated into this guideline in line with NICE procedures for developing

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[10] Since TA100 was published, the licence for capecitabine has been extended to include combination therapy

clinical guidelines, and the evidence to support these recommendations can be found at www.nice.org.uk/TA100.

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4 Management of metastatic disease

The objectives of this chapter were to determine:
- which imaging modality most accurately determines the extent of metastases in patients with colorectal cancer and extrahepatic metastases (e.g. lung, brain, peritoneum)
- which imaging modality(s) most accurately determines the number and extent of metastases preoperatively in patients with colorectal cancer metastasised to the liver
- the effectiveness of treating metastatic disease before, after or at the same time as treating the primary tumour in patients with colorectal cancer presenting with overt synchronous metastatic disease
- the effectiveness of chemotherapy in patients with advanced and metastatic colorectal cancer
- the most effective additional treatment to systemic chemotherapy to achieve cure or long term survival in patients with apparently unresectable metastatic disease.

4.1 Management of patients presenting in stage IV

Approximately 25% of patients with colorectal cancer have metastatic disease at the time of initial presentation and it is thought that their outcome is often worse than for those patients who develop metachronous metastatic disease following apparently curative resection of their primary tumour.

The first question in managing this group of patients is whether the primary tumour needs immediate treatment because of established or impending obstructive symptoms, even in the presence of unresectable metastatic disease (see section 3.2).

The second question is whether or not both the primary tumour and the metastases are surgically resectable with curative intent. If the disease sites are considered resectable then the next questions are whether there should be preoperative or post-operative adjuvant treatments (or a combination of both) and whether the surgery should be a staged or combined procedure? Current practice varies widely including synchronous resections, staged resections with or without initial systemic treatment.

Where metastases are unresectable, currently patients fall into 2 groups:
- the extent of metastatic disease is such that although inoperable at presentation, patients might become resectable with curative intent if they have a good response to chemotherapy
- the extent of metastatic disease is such that patients are highly unlikely to be suitable for potentially curative surgery, even with a good response to chemotherapy

Advances in systemic therapy over the last 10 years have increased the potential for long-term survival and possible cure. However there remains uncertainty as to the best sequence of treatments to achieve optimal outcome.

Clinical question: 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?

Clinical 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 and Jorgensen, 2009; Scheer *et al.*, 2008), one randomised

trial (Nordlinger *et al.*, 2008) and 3 retrospective case series studies, two case matched (Moug *et al.*, 2010; Benoist *et al.*, 2005) and one non-matched case series (Mentha *et al.*, 2008).

<u>Synchronous resection versus staged resection</u>
A well conducted systematic review which included 16 studies (Hillingso and Jorgensen, 2009) 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. The available evidence was considered to be very low quality for all outcomes on GRADE assessment (Table 4.1).

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 results of the pooled analysis show synchronous resection to be significantly better than staged resection in relation to postoperative morbidity (OR=0.68, [95% CI: 0.49-0.81]). On calculating the risk difference, there was no significant difference in the risk of mortality between the two groups (RD, 0.01, [95% CI: -0.01-0.04]). There was no significant difference in 5 year survival for patients undergoing synchronous resection versus patients undergoing staged resection.

Table 4.1 GRADE profile: Quality assessment of studies reporting length of hospital stay (days); postoperative morbidity; postoperative mortality and 5 year survival

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
Quality assessment							
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	VERY LOW
Morbidity							
13[5]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	VERY LOW
Mortality							
14[6]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	VERY LOW
5-year survival							
12[7]	observational studies	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	VERY LOW

Footnotes:
[1] A total of 11 studies included in the systematic review reported on length of hospital stay. 8/11 reported mean length of hospital stay with standard deviations, while 3 studies reported median length of hospital stay (Hillingo and Jorgensen, 2009). 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 and Jorgensen, 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

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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 (Hillingso and Jorgensen, 2009) 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.

[5]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.

[6]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.

[7]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.

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*., 2008) deemed to be relevant and not all included studies were case matched meaning there was no comparison within the individual study. This, together with a non-matched case series study (Mentha *et al*., 2008) and a randomised trial investigating only progression free survival (Nordlinger *et al*., 2008) comprised the evidence base examining chemotherapy versus immediate surgery for patients with colorectal cancer and liver metastases.

Outcome data were available for length of hospital stay, tumour related complications in patients treated initially with chemotherapy, overall survival and progression free survival. The available evidence was considered to be very low to low quality for all outcomes on GRADE assessment (Table 4.2).

One retrospective case series (Benoist *et al*., 2005) aimed at determining the best treatment 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 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*., 2008).

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*., 2008).

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*., 2008).

Scheer *et al*. (2008) reported that for patients that underwent resection of the primary tumour median survival ranged from 14-23 months versus 8.2-22 months for patients treated with chemotherapy as first treatment.

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% (range 21.3-35.3) to 35.4% (range 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).

Table 4.2 GRADE profile: Quality assessment of studies reporting length of hospital stay (days); tumour related complications; overall survival; progression-free survival

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Quality
			**Quality assessment**				
Length of hospital stay							
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	VERY LOW
Tumour related complications							
6	observational studies	serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	VERY LOW
Haemorrhage							
4	observational studies	serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	VERY LOW
Overall survival							
6	observational studies	serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	VERY LOW
1	observational study	very serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	VERY LOW
Progression free survival							
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	LOW

Footnotes

[1] Benoist *et al.* 2005 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*, 2008) 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.

[2] Studies included in the systematic review were retrospective studies and consisted of both comparative and non-comparative studies

[3] 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.

[4] 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.

[5] The intervention under investigation meant that the study was subject to lead time bias, though steps were taken to address this.

[6] The number of events did not accumulate at the expected rate resulting in an under-powered study.

Recommendations

- Prioritise treatment to control symptoms if at any point the patient has symptoms from the primary tumour.
- If both primary and metastatic tumours are considered resectable, anatomical site-specific MDTs should consider initial systemic treatment followed by surgery, after full discussion with the patient. The decision on whether the operations are done at the same time or separately should be made by the anatomical site-specific MDTs in consultation with the patient.

Linking evidence to recommendations

The GDG considered that although overall survival is important to patients, quality of life is held in equal importance. The outcome of operative mortality was also considered important because the recommendations are aiming to prevent untimely deaths and morbidity because of the impact of this endpoint on the patient's ability to have other treatment. Length of hospital stay was not considered a useful outcome because it was determined by local procedures and not controlled for across the studies, therefore there was the potential for bias.

The GDG noted that the evidence as assessed by GRADE methodology as very low.

Despite a lack of evidence for the specific situation of an obstructing tumour, there was GDG agreement that treatment should be given for symptom control. Due to the lack of evidence the GDG believes that at present treatment decisions of this type should be left to the MDTs in consultation with the patient.

The data on initial systemic treatment, suggested that patients presenting in stage IV with non-obstructing primary tumours might benefit in terms of quality of life and overall survival from receiving this. Therefore the GDG decided to recommend that initial systemic treatment be considered.

The GDG noted that outcomes of surgery, such as peri-operative morbidity/mortality, were similar whether the surgery was synchronous or staged. However the GDG agreed that at the individual patient level, if either procedure were high risk, it would be preferable to separate the operations even though the evidence had shown no difference in outcomes between these groups of patients

The topic was not considered a priority for health economic evaluation because there was no appropriate comparator to enable cost-effectiveness analysis to be undertaken.

4.2   Imaging hepatic metastases

Colorectal cancer that has metastasised to the liver may be amenable to surgical resection with long-term survival improvement or curative intent. The expected 5 year survival after such liver surgery now approaches 60%, with 10 year survival close to 30%. Currently, >20% of patients with hepatic colorectal cancer metastases can be considered candidates for hepatectomy with curative intent. However, hepatic resection is a costly procedure with significant morbidity; careful patient selection is crucial to achieve the best clinical outcomes.

Imaging plays three roles in patient selection:
- to detect as many liver metastases as possible and their location, in order to maximise the chance of achieving complete clearance of disease at the time of surgery
- to accurately characterise any benign liver lesions which may be present, so as to avoid unnecessary surgical procedures
- to detect other sites of metastatic disease which may themselves be amenable to treatment, or may render liver resection inappropriate (see section 4.1)

The key question is which imaging modality most accurately determines the number and extent of liver metastases preoperatively, to decide which patients are suitable for radical surgery with curative intent.

Clinical question: In a patient with colorectal cancer metastasised to the liver which imaging modality(s) most accurately determine the number and extent of metastases preoperatively?

Clinical evidence
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 all modalities being 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 micrometastases of <1cm.

Since 2005 a number of studies have been carried out continuing to test the ever-developing technologies of MRI and CT against each other. In the last 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 and CT.

It appears that in a per-patient analysis PET-CT has consistently higher sensitivity in all the studies compared to MRI and CT and pooled analysis supports this with 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 studies compared 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*. (2005) 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 metastases in their analysis. It was not possible to extract data for this relating to hepatic metastases only.

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 Gadolinium- 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.

Recommendation
- If the CT scan shows metastatic disease only in the liver and the patient has no contraindications to further treatment, a specialist hepatobiliary MDT should decide if further imaging to confirm surgery is suitable for the patient - or potentially suitable after further treatment - is needed.

Linking evidence to recommendations
The GDG considered sensitivity and specificity of the investigations to be the most important outcomes. They noted that the overall quality of the diagnostic studies was poor because there was poor reporting of study design parameters, varied study design and possible risk of bias.

The GDG acknowledged that the diagnosis of liver metastases is derived from a CT scan performed as part of the original staging or during follow-up after potentially curative surgery for the primary cancer. The question is : what imaging and what sequence should then be done to confirm the patient is suitable for surgery and to determine the surgical strategy?

The GDG acknowledged that evidence showed CT and MRI are comparable at detecting liver metastases, with sensitivities over 75%. They also noted that from the evidence PET-CT reported consistently higher sensitivity (90%) than the other modalities. However they were aware that PET-CT is more expensive and less widely available than the other modalities and that not all tumours are FDG avid.

The available evidence is unclear whether MRI or PET-CT should be used after a CT scan to confirm the patient with liver metastases suitable for surgery. Therefore the GDG recommended that the opinion of a hepatobiliary MDT is sought. This would then allow a specialist to make the decision on what additional imaging to use, striking a balance between missing patients with resectable disease and excessive inappropriate laparotomies.

Because of this uncertainty, the GDG decided to recommend further research in this area. The focus of this question was on the use of imaging modalities (CT, PET-CT, MRI or ultrasound) for the detection of liver metastases to inform a decision about resectability. An economic analysis of this topic would need to take into account not only accuracy of the imaging modality in detecting metastases, but also downstream consequences on treatment decisions and patient outcomes. An initial search of the clinical literature revealed that most of the relevant studies identified do not report information on resectability or change in patient management in relation to the information obtained by the imaging test. As the decision to resect is based on a number of different considerations, there is insufficient information to model the link between the imaging results and the treatment decision. Therefore the feasibility of conducting a comprehensive cost-effectiveness analysis based on currently available data is limited and the GDG agreed not to pursue development of an economic model for this topic.

> **Research recommendation**
> - A prospective trial should be conducted to investigate the most clinically effective and cost-effective sequence in which to perform MRI and PET-CT, after an initial CT scan, in patients with colorectal cancer that has metastasised to the liver, to determine whether the metastasis is resectable. The outcomes of interest are reduction in inappropriate laparotomies and improvement in overall survival.

4.3   Imaging extra-hepatic metastases

Historically, patients with extra-hepatic metastatic colorectal cancer were considered incurable, treatment was either with palliative intent or best supportive care, and life expectancy was short (typically a few months). Modern chemotherapy, combined with newer interventions in surgery and radiology offer improvements in survival that can be measured in years, and occasionally the possibility of cure.

Extra-hepatic metastases can be suspected at first diagnosis of colorectal cancer, either in the elective or emergency setting (patients presenting with stage IV disease). Alternatively, following apparently curative surgery for primary colorectal cancer, extra-hepatic metastases can be diagnosed during either routine follow-up or between follow-up appointments during investigation of new symptoms.

The issues that determine appropriate treatment for patients with extra-hepatic metastases are:

- patient specific (age, fitness, mode of presentation with colorectal cancer)
- lesion specific: whether or not the detected abnormality represents metastatic cancer or is a benign co-incidental finding
- disease specific (anatomic site(s) of disease, extent of tumour burden)
- the ability to determine the extent and location of their tumour burden.

The common sites of extra-hepatic metastases are distant lymph nodes, peritoneum and lungs. Rare sites of metastases include adrenal glands, central nervous system and bones. Previously, following apparently curative surgery for primary colorectal cancer, extra-hepatic metastases have been detected during follow-up using a combination of clinical examination, blood CEA estimations, endoscopic surveillance and liver ultrasound scans with occasional chest X-ray examinations. Over the past decade and a half there has been a move towards contrast-enhanced CT scanning of chest, abdomen and pelvis. Further information has also been obtained using MRI and PET-CT, both in lesion characterisation and also evaluation of extent and site of extra-hepatic tumour burden.

Having detected extra-hepatic disease, it is important to determine the extent of disease to offer the appropriate treatment strategy. There is uncertainty about the role of metastasectomy for the treatment of resectable lung metastases and this is being investigated in the PulMiCC trial. However, little is known as to which is the most useful investigation or the correct sequence of investigations to accurately determine the extent of tumour burden in patients with extra-hepatic metastatic colorectal cancer.

Clinical question: In a patient with colorectal cancer and extrahepatic metastases (e.g. lung, brain, peritoneum), which imaging modality most accurately determines the extent of metastases?

Clinical evidence
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; Votrubova *et al.*, 2006). None of the studies were designed to directly compare the effectiveness of the imaging techniques in detecting extrahepatic 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 extrahepatic 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%, whole body 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 whole body MRI.

PET/CT versus CT

Selzner et al. 2004 found no difference in the ability of PET/CT or contrast enhanced CT 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.

Two studies (Metser et al., 2010; 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 multi-detector CT 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 multi-detector CT (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 multi-detector CT for the detection of recurrence and metastases (p<0.0001) though again there was no difference in specificity (p=0.56).

Recommendations

- Offer contrast-enhanced CT of the chest, abdomen and pelvis to patients being assessed for metastatic colorectal cancer.
- If intracranial disease is suspected, offer contrast-enhanced MRI scan of the brain. Do not offer imaging of the head, neck and limbs unless involvement of these sites is suspected clinically.
- Discuss all imaging with the patient following review by the appropriate anatomical site-specific MDT.

- If the CT scan shows the patient may have extra-hepatic metastases that could be amenable to further radical surgery, an anatomical site-specific MDT should decide whether a positron emission tomography-CT (PET-CT) scan of the whole body is appropriate.
- If contrast-enhanced CT suggests disease in the pelvis, offer an MRI of the pelvis and discuss in the colorectal cancer MDT.
- If the diagnosis of extra-hepatic recurrence remains uncertain, keep the patient under clinical review and offer repeat imaging at intervals agreed between the healthcare professional and patient.

Linking evidence to recommendations
The GDG considered sensitivity and specificity of the investigations to be the most important outcomes. They noted that there was limited, poor-quality evidence to address this topic. The GDG also observed that imaging technology is improving all the time and it can sometimes be unclear whether results from older imaging studies are generalisable to modern clinical practice.

The GDG noted that CT of the thorax, abdomen and pelvis has high specificity and modest sensitivity for the detection of extra-hepatic metastases, as it covers the organs and viscera at greatest risk for recurrence or metastases from colorectal cancer. The GDG were also aware that CT is widely available throughout the NHS, inexpensive relative to the other modalities and applicable to almost all patients. Therefore the GDG recommended that CT be used initially to determine the extent of extrahepatic metastases.

The GDG considered that isolated asymptomatic metastasis from colorectal cancer to the head, neck or limbs was unusual and therefore did not warrant routine imaging. However, when there is suspicion of intracranial disease, a contrast-enhanced MRI provides greatest sensitivity and specificity and is the investigation of choice.

Because of the relative high cost and limited availability of PET-CT, the GDG considered this was an inappropriate first investigation for detecting extra-hepatic metastases. However, for patients with extra-hepatic metastases thought to be amenable to radical surgery, the GDG considered the increased sensitivity provided by PET-CT could be useful in the avoidance of non-beneficial surgery. Given the lack of studies directly addressing this issue, the GDG agreed it was more appropriate for the decision on whether or not to perform a PET-CT to be left to the site-specialist MDT.

The limited evidence published to date is insufficient to fully define the benefits and limitations of PET-CT in this specialized area of practice. PET-CT is considerably more costly than the other imaging modalities, and in the UK, is available only at a small number of specialist centres. It has increased sensitivity for detecting extra-hepatic metastases beyond that of MRI and CT, but it is unclear whether this benefit has a sufficient impact on patient management to justify the cost. Therefore the GDG decided to recommend further research in this area.

The GDG acknowledged that the pelvis is a common site for recurrence of colorectal cancer. When pelvic recurrence is suspected on CT scan, they agreed that MRI has increased specificity to discriminate between recurrent tumour and complications of treatment. Furthermore it better demonstrates the anatomic relationships of recurrent tumour to pelvic viscera, major blood vessels and bony structures, and thus facilitates the selection for radical surgery with curative intent.

The GDG acknowledged that the use of MRI in addition to CT scanning for pelvic disease was likely to incur substantially higher costs. However the GDG agreed that this balanced against improved patient selection for radical surgery.

The additional use of PET-CT incurs a further substantial increase in cost, but the trade-off is further improved patient selection when radical surgery is being considered, in particular the avoidance of non-beneficial surgery and the costs and complications associated with this.

Research recommendation
- A prospective, multi-centre observational study of the quality, sensitivity, specificity and cost-effectiveness of using PET-CT in the management of patients with colorectal cancer should be conducted.

4.4   Chemotherapy for advanced and metastatic colorectal cancer

The management of locally advanced and metastatic adenocarcinoma of the colon and rectum has advanced markedly over the past 10 years. The introduction of a number of new chemotherapeutic and biological agents has led to significant increases in progression free and overall survival. The clinical efficacy of these agents has been the subject of a number of previous NICE technology appraisals (TA). It is recognised that management of advanced colorectal cancer encompasses a spectrum of no treatment, monotherapy (see section 4.4.3) and combination therapy. This section is specifically focused on combination chemotherapy.

Both oxaliplatin and irinotecan have developed important roles in the management of colorectal cancer – both in combination with fluoropyrimidines and also, for irinotecan, as a single agent.

Over 50,000 patients have now been treated in trials looking at optimal combinations of oxaliplatin and a fluoropyrimidines (5-flourouracil or capecitabine). These data confirm the value of this combination in terms of trial endpoints when compared against single agent fluoropyrimidines. When combinations of oxaliplatin and a fluoropyrimidine are compared against irinotecan combinations then generally the results are equal, albeit with differing toxicities.

Irinotecan appears to have activity both in combination with a fluoropyrimidine and as a single agent. The combination regimens seem to have less toxicity, and a trend to better outcomes than when used as a single agent.

Currently, for patients with advanced metastatic disease, both oxaliplatin and irinotecan can be used to extend disease-free and overall survival. There are a number of less frequent circumstances (for example liver-limited metastatic disease) (see sections 4.1-4.3) where alternative strategies are used but these are with the intention of long-term disease control, rather than palliation. Defining the optimal strategy for sequencing of these agents remains a difficult trial endpoint.

Recommendations on the use of oxaliplatin, irinotecan and raltitrexed were made in NICE TA93[11]. However, since the publication of TA93 in 2005 there has been an expansion in the amount of published trial data and therefore TA93 is being updated within this guideline. The GDG accepted the recommendations of TA93 for the use of irinotecan and oxaliplatin but also wished to address the following issues:
- The value of combining irinotecan with an oral fluoropyrimidine.

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[11] http://guidance.nice.org.uk/TA93

- The optimal sequencing of oxaliplatin and irinotecan combinations.
- The value of raltitrexed in patients who cannot tolerate 5FU/FA based regimens of for whom these are inappropriate.

Due to a lack of trial data on direct comparisons between all relevant drug sequences a Mixed Treatment Comparison (MTC) was chosen to address the optimal sequencing question. This technique allows data from indirect comparisons to be used as evidence (see Figure 4.1).

This update of TA93 does not cover the value of biological agents since recommendations have already been made on their use in TA176[12] and TA212[13].

4.4.1 Oxaliplatin and irinotecan in combination with fluoropyrimidines

Clinical question: What is the effectiveness of oxaliplatin and irinotecan-based chemotherapy regimens for patients with advanced and metastatic colorectal cancer?

This clinical question includes both an update to identify new evidence that has become available after TA93[14] was issued (August 2005) and an expansion to the guideline 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)

Although there are data on the choice of chemotherapy regimens to treat patients with advanced and metastatic colorectal cancer, none of the studies identified by the systematic review provided a comprehensive analysis with which to directly answer the review question.

In the absence of direct, comparative evidence an indirect modelling exercise known as a Mixed Treatment Comparison was conducted to address these issues and make use of all available data. The outcome of this exercise was to inform decision-making regarding optimal combinations and sequences of chemotherapy for the management of advanced colorectal cancer. Full details of this analysis can be found in Appendix 2. 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.

Clinical evidence (see also Appendix 2)
After a review of the available evidence for this topic and consultation with the GDG, the following chemotherapy regimens were considered relevant to include within this clinical question:

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

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[12]http://guidance.nice.org.uk/TA176
[13] http://guidance.nice.org.uk/TA212
[14] http://guidance.nice.org.uk/TA93

The GDG identified ten sequences based on these chemotherapy regimens that were considered relevant to current clinical practice (Table 4.3). Sequences were limited to two lines of treatment.

**Table 4.3: Summary of ten chemotherapy treatment sequences of interest**

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

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).

A total of twenty-three studies formed the evidence network for the analysis of response rate and progress-free survival for first-line treatment (Colucci *et al.*, 2005; Comella *et al.*, 2005; Comella *et al.*, 2009; Cunningham *et al.*, 2009; Diaz-Rubio *et al.*, 2007; Douillard *et al.*, 2000; Ducreux *et al.*, 2010; Falcone *et al.*, 2007; Gennatas *et al.*, 2006; Giachetti *et al.*, 2000; Goldberg *et al.*, 2004; Goldberg *et al.*, 2006; de Gramont *et al.*, 2000; Hochster *et al.*, 2008; Kohne *et al.*, 2005; Kohne *et al.*, 2008; Koopman *et al.*, 2007; Martoni *et al.*, 2006; Porschen *et al.*, 2007, Saltz *et al.*, 2000; Seymour *et al.*, 2007; Souglakos *et al.*, 2006; Tournigand *et al.*, 2004). The evidence network is shown in Figure 4.1.

Figure 4.1: 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.

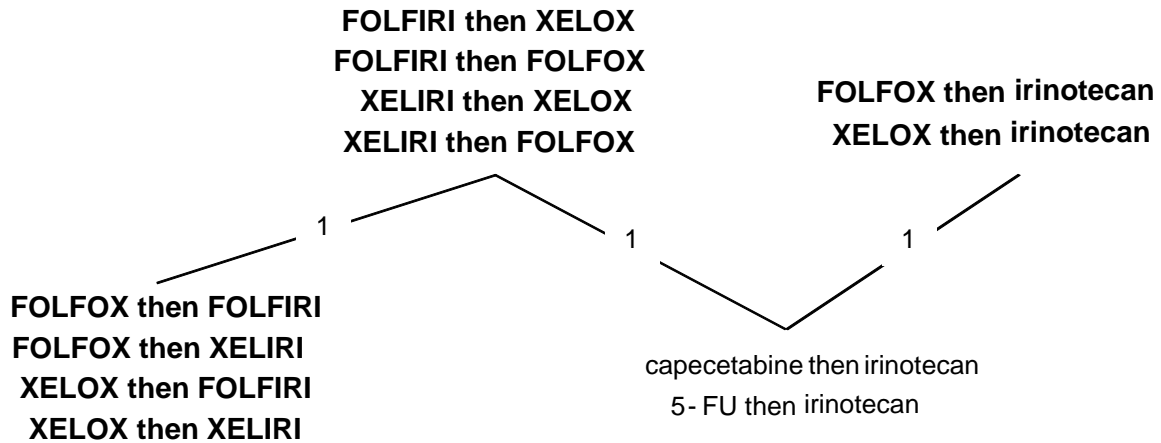The diagnosis and management of colorectal cancer: full guideline (November 2011)
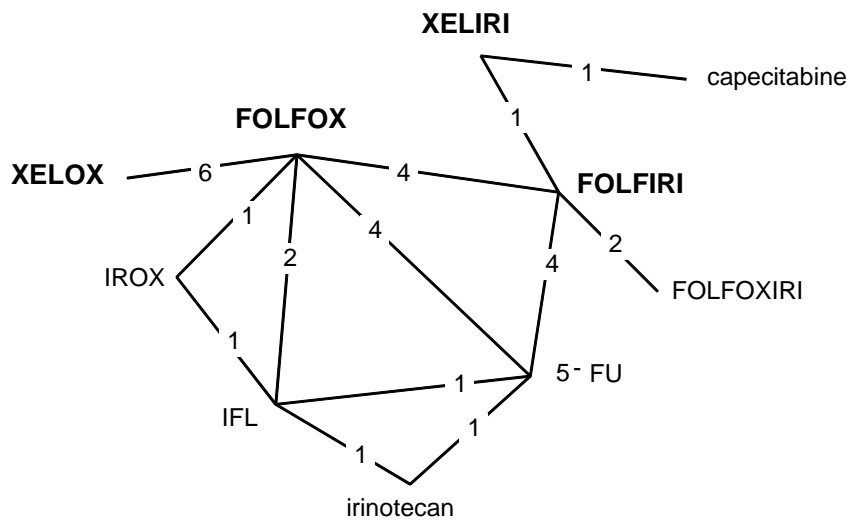
For the analysis of effectiveness of second-line treatment, the search for RCTs identified four studies in which two treatments of interest had been compared specifically as second-line chemotherapy (Haller *et al.*, 2008; Kim *et al.*, 2009; Rothenberg *et al.*, 2008; Rougier *et al.*, 1998). However 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 analysis.

The only other source of data on second-line response rates, PFS and overall survival 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; 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. In order to facilitate the analysis, two important assumptions were explored:

1. the oral and iv fluoropyrimidine formulations (capecitabine and 5-FU) are equally effective when used as part of a combination treatment
2. the first-line study by Cunningham *et al.* 2009 could be considered a quasi-sequenced study because the protocol pre-specified that patients who progressed on first-line treatment should be offered irinotecan as second-line treatment

The validity of these two assumptions was explored using statistical methods and through discussion with GDG members. Using these key assumptions for the analysis, a network of evidence was constructed for the relevant sequences of treatment as shown in Figure 4.2. 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.

Figure 4.2: Network of sequenced studies to inform second-line response rate, progression-free survival and overall survival (assuming equivalent effect of capecitabine and 5-FU).

FOLFIRI then XELOX
FOLFIRI then FOLFOX
XELIRI then XELOX
XELIRI then FOLFOX

FOLFOX then irinotecan
XELOX then irinotecan

1   1   1

FOLFOX then FOLFIRI
FOLFOX then XELIRI
XELOX then FOLFIRI
XELOX then XELIRI

capecetabine then irinotecan
5 - FU then irinotecan

Quality of the evidence

All studies that were identified for inclusion in the mixed or indirect treatment comparison were RCTs and were assessed using the NICE methodology checklist for randomised trials All studies included were considered to be methodologically sound. 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. Using a MTC method however, will allow for inbuilt considerations in the model in order to account for the indirectness of the data.

First-line treatment response rate and progression-free survival

The results of the MTC analysis for first-line treatments are shown in Table 4.3.

Table 4.3: Summary of response rates and PFS for first-line treatments

Treatment	Response rate (OR with 95% CrI)	PFS (HR with 95% CrI)
FOLFOX (reference)	1	1
XELOX	0.79 (0.63, 0.98)	1.07 (0.92, 1.25)
FOLFIRI	0.74 (0.61, 0.91)	1.09 (0.94, 1.26)
XELIRI	0.80 (0.23, 2.89)	1.43 (0.82, 2.48)

Note; For response rate, OR < 1 favours the reference treatment. For PFS, HR > 1 favours the reference treatment.

Second-line treatment response rates, progression-free survival and overall survival
The results of the indirect treatment comparison for sequences are shown in Table 4.4.

Table 4.4: Summary of response rates and PFS for second-line treatments (given as part of a sequence) and overall survival for sequences of treatment

Treatment sequences	Response rate for second-line treatment (OR with 95% CrI)	PFS for second-line treatment (HR with 95% CrI)	Overall survival for sequence of treatment (HR with 95% CrI)
FOLFOX/XELOX then **FOLFIRI/XELIRI** (reference)	1	1	1
FOLFOX/XELOX then **irinotecan**	4.80 (0.75, 18.28)	1.45 (0.94, 2.23)	0.96 (0.68, 1.37)
FOLFIRI/XELIRI then **FOLFOX/XELOX**	5.72 (1.21, 19.67)	1.68 (1.26, 2.23)	0.96 (0.74, 1.24)

Note: For response rate, OR < 1 favours the reference treatment. For PFS and overall survival, HR > 1 favours the reference treatment.

In first-line treatment, the results of the mixed treatment comparison 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.

For the endpoint overall survival, the indirect treatment comparison suggests no differences between the treatment sequences of interest.

Toxicity

Toxicity data was reported in a number of studies, though the consistency of reporting was variable. Commonly reported toxicities included nausea and vomiting, diarrhoea, neutropenia, febrile neutropenia, anaemia, palmar-plantar erythrodysesthesia (PPE), peripheral neuropathy and toxic death. MTC methods were not applied to toxicity data as there was insufficient data to inform the analysis.

For first-line regimens, the grade 3/4 toxicities that were most commonly reported across all treatments included diarrhoea (from 15.6% for FOLFOX to 30.3% for XELIRI), neutropenia (from 7.6% for XELOX to 28.7% for FOLFOX) and peripheral neuropathy (from 16.3% for FOLFOX to 18.3% for XELOX).

In second-line treatment, grade 3/4 neutropenia was one of the most commonly reported toxicities (from 22% for irinotecan to 33% for FOLFOX). It was also noted that single agent irinotecan was associated with a higher rate of grade 3/4 diarrhoea (22%) than the other treatments. Data should be interpreted with caution as only a small number of studies were available to inform regimen-specific toxicity rates in most cases.

<u>Quality of Life</u>

Quality of life was included as an outcome in a total of seven studies; four were first-line studies (Comella *et al.*, 2009; Falcone *et al.*, 2007; Douillard *et al.*, 2000; DeGramont *et al.*, 2000); two were second-line studies (Cunningham *et al*, 1999; Rougier *et al*, 1998) and one was a sequenced study (Koopman *et al.*, 2007).

Only one trial compared two treatments of interest (FOLFOX and XELOX) and only in first line (Comella at al., 2009). To compare quality of life between 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 (EORTC-QLQ-C30 version 3). 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.

Economic evaluation (see also Appendix 2)
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. In first line, patients receive one of four possible irinotecan or oxaliplatin-based combination chemotherapy regimens. Following first-line treatment, the model allows for a proportion of patients to discontinue treatment. The remaining proportion of patients go on to receive one of five possible second-line treatments (Figure 4.3).

Figure 4.3: Basic structure of the cost-effectiveness model. The same structure was applied to all ten treatment sequences in the analysis.
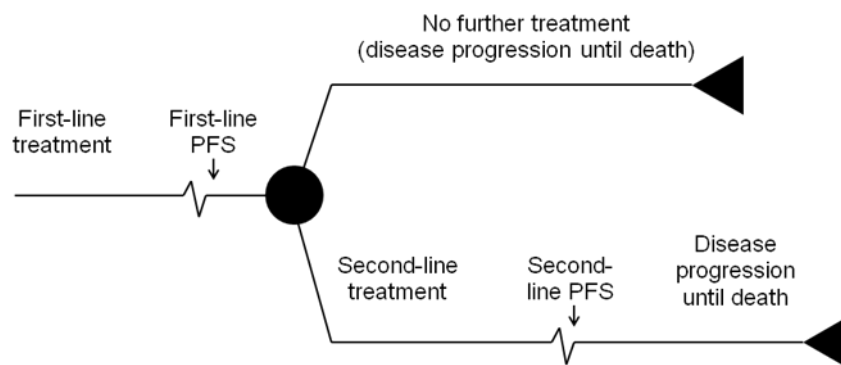
The main effectiveness outcome in the model is quality-adjusted life years (QALYs). The model assumes a lifetime time horizon. Survival time is partitioned in the model using the progression-free survival and overall survival results of the MTC analysis. While receiving chemotherapy and prior to the 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.

The impact of chemotherapy-related toxicities was taken into account in the model both in terms of disutility to the patient as well as cost associated with management. Toxicities in the

cost-effectiveness model were limited to those with most clinical relevance as well as data to support estimates of both the impact on patient well-being and cost. This included febrile neutropenia and grade 3 and 4 diarrhoea and vomiting.

The sources of data inputs for key parameters in the model are summarised briefly in Table 4.5. The model was made probabilistic to take into account the impact of parameter uncertainty on results.

Table 4.5: Key parameters and sources of data inputs for the cost-effectiveness model

Parameter	Source	Parameter uncertainty
PFS and overall survival	Mixed and indirect treatment comparison	Simulations from MTC
Proportion of patients discontinuing after first-line treatment	Review of clinical trials	Fixed
Health state utilities	Published literature (Best *et al.* 2010)	Beta distribution
Health state disutilities for toxicity	Published literature (using proxy estimates from metastatic breast cancer Lloyd *et al.* 2006)	Beta distribution
Toxicity rates	Review of clinical trials	Beta distribution
Toxicity management costs	National PbR tariff, NHS Reference Costs	Fixed
Drug cycles	Review of clinical trials	Gamma / uniform distribution
Drug unit costs	British National Formulary/NHS Commercial Medicines Unit	Fixed
Other healthcare resource use	Published literature (Guest *et al.* 2006)	Fixed
Other healthcare unit costs	National PbR tariff, NHS Reference Costs, PSSRU	Fixed

The results of the mixed and indirect treatment comparisons were used as inputs to conduct a cost-effectiveness analysis. This allowed the sequences to be ranked in order of cost-effectiveness. The total costs and total QALYs in the base case analysis for each of the ten sequences of chemotherapy are summarised in Table 4.6. 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.

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. Compared to the reference strategy, the sequence FOLFOX – FOLFIRI produces 0.019 more QALYs and incurs £2,051 in additional costs. This yields an incremental cost-effectiveness ratio (ICER) of £109,604/QALY.

Table 4.6: Total costs and effectiveness by treatment strategy

Strategy	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER
FOLFOX-irinotecan	£ 16,285	-	0.922	-	-
XELOX-FOLFIRI	£ 16,662	£ 377	0.919	-0.004	Dominated
XELIRI-XELOX	£ 16,798	£ 513	0.819	-0.104	Dominated

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XELOX-XELIRI	£ 16,894	£ 609	0.895	-0.027	Dominated
XELOX-irinotecan	£ 17,328	£ 1,043	0.900	-0.022	Dominated
XELIRI-FOLFOX	£ 17,334	£ 1,048	0.826	-0.096	Dominated
FOLFIRI-XELOX	£ 17,400	£ 1,115	0.903	-0.020	Dominated
FOLFIRI-FOLFOX	£ 17,935	£ 1,650	0.910	-0.012	Dominated
FOLFOX-FOLFIRI	£ 18,336	£ 2,051	0.941	0.019	£109,604/QALY
FOLFOX-XELIRI	£ 18,568	£ 2,283	0.917	-0.005	Dominated

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. This is particularly relevant in the present analysis given that the differences in total QALYs between several strategies are very small. Taking into account parameter uncertainty, probabilistic sensitivity analysis showed 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 willingness to pay (WTP) thresholds. The CEACs (see Appendix 2) 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.
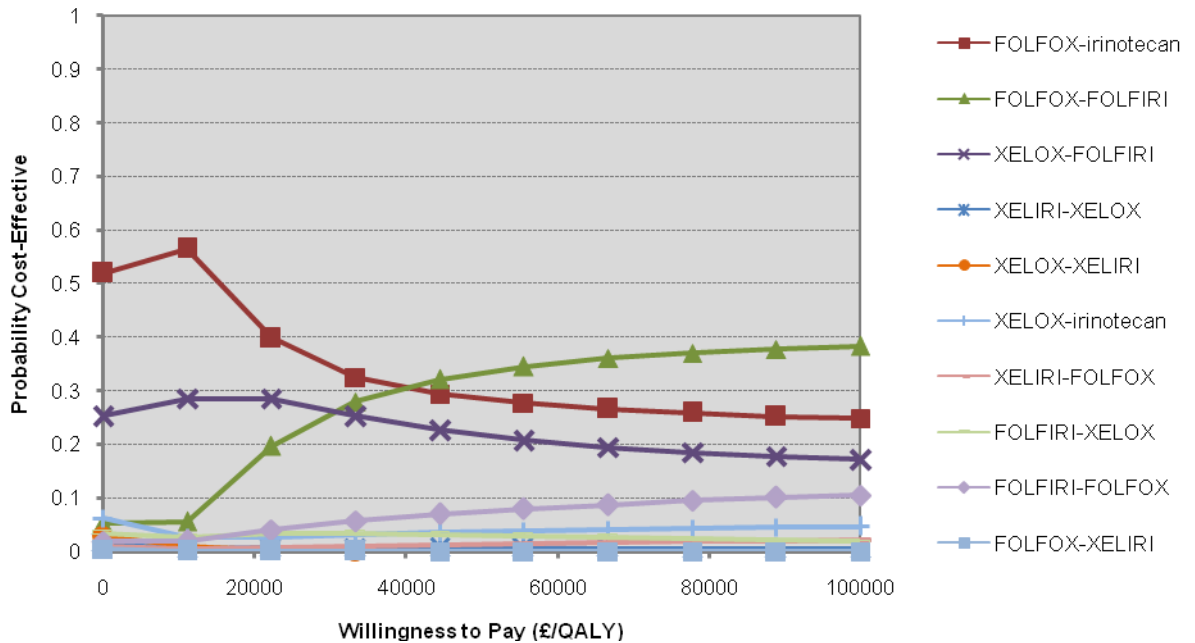
Sensitivity analysis – drug discounts
Currently available data on the impact of price discounts for generic pharmaceutical products across the NHS were applied to the economic analysis (see Table A2.24 in Appendix 2) and these results are presented in Table 4.7.

Table 4.7: Cost-effectiveness results for non-dominated strategies taking into account price discounts for generic pharmaceutical products

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

Subsequent probabilistic sensitivity analysis using these discounted drug prices showed there is greater uncertainty about which strategy has the highest probability of being cost effective. This is shown by the intersecting cost-effectiveness acceptability curves for FOLFOX-irinotecan, FOLFOX-FOLFIRI and XELOX-FOLFIRI over the range of WTP thresholds between approximately £20,000 and £50,000/QALY (Figure 4.4).

Figure 4.4 Cost-effectiveness acceptability curves using discounted drug prices

In this sensitivity analysis, when discounted prices for non-proprietary drugs were taken into account, the ICER for FOLFOX – FOLIRI vs FOLFOX-irinotecan fell to £47,800/QALY. Therefore taking parameter uncertainty and drug discounts into account, the treatment strategies FOLFOX-irinotecan, FOLFOX-FOLFIRI and XELOX-FOLFIRI were associated with the highest probability of being cost effective.

Conclusion

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.

Full details of the methods and results for the mixed treatment comparison and economic evaluation for this topic can be found in Appendix 2.

Recommendations
- When offering multiple chemotherapy drugs to patients with advanced and metastatic colorectal cancer consider one of the following sequences of chemotherapy unless they are contraindicated:
  - FOLFOX (folinic acid plus fluorouracil plus oxaliplatin) as first-line treatment then single agent irinotecan as second-line treatment **or**

- o FOLFOX as first-line treatment then FOLFIRI (folinic acid plus fluorouracil plus irinotecan[15]) as second-line treatment **or**
- o XELOX (capecitabine plus oxaliplatin) as first-line treatment then FOLFIRI (folinic acid plus fluorouracil plus irinotecan[15]) as second-line treatment.
- Decide which combination and sequence of chemotherapy to use after full discussion of the side effects and the patient's preferences.

Linking evidence to recommendations

The GDG considered the outcomes of progression-free survival, and overall survival to be particularly important. The GDG also considered response rate, toxicity and quality of life to be informative. However they noted that data on quality of life were limited. Cost-effectiveness was also considered to be important.

The GDG noted that there was little difference in clinical effectiveness between the sequences of interest. The GDG used Mixed Treatment Comparison (MTC) techniques to inform the clinical and economic analysis for this topic. The rationale for this type of analysis is detailed in Appendix 2.

The quality assessment of the individual trials included in the mixed treatment comparison showed that they were all of high methodological quality. The quality assessment for this MTC 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. Using a MTC method however, will allow for inbuilt considerations in the model in order to account for the indirectness of the data.

The GDG also noted from the base case health economic analysis that FOLFOX – irinotecan emerged as the least costly treatment of the 10 sequences investigated. All other strategies were dominated except FOLFOX – FOLFIRI. However the GDG recognised that because the difference in QALYs between sequences was small, even small changes to the difference in costs had a substantial impact on the ICER. The mean ICER for each sequence within the model was considered by the GDG. However given the uncertainty around these estimates the GDG considered the probability of each sequence being cost effective as the more significant determinant when making their recommendations.

Probabilistic sensitivity analysis using discounted drug prices showed that there is uncertainty about which sequence has the highest probability of being cost effective around a willingness to pay threshold of £20,000 - £30,000/QALY. The GDG also recognised that these discounted drug prices were based on currently available estimates which may change.

Given this uncertainty the GDG could not be sure that the reference strategy (FOLFOX – irinotecan) was the most cost effective at a willingness to pay threshold of £30,000 per QALY gained. They therefore decided to recommend that the three sequences shown by the probabilistic sensitivity analysis to have the highest probability of being cost effective (FOLFOX – irinotecan, FOLFOX – FOLFIRI and XELOX – FOLFIRI) be considered for the

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[15] At the time of publication (November 2011), irinotecan did not have UK marketing authorisation for second-line combination therapy. Informed consent should be obtained and documented.

treatment of patients with advanced and metastatic colorectal cancer, unless clinically contraindicated.

4.4.2 Raltitrexed

Clinical question: What is the most effective treatment for advanced colorectal cancer patients when 5-FU/FA based regimens are not tolerated or inappropriate

Clinical evidence
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 trials (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). Of 20 deaths considered related to raltitrexed, 11 were associated with a major protocol deviation. 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 *et al.*, 2008).

Recommendations
- Consider raltitrexed only for patients with advanced colorectal cancer who are intolerant to 5-fluorouracil and folinic acid or for whom these drugs are not suitable (for example, patients who develop cardiotoxicity). Fully discuss the risks and benefits of raltitrexed with the patient.
- Prospectively collect data on quality of life, toxicity, response rate, progression free survival and overall survival for all patients taking raltitrexed.

Linking evidence to recommendations
The GDG recognised that the population for this question must be "patients who are not able to tolerate 5FU/FA based regimens, or for whom 5FU/FA based regimens are inappropriate", to match the population used in TA93. Whilst this is the licensed indication for raltitrexed and therefore the population of interest, the GDG noted that it is currently not possible to identify those patients who are intolerant to 5FU/FA before they actually receive the drug. Therefore it is also not possible to randomise 5FU/FA intolerant patients to the interventions of interest. Consequently, there will never be any directly relevant evidence with which to answer this question.

Since the GDG agreed the efficacy of raltitrexed was likely to be the same for both 5FU/FA tolerant and intolerant patients, and TA93 had used 'indirect' evidence (from raltitrexed arms of trials comparing raltitrexed with 5FU/FA), a similar 'indirect' approach was used to update the raltitrexed part of TA93.

The GDG acknowledged that the review of the evidence had highlighted that the evidence base for raltitrexed has not changed significantly since TA93 and there was no good quality evidence to address the question being investigated. This lack of good quality evidence also meant it was not possible to conduct robust cost-effectiveness analysis for the use of raltitrexed.

The GDG highlighted that if patients who are intolerant to 5FU/FA are not able to receive raltitrexed, this will severely limit the potential treatment options for this group of patients. Both TA33 and TA93 have recommended that the use of raltitrexed is confined to appropriately designed clinical studies. However trials of raltitrexed in 5FU/FA intolerant patients have not happened so far and are unlikely to happen. The GDG were therefore concerned that the use of raltitrexed is being denied to a specific subgroup in which it is impossible to obtain direct evidence of effectiveness. Consequently they agreed to recommend that raltitrexed can be considered for the subgroup of patients with advanced colorectal cancer who are intolerant to 5FU/FA, so long as the risks and benefits are discussed with the patient and audit data are collected.

4.4.3   *Capecitabine and tegafur with uracil*
The recommendations in this section are from 'Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer', NICE technology appraisal guidance 61 (NICE, 2003)

Recommendations
- Oral therapy with either capecitabine or tegafur with uracil (in combination with folinic acid) is recommended as an option for the first-line treatment of metastatic colorectal cancer.
- The choice of regimen (intravenous 5-fluorouracil and folinic acid or one of the oral therapies) should be made jointly by the individual and the clinician(s) responsible for treatment. The decision should be made after an informed discussion between the clinician(s) and the patient; this discussion should take into account contraindications and the side-effect profile of the agents as well as the clinical condition and preferences of the individual.
- The use of capecitabine or tegafur with uracil to treat metastatic colorectal cancer should be supervised by oncologists who specialise in colorectal cancer.

Linking evidence to recommendations
These recommendations are from 'Guidance on the use of capecitabine and tegafur uracil for metastatic colorectal cancer', NICE technology appraisal guidance 61 (NICE, 2003). They were formulated by the technology appraisal and not by the guideline developers. They have been incorporated into this guideline in line with NICE procedures for developing clinical guidelines, and the evidence to support these recommendations can be found at www.nice.org.uk/TA61.

4.5   Biological agents in metastatic colorectal cancer
Recommendations on 'Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of monastic colorectal cancer' can be found in NICE technology appraisal guidance 212[16].

Recommendations on the use of 'Cetuximab for the first-line treatment of metastatic colorectal cancer' can be found in NICE technology appraisal guidance 176[17].

NICE's advice on the use of 'Cetuximab for the treatment of metastatic colorectal cancer following failure of oxaliplatin-containing chemotherapy (terminated appraisal)' can be found at http://guidance.nice.org.uk/TA150.

Recommendations on the use of 'Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer' can be found in NICE technology appraisal guidance 118[18].

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[16] www.guidance.nice.org.uk/TA212
[17] www.guidance.nice.org.uk/TA176
[18] www.guidance.nice.org.uk/TA118

4.6 Adjuncts to chemotherapy in unresectable metastatic disease

Up to 50% of patients with colorectal cancer will develop liver and/or lung metastases at some time during the course of their disease. Metastases can also arise at other sites in the body. The peritoneum may be the predominant or only route of spread in 10-15% of patients with colorectal cancer. Surgery for metastases is not always possible and, for example, only 10-20% of patients with liver metastases will have disease suitable for liver resection. Where metastatic disease is considered unresectable, systemic combination chemotherapy, with or without biological agents, is the standard of care. Systemic therapy alone can prolong median survival to approximately 2 years, but long term cure is unlikely.

Provided a good response is seen in patients with unresectable liver, lung or peritoneal disease following chemotherapy, then local procedures can be attempted to try to prolong the disease-free interval. These local procedures have been most applied to the liver where radiofrequency ablation (RFA) is the most commonly used local treatment, although conclusive data on the benefits have not yet been published. There are even less data on alternative local procedures such as microwave, laser, cryotherapy, radio-embolisation or stereotactic body radiotherapy (SBRT). Some of these local procedures can also be applied to lung metastases, depending on the size and position of individual lesions. Therefore, for those patients whose metastatic disease is considered unresectable but who have chemo-sensitive disease, the question remains what benefit is there to adding local treatment to consolidate chemotherapy response.

> **Clinical question: What is the most effective additional treatment to systemic chemotherapy to achieve cure or long term survival in patients with apparently unresectable metastatic disease?**

Clinical evidence
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 evidentiary benefits of including such studies was low and would not inform any recommendations regarding the best form of treatment for this patient group.

Research Recommendations
- Prospective studies should investigate and compare the effectiveness of techniques for refining local ablation (radiofrequency ablation, radioembolisation, microwave, cryotherapy, laser and stereotactic radiotherapy) in patients with metastatic colorectal cancer. Outcomes of interest are technical feasibility, local control, disease-free survival, overall survival, toxicity and quality of life.
- Consider patients for entry into NCRN approved studies on local ablative therapies.
- Novel techniques for the treatment of metastatic disease, including peritoneal carcinomatosis, should be carefully audited so that case-mix adjusted outcome data may be collected and evaluated.

Linking evidence to recommendations

The GDG acknowledged that there is currently no evidence available to answer this question. Therefore, the GDG could not recommend a particular treatment to achieve cure or long-term survival in patients with apparently unresectable metastatic disease.

The GDG noted that currently these treatments are being widely used without evidence of valid outcomes and an increasing number of patients are being considered for these interventions. Ongoing trials in this area have had difficulties in recruiting sufficient numbers of patients but with modern practice and increasing availability of these techniques (in a standardised form), the GDG believed there is value in recommending further research because trial recruitment is more likely to be successful.

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5 Ongoing care and support

The objectives of this chapter were to determine:
- the optimal method(s), frequency and duration of follow-up in asymptomatic patients who have undergone treatment with curative intent for colorectal cancer
- the information needs associated with bowel function for patients with colorectal cancer

5.1 Follow-up after apparently curative resection

Conventionally, the rationale for follow-up after curative resection for colorectal cancer recognized that local recurrence and/or metastatic rates were high and that early detection of metachronous disease offered a "second chance" at cure. However, it is increasingly recognized that follow-up may have several additional benefits beyond this conventional model, which include: facilitation of audit; characterisation of late-effects of treatment; and health-related opportunities such as early detection of co-morbidities, screening, and delivery of lifestyle advice. The optimal method of follow-up for each of these endpoints may be different. For the purpose of these guidelines, the optimal method will focus on conventional oncological endpoints. However, what should constitute good clinical practice in terms of follow-up has not been established and there is enormous variation in terms of frequency, duration, clinical setting and interventions employed. It is also not clear to what extent follow-up can be tailored to the risk of recurrence as defined by pathological stage.

Many UK centres use a policy of CT scanning, at variable intervals, with or without serial serum CEA to detect liver and/or lung metastases during the first few years after initial curative resection. This practice has arisen largely as a result of cumulative data at institutional and population levels that patients with resectable liver disease have an approximate 40% to 60% 5-year survival compared with a very low survival prospect at 5-years in those patients left untreated or unsuitable for liver resection. It is clear that early detection of recurrent colorectal cancer following potentially curative resection of the primary tumour confers survival benefit, and in some cases cure. Follow-up may also identify unresectable lesions which may become resectable after combination chemotherapy in around 22% of patients, again raising the possibility of long term survival and an advantage to active follow-up. A similar rationale may be extended to the early detection of local recurrent disease from rectal cancer as 5-year survival rates of 30% to 40% are attainable in specialist centres.

There is currently a paucity of data on quality of life related issues and colorectal cancer follow-up. Moreover, the specific question of whether or not the earlier detection of recurrent disease affects quality of life is complex. Preliminary data suggest that intensive follow-up is not deleterious in terms of quality of life. However, there are still unexplored issues, of which two examples are worth mentioning. First, with ever increasing sensitivity among surveillance tools, there will be inevitable increases in false positive tests. Second, intensive follow-up brings forward the date of recurrence detection.

> **Clinical 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?**

Clinical evidence
Two meta-analyses summarised the results of randomised trials of the use of intensive follow-up after curative resection for colorectal cancer (Tjandra and Chan, 2007; Jeffery *et al.*, 2007). A protocol for intensive follow-up was not defined because studies in the meta-

analysis used different protocols. Thus, the results of the meta-analyses should be interpreted as evaluating the principle of intensive versus less intensive follow-up rather than the assessment of specific follow-up regimens as the included studies are heterogeneous in this regard.

There is moderate quality evidence of significant overall survival benefit at 5 years with intensive follow-up (Tjandra and Chan, 2007; 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 and Chan, 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; Tjandra and Chan, 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; Tjandra and Chan, 2007).

A single prospective comparative cohort study was identified during update searches (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.

Intensive versus less intensive follow-up
From two systematic reviews and meta-analysis (Jeffery *et al.*, 2007; Tjandra and Chan, 2007) more intensive follow-up was associated with improved 5-year overall survival. Jeffery *et al.* (2007) recorded an 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%CI: -0.11 to -0.73]. Tjandra and Chan (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 was very little evidence with which to support the use of any specific tests in follow-up; a single study reported on the use of colonoscopy 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.*, 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).

Table 5.1 GRADE profile: In asymptomatic patients who have undergone treatment with curative intent for colorectal cancer is intensive follow up more effective than less intensive or no follow-up

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				**No of patients**		**Effect**		
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

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Economic evaluation

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 and Olsen, 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 and Olsen, 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 (Table 5.2).

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 in the reviewed publication. Costs of both follow up and treatment of recurrences were included in the analysis. Costs were based on the study-specific treatments and as these trials predated the routine use of adjuvant chemotherapy, 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.

Table 5.2: Modified GRADE profiles for included economic studies

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
Renehan *et al.*, 2004	Patients treated for colorectal cancer	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	Minor limitations
		Intensive follow up (based on 5 trials)	£4758	4.97 life years lost	£2479	0.73 life years gained	£3402 / LYG			
	Comments: Incremental health outcomes were measured in terms of life years gained. There is some uncertainty about the impact that quality adjusting survival would have on the ICER, but this is unlikely to change the conclusion of the study.									
Macafee *et al.*, 2008	Patients who have undergone resection for colorectal cancer	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	Potentially serious limitations
		Intensive follow up (FACS)	£68.6 mi	1412 resectable recurrences	£15.4 mi	853 resectable recurrences	£18,077 / additional resectable recurrence			
	Comments: Effects were measured in terms of the number of resectable recurrences identified. The time horizon was limited to 5 years. An appropriate willingness to pay threshold for interpreting the ICER results is not known.									

Recommendations

- Offer follow-up to all patients with primary colorectal cancer undergoing treatment with curative intent. Start follow-up at a clinic visit 4 to 6 weeks after potentially curative treatment.
- Offer patients regular surveillance with:
  - a minimum of two CTs of the chest, abdomen and pelvis in the first 3 years **and**
  - regular serum carcinoembryonic antigen tests (at least every 6 months in the first 3 years).
- Offer a surveillance colonoscopy at 1 year after initial treatment. If this investigation is normal consider further colonoscopic follow-up after 5 years, and thereafter as determined by cancer networks. The timing of surveillance for patients with subsequent adenomas should be determined by the risk status of the adenoma.
- Start reinvestigation if there is any clinical, radiological or biochemical suspicion of recurrent disease.
- Stop regular follow-up
  - when the patient and healthcare professional have discussed and agreed that the likely benefits no longer outweigh the risks of further tests **or**
  - when the patient cannot tolerate further treatments.

Linking evidence to recommendations

Overall survival was the most consistently reported outcome. Survival with good quality of life was considered the endpoint of most importance to patients and health professionals. All outcomes were considered useful but evidence was limited for some outcomes (for example quality of life and late effects of treatment).

The GDG assessed the benefits of intensive follow-up versus less intensive and found evidence that improved survival is associated with more intensive follow-up. However there was variability in the components and frequency of the different intensive protocols in the evidence.

The GDG considered detection of recurrence to be a critical goal in follow-up because doing so would enable some patients to be cured. Whilst CEA will not detect all recurrence, the GDG considered that its use would be beneficial in achieving this goal. The GDG were also concerned that the use of CT scans and CEA tests for follow-up was inconsistent across cancer networks, and thus, a minimum standard of care had to be recommended based on clinical experience and the need to promote patient confidence. The GDG were not able to recommend one specific protocol from the evidence. Instead they elected to recommend a pragmatic protocol of follow-up.

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.

The GDG also assessed the potential harms, namely increased patient anxieties from intensive testing. The number of studies of this endpoint were few but there was no strong evidence that the intervention of intensive follow-up is associated with increased anxieties across a wide range of patients.

The GDG chose not to recommend further research on oncological outcomes related to follow-up because they were aware that relevant trials were already underway.

The use of intensive follow-up may incur an increased cost on resources, particularly imaging. The trade-off is improved survival and probable improvement in quality of life.

The overall quality of evidence on was assessed as low to moderate by GRADE methodology.

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.

Research recommendation
- Strategies to integrate oncological surveillance with optimising quality of life, reducing late effects, and detecting second cancers in survivors of colorectal cancer should be developed and explored.

5.2   Information about bowel function

Treatment and care needs to take into account patients' individual needs and preferences. Good communication is essential, supported by evidence based information, allowing patients to reach informed decisions about their care. If the patient agrees, families and carers should have the opportunity to be involved in decisions about treatment and care.

Treatment for colorectal cancer often causes a change in bowel function. This can be distressing for patients and have other adverse effects, including dietary restrictions and changes in body image and sexual function. Patients want to know what to expect after surgery, what is normal and when they should seek further medical advice.

Allied to quality of life issues, follow-up allows identification of specific late effects of treatment. For colorectal cancer, bowel function is the commonest late effect but historically has not been addressed in most of the large randomised controlled trials. This is now changing and there are limited data available to inform patients needs in terms of supplying clear, useful information. What is available has mainly evolved from the interest of various types of healthcare professionals but the key question: is what do patients' identify as their information needs?

Clear and effective communication of information can improve wellbeing and quality of life.

Clinical question: In patients with colorectal cancer, what are the information needs associated with bowel function?

Clinical evidence
There were a small number of studies 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 investigating 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 respondents 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.*, 2004; Nikoletti *et al.*, 2008). The best time for the provision of information was considered to be 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).

Two studies which considered patient perspective were identified on update searches (Beaver *et al.*, 2010; 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 this was not limited 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 it was more important to know where their family could go to get help with dealing with their illness. The study also 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 changes 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. 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 consultants 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).

Recommendations
- Before starting treatment, offer all patients information on all treatment options available to them (including no treatment) and the potential benefits and risks of these treatments, including the effect on bowel function.
- Before surgery, offer all patients information about the likelihood of having a stoma, why it might be necessary, and how long it might be needed for.
- Ensure a trained stoma professional gives specific information on the care and management of stomas to all patients considering surgery that might result in a stoma.
- After any treatment, offer all patients specific information on managing the effects of the treatment on their bowel function. This could include information on incontinence, diarrhoea, difficulty emptying bowels, bloating, excess flatus and diet, and where to go for help in the event of symptoms.
- Offer verbal and written information in a way that is clearly understood by patients and free from jargon. Include information about support organisations or internet resources recommended by the clinical team.

Linking evidence to recommendations

The GDG looked for evidence primarily concentrating on the patient perception of information needs, not needs reported by health professionals. There was surprisingly little evidence with only a small number of studies, all of which were qualitative in design and with heterogeneous inclusion and exclusion criteria. Older patients and those with more severe disease were under represented, they may have different needs but the evidence is not clear.

The GDG looked at what information was useful, who should deliver it, when and in what format. The impact of information delivery and quality of life outcomes were also examined. The recommendations are based on the available evidence and the expertise of the GDG. Patients' lives are profoundly altered by the diagnosis and treatment of their bowel cancer. There was a strong agreement in the GDG that more needs to be known from patients about their own information requirements.

Research recommendations
- Further research should be undertaken to determine which side effects, associated with bowel function, patients consider have the greatest impact on their quality of life after treatment.

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6 PROMs for colorectal cancer patients

Research recommendation
- Colorectal cancer-specific patient-reported outcome measures (PROMs) should be developed for use in disease management and to inform outcome measures in future NCRN clinical trials.

Linking evidence to recommendations
Reviewing the evidence for this guideline highlighted the lack of data on patient perspectives on all aspects of treatment. The GDG agreed that it was crucial that these data were collected and therefore recommended that colorectal cancer specific PROMs be developed to inform what patient perspective data should be collected in future NCRN clinical trials.

Appendix 1

Summary of the 5th edition of the TNM staging system for colorectal cancer and comparison with Dukes' stage

Tumour
T1   the tumour is confined to the submucosa
T2   the tumour has grown into (but not through) the muscularis propria
T3   the tumour has grown into (but not through) the serosa
T4   the tumour has penetrated through the serosa and the peritoneal surface. If extending directly into other nearby structures (such as other parts of the bowel or other organs/body structures) it is classified as T4a. If there is perforation of the bowel, it is classified as T4b.

Nodes
N0*   no lymph nodes contain tumour cells
N1^   there are tumour cells in up to 3 regional lymph nodes
N2^   there are tumour cells in 4 or more regional lymph nodes

Metastases
M0   no metastasis to distant organs
M1   metastasis to distant organs

Dukes' stage
Dukes' stage A = T1N0M0 or T2N0M0
Dukes' stage B = T3N0M0 or T4N0M0
Dukes' stage C = any T, N1, M0 or any T, N2, M0
Dukes' stage D = any T, any N, M1

* A tumour nodule in the pericolic or perirectal adipose tissue without evidence of residual lymph node is regarded as a lymph node metastasis if it is >3mm in diameter. If it is <3mm in diameter, it is regarded as discontinuous tumour extension
^If there are tumour cells in non-regional lymph nodes (i.e. in a region of the bowel with a different pattern of lymphatic drainage to that of the tumour), that is regarded as distant metastasis (pM1)

Appendix 2

Mixed treatment comparison and cost-effectiveness analysis for sequences of oxaliplatin and irinotecan-based chemotherapy in the treatment of advanced and metastatic colorectal cancer

1   Introduction

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:

1. the use of irinotecan or oxaliplatin in combination with the oral fluoropyrimidine capecitabine
2. 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 A2.1). Sequences were limited to two lines of treatment.

Table A2.1: Summary of ten chemotherapy treatment sequences of interest

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

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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.

2   Quality of included studies

All studies that were identified for inclusion in the mixed or indirect treatment comparison were RCTs and were assessed using the NICE methodology checklist for randomised trials. This assessment 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 the included studies.

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.

3 Evidence synthesis methods

3.1 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 A2.1. A list of included studies is provided in Table A2.2.

Figure A2.1: 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.
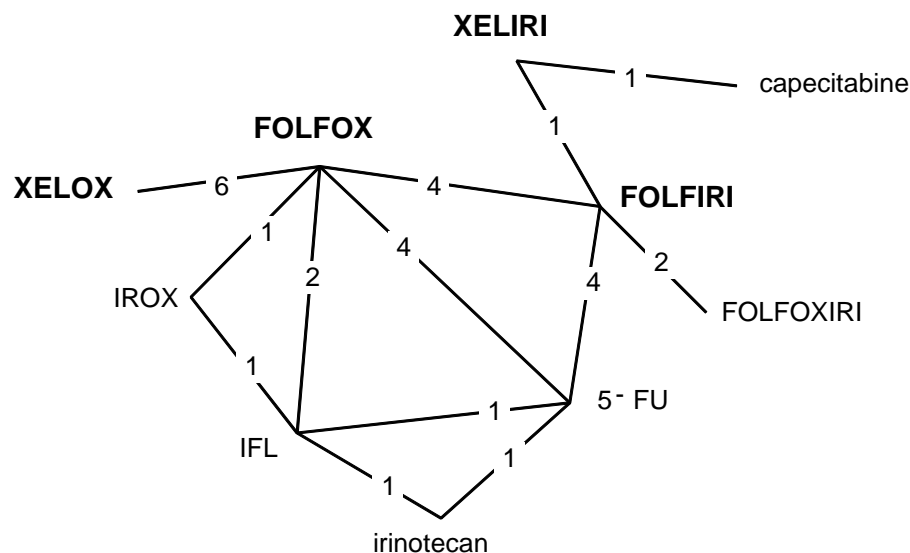
Table A2.2: Studies that informed the MTC for response rate and progression-free survival for first-line treatments.

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

3.1.1 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 $\delta_{jk} \sim \text{N}(d(t_{jk}) - d(t_{j1}), \sigma^2)$ 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.

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3.1.2 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.

3.1.3 First-line progression-free survival relative effects

All twenty-three studies listed in Table A2.2 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

$$y_{jk} \sim \text{Normal}(\delta_{jk}, W_{jk}) \text{ with } \delta_{jk} \sim \text{N}(d(t_{jk})-d(t_{j1}), \sigma^2) \qquad j=1,\ldots,17, \; k=2,3$$

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 and Ades, 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

$$\ln(M_{jk}) \sim \text{Normal}(m_{jk}, V_{jk}) \qquad j=1,\ldots,5, \, k=1,2$$

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 $\delta_{jk} \sim N(d(t_{jk}) - d(t_{j1}), \sigma^2)$, 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.

3.1.4 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; Ducreux *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.

3.2 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 A2.3). 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.

Table A2.3: 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

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

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; 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 A2.4), 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 A2.2. 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 A2.2: Network of sequenced studies to inform second-line response rate, progression-free survival and overall survival (assuming equivalent effect of capecitabine and 5-FU).
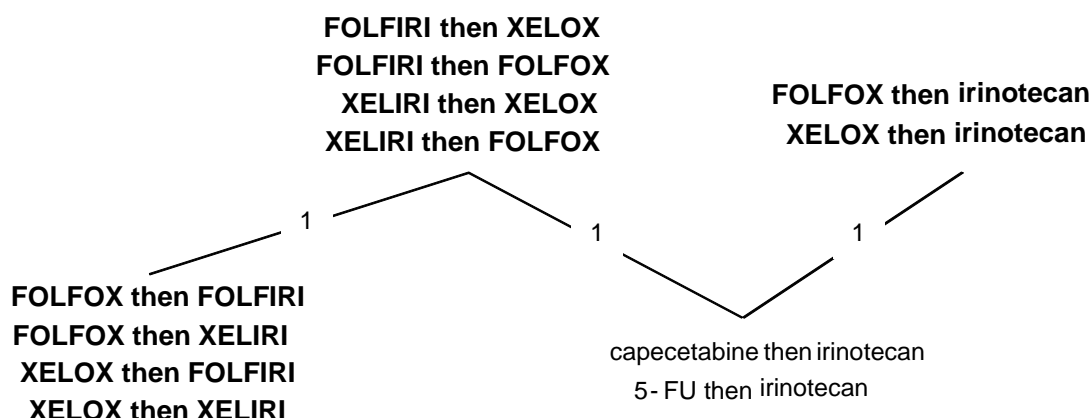

Table A2.4: Sequenced studies included in the MTC analysis to inform second-line response rate, progression-free survival and overall survival.

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

3.2.1 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.

3.2.2 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

$$y_{jk} \sim \text{Normal}(d(t_{jk})\text{-}d(t_{j1}),\ W_{jk})\ \text{with}\ j\text{=}1,2,3,\ k\text{=}2$$

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(λ_{jk})- V_{jk}/2 as before, and ln(λ_{jk})= μ_j+$d(t_{jk})$-$d(t_{j1})$.

3.2.3 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.

3.3 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.

3.4 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, $1/\sigma^2$~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.

4 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.

4.1 First-line treatment response rate

The results for first-line treatment response rate are shown in Tables A2.5 and A2.6.

Table A2.5: 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.

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	

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.

Table A2.6: Posterior summaries of the absolute response rate for first-line treatment (median with 95% credible interval).

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)

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.

4.2 First-line treatment progression-free survival

The results for first-line treatment progression-free survival are shown in Tables A2.7 and A2.8.

Table A2.7: 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.

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	

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.

Table A2.8: 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.

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)

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.

4.3   Second-line treatment response rates for sequences

The results for second-line treatment response rate are shown in Tables A2.9 and A2.10.

Table A2.9: 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.

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	

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.

Table A2.10: 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	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)

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.

4.4   Second-line treatment progression-free survival for sequences

The results for second-line progression-free survival are shown in Tables A2.11 and A2.12.

Table A2.11: 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.

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	

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.

Table A2.12: 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.

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)

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).

4.5 Overall survival for sequences

The results for overall survival for sequences of treatment are shown in Tables A2.13 and A2.14.

Table A2.13: 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.

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	

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.

Table A2.14: 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.

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)

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.

# 5 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 A2.3). 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 A2.3: Basic structure of the cost-effectiveness model. The same structure was applied to all ten treatment sequences in the analysis.
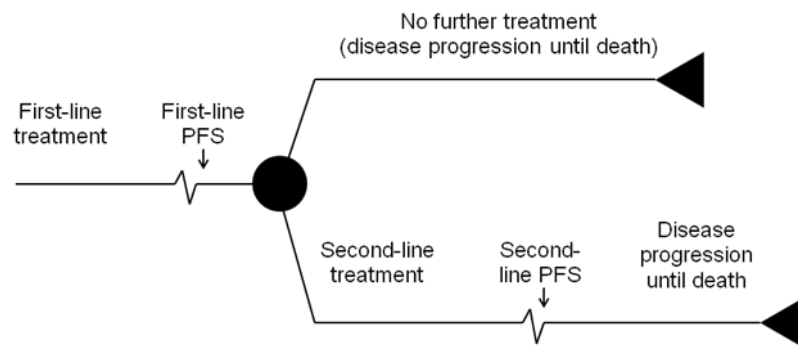
The MTC analysis produced estimates of progression-free survival for each of the first-line treatments. Some assumptions (described in detail above) were made in order to create a connected evidence network to estimate second-line progression-free survival and overall survival for the treatment sequences 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).

6 Cost-effectiveness model inputs

6.1 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.

6.2 Toxicity rates

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 A2.15 and A2.16. 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.

Table A2.15: First-line treatment toxicity rates used in the cost-effectiveness analysis

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,

Treatment	Mean (%)	Standard dev	Distribution	Sources
				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 A2.16: Second-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

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Treatment	Mean (%)	Standard dev	Distribution	Sources
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

6.3   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 A2.17 summarises the utility estimates used in the analysis.

Table A2.17: Utility values used in the cost-effectiveness 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

6.4 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 A2.18).

Table A2.18: Drug doses and administration schedule

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

6.4.1 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 A2.19 and A2.20.

Table A2.19: Drug cost per cycle

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 A2.20: Drug administration 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

* includes equipment costs associated with delivering IV chemotherapy

6.4.2 Number of cycles

The duration of treatment in terms of number of cycles was extracted from the clinical literature (Table A2.21). 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.

Table A2.21: Number of treatment cycles

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

6.5 Cost of adverse event management

Estimates of the cost of management of febrile neutropenia and severe diarrhoea were based on NHS reference costs (Table A2.22). 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.

Table A2.22: Cost of management for febrile neutropenia and grade 3/4 diarrhoea

Toxicity	Cost	Source
Febrile neutropenia	£ 6,278	PbR Tariff 2010-2011 (PA45Z)
Diarrhoea (Grade 3/4)	£ 388	NHS Reference Costs 2008-2009 (FZ45C)

6.6   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 A2.23). Supportive care costs were applied throughout the model during both active treatment and progressive disease.

Table A2.23: Supportive care costs

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)

6.7   Sensitivity analyisis

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 A2.24). 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.

Table A2.24: Comparison of list price and discounted drug cost per cycle

| 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

7 Cost-effectiveness analysis results

7.1 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 A2.25. 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. The scatter plot in Figure A2.4 shows the total costs and total QALYs across simulations for the ten sequences.

Table A2.25: Total costs and effectiveness by treatment strategy (in order of increasing cost)

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

Figure A2.4: Scatter plot showing total costs and total QALYs for all ten treatment sequences (only 1000 of 30,000 simulation results are shown)
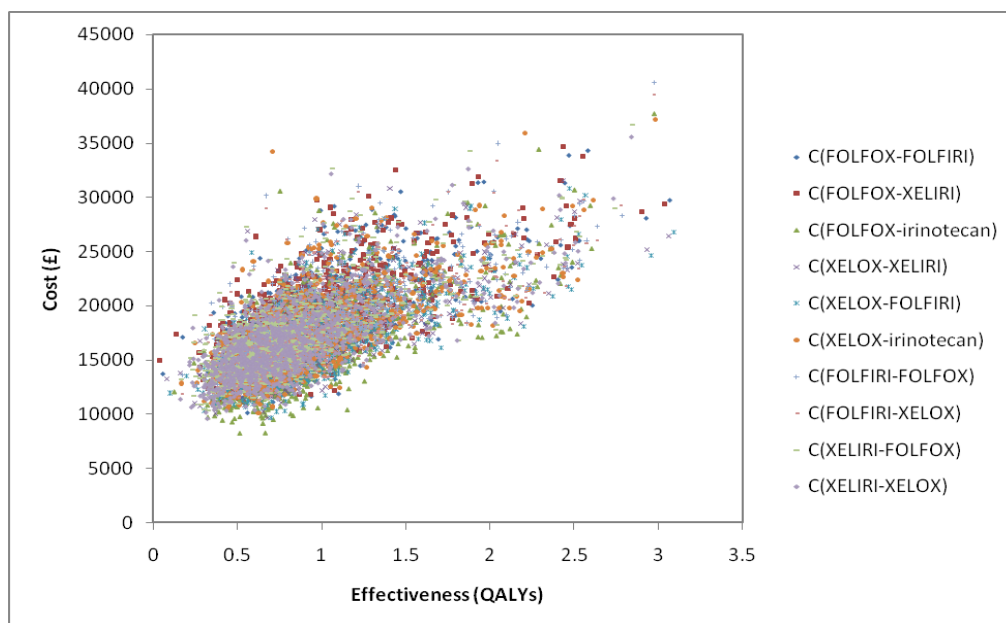

Taking FOLFOX – irinotecan as the reference (least expensive) strategy, all other strategies were shown to be less effective and also more costly (i.e. dominated) except the sequence FOLFOX – FOLFIRI (Table A2.26 and Figure A2.5). Compared to the reference strategy, the sequence FOLFOX – FOLFIRI produces 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.

**Table A2.26: Incremental cost effectiveness results**

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

Figure A2.5: 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).
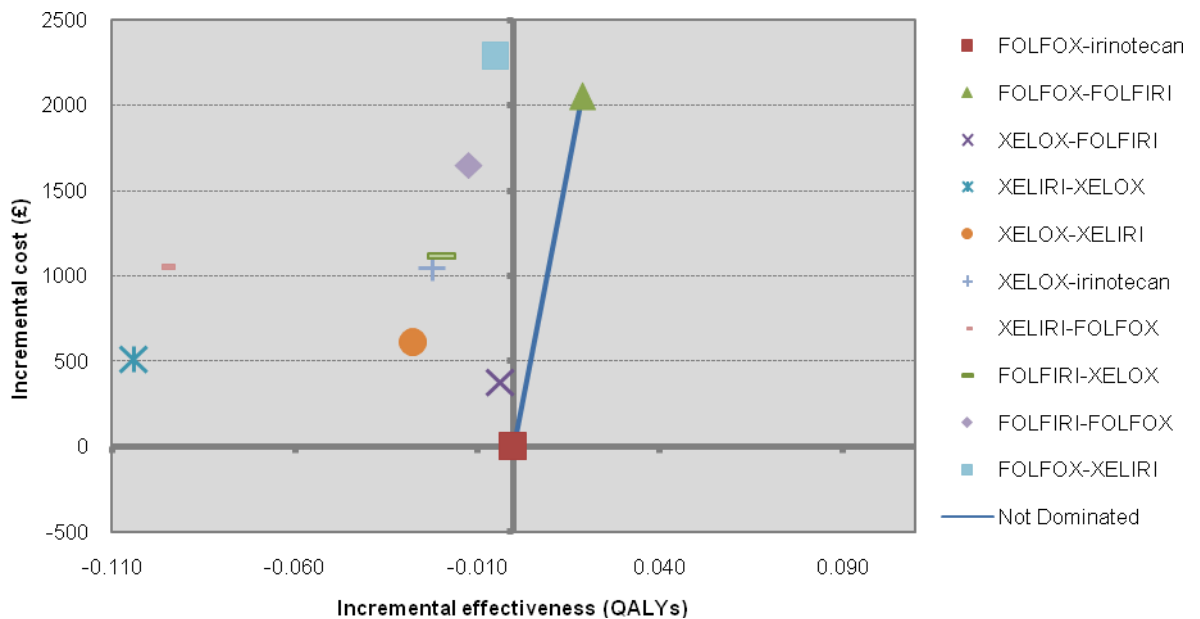
The incremental cost effectiveness results presented above reflect the expected costs and effectiveness estimates for the treatment sequences of interest, however given uncertainty associated with many parameters in the model, we are also interested in the distribution over incremental costs, incremental 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 A2.6).

Figure A2.6: Cost-effectiveness acceptability curves for the base case analysis
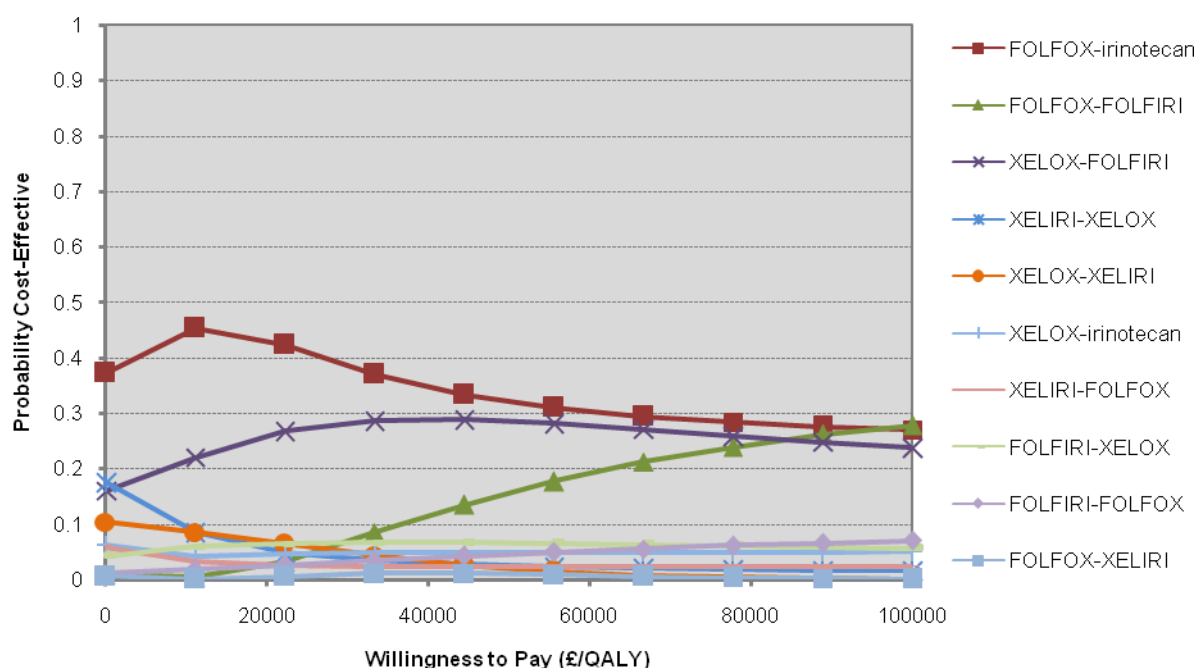

7.2 Sensitivity analysis - drug discounts

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 A2.27).

Table A2.27: Cost-effectiveness results for non-dominated strategies taking into account price discounts for generic pharmaceutical products

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

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 £50,000/QALY (Figure A2.7).

Figure A2.7: Cost-effectiveness acceptability curves using discounted drug prices
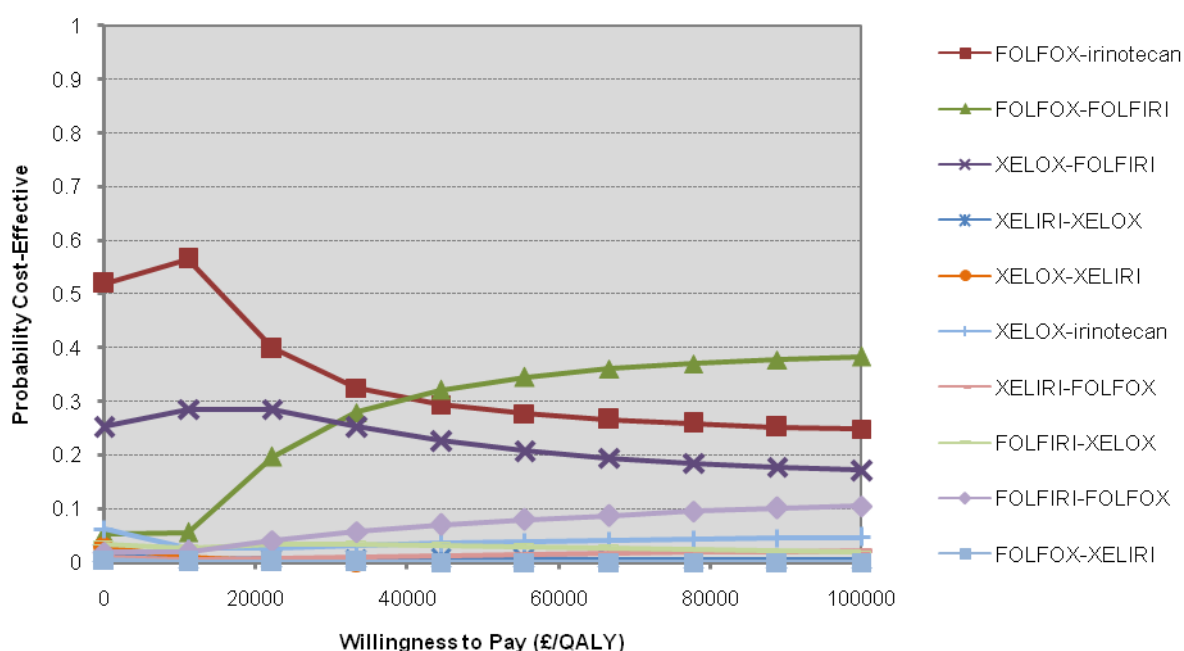
8 Discussion

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.

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Appendix 3

Abbreviations

5FU/FA	5-fluorouracil/folinic acid
APR	abdomino-perineal resection
CEA	carcinoembryonic antigen
CRM	circumferential resection margin
CT	computed tomography
DRE	digital rectal examination
ENT	ear, nose, throat
ESD	endoscopic submucosal dissection
EUS	endoscopic ultrasound
FOLFIRI	irinotecan in combination with 5-flourouracil and folinic acid
FOLFOX	oxaliplatin in combination with 5-flourouracil and folinic acid
GRADE	grading of recommendations, assessment, development and evaluation
MDT	multidisciplinary team
MRI	magnetic resonance imaging
NBOCAP	National Bowel Cancer Audit Programme
NCRN	National Cancer Research Network
PET-CT	positron-emisson tomography fused with computed tomography
PROM	patient reported outcome measure
QALY	quality adjusted life years
RCT	randomised controlled trial
RFA	radiofrequency ablation
SBRT	stereotactic body radiotherapy
SCPRT	short course preoperative radiotherapy
SEMS	self-expanding metal stent
TEMS	transanal endoscopic micro surgery
TME	total mesorectal excision
XELOX	oxaliplatin in combination with capecitabine
XELIRI	irinotecan in combination with capecitabine

Appendix 4

Glossary

Abdomino-perineal resection
A combined operation through the abdomen and perineum which involves the removal of the anus, rectum, and distal sigmoid colon, resulting in the need for a permanent colostomy

Adenoma
A benign tumour of the epithelium arising from the lining of the bowel and resembling a wart-like polyp

Anterior resection
An operation through the abdomen which involves the removal of part of the rectum, preserving the anal canal with a join made between the remaining colon and anal canal.

Barium enema
X-ray examination of the rectum and colon in which an X-ray contrast medium (dye) (usually barium sulfate) is injected through the anus as an enema into the rectum and colon and X-rays are taken

Case series
A series of case reports involving patients who were given similar treatment. Reports of case series usually contain information about individual patients, including demographic information, information on diagnosis, treatment, response to treatment and follow-up.

Circumferential resection margin
Following surgical resection of a length of bowel containing a colorectal cancer, this defines the distance laterally (to the side) between the deepest point of cancer invasion and the edge of the removed bowel. If such a margin of healthy tissue exists then the surgical resection is considered R0, if the cancer comes microscopically into contact with this margin then the resection is considered R1, and if the surgeon has cut across the cancer to remove the surgical specimen then the resection is considered R2.

Chemoradiotherapy
Chemotherapy given concurrently with radiotherapy

Chemotherapy
Drug(s) that kill cells usually when they are dividing. These drugs are usually used in the treatment of cancer.

Colonoscopy
A method of examining the lining of the entire colon (from rectum to ceacum) and obtain tissue samples (biopsies) using an endoscope.

Computed tomography (CT)
A diagnostic imaging technique that uses X-rays and a computer to produce detailed 3 dimensional pictures of cross sections of the body.

Contrast enema study
A generic term used to describe barium enema, but sometimes using X-ray contrast media (dyes) other than barium

CT colonography
A medical imaging procedure which uses x-rays and computers to produce two- and three-dimensional images of the colon (large intestine) from the lowest part, the rectum, all the way to the lower end of the small intestine and display them on a screen.

Endoscopic decompression
Emergency treatment using telescopes of a bowel that has become totally blocked by the presence of a colon cancer that was previously not suspected.

Endoscopic submucosal dissection
Surgical removal of a colorectal adenoma or early cancer using an operating telecsope

Endoscopic ultrasound
Ultrasound examination of the bowel (usually rectum) using an operating telescope to determine how far the tumour has spread into the surrounding healthy tissues.

False negative
An individual that is truly positive for a disease, but which a diagnostic test classifies as disease-free

False positive
An individual that is truly disease-free, but which a diagnostic test classifies as positive for a disease.

Flexible sigmoidoscopy
Endoscopic examination of the lower large bowel and rectum

Hepatectomy
Surgical resection of the liver

Laparoscopic surgery
A minimally invasive surgical approach where the surgeon makes several small incisions to access the interior of the body, using operating telescopes.

Laparotomy
A surgical opening of the abdominal cavity

Local control
Control of cancer at a particular body site.

Local recurrence
The reappearance of cancer cells after treatment, at the same place they were originally found. The reappearance of cancer cells after treatment, at the same place they were originally found.

Magnetic resonance imaging (MRI)
A diagnostic imaging technique that uses powerful electromagnets and a computer to produce well-defined images of the body's internal structures.

Meta-analysis
A method of summarising previous research by reviewing and combining the results of a number of different clinical trials.

Metachronous metastatic disease
Disease that is detected elsewhere in the body after apparently curative surgery for the primary colorectal cancer.

Metastases/Metastatic
Spread of cancer away from the original site to somewhere else in the body, usually via the bloodstream or the lymphatic system.

Morbidity
A diseased condition or state.

Multidisciplinary team (MDT)
A team with members from different healthcare disciplines (including for example, oncology, pathology, radiology, nursing).

Observational study
A non-randomised study that observes the characteristics and outcomes over time of subjects who do and do not take a particular therapy.

Overall survival
The time one lives after a diagnosis of cancer. Often quoted as a percentage chance of living a number of years (e.g. 5 or 10).

Peritoneal carcinomatosis
Cancer that is found/recurs in the peritoneum (lining of the abdominal cavity) at either the time of diagnosis or after apparently curative surgery for primary colorectal cancer

Polyp
A polyp is an abnormal growth of tissue projecting from a mucous membrane. If it is attached to the surface by a narrow elongated stalk it is said to be pedunculated. If no stalk is present it is said to be sessile.

Positive margin (see circumferential resection margin)
Positive margin refers to cancer in which the surgeon is physically unable to remove all of the disease with a margin of healthy normal tissue, and so there is concern that it is possible that cancerous disease might remain/have been left behind.

Positron emission tomography
A diagnostic imaging technique using a radio-active tracer which shows increased tissue metabolism.

Radioembolisation
A technique by which potentially therapeutic radiation can be directly injected (and hopefully be of benefit) into secondary colorectal cancers which have spread to the liver.

Radiofrequency ablation
A minimally invasive, targeted treatment in which a small needle - attached to a device that delivers radiofrequency (RF) energy - is inserted into a tumor. The RF energy is then applied to heat and destroy the cancerous tissue.

Radiotherapy
A treatment for cancer that uses high energy ionising radiation (usually X-rays) to kill cells.

Randomised controlled trials (RCTs)

A clinical trial in which subjects are randomised to different groups for the purpose of studying the effect of a new intervention, for example a drug or other therapy.

Segmental resection

A surgical procedure to remove part of the colon or rectum.

Self-expanding metal stent

A metallic tube, or stent, used in order to hold open a structure in the gastrointestinal tract in order to allow the passage of bowel content if the bowel is blocked (obstructed).

Sensitivity

The proportion of individuals who have disease correctly identified by the study test.

Short course preoperative radiotherapy

Radiotherapy immediately and directly before surgery for rectal cancer, with the intention of reducing the risk of cancer returning after appropriate surgery at the site of the primary rectal cancer in the pelvis.

Specificity

The proportion of individuals who do not have a disease and who are correctly identified by the study test.

Staging

Clinical description of the size and spread of a patient's tumour, fitting into internationally agreed categories.

Stereotactic radiotherapy

A way of giving a high dose of external radiotherapy very precisely to a tumour. It uses a computer and scanning machines to build a picture of the tumour. Then multiple beams of radiotherapy are aimed at the tumour from different directions.

Stoma

A surgically created opening which connects a portion of the body cavity to the outside environment.

Systematic review

A review of the literature carried out in order to address a defined question and using quantitative methods to summarise the results.

Tenesmus

The feeling of wishing to pass a bowel motion when the rectum is empty.

Total mesorectal excision

A standard technique for the treatment of colorectal cancer, devised some 20 years ago. A significant length of the bowel around the tumour is removed, and the removed lymph system scrutinised for cancerous activity.

Transanal endoscopic microsurgery

A surgical technique to remove early rectal cancers using an operative microscope under general anaesthetic

True negative

A negative test result for an individual that is truly negative for a particular disease.

True positive
A positive test result for an individual that is truly positive for a particular disease.

Appendix 5

Guideline scope

1   Guideline title
Colorectal cancer: diagnosis and management of colorectal cancer

1.1 Short title
Colorectal cancer

2   The remit
The Department of Health has asked NICE: 'To prepare a clinical guideline on the diagnosis and management of patients with all stages of primary colorectal cancer. This excludes any population screening and surveillance of high-risk groups, including patients with a family history and patients with inflammatory bowel disease.'

3   Clinical need for the guideline
3.1 Epidemiology
a)   Colorectal cancer is the third most common cancer in the UK, with approximately 32,300 new cases diagnosed and 14,000 deaths in England and Wales each year. Around half of people diagnosed with colorectal cancer survive for at least 5 years after diagnosis.

b)   Occurrence of colorectal cancer is strongly related to age, with 83% of cases arising in people older than 60 years. It is anticipated that as our elderly population increases, colorectal cancer will increase in prevalence.

3.2 Current practice
a)   There are variations in:
- the management of locally advanced disease
- the management of patients presenting with stage IV disease
- the management of symptomatic primary colorectal cancer
- the role of sequenced therapies combining surgery, ablation, chemotherapies and biological agents in advanced disease.

b)   Patients with poor performance status, who are therefore at a greater risk of treatment-related morbidity and mortality, are increasingly being considered for radical interventions. These interventions may be curative but their impact needs to be balanced against the overall prognosis of the patient.

c)   The costs of the radical therapies for colorectal cancer have increased significantly over the past decade, posing a major health economics challenge.

d)   A clinical guideline will help to address these issues and offer guidance on best practice.

4   The guideline
The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

If we are to produce a high-quality guideline within the allotted time it will not be possible to cover the entire care pathway described by the remit (see section 2). Therefore we intend to focus on clinical issues:

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- for which there is uncertainty or disagreement on best practice
- that will have the most significant impact on the clinical service and on the management of patients with colorectal cancer
- that could improve health outcomes and/or make better use of health resources
- that could help to avoid unlawful discrimination and reduce health inequalities.

A list of the prioritised clinical questions (section 4.4) has been developed using advice from the Guideline Development Group chair and clinical lead, attendees at the NICE colorectal cancer stakeholder workshop and registered stakeholders. We acknowledge that there will be some important topics that are not part of the final prioritised list.

The areas that will be addressed by the guideline are described in the following sections.

4.1 Population
4.1.1 Groups that will be covered
a) Adults (18 years and older) with newly diagnosed adenocarcinoma of the colon.
b) Adults with newly diagnosed adenocarcinoma of the rectum.
c) Adults with relapsed adenocarcinoma of the colon.
d) Adults with relapsed adenocarcinoma of the rectum.
e) No patient subgroups needing special consideration have been identified.

4.1.2 Groups that will not be covered
a) Patients with anal cancer.
b) Children (younger than 18) with colorectal cancer.
c) Patients with primary or secondary lymphoma of colon and rectum.
d) Patients with pure small cell carcinoma of colon and rectum.
e) Patients with carcinoid tumours of colon and rectum.
f) Patients with high grade neuroendocrine tumours of colon and rectum.
g) Patients with adenocarcinoma with some neuroendocrine differentiation.
h) Patients with gastrointestinal stromal tumours (GIST) or sarcoma of colon and rectum.

4.2 Healthcare setting
a) Primary care.
b) Secondary care.
c) Tertiary care in cancer centres, and regional centres for specialties such as stenting, surgery for metastatic disease, endorectal therapies, radiotherapy and ablation therapies.
d) NHS hospice care

4.3 Main outcomes
a) Sensitivity of diagnostic tests
b) Specificity of diagnostic tests
c) Overall survival
d) 5 year survival
e) 10 year survival
f) Median survival
g) Disease free survival
h) Treatment related morbidity
i) Treatment related mortality
j) Number and severity of adverse events
k) Quality of life

4.4 Clinical management

4.4.1 Key clinical issues that will be covered

a) Effective diagnostic modalities in establishing a diagnosis of colorectal cancer in patients referred with suspicious symptoms (considering effectiveness of methods in terms of sensitivity and specificity).

b) Tumour staging for defining treatment at all stages of disease in patients with colorectal cancer.

c) Curative treatment for patients with stage I or polyp cancer.

d) Treatment for patients presenting as emergencies with the symptoms of colorectal cancer (such as radical surgery with curative intent, defunctioning stoma or endoscopic stenting).

e) The sequence of local and systemic treatments in patients presenting with locally-advanced colorectal cancer (such as surgery, stenting, radiotherapy and chemotherapy).

f) The sequence of local and systemic treatments in patients presenting with synchronous metastatic disease (such as surgery, stenting, radiotherapy and chemotherapy).

g) Effectiveness of preoperative a) short course radiotherapy and b) chemo-radiotherapy in treating patients with rectal cancer.

h) For patients with stage II and III rectal cancer, the indications for adjuvant chemotherapy after surgery.

i) For patients with high-risk stage II colon cancer, the indications for adjuvant chemotherapy after surgery.

j) The sequence of ablation, surgery, regional therapy and systemic therapy, to achieve cure or long-term survival in patients with apparently incurable metastatic disease.

k) Clinical indications for performing liver metastasectomy in patients with colorectal cancer metastasised to the liver.

l) Clinical indications for performing extrahepatic metastasectomy in patients with colorectal cancer.

m) Chemotherapy for patients with advanced and metastatic disease including an update of NICE technology appraisal guidance 93.

n) Methods and frequencies of follow up after potentially curative treatment for colorectal cancer (primary or metastatic).

o) For patients diagnosed with colorectal cancer what colorectal specific support should be offered.

4.4.2 Clinical issues that will not be covered

a) Population screening.

b) Surveillance of high-risk groups, including patients with a family history of colorectal cancer and patients with inflammatory bowel disease.

4.5 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually only be from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see 'Further information').

4.6 Status

4.6.1 Scope

This is the final scope.

4.6.2 Timing
The development of the guideline recommendations will begin in May 2009.

5 Related NICE guidance
5.1 Published guidance
5.1.1 NICE guidance to be updated
This guideline will update and replace the following NICE guidance.
- Irinotecan, oxaliplatin and raltitrexed for advanced colorectal cancer (review). NICE technology appraisal guidance 93 (2005). Available from www.nice.org.ukTA93.

5.1.2 Other related NICE guidance
- Cetuximab for the treatment of metastatic colorectal cancer following failure of oxaliplatin-containing chemotherapy – terminated appraisal. NICE technology appraisal 150 (2008). See www.nice.org.uk/TA150.
- Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. NICE technology appraisal guidance 118 (2007). Available from www.nice.org.uk/TA118
- Radiofrequency-assisted liver resection. NICE interventional procedure guidance 211 (2007). Available from www.nice.org.uk/IPG211
- Microwave ablation for the treatment of metastases in the liver. NICE interventional procedure guidance 220 (2007). Available from www.nice.org.uk/IPG220
- Laparoscopic surgery for the treatment of colorectal cancer (review). NICE technology appraisal guidance 105 (2006). Available from www.nice.org.uk/TA105
- Preoperative high dose rate brachytherapy for rectal cancer. NICE interventional procedure guidance 201 (2006). Available from www.nice.org.uk/IPG201
- Capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes' C) colon cancer. NICE technology appraisal guidance 100 (2006). Available from www.nice.org.uk/TA100
- Referral guidelines for suspected cancer. NICE clinical guideline 27 (2005). Available from www.nice.org.uk/CG027
- Computed tomographic colonography (virtual colonoscopy). NICE interventional procedure guidance 129 (2005). Available from www.nice.org.uk/IPG129
- Laparoscopic liver resection. NICE interventional procedure guidance 135 (2005). Available from www.nice.org.uk/IPG135
- Improving supportive and palliative care for adults with cancer. Cancer service guidance (2004). Available from: www.nice.org.uk/csgsp
- Improving outcomes in colorectal cancers: manual update. Cancer service guidance (2004). Available from www.nice.org.uk/csgcc
- Selective internal radiation therapy for colorectal metastases in the liver. NICE interventional procedure guidance 93 (2004). Available from www.nice.org.uk/IPG93
- Radiofrequency ablation for the treatment of colorectal metastases in the liver. NICE interventional procedure guidance 92 (2004). Available from www.nice.org.uk/IPG92
- Capecitabine and tegafur uracil for metastatic colorectal cancer. NICE technology appraisal guidance 61 (2003). Available from www.nice.org.uk/TA61

5.2 Guidance under development
NICE is currently developing the following related guidance (details available from the NICE website).
- Cetuximab for the first line treatment of metastatic colorectal cancer. NICE technology appraisal guidance. Publication expected April 2009.
- Irinotecan for the adjuvant treatment of colon cancer. NICE technology appraisal guidance. Publication date to be confirmed.

- Bevacizumab in combination with oxaliplatin and either 5FU or capecitabine for the treatment of metastatic colorectal cancer. NICE technology appraisal guidance. Publication date to be confirmed.

6   Further information

Information on the guideline development process is provided in:

- 'How NICE clinical guidelines are developed: an overview for stakeholders' the public and the NHS'
- 'The guidelines manual'.

These are available from the NICE website (www.nice.org.uk/guidelinesmanual). Information on the progress of the guideline will also be available from the NICE website (www.nice.org.uk).

Appendix 6

People and organisations involved in production of the guideline

6.1   Members of the Guideline Development Group
6.2   Organisations invited to comment on guideline development
6.3   Individuals carrying out literature reviews and complementary work
6.4   Members of the Guideline Review Panel

Appendix 6.1

Members of the Guideline Development Group (GDG)

GDG Chair

Mr Graeme Poston   Consultant Surgeon, Aintree University Hospital NHS
                                     Foundation Trust

GDG Lead Clinician

Dr Diana Tait   Consultant Clinical Oncologist/Associate Medical
                                     Director, Clinical Governance, The Royal Marsden NHS
                                     Foundation Trust

Group Members

Dr Rosaleen Beattie   Medical Director/Consultant in Palliative Medicine, St
                                     John's Hospice, Lancaster (until January 2011)

Dr Clare Byrne   Advanced Nurse Practitioner, Aintree University
                                     Hospital NHS Foundation Trust

Mr John Chapman   Patient/carer member

Mrs Linda Devereux   Associate Director, Merseyside and Cheshire Cancer
                                     Network

Dr Rob Glynne-Jones   Consultant Clinical Oncologist/Macmillan Lead for GI
                                     Oncology, Mount Vernon Cancer Centre

Dr Mark Harrison   Consultant Oncologist, Mount Vernon Cancer Centre

Ms Christine Holman   Patient/carer member

Professor Mohammad Ilyas   Professor of Pathology and Honorary Consultant,
                                     Queens Medical Centre, Nottingham

Dr Timothy Iveson   Consultant Medical Oncologist, Southampton General
                                     Hospital

Dr John Martin   Consultant Gastroenterologist, Charing Cross Hospital,
                                     London

Ms Yvette Perston   Colorectal Clinical Nurse Specialist, Cardiff and Vale
                                     NHS Trust

Mr Andrew Radcliffe   Consultant Colorectal Surgeon, Cardiff and Vale NHS
                                     Trust[19]

Mr Andrew Renehan   Senior Lecturer, University of Manchester /Honorary
                                     Consultant Surgeon, Christie Foundation NHS Trust

Mrs Cheryl Richardson   Superintendent Radiographer (MRI), The Royal
                                     Marsden NHS Foundation Trust

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[19] Retired in May 2010

Mr Nick Ryan	Patient/carer member
Dr Eamon Staunton	GP, Hampshire
Dr Alasdair Taylor	Consultant Radiologist, University Hospitals of Morecambe Bay NHS Trust

Declarations of interest

The Guideline Development Group were asked to declare any possible conflicts of interest which could interfere with their work on the guideline. The interests that were declared are as follows:

GDG Member	Interest Declared	Type of Interest	Decisions Taken
Mr Graeme Poston	Received an honorarium from Pfizer in April 2008 for giving a lecture on the multi-disciplinary management of colorectal cancer	Personal pecuniary non-specific	Declare and can participate in discussion on all topics as not specific to particular drug.
	Received an honorarium from Merck in October 2008 for giving a lecture on the multi-disciplinary management of colorectal cancer.	Personal pecuniary non-specific	Declare and can participate in discussion on all topics as not specific to particular drug.
	Consulted to Biocompatibles in March 2008 on the potential role or regionally targeted chemotherapy injected directly into the blood supply to the liver before liver surgery for secondary colorectal cancer.	Personal pecuniary specific	Declare and must withdraw from discussions on all topics that include regionally targeted chemotherapy until March 2009
	Invited to be the PI for the second round of data analysis of EORTC 40983 (Phase III study of surgery with or without neoadjuvant and adjuvant oxaliplatin, 5FU/leucovorin in patients with resectable colorectal liver metastases.	Personal non-pecuniary	Declare and can participate in discussion on all topics as involvement is for data analysis
	Appointed to the Medical Advisory Board of Beating Bowel Cancer to advise on a campaign to publicise TA179.	Personal non-pecuniary	Declare and can participate in discussion on all topics as no fees are involved.
	Involved in the CLOCC trial (randomized phase II study investigating the role of local treatment of liver metastases by radiofrequency combined with chemotherapy and of chemotherapy alone in patients with unresectable colorectal liver metastases).	Personal non-pecuniary	Declare and must withdraw from discussion on the topic about "the most effective additional treatment to systemic chemotherapy to achieve cure or long term survival in patients with apparently unresectable metastatic disease".
Professor Mohammad Ilyas	Organised a scientific meeting on advances in colorectal cancer which was sponsored by Astra Zeneca.	Non-personal pecuniary non-specific	Declare and can participate in discussions on all topics as the interest is non-specific
	Received an honorarium from A. Menarini Diagnostics in May 2011 for an advisory board on image analysis in pathology	Personal pecuniary non-specific	Declare andcan participate in discussion on all topics as interest is non-specific.
	Will be undertaking evaluation of molecular pathology for the SCOT trial which begins recruitment in July 2011. No funding is being received for this activity.	Personal non-pecuniary	Declare and can participate in discussion on all topics as interest is non-specific.

Dr Timothy Iveson	Received an honorarium from Roche in September 2008 for an advisory board on bevacizumab and the resection of colorectal liver metastases.	Personal pecuniary specific	Declare and must withdraw from discussions on all topics that include bevacizumab until January 2010[20].
	Received an honorarium from Roche in January 2009 for an advisory board on bevacizumab and the treatment of colorectal cancer	Personal pecuniary specific	Declare and must withdraw from discussions on all topics that include bevacizumab until January 2010.
	Joined the advisory board of Bowel Cancer UK in June 2011	Personal non-pecuniary	Declare and can participate in discussion of all topics
	Took over the role of Chief Investigator of the SCOT trial in June 2011. The SCOT trial will investigate different durations of adjuvant chemotherapy in colorectal cancer and will begin recruiting in July 2011.	Personal non-pecuniary	Chairperson's action taken that can participate in discussion of topics on adjuvant chemotherapy since no financial renumeration is being received by the individual or their department; the individual has recently taken over the role of Chief Investigator and was therefore not instrumental in designing the trial protocol; the trial will not start recruitment until after the final GDG meeting; only editorial amendments to the recommendations on adjuvant chemotherapy were considered during the final GDG meeting.
Dr Rob Glynne-Jones	Chief Investigator of XERXES study (phase I/II dose escalation study of IV cetuximab in combination with 5 day weekly oral capecitabine and preoperative radiotherapy in patients with rectal cancer).	Non-personal pecuniary, specific	Declare and must withdraw from discussions on any topics that include cetuximab in combination with capecitabine in rectal cancer[21].
	Medical advisor to Bowel Cancer UK.	Personal non-pecuniary	Declare and can participate in discussion of all topics.
	Attended an advisory board, organised by Roche, on treatment of colorectal cancer in January 2009.	Personal non-pecuniary	Declare and can participate in discussion of all topics since advisory board was non-specific and no fee received.
	Attended an advisory board, organised by Sanofi Aventis, on aflibercept (VEGF trap) in November 2009.	Personal non-pecuniary	Declare and can participate in discussion of all topics since afilbercept not covered by the guideline and no fee received.
	Attended an advisory board, organised by Nucletron, on brachytherapy in January 2010.	Personal non-pecuniary	Declare and can participate in discussion of all topics since brachytherapy not covered by the

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[20] Bevacizumab was not included in any of the topics investigated by the guideline and was therefore not discussed by the GDG.

[21] Cetuximab in combination with capecitabine was not included in any of the topics investigated by the guideline and was therefore not discussed by the GDG.

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			guideline and no fee received.
	Attended an advisory board, organised by Merck, on the management of colorectal cancer in June 2010.	Personal non-pecuniary	Declare and can participate in discussion of all topics since advisory board was non-specific and no fee received.
Dr Mark Harrison	Submitted a trial proposal to NCRN in September 2009 investigating irinotecan + capecitabine vs irinotecan + 5FU/FA for second line treatment of metastatic colorectal cancer.		Free drug support was withdrawn in September 2010 so the trial was terminated before recruitment started. Consequently no conflict of interest.
	Received an honorarium from Roche for attending an advisory board on stomach cancer.	Personal pecuniary non-specific	Declare and can participate in discussions on all topics as the interest is non-specific
	Received an honorarium from Roche for chairing a meeting on angiogenesis in colorectal cancer.	Personal pecuniary specific	Declare and must withdraw from discussions on any topics that angiogenesis in colorectal cancer[22]
Mr Andrew Radcliffe	Received a fee from Sanofi Pasteur MSD for attending an advisory board in March 2011 on the role of HPV vaccination in the prevention of anal cancer.	Personal pecuniary non-specific	Declare and can participate in discussions on all topics as the interest is non-specific.
Mr Andrew Renehan	Received honorariums from Novo Nordisk for attending advisory boards in August and September 2009 and September and October 2010 to discuss insulin analogues and cancer risk.	Personal pecuniary non-specific	Declare and can participate in discussions on all topics as the interest is non-specific.
	Received a fee from Sanofi Pasteur MSD for attending an advisory board in March 2011 on the role of HPV vaccination in the prevention of anal cancer.	Personal pecuniary non-specific	Declare and can participate in discussions on all topics as the interest is non-specific.

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[22] Angiogenesis in colorectal cancer was not included in any of the topics investigated by the guideline and was therefore not discussed by the GDG.

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Appendix 6.2

Organisations invited to comment on guideline development

The following stakeholders registered with NICE and were invited to comment on the scope and the draft version of this guideline.

Abbott GmbH & Co KG
Abbott Laboratories Limited
ACPGBI Nurses Forum
Age Concern England
Airedale NHS Foundation Trust
Almac Diagnostics
American Medical Systems UK
Amgen UK Ltd
Arden Cancer Network
Association for Palliative Medicine of Great Britain and Ireland
Association of British Insurers (ABI)
Association of Cancer Physicians
Association of Chartered Physiotherapists in Oncology and Palliative Care
Association of Clinical Biochemists, The
Association of Clinical Pathologists
Association of Coloproctology of Great Britain and Ireland
Association of Genetic Nurses and Counsellors
Association of Laparoscopic Surgeons of Great Britain and Ireland
Association of Surgeons in Primary Care
Association of the British Pharmaceuticals Industry (ABPI)
AstraZeneca UK Ltd
Barnsley Hospital NHS Foundation Trust
BASO ~ The Association for Cancer Surgery
Beating Bowel Cancer
Beckman Coulter UK Ltd
Belfast Health and Social Care Trust
Birmingham Cancer Network
Birmingham Womens NHS Foundation Trust
BMJ
Bolton PCT
Boston Scientific Limited
Bowel Screening Wales
Brighton and Sussex University Hospitals Trust
Bristol-Myers Squibb Pharmaceuticals Ltd
British Association for Counselling and Psychotherapy
British Geriatrics Society
British National Formulary (BNF)
British Nuclear Medicine Society
British Pain Society
British Psychological Society, The
British Society for Human Genetics
British Society of Gastroenterology
British Society of Gastrointestinal and Abdominal Radiology (BSGAR)
British Society of Interventional Radiology
British Society of Paediatric Gastroenterology, Hepatology & Nutrition (BSPGHAN)
Bullen Healthcare Company Ltd, The
BUPA

Cambridge University Hospitals NHS Foundation Trust (Addenbrookes)
Cancer Care Cymru
Cancer Research UK
Care Quality Commission (CQC)
Central Lancashire PCT
Central South Coast Cancer Network
Christie Hospital NHS Foundation Trust
CIS'ters
CLIC Sargent
CM&D Pharma Limited
Cochrane Pain, Palliative and Support Care Group
College of Occupational Therapists
Coloplast Limted
Connecting for Health
ConvaTec
Daiichi Sankyo UK
Department for Communities and Local Government
Department of Health
Department of Health Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI)
Department of Health, Social Services & Public Safety, Northern Ireland (DHSSPSNI)
Derby-Burton Cancer Network
Derbyshire Mental Health Services NHS Trust
Dorset Cancer Network
East Lancashire Hospitals NHS Trust
East Midlands Cancer Network
Essex Cancer Network
Eusapharma (Europe) Ltd
Ferring International Center
Ferring Pharmaceuticals Ltd
GE Healthcare
Gloucestershire Hospitals NHS Trust
Greater Manchester and Cheshire Cancer Network
Greater Manchester and Cheshire Cardiac and Stroke Network
Greater Midlands Cancer Network
Guerbet Laboratories Ltd
Harrogate and District NHS Foundation Trust
Heart of England NHS Foundation Trust
Hospira UK Limited
Humber and Yorkshire Coast Cancer Network
Institute of Biomedical Science
Johnson & Johnson Medical
Joint Collegiate Council for Oncology
Kent & Medway Cancer Network
Leeds PCT
Leicestershire Northamptonshire and Rutland Cancer Network
Liverpool Community Health

Lothian University Hospitals Trust
Luton & Dunstable Hospital NHS Foundation Trust
Lynns Bowel Cancer Campaign
Macmillan Cancer Support
MAST Group
Maternity Health Links
Medicines and Healthcare Products Regulatory Agency (MHRA)
Merck Serono
Merck Sharp & Dohme Ltd
Ministry of Defence (MoD)
MRC-CTU
National Cancer Research Institute (NCRI)
National Colorectal Cancer Nurses Network
National Council for Palliative Care
National Patient Safety Agency (NPSA)
National Public Health Service for Wales
National Treatment Agency for Substance Misuse
NCC - Cancer
NCC - Mental Health
NCC - National Clinical Guidance Centre (NCGC)
NCC - Women & Children
Nestle Clinical Nutrition
NETSCC, Health Technology Assessment
NHS Bedfordshire
NHS Clinical Knowledge Summaries Service (SCHIN)
NHS Direct
NHS Improvement
NHS Kirklees
NHS Knowsley
NHS Oxfordshire
NHS Plus
NHS Quality Improvement Scotland
NHS Sefton
NHS Sheffield
NHS Western Cheshire
Norgine Pharmaceuticals Ltd
North East London Cancer Network
North Tees and Hartlepool Acute Trust
North Trent Cancer Network
North West London Cancer Network
North Yorkshire and York PCT
Northern Devon Healthcare NHS Trust
Northern Ireland Cancer Network
Northern Ireland Chest Heart & Stroke
Nottingham University Hospitals NHS Trust
Novartis Pharmaceuticals UK Ltd
Nucletron B.V.
Nutricia Clinical Care
Nutricia Ltd (UK)
Ovarian Cancer Action
Patients Council
PERIGON Healthcare Ltd
Pfizer Limited

Pharmacosmos
Plymouth Hospitals NHS Trust
Poole and Bournemouth PCT
Primary Care Society for Gastroenterology (PCSG)
psc-support
QResearch
Randox Laboratories Ltd
Roche Diagnostics
Roche Products Limited
Rotherham NHS Foundation Trust
Royal College of Anaesthetists
Royal College of General Practitioners
Royal College of General Practitioners Wales
Royal College of Midwives
Royal College of Nursing
Royal College of Obstetricians and Gynaecologists
Royal College of Paediatrics and Child Health
Royal College of Pathologists
Royal College of Physicians London
Royal College of Psychiatrists
Royal College of Radiologists
Royal College of Surgeons of England
Royal Pharmaceutical Society of Great Britain
Royal Society of Medicine
Sandwell PCT
Sanofi-Aventis
Scottish Clinical Biochemistry Managed Diagnostic Network
Scottish Intercollegiate Guidelines Network (SIGN)
Sheffield PCT
Sheffield Teaching Hospitals NHS Foundation Trust
Sirtex Medical Europe GmbH
Social Care Institute for Excellence (SCIE)
Society and College of Radiographers
South Asian Health Foundation
South East Wales Cancer Network
Southport & Ormskirk Hospital NHS Trust
Sussex Cancer Network
Teenagers and Young Adults with Cancer (TYAC)
Teva UK Limited
Thames Valley Cancer Network
The Society and College of Radiographers
UCL Partners
UCLH NHS Foundation Trust
University Hospital Birmingham NHS Foundation Trust
Vifor Pharma UK Ltd
Walsall PCT
Warner Chilcott UK
Welsh Assembly Government
Welsh Scientific Advisory Committee (WSAC)

West Hertfordshire PCT & East and North Hertfordshire PCT

Western Cheshire Primary Care Trust

Western Health and Social Care Trust

Wirral University Teaching Hospital NHS Foundation Trust

York Teaching Hospital NHS Foundation Trust

Appendix 6.3

Individuals carrying out literature reviews and complementary work

Overall Co-ordinators
Dr John Graham   Director, National Collaborating Centre for Cancer, Cardiff
Dr Andrew Champion   Centre Manager, National Collaborating Centre for Cancer, Cardiff

Project Manager
Angela Bennett   Assistant Centre Manager, National Collaborating Centre for Cancer, Cardiff

Researcher
Dr Susan O'Connell   Researcher, National Collaborating Centre for Cancer, Cardiff
Dr Karen Francis   Senior Researcher, National Collaborating Centre for Cancer, Cardiff
Miss Angeliki Kontoyannis   Surgical Registrar, Cardiff University

Information Specialist
Sabine Berendse   Information Specialist, National Collaborating Centre for Cancer, Cardiff

Health Economist
Bernadette Li   Research Fellow, London School of Hygiene and Tropical Medicine

Mixed Treatment Comparison
Sofia Dias   Research Associate, School of Social & Community Medicine, University of Bristol

Needs Assessment
Miss Angeliki Kontoyannis   Surgical Registrar, Cardiff University

Appendix 6.4

Members of the Guideline Review Panel

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring its quality. The members of the Guideline Review Panel were as follows:

Dr John Hyslop – Chair
Consultant Radiologist, Royal Cornwall Hospital NHS Trust

Dr Ash Paul
Medical Director, Bedfordshire Primary Care Trust

Mr Kieran Murphy
Health Economics & Reimbursement Manager, Johnson & Johnson Medical Devices & Diagnostics (UK)

Mrs Sarah Fishburn
Lay member

Members of the NICE project team

Dr Judith Richardson
Associate Director, Centre for Clinical Practice Director

Nicole Elliott[23]
Guideline Commissioning Manager

Claire Turner[24]
Guideline Commissioning Manager

Emma Banks[25]
Guidelines Coordinator

Anthony Gildea[26]
Guidelines Coordinator

Ruaraidh Hill
Technical Lead

Prashanth Kandaswamy
Health Economist

Lynne Kincaid, Emilene Coventry
Editor

Barbara Meredith
Patient Involvement Lead

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[23] From October 2008 – July 2009
[24] October 2009 – present
[25] From October 2008 – June 2010
[26] June 2010 – present