Cancer Council Australia

Clinical practice guidelines for the prevention, early detection and management of colorectal cancer

8 Population screening for colorectal cancer

Dec 2016: In progress with authors and not yet on wiki

- Population screening for colorectal cancer: Evidence
  - Evidence: Screening benefit (PSC1a)
  - Evidence: Screening test accuracy (PSC1b)
  - Evidence: Screening cost effectiveness (PSC1c)
  - Evidence: Screening age (PSC1d)
- Population screening for colorectal cancer: Evidence summary and recommendations
- Discussion

9 The symptomatic patient

Chapter and subsections reviewed for 16 October. Currently under review and will be updated on wiki in Jan 2017

- Signs and symptoms predictive of colorectal cancer - SPT1-2a
- Optimal maximum time from referral to diagnosis and treatment - SPT1-2b

10 Risk and screening based on family history

Revisions made 19 January.

- Colorectal cancer risk according to family history FHS2
- Screening strategies for people with a family history of colorectal cancer

11 High-risk familial syndromes

- Familial adenomatous polyposis
- MUTYH associated polyposis
- Lynch syndrome
- Peutz-Jeghers syndrome
- Juvenile polyposis syndrome
- Serrated polyposis syndrome
- Supplement. State- and territory-based familial cancer registries

12 Imaging a patient with a diagnosis of colon/rectal adenocarcinoma

- Colon cancer
- Rectal cancer
- Appendix 1. Rectal MRI cancer report

13 Pathology and staging

Content on wiki, some references outstanding. Pending review PTH content and needs review by medical editor.

- Development of post-surgical staging
- Post-surgical staging following neoadjuvant therapy
- Notable differences between available clinicopathological staging systems
- Selection of a clinicopathological staging system
- Clinical input
- Additional information on pathology reporting
- What is the optimal molecular profiling of colorectal cancer? PTH1

14 Preparation for surgery and peri-operative optimisation

- Multidisciplinary meetings
- Perioperative anaemia management
- Thromboembolic prophylaxis
- Nutritional interventions
- Stomal therapy
- Body temperature
- Enhanced recovery after surgery
- Mechanical bowel preparation with or without antibiotic prophylaxis PRP2-5,7

15 Elective and emergency surgery for colon and rectal cancer

- Optimal approach to elective resection for colon cancers (COL1-2a)
- Optimal approach to elective resection for rectal cancers
  - Optimal approach to elective resection for rectal cancers (COL1-2b)
  - Local versus radical resection for T1-T2 rectal tumours (REC3)
- Emergency management of malignant large bowel obstruction (COLMNG5)
- Peritonectomy with hyperthermic intraperitoneal chemotherapy (COLMNG3)

16 Adjuvant therapy for colon cancer

Content developed by author P.Gibbs and edited, a few queries outstanding for author and needs to be reviewed by WP

- Adjuvant therapy for stage III colon cancer
  - Adjuvant therapy for elderly patients with stage III colon cancer (ADJ1)
- Adjuvant therapy for stage II colon cancer
- Irinotecan and targeted (biological) agents in adjuvant therapy for Stage II and Stage III colon cancer
- Discussion: adjuvant therapy for colon cancer

17 Neoadjuvant and adjuvant therapy for rectal cancer

Content amended post 12/12 meeting and added to wiki. Can have WP comment (to add buttons).

- Neoadjuvant therapy for rectal cancer
  - Short course radiation treatment
  - Neoadjuvant long-course chemoradiation (NEO1b)
- 'Watch and wait' approach after clinical complete response to neoadjuvant chemoradiation (NEO1a)
- Neoadjuvant chemotherapy regimen
- Optimal timing surgery after neoadjuvant therapy
- Adjuvant therapy for rectal cancer
  - Postoperative chemotherapy
  - Postoperative radiation treatment
- Discussion

18 Management of resectable locally recurrent disease and metastatic disease

Content MNG13 and background under development Cherry Koh, MNG14 review being finalised.

- What is the appropriate management of recurrent, resectable colorectal cancer? MNG13
- What is the appropriate management of metastatic resectable colorectal cancer? MNG14

19 Management non-resectable locally recurrence disease and metastatic disease

Background developed but content not yet posted on wiki. Suggest to do post edit.

- What is the impact of different liver directed therapies in patients with unresectable metastatic disease? MNG16
- Synchronous primary in metastatic colorectal cancer MNG17 NARRATIVE

20 Follow-up after curative resection for colorectal cancer

12/12 - needs to be sent to WP and SC, edited

- Rationale for follow-up
- Optimal surveillance protocol (FUR1-2)
- Health professionals performing follow-up and suggested follow-up schedule

21 Psychosocial care

22 Appendices

- Guideline development process
- Clinical question list
- Technical report
- Glossary and abbreviations
- Working party and sub-committee membership
- Conflict of interest register

Any other appendices as required.

Back to top

1 Introduction

1.1 Introduction

Colorectal cancer is a major cause of morbidity and mortality in Australia. It is the second most common cancer diagnosed in both men and women, and is more common in those aged over 50 years. Colorectal cancer is also the second most common cause of cancer death and accounts for 9% of all cancer deaths.[1] This profile of colorectal cancer in Australia highlights the need for guidelines to ensure clinical best practice.

These draft clinical practice guidelines are a revision and update of the 2005 Clinical Practice Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer. They were originally developed in 1999, and since then, have been widely used as a reference and referred to by health practitioners, including general practitioners (GPs) and specialists to guide clinical practice. This current revision and update was commissioned and funded by the Department of Health Commonwealth of Australia.

The guidelines aim to provide information and recommendations to guide practice across the continuum of cancer care including colorectal cancer prevention, screening and diagnosis, clinical aspects of surgery, radiotherapy and chemotherapy, follow-up and psychosocial care. The guidelines also provide an evidence base for the National Bowel Cancer Screening Program.

The update of the guidelines was overseen by a multidisciplinary working party with input by subcommittees. We thank the members of the Working Party, subcommittee, systematic reviewers and all others who contributed to the development of these draft guidelines.

1.2 References

1. ↑ Australian Institute of Health and Welfare. *Cancer in Australia: an overview 2014. [Version updated 16 April 2015] Cancer series No 90. Cat. no. CAN 88.* Canberra: AIHW;.

Back to top

2 Summary of recommendations

This is a summary of the draft recommendations in these guidelines, numbered according to chapter to which they relate. Please note that some chapters do not have associated recommendations.

2.1 Recommendations

2.1.1 Primary Prevention: Chemopreventive candidate agents

2.1.2 Chemopreventive candidate agents

Evidence-based recommendation	Grade
For all people aged 50–70 years who are at average risk of colorectal cancer, aspirin should be actively considered to prevent colorectal cancer. A low dose (100–300 mg per day) is recommended for at least 2.5 years, commencing at age 50 to 70 years. The benefit may extend to older ages with longer duration of use. Benefit for cancer prevention (though shorter for cardiovascular risk) is evident only 10 years after initiation so a life expectancy of at least 10 years should be taken into consideration in the advice to use aspirin. The choice to take aspirin should be personalised based on age, sex and potential reduction in cardiovascular events, cerebrovascular events and thrombotic stroke. The individual should take into account the potential risks of taking aspirin. Aspirin should be avoided in patients with current dyspepsia, any history of peptic ulcer, aspirin allergy, bleeding diathesis, an increased risk of gastrointestinal haemorrhage (such as associated with use of oral anticoagulants or antiplatelet agents), or renal impairment. The benefit in colorectal cancer risk reduction in women over 65 is less clear cut. However, based on limited data available, older women with cardiovascular risk factors may derive a greater overall benefit than harm.	**B**

Practice point
Aspirin should be avoided in patients with uncontrolled hypertension.

Practice point
Breath testing for *Helicobacter pylori* (and treatment for those who test positive) can also be considered, as gastrointestinal toxicity from aspirin is enhanced in the presence of *Helicobacter pylori*.

Evidence-based recommendation	Grade
People who are at high risk of colorectal cancer due to Lynch Syndrome carrier status should be advised to begin aspirin from the commencement of their colonoscopy screening (usually at age 25 years).	**A**

Evidence-based recommendation	Grade
Non-syndromic familial cancer patients should be actively considered for aspirin, bearing in mind the possibility of adverse events. 600 mg/day has been shown to be effective, but lower dose (100 mg/day) may be as effective and is recommended based on the data available at the time of the systematic review.	**B**

Practice point
Where surgery is inappropriate for people with familial adenomatous polyposis, an NSAID (e.g. sulindac) is recommended. (Kim B et al 2011)

Practice point
Without RCT evidence, statins cannot be recommended for chemoprevention at this time.

Practice point
Without RCT evidence, metformin cannot be recommended for chemoprevention at this time.

Practice point
Bisphosphonates cannot be recommended for chemoprevention.

Back to top

2.1.3 Population screening for colorectal cancer

2.1.4 Population screening: Evidence summary and recommendations (PSC1a-d)

Evidence-based recommendation	Grade
Overall population screening strategy The recommended strategy for population screening in Australia, directed at those at average risk of colorectal cancer and without relevant symptoms, is immunochemical faecal occult blood testing every 2 years, starting at age 50 years and continuing to age 74 years.	**C**

Evidence-based recommendation	Grade
Primary screening test An immunochemical faecal occult blood test is recommended as the screening modality for the detection of colorectal cancer in the average-risk population.	**C**

Evidence-based recommendation	Grade
Primary screening test The emerging faecal, blood or serum tests for cancer-specific biomarkers such as DNA are not recommended as population screening modalities for colorectal cancer.	**C**

Evidence-based recommendation	Grade
Primary screening test The use of flexible sigmoidoscopy as a primary screening test is not recommended for population screening in the average-risk population.	**C**

Evidence-based recommendation	Grade
Frequency of testing	**N/A**

Evidence-based recommendation	Grade
Population screening for colorectal cancer using immunochemical faecal blood testing every 2 years is recommended. It is not recommended that the frequency of screening within the NBCSP be increased to yearly.	

Evidence-based recommendation	Grade
Target age group It is recommended that the age range for organised population screening continues to be 50–74 years.	**N/A**

Evidence-based recommendation	Grade
Target age group Starting at age 40 is not recommended for population screening as it is unlikely to be cost-effective.	**N/A**

Evidence-based recommendation	Grade
Target age group Although modelling indicated that it may be cost-effective, starting screening at age 45 is not recommended for population screening because there is a much less favourable ratio of benefits to harms than for 50–74 years.	**N/A**

Evidence-based recommendation	Grade
Target age group Extending the age range to 79 or 84 years is not recommended for population screening as it is unlikely to be cost-effective.	**N/A**

Consensus-based recommendation

Resources should be invested in increasing participation in the existing NBCSP target age group of 50–74, rather than by lowering the starting age of screening, to optimise the balance of effectiveness, cost-effectiveness and ratio of benefits to harms.

Consensus-based recommendation

In people aged 45–49 years who request screening after being fully informed of the benefits and harms of testing, general practitioners (GPs) could offer an immunochemical faecal occult blood test every 2 years during the lead-up to the first routine invitation by the NBCSP at age 50 years.

Practice point

Encouragement by GPs and practice staff substantially boosts participation in colorectal cancer screening. Patient endorsement letters in advance of receiving a test kit, the use of GP reminder systems and practice audit are approaches likely to improve participation rates. Increased participation in the NBCSP will increase the program's effectiveness and cost-effectiveness.

Practice point

GPs have a critically important role in managing the interface between population screening and personalised care. This role includes identifying and advising those who should opt off the NBCSP because of the presence of major comorbidities and limited life expectancy and those who should defer participation for several months because of recent surgery or major illness.

Practice point

Participation in a population screening program is not recommended for people with symptoms such as rectal bleeding or persistent change in bowel habit or with iron-deficiency anaemia, nor for those who should be having regular surveillance or screening based on colonoscopy, e.g. for past colorectal cancer or adenoma, chronic inflammatory bowel disease, a strong family history of colorectal cancer, or a high-risk genetic cancer syndrome (see Risk and screening based on family history of colorectal cancer).

Practice point

Individuals who have had a high-quality colonoscopy performed within the previous two years should allow another two years to elapse (i.e. skip a round) before participating in their next round of iFOBT screening. Colorectal cancer will rarely be present within that interval.

High-quality colonoscopy is defined in the Clinical Practice Guidelines for Surveillance Colonoscopy.

Practice point

GPs have a key role in advising patients who are at average or slightly above average risk that iFOBT is the preferred method of screening. They should discuss the relative harms and benefits of colonoscopy and discourage inappropriate use of colonoscopy as a screening method.

Practice point

Participants with positive iFOBT results should have follow-up investigation unless there was a clear breach in protocol when samples were collected (e.g. menstrual blood loss close to the time of sample collection). Repeating the iFOBT test after a positive result carries the risk of a falsely negative test result on the second occasion because of low levels of bleeding from a cancer or adenoma, intermittent bleeding, or uneven distribution of blood in the stools.

Practice point

Colonoscopy should be performed as promptly as possible after a positive iFOBT to minimise the risk of psychological harm, although there is no evidence that prognosis is worsened within 120 days if cancer is present.

Back to top

2.1.5 The symptomatic patient

2.1.6 Signs and symptoms predictive of colorectal cancer

Evidence-based recommendation	Grade
The urgency of colonoscopy to investigate symptoms suggestive of colorectal cancer should be based on an assessment of patient age, symptom profile and results of simple investigations including full blood count, iron studies and iFOBT (see Table 10.1 for consensus-based colonoscopy triage categories).	**C**

Consensus-based recommendation

In people with symptoms other than overt rectal bleeding, immunochemical faecal occult blood testing (iFOBT) can be used as part of the diagnostic assessment in primary care.

Practice point

Immunochemical faecal occult blood testing (iFOBT) is of particular use in the following circumstances to support diagnostic assessment and inform urgency of colonoscopy:

- people over 50 years with either unexplained weight loss or abdominal pain
- people under 60 years with either altered bowel habit or anaemia.

Back to top

2.1.7 Optimal maximum time from referral to diagnosis and treatment

Evidence-based recommendation	Grade
For patients with symptoms suggestive of colorectal cancer, the total time from first healthcare presentation† to diagnostic colonoscopy should be no more than 120 days. Diagnostic intervals greater than 120 days are associated with poorer clinical outcomes. † First healthcare presentation is defined as the date of presentation in general practice with symptoms suggestive of colorectal cancer or positive iFOBT for screening.	**C**

Evidence-based recommendation	Grade
A diagnostic interval of 120 days should be the maximum time from first healthcare presentation† to diagnostic colonoscopy for triage Categories 1 and 2, whether it is for a patient with symptoms or after a positive iFOBT used for colorectal cancer screening. Diagnostic intervals greater than 120 days are associated with poorer clinical outcomes. † First healthcare presentation is defined as the date of presentation in general practice with symptoms suggestive of colorectal cancer or positive iFOBT for screening.	**D**

Consensus-based recommendation

Triage category 1 patients, whether due to symptoms or positive iFOBT, should continue to be considered most urgent and prioritised for diagnostic colonoscopy, in any model of care at any jurisdictional level.

Practice point

Colonoscopy for symptomatic patients should be performed as promptly as possible after referral from general practice, especially for those meeting triage Category 1 criteria. If cancer is present, there is no evidence that prognosis is worsened within 120 days from first presentation to diagnostic colonoscopy. However, performing colonoscopy as promptly as possible after referral from general practice is to minimise the risk of psychological harm in symptomatic or iFOBT-positive patients who are potentially anxious while awaiting investigation. Prompt scheduling will also help to ensure that any unexpected delays between general practice referral and colonoscopy triaging do not flow on to exceed the 120-day threshold after which prognosis can worsen if cancer is present.

Back to top

2.1.8 Risk and screening based on family history

2.1.9 Colorectal cancer risk according to family history

Evidence-based recommendation	Grade
Category 1 People who have one relative with colorectal cancer diagnosed at age 55 or older should be advised that their own risk of developing colorectal cancer could be up to twice the average risk, but is still not high enough to justify CRC screening by colonoscopy.	**C**

Evidence-based recommendation	Grade
Category 2 People should be advised that their risk of developing colorectal cancer is at least three times higher than average, but could be up to six times higher than average, if they have any of the following: ■ one first-degree relative with colorectal cancer diagnosed before age 55 years ■ two first-degree relatives with colorectal cancer diagnosed at any age ■ one first-degree relative and at least two second-degree relative diagnosed with colorectal cancer at any age.	**C**

Evidence-based recommendation	Grade
Category 3 People should be advised that their risk of colorectal cancer is at least seven times higher than average, but could be up to 10 times higher than average, if they have either of the following: ■ at least three first-degree or second-degree relatives with colorectal cancer, with at least one diagnosed before age 55 years ■ at least three first-degree relatives with colorectal cancer diagnosed at any age.	**C**

Practice point

Approximately 95-98% of the population are in Category 1 (near average risk of developing colorectal cancer).

Practice point

Approximately 65% of those with a family history of colorectal cancer only have a weak family history which means they are category 1 risk.

Practice point

Medical information that patients provide about their relatives is often inaccurate. (St John et al 1993, Love et al 1985, Douglas et al 1999, Ruo et al 2001, Mitchell et al 2004) The percentage of colorectal cancer reports that are correct (positive predictive value) is 86% meaning that reports by relatives are usually true. However, a high proportion of people appear to be unaware that their relatives have had colorectal cancer, with the percentage of all colorectal cancers in first-degree relatives that are reported (sensitivity) being 27%. (Mai 2011).

Practice point

Given the potential importance of an accurate risk prediction for an individual, every effort should be made to collect reliable information.

Practice point

When there is uncertainty on family history, people should be encouraged to seek clarification within their family including details on which relatives have had colorectal cancer and their ages of diagnoses.

Practice point

If a family medical history appears to be significant but diagnoses prove difficult to confirm, it may be appropriate to seek expert help from a familial cancer clinic who have resources available to confirm cancer diagnoses.

Back to top

2.1.10 Screening strategies for people with a family history of colorectal cancer

Practice point

For people with category 1 risk of colorectal cancer with one relative with colorectal cancer, iFOBT should be considered every 2 years from age 45, given the risk of colorectal cancer at this age is approximately equivalent to the population risk at age 50.

Practice point

For people with category 2 risk of colorectal cancer:

- iFOBT should be performed every 2 years from age 40 up to age 50, and colonoscopy should be performed every 5 years from age 50 to age 74.
- low-dose (100 mg) aspirin daily should be considered (see Aspirin).

Practice point

For people in category 2, CT colonography can be offered if colonoscopy is contraindicated (Dachman 2003).

Practice point

Because of the possibility of Lynch syndrome, a complete family history should be taken and updated regularly, and the accuracy of the cancer diagnoses and polyp pathology should be checked carefully.

Practice point

Category 2 can now be met by inclusion of relatives from both sides of the family. Genetic testing is not appropriate at present for people with category 2 risk. Tumour testing for Lynch syndrome-related changes, using immunohistochemistry and microsatellite instability, should be considered when any of the revised Bethesda criteria are met (see Lynch syndrome).

Practice point

As with all forms of screening, those at risk should be carefully checked for the presence of symptoms that might be due to colorectal neoplasia. Where symptoms are present, appropriate diagnostic steps should be taken before entry into a screening program.

Practice point

For people with category 3 risk of colorectal cancer:

- iFOBT should be performed every 2 years from age 35 up to age 45, then 5-yearly colonoscopy from age 45 to age 74.
- Low-dose (100 mg) aspirin daily should be considered (see Aspirin).
- Referral to a genetic centre for hereditary cancer syndromes should be considered. Those carrying their family-specific mutation or having uncertain genetic status require careful cancer screening (see High-risk familial syndromes).

Practice point

Category 3 can now be met by inclusion of relatives from both sides of the family. This is expected to increase the numbers in this category by approximately 50%. Referral to a genetic centre for hereditary cancer syndromes should be prioritised to those with family members with colorectal cancer from the same side of the family.

Practice point
Screening recommendations no longer specify that screening should begin at 10 years younger than the age of first diagnosis of colorectal cancer in the family, as there is no published evidence to support this strategy.

Evidence-based recommendation	Grade
Category 1 For people with a family history of colorectal cancer who are assessed as having category 1 risk, iFOBT should be performed every 2 years from age 50 to age 74. See Population screening for colorectal cancer. For those with one first-degree relative with colorectal cancer, iFOBT every two years from age 45 should be considered.	**C**

Evidence-based recommendation	Grade
Category 2 For category 2 patients, offer iFOBT every 2 years starting at age 40, then colonoscopy every 5 years starting at age 50. CT colonography may be offered if colonoscopy is contraindicated.	**C**

Evidence-based recommendation	Grade
Category 3 For category 3 patients, offer iFOBT every two years starting at age 35, then colonoscopy every five years starting at age 45. CT colonography may be offered if colonoscopy is contraindicated.	**C**

Back to top

2.1.11 High-risk familial syndromes

2.1.12 Familial adenomatous polyposis (FAP)

Practice point

- Colonic surveillance should be offered to:
  - individuals found on genetic testing to carry a pathogenic APC mutation
  - first-degree relatives of patients with FAP or AFAP in whom genetic testing has been declined or is not possible because the family mutation has not been identified.

Surveillance should commence from age 10 to 15 years or earlier if there are gastrointestinal symptoms (Robays and Poppe, 2014). In families with classical FAP, flexible sigmoidoscopy is adequate since adenomas occur simultaneously throughout the colorectum (Syngal et al., 2015; Stoffel et al., 2015; Robays and Poppe, 2014). Once an adenoma is identified, annual colonoscopy should be performed until colectomy is undertaken. In AFAP, surveillance should be by colonoscopy since the first adenomas may only be present in the proximal colon but surveillance can be delayed until 18 years of age (Syngal et al., 2015; Cancer Institute NSW 2016; Robays and Poppe, 2014).

Practice point

- Total colectomy and ileorectal anastomosis should be reserved for patients with rectal adenomas considered easily controllable by endoscopy and < 1000 colonic adenomas. Proctocolectomy with a permanent ileostomy is rarely needed (Syngal et al., 2015). Annual surveillance of the residual rectum or ileal pouch is required following colectomy (Cancer Institute NSW 2016).
- Some patients with AFAP can be managed with colonoscopic polypectomy at one- to two-yearly intervals (Syngal et al., 2015; Balmaña et al., 2013). If surgery is required due to a high number of adenomas, colectomy with ileorectal anastomosis can nearly always be performed, because of the small number of adenomas in the rectum (Syngal et al., 2015; Balmaña et al., 2013)

Back to top

2.1.13 MUTYH-associated polyposis

Practice point

- Referral to a genetics service for germline genetic testing for mutations in MUTYH is indicated for persons with a cumulative count of ≥ 20 colorectal adenomas at any age (Syngal et al., 2015). It is also indicated for siblings of a MUTYH biallelic mutation carrier (Syngal et al., 2015).

Testing may also be considered in patients with ≥ 10 adenomas and any of the following (Syngal et al., 2015) :

- age under 50
- synchronous colorectal cancer
- both adenomatous and serrated polyps where the adenomatous polyps dominate
- family history suggestive of recessive inheritance (e.g. consanguinity in parents or siblings with documented adenomatous polyposis or colorectal cancer).

Clinical practice in some familial cancer clinics would accept patients in these categories even if there are no synchronous adenomas in the proband.

Practice point

Biallelic mutation carriers should have colonoscopy every 2 years starting at age 18 to 20 years (Cancer Institute NSW, 2016; Robays and Poppe, 2014; Balmaña et al., 2013). If polyps are detected, annual colonoscopy may be required to control the polyp burden (Cancer Institute NSW, 2016). If polyps cannot be easily managed colonoscopically, a colectomy with ileorectal anastomosis should be considered and discussed with the patient (Cancer Institute NSW, 2016; Balmaña et al., 2013) The residual rectum requires annual surveillance.

Back to top

2.1.14 Lynch syndrome

Practice point

- All colorectal cancers should be tested for mismatch repair deficiency as a means to subsequently identify Lynch syndrome (Robays and Poppe, 2014; Ladabaum et al., 2015; Giardiello et al., 2014; Rubenstein et al., 2015).

Back to top

Back to top

2.1.15 Juvenile polyposis syndrome

Practice point

In patients with a diagnosis of juvenile polyposis syndrome, colonoscopy should commence at age 12–15 or earlier if symptoms occur (Syngal et al., 2015; Cancer Institute NSW, 2016). It should be repeated every 1 to 3 years depending on polyp burden. Colectomy is indicated if polyps cannot be managed endoscopically (Syngal et al., 2015; Cancer Institute NSW, 2016).

Back to top

2.1.16 Serrated polyposis syndrome

Practice point

Expert opinion is that colonoscopy should be performed every 1 to 3 years with the aim to remove all polyps ≥ 5mm. If the number and size of polyps make it impossible to achieve this, colectomy and ileorectal anastomosis should be considered.(Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW, et al 2015)(Cancer Institute NSW 2016)

Back to top

2.1.17 Imaging a patient with a diagnosis of colon/rectal adenocarcinoma

2.1.18 Imaging for colon cancer

Practice point

CT colonoscopy should be considered for a patient with colon cancer if it has not been possible to view the entire colon by colonoscopy due to the risk of synchronous tumours. (New Zealand Guidelines Group 2011.)

Practice point

If CT shows metastatic disease confined to the liver, MRI of the liver can be considered to assess for resectability, particularly if the background liver parenchyma is abnormal, the patient has recently received chemotherapy, or when a patient cannot have iodinated contrast.

Practice point

For patients with colorectal cancer who have potentially resectable metastatic disease, PET-CT is recommended to detect additional metastases.

Practice point

For patients with stage II and III disease who have undergone initial surgery and/or adjuvant treatment, a suitable approach to imaging surveillance may involve 12-monthly CT of chest, abdomen and pelvis.

Practice point

For patients with stage IV disease who have undergone a resection procedure with curative intent, a suitable approach to imaging surveillance may involve CT of chest, abdomen and pelvis every 6 months.

Back to top

2.1.19 Imaging for rectal cancer

Practice point

MRI of the rectum is the recommended staging investigation for rectal cancer.

Practice point

High-resolution sequences must be performed and must meet accepted criteria.

Practice point

Additional sequences coronal to the anal canal are required for low tumours (Table 7.2).

Practice point

Template reports are recommended, which include all of:

- Distance from anal verge (and puborectalis sling for low tumours)
- Relationship to the peritoneal reflection
- T stage including spread in mm beyond muscularis
- N stage and pelvic lymph nodes using morphological criteria
- EMVI status
- CRM status using 1mm as a cut-off distance.

Back to top

2.1.20 Pathlogy and staging

Back to top

2.1.21 Selection of a clinicopathological staging system

Practice point

TNM staging, ACPS/Concord staging and the data required to stage the patient should all be recorded to allow national and international comparisons.

Back to top

2.1.22 Optimal molecular profiling

Practice point
A suitable tissue block with a high proportion of tumour tissue (preferably over 70%) should be designated for the purpose of further molecular testing if required.

Evidence-based recommendation	Grade
RAS mutation studies should be performed on patients with advanced (metastatic) colorectal cancer in whom anti-EGFR treatment is being considered. Cetuximab and panitumumab should only be considered for the treatment of patients with RAS wild-type metastatic colorectal cancer.	**D**

Evidence-based recommendation	Grade
There is emerging evidence suggesting that BRAF mutation may be associated with poor response to anti-EGFR treatment, and that BRAF mutation studies should therefore be performed on patients with advanced (metastatic) colorectal cancer.	**D**

Back to top

2.1.23 Preparation for surgery and peri-operative optimisation

2.1.24 Multidisciplinary meetings

Practice point
Ideally, all patients with newly diagnosed colorectal cancer should be discussed at a multidisciplinary team meeting.

Practice point
Discussion at a multidisciplinary team meeting is mandatory for high-risk and complex cases such as patients with preoperative rectal cancers, metastatic disease or recurrent disease.

Back to top

2.1.25 Perioperative anaemia management

Practice point

Patients undergoing elective surgery for colorectal cancer should be assessed for anaemia and iron deficiency and any deficiencies should be addressed preoperatively.

Practice point

Intravenous iron should be considered in preference to oral iron preoperatively given its quicker therapeutic effect.

Practice point

Consideration should also be given to treating postoperative functional iron deficiency anaemia with intravenous iron.

Back to top

2.1.26 Thromboembolic prophylaxis

Practice point

All patients undergoing surgery for colorectal cancer should have standard thromboprophylaxis in hospital with compression stockings, unfractionated or low molecular-weight heparin and sequential compression devices. Extended prophylaxis for 28 days can be considered in high risk patients following colorectal cancer surgery.

Back to top

2.1.27 Nutritional interventions

Practice point

Patients undergoing elective surgery for colorectal cancer should be screened for malnutrition.

Practice point

If patients are found to be malnourished, nutritional interventions should be put in place.

Back to top

2.1.28 Stomal therapy

Practice point

Patients undergoing colorectal cancer surgery who may, or will, require a stoma should be seen prior to surgery by a stomal therapist.

Practice point

Patients with stomas should be given postoperative education.

Back to top

2.1.29 Body temperature

Practice point

Perioperative normothermia should ideally be maintained at or above 36.0˚C.

Practice point
The use of warmed IV fluids and forced-air warming can be used to minimise perioperative hypothermia.

Back to top

2.1.30 Enhanced recovery after surgery

Practice point
Patients having elective surgery for colorectal cancer should be managed within an appropriately resourced enhanced recovery after surgery (ERAS) program.

Back to top

2.1.31 Mechanical bowel preparation with or without antibiotic prophylaxis

Evidence-based recommendation	Grade
Mechanical bowel preparation should not be used routinely in colonic surgery. It can be used selectively according to individual patient and tumour characteristics, at the surgeon's discretion.	**D**

Back to top

2.1.32 Elective and emergency surgery for colon and rectal cancer

2.1.33 Optimal approach to elective resection for colon cancers (COL1-2a)

Evidence-based recommendation	Grade
Either an open approach or a laparoscopic approach can be used for the resection of colon cancer.	**D**

Evidence-based recommendation	Grade
Laparoscopic colectomy has post-operative advantages over open colectomy and should be performed when the surgical expertise and hospital infrastructure are available.	**D**

Practice point
Laparoscopic colectomy requires significant additional skills. Surgeons should ensure that they have mastered the necessary techniques before performing laparoscopic colectomy as an independent operator.

Practice point
Laparoscopic colorectal surgery is complex minimally invasive surgery that requires high-resolution video imaging and up-to-date equipment, including instrumentation and energy sources. It should only be undertaken in facilities that provide this infrastructure.

Back to top

2.1.34 Optimal approach to elective resection for rectal cancers (COL1-2b)

Evidence-based recommendation	Grade
Open surgery is the standard approach for resection of rectal cancer. Laparoscopic resection can be considered in selected cases if the surgical expertise (including advanced laparoscopic skills) and hospital infrastructure are available noting that it is a technique that has yet to be proven safe and efficacious in all patients for rectal cancer.	**C**

Practice point
Regardless of the approach utilised, rectal cancer resection must be undertaken by surgeons who have been appropriately trained in surgical resection of rectal cancer, utilising the principles of total mesorectal resection as proposed by Heald. This should include sharp dissection undertaken along the mesorectal plane. Surgical resection undertaken by inadequately trained surgeons is likely to result in inferior oncological outcomes.

Practice point
Case selection is important, as it is suboptimal to generalise the surgical approach for rectal cancer to all patients. Factors such as patient body mass index, tumour stage, and surgeon experience are important considerations when determining whether a laparoscopic or open approach is optimal for the patient.

Practice point
The laparoscopic approach may have a higher potential for an inferior quality TME specimen, as demonstrated by two recent multicentre RCTs, though long-term outcome data are not yet available on these studies (Fleshman et al 2015, Stevenson et al 2015). Two other large multicentre RCTs have reported long-term outcomes with no difference in local recurrence or survival (Jeong et al 2014, Bonjer et al 2015). The surgeon should discuss with the patient the potential impact on oncological outcome of the laparoscopic approach along with the potential improvements on short term recovery.

Back to top

2.1.35 Local versus radical resection for T1-T2 rectal tumours (REC3)

Evidence-based recommendation	Grade
For patients with stage 1 rectal cancer (T1/2, N0, M0), cases should be discussed by a multidisciplinary team to determine optimal management with respect to risk of local recurrence, avoidance of a permanent stoma, and fitness for surgery.	**C**

Evidence-based recommendation	Grade
For patients with T1 tumours local excision can be considered, provided that the tumour can be removed with clear margins and that the treating clinician counsels the patient that: ■ the risk of local recurrence increases as the T1 tumour stage progresses (from T1sm1 to T1sm2, or from T1sm2 to T1sm3) ■ radical resection may be required after histopathological review of the local excision specimen.	**D**

Evidence-based recommendation	Grade
For patients with T2 tumours, consider radical resection as the first option if they are fit for surgery.	C

Practice point

When determining the optimal management strategy for each patient, the multidisciplinary team, treating clinician and patient should discuss the balance of risks (e.g. local recurrence) and benefits (e.g. avoidance of a permanent stoma), with consideration of the individual's fitness for surgery. The treating clinician should explain to the patient that local excision carries a lower risk of perioperative mortality and a lower permanent stoma rate, but is associated with a higher local recurrence rate, which increases as the depth of tumour invasion increases from T1sm1 to T1sm2 to T1sm3 to T2.

Practice point

Radical resection is recommended for patients with T1sm3 tumours, and for those with T2 tumours who are considered fit for radical surgery.

Practice point

The use of transanal endoscopic microsurgery or transanal minimally invasive surgery has not shown any significant advantages over transanal local excision, however it is essential to obtain clear resection margins and the choice of approach to local resection should be determined by the individual surgeon with this factor in mind.

Practice point

Application of radiotherapy before or after local excision of rectal cancer may reduce the risk of local recurrence. However, it may have an adverse effect on bowel function.

Back to top

2.1.36 Emergency management of malignant large bowel obstruction (COLMNG5)

Evidence-based recommendation	Grade
In patients with acute obstruction due to left-sided colorectal cancer who are potentially curative, the use of stenting as a bridge to surgery is not recommended as standard treatment, due to the potential risk of tumour perforation and conversion of a curative case to a palliative case.	**D**

Consensus-based recommendation
The insertion of an intraluminal colonic stent can be considered in large bowel obstruction secondary to colorectal cancer as palliation to relieve large bowel obstruction in patients with incurable metastatic colorectal cancer.

Consensus-based recommendation
For patients with potentially curable left-sided obstructing colonic cancer who are considered to be at increased risk of post-operative mortality, stent placement may be considered as an alternative to emergency surgery.

Consensus-based recommendation
If stenting is considered, it should be discussed by the multidisciplinary team and implications for anti-VEGF systemic therapy should be assessed.

Back to top

2.1.37 Peritonectomy with hyperthermic intraperitoneal chemotherapy (COLMNG3)

Evidence-based recommendation	Grade
For patients with colorectal peritoneal metastases (either synchronous or metachronous to the primary), consider cytoreduction with perioperative	**D**

Evidence-based recommendation	Grade
intraperitoneal chemotherapy. Where this procedure is suitable, offer referral to a centre with the necessary expertise and infrastructure to perform this procedure.	

Evidence-based recommendation	Grade
Cytoreduction surgery and perioperative intraperitoneal chemotherapy should only be offered after due consideration of, and discussion with the patient about, the potential treatment-related mortality and morbidity.	**D**

Practice point

Patients with peritoneal carcinomatosis should be referred to a centre with expertise in the management of peritoneal surface malignancies and should be offered enrolment in a prospective trial, so as to allow further evaluation of cytoreduction and intraperitoneal chemotherapy.

Practice point

Prior to referral, treating clinicians should have an in-depth discussion with every patient about the potential survival advantage and potential treatment-related mortality or morbidity.

Practice point

All patients' cases should be discussed at a multidisciplinary team meeting with clinicians who have expertise in the management of peritoneal metastases, to review the relevant clinical information, previous histology (if applicable) and relevant imaging prior to offering patients cytoreductive surgery and intraperitoneal chemotherapy.

Practice point

All patients offered this procedure in established cytoreduction centres should be asked to give their consent for their patient records to be available for ongoing auditing of clinical outcomes. Patients should also be invited and encouraged to participate in research to enable collection of prospective longitudinal data for clinical and quality-of-life outcomes.

Back to top

2.1.38 Adjuvant therapy for colon cancer

2.1.39 Adjuvant therapy for stage III colon cancer

Practice point

Oxaliplatin in combination with a fluoropyrimidine is standard therapy for young patients (< 70 years) with stage III colon cancer.

Practice point

Capecitabine plus oxaliplatin (XELOX) can be considered as an alternative to FOLFOX for adjuvant treatment for patients with stage III colon cancer.

Back to top

2.1.40 Adjuvant therapy for elderly patients with stage III colon cancer

Consensus-based recommendation

Elderly patients (≥ 70 years) with stage III colon cancer who are fit for adjuvant chemotherapy should receive 6 months of a single-agent fluoropyrimidine (either 5FU or capecitabine).

Practice point

The addition of oxaliplatin to adjuvant fluoropyrimidine-based therapy in elderly patients (≥ 70 years) with stage III colon cancer did not improve survival outcomes.

Practice point

The combination of oxaliplatin and fluoropyrimidine-based therapy in the metastatic setting provides a similar benefit in elderly patients and younger patients. The discordance between the adjuvant and metastatic setting remain unexplained.

Back to top

2.1.41 Adjuvant therapy for stage II colon cancer

Practice point

The optimal approach to adjuvant therapy in stage II colon cancer remains uncertain. Adjuvant therapy can be considered in high-risk patients on a case-by-case basis.

Back to top

2.1.42 Irinotecan and targeted (biological) agents in adjuvant therapy for stage II and stage III colon cancer

Practice point

Neither Irinotecan nor a biological agent (either bevacizumab or cetuximab) should be used as adjuvant therapy for patients with stage II or III colon cancer.

Back to top

2.1.43 Neoadjuvant and adjuvant therapy for rectal cancer

2.1.44 Neoadjuvant therapy for rectal cancer

Practice point

Accurate determination of suitability for neoadjuvant therapy is based on careful preoperative location and staging assessments, and requires optimal quality of care from each aspect of the multidisciplinary team's assessment.

Practice point

'Early' cT3N0 rectal cancer (<1mm extension) is considered potentially suitable for surgery without neoadjuvant treatment in some international guidelines; but requires a high level of confidence in staging investigations and interpretation.

Back to top

2.1.45 Short-course radiation treatment

Practice point

Preoperative (neoadjuvant) radiation treatment (either short-course radiation treatment alone or long-course chemoradiation) is recommended for most patients with stage II and III rectal cancers, to reduce risk of local recurrence.

Practice point

Short-course radiation treatment should be considered if there are clear concerns regarding a patient's physical or psychosocial ability to tolerate long-course chemoradiation.

Practice point
MRI imaging, patient and clinical factors including comorbidity status should be carefully reviewed by the multidisciplinary team. If clinical T4 primary or nodal disease is seen, or tumour extends close to the mesorectal fascia, then long-course chemoradiation is preferable where possible.

Back to top

2.1.46 Neoadjuvant long-course chemoradiation

Evidence-based recommendation	Grade
Consider neoadjuvant chemoradiation for patients with stage II-III rectal cancer where appropriate.	**C**

Practice point
The current standard dose of neoadjuvant chemoradiation is 50–50.4 Gy (boost volume after 45 Gy) with either continuous infusional 5FU or capecitabine.

Practice point
‘Early’ cT3N0 rectal cancer (<1mm extension) is considered potentially suitable for surgery without neoadjuvant treatment in some international guidelines; but requires a high level of confidence in staging investigations and interpretation.

Back to top

2.1.47 'Watch and wait' approach after clinical complete response to neoadjuvant chemoradiation (NEO1a)

Evidence-based recommendation	Grade
	D

Evidence-based recommendation	Grade
For patients with rectal cancer who have had a clinical complete response to neoadjuvant chemoradiation, and planned resection according to the standard recommendation is either not possible or the patient declines it, a 'watch and wait' approach can be considered, provided that: ■ the risks and benefits have been discussed with the multidisciplinary team and the patient ■ the patient is monitored closely for local recurrence ■ the patient is offered an appropriate surgical resection procedure if local recurrence is detected.	

Practice point

A 'watch and wait' approach for patients with clinical complete response following chemoradiation is not considered standard practice. Clinicians and patients who select this option must be aware of increased risk of recurrence necessitating surgical intervention, and the importance of close follow-up.

Practice point

Follow-up and surveillance guidelines for a 'watch and wait' approach, in particular the frequency of follow-up tests, are not established. Testing may include serial CEA measurements, clinical examination, radiological surveillance, and sigmoidoscopy/colonoscopy.

Back to top

2.1.48 Neoadjuvant chemotherapy regimen

Practice point

Infusional fluoropyrimidine is preferable to bolus fluoropyrimidine for use in combination with radiation treatment for rectal cancer.

Practice point

Oral capecitabine or intravenous infusional 5FU are both acceptable agents to combine with radiation treatment for rectal cancer.

Practice point

If capecitabine is considered, patients should be carefully selected to minimise risk of non-compliance or overdosing.

Practice point

Neoadjuvant oxaliplatin with radiation treatment for rectal cancer is not currently regarded as standard therapy. Data for local control or survival benefit are mixed and oxaliplatin is associated with higher toxicity than fluoropyrimidine alone.

Practice point

The role of neoadjuvant systemic chemotherapy is still under investigation and is not regarded as routine.

Practice point

The roles of bevacizumab, panitumumab and cetuximab in the neoadjuvant setting for rectal cancer are uncertain, based on available evidence. These are not currently available for the treatment of non-metastatic rectal cancer, and they are not indicated in this setting.

Back to top

2.1.49 Optimal timing surgery after neoadjuvant therapy

Practice point

Available data for the optimal timing between completion of neoadjuvant C-RT and surgery indicate that surgery at least 6 weeks but by 12 weeks appears to be appropriate, until results from further studies become available.

Practice point

Waiting longer within the 6-12 week time frame to allow optimal pathological downstaging may be selected preferentially, for example for patients with T4 tumours, where maximal downstaging is desirable.

Back to top

2.1.50 Postoperative chemotherapy

Practice point

Strong evidence for benefit of adjuvant chemotherapy for rectal cancer is lacking, even in patients with node positive disease. In disease regarded as high risk, the uncertain benefits of adjuvant chemotherapy should be acknowledged.

Practice point

Patients with upper third rectal tumours (10–15cm from the anal verge) with either cN+ or pN+ findings, are possibly those who may derive any/most benefit from adjuvant chemotherapy.

Practice point

For patients with pathological stage II/III rectal cancer, adjuvant oxaliplatin-based chemotherapy is associated with increased toxicities. Benefits, if any, may be confined to those with stage III disease; but not all data concur.

Practice point
The uncertain benefits of oxaliplatin as adjuvant therapy in rectal cancer should be acknowledged.

Practice point
There are no randomised trials for adjuvant chemotherapy for patients with pathological complete response after chemoradiation followed by surgery. Available evidence suggests that these patients have a very good prognosis and any absolute benefits are likely to be small.

Back to top

2.1.51 Postoperative radiation treatment

Practice point
Patients with higher risk disease post-operatively who did not receive neoadjuvant treatment should be considered for adjuvant pelvic radiotherapy concurrent with 5 fluorouracil chemotherapy.

Back to top

2.1.52 Management of resectable locally recurrent disease and metastatic disease

2.1.53 Management of locally recurrent resectable colorectal cancer

Evidence-based recommendation	Grade
For patients with isolated local recurrence of rectal cancer, consider referral to a centre with the necessary expertise to perform curative surgery (also known as pelvic exenteration).	**D**

Evidence-based recommendation	Grade
Re-operative surgery for locally recurrent rectal cancer should only be offered after due consideration of, and discussion with the patient about, the potential survival advantage, quality-of-life outcomes, and potential treatment-related morbidity.	**D**

Consensus-based recommendation

Patients who have not previously received radiotherapy should be considered for neoadjuvant chemoradiation prior to re-operative surgery.

Practice point

Patients with locally recurrent colorectal cancer should be referred to a centre with the expertise in the management of these cancers.

Practice point

All patients with locally recurrent colorectal cancer should be discussed at a multi-disciplinary team meeting with clinicians who have the expertise in the management of such malignancies. These meetings should review the patient's previous histology and relevant imaging prior to making an appropriate clinical recommendation.

Practice point

Re-operative surgery for locally recurrent colorectal cancer can be associated with significant morbidity. As such, all re-resections should only be offered when cure is considered possible.

Practice point

The key factor in achieving long-term survival in patients with locally recurrent colorectal cancer is a complete resection with clear resection margins (R0 margins), which is an important consideration when making clinical decision about disease resectability.

Back to top

2.1.54 Management of resectable metastatic colorectal cancer (MNG14)

Evidence-based recommendation	Grade
In patients with resectable liver metastases, liver resection should be offered, as this improves overall and progression free survival.	**D**

Evidence-based recommendation	Grade
Patients referred for liver resection should be counselled about the potential complications associated with liver resection in comparison with non-curative treatments.	**D**

Consensus-based recommendation
Patients at higher risk of recurrence should receive adjuvant therapy following liver resection, so as to reduce the likelihood of further local or systemic recurrences.

Consensus-based recommendation
For patients with liver metastases that are considered ‘borderline’ resectable, neoadjuvant chemotherapy should be considered and the case should be discussed by a multidisciplinary team that includes an experienced liver surgeon.

Consensus-based recommendation
In patients with pulmonary metastases, pulmonary resection improves locoregional control and may improve survival.

Consensus-based recommendation
Systemic adjuvant chemotherapy following complete resection of pulmonary metastases may reduce the likelihood of further systemic or local recurrences.

Consensus-based recommendation

In patients with liver and lung metastases, curative treatment may still be feasible. Combined or staged resection of the metastases may be possible provided both the liver and lung metastases can be completely resected and after taking into account the anatomic as well as functional considerations of the remnant liver and lung. Furthermore, lung resection may be considered in patients who have previously undergone a liver resection and vice versa. The use of neoadjuvant chemotherapy with subsequent restaging may also be considered in patients with synchronous liver and lung metastases prior to offering definitive resection.

Consensus-based recommendation

In patients with other isolated metastases, metasectomy may be appropriate in a well-informed patient after appropriate investigations and discussion in a multi-disciplinary team meeting.

Practice point

Patients with liver metastases should be referred to a centre with expertise in the management of these malignancies, for consideration of liver resection, if appropriate.

Practice point

Following curative treatment of liver metastases, patients need ongoing regular follow-up so as to permit early detection of further recurrences that may be amendable to further therapy.

Back to top

2.1.55 Management of non-resectable locally recurrent disease and metastatic disease

2.1.56 Liver-directed therapies for patients with incurable metastatic colorectal cancer

Evidence-based recommendation	Grade
For patients with non-resectable liver metastases of colorectal cancer, liver-directed therapies (selective internal radiation treatment, radiofrequency ablation, hepatic arterial infusion of chemotherapy agents or transarterial chemoembolisation) can be considered in centres with expertise in the specific technique after multidisciplinary team discussion, or in the context of a clinical trial.	**D**

Consensus-based recommendation
In patients with non-resectable liver metastases only (or oligometastatic disease) liver directed techniques can be considered by the MDT based on local experience, patient preference and tumour characteristics. Treating clinicians should have an in-depth discussion with every patient regarding technical complexity, potential outcomes and complications in addition to other therapies available for that patient.

Practice point
All patients with metastatic colorectal cancer should be discussed at a multidisciplinary team meeting with clinicians who have expertise in management of metastatic colorectal cancer.

Practice point
For patients who could be considered surgical candidates if their metastases were smaller, we suggest initial systemic chemotherapy followed by re-evaluation for surgery.

Practice point

Wherever possible, patients considering liver-directed therapies should be enrolled into clinical trials examining these treatments in comparison to standard therapies.

Practice point

SIRT in combination with systemic chemotherapy can be used to prolong the time to liver progression but not improve colorectal cancer survival with most evidence currently in the chemo-refractory patients. At present there is insufficient data to recommend SIRT in the first line setting for patients with non-resectable mCRC.

Insert other pages Back to top

2.1.57 Follow-up after curative resection for colorectal cancer

2.1.58 Rationale for follow-up

Practice point

As there are no reliable indicators of an individual’s risk of synchronous or metachronous lesions, nor of treatable recurrence, all patients who have undergone curative surgery should be offered follow-up if they are fit for further intervention should disease be detected.

Practice point

Patients who are unfit for further surgery or who have advanced disease require appropriate follow-up directed at psychological support and symptom relief.

Back to top

2.1.59 Optimal follow-up surveillance protocol

Evidence-based recommendation	Grade
Intensive follow-up after curative surgery for colorectal cancer should include CEA and CT scan, with the aim of early detection of recurrence or residual disease where there is the possibility for curative resection. PET/CT scan can be used as an effective adjunct for detection of recurrence, especially when the CEA and/or CT scans are suggestive of recurrence.	**D**

Practice point

These recommendations apply only to asymptomatic patients. All patients who develop symptoms should be investigated rigorously.

Practice point

Colonoscopy should be performed at 12 months after surgery to exclude missed lesions. If the initial colonoscopy was incomplete then a colonoscopy should be performed at the latest 6 months after surgery. If the colonoscopy is normal, refer to the Clinical Practice Guidelines for Surveillance Colonoscopy for subsequent colonoscopies.

Practice point

Intensive follow-up for colorectal cancer should be considered for patients who have had potentially curable disease, although optimal modality and frequency are yet to be firmly established.

Practice point

Intensive follow-up can detect recurrences earlier, thus surgical resection for curative intent is possible. However, this is not associated with improved survival.

Practice point

CEA and CT scans are readily accessible and relatively sensitive investigations.

Back to top

2.1.60 Health professionals performing follow-up and suggested follow-up schedule

Practice point

Follow-up can be delivered as a combination of visits to the surgeon or associated gasteroenterologist, with ongoing care by the GP and clinical nurse consultant.

Back to top

2.1.61 Pyschosocial care

2.1.62 Psychosocial care

Practice point

Patients with colorectal cancer should be screened for psychological distress at diagnosis and key points in their disease trajectory.

Practice point

Psychological interventions should be a component of colorectal cancer care, as they can improve the quality of life for patients with cancer.

Practice point

The use of decision aids should be considered for preference-sensitive decisions about treatment for colorectal cancer.

Back to top

This guideline includes evidence-based recommendations (EBR), consensus-based recommendations (CBR) and practice points (PP) as defined in the table below. Recommendations and practice points were developed by working party members and sub-committee members.

Each EBR was assigned a grade by the expert working group, taking into account the volume, consistency, generalisability, applicability and clinical impact of the body of evidence according to NHMRC Level and Grades for Recommendations for Guidelines Developers.[1]

2.1.63 NHMRC approved recommendation types and definitions

Type of recommendation	Definition
Evidence-based recommendation	A recommendation formulated after a systematic review of the evidence, indicating supporting references
Consensus-based recommendation	A recommendation formulated in the absence of quality evidence, after a systematic review of the evidence was conducted and failed to identify admissible evidence on the clinical question
Practice point	A recommendation on a subject that is outside the scope of the search strategy for the systematic review, based on expert opinion and formulated by a consensus process

Source: National Health and Medical Research Council. Procedures and requirements for meeting the NHMRC standard for clinical practice guidelines. Melbourne: National Health and Medical Research Council, 2011

Back to top

2.2 References

1. ↑ National Health and Medical Research Council. *NHMRC levels of evidence and grades for recommendations for guideline developers.* Canberra: National Health and Medical Research Council; 2009 Available from: https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf.

3 Plain-language summary

4 Colorectal cancer in Australia

Contents

4.1 Introduction

In Australia, colorectal cancer is a major cause of morbidity and mortality. In 2014, it was estimated to be the second most commonly diagnosed cancer in Australia (excluding non-melanoma skin cancer) and the second most common cause of cancer mortality (after lung cancer), representing 9% of all deaths from cancer.[1] The risk of being diagnosed with colorectal cancer by the age of 85 years is one in 11 for males and one in 15 for females.[2]

Australia has one of the highest rates of colorectal cancer in the world.[3] The high rates of colorectal cancer in Australia and other developed Western countries are likely to be due in large part to the increased prevalence of established environmental risk factors, including physical inactivity and obesity,[4] smoking,[5] heavy alcohol consumption,[6] and a diet high in red/processed meats[7] and low in fibre.[8]

Back to top

4.2 Incidence and mortality

4.2.1 Population age-standardised rates

Table 1.1 shows the Australian incidence and mortality rates for colorectal cancer in comparison with other countries for the period up to and including 2012.[3]

A total of 14,958 new cases of colorectal cancer were diagnosed in Australia in 2012 (8239 males and 6718 females). In comparison, there were 6985 new cases diagnosed in 1982.[2]

The age-standardised incidence rate for colorectal cancer increased from 58 per 100,000 persons in 1982 to 59 cases per 100,000 persons in 2012 (70 for males and 50 for females).[2]

The introduction of the National Bowel Cancer Screening Program (NBCSP) was expected to result in short-term increases in incidence rates due to the detection of previously undetected cancers in those participating in screening for the first time.[9] However, in the long-term it is expected that the incidence of colorectal cancer in those age groups eligible for population screening will begin to fall, as pre-cancerous lesions are detected and treated before they develop into cancer. This trend has been observed in cervical cancer incidence following the introduction of the National Cervical Screening Program.[10]

In 2013, 4162 deaths from colorectal cancer in Australia (2299 males and 1863 females) were recorded.[i,2] In comparison, there were 2500 deaths recorded in 1968.[2]

The age-standardised mortality rate for colorectal cancer decreased from 31 deaths per 100,000 persons in 1968 to 16 deaths per 100,000 in 2013 (19 for males and 13 for females).[2]

Although the age-standardised incidence rate for colorectal cancer in Australia is amongst the highest in the world, it has barely increased in 30 years, and in comparison with other developed Western countries the proportion of diagnosed patients dying from the disease is low.

[i] Numbers recorded by the Australian Bureau of Statistics (ABS) based on death certificates. These figures probably significantly underestimate the true number of deaths due to colorectal cancer because the coding methods used in various jurisdiction can result in such deaths being attributed to nonspecific cancers such as 'malignant neoplasms of other and unspecified digestive organs' or 'cancers of unknown primary site'.

4.2.1.1 Table 1.1 Incidence and mortality rates for colorectal cancer, selected countries, 2012

Country	Incidence [(a)] (ASRW)	Mortality [(b)] (ASRW)
Australia	38.4	9.0
New Zealand	37.3	15.1
Canada	35.1	10.8
UK	30.2	10.7
USA	25.0	9.2

ASRW: age-standardised rate (standardised to World Standard Population for purpose of international comparison)
(a) Incidence is the number of new cases of colorectal cancer per 100,000 people, age-standardised to the World Standard Population;
(b) Mortality is the number of deaths from colorectal cancer per 100,000 people, age-standardised to the World Standard Population.
Source: GLOBOCAN (2012)[3]

Back to top

4.2.2 Age and sex

The trend in age-specific incidence rates for colorectal cancer in 2012 was similar to that of previous years, with incidence rates rising sharply for those aged 50 years and over, and remaining relatively low for those under 45 years (Figure 1.1).[2] People aged 80 years and over demonstrated the highest incidence rates, with more than 400 newly diagnosed cases per 100,000 population.

4.2.2.1 Figure 1.1 Age-specific incidence rates for colorectal cancer, Australia, 2012

Source: Australian Institute of Health and Welfare (2016).[2] The incidence (or mortality) rate has been age-standardised to the Australian population (ASR) at 30 June 2001.

Figure 1.2 shows the time trends in incidence of colorectal cancer in Australian men and women.[2] Between 2000 and 2012, the age-standardised incidence rates for colorectal cancer demonstrated a gradual decline in both males (1% per year) and females (0.6% per year). However, over the same period the number of newly diagnosed cases of colorectal cancer increased by 20% in males, and 22% in females, due to the increasing size and ageing of the Australian population.[2]

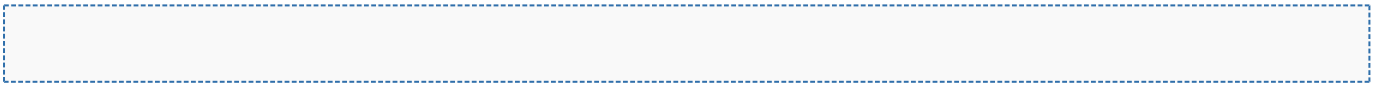
4.2.2.2 Figure 1.2 Age-standardised incidence rates for colorectal cancer, Australia, 1982–2012

Source: Australian Institute of Health and Welfare (2016).[2] The incidence (or mortality) rate has been age-standardised to the Australian population (ASR) at 30 June 2001.

The highest age-specific mortality rates for colorectal cancer in 2013 were observed in the oldest age groups, with those aged 80–84 demonstrating a rate of 144 deaths per 100,000 population, and those aged 85 years and over demonstrating a rate of 220 deaths per 100,000 (Figure 1.3).[2] Approximately 30% of all colorectal cancer deaths occurred in those aged between 50 and 69 years (1198 deaths). However, death from colorectal cancer was relatively uncommon among those aged less than 50 years.[2]

Figure 1.4 shows the time trends in mortality from colorectal cancer in Australian men and women.[2] Between 1994 and 2013 there was a decline in the age-standardised mortality rate, which fell by an average of 2.4% per year overall.[2]

4.2.2.3 Figure 1.3 Age-specific mortality rates for colorectal cancer, Australia, 2013



Source: Australian Institute of Health and Welfare (2016)[2]

4.2.2.4 Figure 1.4 Age-standardised mortality rates for colorectal cancer, Australia, 1968–2013

Source: Australian Institute of Health and Welfare (2016).[2] The incidence (or mortality) rate has been age-standardised to the Australian population (ASR) at 30 June 2001.

Back to top

4.2.3 Socioeconomic status

In the 4 years from 2006 to 2009, those living in the most disadvantaged areas of Australia accounted for the highest age-standardised incidence rate for colorectal cancer (66 per 100,000).[1]

In the 4 years from 2009 to 2012, those living in the most disadvantaged areas of Australia accounted for the highest age-standardised mortality rate[ii] for colorectal cancer (17 per 100,000).[1]

[ii]Age-standardised incidence according to socioeconomic status, jurisdiction and Indigenous status was not consistently reported for all time periods, so direct comparisons between the reporting periods cannot be made.

Back to top

4.2.4 Remoteness area

In the 5 years from 2005 to 2009, people living in Inner regional areas of Australia had the highest age-standardised incidence rate for colorectal cancer (70 per 100,000).[1]

Between 2008 and 2012, age-standardised mortality rates[ii] for colorectal cancer were higher in Inner regional and Outer regional areas of Australia, each with 17 deaths per 100,000. Age-standardised mortality rates were lowest in Very remote areas (11 deaths per 100,000).[1]

[ii] Age-standardised incidence according to socioeconomic status, jurisdiction and Indigenous status was not consistently reported for all time periods, so direct comparisons between the reporting periods cannot be made.

Back to top

4.2.5 State and territory

The incidence of colorectal cancer varied between jurisdictions in the period between 2005 and 2009. Tasmania (75 cases per 100,000 persons) and Queensland (66 cases per 100,000 persons) had the highest age-standardised incidence rates, while Western Australia and the Northern Territory (57 cases per 100,000 persons each) had the lowest.[1]

Between 2008 and 2012, Tasmania had the highest age-standardised mortality rate[ii] for colorectal cancer (20 deaths per 100,000 population), while Western Australia had the lowest (14 deaths per 100,000 population).[1]

[ii] Age-standardised incidence according to socioeconomic status, jurisdiction and Indigenous status was not consistently reported for all time periods, so direct comparisons between the reporting periods cannot be made.

Back to top

4.2.6 Aboriginal and Torres Strait Islander peoples

Between 2005 and 2009, colorectal cancer was the third most commonly diagnosed cancer among Aboriginal and Torres Strait Islander peoples (of the selected cancers reported for Indigenous Australians), with 79 cases per year.[1]

Colorectal cancer is one of the cancers for which the age-standardised incidence rate was lower for Indigenous Australians than non-Indigenous Australians, with a rate ratio of 0.8.[1] It is unclear why there is a lower incidence rate for some cancers among Indigenous Australians. However, it has been suggested that the lower rates of participation in screening and diagnostic testing among Indigenous people may play a role.[1] Indigenous Australians are more likely to have cancers that are diagnosed at a later stage, when the primary site is no longer apparent, which may contribute to lower incidence rates for specific primary sites.[1]

In 2008–2012, the age-standardised mortality rate for colorectal cancer was lower for Aboriginal and Torres Strait Islander people (13 deaths per 100,000) than for non-Indigenous Australians (16 deaths per 100,000), based on National Mortality Database data from New South Wales, Queensland, Western Australia, South Australia and the Northern Territory.[1]

Back to top

4.3 Socioeconomic status

In the 5 years from 2006 to 2010, those living in the most disadvantaged areas of Australia had the highest age-standardised incidence rate for colorectal cancer (67 cases per 100,000 people), while those living in the least disadvantaged areas had the lowest age-standardised incidence rate (59 cases per 100,000).[11]

In the 5 years from 2009 to 2013, those living in the most disadvantaged areas of Australia had the highest age-standardised mortality rate for colorectal cancer (18 deaths per 100,000 people), while those living in the least disadvantaged areas had the lowest age-standardised mortality rate (14 deaths per 100,000).[11]

4.4 Remoteness area

In the 5 years from 2006 to 2010, people living in Outer regional areas of Australia had the highest age-standardised incidence rate for colorectal cancer (69 cases per 100,000 people), while those living in Very remote areas had the lowest age-standardised incidence rate (51 cases per 100,000).[11]

Between 2009 and 2013, age-standardised mortality rates for colorectal cancer were highest in Outer regional areas of Australia, with 17 deaths per 100,000 people. Age-standardised mortality rates were lowest in Very remote areas (12 deaths per 100,000).[11]

4.5 State and territory

The incidence of colorectal cancer varied between jurisdictions in the period between 2006 and 2010. Tasmania (75 cases per 100,000 people) had the highest age-standardised incidence rate, while the Northern Territory (57 cases per 100,000) had the lowest.[11]

Between 2009 and 2013, Tasmania and the Northern Territory had the highest age-standardised mortality rate for colorectal cancer (19 deaths per 100,000 people each), while Western Australia had the lowest age-standardised mortality rate (14 deaths per 100,000).[11]

4.6 Aboriginal and Torres Strait Islander peoples

Between 2006 and 2010, Indigenous Australians had a lower age-standardised incidence rate for colorectal cancer (47 cases per 100,000 people) compared with non-Indigenous Australians (60 cases per 100,000), based on incidence data from New South Wales, Queensland, Western Australia, and the Northern Territory.[11]

It is unclear why there is a lower incidence rate for some cancers among Indigenous Australians. However, it has been suggested that the lower rates of participation in screening and diagnostic testing among Indigenous people may play a role.[1] Indigenous Australians are more likely to have cancers that are diagnosed at a later stage, when the primary site is no longer apparent, which may contribute to lower incidence rates for specific primary sites.[1]

In 2009–2013, the age-standardised mortality rate for colorectal cancer was lower for Indigenous Australians (13 deaths per 100,000 people) than for non-Indigenous Australians (16 deaths per 100,000), based on National Mortality Database data from New South Wales, Queensland, Western Australia, South Australia and the Northern Territory.[11]

4.7 Colorectal cancer screening

The early detection of colorectal cancer through population screening programs is associated with better treatment options, improved prognosis and reduced mortality. A number of randomised controlled trials have shown that population screening programs using the faecal occult blood test (FOBT) can reduce colorectal cancer mortality by 15–33%.[12][13][14][15]

In Australia, screening for colorectal cancer is available through the NBCSP, which was introduced in 2006. The NBCSP aims to reduce the morbidity and mortality from colorectal cancer by actively recruiting and screening the target population for early detection or prevention of the disease using FOBT kits.[11] The program has been phased in gradually, and by 2020 will offer biennial screening for those aged 50 to 74 years.

In addition to the NBSCP, there are a number of other ways that Australians can participate in screening for colorectal cancer. In conjunction with their general practitioner, individuals can purchase a FOBT kit from a pharmacy without a prescription, or obtain a kit from non-government organisations such as the Cancer Council [16] or from community or consumer organisations like Rotary or Bowel Cancer Australia, which run screening programs through pharmacies. In addition, individuals who undergo endoscopic procedures such as sigmoidoscopy or colonoscopy, even when these procedures are not specifically for the purpose of screening for colorectal cancer, may be considered up-to-date with screening. Research suggests that a significant percentage of older Australians may be participating in screening practices such as these, outside of the NBCSP. [16]

Back to top

4.7.1 Screening participation rates in the general population

Of the 2,239,760 FOBT invitation kits that were sent out to eligible individuals between 1 January 2013 and 31 December 2014, a total of 836,457 people participated in the program by returning a completed FOBT for analysis.[11] Therefore, the overall Australia-wide crude participation rate[iii] was 37.0%.[11] Given the significant proportion of older Australians who may be participating in screening practices outside of the NBCSP, however, this may be an underestimate of true population screening rates.[16]

The national participation rate of 37% for 2013–2014 was slightly higher when compared with the previous rolling 2-year period (2012–2013), which had a participation rate of 36%.15 In addition, the participation rate was highest for individuals receiving their second or later (subsequent) screening invitation (41% compared with 35%).[11]

A 2014 study compared the outcomes and cancer characteristics of individuals who had been invited to participate in the NBCSP in 2006–2008, as part of the target population turning 50, 55 or 65 (invitees), with those of individuals aged 50–69 in 2006–2008, but who did not turn 50, 55 or 65 during that period and were therefore not invited to screen then (non-invitees).[17] This study demonstrated that, of those diagnosed with colorectal cancer between 2006 and 2008, non-invitees had a 68% higher risk of colorectal cancer death, compared with NBCSP invitees.[17] For NBCSP invitees specifically, the risk of death from colorectal cancer was more than twice as high in those who did not participate but later had a colorectal cancer diagnosed, compared

with those whose cancer was diagnosed through participation in colorectal cancer screening. In addition, colorectal cancers diagnosed in non-invitees had 38% higher odds of being more advanced than those diagnosed in NBCSP invitees.[17] For NBCSP invitees specifically, those with colorectal cancers detected through screening had 121% higher odds of being diagnosed at an earlier stage, compared with colorectal cancers diagnosed in invitees who did not participate. These findings suggest that the NBCSP is contributing to reducing morbidity and mortality from colorectal cancer in Australia.[17]

[iii] All colorectal screening participation rates (in the general population and by state and territory, age and sex, socioeconomic status and remoteness area) reported in the National Bowel Cancer Screening Program Monitoring Report 2016 were crude participation rates, and age-standardised participation rates were not reported.

Back to top

4.7.2 Screening participation rates by state and territory

In 2013–2014, NBCSP participation rates did vary by state and territory.[11] With the exception of New South Wales (34.5% crude participation rate), Queensland (36.6%) and the Northern Territory (27.6%), all other jurisdictions demonstrated participation rates that were above the overall Australian rate.[11]

While the reasons behind the observed jurisdictional variations in NBCSP participation are unclear, an analysis of participation by socioeconomic status and remoteness areas within each jurisdiction has demonstrated that participation in New South Wales and Queensland was generally lower across all subgroups (including Major cities, and Inner and outer regional areas), compared with the other jurisdictions.[11] These findings suggest that in these jurisdictions, which are larger and therefore have a bigger impact on the Australian participation rate, lower participation was an overall trend.

Back to top

4.7.3 Screening participation rates by age and sex

Participation rates were higher for females than males in each of the four age groups (Figure 1.5), with females 1.2 times more likely than males to participate in colorectal screening (34.7% for males, compared with 40.0% for females).[11]

Given that colorectal cancer risk and incidence is higher in men, this suggests an inequitable pattern of NBCSP participation on the basis of sex. It has been suggested that women may have higher screening rates for colorectal cancer due to the fact that they are involved in, and aware of, other population-based screening programs such as those for cervical cancer and breast cancer, and may therefore better understand the potential benefits of screening.[18]

Participation rates varied between the four target age groups, and were highest for those aged 65–69 years (44.2%), and those aged 60–64 years (43.9%). These were the only two age groups with participation rates above the national average (Figure 1.5).[11]

4.7.3.1 Figure 1.5 Crude participation in the National Bowel Cancer Screening Program, by age and sex, 2013–2014

Source: Data from National Bowel Cancer Screening Program Register as at 31 December 2015(AIHW 2016)[11]

Back to top

4.7.4 Screening participation rates by socioeconomic status

Analysis of NBCSP data according to population-based socioeconomic status quintiles showed that invitees living within areas with the lowest socioeconomic status (areas with the most socioeconomic disadvantage) had lower participation rates, when compared with those living in all other areas rated according to level of socioeconomic status (Figure 1.6).[11]

These results are consistent with the findings of studies in Australia and internationally. A UK study has shown that socioeconomic deprivation has a major effect on participation in screening.[19] It found that people from more economically deprived areas had less interest in and uptake of colorectal cancer screening than their counterparts in less deprived areas.[19] Similarly, a study in South Australia demonstrated a general pattern of lower screening participation in more disadvantaged socioeconomic groups.[18] This study found that key barriers to the NBCSP were lack of knowledge about colorectal cancer and screening tests in general, and the NBCSP in particular, suggesting a need for greater resources for social marketing to increase both awareness and health literacy in this area.[18]

4.7.4.1 Figure 1.6 Crude participation in the National Bowel Cancer Screening Program, by socioeconomic status area, 2013–2014

Source: Data from National Bowel Cancer Screening Program Register as at 31 December 2015(AIHW 2016)[11]

Back to top

4.7.5 Screening participation rates by remoteness area

Over 66% of all participants came from Major cities (with a 36.6% crude participation rate).[11] The proportion participating in screening was highest in Inner regional (40.0%) and Outer regional (38.7%) areas and lowest in Remote and Very remote areas (Figure 1.7).

4.7.5.1 Figure 1.7 Crude participation in the National Bowel Cancer Screening Program, by remoteness area, 2013–2014

Source: Data from National Bowel Cancer Screening Program Register as at 31 December 2015 (AIHW 2016)[11]

Back to top

4.8 Colorectal cancer control in Australia: now and in the future

4.8.1 Survival

In 2008–2012, the 5-year relative survival for colorectal cancer in the Australian population was 68% (67% for males and 69% for females) (Figure 1.8).[11] In people aged 50–74 years (the target age group for the NBCSP), the 5-year relative survival was 72%. In comparison, in 1982–1986, individuals diagnosed with colorectal cancer had a 48% chance of surviving for 5 years compared with those in the general population.[11]

The improvement in colorectal cancer survival rates may be due to a number of factors, such as earlier presentation, earlier diagnosis, and improved treatments including safer and more effective surgical techniques [20] as well as the availability of new chemotherapeutic and biologic treatment agents.[21] Better management of families with Lynch syndrome and Familial Adenomatous Polyposis, more effective colonoscopic surveillance following cancer or adenoma detection, and ad hoc screening by FOBT or colonoscopy may also have contributed to improved colorectal cancer survival rates. It is unlikely that the NBCSP has had a significant impact on the observed increases in 5-year survival, given the small number of years the program has been active, the limited ages screened during those years, and the relatively low participation rates.

At the time of diagnosis, the probability of surviving for at least 5 years was 68%, which increased to 91% and 96% at 5 years and 15 years post-diagnosis, respectively (Figure 1.8).[11]

4.8.1.1 Figure 1.8 Relative survival at diagnosis and 5-year conditional survival from colorectal cancer, Australia, 2008–2012

Conditional relative survival: Conditional survival estimates show the probability of surviving a given number of years provided that an individual has already survived a specified amount of time after diagnosis.
Source: Data from Australian Cancer Database (AIHW 2012)[9]

Back to top

4.8.2 Incidence

Projections for cancer incidence in Australia have been undertaken that involve mathematical extrapolations of past trends with the assumption that the same trend will continue into the future.[9] These projections are not forecasts and do not attempt to allow for future changes in areas such as population screening programs or treatment regimens. For colorectal cancer, projections are based on extrapolation of the trends in incidence up to 2007 and do not take into account the impact of the NBCSP on future incidence.[9]

In males, age-standardised incidence rates for colorectal cancer demonstrated an increasing trend between 1982 and 1996. However, between 1996 and 2007 there was a small but statistically significant reduction of approximately 0.3 cases per 100,000 males per year (Figure 1.9).[9]

While the age-standardised incidence rate for colorectal cancer is expected to fall to approximately 71 cases per 100,000 males by 2020, equating to approximately 10,800 new cases, the estimated number of new cases diagnosed is expected to continue to increase due to projected increases in the size of the elderly population (Figure 1.9). Males aged 45–64 years are expected to show the greatest reductions in colorectal cancer rates, while those aged 85 years and over are expected to show smaller reductions.[9]

4.8.2.1 Figure 1.9 Trends in number of new cases and age-standardised incidence rates(a) for colorectal cancer in Australian males, 1982 to 2007, projected to 2020

(a) Rates are expressed per 100,000 males. ASR: Age standardised rate (standardised to the Australian population as at 30 June 2001) Source: Australian Cancer Database (AIHW 2012)[9]

In females, the age-standardised incidence rate for colorectal cancer demonstrated a slight increase of approximately 0.04 cases per 100,000 females per year between 1982 and 2007 (Figure 1.10), which was not statistically significant.[9]

By 2020, the age-standardised incidence rate for colorectal cancer is expected to remain steady at approximately 54 cases diagnosed per 100,000 females, which is equivalent to approximately 9160 new cases (Figure 1.10).[9] Females aged 45–64 years are expected to show reductions in colorectal cancer rates, although these reductions are unlikely to be as significant as those observed for males in the same age group.[9]

4.8.2.2 Figure 1.10 Trends in number of new cases and age-standardised incidence rates(a) for colorectal cancer in Australian females, 1982 to 2007, projected to 2020

(a) Rates are expressed per 100,000 females. ASR: Age standardised rates (age standardised to the Australian population as at 30 June 2001) Source: AHW Australian Cancer Database (AIHW 2012)[9]

Back to top

4.9 References

1. ↑ 1.00 1.01 1.02 1.03 1.04 1.05 1.06 1.07 1.08 1.09 1.10 1.11 1.12 1.13 Australian Institute of Health and Welfare. *Cancer in Australia: an overview 2014. [Version updated 16 April 2015] Cancer series No 90. Cat. no. CAN 88.* Canberra: AIHW;.
2. ↑ 2.00 2.01 2.02 2.03 2.04 2.05 2.06 2.07 2.08 2.09 2.10 2.11 2.12 2.13 2.14 2.15 2.16 Australian Cancer Incidence and Mortality (ACIM). *Workbook for colorectal cancer.* www.aihw.gov.au/cancer/data/acim_books/index.cfm 2011.

3. ↑ 3.0 3.1 3.2 World Health Organization International Agency for Research on Cancer (IARC). *GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012.* [homepage on the internet]; 2012 [cited 2016 Apr 23]. Available from: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx.
4. ↑ Steins Bisschop CN, van Gils CH, Emaus MJ, Bueno-de-Mesquita HB, Monninkhof EM, Boeing H, et al. *Weight change later in life and colon and rectal cancer risk in participants in the EPIC-PANACEA study.* Am J Clin Nutr 2014 Jan;99(1):139-47 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24225355.
5. ↑ Leufkens AM, Van Duijnhoven FJ, Siersema PD, Boshuizen HC, Vrieling A, Agudo A, et al. *Cigarette smoking and colorectal cancer risk in the European Prospective Investigation into Cancer and Nutrition study.* Clin Gastroenterol Hepatol 2011 Feb;9(2):137-44 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21029790.
6. ↑ Ferrari P, Jenab M, Norat T, Moskal A, Slimani N, Olsen A, et al. *Lifetime and baseline alcohol intake and risk of colon and rectal cancers in the European prospective investigation into cancer and nutrition (EPIC).* Int J Cancer 2007 Nov 1;121(9):2065-72 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17640039.
7. ↑ Norat T, Bingham S, Ferrari P, Slimani N, Jenab M, Mazuir M, et al. *Meat, fish, and colorectal cancer risk: the European Prospective Investigation into cancer and nutrition.* J Natl Cancer Inst 2005 Jun 15;97(12):906-16 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15956652.
8. ↑ Murphy N, Norat T, Ferrari P, Jenab M, Bueno-de-Mesquita B, Skeie G, et al. *Dietary fibre intake and risks of cancers of the colon and rectum in the European prospective investigation into cancer and nutrition (EPIC).* PLoS One 2012;7(6):e39361 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22761771.
9. ↑ 9.00 9.01 9.02 9.03 9.04 9.05 9.06 9.07 9.08 9.09 9.10 Australian Institute of Health and Welfare. *Cancer incidence projections: Australia, 2011 to 2020. Cancer series no. 66. Cat. no. CAN 62.* Canberra: AIHW; 2012.
10. ↑ Australian Institute of Health and Welfare. *Cervical screening in Australia 2012–2013. Cancer series no. 93. Cat. no. CAN 91.* Canberra: AIHW; 2015 Available from: http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=60129550872.
11. ↑ 11.00 11.01 11.02 11.03 11.04 11.05 11.06 11.07 11.08 11.09 11.10 11.11 11.12 11.13 11.14 11.15 11.16 11.17 11.18 11.19 11.20 11.21 11.22 11.23 11.24 Australian Institute of Health and Welfare. *National Bowel Cancer Screening Program: monitoring report 2016. Cancer series no. 98. Cat. no. CAN 97.* Canberra: AIHW; 2016.
12. ↑ Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, et al. *Randomised controlled trial of faecal-occult-blood screening for colorectal cancer.* Lancet 1996 Nov 30;348(9040):1472-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8942775.
13. ↑ Kewenter J, Brevinge H, Engaråas B, Haglind E, Ahrén C. *Results of screening, rescreening, and follow-up in a prospective randomized study for detection of colorectal cancer by fecal occult blood testing. Results for 68,308 subjects.* Scand J Gastroenterol 1994 May;29(5):468-73 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8036464.
14. ↑ Kronborg O, Fenger C, Olsen J, Jørgensen OD, Søndergaard O. *Randomised study of screening for colorectal cancer with faecal-occult-blood test.* Lancet 1996 Nov 30;348(9040):1467-71 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8942774.
15. ↑ Mandel JS, Church TR, Ederer F, Bond JH. *Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood.* J Natl Cancer Inst 1999 Mar 3;91(5):434-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/10070942.

16. ↑ 16.0 16.1 16.2 Zajac, I. T. Flight, I. Turnbull, D. Young, G. Cole, S. Wilson, C.. *Self-reported bowel screening rates in older Australians and the implications for public health screening programs.* Australas Med J 2013;6(8): 411-417.
17. ↑ 17.0 17.1 17.2 17.3 Australian Institute of Health and Welfare. *Analysis of bowel cancer outcomes for the National Bowel Cancer Screening Program. Cat. no. CAN 87.* Canberra: AIHW; 2014.
18. ↑ 18.0 18.1 18.2 Ward PR, Javanparast S, Wilson C. *Equity of colorectal cancer screening: which groups have inequitable participation and what can we do about it?* Aust J Prim Health 2011;17(4):334-46 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22112702.
19. ↑ 19.0 19.1 Whynes DK,Frew EJ, Manghan CM, Scholefield JH, Hardcastle JD. *Colorectal cancer, screening and survival: the influence of socio-economic deprivation.* Public Health 2003;117(6):389-395.
20. ↑ Wiegering, A. Isbert, C. Dietz, U. A. Kunzmann, V. Ackermann, S. Kerscher, A. Maeder, U. Flentje, M. Schlegel, N. Reibetanz, J. Germer, C. T. Klein, I.. *Multimodal therapy in treatment of rectal cancer is associated with improved survival and reduced local recurrence - a retrospective analysis over two decades.* BMC Cancer 2014;14: 816.
21. ↑ Hu CY, Bailey CE, You YN, Skibber JM, Rodriguez-Bigas MA, Feig BW, et al. *Time trend analysis of primary tumor resection for stage IV colorectal cancer: less surgery, improved survival.* JAMA Surg 2015 Mar 1;150(3):245-51 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25588105.

Back to top

5 Primary prevention

Contents

5.1 Background

Colorectal cancer is the second most common non-skin cancer occurring in men and women in Australia, and the second most common cause of cancer death[1]. Although mortality from the disease has been decreasing over recent decades, the incidence is still rising slowly[1]. Many observational studies have provided evidence of dietary associations with colorectal cancer risk. A limited number of randomised controlled trials (RCTs) also support diet and lifestyle advice to reduce colorectal cancer risk. Colorectal cancer is the second most preventable cancer after lung cancer[2]. Table 2.1 shows the proportion of incident colorectal cancer cases diagnosed in 2010 in Australia attributable to lifestyle and environmental factors (all both males and females).

5.1.1 Table 2.1 Proportion of incident colorectal cancer cases diagnosed in Australia attributable to lifestyle and environmental factors

Lifestyle/environmental factor	Proportion (%)
Tobacco smoke	6.4
Alcohol	9.0
Overweight and obesity	9.0
Insufficient physical activity	4.8
Diet – insufficient fibre	17.6
Diet – red and processed meat	17.6
Population attributable fraction combined	49.8

Proportions (%) presented are for the entire Australian population (0–-85+ years), all persons (male/female); Abridged table, adapted from Whiteman et al 2015[2] with permission from the publisher (in progress)

In the adult white population in the USA, it has been estimated that 60% and 59% of colorectal cancer incidence for women and men, respectively, could be prevented by lifestyle factors[3]. However, although these lifestyle and environmental risk factors are well described, there is no data yet available to indicate that interventions to avoid or modify favourably the factors has been less convincing except for some diet studies.

Prevention of colorectal cancer includes:

- primary prevention through chemoprevention, dietary and lifestyle modifications
- early detection and removal of precursor lesions such as the adenomatous polyp.

This chapter focuses on primary prevention, and summarises advances in the knowledge and application of interventions to prevent colorectal cancer, thereby reducing the incidence of the disease.

5.1.2 Contents

Subsections:

Part 1: Dietary and lifestyle strategies

Part 2: Chemopreventive candidate agents

5.2 References

1. ↑ [1.0] [1.1] Australian Institute of Health and Welfare. *Cancer in Australia: an overview 2014. [Version updated 16 April 2015] Cancer series No 90. Cat. no. CAN 88.* Canberra: AIHW;.
2. ↑ [2.0] [2.1] Whiteman DC, Webb PM, Green AC, Neale RE, Fritschi L, Bain CJ, et al. *Cancers in Australia in 2010 attributable to modifiable factors: introduction and overview.* Aust N Z J Public Health 2015 Oct;39 (5):403-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26437722.
3. ↑ Song M, Giovannucci E. *Preventable Incidence and Mortality of Carcinoma Associated With Lifestyle Factors Among White Adults in the United States.* JAMA Oncol 2016 Sep 1;2(9):1154-61 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27196525.

5.1 Introduction: primary prevention

Contents

5.1.1 Background

Colorectal cancer is the second most common non-skin cancer occurring in men and women in Australia, and the second most common cause of cancer death[1]. Although mortality from the disease has been decreasing over recent decades, the incidence is still rising slowly[1]. Many observational studies have provided evidence of dietary associations with colorectal cancer risk. A limited number of randomised controlled trials (RCTs) also support diet and lifestyle advice to reduce colorectal cancer risk. Colorectal cancer is the second most preventable cancer after lung cancer[2]. Table 2.1 shows the proportion of incident colorectal cancer cases diagnosed in 2010 in Australia attributable to lifestyle and environmental factors (all both males and females).

5.1.1.1 Table 2.1 Proportion of incident colorectal cancer cases diagnosed in Australia attributable to lifestyle and environmental factors

Lifestyle/environmental factor	Proportion (%)
Tobacco smoke	6.4
Alcohol	9.0
Overweight and obesity	9.0
Insufficient physical activity	4.8
Diet – insufficient fibre	17.6
Diet – red and processed meat	17.6
Population attributable fraction combined	49.8

Proportions (%) presented are for the entire Australian population (0–-85+ years), all persons (male/female); Abridged table, adapted from Whiteman et al 2015[2] with permission from the publisher (in progress)

In the adult white population in the USA, it has been estimated that 60% and 59% of colorectal cancer incidence for women and men, respectively, could be prevented by lifestyle factors[3]. However, although these lifestyle and environmental risk factors are well described, there is no data yet available to indicate that interventions to avoid or modify favourably the factors has been less convincing except for some diet studies.

Prevention of colorectal cancer includes:

- primary prevention through chemoprevention, dietary and lifestyle modifications
- early detection and removal of precursor lesions such as the adenomatous polyp.

This chapter focuses on primary prevention, and summarises advances in the knowledge and application of interventions to prevent colorectal cancer, thereby reducing the incidence of the disease.

5.1.1.2 Contents

Subsections:

Part 1: Dietary and lifestyle strategies

Part 2: Chemopreventive candidate agents

5.1.2 References

1. ↑ [1.0] [1.1] Australian Institute of Health and Welfare. *Cancer in Australia: an overview 2014. [Version updated 16 April 2015] Cancer series No 90. Cat. no. CAN 88.* Canberra: AIHW;.
2. ↑ [2.0] [2.1] Whiteman DC, Webb PM, Green AC, Neale RE, Fritschi L, Bain CJ, et al. *Cancers in Australia in 2010 attributable to modifiable factors: introduction and overview.* Aust N Z J Public Health 2015 Oct;39 (5):403-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26437722.
3. ↑ Song M, Giovannucci E. *Preventable Incidence and Mortality of Carcinoma Associated With Lifestyle Factors Among White Adults in the United States.* JAMA Oncol 2016 Sep 1;2(9):1154-61 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27196525.

5.2 Dietary and lifestyle strategies

Contents

5.2.1 Overview of evidence (non-systematic literature review)

No systematic reviews on this topic were undertaken in the development of this clinical practice guideline section.

5.2.1.1 Evidence sources

Two comprehensive literature reviews undertaken jointly by the World Cancer Research Fund and the American Institute for Cancer Research have reported the evidence for lifestyle factors in the prevention of cancers:

- the Second Expert Report (SER) on food, nutrition and physical activity in the prevention of cancer (2007)[1]
- the Continuous Update Project (CUP) review of food, nutrition and physical activity in the prevention of colorectal cancer (2011).[2]

The lifestyle and dietary guidance in this chapter is primarily summarised from these reviews. Updated information was included, where available. New systematic reviews were not undertaken for this guideline.

Updated systematic reviews are currently in progress by World Cancer Research Fund/American Institute for Cancer Research.[i]

[i]These guidelines may be updated after 2017 as a result of updated guidance from the World Cancer Research Fund/American Institute for Cancer Research. The provisional publication dates for The Colorectal Cancer Report and the Expert Report are April 2017 and November 2017, respectively.

Back to top

5.2.1.2 Summary of associations between lifestyle factors and colorectal cancer risk

Table 2.2 summarises the World Cancer Research Fund/American Institute for Cancer Research conclusions on the evidence for dietary and lifestyle factors as risk factors for, or protective against, colorectal cancer.[2]

5.2.1.2.1 Table 2.2. Food, nutrition, physical activity and risk of cancers of the colon and the rectum

Strength of association	Decreases risk	Increases risk
Convincing	Physical activity[1, 2] Foods containing dietary fibre[3]	Red meat[4,5] Processed meat[4,6] Alcoholic drinks (men)[7] Body fatness Abdominal fatness Adult attained height[8]

Strength of association	Decreases risk	Increases risk
Probable	Garlic Milk[9] Calcium[10]	Alcoholic drinks (women)[7]
Limited – suggestive	Non-starchy vegetables Fruits Foods containing vitamin D3[12]	Foods containing iron[3,4] Cheese[11] Foods containing animal fats[3] Foods containing sugars[13]
Limited – no conclusion	Fish, glycaemic index, folate, vitamin C, vitamin E, selenium, low fat, dietary pattern	
Substantial effect on risk unlikely	None identified	

1. Physical activity of all types: occupational, household, transport, and recreational.

2. The Panel judges that the evidence is stronger for colon cancer is convincing. No conclusion was drawn for rectal cancer.
3. Includes both foods naturally containing the constituent and foods which have the constituent added. Dietary fibre is contained in plant foods.
4. Although red and processed meats contain iron, the general category of ‘foods containing iron’ comprises many other foods, including those of plant origin.
5. The term ‘red meat’ refers to beef, pork, lamb, and goat from domesticated animals.
6. The term ‘processed meat’ refers to meats preserved by smoking, curing, or salting, or addition of chemical preservatives.
7. The judgements for men and women are different because there are fewer data for women. For colorectal cancers, the effect appears stronger in men than women.
8. Adult attained height is unlikely directly to modify the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth.
9. Milk from cows. Most data are from high-income populations, where calcium can be taken to be a marker for milk/dairy consumption. The Panel judges that a higher intake of dietary calcium is one way in which milk could have a protective effect.
10. The evidence is derived from studies using supplements at a dose of 1200 mg/day.
11. Although both milk and cheese are included in the general category of dairy products, their different nutritional composition and consumption patterns may result in different findings.
12. Found mostly in fortified foods and animal foods.
13. ‘Sugars’ here means all ‘non-milk extrinsic’ sugars, including refined and other added sugars, honey, and as contained in fruit juices and syrups. It does not include sugars naturally present in whole foods such as fruits. It also does not include lactose as contained in animal or human milks.

Source: World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Report. Food, Nutrition, Physical Activity, and the Prevention of Colorectal Cancer. 2011.[2] Seeking permission from publisher, note title amendment.

Back to top

5.2.1.3 Tobacco smoking

The CUP review[2] reported significant associations between daily cigarette consumption, duration, pack years and age of initiation with colorectal cancer incidence, with an increase in risk of 38% for every 40 cigarettes smoked per day.[3] The large European Prospective Investigation into Cancer and Nutrition (EPIC) study found that smokers have an increased risk of colon cancer with most occurring in the proximal rather than distal colon.[4] The incidence of smoking-related colon cancer in the US is now the same for women and men, likely reflecting converging smoking patterns.[5]

Tobacco smoking is considered to be an established cause of colorectal cancer,[6] with 8.1% of colorectal cancer in the UK attributed to tobacco use.[7]

Back to top

5.2.1.4 Obesity and abdominal fatness

The CUP review[2] concluded that cohort studies investigating body mass index published between 2007 and 2011 showed increased risk of colorectal cancer with increased body fatness. The meta-analyses showed increased risks of 2%, 3% and 1% per kg/m2 for colorectal, colon and rectal cancers, respectively. There tended to be a larger effect for men than women and the effect was stronger for the USA and Asia than Europe.

The CUP review[2] agreed with the SER[1] finding that there was convincing evidence that greater body fatness is associated with colorectal cancer risk. Similarly, the CUP review[2] found that all new cohort studies demonstrated that increasing waist circumference and/or waist-to-hip ratio measurements increased risk for colorectal cancer. The meta-analyses showed increased risks of 3%, 5% and 3% (per inch in waist circumference for studies that did not adjust for body mass index) for colorectal, colon and rectal cancers respectively. In the UK, 13% of colorectal cancer has been attributed to overweight and obesity.[7] In the large EPIC cohort study, individuals who gained > 20 kg of weight since age 20 had a 38% higher risk of colon, but not rectal cancer, compared with those whose weight remained stable. In a recent meta-analysis of observational studies, each 5 kg of adult body weight gain was associated with a 4% higher risk of colorectal cancer.[8] This association only applied to those with high attained waist circumference, suggesting fat

accumulation in the abdominal area is important in relation to colorectal cancer risk.[9][10][11][12][13] In the Women's Health Initiative Study, the risk of colorectal cancer in postmenopausal women increased when BMI exceeded 27 kg/m2.[14] A recent review, which included seven studies, found obese patients were more likely to have distal tumours, show intact DNA mismatch repair, and have increased lymph node metastases, compared with normal-weight patients.[15] The incidence of colorectal cancer in individuals under 50 years for whom screening is limited is increasing[16] and the rising prevalence of excess weight may play a role in this trend.[17]

Other recent reviews made similar conclusions, with the risk of colorectal cancer from excess body fatness being stronger in men than women, rectal cancer being less affected by body fatness than colon cancer, and with general and regional fatness both playing a role.[9][10][11][12][13][18] Body and abdominal adiposity may increase risk through systemic effects, in which insulin and oestrogen levels encourage carcinogenesis and discourage apoptosis.[19] Patients with type-2 diabetes are at greater risk of cancers[20], including of the colorectum,[21] but particularly the proximal colon.[22][23]

Back to top

5.2.1.5 Nutrition

5.2.1.5.1 Dietary fibre

Dietary fibre is a heterogeneous group comprising primarily plant-derived structural components not digested by human digestive enzymes, consisting largely of non-starch polysaccharides and resistant starch. The suggested mechanisms for protection from colorectal cancer by high dietary fibre include fibre diluting or adsorbing digesta carcinogens, reducing intestinal transit time, reducing secondary bile acid production, reducing colonic pH and increasing the production of short chain fatty acids.[18] The short-chain fatty acid butyrate may play an important role,[24] as it enhances the deletion of genetically damaged cells by inducing cell cycle arrest, differentiation and apoptosis.[25]

The CUP review[2] concluded that 13 of 18 studies published since the SER (2007)[1] showed decreased risk of colorectal cancer with increased intake of total dietary fibre. The updated meta-analyses showed a 12% decreased risk for men and an 8% decreased risk for women (per 10 g dietary fibre/day), with a 21% decreased risk per three daily servings of wholegrains for colorectal cancer and a 16% decreased risk for colon cancer. The CUP review[2] also reported a further 12 new studies examining colon cancer alone and 10 studies looking at rectal cancer only since SER.[1] Meta-analyses undertaken for the CUP review[2] showed an 11% decrease in colon cancer risk per 10 g of dietary fibre consumed per day. For rectal cancer meta-analyses revealed a trend towards decreased risk that did not reach statistical significance as was reported previously in the SER (2007).[1]

Based on consistent evidence, with clear dose-response relationships for both women and men, the CUP review [2] concluded that the protective effect of dietary fibre had strengthened from 'probable' to 'convincing'. The CUP review[2] agreed with the SER[1] conclusion that evidence of protection from non-starchy fruits and vegetables was limited. The CUP review[2] included a pooled analysis of 756,217 participants from 14 cohort studies, followed up for between 6 and 20 years[26].

Since the CUP review[2] published its conclusions, another large systematic review and meta-analysis confirmed that ingestion of dietary fibre, in particular cereal fibre and whole grains, was inversely associated with risk of colon cancer.[27] The investigators found no association between intake of fruit or vegetable fibre and risk of colorectal cancer, but suggested that level of fibre intake from these sources may have been too low to detect effects. Intake of whole grains did not protect against colorectal cancer in the Norwegian Women Study, although consumption tended to be weakly associated with a lower risk of proximal colon cancer.[28] Intake of whole grain products, in particular whole grain wheat, was found to be associated with a lower incidence of colorectal cancer in the prospective HELGA study.[29]

The large NIH-AARP American cohort study was not included in the CUP review[2] and reported a reduction in risk of colon cancer in adults from high intake of vegetables consumed during ages 12–13 years and during the previous 10 years. High intakes of fruit consumed in the previous 10 years were also protective.[30] A healthy diet can also improve overall survival after diagnosis of colorectal cancer.[31]

Back to top

5.2.1.5.2 Red and processed meat

Based on the findings of nine of 12 studies published between 2007–2011, the CUP review[2] confirmed the SER [1] finding that there was convincing evidence that higher intakes of red meat increase the risk of colorectal cancer. Meta-analysis showed a 17% increase in risk of colorectal cancer per 100 g red meat consumed per day. [32]

The risk of colorectal cancer and rectal cancer differ according to the subtype of red meat consumed.[33] The mechanism underlying the increase in risk may be associated with the presence of haem in red meat, which undergoes endogenous nitrosylation with the formation of potentially carcinogenic N-nitroso compounds,[31] or due to the production of potentially carcinogenic heterocyclic amines and polycyclic aromatic hydrocarbons during the cooking of meat, or the presence of nitrites and nitrates.[34]

In 10 of 13 studies included in the CUP review, increased risk of colorectal cancer with higher intake of processed meat was observed.[2] The meta-analysis showed an 18% increased risk for colorectal cancer and a 24% increased risk of colon cancer per 50 g processed meat/day intake.[2] There was a nonsignificant trend towards increased risk of rectal cancer.

The CUP review[2] concluded there was a dose-response relationship apparent from cohort studies and agreed with the SER that processed meat was a convincing cause of colorectal cancer. These conclusions are further supported by more recent studies confirming red meat consumption is a risk factor for cancer of several sites, including colon and rectum, with no effect of cooking method.[15] Further, the American Institute for Cancer Research working group on red and processed meats classified red meat as ‘probably carcinogenic to humans’ based on limited evidence for positive associations between red meat consumption and colorectal cancer

development, but strong mechanistic evidence. The working group also upgraded their classification for processed meats to 'carcinogenic in humans' based on there being sufficient epidemiological evidence that these meats causes colorectal cancer.[35][36] Others have found an association between cooking method and colorectal cancer and rectal adenoma risk.[34][37] Recent studies have also confirmed a positive association between red processed meat and proximal colon cancer,[34] and that in Europe the negative effect of processed meat was mainly driven by the consumption of sausages.[38]

Back to top

5.2.1.5.3 Other nutrients

The CUP review and SER concluded milk probably protected from colorectal cancer, with a 9% decreased risk for colorectal cancer per 200 g milk consumed/day.[2][1] This conclusion is supported by the EPIC study, which found dairy products protective irrespective of fat content of the products,[39] and a meta-analysis of cohort studies that showed that milk and total dairy products are associated with a reduction in colorectal cancer risk.[40]

However, the CUP review[2] and SER review[1] found that, in six of seven cohort studies, calcium supplements reduced the risk of colorectal cancer, and the CUP panel concluded that calcium probably protected against colorectal cancer. The NIH-AARP Diet and Health study was not included in CUP review,[2] and this large study found that high intake of milk and calcium over the previous 10 years reduced the risk of colon cancer, and that intake of milk was inversely associated with risk of rectal cancer.[30] However a 2013 meta-analysis showed that calcium supplementation (≥ 500 mg/d) did not alter the risk of colorectal cancer (risk ratio [RR] 1•38, 95% confidence interval [CI] 0•89 to 2•15, P = 0•15).[41]

In contrast to the benefits seen for colorectal cancer risk, a recent randomised controlled trial investigating the impact of calcium and vitamin D alone and in combination on metachronous adenoma revealed no significant reduction of risk associated with any of the treatments:[42]

- vitamin D versus no vitamin D (adjusted RR 0.99; 95% CI 0.89 to 1.09)
- calcium versus no calcium (RR 0.95; 95% CI 0.85 to 1.06)
- both vitamin D and calcium versus neither (RR 0.93; 95% CI, 0.80 to 1.08).

The findings for advanced adenomas were similar.[42] There were few serious adverse events.

In combination, the evidence suggests that calcium and vitamin D may elicit their protective effects at points in colorectal carcinogenesis beyond the advanced adenoma stage.

The SER reviewed 15 case-controlled studies on dietary selenium that showed a decreased risk for colorectal cancer with increased serum selenium levels, but no cohort studies were identified.[1] The Panel concluded there was limited evidence that foods containing selenium protect against colorectal cancer. The updated CUP review report included two new cohort studies published since the SER but the results were inconsistent and the report concluded there was inadequate evidence to draw conclusions about the relationship between dietary selenium and colorectal cancer.[2] There were few, relatively small studies investigating selenium supplements and the World Cancer Research Fund concluded the results were inconsistent and the outcomes too limited to draw a conclusion.[1][2]

Back to top

5.2.1.6 Alcohol

The 15 new papers reviewed by the CUP review showed an increased risk with increased intake of ethanol for colorectal cancer and colon cancers.[2] The meta-analyses showed a 10% increased risk for colorectal cancer and rectal cancers, and an 8% increased risk for colon cancer per 10 g ethanol consumed per day. The effect was stronger in men than women, with 11% increased risk in men, compared with 7% in women.

The CUP review[2] agreed with the SER[1] conclusion that the evidence for ethanol from alcoholic drinks as a cause of colorectal cancer in men was convincing, and was probably a cause of colorectal cancer in women. In the UK, 15.5% of colorectal cancers in men and 6.9% in women have been attributed to consumption of alcohol.[7] In a recent meta-analysis, alcohol consumption was associated with an increase of risk of colorectal adenomas which was the same for both sexes and stronger in European than US and Asian studies.[43] In 2010, there were 10,865 colon cancers diagnosed in Australia, of which 868 were attributed to alcohol consumption, with 80% of those diagnosed in men.[44] The European Code against Cancer (4th edition) concluded that even low and moderate alcohol intakes increase the risk of colorectal cancer in a dose-dependent manner.[45]

Alcohol also interacts with tobacco by interfering with the repair of specific DNA mutations caused by smoking, and may also enhance the penetration of other carcinogenic molecules into mucosal surfaces.

Back to top

5.2.1.7 Physical activity

The SER recommended that, to prevent colorectal cancer, people should be moderately physically active (equivalent to brisk walking for at least 30 minutes a day, with the objective of ≥ 60 minutes of moderate or ≥ 30 minutes of vigorous physical activity every day).[1]

The CUP review reviewed the outcomes of cohort studies published since 2007, and concluded that a lower risk of colon cancer was associated with higher overall levels of physical activity, with evidence of a dose-response effect within the range studied.[2][46][47] The effect was strong for colon cancer, but there was no evidence of an effect for rectal cancer. The effect was strong and consistent for men, but less strong in women. The meta-analyses showed that recreational physical activity resulted in an 11% decrease in risk for colorectal and 12% decrease for colon cancer per 30 minutes of exercise per day, with maximum effect observed with approximately 10 hours per week of average-paced walking.[48] Another meta-analysis found a similar inverse relationship between colonic adenoma risk and physical activity.[46][47]

While these effects were independent of any effect of exercise on obesity, additional benefits of longer-term, sustained, moderate physical activity may also be realised through reduced body fatness and may protect against colon cancer by decreasing inflammation, reducing insulin levels and reducing insulin resistance. Physical activity and fewer sitting hours were found to significantly reduce colon cancer risk in both the distal and proximal colon, although results for rectal cancer were mixed.[46][19][49]

Increasing exercise after non-metastatic colorectal cancer treatment was associated with reduced risk of colorectal cancer-specific and overall mortality for women and men[50][51] and lower rectum cancer mortality[19]. In a meta-analysis of prospective studies both prediagnosis and postdiagnosis physical activity was found to reduce the risk of colorectal cancer-specific mortality and all-cause mortality.[52]

Back to top

5.2.2 Summary of key messages based on the World Cancer Research Fund/American Institute for Cancer Research and updated evidence

5.2.2.1 Table 2.3. Key messages regarding primary prevention of colorectal cancer

Factor	Key message
Smoking	Avoid tobacco smoking.
Alcohol	(Men) Avoid alcohol or limit intake to less than 2 standard drinks per day.
	(Women) Avoid alcohol or limit intake to less than 1 standard drink per day.
	Increase intake of cereal fibre, particularly poorly soluble cereal.
	Moderate amounts of lean red meat (up to 100 g/day) can be eaten as part of a mixed diet. Charring of red meat is best avoided and consumption of processed meats should be limited.
	Garlic is probably protective against cancer.
	Milk is probably protective against cancer.
	There is limited evidence that foods containing iron increase risk of cancer.
	There is limited evidence that cheese intake increases risk of cancer.

Factor	Key message
Diet	There is limited evidence that foods containing animal fats increase risk of cancer.
	There is limited evidence that foods containing sugars increase risk of cancer.
	There is limited evidence that non-starchy vegetables and fruits reduce risk of cancer.
	There is limited evidence that foods containing vitamin D reduce risk of cancer.
	There is no evidence that foods containing folate reduce risk of cancer.
	There is no evidence that fish intake reduces risk of cancer.
	There is no evidence that foods containing selenium reduce risk of cancer.
Body fatness	Maintain weight in healthy BMI range.
	Avoid abdominal fatness.
Physical activity	Aim for 30–60 minutes/day of moderate physical activity.
	Avoid sedentary behaviour.

Source: World Cancer Research Fund and American Institute for Cancer Research SER[1] and CUP[2] reports.

Back to top

5.2.3 References

1. ↑ 1.00 1.01 1.02 1.03 1.04 1.05 1.06 1.07 1.08 1.09 1.10 1.11 1.12 1.13 World Cancer Research Fund/American Institute for Cancer Research. *Food, nutrition, physical activity and the prevention of cancer: a global perspective.* 2007 Available from: http://www.dietandcancerreport.org/.
2. ↑ 2.00 2.01 2.02 2.03 2.04 2.05 2.06 2.07 2.08 2.09 2.10 2.11 2.12 2.13 2.14 2.15 2.16 2.17 2.18 2.19 2.20 2.21 2.22 2.23 2.24 2.25 2.26 2.27 World Cancer Research Fund/American Institute for Cancer Research. *Continuous Update Project Report: Food, Nutrition, Physical Activity, and the Prevention of Colorectal Cancer.* WCRF; 2011.
3. ↑ Liang PS, Chen TY, Giovannucci E. *Cigarette smoking and colorectal cancer incidence and mortality: systematic review and meta-analysis.* Int J Cancer 2009 May 15;124(10):2406-15 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19142968.
4. ↑ Leufkens AM, Van Duijnhoven FJ, Siersema PD, Boshuizen HC, Vrieling A, Agudo A, et al. *Cigarette smoking and colorectal cancer risk in the European Prospective Investigation into Cancer and Nutrition study.* Clin Gastroenterol Hepatol 2011 Feb;9(2):137-44 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21029790.
5. ↑ Freedman ND, Abnet CC, Caporaso NE, Fraumeni JF Jr, Murphy G, Hartge P, et al. *Impact of changing US cigarette smoking patterns on incident cancer: risks of 20 smoking-related cancers among the women and men of the NIH-AARP cohort.* Int J Epidemiol 2016 Jun;45(3):846-56 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26411408.
6. ↑ Secretan B, Straif K, Baan R, Grosse Y, El Ghissassi F, Bouvard V, et al. *A review of human carcinogens--Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish.* Lancet Oncol 2009 Nov;10(11):1033-4 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19891056.

7. ↑ 7.0 7.1 7.2 Parkin DM, Boyd L, Walker LC. *16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010.* Br J Cancer 2011 Dec 6;105 Suppl 2:S77-81 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22158327.
8. ↑ Schlesinger S, Lieb W, Koch M, Fedirko V, Dahm CC, Pischon T, et al. *Body weight gain and risk of colorectal cancer: a systematic review and meta-analysis of observational studies.* Obes Rev 2015 Jul;16 (7):607-19 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25925734.
9. ↑ 9.0 9.1 Aleksandrova K, Nimptsch K, Pischon T. *Obesity and colorectal cancer.* Front Biosci (Elite Ed) 2013 Jan 1;5:61-77 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23276970.
10. ↑ 10.0 10.1 Gribovskaja-Rupp I, Kosinski L, Ludwig KA. *Obesity and colorectal cancer.* Clin Colon Rectal Surg 2011 Dec;24(4):229-43 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23204938.
11. ↑ 11.0 11.1 Whitlock K, Gill RS, Birch DW, Karmali S. *The Association between Obesity and Colorectal Cancer.* Gastroenterol Res Pract 2012;2012:768247 Available from: http://www.ncbi.nlm.nih.gov/pubmed /23304128.
12. ↑ 12.0 12.1 Ma Y, Yang Y, Wang F, Zhang P, Shi C, Zou Y, et al. *Obesity and risk of colorectal cancer: a systematic review of prospective studies.* PLoS One 2013;8(1):e53916 Available from: http://www.ncbi. nlm.nih.gov/pubmed/23349764.
13. ↑ 13.0 13.1 Boeing H. *Obesity and cancer--the update 2013.* Best Pract Res Clin Endocrinol Metab 2013 Apr;27(2):219-27 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23731883.
14. ↑ Heo M, Kabat GC, Strickler HD, Lin J, Hou L, Stefanick ML, et al. *Optimal cutoffs of obesity measures in relation to cancer risk in postmenopausal women in the Women's Health Initiative Study.* J Womens Health (Larchmt) 2015 Mar;24(3):218-27 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25587642.
15. ↑ 15.0 15.1 Sinicrope FA, Foster NR, Sargent DJ, O'Connell MJ, Rankin C. *Obesity is an independent prognostic variable in colon cancer survivors.* Clin Cancer Res 2010 Mar 15;16(6):1884-93 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20215553.
16. ↑ Ahnen DJ, Wade SW, Jones WF, Sifri R, Mendoza Silveiras J, Greenamyer J, et al. *The increasing incidence of young-onset colorectal cancer: a call to action.* Mayo Clin Proc 2014 Feb;89(2):216-24 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24393412.
17. ↑ Patel P, De P. *Trends in colorectal cancer incidence and related lifestyle risk factors in 15-49-year-olds in Canada, 1969-2010.* Cancer Epidemiol 2016 Jun;42:90-100 Available from: http://www.ncbi.nlm.nih.gov /pubmed/27060626.
18. ↑ 18.0 18.1 Topping DL, Clifton PM. *Short-chain fatty acids and human colonic function: roles of resistant starch and nonstarch polysaccharides.* Physiol Rev 2001 Jul;81(3):1031-64 Available from: http://www.ncbi. nlm.nih.gov/pubmed/11427691.
19. ↑ 19.0 19.1 19.2 Morrison DS, Parr CL, Lam TH, Ueshima H, Kim HC, Jee SH, et al. *Behavioural and metabolic risk factors for mortality from colon and rectum cancer: analysis of data from the Asia-Pacific Cohort Studies Collaboration.* Asian Pac J Cancer Prev 2013;14(2):1083-7 Available from: http://www.ncbi. nlm.nih.gov/pubmed/23621191.
20. ↑ Anderson AS, Key TJ, Norat T, Scoccianti C, Cecchini M, Berrino F, et al. *European Code against Cancer 4th Edition: Obesity, body fatness and cancer.* Cancer Epidemiol 2015 Dec;39 Suppl 1:S34-45 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26205840.

21. ↑ De Bruijn KM, Arends LR, Hansen BE, Leeflang S, Ruiter R, van Eijck CH. *Systematic review and meta-analysis of the association between diabetes mellitus and incidence and mortality in breast and colorectal cancer.* Br J Surg 2013 Oct;100(11):1421-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24037561.
22. ↑ Limburg PJ, Anderson KE, Johnson TW, Jacobs DR Jr, Lazovich D, Hong CP, et al. *Diabetes mellitus and subsite-specific colorectal cancer risks in the Iowa Women's Health Study.* Cancer Epidemiol Biomarkers Prev 2005 Jan;14(1):133-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15668486.
23. ↑ Lim E, Jones IT, Gibbs P, McLaughlan S, Faragher I, Skinner I, et al. *Subsite-specific colorectal cancer in diabetic and nondiabetic patients.* Cancer Epidemiol Biomarkers Prev 2005 Jun;14(6):1579-82 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15941979.
24. ↑ Cassidy A, Bingham SA, Cummings JH. *Starch intake and colorectal cancer risk: an international comparison.* Br J Cancer 1994 May;69(5):937-42 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8180027.
25. ↑ Hague A, Manning AM, Hanlon KA, Huschtscha LI, Hart D, Paraskeva C. *Sodium butyrate induces apoptosis in human colonic tumour cell lines in a p53-independent pathway: implications for the possible role of dietary fibre in the prevention of large-bowel cancer.* Int J Cancer 1993 Sep 30;55(3):498-505 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8397167.
26. ↑ Koushik A, Hunter DJ, Spiegelman D, Beeson WL, van den Brandt PA, Buring JE, et al. *Fruits, vegetables, and colon cancer risk in a pooled analysis of 14 cohort studies.* J Natl Cancer Inst 2007 Oct 3;99(19):1471-83 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17895473.
27. ↑ Aune D, Chan DS, Lau R, Vieira R, Greenwood DC, Kampman E, et al. *Dietary fibre, whole grains, and risk of colorectal cancer: systematic review and dose-response meta-analysis of prospective studies.* BMJ 2011 Nov 10;343:d6617 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22074852.
28. ↑ Bakken T, Braaten T, Olsen A, Kyrø C, Lund E, Skeie G. *Consumption of Whole-Grain Bread and Risk of Colorectal Cancer among Norwegian Women (the NOWAC Study).* Nutrients 2016 Jan 13;8(1) Available from: http://www.ncbi.nlm.nih.gov/pubmed/26771634.
29. ↑ Kyrø C, Skeie G, Loft S, Landberg R, Christensen J, Lund E, et al. *Intake of whole grains from different cereal and food sources and incidence of colorectal cancer in the Scandinavian HELGA cohort.* Cancer Causes Control 2013 Jul;24(7):1363-74 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23624874.
30. ↑ [30.0] [30.1] Ruder EH, Thiébaut AC, Thompson FE, Potischman N, Subar AF, Park Y, et al. *Adolescent and mid-life diet: risk of colorectal cancer in the NIH-AARP Diet and Health Study.* Am J Clin Nutr 2011 Dec;94(6):1607-19 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22071715.
31. ↑ [31.0] [31.1] Norat T, Bingham S, Ferrari P, Slimani N, Jenab M, Mazuir M, et al. *Meat, fish, and colorectal cancer risk: the European Prospective Investigation into cancer and nutrition.* J Natl Cancer Inst 2005 Jun 15;97(12):906-16 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15956652.
32. ↑ Chan DS, Lau R, Aune D, Vieira R, Greenwood DC, Kampman E, et al. *Red and processed meat and colorectal cancer incidence: meta-analysis of prospective studies.* PLoS One 2011;6(6):e20456 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21674008.
33. ↑ Egeberg R, Olsen A, Christensen J, Halkjær J, Jakobsen MU, Overvad K, et al. *Associations between red meat and risks for colon and rectal cancer depend on the type of red meat consumed.* J Nutr 2013 Apr;143(4):464-72 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23427329.
34. ↑ [34.0] [34.1] [34.2] Miller PE, Lazarus P, Lesko SM, Cross AJ, Sinha R, Laio J, et al. *Meat-related compounds and colorectal cancer risk by anatomical subsite.* Nutr Cancer 2013;65(2):202-26 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23441608.

35. ↑ International Agency for Research on Cancer IARC Working Group. *Volume 114: Consumption of red meat and processed meat.*; 2015.
36. ↑ Bouvard V, Loomis D, Guyton KZ, Grosse Y, Ghissassi FE, Benbrahim-Tallaa L, et al. *Carcinogenicity of consumption of red and processed meat.* Lancet Oncol 2015 Dec;16(16):1599-600 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26514947.
37. ↑ Ferrucci LM, Sinha R, Huang WY, Berndt SI, Katki HA, Schoen RE, et al. *Meat consumption and the risk of incident distal colon and rectal adenoma.* Br J Cancer 2012 Jan 31;106(3):608-16 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22166801.
38. ↑ Parr CL, Hjartåker A, Lund E, Veierød MB. *Meat intake, cooking methods and risk of proximal colon, distal colon and rectal cancer: the Norwegian Women and Cancer (NOWAC) cohort study.* Int J Cancer 2013 Sep 1;133(5):1153-63 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23401013.
39. ↑ Murphy N, Norat T, Ferrari P, Jenab M, Bueno-de-Mesquita B, Skeie G, et al. *Consumption of dairy products and colorectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC).* PLoS One 2013;8(9):e72715 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24023767.
40. ↑ Aune D, Lau R, Chan DS, Vieira R, Greenwood DC, Kampman E, et al. *Dairy products and colorectal cancer risk: a systematic review and meta-analysis of cohort studies.* Ann Oncol 2012 Jan;23(1):37-45 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21617020.
41. ↑ Bristow SM, Bolland MJ, MacLennan GS, Avenell A, Grey A, Gamble GD, et al. *Calcium supplements and cancer risk: a meta-analysis of randomised controlled trials.* Br J Nutr 2013 Oct;110(8):1384-93 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23601861.
42. ↑ [42.0] [42.1] Baron JA, Barry EL, Mott LA, Rees JR, Sandler RS, Snover DC, et al. *A Trial of Calcium and Vitamin D for the Prevention of Colorectal Adenomas.* N Engl J Med 2015 Oct 15;373(16):1519-30 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26465985.
43. ↑ Zhu JZ, Wang YM, Zhou QY, Zhu KF, Yu CH, Li YM. *Systematic review with meta-analysis: alcohol consumption and the risk of colorectal adenoma.* Aliment Pharmacol Ther 2014 Aug;40(4):325-37 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24943329.
44. ↑ Pandeya N, Wilson LF, Webb PM, Neale RE, Bain CJ, Whiteman DC. *Cancers in Australia in 2010 attributable to the consumption of alcohol.* Aust N Z J Public Health 2015 Oct;39(5):408-13 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26437723.
45. ↑ Scoccianti C, Cecchini M, Anderson AS, Berrino F, Boutron-Ruault MC, Espina C, et al. *European Code against Cancer 4th Edition: Alcohol drinking and cancer.* Cancer Epidemiol 2015 Dec;39 Suppl 1:S67-74 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26115567.
46. ↑ [46.0] [46.1] [46.2] Boyle T, Keegel T, Bull F, Heyworth J, Fritschi L. *Physical activity and risks of proximal and distal colon cancers: a systematic review and meta-analysis.* J Natl Cancer Inst 2012 Oct 17;104(20):1548-61 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22914790.
47. ↑ [47.0] [47.1] Robsahm TE, Aagnes B, Hjartåker A, Langseth H, Bray FI, Larsen IK. *Body mass index, physical activity, and colorectal cancer by anatomical subsites: a systematic review and meta-analysis of cohort studies.* Eur J Cancer Prev 2013 Nov;22(6):492-505 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23591454.
48. ↑ Keum N, Bao Y, Smith-Warner SA, Orav J, Wu K, Fuchs CS, et al. *Association of Physical Activity by Type and Intensity With Digestive System Cancer Risk.* JAMA Oncol 2016 Sep 1;2(9):1146-53 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27196375.

49. ↑ Simons CC, Hughes LA, van Engeland M, Goldbohm RA, van den Brandt PA, Weijenberg MP. *Physical activity, occupational sitting time, and colorectal cancer risk in the Netherlands cohort study.* Am J Epidemiol 2013 Mar 15;177(6):514-30 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23420352.
50. ↑ Meyerhardt JA, Giovannucci EL, Holmes MD, Chan AT, Chan JA, Colditz GA, et al. *Physical activity and survival after colorectal cancer diagnosis.* J Clin Oncol 2006 Aug 1;24(22):3527-34 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16822844.
51. ↑ Meyerhardt JA, Giovannucci EL, Ogino S, Kirkner GJ, Chan AT, Willett W, et al. *Physical activity and male colorectal cancer survival.* Arch Intern Med 2009 Dec 14;169(22):2102-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20008694.
52. ↑ Je Y, Jeon JY, Giovannucci EL, Meyerhardt JA. *Association between physical activity and mortality in colorectal cancer: a meta-analysis of prospective cohort studies.* Int J Cancer 2013 Oct 15;133(8):1905-13 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23580314.

Back to top

5.3 Chemopreventive candidate agents

Contents

5.3.1 Background

Chemoprevention is the regular use of drugs to prevent or delay the development of cancers. As chemoprevention strategies require regular use of agents over many years by people who are disease free and may never develop cancers, chemopreventive agents need to be easily administered with a convenient dosing schedule, inexpensive and with very few side effects.

Trials of chemoprevention (calcium, some vitamin supplementation, selenium, statins) have provided mixed evidence of benefit. The strong evidence for benefit has emerged from observational studies of exposure to nonsteroidal anti inflammatory drugs (NSAIDs), especially aspirin.

Results of randomised controlled trials (RCTs) of aspirin in the primary and secondary prevention of colorectal cancer and adenomas are now available and point to a benefit similar to that associated with screening by colonoscopy in people under 70 years of age. Aspirin is cheap, readily available, has other benefits such as cardiovascular protective effects, and a relatively benign side-effects profile, although these side effects increase with age and the benefits for cancer prevention occur only after a latent period of 10 years and are less studied in older people, especially women.

5.3.2 Aspirin

5.3.2.1 Systematic review evidence

In an asymptomatic population at average risk or increased risk of colorectal cancer, what is the cost-benefit ratio of prophylactic Aspirin use in reducing the mortality and incidence of colorectal cancer?

A systematic review was undertaken to evaluate the effectiveness of aspirin in the primary prevention of colorectal cancer in people at average or higher risk. A total of 10 clinical trials reported in 17 articles[1][2][3][4][5][6][7][8][9][10][11][12][13][14][15][16][17] examining effects of aspirin on colorectal cancer outcomes met the criteria and were included in the systematic review. The trials included were specifically of average or high-risk populations.

The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the technical report.

Back to top

5.3.2.1.1 Average-risk population

Five randomised controlled trials compared aspirin use with placebo or no aspirin use.[3][4][5][6][9][10][11][17] Four were at low risk of bias[3][4][9][10][11][17] and one, the British Doctors Aspirin Trial (BDAT),[6] was at high risk of bias.

Three trials recruited participants with a transient ischemic attack or minor ischaemic stroke or those who were at high risk of ischaemic heart disease. Primary endpoints in these trials were various cardiovascular endpoints.[9][10][11][17] Two trials recruited healthy participants.[3][4][5][6]

Based on a weighted average calculation, the average trial duration (duration taking aspirin) was 8.9 years.[3][4][5][6][9][10][11][17]

A limitation to these trials is that none of them had colorectal cancer as the primary endpoint. Secondary study outcomes included colorectal cancer incidence and mortality, gastrointestinal side effects, incidence of other cancers, and fatal or non-fatal cardiovascular events. Most studies did not report on aspirin exposure after the randomised interventional period.

Back to top

5.3.2.1.1.1 Colorectal cancer incidence

Three trials reported a statistically significant reduction in colorectal cancer incidence in average-risk populations.[3][4][5][6][10][11]

The BDAT trial showed a statistically significant reduction in colorectal cancer incidence in those taking 300 mg /day aspirin, compared with no aspirin, at 23 years' follow-up (hazard ratio [HR] 0.7, p = 0.04).[7] The Women's Health Study, which used an aspirin dosage of 100 mg on alternate days, found a statistically significant reduction in colorectal cancer incidence after 16 years' follow-up (HR 0.80, p = 0.021), but not after 10 years' follow-up (RR 0.97).[3][4][5] No difference was found for colon polyps (type not specified) between groups (HR 1.00), though the trial was not colonoscopically controlled.[3][4][5]

Pooled data from the BDAT and the United Kingdom Transient Ischaemic Attack Trial (UK-TIA) trials with up to 23 years' follow-up[7] showed that aspirin use (BDAT used 300 mg/day or 500 mg/day, UK TIA used 300 mg/day or 1200 mg/day) demonstrated a reduction in colorectal cancer incidence (HR 0.74, p = 0.02). This reduction was not seen in the first 10 years after intervention (HR 0.92; 95% confidence interval [CI] 0.56 to1.49). In non-pooled data from the UK-TIA and BDAT trials individually, each showed a reduction in colorectal cancer incidence only after 10 years of follow up (HR 0.50, p = 0.05 and HR 0.64, p = 0.05, respectively).[6][10][11] Pooled analysis of data from the BDAT, SALT, TPT and UK-TIA trials also showed a significant reduction in colorectal cancer incidence in those taking aspirin during the trial period and followed for a median of 18.3

years (HR 0.75 p = 0.02).[8] Subgroup analysis of this pooled dataset also showed that 2.5–5 years of aspirin consumption was just as beneficial as ≥ 5 years of aspirin consumption (HR 0.69 and 0.62 respectively, p = 0.003 for both).[8] In addition, subgroup analysis on the location of cancer showed that, reflecting the incidence data, aspirin was beneficial for preventing proximal colon cancer (HR 0.45, p = 0.001), but not for distal colon cancer (HR 1.10, p = 0.66) or rectal cancer (HR 0.90, p = 0.58), with a median of 18.3 years' follow-up.

It should be noted that these trials (BDAT and UK-TIA) were the pivotal trials demonstrating the secondary protective effects of aspirin against cardiovascular disease. Thus, the benefits of taking aspirin for cancer prevention can be expected to be enhanced by the benefits of protection against adverse cardiovascular outcomes (transient ischaemic attacks, stroke, and heart attacks), especially in those who carry excess risk of these latter outcomes. Modelling of results from the cardiovascular prevention trials to date shows that the cancer prevention effects dominate over the cardiovascular benefits. It must be noted that in these trials the participants were mainly men.[18]

In modelling data reported on the Women's Health Study, aspirin (mean duration 10.1 years) was shown to be associated with a modest decreased 15-year risk of colorectal cancer in women under 65 years, and the highest net benefit was only seen in the 10-year risk of colorectal cancer in women ≥ 65 years of age (number needed to treat [NNT] = 369). In this dataset, cardiovascular benefits dominated over colorectal cancer incidence.[4]

Back to top

5.3.2.1.1.2 Colorectal cancer mortality

Four trials reported individual data for mortality due to colorectal cancer in the average-risk population.[6][9][10][11][17] Only one reported a significant benefit (reduction) in colorectal cancer mortality for those taking aspirin with 17–20 years of follow-up (odds ratio [OR] 0.73; 95% CI 0.49 to 1.10).[9]

A meta-analysis of these trials found aspirin to be beneficial with a median of 18.3 years follow-up (OR 0.66, p = 0.002).[8] Subgroup analysis reported that this benefit was only for those who took 300 mg or less per day during the trial period.[8] The benefit from aspirin consumption was seen irrespective of aspirin consumption duration (≥ 2.5 years' versus ≥ 5 years' duration).

In addition, subgroup analysis on the location of colorectal cancer showed that, reflecting the incidence data, aspirin reduced mortality for proximal colon cancer (HR 0.34, p = 0.001), but not for distal colon (HR 1.21, p = 0.54) or rectal cancer (HR 0.80, p = 0.35), with a median 18.3 years' follow-up.[8] The benefit for proximal cancer is particularly important, given the concern that colonoscopic screening in many studies has not been shown to be protective against proximal colorectal cancer. This failure is thought to be due to poor bowel preparations, incomplete examinations, flat (sessile serrated) polyps easily overlooked, and difficulty completely removing these polyps.

The Women's Health Study[4] did not report on mortality.

Back to top

5.3.2.1.1.3 Adverse effects

Two trials reported adverse effects from aspirin consumption.[3][4][5][10][11]

In the Women's Health Study, those taking aspirin experienced greater gastrointestinal bleeding and peptic ulcers (HR 1.14 and 1.17 respectively, $p < 0.001$) compared with the placebo group.

In UK-TIA, participants taking aspirin at a dosage of 300 mg/day or 1200 mg/day experienced significantly greater gastrointestinal haemorrhage, compared with the placebo group (300 mg/day: OR 1.32; 95% CI 1.06 to 1.65; 1200 mg/day: OR 1.54, 95% CI 1.25 to 1.89).[10][11] Participants taking aspirin also experienced greater upper gastrointestinal symptoms (OR 1.32, $p < 0.05$), and more so with a higher aspirin dose of 1200 mg/day (OR 1.54, $p < 0.05$ compared with 300 mg/day).[10][11] Fatal gastrointestinal bleeding rates did not differ between aspirin and placebo groups.[19]

Trials documented adverse effects well during intervention, but less well during the long periods of follow-up. However, aspirin side effects related to long-term use in other large population studies are well documented, and there is little reason to consider that dose-equivalent side effects would be different for the participants in the trials considered.

Many commentators question the clinical impact of side effects (lower) than the incidence and mortality benefits (higher), leading to analyses that provide estimates of side effects weighted downwards.[4] These point to higher benefit estimates than analyses that do not take this into account.

Back to top

5.3.2.1.2 High-risk population

Five randomised controlled trials compared daily aspirin use with placebo.[1][2][12][14][15][16] Two trials compared lower-dose aspirin (defined as 81 mg/day or 160 mg/day) and higher-dose aspirin (defined as 300 mg /day or 325 mg/day) with placebo.[12][14] The remaining trials compared higher-dose aspirin with placebo (325 mg/day, 600 mg/day, or 300mg/day, respectively)..[1][2][15][16] All studies were at low risk of bias.[1][2][12][14][15][16]

Eligibility requirements for the trials differed. In the Colorectal Adenoma/Carcinoma Prevention Programme 2 (CAPP2) trial, eligible participants were > 25 years of age and proven carriers of a pathologic mismatch-repair mutation or members of a family that met the Amsterdam diagnostic criteria and had a personal history of a cured Lynch syndrome neoplasm but with at least some residual colon or rectum.[1][2] Colonoscopic examination and clearance of polyps within 3 months after recruitment were prerequisites to study entry. The Aspirin/Folate Polyp Prevention Study (AFPPS), the Association pour la Prevention par l'Aspirine du Cancer Colorectal (APACC) study, and the United Kingdom Colorectal Adenoma Prevention Study (ukCAP) recruited participants who had a recent history of sporadic colorectal adenomas and excluded individuals with a history of invasive large-bowel cancer.[12][14][15]

The Colorectal Adenoma Prevention Study (Cancer and Leukemia Group B [CALGB]) trial specifically recruited patients who had been treated for colorectal cancer.[16] Other eligibility criteria for these four trials were similar – all excluded individuals with inflammatory bowel disease, those with a clinical need for aspirin treatment, and those who could not take aspirin.[16][12][14][15]

The trial duration ranged from 1 month to 67 months. Based on a weighted average calculation, the average trial duration (duration taking aspirin) was 2.3 years.[12][14][15][1][2][16]

Study primary outcomes included the detection of at least one adenoma or colorectal carcinoma at follow up. Four trials used adenoma incidence as a primary endpoint.[16][12][14][15] The CAPP2 trial[1][2] had a mean follow-up of 5.5 years, and the other trials had a median follow-up between 31.3 and 47.2 months.[16][12][14][15]

Back to top

5.3.2.1.2.1 Colorectal cancer incidence

For the CAPP2 trial in a high-risk population, no benefit in colorectal cancer incidence was reported after mean follow-up of 29.1 months or 66.1 months (RR 1.0; HR 0.63, p = 0.12, respectively) using intention-to-treat analysis.[1][2] The most convincing benefit was found with per-protocol analysis, where aspirin reduced colorectal cancer incidence after ≥ 2 years on trial treatment compared with placebo (HR 0.41, p = 0.02), with a mean of 66.1 months follow up.[1][2] Analyses including all Lynch Syndrome-associated cancers (colorectal and other cancers) provided the strongest outcome benefit. Both intention-to-treat and per-protocol analyses reported significant benefit after ≥ 2 years on trial treatment compared with placebo (HR 0.65, p = 0.05 and HR 0.45, p = 0.005 respectively) for all Lynch Syndrome-associated cancers.[1][2] Note that there was no effect on adenomas, suggesting that the effect was on the progression of adenomas to cancers.

The AFPPS, APACC, CALGB, and ukCAP trials only report incidence of adenoma and advanced lesions.[16][12][14][15] While the primary endpoint of these trials was the incidence of new adenomas following randomisation and during follow-up, in the pooled meta-analysis, aspirin was shown to significantly reduce the risk of adenoma when comparing any dose of aspirin with placebo (RR 0.83, p = 0.012).[13] A reduction in advanced lesion risk was also reported when comparing any dose of aspirin with placebo (RR 0.72, p = 0.0046) in pooled meta-analysis.[13] In the individual trials, a reduction in adenoma incidence for any dose of aspirin was reported for the CALGB (RR 0.61, 95% CI 0.44 to 0.86)[16] and ukCAP (RR 0.79, 95% CI 0.63 to 0.99) trials[15] only (325 mg /day and 300 mg/day, respectively). However, a reduction in adenoma incidence for any dose of aspirin was not observed in the AFPPS (RR 0.88, p > 0.05)[12] or APACC (RR 0.95, p > 0.05)[14] trials. In the individual trials, a reduction in advanced lesions incidence was reported only in the ukCAP trial (RR 0.63; 95% CI 0.43 to 0.91), but then only for any dose of aspirin compared with placebo.[15]

A significant reduction in the risk of any colorectal adenoma (RR 0.83, p = 0.012) was also reported in pooled meta-analysis comparing only low-dose aspirin (81 mg or 160 mg/day) with placebo in the AFPPS and APACC trials.[13] No risk reduction was reported in pooled data comparing only low-dose aspirin (81 mg or 160 mg/day) with placebo for advanced lesion (RR 0.83, p = 0.57) in the AFPPS and APACC trials.[13] As individual trials, significant risk reduction in the risk of any colorectal adenoma was only reported for the AFPPS trial (RR 0.81; 95% CI 0.69 to 0.96).[12]

A significant risk reduction was reported for advanced lesions when comparing higher-dose aspirin (300 mg or 325 mg/day) with placebo in pooled meta-analysis (RR 0.71, p = 0.0089),[13] but no such difference was found for any colorectal adenoma (RR 0.85, p = 0.099) in the AFPPS, CALGB, ukCAP and APACC trials.[13]

In pooled analysis of the adenoma trials, rates of colorectal cancer did not differ significantly between treatment groups: 9 cases (0.54%, N = 1678) were diagnosed among participants taking aspirin (any dose), compared with 8 cases (0.62%, N = 1289) diagnosed in the placebo groups (p = 0.81).[13]

Back to top

5.3.2.1.2.2 Colorectal cancer mortality

None of the five trials reported colorectal cancer mortality data in the high risk population.[1][2][12][14][15][16]

5.3.2.1.2.3 Adverse effects

In pooled analysis of the AFPPS, APACC, CALGB, and ukCAP trials, stroke was the only adverse event for which a significant (p = 0.002) reduction was reported in the aspirin treatment group compared with the placebo group.[13] The CAPP2 trial did not report statistical analysis of serious adverse events, but there was no numerical difference in adverse outcomes.[1][2]

Back to top

5.3.2.1.3 Additional considerations

5.3.2.1.3.1 Non-RCT evidence

In addition to the evidence from RCTs evaluating long-term aspirin treatment in the prevention of various conditions, there is substantial and consistent evidence from case control studies and cohort studies to support the association between aspirin exposure and colorectal cancer prevention.[7][20]

5.3.2.1.3.2 Cardiovascular benefits

The aligned benefits of cardiovascular and cancer prevention, well demonstrated through the analysis of the BDAT and the UK-TIA, point to synergies in prevention, especially for those who have already sustained a TIA or myocardial ischaemic event. The US Preventive Services Task Force has quantified this benefit and, taking the cancer prevention into account, extends the advice on use of aspirin to also those whose risk of a cardiovascular event is at least a 10% over the following 10 years.[21]

Analysis of the range of data available suggest that the beneficial effects of aspirin are strongest for cancer prevention, dominating over cardiovascular prevention. However, the relative risks of each disease depend on age and sex.

5.3.2.1.3.3 Adverse effects

An analysis of benefits versus risks of aspirin[18] based on pooled data from the BDAT, SALT, TPT and UK-TIA trials,[8] which were predominantly for males, found that the benefits of aspirin use include a reduction in risk of cancer (including colorectal cancer), myocardial infarction and ischemic stroke. The harms include increased risk of haemorrhagic stroke, gastrointestinal bleeding and peptic ulcer. Overall, the estimates of the benefits outweigh the harms. The analysis[18] made the following conclusions:

- Taking aspirin for 15 years is five times more likely to reduce morbidity than increase morbidity.
- Taking aspirin for 10 years is 10 times more likely to prevent death than cause death at age 50 years and five times more likely at age 65 years.
- Among 50-year-old males, one death would be prevented for every 106 men taking aspirin for 10 years.
- Among 50-year-old females, one death would be prevented for every 213 women taking aspirin for 10 years.
- Among 65-year-old males, one death would be prevented for every 46 men taking aspirin for 10 years.
- Among 65-year-old females, one death would be prevented for every 89 women taking aspirin for 10 years.

The side effects of aspirin use are well known. The most useful evidence on treatment-related adverse effects of long-term use comes from sources other than RCTs, because long-term follow-up of studies assessing cancer prevention did not report side effects. From available evidence, it can be concluded that there is a dose relationship, with higher doses associated with more adverse events, and that the rate of adverse events is higher in people aged over 70 years. Covering the risk of gastrointestinal ulceration with a proton pump inhibition can be considered although the benefit with low dose aspirin is controversial.

The following should also be taken into consideration:

- There is non-clinical evidence that gastric mucosal injury is attenuated with repeated administration of aspirin over time.[22]
- Most of the trials excluded patients with risk factors for aspirin use. Therefore, recommendatons for individuals must take account relative contraindications to the use of aspirin.

Notwithstanding the findings of the CAPP2 trial,[1][2] the current dose recommended for prevention of Lynch Syndrome-associated cancers, including colorectal cancer, is 100 mg daily, based on evidence that this lower dose will be effective without the dose-related side effects of the higher dose used in CAPP2. This advice could be modified when results are reported from the current CAPP3 trial, which is investigating the optimal dose of aspirin.[23]

Back to top

5.3.2.2 Evidence summary and recommendations

5.3.2.2.1 Average-risk population evidence summary table

Evidence summary	Level	References
Colorectal cancer incidence and mortality In the post hoc analyses of the cardiovascular prevention trials, predominantly in males, there was evidence for a real but small reduction in incidence and mortality from colorectal cancer commencing 10 years after starting aspirin.	I, II	[3], [24], [5], [6], [7], [8], [25], [10], [11], [17]
Evidence from all trials showed a significant reduction in the incidence of proximal colon cancer compared to distal colon cancer in those taking aspirin. Benefit is attenuated distally.	I, II	[5], [8]
It is not known if the colorectal cancer risk reduction and mortality reduction benefits can be extrapolated to populations without cardiovascular risk. The risk of aspirin in these average risk settings still needs more empirical data.	I	[7], [8]
Aspirin commencement age Most of the studies recruited participants aged 50 years or older. Based on the age range of recruitment into the trials, the evidence supported commencing aspirin between the ages of 50 and 70 years.	I, II	[3], [24], [5], [6], [7], [8], [25], [10], [11], [17]
Aspirin duration Taking aspirin for 2.5 years was shown to be just as effective as taking it for 5 years, when considering colorectal cancer incidence and mortality, but only after a latent period of 10 years. The benefit extends to older ages with longer duration of use.	I	[8]
Aspirin dose and frequency A low dose of aspirin (100–300 mg per day) is as effective at reducing colorectal mortality as a higher dose.	II	[8], [10], [11]

Evidence summary	Level	References
Potential harms of aspirin Aspirin was shown to be associated with increased incidence of the following adverse events: ■ dyspepsia ■ peptic ulcer ■ bleeding diathesis ■ gastrointestinal haemorrhage (such as associated with use of oral anticoagulants or antiplatelet agents). Aspirin should be avoided in those with: ■ aspirin allergy ■ renal impairment.	I, II	[3], [24], [5], [18], [10], [11]
Overall health benefit over harm The overall health benefit over risk depends on the likelihood of a clinically significant bleeding risk, particularly gastrointestinal and intracerebral haemorrhage. The likelihood of health benefit was 5 times greater than the health harm. The likelihood of preventing death is 5 to 10 times greater than the likelihood of causing death. Aspirin demonstrated a benefit in reducing thrombotic strokes.	I, II	[8], [18]
Sex and age considerations The evidence reported from the cardiovascular risk trials was from a predomintantly male population (92%). In the only trial conducted in an average-risk population with cancer as the primary endpoint (which recruited only women at average risk of cardiovascular disease and cancer), there was evidence of colorectal cancer prevention in women under 65 years taking alternate-day 100 mg aspirin. There was a suggestion of overall health benefit in women over 65 years, but not from colorectal cancer prevention.	I, II	[3], [24], [5], [6], [7], [8], [25], [10], [11]

5.3.2.2.2 High-risk population evidence summary table

Evidence summary	Level	References
Colorectal cancer incidence and mortality In the high-risk population (notably, people with Lynch Syndrome), benefits for aspirin compliers were unequivocally greater than risks.	II	[1], [2]
Aspirin dose and frequency The dose demonstrated in the pivotal CAPP2 trial was 600 mg daily taken for at least 2 years.	II	[1], [2]
Adverse events The only adverse event reporting a significant reduction in participants on aspirin compared to placebo was stroke. The CAPP2 trial did not report statistical analysis of serious adverse events but numerically there was no difference in adverse outcomes.	I, II	[1], [2], [13]

5.3.2.2.3 Recommendations

Evidence-based recommendation	Grade
For all people aged 50–70 years who are at average risk of colorectal cancer, aspirin should be actively considered to prevent colorectal cancer. A low dose (100–300 mg per day) is recommended for at least 2.5 years, commencing at age 50 to 70 years. The benefit may extend to older ages with longer duration of use. Benefit for cancer prevention (though shorter for cardiovascular risk) is evident only 10 years after initiaton so a life expectancy of at least 10 years should be taken into consideration in the advice to use aspirin. The choice to take aspirin should be personalised based on age, sex and potential reduction in cardiovascular events, cerebrovascular events and thrombotic stroke. The individual should take into account the potential risks of taking aspirin. Aspirin should be avoided in patients with current dyspepsia, any history of peptic ulcer, aspirin allergy, bleeding diathesis, an increased risk of gastrointestinal haemorrhage (such as associated with use of oral anticoagulants or antiplatelet agents), or renal impairment. The benefit in colorectal cancer risk reduction in women over 65 is less clear cut; however with the limited data available, those older women with cardiovascular risk factors may derive a greater overall benefit than harm.	**B**

Practice point
Aspirin should be avoided in patients with uncontrolled hypertension.

Practice point
Breath testing for *Helicobacter pylori* (and treatment for those who test positive) can also be considered, as gastrointestinal toxicity from aspirin is enhanced in the presence of *Helicobacter pylori*.

Evidence-based recommendation	Grade
People who are at high risk of colorectal cancer due to Lynch Syndrome carrier status should be advised to begin aspirin from the commencement of their colonoscopy screening (usually at age 25 years).	**A**

Evidence-based recommendation	Grade
Non-syndromic familial cancer patients should be actively considered for aspirin, bearing in mind the possibility of adverse events. 600 mg/day has shown to be effective, but lower dose (100 mg/day) may be as effective and is recommended based on the data available at the time of the systematic review.	**B**

Back to top

5.3.2.2.3.1 Considerations in making these recommendations

RCT findings lead to the guarded conclusion that aspirin is effective in the primary prevention of colorectal cancer. After taking into account the observational epidemiological data and other potential benefits, we have made a strong recommendation to consider universal aspirin chemoprevention except where contraindicated, especially for those with excess cardiovascular risk.

Back to top

5.3.2.3 Benefits and harms

With appropriate consideration of risks and benefits for the individual, the benefits are considered to substantially outweigh the harms following implementation of these recommendations.

5.3.2.3.1 Health system implications of these recommendations

5.3.2.3.1.1 Clinical practice

Aspirin is cheap and readily available. The major health system implication is the dissemination of this recommendation to primary care providers. Modelled benefits of colorectal cancer incidence can be anticipated, and due to the differential site-specific preventative benefits of aspirin (proximal) and colonoscopy (better for distal colorectal cancer), the two approaches can be considered complementary.

The national guidelines for managing absolute cardiovascular risk[26] do not recommend aspirin for primary prevention of cardiovascular disease. However, the analyses of the existing cardiovascular prevention trials and the Women's Health Study to now include cancer prevention (especially colorectal), add a new compelling perspective for the use of aspirin in preventative medicine. The current recommendations take a broader view of the benefits of aspirin to include people even at average risk of cardiovascular disease, because of the added benefits from cancer prevention.

Back to top

5.3.2.3.1.2 Resourcing

Education for GPs on the risks and benefits will be needed to engage their support for the recommendations. Renal function will need to be measured if there is doubt about aspirin usage. It is anticipated most dispensing will be over the counter and user paid (rather than reimbursed by the Pharmaceutical Benefits Scheme).

No comment pages found

Back to top

5.3.2.3.1.3 Barriers to implementation

Aspirin is off patent and widely available. However, there professional education is needed about its appropriate use.

Back to top

5.3.2.4 Discussion

5.3.2.4.1 Unresolved issues

The following issues are unresolved:

- The optimal dose for colorectal cancer protection (100 mg/day, 300 mg/day or 600 mg/day) has not been identified. More data are needed before specific recommendations can be made.
- There is a lack of RCTs of aspirin in average-risk populations with CRC as the primary endpoint.
- There is no information on aspirin use in the elderly.
- There is no information on the optimal target age range (including starting and stopping ages) for aspirin use in average-risk populations.
- Better analysis is needed of dose-related risk versus benefit of aspirin use stratified by age as the balance of benefit and harm is unknown in those of 70 years.

Back to top

5.3.2.4.2 Studies currently underway

CAPP3[23] may demonstrate if lower doses of aspirin are as effective for people with Lynch syndrome. People with Lynch syndrome are encouraged to join trials investigating optimal aspirin dose.

The current ongoing ASPREE trial will add information on the primary prevention benefits of low-dose aspirin and its risks in older healthy individuals.[27]

Back to top

5.3.2.4.3 Future research priorities

Future research can help provide clarity about the unresolved questions in regards to the use of aspirin to prevent colorectal cancer.

Back to top

5.3.3 Other chemopreventive candidate agents

5.3.3.1 Overview of evidence (non-systematic literature review)

Two comprehensive literature reviews undertaken jointly by the World Cancer Research Fund and the American Institute for Cancer Research have reported the evidence for chemopreventive candidate agents in the prevention of cancers:

- the Second Expert Report (SER) on food, nutrition and physical activity in the prevention of cancer (2007)[28]

- the Continuous Update Project (CUP) review of food, nutrition and physical activity in the prevention of colorectal cancer (2011).[29]

The information on non-aspirin chemopreventive candidate agents in this chapter is primarily summarised from these reviews. Updated information was included, where available. New systematic reviews were not undertaken for this guideline.

Updated systematic reviews are currently in progress by World Cancer Research Fund/American Institute for Cancer Research.[i]

[i]These guidelines may be updated after 2017 as a result of updated guidance from the World Cancer Research Fund/American Institute for Cancer Research. The provisional publication dates for The Colorectal Cancer Report and the Expert Report are April 2017 and November 2017, respectively.

Back to top

5.3.3.1.1 Nonsteroidal anti-inflammatory drugs (NSAIDs)

There is strong evidence supporting the chemopreventive activity of non-steroidal anti-inflammatory drugs (NSAIDs) other than aspirin against colorectal cancer. However, data on the risk–benefit profile of these drugs are currently insufficient to allow definitive recommendations for their use at a population level for primary cancer prevention.

See High-risk familial syndromes chapter

Practice point

Where surgery is inappropriate for people with with familial adenomatous polyposis, an NSAID (e.g. sulindac) is recommended.Kim B et al 2011

Back to top

5.3.3.1.2 Statins

The commonly prescribed cholesterol-lowering statin drugs have chemopreventive properties. They are very well tolerated and serious adverse effects of these drugs are rare.

Results from a prospective case-control study indicating that the use of statins for more than 5 years was associated with a reduced relative risk of colorectal cancer (OR 0.53; 95% CI 0.38 to 0.74) pointed to the potential colorectal cancer-protective properties of statins.[30] There has now been a number of trials with widely variable findings ranging from strong reduction in colorectal cancer risk to no association between statin usage and colorectal cancer risk. A recent meta-analysis of 27 clinical trials found no benefit from statin use for either incidence or recurrence of a number of cancers, including colorectal cancer.[31] Despite these inconsistent and findings, the accumulating clinical evidence still suggests a significant association between statin usage and reduced colorectal cancer risk.[31]

More nuanced studies suggest statin protection is strongest when consumed for > 3 years or > 5 years in modest doses (e.g. 40 mg simvastatin). The effects seem more reproducible where the lipophilic statins are used.[32]

However, the impact of statin use on colorectal adenoma remains unclear. Statin use was associated with an increased risk of adenoma recurrence in a secondary analysis of a prospective cohort study (RR 1.39; 95% CI 1.04 to 1.46).[33] A negative association between prior statin use and adenoma diagnosis (OR 0.40; 95% CI 0.24 to 0.76) has also been reported in a smaller retrospective case-control study.[34]

More data from randomised control trials with colorectal cancer as a primary end point are required before any clear recommendations for the use of statins for colorectal cancer prevention can be made.

Practice point
Without RCT evidence, statins cannot be recommended for chemoprevention at this time.

Back to top

5.3.3.1.3 Metformin

Patients with diabetes mellitus have an increased risk of colorectal cancer.[35] Metformin is an oral hypoglycaemic drug, widely prescribed for the treatment of type-2 diabetes with few side effects. Metformin lowers intestinal glucose absorption, hepatic glucose production and improves insulin sensitivity in the peripheral tissues, leading to lower levels of circulating insulin.[36] Elevated insulin levels have been associated with an increased risk of colorectal cancer.

Two early meta-analyses of cancer incidence in patients with type-2 diabetes have both shown an inverse association between metformin use and colorectal cancer: RR 0.63 (95% CI 0.50 to 0.79, $p < 0.001$), and RR 0.66 (95% CI 0.49 to 0.88), respectively.[37][38] Since then numerous other meta-analyses and observational studies of metformin use and colorectal cancer risk in diabetes patients have been published showing a range of outcomes, but with a general trend towards metformin being protective. A recent systematic review of the effect on colorectal cancer risk and mortality amongst diabetes patients receiving and not receiving metformin

treatment reported a reduction of colorectal cancer incidence (OR 0.9, 95% CI 0.85 to 0.96) and improved survival (HR 0.68; 95% CI 0.58 to 0.81), while a recent retrospective chart review of 1304 colorectal cancer patients revealed that, amongst those patients with diabetes, those receiving metformin treatments survived significantly longer (overall survival 91% at year 1, 80.5% at year 2) than those taking other treatments (including diet control) (overall survival 80.6% at year 1, 67.4% at year 2) with multivariate analysis suggesting that colorectal cancer patients with diabetes taking treatments other than metformin (diet control, insulin or non-metformin oral hypoglycaemics) had a worse prognosis (HR 1.35; 95% CI 1.039 to 1.753, p = 0.025) than those taking metformin (HR 0.807; 95% CI 0.601 to 1.084, p = 0.154).[39]

Given the increased risk of colorectal cancer associated with type-2 diabetes, metformin's potent hypoglycaemic activity and protective activity against colorectal cancer make it an attractive drug for the management of diabetes patients, particularly amongst those who have had colorectal cancer. Whether metformin can be beneficial in reducing the incidence of or increase survival after colorectal cancer in non-diabetic patients remains unclear and randomised placebo controlled trials to address this question are needed. Of 11 currently active clinical trials listed in the US clinical trials registry that are evaluating the effect of metformin on colorectal cancer risk, four use metformin alone as the intervention, while the others involve the use of metformin as an adjunct to other interventions.

Overall, it is unclear whether metformin is protective against colorectal cancer in non-diabetic populations, either by reducing incidence or increasing survival.

Practice point
Without RCT evidence, metformin cannot be recommended for chemoprevention at this time.

Back to top

5.3.3.1.4 Bisphosphonates

Bisphosphonates are used in treatment of osteoporosis, multiple myeloma, and bone overgrowth in malignancy, and for the prevention or treatment of solid tumour metastases to the bone.[40] Their anti-cancer activity is likely mediated through inhibition of angiogenesis and cell proliferation, induction of cell-cycle arrest and apoptosis in cancer cells, and immune cell activation.[40]

No RCTs have evaluated the use of bisphosphonates in the primary prevention of colorectal cancer. Several observational studies of bisphosphonate use have recorded cancer-related outcomes as secondary end-points. Three studies in women found quite substantial reductions in the risk of colorectal cancer.[41][42][43] In the first, receipt of 2–13 bisphosphonate prescriptions over a period of ≥ 5 years was associated with a reduced risk of colorectal cancer (O 0.84; 95% CI 0.71 to 1.00), while for those receiving ≥ 14 prescriptions over ≥ 5 years the colorectal cancer risk reduction was stronger (OR 0.78; 95% CI 0.65 to 0.94) with the effect significant only

where risedronic acid was the agent used.[41] In the second, colorectal cancer risk was reduced with the use of bisphosphonates for more than 1 year before diagnosis (OR 0.50; 95% CI 0.35 to 0.85).[42] In the third study, a reduced risk of colorectal cancer was again associated with bisphosphonates use (OR 0.50; 95% CI 0.35 to 0.71), with the reduced risk comprising the following components: a lower colorectal cancer incidence (adjusted HR 0.69; 95% CI 0.6 to 0.79) and a lower mortality rate post colorectal cancer diagnosis (HR 0.82; 95% CI 0.70 to 0.97).[43]

In contrast, analyses of data from the Women's Health Initiative and the Nurse's Health Study found no such reduction: adjusted HR 0.88 (95% CI 0.72 to 1.07, p = 0.19) and HR 1.04 (95% CI 0.82 to 1.33), respectively.[44] [45] Further, a recent analysis of the post-diagnostic use of oral bisphosphonates on colorectal cancer mortality revealed no benefits from bisphosphonate use (adjusted HR 1.11; 95% CI 0.80 to 1.54),[46] while a recent meta-analysis of 10 clinical studies comprising four case-control and six cohort studies showed borderline significant colorectal cancer risk reduction from bisphosphonate usage (pooled risk estimate 0.89; 95% CI 0.79 to 1.00, p=0.04).[47]

Meta-analyses of these observational studies are subject to a number of methological limitations that could compromise their findings with respect to colorectal cancer prevention:

- The number of studies was relatively small.
- Colorectal cancer was a secondary end point in studies on osteoporosis prevention.
- Men were underrepresented in study samples.
- A range of different doses and dose durations were used, making any recommendation difficult.

Bisphosphonates are associated with rare but serious adverse events. Evidence from appropriately designed RCTs, including evidence for treatment-related adverse events, is needed before guidance can be given on their use in the prevention of colorectal cancer. Currently there are no clinical trials in the US clinical trials registry investigating bisphosphonates and their impact on colorectal cancer.

More data from randomised control trials with colorectal cancer as a primary end point are required before any clear recommendations for the use of bisphosphonates for colorectal cancer prevention can be made.

Practice point
Bisphosphontes cannot be recommended for chemoprevention.

Back to top

5.3.3.2 References

1. ↑ 1.00 1.01 1.02 1.03 1.04 1.05 1.06 1.07 1.08 1.09 1.10 1.11 1.12 1.13 1.14 1.15 Burn J, Bishop DT, Mecklin JP, Macrae F, Möslein G, Olschwang S, et al. *Effect of aspirin or resistant starch on colorectal neoplasia in the Lynch syndrome.* N Engl J Med 2008 Dec 11;359(24):2567-78 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19073976.
2. ↑ 2.00 2.01 2.02 2.03 2.04 2.05 2.06 2.07 2.08 2.09 2.10 2.11 2.12 2.13 2.14 2.15 Burn J, Gerdes AM, Macrae F, Mecklin JP, Moeslein G, Olschwang S, et al. *Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial.* Lancet 2011 Dec 17;378(9809):2081-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22036019.
3. ↑ 3.00 3.01 3.02 3.03 3.04 3.05 3.06 3.07 3.08 3.09 3.10 3.11 3.12 Cook NR, Lee IM, Gaziano JM, Gordon D, Ridker PM, Manson JE, et al. *Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial.* JAMA 2005 Jul 6;294(1):47-55 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15998890.
4. ↑ 4.00 4.01 4.02 4.03 4.04 4.05 4.06 4.07 4.08 4.09 4.10 4.11 van Kruijsdijk RC, Visseren FL, Ridker PM, Dorresteijn JA, Buring JE, van der Graaf Y, et al. *Individualised prediction of alternate-day aspirin treatment effects on the combined risk of cancer, cardiovascular disease and gastrointestinal bleeding in healthy women.* Heart 2015 Mar;101(5):369-76 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25475110.
5. ↑ 5.00 5.01 5.02 5.03 5.04 5.05 5.06 5.07 5.08 5.09 5.10 5.11 5.12 Cook NR, Lee IM, Zhang SM, Moorthy MV, Buring JE. *Alternate-day, low-dose aspirin and cancer risk: long-term observational follow-up of a randomized trial.* Ann Intern Med 2013 Jul 16;159(2):77-85 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23856681.
6. ↑ 6.00 6.01 6.02 6.03 6.04 6.05 6.06 6.07 6.08 6.09 6.10 Peto R, Gray R, Collins R, Wheatley K, Hennekens C, Jamrozik K, et al. *Randomised trial of prophylactic daily aspirin in British male doctors.* Br Med J (Clin Res Ed) 1988 Jan 30;296(6618):313-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/3125882.
7. ↑ 7.0 7.1 7.2 7.3 7.4 7.5 7.6 7.7 Flossmann E, Rothwell PM, British Doctors Aspirin Trial and the UK-TIA Aspirin Trial. *Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies.* Lancet 2007 May 12;369(9573):1603-13 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17499602.
8. ↑ 8.00 8.01 8.02 8.03 8.04 8.05 8.06 8.07 8.08 8.09 8.10 8.11 8.12 8.13 8.14 Rothwell PM, Wilson M, Elwin CE, Norrving B, Algra A, Warlow CP, et al. *Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials.* Lancet 2010 Nov 20;376(9754):1741-50 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20970847.
9. ↑ 9.0 9.1 9.2 9.3 9.4 9.5 9.6 Meade TW, Wilke HC, Kelleher CC, Roderick PJ, Brennan PJ, Wilson CW, et al. *Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. The Medical Research Council's General Practice Research Framework.* Lancet 1998 Jan 24;351(9098):233-41 Available from: http://www.ncbi.nlm.nih.gov/pubmed/9457092.

10. ↑ 10.00 10.01 10.02 10.03 10.04 10.05 10.06 10.07 10.08 10.09 10.10 10.11 10.12 10.13 10.14 10.15 *United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: interim results. UK-TIA Study Group.* Br Med J (Clin Res Ed) 1988 Jan 30;296(6618):316-20 Available from: http://www.ncbi.nlm.nih.gov/pubmed/2894232.
11. ↑ 11.00 11.01 11.02 11.03 11.04 11.05 11.06 11.07 11.08 11.09 11.10 11.11 11.12 11.13 11.14 11.15 Farrell B, Godwin J, Richards S, Warlow C. *The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results.* J Neurol Neurosurg Psychiatry 1991 Dec;54(12):1044-54 Available from: http://www.ncbi.nlm.nih.gov/pubmed/1783914.
12. ↑ 12.00 12.01 12.02 12.03 12.04 12.05 12.06 12.07 12.08 12.09 12.10 12.11 12.12 Baron JA, Cole BF, Sandler RS, Haile RW, Ahnen D, Bresalier R, et al. *A randomized trial of aspirin to prevent colorectal adenomas.* N Engl J Med 2003 Mar 6;348(10):891-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/12621133.
13. ↑ 13.0 13.1 13.2 13.3 13.4 13.5 13.6 13.7 13.8 13.9 Cole BF, Logan RF, Halabi S, Benamouzig R, Sandler RS, Grainge MJ, et al. *Aspirin for the chemoprevention of colorectal adenomas: meta-analysis of the randomized trials.* J Natl Cancer Inst 2009 Feb 18;101(4):256-66 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19211452.
14. ↑ 14.00 14.01 14.02 14.03 14.04 14.05 14.06 14.07 14.08 14.09 14.10 14.11 Benamouzig R, Deyra J, Martin A, Girard B, Jullian E, Piednoir B, et al. *Daily soluble aspirin and prevention of colorectal adenoma recurrence: one-year results of the APACC trial.* Gastroenterology 2003 Aug;125(2):328-36 Available from: http://www.ncbi.nlm.nih.gov/pubmed/12891533.
15. ↑ 15.00 15.01 15.02 15.03 15.04 15.05 15.06 15.07 15.08 15.09 15.10 15.11 15.12 Logan RF, Grainge MJ, Shepherd VC, Armitage NC, Muir KR, ukCAP Trial Group. *Aspirin and folic acid for the prevention of recurrent colorectal adenomas.* Gastroenterology 2008 Jan;134(1):29-38 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18022173.
16. ↑ 16.00 16.01 16.02 16.03 16.04 16.05 16.06 16.07 16.08 16.09 16.10 16.11 Sandler RS, Halabi S, Baron JA, Budinger S, Paskett E, Keresztes R, et al. *A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer.* N Engl J Med 2003 Mar 6;348(10):883-90 Available from: http://www.ncbi.nlm.nih.gov/pubmed/12621132.
17. ↑ 17.0 17.1 17.2 17.3 17.4 17.5 17.6 17.7 Norrving B, Elwin CE, Peterson B, Blomstrand C, Olsson JE, Nilsson B, et al. *Swedish Aspirin Low-Dose Trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischaemic events. The SALT Collaborative Group.* Lancet 1991 Nov 30;338(8779):1345-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/1682734.
18. ↑ 18.0 18.1 18.2 18.3 18.4 Cuzick J, Thorat MA, Bosetti C, Brown PH, Burn J, Cook NR, et al. *Estimates of benefits and harms of prophylactic use of aspirin in the general population.* Ann Oncol 2015 Jan;26(1):47-57 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25096604.
19. ↑ Chubak J, Kamineni A, Buist DSM, Anderson ML, Whitlock EP. 2015 Sep Available from: http://www.ncbi.nlm.nih.gov/pubmed/26491758.
20. ↑ Hawk ET, Limburg PJ, Viner JL. *Epidemiology and prevention of colorectal cancer.* Surg Clin North Am 2002 Oct;82(5):905-41 Available from: http://www.ncbi.nlm.nih.gov/pubmed/12507200.
21. ↑ Bibbins-Domingo K, U.S. Preventive Services Task Force. *Aspirin Use for the Primary Prevention of Cardiovascular Disease and Colorectal Cancer: U.S. Preventive Services Task Force Recommendation Statement.* Ann Intern Med 2016 Apr 12 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27064677.
22. ↑ St John DJ, Yeomans ND, McDermott FT, De Boer WG. *Adaptation of the gastric mucosa to repeated administration of aspirin in the rat.* Am J Dig Dis 1973 Oct;18(10):881-5 Available from: http://www.ncbi.nlm.nih.gov/pubmed/4582544.

23. ↑ 23.0 23.1 Burn J, Mathers JC, Bishop DT. *Chemoprevention in Lynch syndrome.* Fam Cancer 2013 Dec;12 (4):707-18 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23880960.
24. ↑ 24.0 24.1 24.2 24.3 van Kruijsdijk RC, Visseren FL, Ridker PM, Dorresteijn JA, Buring JE, van der Graaf Y, Cook NR.. *Individualised prediction of alternate-day aspirin treatment effects on the combined risk of cancer, cardiovascular disease and gastrointestinal bleeding in healthy women.* Heart 2015 Mar;101(5): 369-76 Available from: http://www.ncbi.nlm.nih.gov/pubmed/?term=individualised+prediction+of+alternate-day.
25. ↑ 25.0 25.1 25.2 Meade TW, Wilke HC, Kelleher CC, Roderick PJ, Brennan PJ, Wilson CW, et al. *Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. The Medical Research Council's General Practice Research Framework.* Lancet 1998 Jan 24;351(9098):233-41 Available from: http://www.ncbi.nlm.nih.gov/pubmed/9457092.
26. ↑ National Vascular Disease Prevention Alliance. *Guidelines for the management of absolute cardiovascular disease risk.*; 2012.
27. ↑ ASPREE Investigator Group. *Study design of ASPirin in Reducing Events in the Elderly (ASPREE): a randomized, controlled trial.* Contemp Clin Trials 2013 Nov;36(2):555-64 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24113028.
28. ↑ World Cancer Research Fund/American Institute for Cancer Research. *Food, nutrition, physical activity and the prevention of cancer: a global perspective.* 2007 Available from: http://www.dietandcancerreport.org/.
29. ↑ World Cancer Research Fund/American Institute for Cancer Research. *Continuous Update Project Report: Food, Nutrition, Physical Activity, and the Prevention of Colorectal Cancer.* WCRF; 2011.
30. ↑ Poynter JN, Gruber SB, Higgins PD, Almog R, Bonner JD, Rennert HS, et al. *Statins and the risk of colorectal cancer.* N Engl J Med 2005 May 26;352(21):2184-92 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15917383.
31. ↑ 31.0 31.1 Emberson JR, Kearney PM, Blackwell L, Newman C, Reith C, Bhala N, et al. *Lack of effect of lowering LDL cholesterol on cancer: meta-analysis of individual data from 175,000 people in 27 randomised trials of statin therapy.* PLoS One 2012;7(1):e29849 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22276132.
32. ↑ Hague A, Manning AM, Hanlon KA, Huschtscha LI, Hart D, Paraskeva C. *Sodium butyrate induces apoptosis in human colonic tumour cell lines in a p53-independent pathway: implications for the possible role of dietary fibre in the prevention of large-bowel cancer.* Int J Cancer 1993 Sep 30;55(3):498-505 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8397167.
33. ↑ Bertagnolli MM, Hsu M, Hawk ET, Eagle CJ, Zauber AG, Adenoma Prevention with Celecoxib (APC) Study Investigators. *Statin use and colorectal adenoma risk: results from the adenoma prevention with celecoxib trial.* Cancer Prev Res (Phila) 2010 May;3(5):588-96 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20403998.
34. ↑ Broughton T, Sington J, Beales IL. *Statin use is associated with a reduced incidence of colorectal adenomatous polyps.* Int J Colorectal Dis 2013 Apr;28(4):469-76 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23114474.
35. ↑ Larsson SC, Orsini N, Wolk A. *Diabetes mellitus and risk of colorectal cancer: a meta-analysis.* J Natl Cancer Inst 2005 Nov 16;97(22):1679-87 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16288121.
36. ↑ Rizza RA VA. In: Waldman S, Terzic A. *Pharmacology and Therapeutics: principles to practice.* Amsterdam: Elsevier; 2009 Available from: P. 557-70.

37. ↑ Zhang ZJ, Zheng ZJ, Kan H, Song Y, Cui W, Zhao G, et al. *Reduced risk of colorectal cancer with metformin therapy in patients with type 2 diabetes: a meta-analysis.* Diabetes Care 2011 Oct;34(10):2323-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21949223.
38. ↑ Noto H, Goto A, Tsujimoto T, Noda M. *Cancer risk in diabetic patients treated with metformin: a systematic review and meta-analysis.* PLoS One 2012;7(3):e33411 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22448244.
39. ↑ Ramjeesingh R, Orr C, Bricks CS, Hopman WM, Hammad N. *A retrospective study on the role of diabetes and metformin in colorectal cancer disease survival.* Curr Oncol 2016 Apr;23(2):e116-22 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27122979.
40. ↑ [40.0] [40.1] Clarke LC KS. In: Waldman S, Terzic A. *Pharmacology and Therapeutics: principles to practice.* Amsterdam: Elsevier; 2009 Available from: P. 587-610.
41. ↑ [41.0] [41.1] Singh H, Nugent Z, Demers A, Mahmud S, Bernstein C. *Exposure to bisphosphonates and risk of colorectal cancer: a population-based nested case-control study.* Cancer 2012 Mar 1;118(5):1236-43 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21823104.
42. ↑ [42.0] [42.1] Rennert G, Pinchev M, Rennert HS, Gruber SB. *Use of bisphosphonates and reduced risk of colorectal cancer.* J Clin Oncol 2011 Mar 20;29(9):1146-50 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21321296.
43. ↑ [43.0] [43.1] Pazianas M, Abrahamsen B, Eiken PA, Eastell R, Russell RG. *Reduced colon cancer incidence and mortality in postmenopausal women treated with an oral bisphosphonate--Danish National Register Based Cohort Study.* Osteoporos Int 2012 Nov;23(11):2693-701 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22392160.
44. ↑ Passarelli MN, Newcomb PA, LaCroix AZ, Lane DS, Ho GY, Chlebowski RT. *Oral bisphosphonate use and colorectal cancer incidence in the Women's Health Initiative.* J Bone Miner Res 2013 Sep;28(9):2043-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23519920.
45. ↑ Khalili H, Huang ES, Ogino S, Fuchs CS, Chan AT. *A prospective study of bisphosphonate use and risk of colorectal cancer.* J Clin Oncol 2012 Sep 10;30(26):3229-33 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22649131.
46. ↑ Hicks BM, Murray LJ, Hughes C, Cardwell CR. *Post-diagnostic oral bisphosphonate use and colorectal cancer mortality: a population-based cohort study within the UK Clinical Practice Research Datalink.* Br J Cancer 2015 Jun 30;113(1):123-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25989268.
47. ↑ Eiken P, Vestergaard P. *Oral bisphosphonates and colon cancer: an update.* Ther Adv Musculoskelet Dis 2015 Aug;7(4):160-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26288666.

Back to top

5.3.3.3 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search

View PICO	NHMRC Evidence statement form PPR1	Systematic review report PPR1

Back to top

6 Population screening for colorectal cancer

6.1 Background

Background Colorectal cancer provides an excellent model for population screening, fully satisfying the World Health Organisation's principles of screening.1-6 It is an important health problem7, with the risk for the disease increasing with advancing age. Its biology is well understood, effective screening tests are available, outcomes are changed by intervention and, in countries where colorectal cancer is common, there is an economically balanced case in relation to expenditure on health care as a whole.4 Colorectal cancer screening is primarily directed at middle-aged people in good general health, with no symptoms that might indicate colorectal cancer. Invitations to participate in screening therefore should encourage anyone with relevant symptoms to seek medical advice about the need for diagnostic investigation rather than undergoing screening. Ideally, centrally organised population programs take responsibility for identification of those eligible for screening, choice of screening test, the invitation process, provision of screening at no cost to participants, documentation of follow-up investigations, evaluation of outcomes and cost-effectiveness as well as assessment of the quality of each step in the screening pathway.8-11 Screening for colorectal cancer now has widespread acceptance at an international level, although local circumstances affect program design and choice of screening test.12 Most national programs, especially those in Europe, Canada and Australasia, utilise population screening rather than opportunistic screening.13 Colorectal cancer screening in Australia In 1997, the Australian Health Technology Advisory Committee (AHTAC) reviewed the evidence on screening and recommended that Australia should develop a program for the introduction of population screening for colorectal cancer by faecal occult blood testing for the average risk population (well population aged over 50).14 A pilot study conducted in three

regions (2002-2004) indicated that a national program in Australia would meet the criteria of the Australian Cancer Screening Framework and was likely to be well accepted by health professionals and the general public.15 The Australian National Bowel Cancer Screening Program (NBCSP) commenced in 2006. This government-funded population screening program targets men and women in the 50-74 year age range. A step-wise roll out of eligible age groups allowed health services to adjust to the increased demand for colonoscopy (see Table 9.1). Full roll out of biennial screening will be in place by 2020.16 The key elements of the NBCSP are: • use of an immunochemical FOBT (iFOBT) as the screening test; • provision of iFOBT screening at no cost to participants; • distribution of invitations and screening tests by mail; • analysis of screening in a central laboratory; • follow-up of positive test results, mostly by colonoscopy, through the usual care pathway backed up by a central reminder service; • central collection of data and reporting of NBCSP outcomes via regular reports.16 The participant's screening pathway is set out in Appendix 9.1. Table 9.1. Australian National Bowel Cancer Screening Program target populations in 2006-2019 Period Target ages 2006-2008 55 and 65 2008-2013 50, 55 and 65 2013-2014 50, 55, 60 and 65 2015 50, 55, 60, 65, 70 and 74 2016 50, 55, 60, 64, 65, 70, 72 and 74 2017 50, 54, 55, 58, 60, 64, 68, 70, 72, 74 2018 50, 54, 58, 60, 62, 64, 66, 68, 70, 72, 74 2019 onward 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74

Findings to date indicate that the NBCSP is indeed on course to fulfil its aims, as shown by: 1. a favourable shift in pathological stage in screen-detected cancers17-19 2. modelling studies supporting both marked cost-effectiveness20 and a considerable impact on colorectal cancer mortality21, and 3. linkage studies demonstrating that NBCSP invitees, especially those who participated in the program, have a lower risk of dying from colorectal cancer19,22. Screening infrastructure in the NBCSP is being progressively strengthened to improve its efficiency and effectiveness. However, choice of screening test requires regular review as new evidence becomes available about existing and emerging tests. This revision of population screening guidelines provides a review of up-to-date evidence relating to the effectiveness, acceptability, feasibility and cost-effectiveness of a range of currently available screening methods. The review also examines starting and stopping ages for population screening and the frequency with which screening tests should be offered to the target population. 9.1.1 Screening benefit The primary aims of screening are to reduce the morbidity and mortality of the disease through (1) detection of early-stage cancer and (2) prevention of cancer through detection and removal of pre-malignant adenomas.7 Such screening can be provided on an individual basis (opportunistic screening) or for populations through centrally organised programs. Opportunistic screening is preferred in some health settings, particularly in the USA. However, centrally organised screening is designed to promote participation within the target population, irrespective of social determinants of health such as income, level of education, language spoken or geographic location.8 This potentially increases the impact on bowel cancer morbidity and mortality as well as providing more equitable health care for the population. Other advantages of organised screening include more efficient and cost-effective use of resources and the ability to systematically address quality assurance throughout the screening pathway. 9.1.2 Screening test accuracy Numerous screening tests are available, with differing performance, costs, acceptability and risks.14 These include: • stool tests to detect bleeding arising from cancers or adenomas (faecal occult blood tests or FOBTs) or DNA mutations shed by cancer (faecal DNA test) • endoscopic tests to directly visualise mucosal abnormalities (flexible sigmoidoscopy, colonoscopy) • CT colonography (CTC) to detect anatomical abnormalities with x-ray • plasma tests to detect cancer biomarkers. During the 1990s, randomised controlled

trials (RCTs) performed in Minnesota (USA), Nottingham (UK) and Funen (Denmark) showed that FOBTs were an effective method of screening for colorectal cancer25-29, subsequent meta-analyses providing Level I evidence for a 15-30% mortality improvement30,31. High level evidence for effectiveness now has become available for one-time flexible sigmoidoscopy32-35 with reductions in colorectal cancer-related mortality. However, the other modalities have yet to undergo comparable trials and their effectiveness therefore remains speculative. Three RCTs to evaluate colonoscopy are currently in progress.36-38 9.1.3 Screening cost-effectiveness

To achieve its primary aim of reducing cancer-related mortality, a population-based cancer screening program must be acceptable to the target population, feasible within the overall system for delivery of health care and have an acceptable level of cost-effectiveness. The recent evaluation conducted by the US Preventative Services Task Force (USPSTF) used life-years gained a measurement of effectiveness and the number of colonoscopies as a measurement of burden to compare CRC screening strategies using eight different screening test technologies.39 Under the assumption of 100% screening adherence in each case, the evaluation found that 10-yearly colonoscopy screening, 10 yearly sigmoidoscopy screening combined with annual iFOBT, 5-yearly CTC screening and annual iFOBT alone for CRC screening for ages 50-74 years would provide the best balance of benefits to harms in the US context. However, the study did not report on the impact of more realistic compliance assumptions (which could be expected to differ by screening modality and frequency) on either benefits or harms. Furthermore, the cost-effectiveness of the alternate strategies were not considered. The comparative benefits, harms and cost-effectiveness of the NBSCP compared to other potential future alternate or adjunctive options for screening in Australia have not yet been evaluated. A modelling study was therefore conducted to evaluate the health benefits, harms, and cost-effectiveness of colorectal cancer screening with iFOBT versus flexible sigmoidoscopy, colonoscopy, CTC, faecal DNA and plasma biomarkers. This evaluation was supported by the National Health and Medical Research Council. 9.1.4 Screening age The early randomised controlled trials on gFOBT-based screening showed benefit for people aged 45–50 years and upward. Cost-effectiveness studies also demonstrate that age influences cost-effectiveness.16 The risk of colorectal cancer increases with age, as shown in Table 9.2. Together with the observation that risk increases 4-fold between ages of 40 and 50 years, this led to the recommendation that screening of average risk people should commence at age 50 years, a recommendation that is consistent with the deliberations of several major international bodies.16-21 The recently published USPSTF guidelines endorsed 50 years as the starting age for screening and found convincing evidence showing that screening from 50 to 75 years of age reduces mortality from colorectal cancer. They noted that, there was a diminishing benefit and a greater risk of adverse events after age 75. The NBCSP provides screening from age 50 to 74. The starting age was based on the low age-specific incidence of colorectal cancer in those below 50 years of age, even though cases diagnosed at such an early age make a greater contribution to overall years of potential life lost from the disease. This review re-examines evidence on the appropriate age range for screening, stimulated by suggestions of an increase in risk for colorectal cancer in younger people and the longer life expectation for the elderly.

Table 9.2. Absolute risk of colorectal cancer If a person is aged Risk of colorectal cancer over the next 10 years Men Women 30 0.07% 1 in 1400 0.07% 1 in 1400 40 0.3% 1 in 350 0.3% 1 in 350 50 1% 1 in 90 0.8% 1 in 120 60 3% 1 in 35 2% 1 in 60 70 5% 1 in 20 3% 1 in 35 Absolute risk is the observed or calculated probability of the occurrence of colorectal cancer a population. [Ref].

6.1.1 Contents

REFERENCES 1. Wilson J, Junger G. Principles and practices of screening for disease. Geneva, Switzerland1968. Report No.: 34,1968. 2. Gnauck R. World Health Organization criteria for screening. In Colorectal Cancer: Prevention, Epidemiology and Screening. New York: Raven Press; 1980. 3. Schottenfeld D. Fundamental issues in cancer screening. In Colorectal Cancer: Prevention, Epidemiology and Screening. New York: Raven Press; 1980. 4. The Cancer Council Australia, Australian Cancer Network. Chapter 3, Population screening for colorectal cancer, 2005 CCA Guidelines The Prevention, early detection and management of colorectal cancer2005. 5. GP Y. Screening for colorectal cancer – new evidence in the last 10 years. Cancer Forum; 2014. p. 38. 6. Young GP, Symonds EL, Allison JE, et al. Advances in Fecal Occult Blood Tests: the FIT revolution. Digestive diseases and sciences 2015;60:609-22. 7. Cancer Council Australia. Clinical practice guidelines for the prevention, early detection and management of colorectal cancer (CRC) 2nd edition2005. Report No.: ISBN: 0-9775060-1-0. 8. Miles A, Cockburn J, Smith RA, Wardle J. A perspective from countries using organized screening programs. Cancer 2004;101:1201-13. 9. International Agency for Research on Cancer. Chapter 2, European guidelines for quality assurance in colorectal cancer screening and diagnosis, First Edition: International Agency for Research on Cancer; 2010. 10. Benson VS, Atkin WS, Green J, et al. Toward standardizing and reporting colorectal cancer screening indicators on an international level: The International Colorectal Cancer Screening Network. International journal of cancer 2012;130:2961-73. 11. Brawley OW. Colorectal cancer control: providing adequate care to those who need it. Journal of the National Cancer Institute 2014;106:dju075. 12. Flitcroft KL, St John DJ, Howard K, et al. A comparative case study of bowel cancer screening in the UK and Australia: evidence lost in translation? J Med Screen 2011;18:193-203. 13. Schreuders EH, Ruco A, Rabeneck L, et al. Colorectal cancer screening: a global overview of existing programmes. Gut 2015;64:1637-49. 14. Australian Health Technology Advisory Committee. Colorectal Cancer Screening1997. Report No.: ISBN 0 642 27289 1 15. Australian Government Department of Health. The Australian bowel cancer screening pilot program and beyond: final evaluation report2005. 16. Australian Institute of Health and Welfare. National Bowel Cancer Screening Program Monitoring Report 2016. Canberra: AIHW; 2016. Report No.: Cat. No CAN 97. 17. Cole SR, Tucker GR, Osborne JM, et al. Shift to earlier stage at diagnosis as a consequence of the National Bowel Cancer Screening Program. The Medical journal of Australia 2013;198:327-30. 18. Ananda S, Wong H, Faragher I, et al. Survival impact of the Australian National Bowel Cancer Screening Programme. Internal medicine journal 2016;46:166-71. 19. Australian Institute of Health and Welfare, Australian Government Department of Health. Analysis of

colorectal cancer outcomes for the Australian National Bowel Cancer Screening Program. Asia-Pacific journal of clinical oncology 2016;12:22-32. 20. Pignone MP, Flitcroft KL, Howard K, Trevena LJ, Salkeld GP, St John D. Costs and cost-effectiveness of full implementation of a biennial faecal occult blood test screening program for bowel cancer in Australia. The Medical journal of Australia 2011;194:180-5. 21. Cenin DR, St John DJ, Ledger MJ, Slevin T, Lansdorp-Vogelaar I. Optimising the expansion of the National Bowel Cancer Screening Program. The Medical journal of Australia 2014;201:456-61. 22. St John J, Grogan P. Compelling new data on the effectiveness of Australia's National Bowel Cancer Screening Program: A model for best practice? Asia-Pacific journal of clinical oncology 2016;12:7-9. 23. van Rossum LG, van Rijn AF, Laheij RJ, et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. Gastroenterology 2008; 135:82-90. 24. Park DI, Ryu S, Kim YH, et al. Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average risk undergoing colorectal cancer screening. Am J Gastroenterol 2010;105:2017-25. 25. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. N Engl J Med 1993;328:1365-71. 26. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet (London, England) 1996;348:1472-7. 27. Kronborg O, Fenger C, Olsen J, Jørgensen OD, Søndergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet (London, England) 1996;348:1467-71. 28. Mandel JS, Church TR, Ederer F, Bond JH. Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood. Journal of the National Cancer Institute 1999;91:434-7. 29. Mandel JS, Church TR, Bond JH, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. N Engl J Med 2000;343:1603-7. 30. Hewitson P, Glasziou P, Irwig L, Towler B, Watson E. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. The Cochrane database of systematic reviews 2007:Cd001216. 31. Towler B, Irwig L, Glasziou P, Kewenter J, Weller D, Silagy C. A systematic review of the effects of screening for colorectal cancer using the faecal occult blood test, hemoccult. BMJ (Clinical research ed) 1998;317:559-65. 32. Segnan N, Armaroli P, Bonelli L, et al. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial--SCORE. Journal of the National Cancer Institute 2011;103: 1310-22. 33. Elmunzer BJ, Hayward RA, Schoenfeld PS, Saini SD, Deshpande A, Waljee AK. Effect of flexible sigmoidoscopy-based screening on incidence and mortality of colorectal cancer: a systematic review and meta-analysis of randomized controlled trials. PLoS Med 2012;9:e1001352. 34. Schoen RE, Pinsky PF, Weissfeld JL, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med 2012;366: 2345-57. 35. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet (London, England) 2010;375:1624-33. 36. Quintero E, Castells A, Bujanda L, et al. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. N Engl J Med 2012;366:697-706. 37. Bretthauer M, Kaminski MF, Løberg M, et al. Population-Based Colonoscopy Screening for Colorectal Cancer: A Randomized Clinical Trial. JAMA Intern Med 2016. 38. ClinicalTrials.gov. Colonoscopy vs fecal immunochemical test in reducing mortality from colorectal cancer (CONFIRM) [NCT01239082] 2016. 39. Knudsen AB, Zauber AG, Rutter CM, et al. Estimation of Benefits, Burden, and Harms of Colorectal Cancer Screening Strategies: Modeling Study for the US Preventive Services Task Force. JAMA 2016;315:2595-609. 40. International Agency for Research on Cancer. European guidelines for quality assurance in colorectal cancer screening and diagnosis, First Edition: International Agency for Research on Cancer; 2010. 41. Secretariat MA. Fecal Occult Blood Test for Colorectal Cancer Screening: an evidence-based analysis. Toronto, Ontario, Canada: Ministry of Health and Long-Term Care; 2009. 42. Force UPST. Screening for Colorectal Cancer US Preventive Services Task Force Recommendation Statement. JAMA 2016;315: 2564-75. 43. Force USPST. Screening for Colorectal Cancer: U.S. Preventive Services Task Force Recommendation Statement. Annals of Internal Medicine 2008;149:627-37. 44. Jørgensen O, Kronborg O, Fenger C. A randomised study on screening for colorectal cancer using faecal occult blood testing: results after 13 years and seven biennial screening rounds. Gut 2002;50:29-39. 45. Scholefield J, Moss S, Sufi F, Mangham C,

Hardcastle J. Effect of faecal occult blood screening on mortality from colorectal cancer: results from a randomised controlled trial. Gut 2002;50:840-4. 46. Scholefield JH, Moss SM, Mangham CM, Whynes DK, Hardcastle JD. Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up. Gut 2012;61:1036-40. 47. Zheng S, Chen K, Liu X, et al. Cluster Randomization Trial of Sequence Mass Screening for Colorectal Cancer. Dis Colon Rectum 2003;46:51-8. 48. Blom J, Yin L, Liden A, et al. A 9-year follow-up study of participants and nonparticipants in sigmoidoscopy screening: importance of self-selection. Cancer Epidemiol Biomarkers Prev 2008;17:1163-8. 49. Holme O, Loberg M, Kalager M, et al. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. JAMA 2014;312:606-15. 50. Shroff J, Thosani N, Batra S, Singh H, Guha S. Reduced incidence and mortality from colorectal cancer with flexible-sigmoidoscopy screening: a meta-analysis. World J Gastroenterol 2014;20:18466-76. 51. Hoff G, Grotmol T, Skovlund E, Bretthauer M, Norwegian Colorectal Cancer Prevention Study G. Risk of colorectal cancer seven years after flexible sigmoidoscopy screening: randomised controlled trial. BMJ (Clinical research ed) 2009;338: b1846. 52. Castro I, Cubiella J, Rivera C, et al. Fecal immunochemical test accuracy in familial risk colorectal cancer screening. International journal of cancer 2014;134:367-75. 53. Gimeno-Garcia AZ, Quintero E, Nicolas-Perez D, Hernandez-Guerra M, Parra-Blanco A, Jimenez-Sosa A. Screening for familial colorectal cancer with a sensitive immunochemical fecal occult blood test: a pilot study. Eur J Gastroenterol Hepatol 2009;21:1062-7. 54. Ng SC, Ching JY, Chan V, et al. Diagnostic accuracy of faecal immunochemical test for screening individuals with a family history of colorectal cancer. Aliment Pharmacol Ther 2013;38:835-41. 55. Ahlquist DA, Sargent DJ, Loprinzi CL, et al. Stool DNA and occult blood testing for screen detection of colorectal neoplasia. Ann Intern Med 2008;149:441-50, W81. 56. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med 2014;370:1287-97. 57. Redwood DG, Asay ED, Blake ID, et al. Stool DNA Testing for Screening Detection of Colorectal Neoplasia in Alaska Native People. Mayo Clin Proc 2016;91:61-70. 58. Annahazi A, Abraham S, Farkas K, et al. A pilot study on faecal MMP-9: a new noninvasive diagnostic marker of colorectal cancer. British journal of cancer 2016;114:787-92. 59. Church TR, Wandell M, Lofton-Day C, et al. Prospective evaluation of methylated SEPT9 in plasma for detection of asymptomatic colorectal cancer. Gut 2014;63:317-25. 60. Khalid-de Bakker CA, Jonkers DM, Sanduleanu S, et al. Test performance of immunologic fecal occult blood testing and sigmoidoscopy compared with primary colonoscopy screening for colorectal advanced adenomas. Cancer Prev Res (Phila) 2011;4:1563-71. 61. Brenner H, Haug U, Hundt S. Sex differences in performance of fecal occult blood testing. Am J Gastroenterol 2010;105:2457-64. 62. Chiu HM, Lee YC, Tu CH, et al. Association between early stage colon neoplasms and false-negative results from the fecal immunochemical test. Clin Gastroenterol Hepatol 2013;11:832-8 e1-2. 63. de Wijkerslooth TR, Stoop EM, Bossuyt PM, et al. Immunochemical fecal occult blood testing is equally sensitive for proximal and distal advanced neoplasia. Am J Gastroenterol 2012;107:1570-8. 64. Graser A, Stieber P, Nagel D, et al. Comparison of CT colonography, colonoscopy, sigmoidoscopy and faecal occult blood tests for the detection of advanced adenoma in an average risk population. Gut 2009;58:241-8. 65. Hundt S, Haug U, Brenner H. Comparative evaluation of immunochemical fecal occult blood tests for colorectal adenoma detection. Ann Intern Med 2009; 150:162-9. 66. Morikawa T, Kato J, Yamaji Y, Wada R, Mitsushima T, Shiratori Y. A comparison of the immunochemical fecal occult blood test and total colonoscopy in the asymptomatic population. Gastroenterology 2005;129:422-8. 67. Nakazako M. YH, Matsushita H., Sato K., Fujita K., Yamanaka Y., Imai Y. Immunologic Fecal Occult Blood Test for Colorectal Cancer Screening. Japan Med Assoc J 2006;49:203-7. 68. Parra-Blanco A, Gimeno-Garcia AZ, Quintero E, et al. Diagnostic accuracy of immunochemical versus guaiac faecal occult blood tests for colorectal cancer screening. J Gastroenterol 2010;45:703-12. 69. Terhaar sive Droste JS, Oort FA, van der Hulst RW, et al. Higher fecal immunochemical test cutoff levels: lower positivity rates but still acceptable detection rates for early-stage colorectal cancers. Cancer Epidemiol Biomarkers Prev 2011; 20:272-80. 70. Viana Freitas BR, Kibune Nagasako C, Pavan CR, et al. Immunochemical fecal occult blood test for detection of advanced colonic adenomas and colorectal cancer: comparison with colonoscopy results.

Gastroenterol Res Pract 2013;2013:384561. 71. Brenner H, Tao S. Superior diagnostic performance of faecal immunochemical tests for haemoglobin in a head-to-head comparison with guaiac based faecal occult blood test among 2235 participants of screening colonoscopy. Eur J Cancer 2013;49:3049-54. 72. Chen Y-Y, Chen T-H, Su M-Y, et al. Accuracy of immunochemical fecal occult blood test for detecting colorectal neoplasms in individuals undergoing health check-ups. Adv Digest Med 2014;1:74-9. 73. Hernandez V, Cubiella J, Gonzalez-Mao MC, et al. Fecal immunochemical test accuracy in average-risk colorectal cancer screening. World J Gastroenterol 2014;20: 1038-47. 74. Kato J, Morikawa T, Kuriyama M, et al. Combination of sigmoidoscopy and a fecal immunochemical test to detect proximal colon neoplasia. Clin Gastroenterol Hepatol 2009;7:1341-6. 75. Lee YH, Hur M, Kim H, et al. Optimal cut-off concentration for a faecal immunochemical test for haemoglobin by Hemo Techt NS-Plus C15 system for the colorectal cancer screening. Clin Chem Lab Med 2015;53:e69-71. 76. Levy BT, Bay C, Xu Y, et al. Test characteristics of faecal immunochemical tests (FIT) compared with optical colonoscopy. J Med Screen 2014; 21:133-43. 77. Omata F, Shintani A, Isozaki M, Masuda K, Fujita Y, Fukui T. Diagnostic performance of quantitative fecal immunochemical test and multivariate prediction model for colorectal neoplasms in asymptomatic individuals. Eur J Gastroenterol Hepatol 2011;23:1036-41. 78. Elsafi SH, Alqahtani NI, Zakary NY, Al Zahrani EM. The sensitivity, specificity, predictive values, and likelihood ratios of fecal occult blood test for the detection of colorectal cancer in hospital settings. Clin Exp Gastroenterol 2015;8:279-84. 79. Lee YC, Chiu HM, Chiang TH, et al. Accuracy of faecal occult blood test and Helicobacter pylori stool antigen test for detection of upper gastrointestinal lesions. BMJ Open 2013;3:e003989. 80. Nakajima M, Saito H, Soma Y, Sobue T, Tanaka M, Munakata A. Prevention of advanced colorectal cancer by screening using the immunochemical faecal occult blood test: a case–control study. British journal of cancer 2003;89:23-8. 81. Saito H, Soma Y, Nakajima M, et al. A case-control study evaluating occult blood screening for colorectal cancer with hemoccult test and an immunochemical hemagglutination test. Oncology reports 2000;7:815-9. 82. Saito H, Soma Y, Koeda J, et al. Reduction in risk of mortality from colorectal cancer by fecal occult blood screening with immunochemical hemagglutination test. A case-control study. International journal of cancer 1995;61:465-9. 83. Cole SR, Young GP, Esterman A, Cadd B, Morcom J. A randomised trial of the impact of new faecal haemoglobin test technologies on population participation in screening for colorectal cancer. The Medical journal of Australia 2003; 10:117-22. 84. Macrae FA, Hill DJ, St. John DJB, Ambikapathy A, Garner JF. Predicting colon cancer screening behavior from health beliefs. Prev Med 1984;13:115-26. 85. Cole SR, Young GP. Effect of dietary restriction on participation in faecal occult blood test screening for colorectal cancer. The Medical journal of Australia 2001; 175:195-8. 86. McCusker J, Morrow GR. Factors related to the use of cancer early detection techniques. Prev Med 1980;9:388-97. 87. Salkeld GP, Solomon MJ, Short L, Ward J. Measuring the importance of attributes that influence consumer attitudes to colorectal cancer screening. ANZ J Surg 2003;73:128-32. 88. Wardle J, Pope R. The psychological costs of screening for cancer. J Psychosom Res 1992;36:609-24. 89. Lindholm E, Berglund B, Kewenter J, Haglind E. Worry associated with screening for colorectal carcinomas. Scand J Gastroenterol 1997; 32:238-45. 90. Parker MA, Robinson MH, Scholefield JH, Hardcastle JD. Psychiatric morbidity and screening for colorectal cancer. J Med Screen 2002;9:7-10. 91. Wardle J, Taylor T, Sutton S, Atkin W. Does publicity about cancer screening raise fear of cancer? Randomised trial of the psychological effect of information about cancer screening. BMJ (Clinical research ed) 1999;319:1037-8.

6.1 Introduction: population screening for colorectal cancer

6.1.1 Background

Background Colorectal cancer provides an excellent model for population screening, fully satisfying the World Health Organisation's principles of screening.1-6 It is an important health problem7, with the risk for the disease increasing with advancing age. Its biology is well understood, effective screening tests are available, outcomes are changed by intervention and, in countries where colorectal cancer is common, there is an economically balanced case in relation to expenditure on health care as a whole.4 Colorectal cancer screening is primarily directed at middle-aged people in good general health, with no symptoms that might indicate colorectal cancer. Invitations to participate in screening therefore should encourage anyone with relevant symptoms to seek medical advice about the need for diagnostic investigation rather than undergoing screening. Ideally, centrally organised population programs take responsibility for identification of those eligible for screening, choice of screening test, the invitation process, provision of screening at no cost to participants, documentation of follow-up investigations, evaluation of outcomes and cost-effectiveness as well as assessment of the quality of each step in the screening pathway.8-11 Screening for colorectal cancer now has widespread acceptance at an international level, although local circumstances affect program design and choice of screening test.12 Most national programs, especially those in Europe, Canada and Australasia, utilise population screening rather than opportunistic screening.13 Colorectal cancer screening in Australia In 1997, the Australian Health Technology Advisory Committee (AHTAC) reviewed the evidence on screening and recommended that Australia should develop a program for the introduction of population screening for colorectal cancer by faecal occult blood testing for the average risk population (well population aged over 50).14 A pilot study conducted in three regions (2002-2004) indicated that a national program in Australia would meet the criteria of the Australian Cancer Screening Framework and was likely to be well accepted by health professionals and the general public.15 The Australian National Bowel Cancer Screening Program (NBCSP) commenced in 2006. This government-funded population screening program targets men and women in the 50-74 year age range. A step-wise roll out of eligible age groups allowed health services to adjust to the increased demand for colonoscopy (see Table 9.1). Full roll out of biennial screening will be in place by 2020.16 The key elements of the NBCSP are: • use of an immunochemical FOBT (iFOBT) as the screening test; • provision of iFOBT screening at no cost to participants; • distribution of invitations and screening tests by mail; • analysis of screening in a central laboratory; • follow-up of positive test results, mostly by colonoscopy, through the usual care pathway backed up by a central reminder service; • central collection of data and reporting of NBCSP outcomes via regular reports.16 The participant's screening pathway is set out in Appendix 9.1. Table 9.1. Australian National Bowel Cancer Screening Program target populations in 2006-2019 Period Target ages 2006-2008 55 and 65 2008-2013 50, 55 and 65 2013-2014 50, 55, 60 and 65 2015 50, 55, 60, 65, 70 and 74 2016 50, 55, 60, 64, 65, 70, 72 and 74 2017 50, 54, 55, 58, 60, 64, 68, 70, 72, 74 2018 50, 54, 58, 60, 62, 64, 66, 68, 70, 72, 74 2019 onward 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74

Findings to date indicate that the NBCSP is indeed on course to fulfil its aims, as shown by: 1. a favourable shift in pathological stage in screen-detected cancers17-19 2. modelling studies supporting both marked cost-effectiveness20 and a considerable impact on colorectal cancer mortality21, and 3. linkage studies demonstrating that NBCSP invitees, especially those who participated in the program, have a lower risk of dying from colorectal cancer19,22. Screening infrastructure in the NBCSP is being progressively strengthened to improve its efficiency and effectiveness. However, choice of screening test requires regular review as new evidence becomes available about existing and emerging tests. This revision of population screening guidelines provides a review of up-to-date evidence relating to the effectiveness, acceptability, feasibility and cost-

effectiveness of a range of currently available screening methods. The review also examines starting and stopping ages for population screening and the frequency with which screening tests should be offered to the target population. 9.1.1 Screening benefit The primary aims of screening are to reduce the morbidity and mortality of the disease through (1) detection of early-stage cancer and (2) prevention of cancer through detection and removal of pre-malignant adenomas.7 Such screening can be provided on an individual basis (opportunistic screening) or for populations through centrally organised programs. Opportunistic screening is preferred in some health settings, particularly in the USA. However, centrally organised screening is designed to promote participation within the target population, irrespective of social determinants of health such as income, level of education, language spoken or geographic location.8 This potentially increases the impact on bowel cancer morbidity and mortality as well as providing more equitable health care for the population. Other advantages of organised screening include more efficient and cost-effective use of resources and the ability to systematically address quality assurance throughout the screening pathway. 9.1.2 Screening test accuracy Numerous screening tests are available, with differing performance, costs, acceptability and risks.14 These include: • stool tests to detect bleeding arising from cancers or adenomas (faecal occult blood tests or FOBTs) or DNA mutations shed by cancer (faecal DNA test) • endoscopic tests to directly visualise mucosal abnormalities (flexible sigmoidoscopy, colonoscopy) • CT colonography (CTC) to detect anatomical abnormalities with x-ray • plasma tests to detect cancer biomarkers. During the 1990s, randomised controlled trials (RCTs) performed in Minnesota (USA), Nottingham (UK) and Funen (Denmark) showed that FOBTs were an effective method of screening for colorectal cancer25-29, subsequent meta-analyses providing Level I evidence for a 15-30% mortality improvement30,31. High level evidence for effectiveness now has become available for one-time flexible sigmoidoscopy32-35 with reductions in colorectal cancer-related mortality. However, the other modalities have yet to undergo comparable trials and their effectiveness therefore remains speculative. Three RCTs to evaluate colonoscopy are currently in progress.36-38 9.1.3 Screening cost-effectiveness

To achieve its primary aim of reducing cancer-related mortality, a population-based cancer screening program must be acceptable to the target population, feasible within the overall system for delivery of health care and have an acceptable level of cost-effectiveness. The recent evaluation conducted by the US Preventative Services Task Force (USPSTF) used life-years gained a measurement of effectiveness and the number of colonoscopies as a measurement of burden to compare CRC screening strategies using eight different screening test technologies.39 Under the assumption of 100% screening adherence in each case, the evaluation found that 10-yearly colonoscopy screening, 10 yearly sigmoidoscopy screening combined with annual iFOBT, 5-yearly CTC screening and annual iFOBT alone for CRC screening for ages 50-74 years would provide the best balance of benefits to harms in the US context. However, the study did not report on the impact of more realistic compliance assumptions (which could be expected to differ by screening modality and frequency) on either benefits or harms. Furthermore, the cost-effectiveness of the alternate strategies were not considered. The comparative benefits, harms and cost-effectiveness of the NBSCP compared to other potential future alternate or adjunctive options for screening in Australia have not yet been evaluated. A modelling study was therefore conducted to evaluate the health benefits, harms, and cost-effectiveness of colorectal cancer screening with iFOBT versus flexible sigmoidoscopy, colonoscopy, CTC, faecal DNA and plasma biomarkers. This evaluation was supported by the National Health and Medical Research Council. 9.1.4 Screening age The early randomised controlled trials on gFOBT-based screening showed benefit for people aged 45–50 years and upward. Cost-effectiveness studies also demonstrate that age influences cost-effectiveness.16 The risk of colorectal cancer increases with age, as shown in Table 9.2. Together with the observation that risk increases 4-fold between ages of 40 and 50 years, this led to the recommendation that screening of average risk people should commence at age 50 years, a recommendation that is consistent with the deliberations of several major international bodies.16-21 The recently published USPSTF guidelines endorsed 50 years as the starting age for

screening and found convincing evidence showing that screening from 50 to 75 years of age reduces mortality from colorectal cancer. They noted that, there was a diminishing benefit and a greater risk of adverse events after age 75. The NBCSP provides screening from age 50 to 74. The starting age was based on the low age-specific incidence of colorectal cancer in those below 50 years of age, even though cases diagnosed at such an early age make a greater contribution to overall years of potential life lost from the disease. This review re-examines evidence on the appropriate age range for screening, stimulated by suggestions of an increase in risk for colorectal cancer in younger people and the longer life expectation for the elderly.

Table 9.2. Absolute risk of colorectal cancer If a person is aged Risk of colorectal cancer over the next 10 years Men Women 30 0.07% 1 in 1400 0.07% 1 in 1400 40 0.3% 1 in 350 0.3% 1 in 350 50 1% 1 in 90 0.8% 1 in 120 60 3% 1 in 35 2% 1 in 60 70 5% 1 in 20 3% 1 in 35 Absolute risk is the observed or calculated probability of the occurrence of colorectal cancer a population. [Ref].

6.1.1.1 Contents

- Population screening for colorectal cancer: Evidence
  - Evidence: Screening benefit (PSC1a)
  - Evidence: Screening test accuracy (PSC1b)
  - Evidence: Screening cost effectiveness (PSC1c)
  - Evidence: Screening age (PSC1d)
- Population screening for colorectal cancer: Evidence summary and recommendations
- Discussion

REFERENCES 1. Wilson J, Junger G. Principles and practices of screening for disease. Geneva, Switzerland1968. Report No.: 34,1968. 2. Gnauck R. World Health Organization criteria for screening. In Colorectal Cancer: Prevention, Epidemiology and Screening. New York: Raven Press; 1980. 3. Schottenfeld D. Fundamental issues in cancer screening. In Colorectal Cancer: Prevention, Epidemiology and Screening. New York: Raven Press; 1980. 4. The Cancer Council Australia, Australian Cancer Network. Chapter 3, Population screening for colorectal cancer, 2005 CCA Guidelines The Prevention, early detection and management of colorectal cancer2005. 5. GP Y. Screening for colorectal cancer – new evidence in the last 10 years. Cancer Forum; 2014. p. 38. 6. Young GP, Symonds EL, Allison JE, et al. Advances in Fecal Occult Blood Tests: the FIT revolution. Digestive diseases and sciences 2015;60:609-22. 7. Cancer Council Australia. Clinical practice guidelines for the prevention, early detection and management of colorectal cancer (CRC) 2nd edition2005. Report No.: ISBN: 0-9775060-1-0. 8. Miles A, Cockburn J, Smith RA, Wardle J. A perspective from countries using organized screening programs. Cancer 2004;101:1201-13. 9. International Agency for Research on Cancer. Chapter 2, European guidelines for quality assurance in colorectal cancer screening and diagnosis, First Edition: International Agency for Research on Cancer; 2010. 10. Benson VS, Atkin WS, Green J, et al. Toward standardizing and reporting colorectal cancer screening indicators on an international level: The International Colorectal Cancer Screening Network.

International journal of cancer 2012;130:2961-73. 11. Brawley OW. Colorectal cancer control: providing adequate care to those who need it. Journal of the National Cancer Institute 2014;106:dju075. 12. Flitcroft KL, St John DJ, Howard K, et al. A comparative case study of bowel cancer screening in the UK and Australia: evidence lost in translation? J Med Screen 2011;18:193-203. 13. Schreuders EH, Ruco A, Rabeneck L, et al. Colorectal cancer screening: a global overview of existing programmes. Gut 2015;64:1637-49. 14. Australian Health Technology Advisory Committee. Colorectal Cancer Screening1997. Report No.: ISBN 0 642 27289 1 15. Australian Government Department of Health. The Australian bowel cancer screening pilot program and beyond: final evaluation report2005. 16. Australian Institute of Health and Welfare. National Bowel Cancer Screening Program Monitoring Report 2016. Canberra: AIHW; 2016. Report No.: Cat. No CAN 97. 17. Cole SR, Tucker GR, Osborne JM, et al. Shift to earlier stage at diagnosis as a consequence of the National Bowel Cancer Screening Program. The Medical journal of Australia 2013;198:327-30. 18. Ananda S, Wong H, Faragher I, et al. Survival impact of the Australian National Bowel Cancer Screening Programme. Internal medicine journal 2016;46:166-71. 19. Australian Institute of Health and Welfare, Australian Government Department of Health. Analysis of colorectal cancer outcomes for the Australian National Bowel Cancer Screening Program. Asia-Pacific journal of clinical oncology 2016;12:22-32. 20. Pignone MP, Flitcroft KL, Howard K, Trevena LJ, Salkeld GP, St John D. Costs and cost-effectiveness of full implementation of a biennial faecal occult blood test screening program for bowel cancer in Australia. The Medical journal of Australia 2011;194:180-5. 21. Cenin DR, St John DJ, Ledger MJ, Slevin T, Lansdorp-Vogelaar I. Optimising the expansion of the National Bowel Cancer Screening Program. The Medical journal of Australia 2014;201:456-61. 22. St John J, Grogan P. Compelling new data on the effectiveness of Australia's National Bowel Cancer Screening Program: A model for best practice? Asia-Pacific journal of clinical oncology 2016;12:7-9. 23. van Rossum LG, van Rijn AF, Laheij RJ, et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. Gastroenterology 2008;135:82-90. 24. Park DI, Ryu S, Kim YH, et al. Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average risk undergoing colorectal cancer screening. Am J Gastroenterol 2010;105:2017-25. 25. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. N Engl J Med 1993;328:1365-71. 26. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet (London, England) 1996;348:1472-7. 27. Kronborg O, Fenger C, Olsen J, Jørgensen OD, Søndergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet (London, England) 1996;348:1467-71. 28. Mandel JS, Church TR, Ederer F, Bond JH. Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood. Journal of the National Cancer Institute 1999;91:434-7. 29. Mandel JS, Church TR, Bond JH, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. N Engl J Med 2000;343:1603-7. 30. Hewitson P, Glasziou P, Irwig L, Towler B, Watson E. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. The Cochrane database of systematic reviews 2007:Cd001216. 31. Towler B, Irwig L, Glasziou P, Kewenter J, Weller D, Silagy C. A systematic review of the effects of screening for colorectal cancer using the faecal occult blood test, hemoccult. BMJ (Clinical research ed) 1998;317:559-65. 32. Segnan N, Armaroli P, Bonelli L, et al. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial--SCORE. Journal of the National Cancer Institute 2011;103:1310-22. 33. Elmunzer BJ, Hayward RA, Schoenfeld PS, Saini SD, Deshpande A, Waljee AK. Effect of flexible sigmoidoscopy-based screening on incidence and mortality of colorectal cancer: a systematic review and meta-analysis of randomized controlled trials. PLoS Med 2012;9:e1001352. 34. Schoen RE, Pinsky PF, Weissfeld JL, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med 2012;366:2345-57. 35. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet (London, England) 2010;375:1624-33. 36. Quintero E, Castells A, Bujanda L, et al. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. N Engl J Med 2012;366:697-706. 37. Bretthauer M, Kaminski MF, Løberg M, et al. Population-Based

Colonoscopy Screening for Colorectal Cancer: A Randomized Clinical Trial. JAMA Intern Med 2016. 38. ClinicalTrials.gov. Colonoscopy vs fecal immunochemical test in reducing mortality from colorectal cancer (CONFIRM) [NCT01239082] 2016. 39. Knudsen AB, Zauber AG, Rutter CM, et al. Estimation of Benefits, Burden, and Harms of Colorectal Cancer Screening Strategies: Modeling Study for the US Preventive Services Task Force. JAMA 2016;315:2595-609. 40. International Agency for Research on Cancer. European guidelines for quality assurance in colorectal cancer screening and diagnosis, First Edition: International Agency for Research on Cancer; 2010. 41. Secretariat MA. Fecal Occult Blood Test for Colorectal Cancer Screening: an evidence-based analysis. Toronto, Ontario, Canada: Ministry of Health and Long-Term Care; 2009. 42. Force UPST. Screening for Colorectal Cancer US Preventive Services Task Force Recommendation Statement. JAMA 2016;315: 2564-75. 43. Force USPST. Screening for Colorectal Cancer: U.S. Preventive Services Task Force Recommendation Statement. Annals of Internal Medicine 2008;149:627-37. 44. Jørgensen O, Kronborg O, Fenger C. A randomised study on screening for colorectal cancer using faecal occult blood testing: results after 13 years and seven biennial screening rounds. Gut 2002;50:29-39. 45. Scholefield J, Moss S, Sufi F, Mangham C, Hardcastle J. Effect of faecal occult blood screening on mortality from colorectal cancer: results from a randomised controlled trial. Gut 2002;50:840-4. 46. Scholefield JH, Moss SM, Mangham CM, Whynes DK, Hardcastle JD. Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up. Gut 2012;61:1036-40. 47. Zheng S, Chen K, Liu X, et al. Cluster Randomization Trial of Sequence Mass Screening for Colorectal Cancer. Dis Colon Rectum 2003;46:51-8. 48. Blom J, Yin L, Liden A, et al. A 9-year follow-up study of participants and nonparticipants in sigmoidoscopy screening: importance of self-selection. Cancer Epidemiol Biomarkers Prev 2008;17:1163-8. 49. Holme O, Loberg M, Kalager M, et al. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. JAMA 2014;312:606-15. 50. Shroff J, Thosani N, Batra S, Singh H, Guha S. Reduced incidence and mortality from colorectal cancer with flexible-sigmoidoscopy screening: a meta-analysis. World J Gastroenterol 2014;20:18466-76. 51. Hoff G, Grotmol T, Skovlund E, Bretthauer M, Norwegian Colorectal Cancer Prevention Study G. Risk of colorectal cancer seven years after flexible sigmoidoscopy screening: randomised controlled trial. BMJ (Clinical research ed) 2009;338: b1846. 52. Castro I, Cubiella J, Rivera C, et al. Fecal immunochemical test accuracy in familial risk colorectal cancer screening. International journal of cancer 2014;134:367-75. 53. Gimeno-Garcia AZ, Quintero E, Nicolas-Perez D, Hernandez-Guerra M, Parra-Blanco A, Jimenez-Sosa A. Screening for familial colorectal cancer with a sensitive immunochemical fecal occult blood test: a pilot study. Eur J Gastroenterol Hepatol 2009;21:1062-7. 54. Ng SC, Ching JY, Chan V, et al. Diagnostic accuracy of faecal immunochemical test for screening individuals with a family history of colorectal cancer. Aliment Pharmacol Ther 2013;38:835-41. 55. Ahlquist DA, Sargent DJ, Loprinzi CL, et al. Stool DNA and occult blood testing for screen detection of colorectal neoplasia. Ann Intern Med 2008;149:441-50, W81. 56. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med 2014;370:1287-97. 57. Redwood DG, Asay ED, Blake ID, et al. Stool DNA Testing for Screening Detection of Colorectal Neoplasia in Alaska Native People. Mayo Clin Proc 2016;91:61-70. 58. Annahazi A, Abraham S, Farkas K, et al. A pilot study on faecal MMP-9: a new noninvasive diagnostic marker of colorectal cancer. British journal of cancer 2016;114:787-92. 59. Church TR, Wandell M, Lofton-Day C, et al. Prospective evaluation of methylated SEPT9 in plasma for detection of asymptomatic colorectal cancer. Gut 2014;63:317-25. 60. Khalid-de Bakker CA, Jonkers DM, Sanduleanu S, et al. Test performance of immunologic fecal occult blood testing and sigmoidoscopy compared with primary colonoscopy screening for colorectal advanced adenomas. Cancer Prev Res (Phila) 2011;4:1563-71. 61. Brenner H, Haug U, Hundt S. Sex differences in performance of fecal occult blood testing. Am J Gastroenterol 2010;105:2457-64. 62. Chiu HM, Lee YC, Tu CH, et al. Association between early stage colon neoplasms and false-negative results from the fecal immunochemical test. Clin Gastroenterol Hepatol 2013;11:832-8 e1-2. 63. de Wijkerslooth TR, Stoop EM, Bossuyt PM, et al. Immunochemical fecal occult blood testing is equally sensitive for proximal and distal advanced neoplasia. Am J Gastroenterol 2012;107:1570-8. 64. Graser A, Stieber P, Nagel D, et al. Comparison of

CT colonography, colonoscopy, sigmoidoscopy and faecal occult blood tests for the detection of advanced adenoma in an average risk population. Gut 2009;58:241-8. 65. Hundt S, Haug U, Brenner H. Comparative evaluation of immunochemical fecal occult blood tests for colorectal adenoma detection. Ann Intern Med 2009; 150:162-9. 66. Morikawa T, Kato J, Yamaji Y, Wada R, Mitsushima T, Shiratori Y. A comparison of the immunochemical fecal occult blood test and total colonoscopy in the asymptomatic population. Gastroenterology 2005;129:422-8. 67. Nakazako M. YH, Matsushita H., Sato K., Fujita K., Yamanaka Y., Imai Y. Immunologic Fecal Occult Blood Test for Colorectal Cancer Screening. Japan Med Assoc J 2006;49:203-7. 68. Parra-Blanco A, Gimeno-Garcia AZ, Quintero E, et al. Diagnostic accuracy of immunochemical versus guaiac faecal occult blood tests for colorectal cancer screening. J Gastroenterol 2010;45:703-12. 69. Terhaar sive Droste JS, Oort FA, van der Hulst RW, et al. Higher fecal immunochemical test cutoff levels: lower positivity rates but still acceptable detection rates for early-stage colorectal cancers. Cancer Epidemiol Biomarkers Prev 2011; 20:272-80. 70. Viana Freitas BR, Kibune Nagasako C, Pavan CR, et al. Immunochemical fecal occult blood test for detection of advanced colonic adenomas and colorectal cancer: comparison with colonoscopy results. Gastroenterol Res Pract 2013;2013:384561. 71. Brenner H, Tao S. Superior diagnostic performance of faecal immunochemical tests for haemoglobin in a head-to-head comparison with guaiac based faecal occult blood test among 2235 participants of screening colonoscopy. Eur J Cancer 2013;49:3049-54. 72. Chen Y-Y, Chen T-H, Su M-Y, et al. Accuracy of immunochemical fecal occult blood test for detecting colorectal neoplasms in individuals undergoing health check-ups. Adv Digest Med 2014;1:74-9. 73. Hernandez V, Cubiella J, Gonzalez-Mao MC, et al. Fecal immunochemical test accuracy in average-risk colorectal cancer screening. World J Gastroenterol 2014;20: 1038-47. 74. Kato J, Morikawa T, Kuriyama M, et al. Combination of sigmoidoscopy and a fecal immunochemical test to detect proximal colon neoplasia. Clin Gastroenterol Hepatol 2009;7:1341-6. 75. Lee YH, Hur M, Kim H, et al. Optimal cut-off concentration for a faecal immunochemical test for haemoglobin by Hemo Techt NS-Plus C15 system for the colorectal cancer screening. Clin Chem Lab Med 2015;53:e69-71. 76. Levy BT, Bay C, Xu Y, et al. Test characteristics of faecal immunochemical tests (FIT) compared with optical colonoscopy. J Med Screen 2014; 21:133-43. 77. Omata F, Shintani A, Isozaki M, Masuda K, Fujita Y, Fukui T. Diagnostic performance of quantitative fecal immunochemical test and multivariate prediction model for colorectal neoplasms in asymptomatic individuals. Eur J Gastroenterol Hepatol 2011;23:1036-41. 78. Elsafi SH, Alqahtani NI, Zakary NY, Al Zahrani EM. The sensitivity, specificity, predictive values, and likelihood ratios of fecal occult blood test for the detection of colorectal cancer in hospital settings. Clin Exp Gastroenterol 2015;8:279-84. 79. Lee YC, Chiu HM, Chiang TH, et al. Accuracy of faecal occult blood test and Helicobacter pylori stool antigen test for detection of upper gastrointestinal lesions. BMJ Open 2013;3:e003989. 80. Nakajima M, Saito H, Soma Y, Sobue T, Tanaka M, Munakata A. Prevention of advanced colorectal cancer by screening using the immunochemical faecal occult blood test: a case–control study. British journal of cancer 2003;89:23-8. 81. Saito H, Soma Y, Nakajima M, et al. A case-control study evaluating occult blood screening for colorectal cancer with hemoccult test and an immunochemical hemagglutination test. Oncology reports 2000;7:815-9. 82. Saito H, Soma Y, Koeda J, et al. Reduction in risk of mortality from colorectal cancer by fecal occult blood screening with immunochemical hemagglutination test. A case-control study. International journal of cancer 1995;61:465-9. 83. Cole SR, Young GP, Esterman A, Cadd B, Morcom J. A randomised trial of the impact of new faecal haemoglobin test technologies on population participation in screening for colorectal cancer. The Medical journal of Australia 2003; 10:117-22. 84. Macrae FA, Hill DJ, St. John DJB, Ambikapathy A, Garner JF. Predicting colon cancer screening behavior from health beliefs. Prev Med 1984;13:115-26. 85. Cole SR, Young GP. Effect of dietary restriction on participation in faecal occult blood test screening for colorectal cancer. The Medical journal of Australia 2001; 175:195-8. 86. McCusker J, Morrow GR. Factors related to the use of cancer early detection techniques. Prev Med 1980;9:388-97. 87. Salkeld GP, Solomon MJ, Short L, Ward J. Measuring the importance of attributes that influence consumer attitudes to colorectal cancer screening. ANZ J Surg 2003;73:128-32. 88. Wardle J, Pope R. The psychological costs of screening for cancer. J Psychosom Res 1992;36:609-24. 89. Lindholm E, Berglund B,

Kewenter J, Haglind E. Worry associated with screening for colorectal carcinomas. Scand J Gastroenterol 1997; 32:238-45. 90. Parker MA, Robinson MH, Scholefield JH, Hardcastle JD. Psychiatric morbidity and screening for colorectal cancer. J Med Screen 2002;9:7-10. 91. Wardle J, Taylor T, Sutton S, Atkin W. Does publicity about cancer screening raise fear of cancer? Randomised trial of the psychological effect of information about cancer screening. BMJ (Clinical research ed) 1999;319:1037-8.

6.2 Evidence: Population screening for CRC

Systematic reviews and modelling were performed to address screening:

- benefit (PSC1a)
- test accuracy (PSC1b)
- cost effectiveness (PSC1c)
- age (PSC1d).

Back to top

6.2.1 Evidence: Screening benefit (PSC1a)

Contents

6.2.1.1 Evidence: screening beenfit

In persons without a colorectal cancer diagnosis or symptoms that might indicate colorectal cancer, which screening modality (immunochemical FOBT, flexible sigmoidoscopy, colonoscopy, CT colonography, faecal or blood biomarkers, or any combinations) compared with no screening, reduce colorectal cancer mortality, or the incidence of metastases at diagnosis? (PICO question PSC1a) A systematic review was performed to update the 2005 Australian Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer.7 We chose to adapt two guidelines, the European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis and the Ontario guidelines assessing the Fecal Occult Blood Test for Colorectal Cancer

Screening40,41, which represent the literature covering this PICO question from 2004 to 2010, and update these guidelines up to 31 August 2016. The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical Report. While this systematic review was in preparation, the US Preventive Services Task Force (PSTF) published the 2016 update42 of the 2008 USPSTF Colorectal Cancer Screening guideline43. The literature described in the 2016 edition42 is also covered in this review. At the time of publication of the Australian Guidelines7, the only high level evidence was from 3 RCTs.25-28,44,45 All 3 RCTs used Hemoccult, a guaiac faecal occult blood test. These trials collectively reported that screening for faecal occult blood reduced overall mortality from colorectal cancer on the basis of intention-to-screen by 15–33%. These findings are further supported by a 2012 update from the Nottingham study46 which, after a median of 19.5 years follow-up, reported a colorectal cancer-specific mortality reduction of 13%. To date, only one published RCT47 compares iFOBT to no screening in a population based setting. In this study, 94,423 individuals were offered once-only iFOBT screening and follow-up was 8 years. In this update review, five level II studies reported randomised controlled trials comparing asymptomatic population receiving flexible sigmoidoscopy with no screening (no contact). No other asymptomatic population RCTs were found comparing any other screening methodology to no screening. Our review also included a pooled meta-analysis from the UKFSS, NORCCAP, SCORE and PLCO trials.(ref# Shroff 2014) This meta-analysis was at low risk of bias, and reported colorectal cancer-specific mortality, with subgroup analysis for distal and proximal disease. Overall mortality None of the screening RCTs25-27,32,34,47-49, whether based on screening by FOBT or flexible sigmoidoscopy, had the statistical power to show any significant difference in overall mortality. Colorectal cancer-specific mortality As reported in the 2005 Colorectal Cancer guidelines4,7, three level II RCTs reported colorectal cancer-specific mortality in gFOBT screening trials.25-27 These trials collectively reported that screening for faecal occult blood reduced overall mortality from colorectal cancer on the basis of intention-to-screen by 15–33%. The 2012 update from the Nottingham trial46 reported a colorectal cancer-specific mortality reduction of 13%. The Zheng 200347 trial reported a statistically significant 32% reduction in rectal cancer mortality (poisson test U=2.5, p<0.05, log-rank test p=0.003), but no reduction in colonic (log-rank test, P=0.222) or overall colorectal cancer-specific mortality. In this update review, the UKFSS35, Blom 200848, and PLCO34 trials all reported a statistically significant reduction in colorectal cancer specific mortality in the screened group compared to no screening. The relative reduction in colorectal cancer specific mortality varied from HR=0.5735 to RR=0.7434. In the final NORCCAP trial report49, intention-to-treat analysis showed a significant reduction in colorectal cancer-specific mortality (HR=0.73, p=0.02) in the screened group. The NORCCAP trial is unique among these RCTs as 50% of those screened had an iFOBT in addition to flexible sigmoidoscope. 49 In sub-analysis of the screening modality, the overall reduction in colorectal cancer-specific mortality was only statistically significant for those who had flexible sigmoidoscopy and iFOBT (HR=0.62, p=0.01) and not for flexible sigmoidoscopy alone (HR=0.84, p=0.30). In a meta-analysis by Shroff 201450, the pooled data from the UKFSS35, NORCCAP51, SCORE32, and PLCO34 trials showed a statistically significant (95% CI = 0.65-0.80) 28% relative risk reduction (RR = 0.72) in colorectal cancer-specific mortality for the flexible sigmoidoscopy screened group, compared to the non-screening group in a population of 337,905 participants with an average weighted median follow-up period of 10.8 years. All populations included in this update systematic review32,34,35,47-51, were asymptomatic and from Western countries (UK, Sweden, Norway, USA, Italy), except the Zheng 2003 study, which was on a Chinese population47. The early gFOBT screening trials28,44,45 included participants from USA, UK, and Denmark. In three sigmoidoscopy trials32,34,35, those involved were volunteers who expressed willingness to accept flexible sigmoidoscopy if randomised to the screening arm. Because of this, the reported participation rates may over-estimate rates achievable in the general population. Application of the evidence on screening benefit To date, the only RCT level evidence comparing screening with an unscreened control group comes from 3 large gFOBT trials25-27 first reported in the 1990s, one iFOBT trial47, and the recent flexible sigmoidoscopy trials32,34,35,48-51. Currently, many countries around

the world, including Australia, New Zealand, Canada, and a number of European countries have established national population based bowel cancer screening programs which utilise either gFOBT or iFOBT for screening. The use of FOBT is the preferred screening modality in those countries, based on the available evidence and their own screening experience. An advantage of FOBT is that the test kit can be posted in the mail to the participant, with collection of tiny samples at home and return of these samples by mail. As reported in the 2010 European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis40, iFOBTs have the added advantage that they specifically detect human globin, and there is no need to change diet or medication prior to testing. The analysis of many iFOBTs is automated and a number of them allow quantitative analysis of haemoglobin. In contrast, flexible sigmoidoscopy is an invasive procedure, requiring a highly trained workforce and special facilities. There are particular concerns about its acceptability and feasibility in the Australian setting as well as its cost-effectiveness.

6.2.1.2 See the Evidence summary and recommendations section for guidance resulting from this systematic review.

6.2.1.3 References

1. Wilson J, Junger G. Principles and practices of screening for disease. Geneva, Switzerland1968. Report No.: 34,1968. 2. Gnauck R. World Health Organization criteria for screening. In Colorectal Cancer: Prevention, Epidemiology and Screening. New York: Raven Press; 1980. 3. Schottenfeld D. Fundamental issues in cancer screening. In Colorectal Cancer: Prevention, Epidemiology and Screening. New York: Raven Press; 1980. 4. The Cancer Council Australia, Australian Cancer Network. Chapter 3, Population screening for colorectal cancer, 2005 CCA Guidelines The Prevention, early detection and management of colorectal cancer2005. 5. GP Y. Screening for colorectal cancer – new evidence in the last 10 years. Cancer Forum; 2014. p. 38. 6. Young GP, Symonds EL, Allison JE, et al. Advances in Fecal Occult Blood Tests: the FIT revolution. Digestive diseases and sciences 2015;60:609-22. 7. Cancer Council Australia. Clinical practice guidelines for the prevention, early detection and management of colorectal cancer (CRC) 2nd edition2005. Report No.: ISBN: 0-9775060-1-0. 8. Miles A, Cockburn J, Smith RA, Wardle J. A perspective from countries using organized screening programs. Cancer 2004;101:1201-13. 9. International Agency for Research on Cancer. Chapter 2, European guidelines for quality assurance in colorectal cancer screening and diagnosis, First Edition: International Agency for Research on Cancer; 2010. 10. Benson VS, Atkin WS, Green J, et al. Toward standardizing and reporting colorectal cancer screening indicators on an international level: The International Colorectal Cancer Screening Network. International journal of cancer 2012;130:2961-73. 11. Brawley OW. Colorectal cancer control: providing adequate care to those who need it. Journal of the National Cancer Institute 2014;106:dju075. 12. Flitcroft KL, St John DJ, Howard K, et al. A comparative case study of bowel cancer screening in the UK and Australia: evidence lost in translation? J Med Screen 2011;18:193-203. 13. Schreuders EH, Ruco A, Rabeneck L, et al. Colorectal cancer screening: a global overview of existing programmes. Gut 2015;64:1637-49. 14. Australian Health Technology Advisory Committee. Colorectal Cancer Screening1997. Report No.: ISBN 0 642 27289 1 15. Australian Government Department of Health. The Australian bowel cancer screening pilot program and beyond: final evaluation report2005. 16. Australian Institute of Health and Welfare. National Bowel Cancer Screening Program Monitoring Report 2016. Canberra: AIHW; 2016. Report No.: Cat. No CAN 97. 17. Cole SR, Tucker GR, Osborne JM, et al. Shift to earlier stage at diagnosis as a consequence of the National Bowel Cancer Screening Program. The Medical journal of Australia 2013;198:327-30. 18. Ananda S, Wong H, Faragher I, et al. Survival

impact of the Australian National Bowel Cancer Screening Programme. Internal medicine journal 2016;46:166-71. 19. Australian Institute of Health and Welfare, Australian Government Department of Health. Analysis of colorectal cancer outcomes for the Australian National Bowel Cancer Screening Program. Asia-Pacific journal of clinical oncology 2016;12:22-32. 20. Pignone MP, Flitcroft KL, Howard K, Trevena LJ, Salkeld GP, St John D. Costs and cost-effectiveness of full implementation of a biennial faecal occult blood test screening program for bowel cancer in Australia. The Medical journal of Australia 2011;194:180-5. 21. Cenin DR, St John DJ, Ledger MJ, Slevin T, Lansdorp-Vogelaar I. Optimising the expansion of the National Bowel Cancer Screening Program. The Medical journal of Australia 2014;201:456-61. 22. St John J, Grogan P. Compelling new data on the effectiveness of Australia's National Bowel Cancer Screening Program: A model for best practice? Asia-Pacific journal of clinical oncology 2016;12:7-9. 23. van Rossum LG, van Rijn AF, Laheij RJ, et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. Gastroenterology 2008; 135:82-90. 24. Park DI, Ryu S, Kim YH, et al. Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average risk undergoing colorectal cancer screening. Am J Gastroenterol 2010;105:2017-25. 25. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. N Engl J Med 1993;328:1365-71. 26. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet (London, England) 1996;348:1472-7. 27. Kronborg O, Fenger C, Olsen J, Jørgensen OD, Søndergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet (London, England) 1996;348:1467-71. 28. Mandel JS, Church TR, Ederer F, Bond JH. Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood. Journal of the National Cancer Institute 1999;91:434-7. 29. Mandel JS, Church TR, Bond JH, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. N Engl J Med 2000;343:1603-7. 30. Hewitson P, Glasziou P, Irwig L, Towler B, Watson E. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. The Cochrane database of systematic reviews 2007:Cd001216. 31. Towler B, Irwig L, Glasziou P, Kewenter J, Weller D, Silagy C. A systematic review of the effects of screening for colorectal cancer using the faecal occult blood test, hemoccult. BMJ (Clinical research ed) 1998;317:559-65. 32. Segnan N, Armaroli P, Bonelli L, et al. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial--SCORE. Journal of the National Cancer Institute 2011;103: 1310-22. 33. Elmunzer BJ, Hayward RA, Schoenfeld PS, Saini SD, Deshpande A, Waljee AK. Effect of flexible sigmoidoscopy-based screening on incidence and mortality of colorectal cancer: a systematic review and meta-analysis of randomized controlled trials. PLoS Med 2012;9:e1001352. 34. Schoen RE, Pinsky PF, Weissfeld JL, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med 2012;366: 2345-57. 35. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet (London, England) 2010;375:1624-33. 36. Quintero E, Castells A, Bujanda L, et al. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. N Engl J Med 2012;366:697-706. 37. Bretthauer M, Kaminski MF, Løberg M, et al. Population-Based Colonoscopy Screening for Colorectal Cancer: A Randomized Clinical Trial. JAMA Intern Med 2016. 38. ClinicalTrials.gov. Colonoscopy vs fecal immunochemical test in reducing mortality from colorectal cancer (CONFIRM) [NCT01239082] 2016. 39. Knudsen AB, Zauber AG, Rutter CM, et al. Estimation of Benefits, Burden, and Harms of Colorectal Cancer Screening Strategies: Modeling Study for the US Preventive Services Task Force. JAMA 2016;315:2595-609. 40. International Agency for Research on Cancer. European guidelines for quality assurance in colorectal cancer screening and diagnosis, First Edition: International Agency for Research on Cancer; 2010. 41. Secretariat MA. Fecal Occult Blood Test for Colorectal Cancer Screening: an evidence-based analysis. Toronto, Ontario, Canada: Ministry of Health and Long-Term Care; 2009. 42. Force UPST. Screening for Colorectal Cancer US Preventive Services Task Force Recommendation Statement. JAMA 2016;315: 2564-75. 43. Force USPST. Screening for Colorectal Cancer: U.S. Preventive Services Task Force Recommendation Statement. Annals of Internal Medicine 2008;149:627-37. 44. Jørgensen O, Kronborg O,

Fenger C. A randomised study on screening for colorectal cancer using faecal occult blood testing: results after 13 years and seven biennial screening rounds. Gut 2002;50:29-39. 45. Scholefield J, Moss S, Sufi F, Mangham C, Hardcastle J. Effect of faecal occult blood screening on mortality from colorectal cancer: results from a randomised controlled trial. Gut 2002;50:840-4. 46. Scholefield JH, Moss SM, Mangham CM, Whynes DK, Hardcastle JD. Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up. Gut 2012;61:1036-40. 47. Zheng S, Chen K, Liu X, et al. Cluster Randomization Trial of Sequence Mass Screening for Colorectal Cancer. Dis Colon Rectum 2003;46:51-8. 48. Blom J, Yin L, Liden A, et al. A 9-year follow-up study of participants and nonparticipants in sigmoidoscopy screening: importance of self-selection. Cancer Epidemiol Biomarkers Prev 2008;17:1163-8. 49. Holme O, Loberg M, Kalager M, et al. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. JAMA 2014;312:606-15. 50. Shroff J, Thosani N, Batra S, Singh H, Guha S. Reduced incidence and mortality from colorectal cancer with flexible-sigmoidoscopy screening: a meta-analysis. World J Gastroenterol 2014;20:18466-76. 51. Hoff G, Grotmol T, Skovlund E, Bretthauer M, Norwegian Colorectal Cancer Prevention Study G. Risk of colorectal cancer seven years after flexible sigmoidoscopy screening: randomised controlled trial. BMJ (Clinical research ed) 2009;338: b1846. 52. Castro I, Cubiella J, Rivera C, et al. Fecal immunochemical test accuracy in familial risk colorectal cancer screening. International journal of cancer 2014;134:367-75. 53. Gimeno-Garcia AZ, Quintero E, Nicolas-Perez D, Hernandez-Guerra M, Parra-Blanco A, Jimenez-Sosa A. Screening for familial colorectal cancer with a sensitive immunochemical fecal occult blood test: a pilot study. Eur J Gastroenterol Hepatol 2009;21:1062-7. 54. Ng SC, Ching JY, Chan V, et al. Diagnostic accuracy of faecal immunochemical test for screening individuals with a family history of colorectal cancer. Aliment Pharmacol Ther 2013;38:835-41. 55. Ahlquist DA, Sargent DJ, Loprinzi CL, et al. Stool DNA and occult blood testing for screen detection of colorectal neoplasia. Ann Intern Med 2008;149:441-50, W81. 56. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med 2014;370:1287-97. 57. Redwood DG, Asay ED, Blake ID, et al. Stool DNA Testing for Screening Detection of Colorectal Neoplasia in Alaska Native People. Mayo Clin Proc 2016;91:61-70. 58. Annahazi A, Abraham S, Farkas K, et al. A pilot study on faecal MMP-9: a new noninvasive diagnostic marker of colorectal cancer. British journal of cancer 2016;114:787-92. 59. Church TR, Wandell M, Lofton-Day C, et al. Prospective evaluation of methylated SEPT9 in plasma for detection of asymptomatic colorectal cancer. Gut 2014;63:317-25. 60. Khalid-de Bakker CA, Jonkers DM, Sanduleanu S, et al. Test performance of immunologic fecal occult blood testing and sigmoidoscopy compared with primary colonoscopy screening for colorectal advanced adenomas. Cancer Prev Res (Phila) 2011;4:1563-71. 61. Brenner H, Haug U, Hundt S. Sex differences in performance of fecal occult blood testing. Am J Gastroenterol 2010;105:2457-64. 62. Chiu HM, Lee YC, Tu CH, et al. Association between early stage colon neoplasms and false-negative results from the fecal immunochemical test. Clin Gastroenterol Hepatol 2013;11:832-8 e1-2. 63. de Wijkerslooth TR, Stoop EM, Bossuyt PM, et al. Immunochemical fecal occult blood testing is equally sensitive for proximal and distal advanced neoplasia. Am J Gastroenterol 2012;107:1570-8. 64. Graser A, Stieber P, Nagel D, et al. Comparison of CT colonography, colonoscopy, sigmoidoscopy and faecal occult blood tests for the detection of advanced adenoma in an average risk population. Gut 2009;58:241-8. 65. Hundt S, Haug U, Brenner H. Comparative evaluation of immunochemical fecal occult blood tests for colorectal adenoma detection. Ann Intern Med 2009; 150:162-9. 66. Morikawa T, Kato J, Yamaji Y, Wada R, Mitsushima T, Shiratori Y. A comparison of the immunochemical fecal occult blood test and total colonoscopy in the asymptomatic population. Gastroenterology 2005;129:422-8. 67. Nakazako M. YH, Matsushita H., Sato K., Fujita K., Yamanaka Y., Imai Y. Immunologic Fecal Occult Blood Test for Colorectal Cancer Screening. Japan Med Assoc J 2006;49:203-7. 68. Parra-Blanco A, Gimeno-Garcia AZ, Quintero E, et al. Diagnostic accuracy of immunochemical versus guaiac faecal occult blood tests for colorectal cancer screening. J Gastroenterol 2010;45:703-12. 69. Terhaar sive Droste JS, Oort FA, van der Hulst RW, et al. Higher fecal immunochemical test cutoff levels: lower positivity rates but still acceptable detection rates for early-stage colorectal cancers. Cancer Epidemiol Biomarkers Prev 2011;

20:272-80. 70. Viana Freitas BR, Kibune Nagasako C, Pavan CR, et al. Immunochemical fecal occult blood test for detection of advanced colonic adenomas and colorectal cancer: comparison with colonoscopy results. Gastroenterol Res Pract 2013;2013:384561. 71. Brenner H, Tao S. Superior diagnostic performance of faecal immunochemical tests for haemoglobin in a head-to-head comparison with guaiac based faecal occult blood test among 2235 participants of screening colonoscopy. Eur J Cancer 2013;49:3049-54. 72. Chen Y-Y, Chen T-H, Su M-Y, et al. Accuracy of immunochemical fecal occult blood test for detecting colorectal neoplasms in individuals undergoing health check-ups. Adv Digest Med 2014;1:74-9. 73. Hernandez V, Cubiella J, Gonzalez-Mao MC, et al. Fecal immunochemical test accuracy in average-risk colorectal cancer screening. World J Gastroenterol 2014;20: 1038-47. 74. Kato J, Morikawa T, Kuriyama M, et al. Combination of sigmoidoscopy and a fecal immunochemical test to detect proximal colon neoplasia. Clin Gastroenterol Hepatol 2009;7:1341-6. 75. Lee YH, Hur M, Kim H, et al. Optimal cut-off concentration for a faecal immunochemical test for haemoglobin by Hemo Techt NS-Plus C15 system for the colorectal cancer screening. Clin Chem Lab Med 2015;53:e69-71. 76. Levy BT, Bay C, Xu Y, et al. Test characteristics of faecal immunochemical tests (FIT) compared with optical colonoscopy. J Med Screen 2014; 21:133-43. 77. Omata F, Shintani A, Isozaki M, Masuda K, Fujita Y, Fukui T. Diagnostic performance of quantitative fecal immunochemical test and multivariate prediction model for colorectal neoplasms in asymptomatic individuals. Eur J Gastroenterol Hepatol 2011;23:1036-41. 78. Elsafi SH, Alqahtani NI, Zakary NY, Al Zahrani EM. The sensitivity, specificity, predictive values, and likelihood ratios of fecal occult blood test for the detection of colorectal cancer in hospital settings. Clin Exp Gastroenterol 2015;8:279-84. 79. Lee YC, Chiu HM, Chiang TH, et al. Accuracy of faecal occult blood test and Helicobacter pylori stool antigen test for detection of upper gastrointestinal lesions. BMJ Open 2013;3:e003989. 80. Nakajima M, Saito H, Soma Y, Sobue T, Tanaka M, Munakata A. Prevention of advanced colorectal cancer by screening using the immunochemical faecal occult blood test: a case–control study. British journal of cancer 2003;89:23-8. 81. Saito H, Soma Y, Nakajima M, et al. A case-control study evaluating occult blood screening for colorectal cancer with hemoccult test and an immunochemical hemagglutination test. Oncology reports 2000;7:815-9. 82. Saito H, Soma Y, Koeda J, et al. Reduction in risk of mortality from colorectal cancer by fecal occult blood screening with immunochemical hemagglutination test. A case-control study. International journal of cancer 1995;61:465-9. 83. Cole SR, Young GP, Esterman A, Cadd B, Morcom J. A randomised trial of the impact of new faecal haemoglobin test technologies on population participation in screening for colorectal cancer. The Medical journal of Australia 2003; 10:117-22. 84. Macrae FA, Hill DJ, St. John DJB, Ambikapathy A, Garner JF. Predicting colon cancer screening behavior from health beliefs. Prev Med 1984;13:115-26. 85. Cole SR, Young GP. Effect of dietary restriction on participation in faecal occult blood test screening for colorectal cancer. The Medical journal of Australia 2001; 175:195-8. 86. McCusker J, Morrow GR. Factors related to the use of cancer early detection techniques. Prev Med 1980;9:388-97. 87. Salkeld GP, Solomon MJ, Short L, Ward J. Measuring the importance of attributes that influence consumer attitudes to colorectal cancer screening. ANZ J Surg 2003;73:128-32. 88. Wardle J, Pope R. The psychological costs of screening for cancer. J Psychosom Res 1992;36:609-24. 89. Lindholm E, Berglund B, Kewenter J, Haglind E. Worry associated with screening for colorectal carcinomas. Scand J Gastroenterol 1997; 32:238-45. 90. Parker MA, Robinson MH, Scholefield JH, Hardcastle JD. Psychiatric morbidity and screening for colorectal cancer. J Med Screen 2002;9:7-10. 91. Wardle J, Taylor T, Sutton S, Atkin W. Does publicity about cancer screening raise fear of cancer? Randomised trial of the psychological effect of information about cancer screening. BMJ (Clinical research ed) 1999;319:1037-8.

Back to top

6.2.1.4 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search

View PICO	NHMRC Evidence statement form PSC1a	Systematic review report PSC1a	Modelling report PSC1c	Modelling report PSC1d

Back to top

6.2.2 Evidence: Screening test accuracy (PSC1b)

Contents

6.2.2.1 Evidence: Screening test accuracy

For persons without a colorectal cancer diagnosis or symptoms that might indicate colorectal cancer, which screening modality (immunochemical FOBT, flexible sigmoidoscopy, colonoscopy, faecal or blood biomarkers, or any combinations) performs best in detecting colorectal cancer, and does the diagnostic performance change with family history, age, or gender? (PICO PSC1b) A systematic review was performed to update the 2005 Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer7. We chose to adapt the European and Ontario guidelines40,41, which represent the literature covering this PICO question from 2004 to 2010, and update these guidelines up to 31st August 2016. The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report. While this systematic review was in preparation, the US Preventive Services Task Force (PSTF) published the 2016 update42 of the 2008 USPSTF Colorectal Cancer Screening guideline43. The literature described in the 2016 edition42 is also covered in this review. This update systematic review includes 29 diagnosis accuracy studies reporting the performance of colorectal cancer screening modalities, including iFOBT, faecal or serum biomarkers for the detection of colorectal cancer and/or advanced adenoma. All studies used colonoscopy as the reference standard and all

participants underwent colonoscopy. Three studies52-54 (1,333 participants in total) reported the performance of iFOBT at detecting colorectal cancer and/or advanced adenoma in an above average risk population with known family history of colorectal cancer. The majority of studies (26 in total) used immunochemical based-FOB tests (iFOBT) of various brands. Very few studies report blood/serum or faecal biomarkers. Only 3 studies55-57 reported the performance of multi-target stool DNA tests. One study58 reported the diagnostic performance of faecal MMP-9 protein, and another59 reported the diagnostic performance of plasma methylated SEPT9 DNA. Several studies reported the diagnostic performance of iFOBT59,60 or SEPT9 protein59 depending on participant age, and a few studies reported the diagnostic performance for iFOBT60,61 or SEPT9 protein59 by gender. Immunochemical Faecal Occult Blood test (iFOBT) The diagnostic performance for detection of colorectal cancer using iFOBT was reported across 20 studies, most of which used an Eiken branded test kit. All studies consistently reported a sensitivity of greater than 50%, with most studies reported sensitivities in the 60-85% range. Specificity was consistently high across all 20 studies and ranged from 85-100%. The positive predictive value ranged from 1-25%, with the majority of studies reporting single digit values. Negative predictive value was consistently above 99% for most studies. The diagnostic performance for detection of advanced adenomas using iFOBT was reported in 13 studies24,56,57,60,62-70 and many different brands. Sensitivities reported were lower than for colorectal cancer, the majority of studies reporting 20-40% sensitivity. Specificity was consistently high and most studies reported >85%. Most studies reported a positive predictive value ranging from 20-40%. Negative predictive value was consistently >90%. The diagnostic performance for detection of colorectal cancer and/or advanced adenomas was reported in 10 studies.52,54,61,71-77 Sensitivities reported ranged from 5-75%, but was consistently reported from 40-60%. Specificity was >80% in most studies, and positive predictive value was <30% in most studies. Negative predictive value was >90% for all studies. Only three studies52-54 reported the diagnostic performance of iFOBT in an above average risk populations with known family history of colorectal cancer, for the detection of colorectal cancer and/or advanced adenoma. No studies reported the use of biomarker assays in this above average risk population. Faecal biomarker (DNA) One study reported the diagnostic performance of 2 stool DNA tests55 for the detection of colorectal cancer. In addition, Imperiale et al 201456 and Redwood et al 201657 reported different multitarget stool-DNA assays to detect colorectal cancer. Both multi-target stool DNA tests outperformed other stool DNA tests, the former reporting sensitivities above 90%, and the later ranging from 25-58%. Specificities were above 84% for all tests reported. Two studies reported the diagnostic performance of stool DNA tests55,57 at detecting advanced adenomas. Reported sensitivities ranged from 17-46% and specificities 84-96%. In a study by Imperiale et al 201456, the diagnostic performance for detection of colorectal cancer and/or advanced adenomas using a multitarget stool DNA assay was reported. Sensitivity, and specificity were 42.4% and 86.6% respectively.56 No studies reported the use of faecal biomarker assays in an above average risk population. Blood biomarkers A single study59 reported the diagnostic performance of a plasma methylated SEPT9 DNA assay for the detection of colorectal cancer or advanced adenomas. Sensitivities ranged from 48%-56% and specificity ranged from 89% to 92% depending on age (<65 vs ≥65 years) or gender analysis for detection of colorectal cancer. Sensitivities ranged from 4.6%-13% and specificity ranged from 88.6%-92.6% depending on age (<65 vs ≥65 years) or gender analysis for detection of advanced adenomas. No studies specifically reported the diagnostic performance of blood biomarker assays for advance neoplasms (i.e. the combination of cancer and advanced adenomas) or in participants with above average risk of colorectal cancer.

6.2.2.2 See the Evidence summary and recommendations section for guidance resulting from this systematic review.

6.2.2.3 References

1. Wilson J, Junger G. Principles and practices of screening for disease. Geneva, Switzerland1968. Report No.: 34,1968. 2. Gnauck R. World Health Organization criteria for screening. In Colorectal Cancer: Prevention, Epidemiology and Screening. New York: Raven Press; 1980. 3. Schottenfeld D. Fundamental issues in cancer screening. In Colorectal Cancer: Prevention, Epidemiology and Screening. New York: Raven Press; 1980. 4. The Cancer Council Australia, Australian Cancer Network. Chapter 3, Population screening for colorectal cancer, 2005 CCA Guidelines The Prevention, early detection and management of colorectal cancer2005. 5. GP Y. Screening for colorectal cancer – new evidence in the last 10 years. Cancer Forum; 2014. p. 38. 6. Young GP, Symonds EL, Allison JE, et al. Advances in Fecal Occult Blood Tests: the FIT revolution. Digestive diseases and sciences 2015;60:609-22. 7. Cancer Council Australia. Clinical practice guidelines for the prevention, early detection and management of colorectal cancer (CRC) 2nd edition2005. Report No.: ISBN: 0-9775060-1-0. 8. Miles A, Cockburn J, Smith RA, Wardle J. A perspective from countries using organized screening programs. Cancer 2004;101:1201-13. 9. International Agency for Research on Cancer. Chapter 2, European guidelines for quality assurance in colorectal cancer screening and diagnosis, First Edition: International Agency for Research on Cancer; 2010. 10. Benson VS, Atkin WS, Green J, et al. Toward standardizing and reporting colorectal cancer screening indicators on an international level: The International Colorectal Cancer Screening Network. International journal of cancer 2012;130:2961-73. 11. Brawley OW. Colorectal cancer control: providing adequate care to those who need it. Journal of the National Cancer Institute 2014;106:dju075. 12. Flitcroft KL, St John DJ, Howard K, et al. A comparative case study of bowel cancer screening in the UK and Australia: evidence lost in translation? J Med Screen 2011;18:193-203. 13. Schreuders EH, Ruco A, Rabeneck L, et al. Colorectal cancer screening: a global overview of existing programmes. Gut 2015;64:1637-49. 14. Australian Health Technology Advisory Committee. Colorectal Cancer Screening1997. Report No.: ISBN 0 642 27289 1 15. Australian Government Department of Health. The Australian bowel cancer screening pilot program and beyond: final evaluation report2005. 16. Australian Institute of Health and Welfare. National Bowel Cancer Screening Program Monitoring Report 2016. Canberra: AIHW; 2016. Report No.: Cat. No CAN 97. 17. Cole SR, Tucker GR, Osborne JM, et al. Shift to earlier stage at diagnosis as a consequence of the National Bowel Cancer Screening Program. The Medical journal of Australia 2013;198:327-30. 18. Ananda S, Wong H, Faragher I, et al. Survival impact of the Australian National Bowel Cancer Screening Programme. Internal medicine journal 2016;46:166-71. 19. Australian Institute of Health and Welfare, Australian Government Department of Health. Analysis of colorectal cancer outcomes for the Australian National Bowel Cancer Screening Program. Asia-Pacific journal of clinical oncology 2016;12:22-32. 20. Pignone MP, Flitcroft KL, Howard K, Trevena LJ, Salkeld GP, St John D. Costs and cost-effectiveness of full implementation of a biennial faecal occult blood test screening program for bowel cancer in Australia. The Medical journal of Australia 2011;194:180-5. 21. Cenin DR, St John DJ, Ledger MJ, Slevin T, Lansdorp-Vogelaar I. Optimising the expansion of the National Bowel Cancer Screening Program. The Medical journal of Australia 2014;201:456-61. 22. St John J, Grogan P. Compelling new data on the effectiveness of Australia's National Bowel Cancer Screening Program: A model for best practice? Asia-Pacific journal of clinical oncology 2016;12:7-9. 23. van Rossum LG, van Rijn AF, Laheij RJ, et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. Gastroenterology 2008; 135:82-90. 24. Park DI, Ryu S, Kim YH, et al. Comparison of guaiac-based and quantitative immunochemical

fecal occult blood testing in a population at average risk undergoing colorectal cancer screening. Am J Gastroenterol 2010;105:2017-25. 25. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. N Engl J Med 1993;328:1365-71. 26. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet (London, England) 1996;348:1472-7. 27. Kronborg O, Fenger C, Olsen J, Jørgensen OD, Søndergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet (London, England) 1996;348:1467-71. 28. Mandel JS, Church TR, Ederer F, Bond JH. Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood. Journal of the National Cancer Institute 1999;91:434-7. 29. Mandel JS, Church TR, Bond JH, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. N Engl J Med 2000;343:1603-7. 30. Hewitson P, Glasziou P, Irwig L, Towler B, Watson E. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. The Cochrane database of systematic reviews 2007:Cd001216. 31. Towler B, Irwig L, Glasziou P, Kewenter J, Weller D, Silagy C. A systematic review of the effects of screening for colorectal cancer using the faecal occult blood test, hemoccult. BMJ (Clinical research ed) 1998;317:559-65. 32. Segnan N, Armaroli P, Bonelli L, et al. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial--SCORE. Journal of the National Cancer Institute 2011;103: 1310-22. 33. Elmunzer BJ, Hayward RA, Schoenfeld PS, Saini SD, Deshpande A, Waljee AK. Effect of flexible sigmoidoscopy-based screening on incidence and mortality of colorectal cancer: a systematic review and meta-analysis of randomized controlled trials. PLoS Med 2012;9:e1001352. 34. Schoen RE, Pinsky PF, Weissfeld JL, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med 2012;366: 2345-57. 35. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet (London, England) 2010;375:1624-33. 36. Quintero E, Castells A, Bujanda L, et al. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. N Engl J Med 2012;366:697-706. 37. Bretthauer M, Kaminski MF, Løberg M, et al. Population-Based Colonoscopy Screening for Colorectal Cancer: A Randomized Clinical Trial. JAMA Intern Med 2016. 38. ClinicalTrials.gov. Colonoscopy vs fecal immunochemical test in reducing mortality from colorectal cancer (CONFIRM) [NCT01239082] 2016. 39. Knudsen AB, Zauber AG, Rutter CM, et al. Estimation of Benefits, Burden, and Harms of Colorectal Cancer Screening Strategies: Modeling Study for the US Preventive Services Task Force. JAMA 2016;315:2595-609. 40. International Agency for Research on Cancer. European guidelines for quality assurance in colorectal cancer screening and diagnosis, First Edition: International Agency for Research on Cancer; 2010. 41. Secretariat MA. Fecal Occult Blood Test for Colorectal Cancer Screening: an evidence-based analysis. Toronto, Ontario, Canada: Ministry of Health and Long-Term Care; 2009. 42. Force UPST. Screening for Colorectal Cancer US Preventive Services Task Force Recommendation Statement. JAMA 2016;315: 2564-75. 43. Force USPST. Screening for Colorectal Cancer: U.S. Preventive Services Task Force Recommendation Statement. Annals of Internal Medicine 2008;149:627-37. 44. Jørgensen O, Kronborg O, Fenger C. A randomised study on screening for colorectal cancer using faecal occult blood testing: results after 13 years and seven biennial screening rounds. Gut 2002;50:29-39. 45. Scholefield J, Moss S, Sufi F, Mangham C, Hardcastle J. Effect of faecal occult blood screening on mortality from colorectal cancer: results from a randomised controlled trial. Gut 2002;50:840-4. 46. Scholefield JH, Moss SM, Mangham CM, Whynes DK, Hardcastle JD. Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up. Gut 2012;61:1036-40. 47. Zheng S, Chen K, Liu X, et al. Cluster Randomization Trial of Sequence Mass Screening for Colorectal Cancer. Dis Colon Rectum 2003;46:51-8. 48. Blom J, Yin L, Liden A, et al. A 9-year follow-up study of participants and nonparticipants in sigmoidoscopy screening: importance of self-selection. Cancer Epidemiol Biomarkers Prev 2008;17:1163-8. 49. Holme O, Loberg M, Kalager M, et al. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. JAMA 2014;312:606-15. 50. Shroff J, Thosani N, Batra S, Singh H, Guha S. Reduced incidence and mortality from colorectal cancer with flexible-sigmoidoscopy screening: a meta-analysis. World J Gastroenterol 2014;20:18466-76. 51. Hoff G, Grotmol

T, Skovlund E, Bretthauer M, Norwegian Colorectal Cancer Prevention Study G. Risk of colorectal cancer seven years after flexible sigmoidoscopy screening: randomised controlled trial. BMJ (Clinical research ed) 2009;338: b1846. 52. Castro I, Cubiella J, Rivera C, et al. Fecal immunochemical test accuracy in familial risk colorectal cancer screening. International journal of cancer 2014;134:367-75. 53. Gimeno-Garcia AZ, Quintero E, Nicolas-Perez D, Hernandez-Guerra M, Parra-Blanco A, Jimenez-Sosa A. Screening for familial colorectal cancer with a sensitive immunochemical fecal occult blood test: a pilot study. Eur J Gastroenterol Hepatol 2009;21:1062-7. 54. Ng SC, Ching JY, Chan V, et al. Diagnostic accuracy of faecal immunochemical test for screening individuals with a family history of colorectal cancer. Aliment Pharmacol Ther 2013;38:835-41. 55. Ahlquist DA, Sargent DJ, Loprinzi CL, et al. Stool DNA and occult blood testing for screen detection of colorectal neoplasia. Ann Intern Med 2008;149:441-50, W81. 56. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med 2014;370:1287-97. 57. Redwood DG, Asay ED, Blake ID, et al. Stool DNA Testing for Screening Detection of Colorectal Neoplasia in Alaska Native People. Mayo Clin Proc 2016;91:61-70. 58. Annahazi A, Abraham S, Farkas K, et al. A pilot study on faecal MMP-9: a new noninvasive diagnostic marker of colorectal cancer. British journal of cancer 2016;114:787-92. 59. Church TR, Wandell M, Lofton-Day C, et al. Prospective evaluation of methylated SEPT9 in plasma for detection of asymptomatic colorectal cancer. Gut 2014;63:317-25. 60. Khalid-de Bakker CA, Jonkers DM, Sanduleanu S, et al. Test performance of immunologic fecal occult blood testing and sigmoidoscopy compared with primary colonoscopy screening for colorectal advanced adenomas. Cancer Prev Res (Phila) 2011;4:1563-71. 61. Brenner H, Haug U, Hundt S. Sex differences in performance of fecal occult blood testing. Am J Gastroenterol 2010;105:2457-64. 62. Chiu HM, Lee YC, Tu CH, et al. Association between early stage colon neoplasms and false-negative results from the fecal immunochemical test. Clin Gastroenterol Hepatol 2013;11:832-8 e1-2. 63. de Wijkerslooth TR, Stoop EM, Bossuyt PM, et al. Immunochemical fecal occult blood testing is equally sensitive for proximal and distal advanced neoplasia. Am J Gastroenterol 2012;107:1570-8. 64. Graser A, Stieber P, Nagel D, et al. Comparison of CT colonography, colonoscopy, sigmoidoscopy and faecal occult blood tests for the detection of advanced adenoma in an average risk population. Gut 2009;58:241-8. 65. Hundt S, Haug U, Brenner H. Comparative evaluation of immunochemical fecal occult blood tests for colorectal adenoma detection. Ann Intern Med 2009; 150:162-9. 66. Morikawa T, Kato J, Yamaji Y, Wada R, Mitsushima T, Shiratori Y. A comparison of the immunochemical fecal occult blood test and total colonoscopy in the asymptomatic population. Gastroenterology 2005;129:422-8. 67. Nakazako M. YH, Matsushita H., Sato K., Fujita K., Yamanaka Y., Imai Y. Immunologic Fecal Occult Blood Test for Colorectal Cancer Screening. Japan Med Assoc J 2006;49:203-7. 68. Parra-Blanco A, Gimeno-Garcia AZ, Quintero E, et al. Diagnostic accuracy of immunochemical versus guaiac faecal occult blood tests for colorectal cancer screening. J Gastroenterol 2010;45:703-12. 69. Terhaar sive Droste JS, Oort FA, van der Hulst RW, et al. Higher fecal immunochemical test cutoff levels: lower positivity rates but still acceptable detection rates for early-stage colorectal cancers. Cancer Epidemiol Biomarkers Prev 2011; 20:272-80. 70. Viana Freitas BR, Kibune Nagasako C, Pavan CR, et al. Immunochemical fecal occult blood test for detection of advanced colonic adenomas and colorectal cancer: comparison with colonoscopy results. Gastroenterol Res Pract 2013;2013:384561. 71. Brenner H, Tao S. Superior diagnostic performance of faecal immunochemical tests for haemoglobin in a head-to-head comparison with guaiac based faecal occult blood test among 2235 participants of screening colonoscopy. Eur J Cancer 2013;49:3049-54. 72. Chen Y-Y, Chen T-H, Su M-Y, et al. Accuracy of immunochemical fecal occult blood test for detecting colorectal neoplasms in individuals undergoing health check-ups. Adv Digest Med 2014;1:74-9. 73. Hernandez V, Cubiella J, Gonzalez-Mao MC, et al. Fecal immunochemical test accuracy in average-risk colorectal cancer screening. World J Gastroenterol 2014;20: 1038-47. 74. Kato J, Morikawa T, Kuriyama M, et al. Combination of sigmoidoscopy and a fecal immunochemical test to detect proximal colon neoplasia. Clin Gastroenterol Hepatol 2009;7:1341-6. 75. Lee YH, Hur M, Kim H, et al. Optimal cut-off concentration for a faecal immunochemical test for haemoglobin by Hemo Techt NS-Plus C15 system for the colorectal cancer screening. Clin Chem Lab Med 2015;53:e69-71. 76. Levy BT, Bay C, Xu Y, et al.

Test characteristics of faecal immunochemical tests (FIT) compared with optical colonoscopy. J Med Screen 2014; 21:133-43. 77. Omata F, Shintani A, Isozaki M, Masuda K, Fujita Y, Fukui T. Diagnostic performance of quantitative fecal immunochemical test and multivariate prediction model for colorectal neoplasms in asymptomatic individuals. Eur J Gastroenterol Hepatol 2011;23:1036-41. 78. Elsafi SH, Alqahtani NI, Zakary NY, Al Zahrani EM. The sensitivity, specificity, predictive values, and likelihood ratios of fecal occult blood test for the detection of colorectal cancer in hospital settings. Clin Exp Gastroenterol 2015;8:279-84. 79. Lee YC, Chiu HM, Chiang TH, et al. Accuracy of faecal occult blood test and Helicobacter pylori stool antigen test for detection of upper gastrointestinal lesions. BMJ Open 2013;3:e003989. 80. Nakajima M, Saito H, Soma Y, Sobue T, Tanaka M, Munakata A. Prevention of advanced colorectal cancer by screening using the immunochemical faecal occult blood test: a case–control study. British journal of cancer 2003;89:23-8. 81. Saito H, Soma Y, Nakajima M, et al. A case-control study evaluating occult blood screening for colorectal cancer with hemoccult test and an immunochemical hemagglutination test. Oncology reports 2000;7:815-9. 82. Saito H, Soma Y, Koeda J, et al. Reduction in risk of mortality from colorectal cancer by fecal occult blood screening with immunochemical hemagglutination test. A case-control study. International journal of cancer 1995;61:465-9. 83. Cole SR, Young GP, Esterman A, Cadd B, Morcom J. A randomised trial of the impact of new faecal haemoglobin test technologies on population participation in screening for colorectal cancer. The Medical journal of Australia 2003; 10:117-22. 84. Macrae FA, Hill DJ, St. John DJB, Ambikapathy A, Garner JF. Predicting colon cancer screening behavior from health beliefs. Prev Med 1984;13:115-26. 85. Cole SR, Young GP. Effect of dietary restriction on participation in faecal occult blood test screening for colorectal cancer. The Medical journal of Australia 2001; 175:195-8. 86. McCusker J, Morrow GR. Factors related to the use of cancer early detection techniques. Prev Med 1980;9:388-97. 87. Salkeld GP, Solomon MJ, Short L, Ward J. Measuring the importance of attributes that influence consumer attitudes to colorectal cancer screening. ANZ J Surg 2003;73:128-32. 88. Wardle J, Pope R. The psychological costs of screening for cancer. J Psychosom Res 1992;36:609-24. 89. Lindholm E, Berglund B, Kewenter J, Haglind E. Worry associated with screening for colorectal carcinomas. Scand J Gastroenterol 1997; 32:238-45. 90. Parker MA, Robinson MH, Scholefield JH, Hardcastle JD. Psychiatric morbidity and screening for colorectal cancer. J Med Screen 2002;9:7-10. 91. Wardle J, Taylor T, Sutton S, Atkin W. Does publicity about cancer screening raise fear of cancer? Randomised trial of the psychological effect of information about cancer screening. BMJ (Clinical research ed) 1999;319:1037-8.

Back to top

6.2.2.4 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search

View PICO	NHMRC Evidence statement form PSC1b	Systematic review report PSC1b	Modelling report PSC1c	Modelling report PSC1d

Back to top

6.2.3 Evidence: Screening cost effectiveness (PSC1c)

Contents

6.2.3.1 Evidence: Screening cost effectiveness

In persons without a bowel cancer diagnosis or symptoms that might indicate bowel cancer, what is the most cost-effective, feasible and acceptable screening modality (immunochemical FOBT, flexible sigmoidoscopy, colonoscopy, CT colonography, faecal or blood biomarkers, or any combinations) compared with no screening? (PICO PSC1c) A comprehensive validated model of colorectal cancer development and bowel screening ('Policy1-Bowel') was used to simulate the NBCSP and alternative screening approaches (see Table 9.3). Details of the methods and result can be found in the Technical Report. The strategies were evaluated in context of (i) a scenario assuming perfect adherence to screening, follow-up and surveillance recommendations (Scenario 1); (ii) a scenario assuming high (but imperfect) participation (Scenario 2) and (iii) a scenario assuming lower participation (Scenario 3). Specific participation assumptions differed according to modality but were derived based on currently observed screening participation in Australia and expert opinion for new modalities.

Table 9.3. Screening strategies evaluated Insert large table

NB I presume that the findings on annual FOBT and FS once only at age 55 be included (??)

Colorectal cancer incidence and mortality reductions When assuming perfect adherence to screening, follow-up and surveillance recommendations, colorectal cancer screening was predicted to reduce colorectal cancer incidence by 38-67% and to reduce colorectal cancer mortality by 49-82%. Six strategies predicted a greater than 75% reduction in colorectal cancer mortality in perfectly compliant cohorts (or individuals) – these were 2-yearly fDNA (faecal DNA test) screening at 50-74 years (82%), 10-yearly colonoscopy screening at 55, 65 and 75 year-old (77%), once-off colonoscopy screening at age 50 combined with 2-yearly iFOBT screening at 52-74 years (80%), and 2-yearly iFOBT screening for 50-74 years with/without adjunctive sigmoidoscopy for individuals with negative iFOBT results (75-79%). After accounting for realistic compliance to screening, follow-up and surveillance recommendations, the screening strategies were predicted to reduce colorectal cancer incidence by 13-41% in Scenario 2 (higher participation) and by 6-26% in Scenario 3 (lower participation) ; colorectal cancer mortality rates were reduced by 17-63% and 8-44%, respectively. Six strategies predicted a greater than

50% mortality reduction in Scenario 2 (higher participation) and greater than 35% reduction in Scenario 3 (lower participation): these were 2-yearly fDNA screening (63% in Scenario 2; 44% in Scenario 3), once-off colonoscopy screening at age 50 combined with 2-yearly iFOBT screening at 52-74 years (57% in Scenario 2; 39% in Scenario 3), and 2-yearly iFOBT screening for 50-74 years with/without adjunct sigmoidoscopy screening for individuals with negative iFOBT, or 2-yearly iFOBT with plasma DNA test (pDNA) for under-screened individuals, assuming that the offer of pDNA does not induce any 'leakage' (participation drop) in iFOBT screening - a favourable assumption (52-56% in Scenario 2; 36-39% in Scenario 3). Cost-effectiveness The estimated life-years, lifetime cost and the cost-effectiveness ratio compared to no screening for each strategy were modelled. When compared with no screening, all except the three strategies assuming 2-yearly pDNA testing and 2- or 5-yearly fDNA testing were estimated to be associated with an cost-effectiveness ratio less than the indicative willingness-to-pay (WTP) threshold in Australia of $50,000 per life-year saved (LYS) in all three scenarios. Screening with 10-yearly computed tomography colonoscopy (CTC) at 55, 65 and 75 years was predicted to be cost-saving (i.e. cost less than no screening due to savings in cancer treatment costs) in all scenarios. Given the indicative WTP threshold, only 10-yearly CTC screening and 2-yearly iFOBT at 50-74 years would be cost-effective in all scenarios and 2-yearly iFOBT screening was predicted to be associated with significantly greater life-years savings (i.e. was significantly more effective) than 10-yearly CTC screening. Strategies assuming 2-yearly screening with iFOBT and adjunct sigmoidoscopy for individuals with negative iFOBT were also found to be cost-effective in Scenarios 2 and 3. Overall, 2-yearly iFOBT screening at 50-74 years with or without adjunct sigmoidoscopy screening was predicted to be the most cost-effective strategy under the WTP threshold. Resource utilisation Modelling analysis was used to estimate the number of iFOBT test, pDNA, tests fDNA tests, colonoscopy, sigmoidoscopy and CTC tests in the lifetime of 100,000 persons alive at 40 years for each strategy. In all participation scenarios, 10-yearly colonoscopy screening, once-off colonoscopy screening at 50 year-old combined with 2-yearly iFOBT screening, and 2-yearly fDNA screening were predicted to lead to the highest number of colonoscopy procedures. Screening with sigmoidoscopy or CTC at a 10-yearly interval were estimated to lead to the lowest number of colonoscopies. Number-needed-to-colonoscope (NNC) Strategies assuming 2-yearly pDNA screening, 10- yearly colonoscopy screening and once-off colonoscopy screening at 50 years combined with 2-yearly iFOBT screening were estimated to be associated with the highest NNC ratio per colorectal cancer case or colorectal cancer death prevented, compared to the other strategies. When compared to 2-yearly iFOBT screening, five strategies (fDNA2y, COL@50_iFOBT2y, iFOBT2y+SIG@50, iFOBT2y+SIG@54_64_74, and iFOBT2y+plasmaDNA) were found to have fewer colorectal cancer deaths but also higher numbers of colonoscopies in all scenarios. Thus, these five strategies were estimated to be associated with a higher NNC per colorectal cancer death prevented compared to 2 yearly iFOBT (277-1,133 in Scenario 1, 111-379 in Scenario 2, and 107-203 in Scenario 3). No strategy was found to have both fewer colorectal cancer deaths and fewer colonoscopies than 2 yearly iFOBT, implying that the 2016 current NBCSP has an optimal balance of benefits and harms, given the strategies considered in this evaluation.

6.2.3.2 See the Evidence summary and recommendations section for guidance resulting from this modelling.

6.2.3.3 References

1. Wilson J, Junger G. Principles and practices of screening for disease. Geneva, Switzerland1968. Report No.: 34,1968. 2. Gnauck R. World Health Organization criteria for screening. In Colorectal Cancer: Prevention, Epidemiology and Screening. New York: Raven Press; 1980. 3. Schottenfeld D. Fundamental issues in cancer

screening. In Colorectal Cancer: Prevention, Epidemiology and Screening. New York: Raven Press; 1980. 4. The Cancer Council Australia, Australian Cancer Network. Chapter 3, Population screening for colorectal cancer, 2005 CCA Guidelines The Prevention, early detection and management of colorectal cancer2005. 5. GP Y. Screening for colorectal cancer – new evidence in the last 10 years. Cancer Forum; 2014. p. 38. 6. Young GP, Symonds EL, Allison JE, et al. Advances in Fecal Occult Blood Tests: the FIT revolution. Digestive diseases and sciences 2015;60:609-22. 7. Cancer Council Australia. Clinical practice guidelines for the prevention, early detection and management of colorectal cancer (CRC) 2nd edition2005. Report No.: ISBN: 0-9775060-1-0. 8. Miles A, Cockburn J, Smith RA, Wardle J. A perspective from countries using organized screening programs. Cancer 2004;101:1201-13. 9. International Agency for Research on Cancer. Chapter 2, European guidelines for quality assurance in colorectal cancer screening and diagnosis, First Edition: International Agency for Research on Cancer; 2010. 10. Benson VS, Atkin WS, Green J, et al. Toward standardizing and reporting colorectal cancer screening indicators on an international level: The International Colorectal Cancer Screening Network. International journal of cancer 2012;130:2961-73. 11. Brawley OW. Colorectal cancer control: providing adequate care to those who need it. Journal of the National Cancer Institute 2014;106:dju075. 12. Flitcroft KL, St John DJ, Howard K, et al. A comparative case study of bowel cancer screening in the UK and Australia: evidence lost in translation? J Med Screen 2011;18:193-203. 13. Schreuders EH, Ruco A, Rabeneck L, et al. Colorectal cancer screening: a global overview of existing programmes. Gut 2015;64:1637-49. 14. Australian Health Technology Advisory Committee. Colorectal Cancer Screening1997. Report No.: ISBN 0 642 27289 1 15. Australian Government Department of Health. The Australian bowel cancer screening pilot program and beyond: final evaluation report2005. 16. Australian Institute of Health and Welfare. National Bowel Cancer Screening Program Monitoring Report 2016. Canberra: AIHW; 2016. Report No.: Cat. No CAN 97. 17. Cole SR, Tucker GR, Osborne JM, et al. Shift to earlier stage at diagnosis as a consequence of the National Bowel Cancer Screening Program. The Medical journal of Australia 2013;198:327-30. 18. Ananda S, Wong H, Faragher I, et al. Survival impact of the Australian National Bowel Cancer Screening Programme. Internal medicine journal 2016;46:166-71. 19. Australian Institute of Health and Welfare, Australian Government Department of Health. Analysis of colorectal cancer outcomes for the Australian National Bowel Cancer Screening Program. Asia-Pacific journal of clinical oncology 2016;12:22-32. 20. Pignone MP, Flitcroft KL, Howard K, Trevena LJ, Salkeld GP, St John D. Costs and cost-effectiveness of full implementation of a biennial faecal occult blood test screening program for bowel cancer in Australia. The Medical journal of Australia 2011;194:180-5. 21. Cenin DR, St John DJ, Ledger MJ, Slevin T, Lansdorp-Vogelaar I. Optimising the expansion of the National Bowel Cancer Screening Program. The Medical journal of Australia 2014;201:456-61. 22. St John J, Grogan P. Compelling new data on the effectiveness of Australia's National Bowel Cancer Screening Program: A model for best practice? Asia-Pacific journal of clinical oncology 2016;12:7-9. 23. van Rossum LG, van Rijn AF, Laheij RJ, et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. Gastroenterology 2008; 135:82-90. 24. Park DI, Ryu S, Kim YH, et al. Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average risk undergoing colorectal cancer screening. Am J Gastroenterol 2010;105:2017-25. 25. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. N Engl J Med 1993;328:1365-71. 26. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet (London, England) 1996;348:1472-7. 27. Kronborg O, Fenger C, Olsen J, Jørgensen OD, Søndergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet (London, England) 1996;348:1467-71. 28. Mandel JS, Church TR, Ederer F, Bond JH. Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood. Journal of the National Cancer Institute 1999;91:434-7. 29. Mandel JS, Church TR, Bond JH, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. N Engl J Med 2000;343:1603-7. 30. Hewitson P, Glasziou P, Irwig L, Towler B, Watson E. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. The Cochrane database of systematic reviews 2007:Cd001216.

31. Towler B, Irwig L, Glasziou P, Kewenter J, Weller D, Silagy C. A systematic review of the effects of screening for colorectal cancer using the faecal occult blood test, hemoccult. BMJ (Clinical research ed) 1998;317:559-65. 32. Segnan N, Armaroli P, Bonelli L, et al. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial--SCORE. Journal of the National Cancer Institute 2011;103: 1310-22. 33. Elmunzer BJ, Hayward RA, Schoenfeld PS, Saini SD, Deshpande A, Waljee AK. Effect of flexible sigmoidoscopy-based screening on incidence and mortality of colorectal cancer: a systematic review and meta-analysis of randomized controlled trials. PLoS Med 2012;9:e1001352. 34. Schoen RE, Pinsky PF, Weissfeld JL, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med 2012;366: 2345-57. 35. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet (London, England) 2010;375:1624-33. 36. Quintero E, Castells A, Bujanda L, et al. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. N Engl J Med 2012;366:697-706. 37. Bretthauer M, Kaminski MF, Løberg M, et al. Population-Based Colonoscopy Screening for Colorectal Cancer: A Randomized Clinical Trial. JAMA Intern Med 2016. 38. ClinicalTrials.gov. Colonoscopy vs fecal immunochemical test in reducing mortality from colorectal cancer (CONFIRM) [NCT01239082] 2016. 39. Knudsen AB, Zauber AG, Rutter CM, et al. Estimation of Benefits, Burden, and Harms of Colorectal Cancer Screening Strategies: Modeling Study for the US Preventive Services Task Force. JAMA 2016;315:2595-609. 40. International Agency for Research on Cancer. European guidelines for quality assurance in colorectal cancer screening and diagnosis, First Edition: International Agency for Research on Cancer; 2010. 41. Secretariat MA. Fecal Occult Blood Test for Colorectal Cancer Screening: an evidence-based analysis. Toronto, Ontario, Canada: Ministry of Health and Long-Term Care; 2009. 42. Force UPST. Screening for Colorectal Cancer US Preventive Services Task Force Recommendation Statement. JAMA 2016;315: 2564-75. 43. Force USPST. Screening for Colorectal Cancer: U.S. Preventive Services Task Force Recommendation Statement. Annals of Internal Medicine 2008;149:627-37. 44. Jørgensen O, Kronborg O, Fenger C. A randomised study on screening for colorectal cancer using faecal occult blood testing: results after 13 years and seven biennial screening rounds. Gut 2002;50:29-39. 45. Scholefield J, Moss S, Sufi F, Mangham C, Hardcastle J. Effect of faecal occult blood screening on mortality from colorectal cancer: results from a randomised controlled trial. Gut 2002;50:840-4. 46. Scholefield JH, Moss SM, Mangham CM, Whynes DK, Hardcastle JD. Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up. Gut 2012;61:1036-40. 47. Zheng S, Chen K, Liu X, et al. Cluster Randomization Trial of Sequence Mass Screening for Colorectal Cancer. Dis Colon Rectum 2003;46:51-8. 48. Blom J, Yin L, Liden A, et al. A 9-year follow-up study of participants and nonparticipants in sigmoidoscopy screening: importance of self-selection. Cancer Epidemiol Biomarkers Prev 2008;17:1163-8. 49. Holme O, Loberg M, Kalager M, et al. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. JAMA 2014;312:606-15. 50. Shroff J, Thosani N, Batra S, Singh H, Guha S. Reduced incidence and mortality from colorectal cancer with flexible-sigmoidoscopy screening: a meta-analysis. World J Gastroenterol 2014;20:18466-76. 51. Hoff G, Grotmol T, Skovlund E, Bretthauer M, Norwegian Colorectal Cancer Prevention Study G. Risk of colorectal cancer seven years after flexible sigmoidoscopy screening: randomised controlled trial. BMJ (Clinical research ed) 2009;338: b1846. 52. Castro I, Cubiella J, Rivera C, et al. Fecal immunochemical test accuracy in familial risk colorectal cancer screening. International journal of cancer 2014;134:367-75. 53. Gimeno-Garcia AZ, Quintero E, Nicolas-Perez D, Hernandez-Guerra M, Parra-Blanco A, Jimenez-Sosa A. Screening for familial colorectal cancer with a sensitive immunochemical fecal occult blood test: a pilot study. Eur J Gastroenterol Hepatol 2009;21:1062-7. 54. Ng SC, Ching JY, Chan V, et al. Diagnostic accuracy of faecal immunochemical test for screening individuals with a family history of colorectal cancer. Aliment Pharmacol Ther 2013;38:835-41. 55. Ahlquist DA, Sargent DJ, Loprinzi CL, et al. Stool DNA and occult blood testing for screen detection of colorectal neoplasia. Ann Intern Med 2008;149:441-50, W81. 56. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med 2014;370:1287-97. 57. Redwood DG, Asay ED, Blake ID, et al. Stool

DNA Testing for Screening Detection of Colorectal Neoplasia in Alaska Native People. Mayo Clin Proc 2016;91:61-70. 58. Annahazi A, Abraham S, Farkas K, et al. A pilot study on faecal MMP-9: a new noninvasive diagnostic marker of colorectal cancer. British journal of cancer 2016;114:787-92. 59. Church TR, Wandell M, Lofton-Day C, et al. Prospective evaluation of methylated SEPT9 in plasma for detection of asymptomatic colorectal cancer. Gut 2014;63:317-25. 60. Khalid-de Bakker CA, Jonkers DM, Sanduleanu S, et al. Test performance of immunologic fecal occult blood testing and sigmoidoscopy compared with primary colonoscopy screening for colorectal advanced adenomas. Cancer Prev Res (Phila) 2011;4:1563-71. 61. Brenner H, Haug U, Hundt S. Sex differences in performance of fecal occult blood testing. Am J Gastroenterol 2010;105:2457-64. 62. Chiu HM, Lee YC, Tu CH, et al. Association between early stage colon neoplasms and false-negative results from the fecal immunochemical test. Clin Gastroenterol Hepatol 2013;11:832-8 e1-2. 63. de Wijkerslooth TR, Stoop EM, Bossuyt PM, et al. Immunochemical fecal occult blood testing is equally sensitive for proximal and distal advanced neoplasia. Am J Gastroenterol 2012;107:1570-8. 64. Graser A, Stieber P, Nagel D, et al. Comparison of CT colonography, colonoscopy, sigmoidoscopy and faecal occult blood tests for the detection of advanced adenoma in an average risk population. Gut 2009;58:241-8. 65. Hundt S, Haug U, Brenner H. Comparative evaluation of immunochemical fecal occult blood tests for colorectal adenoma detection. Ann Intern Med 2009; 150:162-9. 66. Morikawa T, Kato J, Yamaji Y, Wada R, Mitsushima T, Shiratori Y. A comparison of the immunochemical fecal occult blood test and total colonoscopy in the asymptomatic population. Gastroenterology 2005;129:422-8. 67. Nakazako M. YH, Matsushita H., Sato K., Fujita K., Yamanaka Y., Imai Y. Immunologic Fecal Occult Blood Test for Colorectal Cancer Screening. Japan Med Assoc J 2006;49:203-7. 68. Parra-Blanco A, Gimeno-Garcia AZ, Quintero E, et al. Diagnostic accuracy of immunochemical versus guaiac faecal occult blood tests for colorectal cancer screening. J Gastroenterol 2010;45:703-12. 69. Terhaar sive Droste JS, Oort FA, van der Hulst RW, et al. Higher fecal immunochemical test cutoff levels: lower positivity rates but still acceptable detection rates for early-stage colorectal cancers. Cancer Epidemiol Biomarkers Prev 2011; 20:272-80. 70. Viana Freitas BR, Kibune Nagasako C, Pavan CR, et al. Immunochemical fecal occult blood test for detection of advanced colonic adenomas and colorectal cancer: comparison with colonoscopy results. Gastroenterol Res Pract 2013;2013:384561. 71. Brenner H, Tao S. Superior diagnostic performance of faecal immunochemical tests for haemoglobin in a head-to-head comparison with guaiac based faecal occult blood test among 2235 participants of screening colonoscopy. Eur J Cancer 2013;49:3049-54. 72. Chen Y-Y, Chen T-H, Su M-Y, et al. Accuracy of immunochemical fecal occult blood test for detecting colorectal neoplasms in individuals undergoing health check-ups. Adv Digest Med 2014;1:74-9. 73. Hernandez V, Cubiella J, Gonzalez-Mao MC, et al. Fecal immunochemical test accuracy in average-risk colorectal cancer screening. World J Gastroenterol 2014;20: 1038-47. 74. Kato J, Morikawa T, Kuriyama M, et al. Combination of sigmoidoscopy and a fecal immunochemical test to detect proximal colon neoplasia. Clin Gastroenterol Hepatol 2009;7:1341-6. 75. Lee YH, Hur M, Kim H, et al. Optimal cut-off concentration for a faecal immunochemical test for haemoglobin by Hemo Techt NS-Plus C15 system for the colorectal cancer screening. Clin Chem Lab Med 2015;53:e69-71. 76. Levy BT, Bay C, Xu Y, et al. Test characteristics of faecal immunochemical tests (FIT) compared with optical colonoscopy. J Med Screen 2014; 21:133-43. 77. Omata F, Shintani A, Isozaki M, Masuda K, Fujita Y, Fukui T. Diagnostic performance of quantitative fecal immunochemical test and multivariate prediction model for colorectal neoplasms in asymptomatic individuals. Eur J Gastroenterol Hepatol 2011;23:1036-41. 78. Elsafi SH, Alqahtani NI, Zakary NY, Al Zahrani EM. The sensitivity, specificity, predictive values, and likelihood ratios of fecal occult blood test for the detection of colorectal cancer in hospital settings. Clin Exp Gastroenterol 2015;8:279-84. 79. Lee YC, Chiu HM, Chiang TH, et al. Accuracy of faecal occult blood test and Helicobacter pylori stool antigen test for detection of upper gastrointestinal lesions. BMJ Open 2013;3:e003989. 80. Nakajima M, Saito H, Soma Y, Sobue T, Tanaka M, Munakata A. Prevention of advanced colorectal cancer by screening using the immunochemical faecal occult blood test: a case–control study. British journal of cancer 2003;89:23-8. 81. Saito H, Soma Y, Nakajima M, et al. A case-control study evaluating occult blood screening for colorectal cancer with hemoccult test and an

immunochemical hemagglutination test. Oncology reports 2000;7:815-9. 82. Saito H, Soma Y, Koeda J, et al. Reduction in risk of mortality from colorectal cancer by fecal occult blood screening with immunochemical hemagglutination test. A case-control study. International journal of cancer 1995;61:465-9. 83. Cole SR, Young GP, Esterman A, Cadd B, Morcom J. A randomised trial of the impact of new faecal haemoglobin test technologies on population participation in screening for colorectal cancer. The Medical journal of Australia 2003; 10:117-22. 84. Macrae FA, Hill DJ, St. John DJB, Ambikapathy A, Garner JF. Predicting colon cancer screening behavior from health beliefs. Prev Med 1984;13:115-26. 85. Cole SR, Young GP. Effect of dietary restriction on participation in faecal occult blood test screening for colorectal cancer. The Medical journal of Australia 2001; 175:195-8. 86. McCusker J, Morrow GR. Factors related to the use of cancer early detection techniques. Prev Med 1980;9:388-97. 87. Salkeld GP, Solomon MJ, Short L, Ward J. Measuring the importance of attributes that influence consumer attitudes to colorectal cancer screening. ANZ J Surg 2003;73:128-32. 88. Wardle J, Pope R. The psychological costs of screening for cancer. J Psychosom Res 1992;36:609-24. 89. Lindholm E, Berglund B, Kewenter J, Haglind E. Worry associated with screening for colorectal carcinomas. Scand J Gastroenterol 1997; 32:238-45. 90. Parker MA, Robinson MH, Scholefield JH, Hardcastle JD. Psychiatric morbidity and screening for colorectal cancer. J Med Screen 2002;9:7-10. 91. Wardle J, Taylor T, Sutton S, Atkin W. Does publicity about cancer screening raise fear of cancer? Randomised trial of the psychological effect of information about cancer screening. BMJ (Clinical research ed) 1999;319:1037-8.

Back to top

6.2.3.4 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	Modelling report PSC1c

Back to top

6.2.4 Evidence: Screening age (PSC1d)

Contents

6.2.4.1 Evidence: Screening age

Is population screening starting at an earlier age more effective and as feasible, acceptable and cost-effective as screening starting at age 50 yr? In population screening, do the harms outweigh the benefits if routine screening is continued beyond the age of 75yr? (PICO PSC1d) Randomised clinical trials25-27,32,34,35,47-49,51 have demonstrated that population based colorectal cancer screening reduces colorectal cancer mortality for average risk individuals aged between 50-75 years. To date no population based colorectal cancer screening trials have specifically reported the effectiveness for population screening in average risk individuals less than 50 years, or greater than 75 years. To address the above PICO question, a modelling evaluation was used to focus on assessing the benefit, harms and cost-effectiveness of colorectal cancer screening in people aged 50-74 years with 2-yearly iFOBT (the current NBCSP program) in comparison to potential alternatives for colorectal cancer screening in Australia (inviting people from age 40 or 45 (vs. 50 years) and/or continuing screening to age 79 or 84 years (vs. 74 years), considering a range of other screening technologies and/or screening intervals. Health outcomes Using biennial iFOBT screening for those 50-74 years of age as the screening strategy, the colorectal cancer incidence rate and colorectal cancer mortality rate were predicted to be reduced by 8-12% and 15-28%, respectively if screening began at 40 years, and 2-4% and 8-17%, respectively if the screening cessation age was extended to 84-years. The incidence and mortality reductions were estimated to be 10-17% and 22-44%, respectively, if the screening age range was widened from 50-74 years to 40-84 years. Cost-effectiveness The estimated life-years, lifetime cost and the cost-effectiveness ratio compared to biennial iFOBT screening at 50-74 years for each strategy are summarised in Table 9.4. According to the indicative willingness to pay-threshold (WTP) of $50,000 per life-year saved (LYS) in Australia, none of the alternative screening age ranges (50-74 years vs 40-74 years vs 50-84 years vs 40-84 years) was considered to be cost-effective when we assumed perfect screening adherence (Scenario 1); however strategies assuming screening starting earlier from 40 years alone or combined with stopping screening at later age were found to be cost-effective in Scenarios 2 and 3.

Table 9.4. Model estimated discounted lifetime cost, life-years and cost-effectiveness ratio of strategies assuming biennial iFOBT screening at various age ranges Insert large table

Resource utilisation An approximate of 1.0 million iFOBT tests and 127,314 colonoscopies were estimated to occur in the current NBCSP for biennial iFOBT screening at 50-74 years in Scenario 1 if there were perfect screening adherence; 720,391 iFOBT tests and 66,681 colonoscopies were predicted in Scenario 2 and 471,954 iFOBT tests and 44,747 colonoscopies were predicted in Scenario 3. Extending the screening age-range resulted an increased resource utilisation. Compared to the current NBCSP program, the number of iFOBT test and colonoscopies were estimated to increase by 42-52% and 28-38%, respectively if the screening start age was lowered from 50 years to 40 years, and by 22-36% and 42-64%, respectively if the screening cessation age was extended to 84 years. Overall iFOBT and colonoscopy numbers were predicted to increase by 66-91% and 72-108%, respectively if the screening age range was widened to 40-84 years. Number-needed-to-colonoscope (NNC) The current NBCSP was predicted to be associated with an NNC of 28 per case prevented and 56 NNC per death prevented compared to no screening in Scenario 1, and 22 per case prevented and 39-41 per death prevented in Scenarios 2 and 3 (when compared to no screening). Using our modelling analysis, we estimated

the number of additional colonoscopies required to prevent one additional colorectal cancer case/colorectal death for each strategy compared with biennial iFOBT screening. The NNC for the age-extensions of the NBCSP are up to 4-5 times higher than that the baseline NNC for the existing NBCSP. At current levels of participation, starting from age forty would be associated with an additional 67 colonoscopies for each additional death prevented, compared to 59 colonoscopies per death prevented for the existing program screening age range. Results and comments for screening starting at age 45?

Back to top

6.2.4.2 See the Evidence summary and recommendations section for guidance resulting from this modelling.

6.2.4.3 References

1. Wilson J, Junger G. Principles and practices of screening for disease. Geneva, Switzerland1968. Report No.: 34,1968. 2. Gnauck R. World Health Organization criteria for screening. In Colorectal Cancer: Prevention, Epidemiology and Screening. New York: Raven Press; 1980. 3. Schottenfeld D. Fundamental issues in cancer screening. In Colorectal Cancer: Prevention, Epidemiology and Screening. New York: Raven Press; 1980. 4. The Cancer Council Australia, Australian Cancer Network. Chapter 3, Population screening for colorectal cancer, 2005 CCA Guidelines The Prevention, early detection and management of colorectal cancer2005. 5. GP Y. Screening for colorectal cancer – new evidence in the last 10 years. Cancer Forum; 2014. p. 38. 6. Young GP, Symonds EL, Allison JE, et al. Advances in Fecal Occult Blood Tests: the FIT revolution. Digestive diseases and sciences 2015;60:609-22. 7. Cancer Council Australia. Clinical practice guidelines for the prevention, early detection and management of colorectal cancer (CRC) 2nd edition2005. Report No.: ISBN: 0-9775060-1-0. 8. Miles A, Cockburn J, Smith RA, Wardle J. A perspective from countries using organized screening programs. Cancer 2004;101:1201-13. 9. International Agency for Research on Cancer. Chapter 2, European guidelines for quality assurance in colorectal cancer screening and diagnosis, First Edition: International Agency for Research on Cancer; 2010. 10. Benson VS, Atkin WS, Green J, et al. Toward standardizing and reporting colorectal cancer screening indicators on an international level: The International Colorectal Cancer Screening Network. International journal of cancer 2012;130:2961-73. 11. Brawley OW. Colorectal cancer control: providing adequate care to those who need it. Journal of the National Cancer Institute 2014;106:dju075. 12. Flitcroft KL, St John DJ, Howard K, et al. A comparative case study of bowel cancer screening in the UK and Australia: evidence lost in translation? J Med Screen 2011;18:193-203. 13. Schreuders EH, Ruco A, Rabeneck L, et al. Colorectal cancer screening: a global overview of existing programmes. Gut 2015;64:1637-49. 14. Australian Health Technology Advisory Committee. Colorectal Cancer Screening1997. Report No.: ISBN 0 642 27289 1 15. Australian Government Department of Health. The Australian bowel cancer screening pilot program and beyond: final evaluation report2005. 16. Australian Institute of Health and Welfare. National Bowel Cancer Screening Program Monitoring Report 2016. Canberra: AIHW; 2016. Report No.: Cat. No CAN 97. 17. Cole SR, Tucker GR, Osborne JM, et al. Shift to earlier stage at diagnosis as a consequence of the National Bowel Cancer Screening Program. The Medical journal of Australia 2013;198:327-30. 18. Ananda S, Wong H, Faragher I, et al. Survival impact of the Australian National Bowel Cancer Screening Programme. Internal medicine journal 2016;46:166-71. 19. Australian Institute of Health and Welfare, Australian Government Department of Health. Analysis of colorectal cancer outcomes for the Australian National Bowel Cancer Screening Program. Asia-Pacific journal of clinical oncology 2016;12:22-32. 20. Pignone MP, Flitcroft KL, Howard K, Trevena LJ, Salkeld GP, St John D. Costs and cost-effectiveness of full implementation of a biennial faecal occult blood test screening program for bowel

cancer in Australia. The Medical journal of Australia 2011;194:180-5. 21. Cenin DR, St John DJ, Ledger MJ, Slevin T, Lansdorp-Vogelaar I. Optimising the expansion of the National Bowel Cancer Screening Program. The Medical journal of Australia 2014;201:456-61. 22. St John J, Grogan P. Compelling new data on the effectiveness of Australia's National Bowel Cancer Screening Program: A model for best practice? Asia-Pacific journal of clinical oncology 2016;12:7-9. 23. van Rossum LG, van Rijn AF, Laheij RJ, et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. Gastroenterology 2008; 135:82-90. 24. Park DI, Ryu S, Kim YH, et al. Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average risk undergoing colorectal cancer screening. Am J Gastroenterol 2010;105:2017-25. 25. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. N Engl J Med 1993;328:1365-71. 26. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet (London, England) 1996;348:1472-7. 27. Kronborg O, Fenger C, Olsen J, Jørgensen OD, Søndergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet (London, England) 1996;348:1467-71. 28. Mandel JS, Church TR, Ederer F, Bond JH. Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood. Journal of the National Cancer Institute 1999;91:434-7. 29. Mandel JS, Church TR, Bond JH, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. N Engl J Med 2000;343:1603-7. 30. Hewitson P, Glasziou P, Irwig L, Towler B, Watson E. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. The Cochrane database of systematic reviews 2007:Cd001216. 31. Towler B, Irwig L, Glasziou P, Kewenter J, Weller D, Silagy C. A systematic review of the effects of screening for colorectal cancer using the faecal occult blood test, hemoccult. BMJ (Clinical research ed) 1998;317:559-65. 32. Segnan N, Armaroli P, Bonelli L, et al. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial--SCORE. Journal of the National Cancer Institute 2011;103: 1310-22. 33. Elmunzer BJ, Hayward RA, Schoenfeld PS, Saini SD, Deshpande A, Waljee AK. Effect of flexible sigmoidoscopy-based screening on incidence and mortality of colorectal cancer: a systematic review and meta-analysis of randomized controlled trials. PLoS Med 2012;9:e1001352. 34. Schoen RE, Pinsky PF, Weissfeld JL, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med 2012;366: 2345-57. 35. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet (London, England) 2010;375:1624-33. 36. Quintero E, Castells A, Bujanda L, et al. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. N Engl J Med 2012;366:697-706. 37. Bretthauer M, Kaminski MF, Løberg M, et al. Population-Based Colonoscopy Screening for Colorectal Cancer: A Randomized Clinical Trial. JAMA Intern Med 2016. 38. ClinicalTrials.gov. Colonoscopy vs fecal immunochemical test in reducing mortality from colorectal cancer (CONFIRM) [NCT01239082] 2016. 39. Knudsen AB, Zauber AG, Rutter CM, et al. Estimation of Benefits, Burden, and Harms of Colorectal Cancer Screening Strategies: Modeling Study for the US Preventive Services Task Force. JAMA 2016;315:2595-609. 40. International Agency for Research on Cancer. European guidelines for quality assurance in colorectal cancer screening and diagnosis, First Edition: International Agency for Research on Cancer; 2010. 41. Secretariat MA. Fecal Occult Blood Test for Colorectal Cancer Screening: an evidence-based analysis. Toronto, Ontario, Canada: Ministry of Health and Long-Term Care; 2009. 42. Force UPST. Screening for Colorectal Cancer US Preventive Services Task Force Recommendation Statement. JAMA 2016;315: 2564-75. 43. Force USPST. Screening for Colorectal Cancer: U.S. Preventive Services Task Force Recommendation Statement. Annals of Internal Medicine 2008;149:627-37. 44. Jørgensen O, Kronborg O, Fenger C. A randomised study on screening for colorectal cancer using faecal occult blood testing: results after 13 years and seven biennial screening rounds. Gut 2002;50:29-39. 45. Scholefield J, Moss S, Sufi F, Mangham C, Hardcastle J. Effect of faecal occult blood screening on mortality from colorectal cancer: results from a randomised controlled trial. Gut 2002;50:840-4. 46. Scholefield JH, Moss SM, Mangham CM, Whynes DK, Hardcastle JD. Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up. Gut

2012;61:1036-40. 47. Zheng S, Chen K, Liu X, et al. Cluster Randomization Trial of Sequence Mass Screening for Colorectal Cancer. Dis Colon Rectum 2003;46:51-8. 48. Blom J, Yin L, Liden A, et al. A 9-year follow-up study of participants and nonparticipants in sigmoidoscopy screening: importance of self-selection. Cancer Epidemiol Biomarkers Prev 2008;17:1163-8. 49. Holme O, Loberg M, Kalager M, et al. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. JAMA 2014;312:606-15. 50. Shroff J, Thosani N, Batra S, Singh H, Guha S. Reduced incidence and mortality from colorectal cancer with flexible-sigmoidoscopy screening: a meta-analysis. World J Gastroenterol 2014;20:18466-76. 51. Hoff G, Grotmol T, Skovlund E, Bretthauer M, Norwegian Colorectal Cancer Prevention Study G. Risk of colorectal cancer seven years after flexible sigmoidoscopy screening: randomised controlled trial. BMJ (Clinical research ed) 2009;338: b1846. 52. Castro I, Cubiella J, Rivera C, et al. Fecal immunochemical test accuracy in familial risk colorectal cancer screening. International journal of cancer 2014;134:367-75. 53. Gimeno-Garcia AZ, Quintero E, Nicolas-Perez D, Hernandez-Guerra M, Parra-Blanco A, Jimenez-Sosa A. Screening for familial colorectal cancer with a sensitive immunochemical fecal occult blood test: a pilot study. Eur J Gastroenterol Hepatol 2009;21:1062-7. 54. Ng SC, Ching JY, Chan V, et al. Diagnostic accuracy of faecal immunochemical test for screening individuals with a family history of colorectal cancer. Aliment Pharmacol Ther 2013;38:835-41. 55. Ahlquist DA, Sargent DJ, Loprinzi CL, et al. Stool DNA and occult blood testing for screen detection of colorectal neoplasia. Ann Intern Med 2008;149:441-50, W81. 56. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med 2014;370:1287-97. 57. Redwood DG, Asay ED, Blake ID, et al. Stool DNA Testing for Screening Detection of Colorectal Neoplasia in Alaska Native People. Mayo Clin Proc 2016;91:61-70. 58. Annahazi A, Abraham S, Farkas K, et al. A pilot study on faecal MMP-9: a new noninvasive diagnostic marker of colorectal cancer. British journal of cancer 2016;114:787-92. 59. Church TR, Wandell M, Lofton-Day C, et al. Prospective evaluation of methylated SEPT9 in plasma for detection of asymptomatic colorectal cancer. Gut 2014;63:317-25. 60. Khalid-de Bakker CA, Jonkers DM, Sanduleanu S, et al. Test performance of immunologic fecal occult blood testing and sigmoidoscopy compared with primary colonoscopy screening for colorectal advanced adenomas. Cancer Prev Res (Phila) 2011;4:1563-71. 61. Brenner H, Haug U, Hundt S. Sex differences in performance of fecal occult blood testing. Am J Gastroenterol 2010;105:2457-64. 62. Chiu HM, Lee YC, Tu CH, et al. Association between early stage colon neoplasms and false-negative results from the fecal immunochemical test. Clin Gastroenterol Hepatol 2013;11:832-8 e1-2. 63. de Wijkerslooth TR, Stoop EM, Bossuyt PM, et al. Immunochemical fecal occult blood testing is equally sensitive for proximal and distal advanced neoplasia. Am J Gastroenterol 2012;107:1570-8. 64. Graser A, Stieber P, Nagel D, et al. Comparison of CT colonography, colonoscopy, sigmoidoscopy and faecal occult blood tests for the detection of advanced adenoma in an average risk population. Gut 2009;58:241-8. 65. Hundt S, Haug U, Brenner H. Comparative evaluation of immunochemical fecal occult blood tests for colorectal adenoma detection. Ann Intern Med 2009; 150:162-9. 66. Morikawa T, Kato J, Yamaji Y, Wada R, Mitsushima T, Shiratori Y. A comparison of the immunochemical fecal occult blood test and total colonoscopy in the asymptomatic population. Gastroenterology 2005;129:422-8. 67. Nakazako M. YH, Matsushita H., Sato K., Fujita K., Yamanaka Y., Imai Y. Immunologic Fecal Occult Blood Test for Colorectal Cancer Screening. Japan Med Assoc J 2006;49:203-7. 68. Parra-Blanco A, Gimeno-Garcia AZ, Quintero E, et al. Diagnostic accuracy of immunochemical versus guaiac faecal occult blood tests for colorectal cancer screening. J Gastroenterol 2010;45:703-12. 69. Terhaar sive Droste JS, Oort FA, van der Hulst RW, et al. Higher fecal immunochemical test cutoff levels: lower positivity rates but still acceptable detection rates for early-stage colorectal cancers. Cancer Epidemiol Biomarkers Prev 2011; 20:272-80. 70. Viana Freitas BR, Kibune Nagasako C, Pavan CR, et al. Immunochemical fecal occult blood test for detection of advanced colonic adenomas and colorectal cancer: comparison with colonoscopy results. Gastroenterol Res Pract 2013;2013:384561. 71. Brenner H, Tao S. Superior diagnostic performance of faecal immunochemical tests for haemoglobin in a head-to-head comparison with guaiac based faecal occult blood test among 2235 participants of screening colonoscopy. Eur J Cancer 2013;49:3049-54. 72. Chen Y-Y, Chen T-H, Su

M-Y, et al. Accuracy of immunochemical fecal occult blood test for detecting colorectal neoplasms in individuals undergoing health check-ups. Adv Digest Med 2014;1:74-9. 73. Hernandez V, Cubiella J, Gonzalez-Mao MC, et al. Fecal immunochemical test accuracy in average-risk colorectal cancer screening. World J Gastroenterol 2014;20: 1038-47. 74. Kato J, Morikawa T, Kuriyama M, et al. Combination of sigmoidoscopy and a fecal immunochemical test to detect proximal colon neoplasia. Clin Gastroenterol Hepatol 2009;7:1341-6. 75. Lee YH, Hur M, Kim H, et al. Optimal cut-off concentration for a faecal immunochemical test for haemoglobin by Hemo Techt NS-Plus C15 system for the colorectal cancer screening. Clin Chem Lab Med 2015;53:e69-71. 76. Levy BT, Bay C, Xu Y, et al. Test characteristics of faecal immunochemical tests (FIT) compared with optical colonoscopy. J Med Screen 2014; 21:133-43. 77. Omata F, Shintani A, Isozaki M, Masuda K, Fujita Y, Fukui T. Diagnostic performance of quantitative fecal immunochemical test and multivariate prediction model for colorectal neoplasms in asymptomatic individuals. Eur J Gastroenterol Hepatol 2011;23:1036-41. 78. Elsafi SH, Alqahtani NI, Zakary NY, Al Zahrani EM. The sensitivity, specificity, predictive values, and likelihood ratios of fecal occult blood test for the detection of colorectal cancer in hospital settings. Clin Exp Gastroenterol 2015;8:279-84. 79. Lee YC, Chiu HM, Chiang TH, et al. Accuracy of faecal occult blood test and Helicobacter pylori stool antigen test for detection of upper gastrointestinal lesions. BMJ Open 2013;3:e003989. 80. Nakajima M, Saito H, Soma Y, Sobue T, Tanaka M, Munakata A. Prevention of advanced colorectal cancer by screening using the immunochemical faecal occult blood test: a case–control study. British journal of cancer 2003;89:23-8. 81. Saito H, Soma Y, Nakajima M, et al. A case-control study evaluating occult blood screening for colorectal cancer with hemoccult test and an immunochemical hemagglutination test. Oncology reports 2000;7:815-9. 82. Saito H, Soma Y, Koeda J, et al. Reduction in risk of mortality from colorectal cancer by fecal occult blood screening with immunochemical hemagglutination test. A case-control study. International journal of cancer 1995;61:465-9. 83. Cole SR, Young GP, Esterman A, Cadd B, Morcom J. A randomised trial of the impact of new faecal haemoglobin test technologies on population participation in screening for colorectal cancer. The Medical journal of Australia 2003; 10:117-22. 84. Macrae FA, Hill DJ, St. John DJB, Ambikapathy A, Garner JF. Predicting colon cancer screening behavior from health beliefs. Prev Med 1984;13:115-26. 85. Cole SR, Young GP. Effect of dietary restriction on participation in faecal occult blood test screening for colorectal cancer. The Medical journal of Australia 2001; 175:195-8. 86. McCusker J, Morrow GR. Factors related to the use of cancer early detection techniques. Prev Med 1980;9:388-97. 87. Salkeld GP, Solomon MJ, Short L, Ward J. Measuring the importance of attributes that influence consumer attitudes to colorectal cancer screening. ANZ J Surg 2003;73:128-32. 88. Wardle J, Pope R. The psychological costs of screening for cancer. J Psychosom Res 1992;36:609-24. 89. Lindholm E, Berglund B, Kewenter J, Haglind E. Worry associated with screening for colorectal carcinomas. Scand J Gastroenterol 1997; 32:238-45. 90. Parker MA, Robinson MH, Scholefield JH, Hardcastle JD. Psychiatric morbidity and screening for colorectal cancer. J Med Screen 2002;9:7-10. 91. Wardle J, Taylor T, Sutton S, Atkin W. Does publicity about cancer screening raise fear of cancer? Randomised trial of the psychological effect of information about cancer screening. BMJ (Clinical research ed) 1999;319:1037-8.

Back to top

6.2.4.4 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	Modelling report PSC1d

Back to top

6.3 Evidence summary, recommendations and considerations

Contents

6.3.1 Evidence summary table

table to be inserted with statements

6.3.2 Recommendations

Recs to be inserted

6.3.3 Considerations in making these recommendations

Screening benefit (PSC1a) With the widespread availability of evidence-based colorectal cancer screening in many countries including Australia (NBCSP), it would be unethical to initiate new randomised controlled trials to compare screening by iFOBT with no screening (NHMRC National Statement on Ethical Conduct in Human Research 2007 (Updated May 2015), cause 3.3.10). There is supporting level II evidence from the Zheng 200347 RCT, 3 large gFOBT RCTs25-27 from the 1990s, as well as 3 case-control studies80-82 on the effectiveness of

FOBT as a population based screening modality. Whilst population-based trials of iFOBT have not been as comprehensive as for gFOBT, the European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis (2010)40 recommends population screening with iFOBT over gFOBt on the basis of: (1) superior performance (e.g. sensitivity and specificity) in detecting cancers and adenomas; (2) greater acceptability to participants and (3) comparable complication rates and costs.23 The success of FOBT screening for bowel cancer in the Australian population was reported in the 2012 Analysis of Bowel Cancer Outcomes for the National Bowel Cancer Screening Program19. In this report, bowel cancer mortality was compared between people in the NBCSP invitee and the never-invited groups in an intention-to-screen bowel cancer mortality analysis. Of the 10,080 never-invited people with a bowel cancer diagnosis, 1,973 (19.6%) had died of bowel cancer before 2012. Of the 2,609 people in the NBCSP invitee group with a bowel cancer diagnosis, 298 (11.4%) had died of bowel cancer by the same date (HR=1.77, 95% CI: 1.57–2.00). The mean follow-up time to bowel cancer death for all diagnoses was 18.6 months (range 0–64.3 months, SD=13.9 months). Screening test accuracy (PSC1b) In Australia, weather conditions and geographic factors may affect performance of iFOBTs. High temperatures and delays to sample analysis may each reduce test sensitivity for cancer and advanced adenomas. This is of special importance in remote regions and during summer months in most parts of Australia. Participation rates may also be lower than desirable, due to linguistic and cultural factors, and an unwillingness to be involved in cancer prevention programs. Screening cost effectiveness (PSC1c) and screening age (PSC1d) The “Policy1-Bowel” model was used to simulate the NBCSP and alternative screening approaches. Calculated rates of colorectal cancer incidence and mortality, survival figures for colorectal cancer, the probability of dying from other causes and population size and projected size were all derived from Australian data. The costs of screening, investigation and stage-specific treatment all related to Australia. In addition, cost-effectiveness assessment related to the willingness-to-pay threshold of $AUD 50,000/LYS used in Australia. The findings therefore relate to population screening in Australia. Although findings may apply to other countries, the closeness will depend on similarities to Australia, including level of risk for colorectal cancer and the design and costs of their health services. Health system implications Clinical practice GPs have a critically important role in managing the interface between population screening and personalised care, identifying and advising those who should opt out because of major co-morbidities and limited life expectancy, the presence of special risk factors, recent colonoscopy for whatever reason, and those who should defer the invitation until they recover from recent surgery or major illness. GPs can also promote participation in the NBCSP, discuss the significance of positive screening test results to their patients, arrange colonoscopy, and discuss further management and interacting with the central register. Add info: (2) Expressing concern about the common practice of repeating the screening test after a positive result; and (3) the importance of prompt follow-up colonoscopy in those having positive screening tests. Colonoscopy services urgently need to introduce booking systems that give priority to these and othe high-risk groups to put this into effect. - their role in advising invitees on action to take - whether to proceed with screening, to defer or opt out of the NBCSP, to undergo diagnostic investigations because of symptoms etc; Resourcing PSC1a: Continued expansion of the NBCSP to complete rollout of biennial screening by 2020; Expansion of public awareness campaigns and promotion of the NBCSP to GPs to boost participation rates; Exploration of alternative screening pathways to boost participation rates in the indigenous population and other disadvantaged groups. PSC1b: (1) Highly desirable to establish centralised adenoma registers to evaluate the extent and significance of detection of adenomas in the NBCSP, to predict the likely contribution of adenoma resection to incidence and mortality reduction in colorectal cancer, and to support quality improvement in the high volume and costly area of colonoscopic post-polypectomy surveillance; PSC1c: Confirmation of the importance of the NBCSP but no specific implications for resources; PSC1d: Confirmation of the appropriateness of the present age range in the NBCSP without any resource implications. Barriers to implementation Barriers to participation in FOBT screening fall into several categories, including: inconvenience of the testing process, aversion to manipulating faeces, lack of perceived benefit of

screening, fear of a diagnosis of cancer, cost, views about personal invulnerability, and cultural beliefs and attitudes.83,84 Recent studies have demonstrated that several of these barriers can be at least partially overcome so as to improve participation. Use of iFOBTs, which require no change in diet or medication, simplifying the method of stool sampling and endorsement of screening by a person's own general practitioner all lead to a significant improvement in participation.85-87 Appropriate public education and promotion is usually necessary to enhance participation rates. Adverse psychological effects on individuals can range from the trauma of identification of disease in symptom-free, healthy individuals, to stress among people in whom cancer is suspected although later discounted, to more subtle concerns of participants during the screening process.88 Health care professionals must recognise the potential adverse psychological effects of screening, although several studies have shown no evidence of long-term harm after screening.89-91 Despite the possibility of adverse psychological consequences of screening, the stress generated by diagnosis of an advanced cancer when there has been no opportunity for early detection by screening also needs to be taken into consideration. Screening test accuracy In the NBCSP, screening tests are analysed in a central national laboratory, simplifying quality assurance. The major concerns relates to the adverse effects of high temperature on samples before return to the laboratory. This applies especially in summer months and in remote areas with poor postal services.

6.3.4 References

1. Wilson J, Junger G. Principles and practices of screening for disease. Geneva, Switzerland1968. Report No.: 34,1968. 2. Gnauck R. World Health Organization criteria for screening. In Colorectal Cancer: Prevention, Epidemiology and Screening. New York: Raven Press; 1980. 3. Schottenfeld D. Fundamental issues in cancer screening. In Colorectal Cancer: Prevention, Epidemiology and Screening. New York: Raven Press; 1980. 4. The Cancer Council Australia, Australian Cancer Network. Chapter 3, Population screening for colorectal cancer, 2005 CCA Guidelines The Prevention, early detection and management of colorectal cancer2005. 5. GP Y. Screening for colorectal cancer – new evidence in the last 10 years. Cancer Forum; 2014. p. 38. 6. Young GP, Symonds EL, Allison JE, et al. Advances in Fecal Occult Blood Tests: the FIT revolution. Digestive diseases and sciences 2015;60:609-22. 7. Cancer Council Australia. Clinical practice guidelines for the prevention, early detection and management of colorectal cancer (CRC) 2nd edition2005. Report No.: ISBN: 0-9775060-1-0. 8. Miles A, Cockburn J, Smith RA, Wardle J. A perspective from countries using organized screening programs. Cancer 2004;101:1201-13. 9. International Agency for Research on Cancer. Chapter 2, European guidelines for quality assurance in colorectal cancer screening and diagnosis, First Edition: International Agency for Research on Cancer; 2010. 10. Benson VS, Atkin WS, Green J, et al. Toward standardizing and reporting colorectal cancer screening indicators on an international level: The International Colorectal Cancer Screening Network. International journal of cancer 2012;130:2961-73. 11. Brawley OW. Colorectal cancer control: providing adequate care to those who need it. Journal of the National Cancer Institute 2014;106:dju075. 12. Flitcroft KL, St John DJ, Howard K, et al. A comparative case study of bowel cancer screening in the UK and Australia: evidence lost in translation? J Med Screen 2011;18:193-203. 13. Schreuders EH, Ruco A, Rabeneck L, et al. Colorectal cancer screening: a global overview of existing programmes. Gut 2015;64:1637-49. 14. Australian Health Technology Advisory Committee. Colorectal Cancer Screening1997. Report No.: ISBN 0 642 27289 1 15. Australian Government Department of Health. The Australian bowel cancer screening pilot program and beyond: final evaluation report2005. 16. Australian Institute of Health and Welfare. National Bowel Cancer Screening Program Monitoring Report 2016. Canberra: AIHW; 2016. Report No.: Cat. No CAN 97. 17. Cole SR, Tucker GR, Osborne JM, et al. Shift to earlier stage at diagnosis as a consequence of the National Bowel Cancer Screening Program. The Medical journal of Australia 2013;198:327-30. 18. Ananda S, Wong H, Faragher I, et al. Survival

impact of the Australian National Bowel Cancer Screening Programme. Internal medicine journal 2016;46:166-71. 19. Australian Institute of Health and Welfare, Australian Government Department of Health. Analysis of colorectal cancer outcomes for the Australian National Bowel Cancer Screening Program. Asia-Pacific journal of clinical oncology 2016;12:22-32. 20. Pignone MP, Flitcroft KL, Howard K, Trevena LJ, Salkeld GP, St John D. Costs and cost-effectiveness of full implementation of a biennial faecal occult blood test screening program for bowel cancer in Australia. The Medical journal of Australia 2011;194:180-5. 21. Cenin DR, St John DJ, Ledger MJ, Slevin T, Lansdorp-Vogelaar I. Optimising the expansion of the National Bowel Cancer Screening Program. The Medical journal of Australia 2014;201:456-61. 22. St John J, Grogan P. Compelling new data on the effectiveness of Australia's National Bowel Cancer Screening Program: A model for best practice? Asia-Pacific journal of clinical oncology 2016;12:7-9. 23. van Rossum LG, van Rijn AF, Laheij RJ, et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. Gastroenterology 2008; 135:82-90. 24. Park DI, Ryu S, Kim YH, et al. Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average risk undergoing colorectal cancer screening. Am J Gastroenterol 2010;105:2017-25. 25. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. N Engl J Med 1993;328:1365-71. 26. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet (London, England) 1996;348:1472-7. 27. Kronborg O, Fenger C, Olsen J, Jørgensen OD, Søndergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet (London, England) 1996;348:1467-71. 28. Mandel JS, Church TR, Ederer F, Bond JH. Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood. Journal of the National Cancer Institute 1999;91:434-7. 29. Mandel JS, Church TR, Bond JH, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. N Engl J Med 2000;343:1603-7. 30. Hewitson P, Glasziou P, Irwig L, Towler B, Watson E. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. The Cochrane database of systematic reviews 2007:Cd001216. 31. Towler B, Irwig L, Glasziou P, Kewenter J, Weller D, Silagy C. A systematic review of the effects of screening for colorectal cancer using the faecal occult blood test, hemoccult. BMJ (Clinical research ed) 1998;317:559-65. 32. Segnan N, Armaroli P, Bonelli L, et al. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial--SCORE. Journal of the National Cancer Institute 2011;103: 1310-22. 33. Elmunzer BJ, Hayward RA, Schoenfeld PS, Saini SD, Deshpande A, Waljee AK. Effect of flexible sigmoidoscopy-based screening on incidence and mortality of colorectal cancer: a systematic review and meta-analysis of randomized controlled trials. PLoS Med 2012;9:e1001352. 34. Schoen RE, Pinsky PF, Weissfeld JL, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med 2012;366: 2345-57. 35. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet (London, England) 2010;375:1624-33. 36. Quintero E, Castells A, Bujanda L, et al. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. N Engl J Med 2012;366:697-706. 37. Bretthauer M, Kaminski MF, Løberg M, et al. Population-Based Colonoscopy Screening for Colorectal Cancer: A Randomized Clinical Trial. JAMA Intern Med 2016. 38. ClinicalTrials.gov. Colonoscopy vs fecal immunochemical test in reducing mortality from colorectal cancer (CONFIRM) [NCT01239082] 2016. 39. Knudsen AB, Zauber AG, Rutter CM, et al. Estimation of Benefits, Burden, and Harms of Colorectal Cancer Screening Strategies: Modeling Study for the US Preventive Services Task Force. JAMA 2016;315:2595-609. 40. International Agency for Research on Cancer. European guidelines for quality assurance in colorectal cancer screening and diagnosis, First Edition: International Agency for Research on Cancer; 2010. 41. Secretariat MA. Fecal Occult Blood Test for Colorectal Cancer Screening: an evidence-based analysis. Toronto, Ontario, Canada: Ministry of Health and Long-Term Care; 2009. 42. Force UPST. Screening for Colorectal Cancer US Preventive Services Task Force Recommendation Statement. JAMA 2016;315: 2564-75. 43. Force USPST. Screening for Colorectal Cancer: U.S. Preventive Services Task Force Recommendation Statement. Annals of Internal Medicine 2008;149:627-37. 44. Jørgensen O, Kronborg O,

Fenger C. A randomised study on screening for colorectal cancer using faecal occult blood testing: results after 13 years and seven biennial screening rounds. Gut 2002;50:29-39. 45. Scholefield J, Moss S, Sufi F, Mangham C, Hardcastle J. Effect of faecal occult blood screening on mortality from colorectal cancer: results from a randomised controlled trial. Gut 2002;50:840-4. 46. Scholefield JH, Moss SM, Mangham CM, Whynes DK, Hardcastle JD. Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up. Gut 2012;61:1036-40. 47. Zheng S, Chen K, Liu X, et al. Cluster Randomization Trial of Sequence Mass Screening for Colorectal Cancer. Dis Colon Rectum 2003;46:51-8. 48. Blom J, Yin L, Liden A, et al. A 9-year follow-up study of participants and nonparticipants in sigmoidoscopy screening: importance of self-selection. Cancer Epidemiol Biomarkers Prev 2008;17:1163-8. 49. Holme O, Loberg M, Kalager M, et al. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. JAMA 2014;312:606-15. 50. Shroff J, Thosani N, Batra S, Singh H, Guha S. Reduced incidence and mortality from colorectal cancer with flexible-sigmoidoscopy screening: a meta-analysis. World J Gastroenterol 2014;20:18466-76. 51. Hoff G, Grotmol T, Skovlund E, Bretthauer M, Norwegian Colorectal Cancer Prevention Study G. Risk of colorectal cancer seven years after flexible sigmoidoscopy screening: randomised controlled trial. BMJ (Clinical research ed) 2009;338: b1846. 52. Castro I, Cubiella J, Rivera C, et al. Fecal immunochemical test accuracy in familial risk colorectal cancer screening. International journal of cancer 2014;134:367-75. 53. Gimeno-Garcia AZ, Quintero E, Nicolas-Perez D, Hernandez-Guerra M, Parra-Blanco A, Jimenez-Sosa A. Screening for familial colorectal cancer with a sensitive immunochemical fecal occult blood test: a pilot study. Eur J Gastroenterol Hepatol 2009;21:1062-7. 54. Ng SC, Ching JY, Chan V, et al. Diagnostic accuracy of faecal immunochemical test for screening individuals with a family history of colorectal cancer. Aliment Pharmacol Ther 2013;38:835-41. 55. Ahlquist DA, Sargent DJ, Loprinzi CL, et al. Stool DNA and occult blood testing for screen detection of colorectal neoplasia. Ann Intern Med 2008;149:441-50, W81. 56. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med 2014;370:1287-97. 57. Redwood DG, Asay ED, Blake ID, et al. Stool DNA Testing for Screening Detection of Colorectal Neoplasia in Alaska Native People. Mayo Clin Proc 2016;91:61-70. 58. Annahazi A, Abraham S, Farkas K, et al. A pilot study on faecal MMP-9: a new noninvasive diagnostic marker of colorectal cancer. British journal of cancer 2016;114:787-92. 59. Church TR, Wandell M, Lofton-Day C, et al. Prospective evaluation of methylated SEPT9 in plasma for detection of asymptomatic colorectal cancer. Gut 2014;63:317-25. 60. Khalid-de Bakker CA, Jonkers DM, Sanduleanu S, et al. Test performance of immunologic fecal occult blood testing and sigmoidoscopy compared with primary colonoscopy screening for colorectal advanced adenomas. Cancer Prev Res (Phila) 2011;4:1563-71. 61. Brenner H, Haug U, Hundt S. Sex differences in performance of fecal occult blood testing. Am J Gastroenterol 2010;105:2457-64. 62. Chiu HM, Lee YC, Tu CH, et al. Association between early stage colon neoplasms and false-negative results from the fecal immunochemical test. Clin Gastroenterol Hepatol 2013;11:832-8 e1-2. 63. de Wijkerslooth TR, Stoop EM, Bossuyt PM, et al. Immunochemical fecal occult blood testing is equally sensitive for proximal and distal advanced neoplasia. Am J Gastroenterol 2012;107:1570-8. 64. Graser A, Stieber P, Nagel D, et al. Comparison of CT colonography, colonoscopy, sigmoidoscopy and faecal occult blood tests for the detection of advanced adenoma in an average risk population. Gut 2009;58:241-8. 65. Hundt S, Haug U, Brenner H. Comparative evaluation of immunochemical fecal occult blood tests for colorectal adenoma detection. Ann Intern Med 2009; 150:162-9. 66. Morikawa T, Kato J, Yamaji Y, Wada R, Mitsushima T, Shiratori Y. A comparison of the immunochemical fecal occult blood test and total colonoscopy in the asymptomatic population. Gastroenterology 2005;129:422-8. 67. Nakazako M. YH, Matsushita H., Sato K., Fujita K., Yamanaka Y., Imai Y. Immunologic Fecal Occult Blood Test for Colorectal Cancer Screening. Japan Med Assoc J 2006;49:203-7. 68. Parra-Blanco A, Gimeno-Garcia AZ, Quintero E, et al. Diagnostic accuracy of immunochemical versus guaiac faecal occult blood tests for colorectal cancer screening. J Gastroenterol 2010;45:703-12. 69. Terhaar sive Droste JS, Oort FA, van der Hulst RW, et al. Higher fecal immunochemical test cutoff levels: lower positivity rates but still acceptable detection rates for early-stage colorectal cancers. Cancer Epidemiol Biomarkers Prev 2011;

20:272-80. 70. Viana Freitas BR, Kibune Nagasako C, Pavan CR, et al. Immunochemical fecal occult blood test for detection of advanced colonic adenomas and colorectal cancer: comparison with colonoscopy results. Gastroenterol Res Pract 2013;2013:384561. 71. Brenner H, Tao S. Superior diagnostic performance of faecal immunochemical tests for haemoglobin in a head-to-head comparison with guaiac based faecal occult blood test among 2235 participants of screening colonoscopy. Eur J Cancer 2013;49:3049-54. 72. Chen Y-Y, Chen T-H, Su M-Y, et al. Accuracy of immunochemical fecal occult blood test for detecting colorectal neoplasms in individuals undergoing health check-ups. Adv Digest Med 2014;1:74-9. 73. Hernandez V, Cubiella J, Gonzalez-Mao MC, et al. Fecal immunochemical test accuracy in average-risk colorectal cancer screening. World J Gastroenterol 2014;20: 1038-47. 74. Kato J, Morikawa T, Kuriyama M, et al. Combination of sigmoidoscopy and a fecal immunochemical test to detect proximal colon neoplasia. Clin Gastroenterol Hepatol 2009;7:1341-6. 75. Lee YH, Hur M, Kim H, et al. Optimal cut-off concentration for a faecal immunochemical test for haemoglobin by Hemo Techt NS-Plus C15 system for the colorectal cancer screening. Clin Chem Lab Med 2015;53:e69-71. 76. Levy BT, Bay C, Xu Y, et al. Test characteristics of faecal immunochemical tests (FIT) compared with optical colonoscopy. J Med Screen 2014; 21:133-43. 77. Omata F, Shintani A, Isozaki M, Masuda K, Fujita Y, Fukui T. Diagnostic performance of quantitative fecal immunochemical test and multivariate prediction model for colorectal neoplasms in asymptomatic individuals. Eur J Gastroenterol Hepatol 2011;23:1036-41. 78. Elsafi SH, Alqahtani NI, Zakary NY, Al Zahrani EM. The sensitivity, specificity, predictive values, and likelihood ratios of fecal occult blood test for the detection of colorectal cancer in hospital settings. Clin Exp Gastroenterol 2015;8:279-84. 79. Lee YC, Chiu HM, Chiang TH, et al. Accuracy of faecal occult blood test and Helicobacter pylori stool antigen test for detection of upper gastrointestinal lesions. BMJ Open 2013;3:e003989. 80. Nakajima M, Saito H, Soma Y, Sobue T, Tanaka M, Munakata A. Prevention of advanced colorectal cancer by screening using the immunochemical faecal occult blood test: a case–control study. British journal of cancer 2003;89:23-8. 81. Saito H, Soma Y, Nakajima M, et al. A case-control study evaluating occult blood screening for colorectal cancer with hemoccult test and an immunochemical hemagglutination test. Oncology reports 2000;7:815-9. 82. Saito H, Soma Y, Koeda J, et al. Reduction in risk of mortality from colorectal cancer by fecal occult blood screening with immunochemical hemagglutination test. A case-control study. International journal of cancer 1995;61:465-9. 83. Cole SR, Young GP, Esterman A, Cadd B, Morcom J. A randomised trial of the impact of new faecal haemoglobin test technologies on population participation in screening for colorectal cancer. The Medical journal of Australia 2003; 10:117-22. 84. Macrae FA, Hill DJ, St. John DJB, Ambikapathy A, Garner JF. Predicting colon cancer screening behavior from health beliefs. Prev Med 1984;13:115-26. 85. Cole SR, Young GP. Effect of dietary restriction on participation in faecal occult blood test screening for colorectal cancer. The Medical journal of Australia 2001; 175:195-8. 86. McCusker J, Morrow GR. Factors related to the use of cancer early detection techniques. Prev Med 1980;9:388-97. 87. Salkeld GP, Solomon MJ, Short L, Ward J. Measuring the importance of attributes that influence consumer attitudes to colorectal cancer screening. ANZ J Surg 2003;73:128-32. 88. Wardle J, Pope R. The psychological costs of screening for cancer. J Psychosom Res 1992;36:609-24. 89. Lindholm E, Berglund B, Kewenter J, Haglind E. Worry associated with screening for colorectal carcinomas. Scand J Gastroenterol 1997; 32:238-45. 90. Parker MA, Robinson MH, Scholefield JH, Hardcastle JD. Psychiatric morbidity and screening for colorectal cancer. J Med Screen 2002;9:7-10. 91. Wardle J, Taylor T, Sutton S, Atkin W. Does publicity about cancer screening raise fear of cancer? Randomised trial of the psychological effect of information about cancer screening. BMJ (Clinical research ed) 1999;319:1037-8.

Back to top

6.4 Discussion

6.4.1 Discussion

The National Bowel Cancer Screening Program (NBCSP) in Australia was initiated in 2006(ref#1). From 2020 onwards, the program will offer biennial colorectal (CRC) screening using immunochemical Faecal Occult Blood testing (iFOBT) for Australians aged between 50 and 74 years. However, some stakeholders have called for an earlier age of starting screening, and a recent report suggested that biennial iFOBT screening at age 40-70 years is cost-effective when compared to no screening(ref#4). However, systematic evaluation of the impact in terms of benefits and harms, as well as the cost-effectiveness of potential age extensions of the program (either to younger or older ages) has been performed. Consistent with the current NBCSP recommendations, an evaluation conducted by US Preventative Services Task Force (USPSTF) in 2008 considered the optimal age to begin and to stop colorectal cancer screening, and recommended that screening be conducted from age 50 to 75 years(ref#2). The same screening age range was also recommended in an updated 2016 evaluation.3 The latter study found that lowering the screening start age from 50 years to 45 years would yield as a relatively small gain in terms of life-years but would require a large increase in the number of colonoscopies required (ref#3). Possible outline for the Discussion (J St J)

In 2015, the Australian Commonwealth Department of Health commissioned a systematic review to update the 2005 NHMRC-approved Clinical Practice Guidelines for the Prevention, Early detection and Management of Colorectal Cancer. This update included review of the guidelines on population screening for colorectal cancer.

Summarise approaches to screening - population and opportunistic. The decision to adopt centrally organised screening under the direction of the Commonwealth Department - in collaboration with the States and territories which have responsibility for public hospital services, including provision of colonoscopy in the public sector.

Reasons for the decision - including Australia’s favourable experience with organised screening for breast cancer and cervical cancer in Australia - programs started in 1991.

Recognition of the importance of taking an evidence-based approach when dealing with a large population - target population 8 million and rising - the responsibility of approaching healthy individuals - encouraging them to participate - a program with recognised harms as well as benefits.

Constraints with choice of test for such a large population

Choice of a FOBT - Level 1 evidence available in 2006 - decision to offer second-yearly testing as in most of the RCTs

Choice of an iFOBT at the outset - advantages over a gFOBT - especially with test sensitivity for cancer and acceptability to the population - no need for special diet or change in medication. Analysis in a central laboratory - to facilitate quality assurance

Choice of an age range of 50-74 yr for the Program. Phased introduction of screening because of concerns about capacity of colonoscopy services , especially in the public sector. Initiatives to provide high quality colonoscopy, to improve opportunities for training in colonoscopy and to assess the capacity of colonoscopy services.

The decision to adopt usual care for follow-up of screening tests - the desirability of involving GPs in the NBCSP - but introducing challenges with data retrieval and reporting of outcomes - option of referral for colonoscopy in either the public or private system.

Stakeholders now questioning the decision to offer second-yearly testing rather than annual testing.

Also questioning the starting age of 50 yr, preferring a starting age of 40 or 45 yr.

Also, questions about the type of screening test - mounting evidence for flexible sigmoidoscopy, US guidelines promoting primary colonoscopy as the best method for opportunistic screening, interest in the emerging faecal and blood-based tests for detection of cancer-specific markers.

Review of our methodology - systematic literature review for high level evidence - formulation of PICO questions - commissioning of microsimulation modelling to investigate cost-effectiveness and to address questions about a range of screening strategies - type of test, frequency of testing.

Discussion about the limited opportunities to perform RCTs now that screening is known to reduce mortality - quote NHMRC views on this - three RCTs assessing colonoscopic screening in progress but only one involves no screening in the control arm - list references.

The emerging role of microsimulation modelling - and where it fits in the evidence ladder - give examples and list references of a number of recent studies designed to address specific questions about screening practices - while recognising their limitations , they allow recommendations to be based on structured and formal methods rather than just the opinion of a small number of experts - modelling provides insights that can not be obtained though expert opinion alone.

With population screening, recognition of the need for evidence about effectiveness of tests; their acceptability to the target population; the feasibility of providing the test with regard to workforce and cost and the impact that choice of a test may have on other health services; and the cost-effectveness of screening based on that test. All four critically important in a population screening program.

Discuss our findings on choice of test - especially FS - Level 1 evidence for FS - reasons for dismissing it - concerns about participation levels - currently not feasible in the Australian setting - importantly,

Discuss reasons for rejecting annual iFOBT - not cost-effective - logistic aspects - the impossibility of issuing and following 8 million invitations each year - too frequent for participants - no sooner finished one than they receive the next test (a soft point but real, even so).

Discuss starting age - staying with 50 - will need careful wording - demonstrates how modelling can provide useful perspective of decision. And we should refer to the recommendation to start screening at 40 in those with a low-risk family history of colorectal cancer.

Screening after age 75 - recognising lower ratio of benefits to harms - greater likelihood of co-morbidities - but also the growing number of elderly, health conscious people who appreciate their relatively high risk for CRC - the place for opportunistic screening directed by their GP - another area where opportunistic screening interfaces with population screening.

Finish with a brief conclusion and note the need for ongoing reviews of the evidence. Unresolved issues Does the inappropriately high rate of colonoscopy in Australia reduce effectiveness of the NBCSP? (Hooi) Monitoring of evidence of changing epidemiology, including incidence at younger age and changes in distribution of cancer within the large bowel (Hooi) E.g. you mentioned there are special considerations when screening for sessile serrated lesions, as the FOBT not suitable (including levels of bleeding and place of FOBT vs other methods - colonoscopy, DNA markers) – James, you could draft a Practice Point about this as well. The recommended age range for the NBCSP The frequency of screening Screening in those below the lower age limit or over the upper age limit A reminder but not for inclusion in the text: Some national programs are able to exclude people before invitations are issued - filtering out those with co-morbidities that limit life expectancy, those already having surveillance colonoscopy for cancer or adenoma follow-up etc. In Australia, the NBCSP does not as yet have access to clinical information, everyone aged between 50 and 74 yr receiving invitations to screen. Clinical differences between invited populations make it difficult to compare participation rates for national programs. Studies currently underway Points to potentially cover here: • development of biomarker tests (blood or faecal, DNA or protein) • colonoscopy screening RCT (references 36-38) Future research priorities Insert suggestions for further research priorities. E.g evaluation of new approaches to screening, such as combining screening methods or evaluation of newly developed screening tests. James, we feel that your comments re tailoring screening to allow for differences in risk would be more appropriate for Mark’s family history screening chapter.

Back to top

6.4.2 References

1. Wilson J, Junger G. Principles and practices of screening for disease. Geneva, Switzerland1968. Report No.: 34,1968. 2. Gnauck R. World Health Organization criteria for screening. In Colorectal Cancer: Prevention, Epidemiology and Screening. New York: Raven Press; 1980. 3. Schottenfeld D. Fundamental issues in cancer screening. In Colorectal Cancer: Prevention, Epidemiology and Screening. New York: Raven Press; 1980. 4. The Cancer Council Australia, Australian Cancer Network. Chapter 3, Population screening for colorectal cancer, 2005 CCA Guidelines The Prevention, early detection and management of colorectal cancer2005. 5. GP Y. Screening for colorectal cancer – new evidence in the last 10 years. Cancer Forum; 2014. p. 38. 6. Young GP, Symonds EL, Allison JE, et al. Advances in Fecal Occult Blood Tests: the FIT revolution. Digestive diseases and sciences 2015;60:609-22. 7. Cancer Council Australia. Clinical practice guidelines for the prevention, early detection and management of colorectal cancer (CRC) 2nd edition2005. Report No.: ISBN: 0-9775060-1-0. 8. Miles A, Cockburn J, Smith RA, Wardle J. A perspective from countries using organized screening programs. Cancer 2004;101:1201-13. 9. International Agency for Research on Cancer. Chapter 2, European guidelines for quality assurance in colorectal cancer screening and diagnosis, First Edition: International Agency for Research on Cancer; 2010. 10. Benson VS, Atkin WS, Green J, et al. Toward standardizing and reporting colorectal cancer screening indicators on an international level: The International Colorectal Cancer Screening Network. International journal of cancer 2012;130:2961-73. 11. Brawley OW. Colorectal cancer control: providing adequate care to those who need it. Journal of the National Cancer Institute 2014;106:dju075. 12. Flitcroft KL, St John DJ, Howard K, et al. A comparative case study of bowel cancer screening in the UK and Australia: evidence lost in translation? J Med Screen 2011;18:193-203. 13. Schreuders EH, Ruco A, Rabeneck L, et al. Colorectal cancer screening: a global overview of existing programmes. Gut 2015;64:1637-49. 14. Australian Health Technology Advisory Committee. Colorectal Cancer Screening1997. Report No.: ISBN 0 642 27289 1 15. Australian Government Department of Health. The Australian bowel cancer screening pilot program and beyond: final evaluation report2005. 16. Australian Institute of Health and Welfare. National Bowel Cancer Screening

Program Monitoring Report 2016. Canberra: AIHW; 2016. Report No.: Cat. No CAN 97. 17. Cole SR, Tucker GR, Osborne JM, et al. Shift to earlier stage at diagnosis as a consequence of the National Bowel Cancer Screening Program. The Medical journal of Australia 2013;198:327-30. 18. Ananda S, Wong H, Faragher I, et al. Survival impact of the Australian National Bowel Cancer Screening Programme. Internal medicine journal 2016;46:166-71. 19. Australian Institute of Health and Welfare, Australian Government Department of Health. Analysis of colorectal cancer outcomes for the Australian National Bowel Cancer Screening Program. Asia-Pacific journal of clinical oncology 2016;12:22-32. 20. Pignone MP, Flitcroft KL, Howard K, Trevena LJ, Salkeld GP, St John D. Costs and cost-effectiveness of full implementation of a biennial faecal occult blood test screening program for bowel cancer in Australia. The Medical journal of Australia 2011;194:180-5. 21. Cenin DR, St John DJ, Ledger MJ, Slevin T, Lansdorp-Vogelaar I. Optimising the expansion of the National Bowel Cancer Screening Program. The Medical journal of Australia 2014;201:456-61. 22. St John J, Grogan P. Compelling new data on the effectiveness of Australia's National Bowel Cancer Screening Program: A model for best practice? Asia-Pacific journal of clinical oncology 2016;12:7-9. 23. van Rossum LG, van Rijn AF, Laheij RJ, et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. Gastroenterology 2008;135:82-90. 24. Park DI, Ryu S, Kim YH, et al. Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average risk undergoing colorectal cancer screening. Am J Gastroenterol 2010;105:2017-25. 25. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. N Engl J Med 1993;328:1365-71. 26. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet (London, England) 1996;348:1472-7. 27. Kronborg O, Fenger C, Olsen J, Jørgensen OD, Søndergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet (London, England) 1996;348:1467-71. 28. Mandel JS, Church TR, Ederer F, Bond JH. Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood. Journal of the National Cancer Institute 1999;91:434-7. 29. Mandel JS, Church TR, Bond JH, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. N Engl J Med 2000;343:1603-7. 30. Hewitson P, Glasziou P, Irwig L, Towler B, Watson E. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. The Cochrane database of systematic reviews 2007:Cd001216. 31. Towler B, Irwig L, Glasziou P, Kewenter J, Weller D, Silagy C. A systematic review of the effects of screening for colorectal cancer using the faecal occult blood test, hemoccult. BMJ (Clinical research ed) 1998;317:559-65. 32. Segnan N, Armaroli P, Bonelli L, et al. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial--SCORE. Journal of the National Cancer Institute 2011;103:1310-22. 33. Elmunzer BJ, Hayward RA, Schoenfeld PS, Saini SD, Deshpande A, Waljee AK. Effect of flexible sigmoidoscopy-based screening on incidence and mortality of colorectal cancer: a systematic review and meta-analysis of randomized controlled trials. PLoS Med 2012;9:e1001352. 34. Schoen RE, Pinsky PF, Weissfeld JL, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med 2012;366:2345-57. 35. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet (London, England) 2010;375:1624-33. 36. Quintero E, Castells A, Bujanda L, et al. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. N Engl J Med 2012;366:697-706. 37. Bretthauer M, Kaminski MF, Løberg M, et al. Population-Based Colonoscopy Screening for Colorectal Cancer: A Randomized Clinical Trial. JAMA Intern Med 2016. 38. ClinicalTrials.gov. Colonoscopy vs fecal immunochemical test in reducing mortality from colorectal cancer (CONFIRM) [NCT01239082] 2016. 39. Knudsen AB, Zauber AG, Rutter CM, et al. Estimation of Benefits, Burden, and Harms of Colorectal Cancer Screening Strategies: Modeling Study for the US Preventive Services Task Force. JAMA 2016;315:2595-609. 40. International Agency for Research on Cancer. European guidelines for quality assurance in colorectal cancer screening and diagnosis, First Edition: International Agency for Research on Cancer; 2010. 41. Secretariat MA. Fecal Occult Blood Test for Colorectal Cancer Screening: an evidence-based analysis. Toronto, Ontario, Canada: Ministry of Health and Long-Term Care; 2009. 42. Force UPST.

Screening for Colorectal Cancer US Preventive Services Task Force Recommendation Statement. JAMA 2016;315: 2564-75. 43. Force USPST. Screening for Colorectal Cancer: U.S. Preventive Services Task Force Recommendation Statement. Annals of Internal Medicine 2008;149:627-37. 44. Jørgensen O, Kronborg O, Fenger C. A randomised study on screening for colorectal cancer using faecal occult blood testing: results after 13 years and seven biennial screening rounds. Gut 2002;50:29-39. 45. Scholefield J, Moss S, Sufi F, Mangham C, Hardcastle J. Effect of faecal occult blood screening on mortality from colorectal cancer: results from a randomised controlled trial. Gut 2002;50:840-4. 46. Scholefield JH, Moss SM, Mangham CM, Whynes DK, Hardcastle JD. Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up. Gut 2012;61:1036-40. 47. Zheng S, Chen K, Liu X, et al. Cluster Randomization Trial of Sequence Mass Screening for Colorectal Cancer. Dis Colon Rectum 2003;46:51-8. 48. Blom J, Yin L, Liden A, et al. A 9-year follow-up study of participants and nonparticipants in sigmoidoscopy screening: importance of self-selection. Cancer Epidemiol Biomarkers Prev 2008;17:1163-8. 49. Holme O, Loberg M, Kalager M, et al. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. JAMA 2014;312:606-15. 50. Shroff J, Thosani N, Batra S, Singh H, Guha S. Reduced incidence and mortality from colorectal cancer with flexible-sigmoidoscopy screening: a meta-analysis. World J Gastroenterol 2014;20:18466-76. 51. Hoff G, Grotmol T, Skovlund E, Bretthauer M, Norwegian Colorectal Cancer Prevention Study G. Risk of colorectal cancer seven years after flexible sigmoidoscopy screening: randomised controlled trial. BMJ (Clinical research ed) 2009;338: b1846. 52. Castro I, Cubiella J, Rivera C, et al. Fecal immunochemical test accuracy in familial risk colorectal cancer screening. International journal of cancer 2014;134:367-75. 53. Gimeno-Garcia AZ, Quintero E, Nicolas-Perez D, Hernandez-Guerra M, Parra-Blanco A, Jimenez-Sosa A. Screening for familial colorectal cancer with a sensitive immunochemical fecal occult blood test: a pilot study. Eur J Gastroenterol Hepatol 2009;21:1062-7. 54. Ng SC, Ching JY, Chan V, et al. Diagnostic accuracy of faecal immunochemical test for screening individuals with a family history of colorectal cancer. Aliment Pharmacol Ther 2013;38:835-41. 55. Ahlquist DA, Sargent DJ, Loprinzi CL, et al. Stool DNA and occult blood testing for screen detection of colorectal neoplasia. Ann Intern Med 2008;149:441-50, W81. 56. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med 2014;370:1287-97. 57. Redwood DG, Asay ED, Blake ID, et al. Stool DNA Testing for Screening Detection of Colorectal Neoplasia in Alaska Native People. Mayo Clin Proc 2016;91:61-70. 58. Annahazi A, Abraham S, Farkas K, et al. A pilot study on faecal MMP-9: a new noninvasive diagnostic marker of colorectal cancer. British journal of cancer 2016;114:787-92. 59. Church TR, Wandell M, Lofton-Day C, et al. Prospective evaluation of methylated SEPT9 in plasma for detection of asymptomatic colorectal cancer. Gut 2014;63:317-25. 60. Khalid-de Bakker CA, Jonkers DM, Sanduleanu S, et al. Test performance of immunologic fecal occult blood testing and sigmoidoscopy compared with primary colonoscopy screening for colorectal advanced adenomas. Cancer Prev Res (Phila) 2011;4:1563-71. 61. Brenner H, Haug U, Hundt S. Sex differences in performance of fecal occult blood testing. Am J Gastroenterol 2010;105:2457-64. 62. Chiu HM, Lee YC, Tu CH, et al. Association between early stage colon neoplasms and false-negative results from the fecal immunochemical test. Clin Gastroenterol Hepatol 2013;11:832-8 e1-2. 63. de Wijkerslooth TR, Stoop EM, Bossuyt PM, et al. Immunochemical fecal occult blood testing is equally sensitive for proximal and distal advanced neoplasia. Am J Gastroenterol 2012;107:1570-8. 64. Graser A, Stieber P, Nagel D, et al. Comparison of CT colonography, colonoscopy, sigmoidoscopy and faecal occult blood tests for the detection of advanced adenoma in an average risk population. Gut 2009;58:241-8. 65. Hundt S, Haug U, Brenner H. Comparative evaluation of immunochemical fecal occult blood tests for colorectal adenoma detection. Ann Intern Med 2009; 150:162-9. 66. Morikawa T, Kato J, Yamaji Y, Wada R, Mitsushima T, Shiratori Y. A comparison of the immunochemical fecal occult blood test and total colonoscopy in the asymptomatic population. Gastroenterology 2005;129:422-8. 67. Nakazako M. YH, Matsushita H., Sato K., Fujita K., Yamanaka Y., Imai Y. Immunologic Fecal Occult Blood Test for Colorectal Cancer Screening. Japan Med Assoc J 2006;49:203-7. 68. Parra-Blanco A, Gimeno-Garcia AZ, Quintero E, et al. Diagnostic accuracy of immunochemical versus guaiac

faecal occult blood tests for colorectal cancer screening. J Gastroenterol 2010;45:703-12. 69. Terhaar sive Droste JS, Oort FA, van der Hulst RW, et al. Higher fecal immunochemical test cutoff levels: lower positivity rates but still acceptable detection rates for early-stage colorectal cancers. Cancer Epidemiol Biomarkers Prev 2011; 20:272-80. 70. Viana Freitas BR, Kibune Nagasako C, Pavan CR, et al. Immunochemical fecal occult blood test for detection of advanced colonic adenomas and colorectal cancer: comparison with colonoscopy results. Gastroenterol Res Pract 2013;2013:384561. 71. Brenner H, Tao S. Superior diagnostic performance of faecal immunochemical tests for haemoglobin in a head-to-head comparison with guaiac based faecal occult blood test among 2235 participants of screening colonoscopy. Eur J Cancer 2013;49:3049-54. 72. Chen Y-Y, Chen T-H, Su M-Y, et al. Accuracy of immunochemical fecal occult blood test for detecting colorectal neoplasms in individuals undergoing health check-ups. Adv Digest Med 2014;1:74-9. 73. Hernandez V, Cubiella J, Gonzalez-Mao MC, et al. Fecal immunochemical test accuracy in average-risk colorectal cancer screening. World J Gastroenterol 2014;20: 1038-47. 74. Kato J, Morikawa T, Kuriyama M, et al. Combination of sigmoidoscopy and a fecal immunochemical test to detect proximal colon neoplasia. Clin Gastroenterol Hepatol 2009;7:1341-6. 75. Lee YH, Hur M, Kim H, et al. Optimal cut-off concentration for a faecal immunochemical test for haemoglobin by Hemo Techt NS-Plus C15 system for the colorectal cancer screening. Clin Chem Lab Med 2015;53:e69-71. 76. Levy BT, Bay C, Xu Y, et al. Test characteristics of faecal immunochemical tests (FIT) compared with optical colonoscopy. J Med Screen 2014; 21:133-43. 77. Omata F, Shintani A, Isozaki M, Masuda K, Fujita Y, Fukui T. Diagnostic performance of quantitative fecal immunochemical test and multivariate prediction model for colorectal neoplasms in asymptomatic individuals. Eur J Gastroenterol Hepatol 2011;23:1036-41. 78. Elsafi SH, Alqahtani NI, Zakary NY, Al Zahrani EM. The sensitivity, specificity, predictive values, and likelihood ratios of fecal occult blood test for the detection of colorectal cancer in hospital settings. Clin Exp Gastroenterol 2015;8:279-84. 79. Lee YC, Chiu HM, Chiang TH, et al. Accuracy of faecal occult blood test and Helicobacter pylori stool antigen test for detection of upper gastrointestinal lesions. BMJ Open 2013;3:e003989. 80. Nakajima M, Saito H, Soma Y, Sobue T, Tanaka M, Munakata A. Prevention of advanced colorectal cancer by screening using the immunochemical faecal occult blood test: a case–control study. British journal of cancer 2003;89:23-8. 81. Saito H, Soma Y, Nakajima M, et al. A case-control study evaluating occult blood screening for colorectal cancer with hemoccult test and an immunochemical hemagglutination test. Oncology reports 2000;7:815-9. 82. Saito H, Soma Y, Koeda J, et al. Reduction in risk of mortality from colorectal cancer by fecal occult blood screening with immunochemical hemagglutination test. A case-control study. International journal of cancer 1995;61:465-9. 83. Cole SR, Young GP, Esterman A, Cadd B, Morcom J. A randomised trial of the impact of new faecal haemoglobin test technologies on population participation in screening for colorectal cancer. The Medical journal of Australia 2003; 10:117-22. 84. Macrae FA, Hill DJ, St. John DJB, Ambikapathy A, Garner JF. Predicting colon cancer screening behavior from health beliefs. Prev Med 1984;13:115-26. 85. Cole SR, Young GP. Effect of dietary restriction on participation in faecal occult blood test screening for colorectal cancer. The Medical journal of Australia 2001; 175:195-8. 86. McCusker J, Morrow GR. Factors related to the use of cancer early detection techniques. Prev Med 1980;9:388-97. 87. Salkeld GP, Solomon MJ, Short L, Ward J. Measuring the importance of attributes that influence consumer attitudes to colorectal cancer screening. ANZ J Surg 2003;73:128-32. 88. Wardle J, Pope R. The psychological costs of screening for cancer. J Psychosom Res 1992;36:609-24. 89. Lindholm E, Berglund B, Kewenter J, Haglind E. Worry associated with screening for colorectal carcinomas. Scand J Gastroenterol 1997; 32:238-45. 90. Parker MA, Robinson MH, Scholefield JH, Hardcastle JD. Psychiatric morbidity and screening for colorectal cancer. J Med Screen 2002;9:7-10. 91. Wardle J, Taylor T, Sutton S, Atkin W. Does publicity about cancer screening raise fear of cancer? Randomised trial of the psychological effect of information about cancer screening. BMJ (Clinical research ed) 1999;319:1037-8.

7 The symptomatic patient

7.1 Background

In Australia approximately 75% of bowel cancers are diagnosed symptomatically, although this may fall with the implementation of biennial screening through the National Bowel Cancer Screening Program (NBCSP).[1] The majority of people with symptomatic colorectal cancer first present to general practice. General practitioners (GPs) are faced with the challenge of identifying patients with symptoms that are due to colorectal cancer amongst the many people with similar symptoms that are caused by benign conditions. A recent study from Victoria found that over a third of patients with colorectal cancer had taken more than 3 months from developing symptoms to seeing a hospital specialist.[2] This finding may reflect poor community symptom awareness, later GP referral or limited access to colonoscopy services.

There is significant growth in demand for colonoscopy, with almost 600,000 Medical Benefits Schedule (MBS)-funded colonoscopies performed in Australia in 2013–2014 and significant problems of managing demand in the public hospital system.[3] The majority of these colonoscopies are likely to be for people with symptoms. Guidance is needed, therefore, to inform selection of patients in primary care who warrant referral for investigation of symptoms suggestive of colorectal cancer. Guidance is also needed in endoscopy units to inform triage of patients with symptoms suggestive of colorectal cancer, and determine the appropriateness and urgency for colonoscopy.

7.1.1 Contents

Sections:

- Signs and symptoms predictive of colorectal cancer
- Optimal maximum time from referral to diagnosis and treatment

7.2 References

1. ↑ Australian Institute of Health and Welfare. *National Bowel Cancer Screening Program: monitoring report 2016. Cancer series no. 98. Cat. no. CAN 97.* Canberra: AIHW; 2016.
2. ↑ Lacey K, Bishop JF, Cross HL, Chondros P, Lyratzopoulos G, Emery JD. *Presentations to general practice before a cancer diagnosis in Victoria: a cross-sectional survey.* Med J Aust 2016 Jul 18;205(2):66-71 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27456447.

3. ↑ Australian Commission on Safety and Quality in Health Care. *Australian atlas of healthcare variation.* [homepage on the internet]; 2016 Available from: http://www.safetyandquality.gov.au/atlas.

7.1 Introduction: the symptomatic patient

7.1.1 Background

In Australia approximately 75% of bowel cancers are diagnosed symptomatically, although this may fall with the implementation of biennial screening through the National Bowel Cancer Screening Program (NBCSP).[1] The majority of people with symptomatic colorectal cancer first present to general practice. General practitioners (GPs) are faced with the challenge of identifying patients with symptoms that are due to colorectal cancer amongst the many people with similar symptoms that are caused by benign conditions. A recent study from Victoria found that over a third of patients with colorectal cancer had taken more than 3 months from developing symptoms to seeing a hospital specialist.[2] This finding may reflect poor community symptom awareness, later GP referral or limited access to colonoscopy services.

There is significant growth in demand for colonoscopy, with almost 600,000 Medical Benefits Schedule (MBS)-funded colonoscopies performed in Australia in 2013–2014 and significant problems of managing demand in the public hospital system.[3] The majority of these colonoscopies are likely to be for people with symptoms. Guidance is needed, therefore, to inform selection of patients in primary care who warrant referral for investigation of symptoms suggestive of colorectal cancer. Guidance is also needed in endoscopy units to inform triage of patients with symptoms suggestive of colorectal cancer, and determine the appropriateness and urgency for colonoscopy.

7.1.1.1 Contents

Sections:

- Signs and symptoms predictive of colorectal cancer
- Optimal maximum time from referral to diagnosis and treatment

7.1.2 References

1. ↑ Australian Institute of Health and Welfare. *National Bowel Cancer Screening Program: monitoring report 2016. Cancer series no. 98. Cat. no. CAN 97.* Canberra: AIHW; 2016.

2. ↑ Lacey K, Bishop JF, Cross HL, Chondros P, Lyratzopoulos G, Emery JD. *Presentations to general practice before a cancer diagnosis in Victoria: a cross-sectional survey.* Med J Aust 2016 Jul 18;205(2):66-71 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27456447.
3. ↑ Australian Commission on Safety and Quality in Health Care. *Australian atlas of healthcare variation.* [homepage on the internet]; 2016 Available from: http://www.safetyandquality.gov.au/atlas.

7.2 Signs & symptoms predictive of CRC

Contents

7.2.1 Evidence

In symptomatic patients without a colorectal cancer diagnosis, what signs or symptoms (persistent changed bowel movements, persistent diarrhoea or constipation, unexplained rectal bleeding, general or localised abdominal pain, unexplained palpable abdominal or rectal mass, unexplained weight loss, iron deficient anaemia, tiredness, fatigue, or any combination) correlate best with a diagnosis of colorectal cancer?

7.2.1.1 Systematic review evidence

A systematic review of the predictive value of signs and symptoms of colorectal cancer was recently undertaken to inform the UK National Institute for Health and Care Excellence (NICE) guidelines[1]. We updated the NICE systematic review to March 2016, identifying two new relevant papers.[2][3] The systematic reviews and meta-analyses focused on the positive predictive values of individual symptoms, signs and combinations of symptoms and, where possible, stratified these by age and sex. Some studies also included levels of haemoglobin and markers of iron deficiency from a full blood count.

Due to the nature of the research question, the studies included used mainly case-control and cohort designs and are therefore subject to several biases, including patient selection, non-consecutive patient sampling and missing data, especially in relation to specification of symptoms. All studies were conducted on Western populations, with the majority based on European populations, particularly in the UK. Only one study was conducted in Australia.[4] However, the evidence is likely to be generalisable to the Australian average risk population presenting in primary care.

The NICE guidelines[1] aimed to identify symptoms associated with a positive predictive value of at least 3% to inform selection for urgent referral for investigation of colorectal cancer. This threshold should be compared against the current positive predictive value of 3.5% for a positive faecal immunochemical occult blood test (FOBT) in the Australian National Bowel Cancer Screening Programme. For those patients with symptoms associated with a positive predictive value of below 3%, NICE developed a health economic model to test different diagnostic strategies in primary care. Specifically, they modelled the following tests in people aged 40 years and over with a change in bowel habit:

- faecal occult blood test using guaiac test
- faecal occult blood test using the FiT
- barium enema
- colonoscopy
- flexible sigmoidoscopy
- CT colonography.

At a threshold of GBP20,000 (approximately $40,000) per quality-adjusted life year (QALY),[1] FOBT was the most cost-effective test in people aged 40 years and over with a change in bowel habit.

Back to top

7.2.2 Evidence summary and recommendations

7.2.2.1 Meta-analyses

Evidence summary	Level	References
Rectal bleeding presenting in primary care was associated with a PPV for	II, III-	[5], [6], [7], [8], [9], [10]

Evidence summary	Level	References
colorectal cancer of up to 4.8% (95% CI 3.3 to 6.8). This PPV tended to increase with age in both men and women.	2, III-3	[11], [4], [12], [13], [14], [15], [16], [17], [18]
Abdominal pain presenting in primary care was associated with a PPV for colorectal cancer of up to 2.0% (95% CI 0.5 to 7.6). This PPV tended to increase with age in both men and women.	III-2, III-3	[5], [19], [10], [14]
Anaemia presenting in primary care was associated with a PPV for colorectal cancer of up to 5.8% (95% CI 2.6 to 12.0). This PPV tended to increase with age in both men and women. Two new studies since the meta-analysis estimated the PPV for anaemia in referred populations as 10.2% (95% CI 4.6 to 17.3) and 12.0% (95% CI 8.0 to 16.0).	II, III-2, III-3, IV	[5], [20], [21], [22], [14], [23], [24]
Weight loss presenting in primary care was associated with a PPV for colorectal cancer of up to 3% (95% CI 0.3 to 22.9). This PPV tended to increase with age in both men and women. One new study since the meta-analysis estimated the PPV for weight loss in a referred population as 5.2% (95% CI = 2.5 to 9.2).	II, III-2, III-3	[5], [10], [14]
Dyspepsia presenting in primary care was associated with a PPV for colorectal cancer of up to 0.6% (95% CI 0.3 to 1.4).	III-2	[25], [26], [27]

PPV: positive predictive value; CI: confidence interval

7.2.2.2 Individual studies

Evidence summary	Level	References
Constipation presenting in primary care in two studies was associated with a PPV for colorectal cancer of 0.4–2.5%. In one further small study in selected patients the estimated PPV was 15.7% (95% CI 10.2 to 23.2).	II, III-2, III-3	[28], [14], [2]
Change in bowel habit presenting in primary care in two studies was associated with a PPV for colorectal cancer of 2.8–2.9%. This PPV tended to increase with age in both men and women. In one further small study in selected patients the estimated PPV was 14% (95% CI 6.7 to 23.3%).	III-2	[10], [5], [14]

PPV: positive predictive value; CI: confidence interval

7.2.2.3 Combination of symptoms

Evidence summary	Level	References
Nine studies that examined the PPVs for rectal bleeding in combination with other symptoms reported wide-ranging estimates. Some studies reported other combinations of symptoms. Combinations associated with higher estimated PPVs included: ■ abdominal tenderness and abnormal rectal examination (PPV 5.8%; 95% CI not reported) ■ dyspepsia with anaemia (PPV 13.5%; 95% CI 5 to 29.57%). Several of the estimates from these studies are likely to be artificially inflated due to small numbers of participants with specific combinations of symptoms.	III-2, III-3, IV	[28], [12], [7], [4], [13], [16], [17], [8], [27]

PPV: positive predictive value; CI: confidence interval

7.2.2.4 Combinations of symptoms and baseline risk factors predicting prevalent cancer

The QCancer colorectal cancer risk prediction model[10] incorporates the following variables for men and women to calculate positive predictive values for combinations of multiple symptoms and baseline risk factors:

- **Women**: age, family history of gastrointestinal cancer, abdominal pain, appetite loss, rectal bleeding, weight loss, anaemia (< 11 g/dL).
- **Men**: age, family history of gastrointestinal cancer, alcohol consumption, abdominal pain, appetite loss, rectal bleeding, weight loss, anaemia (< 11 g/dL), change in bowel habit.

On internal validation the QCancer model showed good discrimination; the area under receiver operating curve (ROC) statistics were 0.89 for women and 0.91 for men. In an independent external validation study the ROC statistics were 0.92 for women and 0.91, and the risk prediction model explained 68% and 66% of the variation in women and men, respectively.[5]

Evidence-based recommendation	Grade
The urgency of colonoscopy to investigate symptoms suggestive of colorectal cancer should be based on an assessment of patient age, symptom profile and results of simple investigations including full blood count, iron studies and FiT (see Table 10.1 for consensus-based colonoscopy triage categories).	**C**

7.2.2.5 Consensus-based colonoscopy triage categories

Table 10.1 presents triage categories to determine urgency and need for colonoscopy based on symptom profile, patient age and results from investigations available in primary care.

The guideline development group applied evidence about the predictive value of individual and combinations of symptoms, including allowance for patient age, to inform the development of colonoscopy triage categories. They build on Victorian draft guidelines for colonoscopy triage. The guideline development group discussed the use of additional investigations in primary care to support triage which had been informed by the NICE guidelines and had undergone extensive expert consultation.

In addition to its traditional use as a screening test in asymptomatic patients, FiT is potentially useful for assessing risk in symptomatic patients, especially those who have not recently participated in the NBCSP. In addition to the NICE[1]modelling study (see Systematic review evidence), we considered new evidence about the use of FiT and calprotectin in patients with bowel symptoms referred from primary care. This demonstrated that a negative FiT can be useful in ruling out significant bowel disease, including colorectal cancer.[29] The study also showed that faecal calprotectin is a useful test in distinguishing patients with inflammatory bowel disease (IBD) and irritable bowel syndrome, consistent with international guidance on using this test to rule out IBD.[30]

7.2.2.5.1 Table 10.1. Colonoscopy triage categories

Category 1	Category 2	Category 3	No colonoscopy indicated
Positive faecal occult blood test (FiT +ve)			
Anaemia and any one of: ■ ≥ 60 years ■ Rectal bleeding	**Anaemia** and all of: ■ No GI symptoms ■ FiT –ve ■ No likely non-GI cause identified	**Anaemia** and all of: ■ No GI symptoms ■ FiT –ve ■ Likely non-GI cause ■ Age ≥ 50 years	**Anaemia** and all of: ■ No GI symptoms ■ FiT –ve ■ Untreated likely non-GI cause (e.g, menorrhagia, diet) ■ Age ≤ 50 years
Rectal bleeding < 12 months and any one of: ■ ≥ 50 years	**Rectal bleeding < 12 months** and all of: ■ No other GI symptoms ■ < 50 years		

■ Abdominal pain ■ Altered bowel habit > 6/52 ■ Unexplained weight loss	■ No cause identified on rigid sigmoidoscopy	**Rectal bleeding ≥ 12 months** and all of: ■ No other GI symptoms ■ No cause identified on rigid sigmoidoscopy	**Rectal bleeding ≥ 12 months** and all of: ■ No other GI symptoms ■ Likely cause identified on rigid sigmoidoscopy
Altered bowel habit > 6/52 and any one of: ■ ≥ 60 years ■ Rectal bleeding < 12 months ■ FiT or calprotectin +ve*	**Altered bowel habit > 6/52** and all of: ■ 40–60 years ■ FiT and calprotectin –ve* ■ Abdominal pain or unexplained weight loss	**Altered bowel habit > 6/52** and either: ■ 40–60 years and no other GI symptoms or: ■ < 40 years with abdominal pain or unexplained weight loss	
Unexplained abdominal pain and any one of: ■ Rectal bleeding ■ Unexplained weight loss ■ FiT or calprotectin +ve*	**Unexplained abdominal pain** and all of: ■ ≥ 40 years ■ FiT and calprotectin –ve* ■ Altered bowel habit > 6/52 and < 60 years	**Unexplained abdominal pain** and either: ■ ≥ 40 years and no other GI symptoms or: ■ < 40 years with altered bowel habit > 6/52	A resolved episode of acute abdominal pain** or Diverticulitis with typical CT features and no other GI symptoms
Unexplained weight loss and any one of: ■ Rectal bleeding ■ Abdominal pain ■ FiT or calprotectin +ve*	**Unexplained weight loss** and all of: ■ ≥ 40 years ■ FiT and calprotectin –ve* ■ Altered bowel habit > 6/52 and < 60 years		**Unexplained weight loss** and all of: ■ no other GI symptoms ■ normal examination ■ normal full blood count and iron studies ■ FiT and calprotectin –ve*

Mass palpable on abdominal or rectal examination or on rigid sigmoidoscopy			

GI: gastrointestinal; > 6/52: symptom present for more than 6 weeks per episode; CT: computed tomography NB. Faecal calprotectin is a useful test in distinguishing patients with inflammatory bowel disease and irritable bowel syndrome, but has no role in detecting colorectal cancer.
**Abdominal pain present for less than 5 weeks should be assessed and treated, with consideration of colonoscopy if no response.

Consensus-based recommendation

In people with symptoms other than overt rectal bleeding, faecal immunochemical occult blood testing (FiT) is a useful part of the diagnostic assessment in primary care

Practice point

Faecal immunochemical occult blood testing (FiT) is of particular use in the following circumstances to support diagnostic assessment and inform urgency of colonoscopy:

- people over 50 years with either unexplained weight loss or abdominal pain
- people under 60 years with either altered bowel habit or anaemia.

Back to top

7.2.3 Benefits and harms

The recommendations aim to support a rational process to determine the urgency of colonoscopies, particularly in the context of long waiting lists for colonoscopy in the public hospital system. It should be noted that no symptoms are strongly predictive of colorectal cancer, nor are there any symptoms which rule out cancer. Thus it remains possible that even patients in Category 3, who have ‘low risk but not no risk’ symptoms, may eventually be diagnosed with colorectal cancer. Those patients who do not meet criteria for colonoscopy should be reviewed by their GP and reconsider the need for investigation if new symptoms or signs have developed.

Back to top

7.2.4 Health system implications

7.2.4.1 Clinical practice

The triage categories, while moderately complex, are designed for use by endoscopy units to assess the urgency of referrals for colonoscopy. GPs should apply this evidence to inform their use of simple investigations in primary care (full blood count, iron studies and FiT) as part of their assessment of patients with symptoms suggestive of colorectal cancer. It should also be noted which patients are identified in this guideline as not requiring referral for colonoscopy.

7.2.4.2 Resourcing

Health services and endoscopy units should consider implementing specific GP referral proformas designed to capture the information needed to apply the triage criteria.[31]

Endoscopy units may need dedicated staff to apply the triage criteria consistently.

7.2.4.3 Barriers to implementation

Primary Health Networks should support this implementation in general practice as part of the national Optimal Care Pathways for colorectal cancer.[32]

Back to top

7.2.5 Discussion

7.2.5.1 Unresolved issues

Timely diagnosis of colorectal cancer is important for improving survival. The triage criteria are designed to improve the efficiency of the referral and triage processes for people with symptoms suggestive of colorectal cancer, but further evidence is required on the impacts of their implementation.

7.2.5.2 Studies currently underway

The Victorian colonoscopy guidelines are currently being piloted to assess their feasibility of implementation.

7.2.5.3 Future research priorities

Further research is needed to determine how best to reduce missed opportunities for colorectal cancer diagnosis in primary care, applying the evidence about symptoms as predictors of colorectal cancer risk.

The colonoscopy triage criteria are based on current best evidence. The following further research is needed to evaluate their implementation:

- prospective, comparative validation studies measuring clinical outcomes
- studies assessing the impact on waiting times, diagnostic intervals and colorectal cancer outcomes.

See also: Optimal maximum time from referral to diagnosis and treatment.

Back to top

7.2.6 References

1. ↑ 1.0 1.1 1.2 1.3 National Institute for Health and Care Excellence. *Suspected cancer: referral and recognition.* National Collaborating Centre for Cancer; 2015 Available from: https://www.nice.org.uk/guidance/ng12.
2. ↑ 2.0 2.1 Rodríguez-Alonso L, Rodríguez-Moranta F, Ruiz-Cerulla A, Lobatón T, Arajol C, Binefa G, et al. *An urgent referral strategy for symptomatic patients with suspected colorectal cancer based on a quantitative immunochemical faecal occult blood test.* Dig Liver Dis 2015 Sep;47(9):797-804 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26055489.
3. ↑ Chowdhury ATMD, Longcroft-Wheaton G, Davis A, Massey D, Goggin P. *Role of faecal occult bloods in the diagnosis of iron deficiency anaemia.* Frontline Gastroenterology 2014 Oct 1;5(4):231-36.
4. ↑ 4.0 4.1 4.2 Mant, A. Bokey, E. L. Chapuis, P. H. Killingback, M. Hughes, W. Koorey, S. G. Cook, I. Goulston, K. J. Dent, O. F.. *Rectal bleeding. Do other symptoms aid in diagnosis?* Dis Colon Rectum 1989;32(3): 191-196.
5. ↑ 5.0 5.1 5.2 5.3 5.4 5.5 Collins GS, Altman DG. *Identifying patients with undetected colorectal cancer: an independent validation of QCancer (Colorectal).* Br J Cancer 2012 Jul 10;107(2):260-5 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22699822.
6. ↑ du Toit J, Hamilton W, Barraclough K. *Risk in primary care of colorectal cancer from new onset rectal bleeding: 10 year prospective study.* BMJ 2006 Jul 8;333(7558):69-70 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16790459.
7. ↑ 7.0 7.1 Ellis BG, Thompson MR. *Factors identifying higher risk rectal bleeding in general practice.* Br J Gen Pract 2005 Dec;55(521):949-55 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16378565.
8. ↑ 8.0 8.1 Fijten GH, Starmans R, Muris JW, Schouten HJ, Blijham GH, Knottnerus JA. *Predictive value of signs and symptoms for colorectal cancer in patients with rectal bleeding in general practice.* Fam Pract 1995 Sep;12(3):279-86 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8536830.
9. ↑ Helfand M, Marton KI, Zimmer-Gembeck MJ, Sox HC Jr. *History of visible rectal bleeding in a primary care population. Initial assessment and 10-year follow-up.* JAMA 1997 Jan 1;277(1):44-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8980209.
10. ↑ 10.0 10.1 10.2 10.3 10.4 Hippisley-Cox J, Coupland C. *Identifying patients with suspected colorectal cancer in primary care: derivation and validation of an algorithm.* Br J Gen Pract 2012 Jan;62(594):e29-37 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22520670.
11. ↑ Jones R, Latinovic R, Charlton J, Gulliford MC. *Alarm symptoms in early diagnosis of cancer in primary care: cohort study using General Practice Research Database.* BMJ 2007 May 19;334(7602):1040 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17493982.
12. ↑ 12.0 12.1 Metcalf JV, Smith J, Jones R, Record CO. *Incidence and causes of rectal bleeding in general practice as detected by colonoscopy.* Br J Gen Pract 1996 Mar;46(404):161-4 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8731622.

13. ↑ 13.0 13.1 Norrelund N, Norrelund H. *Colorectal cancer and polyps in patients aged 40 years and over who consult a GP with rectal bleeding.* Fam Pract 1996 Apr;13(2):160-5 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8732328.
14. ↑ 14.0 14.1 14.2 14.3 14.4 14.5 Panzuto, F. Chiriatti, A. Bevilacqua, S. Giovannetti, P. Russo, G. Impinna, S. Pistilli, F. Capurso, G. Annibale, B. Delle Fave, G.. *Symptom-based approach to colorectal cancer: survey of primary care physicians in Italy.* Dig Liver Dis 2003;35(12): 869-875.
15. ↑ Parker C, Hippisley-Cox J, Coupland C, Vinogradova Y. *Rectal and postmenopausal bleeding: consultation and referral of patients with and without severe mental health problems.* Br J Gen Pract 2007 May;57(538):371-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17504587.
16. ↑ 16.0 16.1 Robertson R, Campbell C, Weller DP, Elton R, Mant D, Primrose J, et al. *Predicting colorectal cancer risk in patients with rectal bleeding.* Br J Gen Pract 2006 Oct;56(531):763-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17007706.
17. ↑ 17.0 17.1 Wauters H, Van Casteren V, Buntinx F. *Rectal bleeding and colorectal cancer in general practice: diagnostic study.* BMJ 2000 Oct 21;321(7267):998-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/11039968.
18. ↑ Heintze C, Matysiak-Klose D, Kröhn T, Wolf U, Brand A, Meisner C, et al. *Diagnostic work-up of rectal bleeding in general practice.* Br J Gen Pract 2005 Jan;55(510):14-9; discussion 18 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15667760.
19. ↑ Bellentani, S. Baldoni, P. Petrella, S. Tata, C. Armocida, C. Marchegiano, P. Saccoccio, G. Manenti, F.. *A simple score for the identification of patients at high risk of organic diseases of the colon in the family doctor consulting room. The Local IBS Study Group.* Fam Pract 1990;7(4): 307-312.
20. ↑ Droogendijk J, Beukers R, Berendes PB, Tax MG, Sonneveld P, Levin MD. *Screening for gastrointestinal malignancy in patients with iron deficiency anemia by general practitioners: an observational study.* Scand J Gastroenterol 2011 Sep;46(9):1105-10 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21726115.
21. ↑ Farrus Palou, M. Perez Ocana, A. Mayer Pujadas, M. A. Piquer Gibert, M. Mundet Tuduri, X. Iglesias Rodal, M.. *Anemia in primary care: etiology and morphological characteristics.* Aten Primaria 2000;25(4): 230-235.
22. ↑ Lucas CA, Logan EC, Logan RF. *Audit of the investigation and outcome of iron-deficiency anaemia in one health district.* J R Coll Physicians Lond 1996 Jan;30(1):33-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8745360.
23. ↑ Stellon AJ, Kenwright SE. *Iron deficiency anaemia in general practice: presentations and investigations.* Br J Clin Pract 1997 Mar;51(2):78-80 Available from: http://www.ncbi.nlm.nih.gov/pubmed/9158249.
24. ↑ Yates JM, Logan EC, Stewart RM. *Iron deficiency anaemia in general practice: clinical outcomes over three years and factors influencing diagnostic investigations.* Postgrad Med J 2004 Jul;80(945):405-10 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15254305.
25. ↑ Hallissey MT, Allum WH, Jewkes AJ, Ellis DJ, Fielding JW. *Early detection of gastric cancer.* BMJ 1990 Sep 15;301(6751):513-5 Available from: http://www.ncbi.nlm.nih.gov/pubmed/2207416.
26. ↑ Heikkinen M, Pikkarainen P, Takala J, Räsänen H, Julkunen R. *Etiology of dyspepsia: four hundred unselected consecutive patients in general practice.* Scand J Gastroenterol 1995 Jun;30(6):519-23 Available from: http://www.ncbi.nlm.nih.gov/pubmed/7569757.

27. ↑ [27.0] [27.1] Meineche-Schmidt V, Jørgensen T. *'Alarm symptoms' in patients with dyspepsia: a three-year prospective study from general practice.* Scand J Gastroenterol 2002 Sep;37(9):999-1007 Available from: http://www.ncbi.nlm.nih.gov/pubmed/12374244.
28. ↑ [28.0] [28.1] Hamilton W, Round A, Sharp D, Peters TJ. *Clinical features of colorectal cancer before diagnosis: a population-based case-control study.* Br J Cancer 2005 Aug 22;93(4):399-405 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16106247.
29. ↑ Mowat C, Digby J, Strachan JA, Wilson R, Carey FA, Fraser CG, et al. *Faecal haemoglobin and faecal calprotectin as indicators of bowel disease in patients presenting to primary care with bowel symptoms.* Gut 2016 Sep;65(9):1463-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26294695.
30. ↑ National Institute for Health and Care Excellence. *Faecal calprotectin diagnostic tests for inflammatory diseases of the bowel.* UK: NICE; 2013 Available from: https://www.nice.org.uk/guidance/dg11.
31. ↑ Akbari A, Mayhew A, Al-Alawi MA, Grimshaw J, Winkens R, Glidewell E, et al. *Interventions to improve outpatient referrals from primary care to secondary care.* Cochrane Database Syst Rev 2008 Oct 8;(4): CD005471 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18843691.
32. ↑ Cancer Council Victoria. *Optimal care pathway for people with colorectal cancer.*; 2014 Available from: www.cancer.org.au/ocp.

7.2.7 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search

View PICO	NHMRC Evidence statement form SPT1-2a	Systematic review report SPT1-2a

Back to top

7.3 Optimal max time from referral to diagnosis and treatment

Contents

7.3.1 Background

Intuitively, it would be expected that diagnosing cancer quickly would be beneficial, as tumours grow and are more likely to metastasise with time. Indeed, perception of a 'delayed diagnosis' of cancer is a leading cause of medicolegal complaints in primary and ambulatory care, on the assumption that harm occurred as a result of late diagnosis.[1]

7.3.1.1 The diagnostic pathway

So-called delays in cancer diagnosis can occur at various points along the diagnostic pathway:[2] Patients may take time appraising their symptoms before seeking healthcare, they may experience multiple visits to their GP about their symptoms before referral for specialist diagnostic tests,[3] and there may be long waiting times to access these diagnostic tests. This latter point along the diagnostic pathway, from GP referral to diagnosis, is the focus of this section.

Access to timely colonoscopy is an important contributor to the overall diagnostic interval for colorectal cancer (defined usually as the time a patient first presents to healthcare until the time of diagnosis).[4]

7.3.1.2 Methodological issues

Proving that earlier detection of symptomatic cancer matters is epidemiologically challenging. The 'waiting time paradox' describes the phenomenon in which patients with late stage cancers present with severe symptoms and are therefore often diagnosed promptly, but have poorer outcomes.[5]This type of confounding by indication is an important source of bias in studies examining the effect of time to diagnosis on outcomes in symptomatic

cancer populations. Many studies that have examined associations between the diagnostic interval and clinical outcomes have assumed a linear relationship between time to diagnosis and mortality. Their analyses, therefore, have not accounted for potential effects of the waiting time paradox. More recent studies, led by researchers at Aarhus University, have introduced the use of spline regression to allow for flexible associations between the diagnostic interval and clinical outcome.[6][7] These important methodological considerations must be taken into account when interpreting the evidence, which includes apparently inconsistent findings. When making recommendations, we applied greater weight to studies that attempted to account for the waiting time paradox.

Back to top

7.3.2 Evidence

In symptomatic patients without a colorectal cancer diagnosis, what is the optimal maximum diagnostic interval that achieves better than or equivalent outcomes in terms of survival, mortality, and diagnosis of metastatic disease?

No comment pages found

7.3.2.1 Systematic review evidence

Nine studies[8][9][10][7][6][11][12][13][14]examined the effect of the diagnostic interval on colorectal cancer related outcomes including mortality, cancer specific survival and mortality, and stage of tumour at diagnosis. Seven studies[8][9][10][6][7][11][12]had a moderate risk of bias and two had a high risk of bias.[13][14]

No comment pages found

7.3.2.1.1 Mortality

A Canadian retrospective cohort study[10] found that diagnostic interval had no significant effect of diagnostic interval length on colorectal cancer mortality with 1–6 years follow-up.

Danish prospective population-based cohort studies in primary care,[7][11] a UK retrospective cohort study,[9] and a study that included one retrospective and two prospective primary care cohort studies conducted in Denmark and the UK[6] reported significantly higher 3- and 5-year mortality rates associated with shorter waiting periods (all < 1 month). These findings are consistent with the ‘waiting time paradox’ where patients with severe symptoms associated with later stage disease are diagnosed promptly.

Three Danish and UK primary care cohort studies[6] reported U-shaped associations between diagnostic interval and overall mortality (at 3 or 5 years) using spline regression analyses. Analysis of combined datasets found that higher 5-year mortality was associated with diagnostic intervals greater than 130 days (HR=1.28 95% CI 1.28-1.55).

A large US retrospective study of > 9,000 patients diagnosed with colorectal cancer between 1998 and 2005[8] found that, for patients with colon cancer only, diagnostic intervals of ≥ 8 months compared with 14–59 days showed a significant effect on overall mortality (OR 1.31, 95% CI 1.08 to 1.58). For local stage rectal cancer, mortality was higher for diagnostic intervals < 2 weeks and 2–4 months, compared with 14–59 days, consistent with the U-shaped associations demonstrated in UK and Danish populations.[6][7][11]

7.3.2.1.2 Colorectal cancer-specific mortality

In an analysis of a large US dataset of medical records for adults aged ≥ 66 years with invasive colon or rectal cancer,[8]colorectal cancer-specific mortality was reported separately for patients diagnosed with either colon cancer or rectal cancer.[8] For those diagnosed with colon cancer, in unadjusted analysis, higher mortality was reported for shorter diagnostic delay (< 2 weeks), compared with 14–59 days (OR 1.27, $p < 0.05$). Significantly higher mortality was reported when comparing short diagnostic interval (14–59 days) with longer diagnostic intervals of 4–8 months and ≥ 8 months (OR 0.76, $p < 0.05$, and OR 0.82, $p < 0.05$, respectively), thus failing to demonstrate any evidence of a U-shaped association between interval and colorectal cancer-specific mortality.

A cohort study comparing outcomes in patients with early and late diagnosis[14] reported significantly higher 5-year cancer-specific survival for a diagnostic interval ≥ 50 days compared with < 50 days when all participants were included in the analysis (94% versus 73%, respectively, $p = 0.007$).[14] No attempt was made to account for the waiting time paradox in this study.

7.3.2.1.3 Tumour stage at diagnosis

Four studies[12][13][14][10] examined associations between diagnostic intervals and tumour stage but only one [10] conducted analyses to account for a potential waiting time paradox.

A retrospective cohort study[12] compared stages for three interval cut-offs (> 41 days, > 60 days, > 90 days), assuming a linear effect of time. Shorter intervals were associated with more advanced stage disease.[12]

Another retrospective cohort study[13] reported shorter diagnostic intervals were associated with earlier stages of cancer, however this effect was non-significant.[13]

A cohort study comparing outcomes in patients with early and late diagnosis[14] reported greater rates of Dukes' stage A cancer in participants with a diagnostic interval ≥ 50 days (57.1%) compared with < 50 days (15.2%, $p = 0.006$).[14]

A large Canadian retrospective cohort study[10] reported higher rates of stage III/IV colorectal cancer for participants with a diagnostic interval < 15 days compared with 51 to < 116 days or ≥ 116 days (OR 0.59, CI 0.39 to 0.89 and OR 0.50, CI 0.33 to 0.75, respectively) but not 15 to < 51 days, consistent with a U-shaped association between diagnostic interval and clinical outcome.[10]

7.3.2.1.4 Summary

The studies that performed analyses to account for the waiting time paradox found potentially important U-shaped associations between diagnostic intervals and (1) overall mortality[6][7][11][8] and (2) late-stage disease at diagnosis,[10] but not colorectal cancer-specific mortality[8] The following cut-off intervals for first presentation to healthcare to diagnosis were associated with poorer outcomes:

- 130 days in the largest study combining three datasets from Danish and UK primary care cohorts[6]
- 8 months (approximately 243 days) in a large US retrospective study[8]
- 116 days in a Canadian retrospective study from population-based cancer registry and administrative database.[10]

In the Australian setting, the presentation–diagnosis interval would most commonly represent the time from GP consultation to diagnostic colonoscopy (or other diagnostic procedure) in specialist care.

Back to top

7.3.3 Evidence summary and recommendations

Evidence summary	Level	References
Analyses of cohort data have reported U-shaped associations between diagnostic interval and (1) overall mortality and (2) late-stage disease at diagnosis, but not colorectal cancer-specific mortality.	III-2	[11], [7], [6], [8], [10]
Diagnostic interval cut-off points associated with poorer outcomes range between 116 days and 8 months.	III-2	[6], [8], [10]

Evidence-based recommendation	Grade
For patients with symptoms suggestive of colorectal cancer, the total time from first healthcare presentation to diagnostic colonoscopy should be no greater than 120 days.	**C**

Evidence-based recommendation	Grade
The maximum time from referral to diagnostic colonoscopy for Category 1 should be 60 days. This should be the same maximum interval, whether it is for a patient with symptoms or a positive FiT used for colorectal cancer screening.	**D**

7.3.3.1 Considerations in making these recommendations

These recommendations are based on the consensus of the guideline development group and interpretation of the best available evidence. There is evidence to suggest that a greater proportion of the diagnostic interval occurs from the point of referral to colonoscopy, rather than in primary care, especially where there is poorer access to colonoscopy. However, for simplicity we have assumed a maximum of 60 days from first presentation in general practice to referral, and 60 days from referral to diagnostic colonoscopy.

Back to top

7.3.4 Benefits and harms

The current national performance indicator within the NBCSP aims for a colonoscopy to be performed within 30 days from referral for a positive FiT. Our recommendation is that all Category 1 colonoscopies (screen positive FiT or symptomatic patients) should be performed no later than 60 days from referral. We discussed whether to include Category 2 colonoscopies within this recommended timeframe, as there will be a small proportion of people with colorectal cancer in this group. However, it was felt that current public hospital endoscopy services would not be able to achieve this.

Back to top

7.3.5 Health system implications

7.3.5.1 Clinical practice

GPs will need to remain alert to the possibility of colorectal cancer as a possible cause of a patient’s symptoms and investigate and refer promptly based on the evidence summarised in the previous section.

7.3.5.2 Resourcing

Endoscopy services will need to establish clear diagnostic pathways for patients with suspected colorectal cancer and establish systems to apply the triage criteria and organise timely colonoscopy, especially for those meeting Category 1 criteria.

7.3.5.3 Barriers to implementation

This is in the context of the roll-out of the biennial NBCSP, due to be fully implemented by 2020 which will place additional demand for colonoscopy.

Back to top

7.3.6 Discussion

7.3.6.1 Unresolved issues

Timely diagnosis of colorectal cancer is important for improving survival. While there are inevitable limitations in defining the optimal maximum time to diagnose someone with suspected colorectal cancer, we have applied the current best evidence to make our recommendations. The triage criteria and associated maximum intervals for Category 1 patients are designed to improve the efficiency of the referral and triage processes for people with symptoms suggestive of colorectal cancer.

7.3.6.2 Studies currently underway

The authors are not aware of any studies underway that may provide more information on this topic.

No comment pages found

7.3.6.3 Future research priorities

Further well-designed research, which accounts for the waiting time paradox, is needed to confirm the estimates of minimum diagnostic intervals associated with poorer colorectal cancer outcomes. In addition, studies should monitor the impact of the implementation of colonoscopy triage categories on waiting times, diagnostic intervals and colorectal cancer outcomes.

Back to top

7.3.7 References

1. ↑ Wallace, E. Lowry, J. Smith, S. M. Fahey, T.. *The epidemiology of malpractice claims in primary care: a systematic review.* BMJ Open 2013;3(7).
2. ↑ Walter F, Webster A, Scott S, Emery J. *The Andersen Model of Total Patient Delay: a systematic review of its application in cancer diagnosis.* J Health Serv Res Policy 2012 Apr;17(2):110-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22008712.
3. ↑ Lyratzopoulos G, Neal RD, Barbiere JM, Rubin GP, Abel GA. *Variation in number of general practitioner consultations before hospital referral for cancer: findings from the 2010 National Cancer Patient Experience Survey in England.* Lancet Oncol 2012 Apr;13(4):353-65 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22365494.
4. ↑ Weller D, Vedsted P, Rubin G, Walter FM, Emery J, Scott S, et al. *The Aarhus statement: improving design and reporting of studies on early cancer diagnosis.* Br J Cancer 2012 Mar 27;106(7):1262-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22415239.
5. ↑ Neal RD, Tharmanathan P, France B, Din NU, Cotton S, Fallon-Ferguson J, et al. *Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review.* Br J Cancer 2015 Mar 31;112 Suppl 1:S92-107 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25734382.

6. ↑ 6.0 6.1 6.2 6.3 6.4 6.5 6.6 6.7 6.8 6.9 Tørring ML, Frydenberg M, Hamilton W, Hansen RP, Lautrup MD, Vedsted P. *Diagnostic interval and mortality in colorectal cancer: U-shaped association demonstrated for three different datasets.* J Clin Epidemiol 2012 Jun;65(6):669-78 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22459430.
7. ↑ 7.0 7.1 7.2 7.3 7.4 7.5 7.6 Tørring ML, Frydenberg M, Hansen RP, Olesen F, Hamilton W, Vedsted P. *Time to diagnosis and mortality in colorectal cancer: a cohort study in primary care.* Br J Cancer 2011 Mar 15;104(6):934-40 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21364593.
8. ↑ 8.0 8.1 8.2 8.3 8.4 8.5 8.6 8.7 8.8 8.9 Pruitt SL, Harzke AJ, Davidson NO, Schootman M. *Do diagnostic and treatment delays for colorectal cancer increase risk of death?* Cancer Causes Control 2013 May;24(5):961-77 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23446843.
9. ↑ 9.0 9.1 9.2 Redaniel MT, Martin RM, Ridd MJ, Wade J, Jeffreys M. *Diagnostic intervals and its association with breast, prostate, lung and colorectal cancer survival in England: historical cohort study using the Clinical Practice Research Datalink.* PLoS One 2015;10(5):e0126608 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25933397.
10. ↑ 10.00 10.01 10.02 10.03 10.04 10.05 10.06 10.07 10.08 10.09 10.10 Singh H, Shu E, Demers A, Bernstein CN, Griffith J, Fradette K. *Trends in time to diagnosis of colon cancer and impact on clinical outcomes.* Can J Gastroenterol 2012 Dec;26(12):877-80 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23248786.
11. ↑ 11.0 11.1 11.2 11.3 11.4 11.5 Tørring ML, Frydenberg M, Hansen RP, Olesen F, Vedsted P. *Evidence of increasing mortality with longer diagnostic intervals for five common cancers: a cohort study in primary care.* Eur J Cancer 2013 Jun;49(9):2187-98 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23453935.
12. ↑ 12.0 12.1 12.2 12.3 12.4 Wattacheril J, Kramer JR, Richardson P, Havemann BD, Green LK, Le A, et al. *Lagtimes in diagnosis and treatment of colorectal cancer: determinants and association with cancer stage and survival.* Aliment Pharmacol Ther 2008 Nov 1;28(9):1166-74 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18691351.
13. ↑ 13.0 13.1 13.2 13.3 13.4 Gómez-Domínguez E, Trapero-Marugán M, del Pozo AJ, Cantero J, Gisbert JP, Maté J. *The colorectal carcinoma prognosis factors. Significance of diagnosis delay.* Rev Esp Enferm Dig 2006 May;98(5):322-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16944992.
14. ↑ 14.0 14.1 14.2 14.3 14.4 14.5 14.6 Rupassara KS, Ponnusamy S, Withanage N, Milewski PJ. *A paradox explained? Patients with delayed diagnosis of symptomatic colorectal cancer have good prognosis.* Colorectal Dis 2006 Jun;8(5):423-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16684087.

Back to top

7.3.8 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search

View PICO	NHMRC Evidence statement form SPT1-2b	Systematic review report SPT1-2b

Back to top

8 Risk and screening based on family history

The fact that family history of colorectal cancer is a risk factor for the disease implicates hereditary risk factors. Genes have been identified that, when inherited in a mutated form, substantially increase the risk of colorectal cancer. The best studied of these genes include:

- the DNA mismatch repair genes MLH1, MSH2, MSH6 and PMS2, mutations of which cause the hereditary cancer predisposition of Lynch syndrome (previously known as hereditary non-polyposis colorectal cancer)
- the APC gene, mutation of which causes familial adenomatous polyposis (FAP)
- the DNA base excision repair gene MUTYH, mutation of which causes attenuated familial adenomatous polyposis.

These genetic disorders have an autosomal-dominant mode of transmission (mismatch repair genes and APC) or autosomal-recessive mode of transmission (MUTYH) within families, and carry a very high risk for cancer (see High-risk familial syndromes).

However, mutations in these genes account for only a minority (less than 5%) of all colorectal cancer cases and at most, only explain half of the reason that family history is a risk factor for colorectal cancer.[1] The remainder of the observed increases in risk may be due in part to mutations in yet-to-be-discovered genes for colorectal cancer,[2] common polygenic factors such as single-nucleotide polymorphisms[3][4] or dietary and lifestyle factors that are shared by family members.

Assessment of family history of colorectal cancer has two roles in cancer prevention and early detection:

- to determine who should be tested for mutations in these genes.
- to inform decisions about the optimal timing, frequency and modality of screening.

This chapter provides estimates of risk of colorectal cancer and screening recommendations for the large number of people in the community who have a family history of colorectal cancer, but whose family history does not have the clinical features suggestive of high-risk familial syndromes. For information on surveillance strategies for specific high-risk familial syndromes, see:

- Familial adenomatous polyposis
- MUTYH associated polyposis
- Lynch syndrome
- Peutz-Jeghers syndrome
- Juvenile polyposis syndrome
- Serrated polyposis syndrome

8.1 Contents

Subsections:

8.2 References

1. ↑ Aaltonen L, Johns L, Järvinen H, Mecklin JP, Houlston R. *Explaining the familial colorectal cancer risk associated with mismatch repair (MMR)-deficient and MMR-stable tumors.* Clin Cancer Res 2007 Jan 1;13 (1):356-61 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17200375.
2. ↑ Win AK, Jenkins MA, Dowty JG, Antoniou AC, Lee A, Giles GG, et al. *Prevalence and Penetrance of Major Genes and Polygenes for Colorectal Cancer.* Cancer Epidemiol Biomarkers Prev 2016 Oct 31 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27799157.
3. ↑ Hsu L, Jeon J, Brenner H, Gruber SB, Schoen RE, Berndt SI, et al. *A model to determine colorectal cancer risk using common genetic susceptibility loci.* Gastroenterology 2015 Jun;148(7):1330-9.e14 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25683114.
4. ↑ Jenkins MA, Makalic E, Dowty JG, Schmidt DF, Dite GS, MacInnis RJ, et al. *Quantifying the utility of single nucleotide polymorphisms to guide colorectal cancer screening.* Future Oncol 2016 Feb;12(4):503-13 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26846999.

8.1 Introduction: Risk and screening based on family history

The fact that family history of colorectal cancer is a risk factor for the disease implicates hereditary risk factors. Genes have been identified that, when inherited in a mutated form, substantially increase the risk of colorectal cancer. The best studied of these genes include:

- the DNA mismatch repair genes MLH1, MSH2, MSH6 and PMS2, mutations of which cause the hereditary cancer predisposition of Lynch syndrome (previously known as hereditary non-polyposis colorectal cancer)
- the APC gene, mutation of which causes familial adenomatous polyposis (FAP)
- the DNA base excision repair gene MUTYH, mutation of which causes attenuated familial adenomatous polyposis.

These genetic disorders have an autosomal-dominant mode of transmission (mismatch repair genes and APC) or autosomal-recessive mode of transmission (MUTYH) within families, and carry a very high risk for cancer (see High-risk familial syndromes).

However, mutations in these genes account for only a minority (less than 5%) of all colorectal cancer cases and at most, only explain half of the reason that family history is a risk factor for colorectal cancer.[1] The remainder of the observed increases in risk may be due in part to mutations in yet-to-be-discovered genes for colorectal cancer,[2] common polygenic factors such as single-nucleotide polymorphisms[3][4] or dietary and lifestyle factors that are shared by family members.

Assessment of family history of colorectal cancer has two roles in cancer prevention and early detection:

- to determine who should be tested for mutations in these genes.
- to inform decisions about the optimal timing, frequency and modality of screening.

This chapter provides estimates of risk of colorectal cancer and screening recommendations for the large number of people in the community who have a family history of colorectal cancer, but whose family history does not have the clinical features suggestive of high-risk familial syndromes. For information on surveillance strategies for specific high-risk familial syndromes, see:

- Familial adenomatous polyposis
- MUTYH associated polyposis
- Lynch syndrome
- Peutz-Jeghers syndrome
- Juvenile polyposis syndrome
- Serrated polyposis syndrome

8.1.1 Contents

Subsections:

- Colorectal cancer risk according to family history FHS2
- Screening strategies for people with a family history of colorectal cancer

8.1.2 References

1. ↑ Aaltonen L, Johns L, Järvinen H, Mecklin JP, Houlston R. *Explaining the familial colorectal cancer risk associated with mismatch repair (MMR)-deficient and MMR-stable tumors.* Clin Cancer Res 2007 Jan 1;13 (1):356-61 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17200375.
2. ↑ Win AK, Jenkins MA, Dowty JG, Antoniou AC, Lee A, Giles GG, et al. *Prevalence and Penetrance of Major Genes and Polygenes for Colorectal Cancer.* Cancer Epidemiol Biomarkers Prev 2016 Oct 31 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27799157.
3. ↑ Hsu L, Jeon J, Brenner H, Gruber SB, Schoen RE, Berndt SI, et al. *A model to determine colorectal cancer risk using common genetic susceptibility loci.* Gastroenterology 2015 Jun;148(7):1330-9.e14 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25683114.
4. ↑ Jenkins MA, Makalic E, Dowty JG, Schmidt DF, Dite GS, MacInnis RJ, et al. *Quantifying the utility of single nucleotide polymorphisms to guide colorectal cancer screening.* Future Oncol 2016 Feb;12(4):503-13 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26846999.

8.2 Colorectal cancer risk according to family history (FHS2)

Back to top

Contents

8.2.1 Background

The best evidence for the association between colorectal cancer risk and family history of the disease comes from studies that compare the risk of colorectal cancer in people with and without a family history of colorectal cancer. Ideally, these studies should control for any other differences between people with and without a family history, and for other risk factors for colorectal cancer – either by matching or by use of statistical methods.

Such studies consistently report an elevated risk of colorectal cancer associated with family history. The strength of this association increases with the number of relatives with colorectal cancer, the closeness of the genetic relationship of the relative(s) with colorectal cancer to the person, and the age at which the relative(s) is diagnosed with colorectal cancer.

Early studies indicated that first-degree relatives of patients with common colorectal cancer had a three- to four-fold increase in lifetime risk for colorectal cancer.[1][2] However, more recent studies of cancer incidence, which included appropriately matched control groups and used stringent methods for collection of family cancer data in relatives, reported an approximate doubling of lifetime risk:

- A Danish cohort study of people diagnosed with colorectal cancer before age 60 years reported that, compared with the general population, the risk of colorectal cancer was 1.6 times higher among patients' mothers and 1.9 times higher among patients' fathers.[3]
- An Australian case-control study comparing cancer risk in relatives of colorectal cancer patients and relatives of matched control patients reported that the risk of common colorectal cancer was 1.8 times higher among people with only one relative with colorectal cancer, compared with relatives of controls.[4]
- A US prospective cohort study of people without known colorectal cancer reported that the age-adjusted relative risk of colorectal cancer for men and women with affected first-degree relatives was 1.72, compared with those without a family history of the disease.[5]
- A US case-control study that compared people with colon cancer with matched controls reported that the risk of colon cancer was 2.2 times higher among patients with a second-degree or third-degree relative with colon cancer than those with no family history.[6]

In contrast to these modest levels of increased risk, colorectal cancer risk was shown to be substantially (three- to six-fold) greater for those who have a first-degree relative with colorectal cancer diagnosed at an early age (below 45 or 55 years) or when two close relatives have had colorectal cancer, irrespective of the age at diagnosis.[4][5][6]

For information on risk associated with specific high-risk familial syndromes, see High-risk familial syndromes.

8.2.2 Systematic review evidence

For individuals, has a family history of colorectal cancer been shown to be reliably associated with an increase in risk of occurrence of or death from colorectal cancer when compared to individuals who do not have a family history of colorectal cancer?

A systematic review of cohort studies was undertaken to update the evidence, since the establishment of the previous guidelines[7], to determine the risk of colorectal cancer for relatives of patients with colorectal cancer. Cohort studies are less subject to recall misclassification than case-control studies in which people with colorectal cancer more likely to report any existing family history than controls.

The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report. hyperlink

Six studies were identified: one analysis of pooled data from two prospective cohort studies[8], three prospective cohort studies[9][10][11] and two retrospective cohort studies.[12][13] All measured colorectal cancer outcomes (diagnosis or mortality) for people without a colorectal cancer diagnosis (or symptoms that might indicate colorectal cancer) at time of recruitment, and assessed risk according to the individual's independently confirmed family history of colorectal cancer. An additional modelling study was also identified.[14]

Of the cohort studies, one15 was deemed to have a low risk of bias[11], two were deemed to have a moderate risk of bias[9][13], and three were deemed to have a high risk of bias.[10][8][12]

8.2.2.1 Increased risk of colorectal cancer by family history

Overall, cohort studies show that people with a family member diagnosed with colorectal cancer have an increased risk of colorectal cancer, compared with the general population. Estimated increases in risk depend on the age at which the family member was diagnosed, and the number of first-degree and second-degree relatives with colorectal cancer (Table 5.1).

Individual colorectal cancer risk (personal risk) could, in theory, be estimated based on a person's specific family history and personal screening recommendations could be devised based on this increased risk. However, for practical reasons, only three categories of risk have been developed (Table 5.2), each with screening recommendations based on the average risk for that category.

8.2.2.1.1 Table 5.1. Increased risk of colorectal cancer based on family history: results from cohort studies published since 2005

Family history of colorectal cancer	Increased risk compared with the average risk
No family history	0.86[13] (14% decrease)
1 or more first-degree relative diagnosed at any age	1.4[12] – 2.1[10] 2.05[13] (40–110% increase)
1 first-degree relative diagnosed before age 50	3.3[13] (230% increase)
1 first-degree relative diagnosed between ages 50 and 60	2.2[12] to 2.5[13] (120–150% increase)
2 or more first-degree relatives	3.0[13] (200% increase)
No first-degree relative, at least one second-degree relative	1.1-1.5[13] (10–50% increase)

8.2.2.2 Category 1 — those near average risk

Lifetime risk is to age 75 years: approximately 5% to 10%

Asymptomatic people fit into this category if they have either of the following[4][5][6][8][10][12][14][15]:

- no first- or second-degree relative with colorectal cancer
- one first-degree or one first and one second-degree relative with colorectal cancer diagnosed at age 55 years or older.

For those with an affected first-degree relative, risk is double the average risk, although most of that extra risk is expressed after the age of 60 years. When the affected relative is second-degree (e.g. a grandparent, uncle or aunt), lifetime risk is only up to 1.5 times higher than average.[13][6]

8.2.2.3 Category 2 — those at moderately increased risk

Lifetime risk to age 75 years: approximately 15–30%

Asymptomatic people fit into this category if they have none of the high-risk features listed in category 3 and have either of the following:

- one first-degree relative with colorectal cancer diagnosed before the age of 55 years[4][6][13][16][17][18]
- two first-degree relatives or one first-degree relative and at least two second-degree relative diagnosed with colorectal cancer at 55 years or older.[13][17][18][19]

Relative risk in these two situations is increased to 3–6 times average risk. For the majority of people in this category, the risk of colorectal cancer is 3–4 times higher than average.

8.2.2.4 Category 3 — those at potentially high risk

Lifetime risk to age 75: approximately 30–40%

Asymptomatic people fit into this category if they have any of the following:

- at least three first-degree relatives diagnosed with colorectal cancer at 55 years or older[13]
- at least three first-degree or second-degree relative with colorectal cancer with at least one diagnosed before age 55 years.

This category excludes people with confirmed or suspected Lynch syndrome based on testing of a colorectal cancer in the family, or a relative with FAP.

For guidance on managing risk in people in category 3 with a known or suspected genetic syndrome, see High-risk familial syndromes.

Relative risk for category 3 is 7–10 times average risk. For the majority of people in this category, the risk of colorectal cancer is 7 times higher than average.

8.2.2.4.1 Table 5.2. Relative risk of colorectal cancer based on family history

Category	Family history	Relative risk
1	No family history No first- or second-degree relative with colorectal cancer One first-degree relative with colorectal cancer diagnosed at 55 years or older One first-degree and one second-degree with colorectal cancer diagnosed at 55 years or older	Up to 2-fold
2	One first-degree relative with colorectal cancer diagnosed under 55 years Two first-degree relatives with colorectal cancer diagnosed at 55 years or older One first-degree relative and at least two second-degree relative with colorectal cancer diagnosed at 55 years or older	3- to 6-fold
	At least three first-degree or second-degree relatives with colorectal cancer, with at least one diagnosed under 55 years	

Category	Family history	Relative risk
3	At least three first-degree relatives with colorectal cancer diagnosed at 55 years or older	7- to 10-fold

Sources: St John et al (1993)[4], Fuchs et al (1994)[5], Slattery et al (1994)[6], Bass et al (2008)[9], Schoen et al (2015)[11], Taylor et al (2011)[13], Lynch et al (2003)[15], Hall et al (1996)[16], Leu et al (2008)[14], Benhamiche-Bouvier et al (2000)[17], Sandhu et al (2001)[18], Aitken et al (1996)[19], Anderson et al (2003)[20]

Note: Relative risk is the ratio of the risk of developing colorectal cancer in a particular exposed group to the average risk in the whole population.

8.2.3 Evidence summary and recommendations

Evidence summary	Level	References
Category 1 – Those near average risk Approximately 95–98% of all people are in this category. The risk of colorectal cancer ranges from slightly below average to slightly above average, which is approximately two-fold the average risk. At least 90% of people in this category will never be diagnosed with colorectal cancer.	III-2	[19], [20], [21], [22], [23], [24], [25], [26]
Category 2 – Those at moderately increase risk Approximately 2–5% of all people are in this category. The risk of colorectal cancer is approximately three- to six-fold higher than average. Approximately 15–30% of people in this group will develop colorectal cancer in their lifetime.	II, III-2	[4], [6], [16], [17], [18], [19]
Category 3 – Those at potentially high risk Less than 1% of all people are in this category. The risk of colorectal cancer is approximately seven to ten-fold higher than average. Approximately 30–40% of people in this group will develop colorectal cancer in their lifetime.	II, III-2	[27], [28], [29], [30]

Evidence-based recommendation	Grade
People who have one relative with colorectal cancer diagnosed at age 55 or older should be advised that their own risk of developing colorectal cancer could be up to twice the average risk, but is still low.	**C**

Evidence-based recommendation	Grade
People should be advised that their risk of developing colorectal cancer is at least three times higher than average, but could be up to six times higher than average, if they have any of the following: ■ one first-degree relative with colorectal cancer diagnosed before age 55 years ■ two first-degree relatives with colorectal cancer diagnosed at age 55 years or older ■ one first-degree relative and at least two second-degree relative diagnosed with colorectal cancer at age 55 years or older.	**C**

Evidence-based recommendation	Grade
People should be advised that their risk of colorectal cancer is at least seven times higher than average, but could be up to 10 times higher than average, if they have either of the following: ■ at least three two first-degree or second-degree relatives with colorectal cancer, with at least one diagnosed before age 55 years ■ at least three first-degree relatives with colorectal cancer diagnosed at 55 years or older	**C**

Practice point

Medical information that patients provide about their relatives is often inaccurate.[4][31][32][33][34] The sensitivity of self-report of colorectal cancer in a first-degree relative is reported at 27% (percentage of all colorectal cancers in first-degree relatives that are reported) and the positive predictive value is 86% (percentage of reports that are correct).39.

Practice point

Given the potential importance of an accurate risk prediction for an individual, every effort should be made to collect reliable information.

Practice point

When there is uncertainty, more detailed information should be obtained from other family members, from death certificates, or from medical records.

Practice point

If a family medical history appears to be significant but diagnoses prove difficult to confirm, it may be appropriate to seek expert help from a familial cancer clinic.

8.2.4 Health system implications

8.2.4.1 Clinical practice

[insert if required. Suggest: No implications for clinical practice are envisaged. Or: Something re: referrals to familial cancer clinics?]

8.2.4.2 Resourcing

[Insert text here.] There are no known resourcing implications.

8.2.4.3 Barriers to implementation

[Insert text here. If no barriers, suggest: No barriers to the implementation of these recommendations are envisaged.]

8.2.5 Discussion

8.2.5.1 Unresolved issues

The effect of a family history of adenoma on colorectal cancer risk is unknown, although increased risk is likely. There is no, or virtually no evidence from which to determine the effect of family history of adenomas or advanced adenomas on colorectal cancer risk. Because of the increasing uptake of colonoscopy in the population, recent studies of family history as a risk factor may be underestimating the true association of colorectal cancer risk with family history of the disease, and therefore older studies may be more relevant to these guidelines.

8.2.5.2 Studies currently underway

We are not aware of any current trials that would provide more data on this question.

8.2.5.3 Future research priorities

Inherent difficulties in deciding the demarcation between categories or the number of categories argues for an algorithm that summarises the family history of colorectal cancer into a risk score that can then be used to decide age and modality of screening.

Identifying the causes for familial risk of colorectal cancer will assist the evaluation of risk within these risk categories, so that more personalised screening can be recommended based on more precise estimates of risk.

8.2.6 References

1. ↑ WOOLF CM. *A genetic study of carcinoma of the large intestine.* Am J Hum Genet 1958 Mar;10(1):42-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/13520697.
2. ↑ Lovett E. *Family studies in cancer of the colon and rectum.* Br J Surg 1976 Jan;63(1):13-18 Available from: http://www.ncbi.nlm.nih.gov/pubmed/1267868.
3. ↑ Søndergaard JO, Bülow S, Lynge E. *Cancer incidence among parents of patients with colorectal cancer.* Int J Cancer 1991 Jan 21;47(2):202-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/1988364.
4. ↑ 4.0 4.1 4.2 4.3 4.4 4.5 4.6 St John DJ, McDermott FT, Hopper JL, Debney EA, Johnson WR, Hughes ES. *Cancer risk in relatives of patients with common colorectal cancer.* Ann Intern Med 1993 May 15;118(10):785-90 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8470852.
5. ↑ 5.0 5.1 5.2 5.3 Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Speizer FE, Willett WC. *A prospective study of family history and the risk of colorectal cancer.* N Engl J Med 1994 Dec 22;331(25):1669-74 Available from: http://www.ncbi.nlm.nih.gov/pubmed/7969357.
6. ↑ 6.0 6.1 6.2 6.3 6.4 6.5 6.6 Slattery ML, Kerber RA. *Family history of cancer and colon cancer risk: the Utah Population Database.* J Natl Cancer Inst 1994 Nov 2;86(21):1618-26 Available from: http://www.ncbi.nlm.nih.gov/pubmed/7932826.
7. ↑ Australian Cancer Network Colorectal Cancer Guidelines Revision Committee. *Clinical practice guidelines for the prevention, early detection and management of colorectal cancer.* The Cancer Council Australia and Australian Cancer Network 2005.
8. ↑ 8.0 8.1 8.2 Wei EK, Giovannucci E, Wu K, Rosner B, Fuchs CS, Willett WC, et al. *Comparison of risk factors for colon and rectal cancer.* Int J Cancer 2004 Jan 20;108(3):433-42 Available from: http://www.ncbi.nlm.nih.gov/pubmed/14648711.
9. ↑ 9.0 9.1 9.2 Bass AJ, Meyerhardt JA, Chan JA, Giovannucci EL, Fuchs CS. *Family history and survival after colorectal cancer diagnosis.* Cancer 2008 Mar 15;112(6):1222-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18219663.
10. ↑ 10.0 10.1 10.2 10.3 Murphy G, Shu XO, Gao YT, Ji BT, Cook MB, Yang G, et al. *Family cancer history affecting risk of colorectal cancer in a prospective cohort of Chinese women.* Cancer Causes Control 2009 Oct;20(8):1517-21 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19418234.
11. ↑ 11.0 11.1 11.2 Schoen RE, Razzak A, Yu KJ, Berndt SI, Firl K, Riley TL, et al. *Incidence and mortality of colorectal cancer in individuals with a family history of colorectal cancer.* Gastroenterology 2015 Nov;149(6):1438-1445.e1 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26255045.

12. ↑ 12.0 12.1 12.2 12.3 12.4 Stefansson T, Moller PH, Sigurdsson F, Steingrimsson E, Eldon BJ. *Familial risk of colon and rectal cancer in Iceland: evidence for different etiologic factors?* Int J Cancer 2006 Jul 15;119(2): 304-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16477631.
13. ↑ 13.00 13.01 13.02 13.03 13.04 13.05 13.06 13.07 13.08 13.09 13.10 13.11 13.12 Taylor DP, Stoddard GJ, Burt RW, Williams MS, Mitchell JA, Haug PJ, et al. *How well does family history predict who will get colorectal cancer? Implications for cancer screening and counseling.* Genet Med 2011 May;13(5):385-91 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21270638.
14. ↑ 14.0 14.1 14.2 Leu M, Reilly M, Czene K. *Evaluation of bias in familial risk estimates: a study of common cancers using Swedish population-based registers.* J Natl Cancer Inst 2008 Sep 17;100(18):1318-25 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18780865.
15. ↑ 15.0 15.1 Lynch KL, Ahnen DJ, Byers T, Weiss DG, Lieberman DA. *First-degree relatives of patients with advanced colorectal adenomas have an increased prevalence of colorectal cancer.* Clin Gastroenterol Hepatol 2003 Mar;1(2):96-102 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15017501.
16. ↑ 16.0 16.1 16.2 Hall NR, Bishop DT, Stephenson BM, Finan PJ. *Hereditary susceptibility to colorectal cancer. Relatives of early onset cases are particularly at risk.* Dis Colon Rectum 1996 Jul;39(7):739-43 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8674364.
17. ↑ 17.0 17.1 17.2 17.3 Benhamiche-Bouvier AM, Lejeune C, Jouve JL, Manfredi S, Bonithon-Kopp C, Faivre J. *Family history and risk of colorectal cancer: implications for screening programmes.* J Med Screen 2000;7 (3):136-40 Available from: http://www.ncbi.nlm.nih.gov/pubmed/11126162.
18. ↑ 18.0 18.1 18.2 18.3 Sandhu MS, Luben R, Khaw KT. *Prevalence and family history of colorectal cancer: implications for screening.* J Med Screen 2001;8(2):69-72 Available from: http://www.ncbi.nlm.nih.gov /pubmed/11480446.
19. ↑ 19.0 19.1 19.2 19.3 Aitken JF, Bain CJ, Ward M, Siskind V, MacLennan R. *Risk of colorectal adenomas in patients with a family history of colorectal cancer: some implications for screening programmes.* Gut 1996 Jul;39(1):105-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8881819.
20. ↑ 20.0 20.1 Anderson JC, Attam R, Alpern Z, Messina CR, Hubbard P, Grimson R, et al. *Prevalence of colorectal neoplasia in smokers.* Am J Gastroenterol 2003 Dec;98(12):2777-83 Available from: http://www. ncbi.nlm.nih.gov/pubmed/14687832.
21. ↑ Pedersen A, Johansen C, Grønbaek M. *Relations between amount and type of alcohol and colon and rectal cancer in a Danish population based cohort study.* Gut 2003 Jun;52(6):861-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/12740343.
22. ↑ Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. *Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults.* N Engl J Med 2003 Apr 24;348(17):1625-38 Available from: http://www.ncbi.nlm.nih.gov/pubmed/12711737.
23. ↑ Grossman S, Milos ML. *Colonoscopic screening of persons with suspected risk factors for colon cancer. I. Family history.* Gastroenterology 1988 Feb;94(2):395-400 Available from: http://www.ncbi.nlm.nih.gov /pubmed/3335314.
24. ↑ Luchtefeld MA, Syverson D, Solfelt M, MacKeigan JM, Krystosek R, Waller J, et al. *Is colonoscopic screening appropriate in asymptomatic patients with family history of colon cancer?* Dis Colon Rectum 1991 Sep;34(9):763-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/1914741.

25. ↑ Rex DK, Lehman GA, Ulbright TM, Smith JJ, Pound DC, Hawes RH, et al. *Colonic neoplasia in asymptomatic persons with negative fecal occult blood tests: influence of age, gender, and family history.* Am J Gastroenterol 1993 Jun;88(6):825-31 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8503374.
26. ↑ Hunt LM, Rooney PS, Hardcastle JD, Armitage NC. *Endoscopic screening of relatives of patients with colorectal cancer.* Gut 1998 Jan;42(1):71-5 Available from: http://www.ncbi.nlm.nih.gov/pubmed/9505888.
27. ↑ Rhodes M, Bradburn DM. *Overview of screening and management of familial adenomatous polyposis.* Gut 1992 Jan;33(1):125-31 Available from: http://www.ncbi.nlm.nih.gov/pubmed/1310949.
28. ↑ Lynch HT, Smyrk T. *Hereditary nonpolyposis colorectal cancer (Lynch syndrome). An updated review.* Cancer 1996 Sep 15;78(6):1149-67 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8826936.
29. ↑ Järvinen HJ. *Epidemiology of familial adenomatous polyposis in Finland: impact of family screening on the colorectal cancer rate and survival.* Gut 1992 Mar;33(3):357-60 Available from: http://www.ncbi.nlm.nih.gov/pubmed/1314763.
30. ↑ Järvinen HJ, Mecklin JP, Sistonen P. *Screening reduces colorectal cancer rate in families with hereditary nonpolyposis colorectal cancer.* Gastroenterology 1995 May;108(5):1405-11 Available from: http://www.ncbi.nlm.nih.gov/pubmed/7729632.
31. ↑ Love RR, Evans AM, Josten DM. *The accuracy of patient reports of a family history of cancer.* J Chronic Dis 1985;38(4):289-93 Available from: http://www.ncbi.nlm.nih.gov/pubmed/3998045.
32. ↑ Douglas FS, O'Dair LC, Robinson M, Evans DG, Lynch SA. *The accuracy of diagnoses as reported in families with cancer: a retrospective study.* J Med Genet 1999 Apr;36(4):309-12 Available from: http://www.ncbi.nlm.nih.gov/pubmed/10227399.
33. ↑ Ruo L, Cellini C, La-Calle JP Jr, Murray M, Thaler HT, Quan SH, et al. *Limitations of family cancer history assessment at initial surgical consultation.* Dis Colon Rectum 2001 Jan;44(1):98-103; discussion 103-4 Available from: http://www.ncbi.nlm.nih.gov/pubmed/11805570.
34. ↑ Mitchell RJ, Brewster D, Campbell H, Porteous ME, Wyllie AH, Bird CC, et al. *Accuracy of reporting of family history of colorectal cancer.* Gut 2004 Feb;53(2):291-5 Available from: http://www.ncbi.nlm.nih.gov/pubmed/14724166.

Back to top

8.2.7 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search

View PICO	NHMRC Evidence statement form FHS1	Systematic review report FHS1

Back to top

8.3 Screening strategies for people with a family history of colorectal cancer

Contents

8.3.1 Background

A family history of colorectal cancer means a person’s probability of developing colorectal cancer could be several times higher than that of someone without a family history (see Colorectal cancer risk according to family history). However, family history in itself is not a good predictor of colorectal cancer,[1] because the increased risk is applied to an average risk of colorectal cancer that is very low (lifetime risk approximately 5%), resulting in an absolute risk in those with a family history that is still low. Nevertheless, family history can be used to stratify people without a diagnosis or symptoms of colorectal cancer into risk categories in which the number of expected colorectal cancers or adenomas is high enough to warrant more intensive screening than

the general population. Based on this, current practice in Australia and in many other countries to have more intensive or frequent screening for those with stronger family history. The majority of screening guidelines recommend biennial FOBT or 10-yearly colonoscopy for the lowest category of risk, 5-yearly colonoscopy for the middle category of risk and annual or biannual colonoscopy of the highest category of risk.[2][3] The majority of screening guidelines recommend screening to begin at age 50 for all risk categories or 10 years before the youngest age of colorectal cancer diagnosis in a relative.

Risk categories are defined in Colorectal cancer risk according to family history

Previous Australian guidelines[4] recommended more intense screening for people at moderately increased risk (category 2) and people at potentially high risk (category 3) due to family history. Recommendations for category 2 included 5-yearly colonoscopy beginning at age 50 years (or 10 years earlier than youngest age of relative at diagnosis) and consideration of faecal occult blood testing (FOBT) between colonoscopies.[4] Recommendations for category 3 were based on family risk profile according to familial syndrome, and included flexible sigmoidoscopy every 1–2 years for familial adenomatous polyposis (FAP), and 2-yearly colonoscopy with additional FOBT for Lynch syndrome.[4]

Based on this recent systematic review, and given that there is sufficient evidence to support screening for 50 year-olds at average risk using iFOBT every 2 years (see General population screening), earlier commencement of 2-yearly iFOBT is justified for people with an increased risk based on their family history.

The estimation of absolute risk, calculated as the probability that person of specific age and family history will develop colorectal cancer in the next 10 years, is a valid way to quantify risk. Screening regimens could be based on absolute risk on the principle of ‘equal risk, equal screening’, whereby an individual with a strong family history starts screening at a younger age because their absolute risk reaches the screening threshold earlier than someone with a lesser family history.

8.3.2 Overview of evidence

What is the effect of screening on risk of colorectal cancer incidence and mortality and how does it vary by family history (various categories)?

Guidance in this section is based the 2005 edition of this guideline,[4] the systematic reviews performed for the Colorectal cancer risk according to family history and Evidence for benefit from population screening sections, selected subsequent articles and international guidelines, and adapted based on consensus. X-ref to guidelines development chapter

It should be noted that the following recommendations are based on studies of cancer risk and on yield of lesions in screening studies, not on randomised controlled trials with colorectal cancer mortality as the outcome.

8.3.2.1 Effectiveness of screening in patients younger than 50 years

One study was identified that evaluated the effectiveness of FOBT prior to age 50 years.[5] This study correlated the results of FOBT tests with colonoscopy findings in 6096 asymptomatic patients aged 40 and over in Taiwan. It reported that a single immunochemical FOBT test for colorectal cancer in patients aged 40–49 years had a 60% sensitivity with a positive predictive value of 7.1%.[5]

A second study compared the results of FOBTs conducted in a large (n = 513,283) Taiwanese cohort between 1994 and 2008 with data from the Taiwan cancer registry.[6] One in seven colorectal cancers in people aged over 40 years occurred in the 40–49 years age group. 43 The study reported that, among people with a positive FOBT, that the hazard ratio (HR) for colorectal cancer was 2.3 times higher for those aged 40–44 years, and 5.7 higher for those aged 45–40 years, than for those aged 50–54 years.[6]

8.3.2.2 Absolute risk

The 10-year risk of colorectal cancer for the average population, those at two-fold risk (both Category 1) and those at three- and six-fold increased risk (Category 2) and those at seven- and ten-fold risk, can be calculated from population-based statistics (Table 5.3). The 10-year colorectal cancer risk for a 40 year-old at three-fold risk is the same as the 10-year colorectal cancer risk for a 35 year-old at seven-fold risk which is the same as the 10-year colorectal cancer risk for a 50 year-old at average risk. For people in category 2, the 10-year risk of colorectal cancer from age 50 is 3% or higher.

8.3.2.2.1 Table 5.3. Ten-year absolute risks of colorectal cancer (%) based on age and level of increased risk due to family history

Increased risk due to family history (RR)	30	35	40	45	50
1 (average)	0.073	0.15	1.29	0.6	1.0
2	0.15	0.29	0.59	1.1	1.9
3	0.22	0.44	0.88	1.6	2.9
6	0.44	0.88	1.8	3.3	5.7
7	0.51	1.0	2.0	3.8	6.6
10	0.73	1.5	2.9	5.4	9.3

RR: relative risk; the risk of colorectal cancer relative to the average risk in the population. Estimates are based on the assumption that the relative risk is the same for all age groups.

The blue shaded cells represent risks approximately equivalent to the risk of a 50 year-old at average risk who are recommended to begin 2-yearly FOBT screening.

Source: Incidence data from AIHW Australian colorectal cancer incidence for males and females combined for the year 2000.[7]

8.3.3 Screening by risk category

Table defining risk categories here: drop in from risk section above when final (unless define each category under subhead below)

8.3.3.1 Category 1 — Those near average risk'

If not above: boxed definition of category 1: drop in from risk section above when final

The yield of clinically significant lesions at screening colonoscopy is low (see Colorectal cancer risk according to family history).[8][9][10][11][12] A number of organisations, including the American Cancer Society and the American Gastroenterological Association, do not consider that risk of colorectal cancer justifies more invasive screening than that recommended for the general population.[13][14] The 1997 Australian Health Technology Advisory Committee (AHTAC) Report on Colorectal Cancer Screening concluded that recommendations for people in this category should be the same as for the average-risk population.[15]

Practice point

For people with a family history of colorectal cancer who are assessed as having category 1 risk:

- FOBT should be performed every 2 years from age 50 to age 74
- sigmoidoscopy (preferably flexible sigmoidoscopy) every 5 years from the age of 50 years should also be considered.

8.3.3.2 Category 2 — Those at moderately increased risk

If not above: boxed definition of category 2: drop in from risk section above when final

People in this group who do not have a known or suspected genetic syndrome have a 10-year risk of colorectal cancer approximately 10 years younger than people from category 1 (see Colorectal cancer risk according to family history). Therefore, their risk of colorectal cancer at age 40 is approximately 0.88% to 1.8%, and approximately equivalent to the risk for people in category 1 at age 50 (1.0%). Accordingly, 2-yearly screening from age 40 is appropriate. By age 50 their 10-year colorectal cancer risk is approximately 2.9 to 5.7%, which is sufficiently high to warrant screening by 5-yearly colonoscopy.

Practice point

For people with category 2 risk of colorectal cancer:

- FOBT should be performed every 2 years from age 40, and colonoscopy should be performed every 5 years from age 50 to age 74.
- low-dose (100 mg) aspirin daily should be considered (see Aspirin).

Practice point

People in category 2 should be advised that colonoscopy is an invasive procedure and the risks should be explained. Flexible sigmoidoscopy and double-contrast barium enema[15] or CT colonography can be offered if colonoscopy is contraindicated.[16]

Practice point

Because of the possibility Lynch syndrome, a complete family history should be taken and updated regularly, and the accuracy of the cancer diagnoses and polyp pathology should be checked carefully.

Practice point

Genetic testing is not appropriate at present for people with category 2 risk. Tumour testing for Lynch syndrome-related changes, using immunohistochemistry and microsatellite instability, should be considered when any of the revised Bethesda criteria are met (see Lynch syndrome).

Practice point

As with all forms of screening, those at risk should be carefully checked for the presence of symptoms that might be due to colorectal neoplasia. Where symptoms are present, appropriate diagnostic steps should be taken before entry into a screening program.

Practice point

Family members should be considered for genetic testing. Those shown to carry their family-specific mutation or having uncertain genetic status require careful cancer screening (see High-risk familial syndromes).

8.3.3.3 Category 3 — those at potentially high risk

If not above: boxed definition of category 3: drop in from risk section above when final

The risk for some people with three (or more) relatives with colorectal cancer may be difficult to categorise, especially if all cases of colorectal cancer occur at an advanced age, are confined to one generation of the family, and if no-one in the family has had any of the extra-colonic cancers associated with Lynch syndrome.49 If there is uncertainty about their mutation status, it may be safer to categorise people as having suspected (or possible) Lynch syndrome. New diagnoses of cancer in the family or results of microsatellite instability, immunohistochemical staining or genetic testing may clarify the situation. People in this group who do not have a known or suspected genetic syndrome have a 10-year risk of colorectal cancer approximately 15 years younger than people from category 1 (see Colorectal cancer risk according to family history). Therefore, their risk of colorectal cancer at age 35 is approximately 1.0% to 1.5%, and approximately equivalent to the risk for people in category 1 at age 50 (1.0%). Accordingly, 2-yearly screening from age 35 is appropriate. By age 45 their 10-year colorectal cancer risk is approximately 3.8% to 5.4%, which is sufficiently high to warrant screening by 5-yearly colonoscopy.

Practice point

For people with category 3 risk of colorectal cancer:

- iFOBT should be performed every 2 years from age 35, then yearly or 5-yearly colonoscopy from age 45 to age 74.
- low-dose (100 mg) aspirin daily should be considered (see Aspirin).
- Genetic testing for hereditary cancer syndromes should be considered . Those carrying their family-specific mutation or having uncertain genetic status require careful cancer screening (see High-risk familial syndromes).

8.3.4 Evidence summary and recommendations

Evidence summary	Level	References
Category 1 - Those at or slightly above average risk The yield of clinically significant lesions at screening colonoscopy is low, so population-based screening is appropriate.	II, III-2	[8], [9], [10], [11], [12]
Category 2 - Those at moderately increase risk The risk of colorectal cancer is as high at age 40 as the general population is at age 50, so population-based screening is appropriate till age 50. The 10-year risk of colorectal cancer from age 50 is at least 3%, so five-yearly colonoscopy is justified from age 50.	II, III-2	[17], [18], [19], [20], [21], [8]

Evidence summary	Level	References
Category 3 - Those at potentially high risk Fewer than 5% of colorectal cancers occur under category 3 conditions. Members of families with either FAP or definite or suspected Lynch syndrome are at potentially high risk for colorectal cancer and, depending on the syndrome, for cancer at certain other sites. The risk of colorectal cancer is as high at age 35 as the general population is at age 50, so population-based screening is appropriate till age 45. The 10-year risk of colorectal cancer from age 45 is at least 3%, so five-yearly colonoscopy is justified from age 45.	II, III-2	[22], [23], [24], [25]

Evidence-based recommendation	Grade
For category 1 patients, faecal occult blood testing (FOBT) should be given every second year from the age of 50 years.	**C**

Evidence-based recommendation	Grade
For category 1 patients, consider sigmoidoscopy (preferably flexible) every five years from the age of 50 years for individuals at average risk.	**C**

Evidence-based recommendation	Grade
For category 2 patients, offer iFOBT every two years starting at age 40, then colonoscopy every five years starting at age 50. Flexible sigmoidoscopy and double-contrast barium enema or CT colonography may be offered if colonoscopy is contraindicated.	**C**

Evidence-based recommendation	Grade
For category 3 patients, offer iFOBT every two years starting at age 35, then colonoscopy every five years starting at age 45. Flexible sigmoidoscopy and double-contrast barium enema or CT colonography may be offered if colonoscopy is contraindicated.	**C**

8.3.5 Health system implications

8.3.5.1 Clinical practice

These guidelines differ from the previous guidelines in in a number of ways.[4] There have been some minor changes in the family history inclusion criteria for category 2; the genetic syndromes have been removed from category 3 and as a consequence colonoscopy screening for category 3 is now five yearly; and the age at which screening begins is now uniform and younger for category 2 and category 3.

8.3.5.2 Resourcing

Insert text here. [To be drafted when recommendations finalised]

8.3.5.3 Barriers to implementation

There may be some resistance to the change in recommendations which have been in use for over 10 years.

8.3.6 Discussion

8.3.6.1 Unresolved issues

The optimal age to stop screening is not known. Health economic research is needed to determine whether the benefits of iFOBT screening or colonoscopy screening beyond age 74 years outweigh the inherent risks. Further research is needed, either observational studies or health economic research, to determine whether the youngest age of colorectal cancer diagnosis should be used as an indicator of the age to begin screening unaffected relatives. Previous guidelines have recommended screening 10 years younger than the age of the youngest relative at colorectal cancer diagnosis, but there is no evidence available to support this recommendation. Only a small number of studies examined the performance of colorectal cancer screening before age 50. Guidance presented here are based on the few studies that provide sensitivity estimates for colorectal cancer for those younger than age 50 that are similar to sensitivity estimates for ages 50 and over.[5] [6]

8.3.6.2 Studies currently underway

We are not aware of any current clinical trial that would provide more data on this question.

8.3.6.3 Future research priorities

Health economic research is needed to assess the cost effectiveness of screening for various categories of family history. In the absence of trials and observational studies for the effectiveness of screening strategies in people at elevated risk of colorectal cancer due to family history, cost-effectiveness analysis is appropriate to determine screening guidelines for the risk categories.

8.3.7 References

1. ↑ Taylor DP, Stoddard GJ, Burt RW, Williams MS, Mitchell JA, Haug PJ, et al. *How well does family history predict who will get colorectal cancer? Implications for cancer screening and counseling.* Genet Med 2011 May;13(5):385-91 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21270638.
2. ↑ Medical Advisory Secretariat. *Fecal Occult Blood Test for Colorectal Cancer Screening: an evidence-based analysis.* Toronto, Ontario: Canada: Ministry of Health and Long-Term Care; 2009.
3. ↑ International Agency for Research on Cancer. *European guidelines for quality assurance in colorectal cancer screening and diagnosis.* First Edition: International Agency for Research on Cancer; 2010.
4. ↑ 4.0 4.1 4.2 4.3 4.4 Australian Cancer Network Colorectal Cancer Guidelines Revision Committee. *Clinical practice guidelines for the prevention, early detection and management of colorectal cancer.* The Cancer Council Australia and Australian Cancer Network 2005.
5. ↑ 5.0 5.1 5.2 Chen Y-Y, Chen T-H, Su M-Y, Ning H-C, Kuo C-J, Lin W-P, et al.. *Accuracy of immunochemical fecal occult blood test for detecting colorectal neoplasms in individuals undergoing health check-ups.* Advances in Digestive Medicine 2014 Sep;Volume 1, Issue 3, Pages 74–79 Available from: http://www.aidm-online.com/article/S2351-9797(14)00045-0/abstract.
6. ↑ 6.0 6.1 6.2 Chen CH, Tsai MK, Wen CP. *Extending Colorectal Cancer Screening to Persons Aged 40 to 49 Years With Immunochemical Fecal Occult Blood Test: A Prospective Cohort Study of 513,283 Individuals.* J Clin Gastroenterol 2016 Oct;50(9):761-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26905605.
7. ↑ AIHW & Australasian Association of Cancer Registries. *Cancer in Australia 2000. Cancer Series. Cat. no. CAN 18.* Canberra: AIHW; 2003.
8. ↑ 8.0 8.1 8.2 Aitken JF, Bain CJ, Ward M, Siskind V, MacLennan R. *Risk of colorectal adenomas in patients with a family history of colorectal cancer: some implications for screening programmes.* Gut 1996 Jul;39 (1):105-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8881819.
9. ↑ 9.0 9.1 Grossman S, Milos ML. *Colonoscopic screening of persons with suspected risk factors for colon cancer. I. Family history.* Gastroenterology 1988 Feb;94(2):395-400 Available from: http://www.ncbi.nlm.nih.gov/pubmed/3335314.
10. ↑ 10.0 10.1 Luchtefeld MA, Syverson D, Solfelt M, MacKeigan JM, Krystosek R, Waller J, et al. *Is colonoscopic screening appropriate in asymptomatic patients with family history of colon cancer?* Dis Colon Rectum 1991 Sep;34(9):763-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/1914741.
11. ↑ 11.0 11.1 Rex DK, Lehman GA, Ulbright TM, Smith JJ, Pound DC, Hawes RH, et al. *Colonic neoplasia in asymptomatic persons with negative fecal occult blood tests: influence of age, gender, and family history.* Am J Gastroenterol 1993 Jun;88(6):825-31 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8503374.
12. ↑ 12.0 12.1 Hunt LM, Rooney PS, Hardcastle JD, Armitage NC. *Endoscopic screening of relatives of patients with colorectal cancer.* Gut 1998 Jan;42(1):71-5 Available from: http://www.ncbi.nlm.nih.gov/pubmed/9505888.
13. ↑ Smith RA, Cokkinides V, von Eschenbach AC, Levin B, Cohen C, Runowicz CD, et al. *American Cancer Society guidelines for the early detection of cancer.* CA Cancer J Clin 2002 Jan;52(1):8-22 Available from: http://www.ncbi.nlm.nih.gov/pubmed/11814067.
14. ↑ Winawer S, Fletcher R, Rex D, Bond J, Burt R, Ferrucci J, et al. *Colorectal cancer screening and surveillance: clinical guidelines and rationale-Update based on new evidence.* Gastroenterology 2003 Feb; 124(2):544-60 Available from: http://www.ncbi.nlm.nih.gov/pubmed/12557158.

15. ↑ [15.0] [15.1] Australian Health Technology Advisory Committee (AHTAC). *Colorectal cancer screening: a report of the Australian Health Technology Advisory Committee.* Canberra, Australia: Commonwealth Department of Health and Family Services; 1997 [cited 2016 Dec 15].
16. ↑ Dachman AH, Yoshida H. *Virtual colonoscopy: past, present, and future.* Radiol Clin North Am 2003 Mar; 41(2):377-93 Available from: http://www.ncbi.nlm.nih.gov/pubmed/12659344.
17. ↑ St John DJ, McDermott FT, Hopper JL, Debney EA, Johnson WR, Hughes ES. *Cancer risk in relatives of patients with common colorectal cancer.* Ann Intern Med 1993 May 15;118(10):785-90 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8470852.
18. ↑ Slattery ML, Kerber RA. *Family history of cancer and colon cancer risk: the Utah Population Database.* J Natl Cancer Inst 1994 Nov 2;86(21):1618-26 Available from: http://www.ncbi.nlm.nih.gov/pubmed /7932826.
19. ↑ Hall NR, Bishop DT, Stephenson BM, Finan PJ. *Hereditary susceptibility to colorectal cancer. Relatives of early onset cases are particularly at risk.* Dis Colon Rectum 1996 Jul;39(7):739-43 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8674364.
20. ↑ Benhamiche-Bouvier AM, Lejeune C, Jouve JL, Manfredi S, Bonithon-Kopp C, Faivre J. *Family history and risk of colorectal cancer: implications for screening programmes.* J Med Screen 2000;7(3):136-40 Available from: http://www.ncbi.nlm.nih.gov/pubmed/11126162.
21. ↑ Sandhu MS, Luben R, Khaw KT. *Prevalence and family history of colorectal cancer: implications for screening.* J Med Screen 2001;8(2):69-72 Available from: http://www.ncbi.nlm.nih.gov/pubmed/11480446.
22. ↑ Rhodes M, Bradburn DM. *Overview of screening and management of familial adenomatous polyposis.* Gut 1992 Jan;33(1):125-31 Available from: http://www.ncbi.nlm.nih.gov/pubmed/1310949.
23. ↑ Lynch HT, Smyrk T. *Hereditary nonpolyposis colorectal cancer (Lynch syndrome). An updated review.* Cancer 1996 Sep 15;78(6):1149-67 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8826936.
24. ↑ Järvinen HJ. *Epidemiology of familial adenomatous polyposis in Finland: impact of family screening on the colorectal cancer rate and survival.* Gut 1992 Mar;33(3):357-60 Available from: http://www.ncbi.nlm. nih.gov/pubmed/1314763.
25. ↑ Järvinen HJ, Mecklin JP, Sistonen P. *Screening reduces colorectal cancer rate in families with hereditary nonpolyposis colorectal cancer.* Gastroenterology 1995 May;108(5):1405-11 Available from: http://www. ncbi.nlm.nih.gov/pubmed/7729632.

Back to top

9 High-risk familial syndromes

Contents

9.1 Background

Approximately 5% of all colorectal cancers and 10–15% of colorectal cancers diagnosed before age 50 years are caused by high-risk germline mutations.[1][2] Genetic knowledge is rapidly expanding and new discoveries are likely to explain cases of heritable predisposition for which a mutation cannot currently be identified. For example, polymerase proofreading-associated polyposis (PPAP) has recently been described and accounts for a small number of families with polyposis.[3] Similarly, mutations in NTHL1 have been found to cause a rare autosomal recessive form of polyposis.[4]

Genetic testing for familial cancer syndromes is under going rapid change as technology improves and costs for more extensive testing strategies drop. Testing strategies are moving towards testing a panel of genes covering all polyposis conditions, or a non-polyposis Lynch panel, or both where the phenotype is unclear. Some centres offer whole exome sequencing but with analysis only of those genes which are appropriate to the clinical presentation. Large deletions, which are common causes some syndromes are not reliably detected by sequencing either in panels or examone sequencing and still need gene specific testing using the technique of MLPA. These *next gen* strategies are now cheaper than traditional Sanger sequencing of individual genes chosen to match the phenotype, with the likelihood that multiple genes will need to be tested sequentially.

9.1.1 Table 6.1 Familial syndromes associated with increased risk of colorectal cancer

Syndrome	Gene responsible	Inheritance	Typical phenotype	Extracolonic manifestations
Lynch syndrome*	*MSH2, MLH1, MSH6* or *PMS2*, *EPCAM*	Autosomal dominant	Early onset colorectal cancer, particularly in the proximal colon. The incidence of adenomas is not high but those that do arise have a high risk of rapidly progressing to malignancy. Cancers display microsatellite instability	Endometrial, ovarian, gastric, pancreatic, urothelial, renal pelvic, small intestine, biliary tract, brain, sebaceous gland adenomas and keratoacanthomas
Familial adenomatous polyposis (FAP)*	*APC*	Autosomal dominant	> 100 adenomas	Duodenal, gastric, desmoid, brain, thyroid, hepatoblastoma
Attenuated		Autosomal	> 10 adenomas before age 30	

Syndrome	Gene responsible	Inheritance	Typical phenotype	Extracolonic manifestations
FAP (AFAP)	*APC*	dominant	years or 20–100 adenomas	Duodenal, gastric
MUTYH-associated polyposis	*MUTYH*	Autosomal recessive	Usually 20–100 adenomas but may have > 100	Duodenal, gastric
Polymerase proofreading-associated polyposis (PPAP)	*POLD1* or *POLE*	Autosomal dominant	10–100 adenomas and variable number of serrated polyps	Endometrial
NTHL1-associated polyposis (NAP)	*NTHL1*	Autosomal recessive	8–50 adenomatous polyps	Endometrial
Peutz-Jeghers syndrome	*STK11*	Autosomal dominant	Histologically characteristic hamartomatous polyps throughout gastrointestinal tract and mucocutaneous pigmentation	Upper gastrointestinal and small intestine, breast, gynaecological, pancreas
Juvenile polyposis syndrome	*SMAD4* or *BMPR1A*	Autosomal dominant	Histologically characteristic hamartomatous polyps throughout gastrointestinal tract; polyps of mixed histology may also be present	Upper gastrointestinal and small intestine but no evidence of excess risk for extra-gastrointestinal cancers
Serrated polyposis syndrome	Unknown	Unclear and low penetrance	At least 5 serrated polyps proximal to the sigmoid with ≥ 2 of these > 10 mm or > 20 serrated polyps of any size but distributed throughout the colon	Nil known
Cowden		Autosomal	Some patients develop adenomas and hyperplastic polyps in addition to colonic hamartomas.	Breast, endometrial, thyroid, renal, skin lesions (trichilemmoma, papilloma): A

Syndrome	Gene responsible	Inheritance	Typical phenotype	Extracolonic manifestations
syndrome	*PTEN*	dominant	There is no evidence that all families with PTEN are at high risk of bowel cancer. Families with a history of colorectal cancer should follow screening guidelines based on their family history.	sensitive indicator of Cowden's Syndrome is head circumference, representing macrocephaly.

*Note on nomenclature Historically, eponymous names were used to refer to specific clinical phenotypes in an individual patient, but now that the genetic basis of FAP and LS is known they should be avoided.

- Gardner Syndrome refers to classic FAP where intestinal polyposis is associated with extra-intestinal manifestations including osteomas (typically of the skull), fibromas, epidermoid cysts and desmoid tumours.
- Muir-Torre syndrome refers to Lynch syndrome associated with sebaceous gland tumours such as sebaceous epitheliomas, sebaceous adenomas, sebaceous carcinomas and keratoacanthomas.
- Turcot syndrome (brain tumour – polyposis syndrome) refers to the occurrence of multiple colorectal adenomas and a primary brain tumour. It can also be associated with cafe-au-lait spots. Turcot syndrome is associated with at least 2 distinct types of germline defects:
    - Type I is associated with a mutation in one of the mismatch repair genes and gliomas (predominantly astrocytomas) and accounts for about one third of cases.
    - Type 2, which accounts for two thirds of cases, is associated with a mutation in the APC gene (FAP variant) and medulloblastoma is the most common type of brain tumour.

Back to top

9.1.2 Principles of management

The optimal management of individuals with, or at risk of, a familial colorectal cancer syndrome is dependent upon determining which syndrome is present. The provisional diagnosis should be based on well verified clinical and pathological data concerning the index patient and other affected members of the family. The diagnosis may ultimately be confirmed by the demonstration of a causative germline mutation.

Care is focused on the family as well as individual patients. It aims to reduce cancer morbidity and mortality by offering information about the risk of colorectal and other cancers and evidenced-based interventions to reduce this risk. There is evidence that participation in regular surveillance programs reduces cancer mortality in individuals carrying mutations causing familial adenomatous polyposis and Lynch syndrome.[5] Screening has not been shown to be beneficial for other rarer familial colorectal cancer syndromes. This is likely a result of small numbers in studied cohorts.

Back to top

9.1.3 Multidisciplinary approach

Patients with these syndromes benefit from management through familial cancer clinics that include geneticists, genetic counsellors, family based databases and multidisciplinary collaboration with gastroenterologists, colorectal surgeons and pathologists. The personal history of cancer and polyps in the index patient needs to be established and, if necessary, pathology review arranged. A detailed family history (pedigree) is collected and confirmed, where possible, by obtaining histological reports, clinical records, cancer registry information and/or death certificates. A provisional diagnosis is then reached and germline genetic testing arranged with pre- and post-test genetic counselling. Based on this, the diagnosis is refined and management recommendations made.

The index patient is supported in advising family members of the diagnosis and, where available, the benefits of predictive testing and surveillance. Communication is of utmost importance in the clinic with pre- and post-test counselling of patients and clear lines of communication with treating health professionals outside the familial cancer clinic.

Family registries have been associated with reduced cancer incidence within families. State-based familial cancer registries have been established in Australia (see Supplement. State- and territory-based familial cancer registries).

9.1.4 Contents

Subsections:

- Familial adenomatous polyposis
- MUTYH associated polyposis
- Lynch syndrome
- Peutz-Jeghers syndrome
- Juvenile polyposis syndrome
- Serrated polyposis syndrome
- Supplement. State- and territory-based familial cancer registries

Back to top

9.2 References

1. ↑ Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW, et al. *ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes.* Am J Gastroenterol 2015 Feb; 110(2):223-62; quiz 263 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25645574.

2. ↑ Stoffel EM, Mangu PB, Gruber SB, Hamilton SR, Kalady MF, Lau MW, et al, 2015. *Hereditary colorectal cancer syndromes: American Society of Clinical Oncology Clinical Practice Guideline endorsement of the familial risk-colorectal cancer: European Society for Medical Oncology Clinical Practice Guidelines.* Journal of Clinical Oncology 2015;33: 209-17 Available from: http://jco.ascopubs.org/content/early/2014/12/01/JCO.2014.58.1322.full.pdf.
3. ↑ Church JM. *Polymerase proofreading-associated polyposis: a new, dominantly inherited syndrome of hereditary colorectal cancer predisposition.* Dis Colon Rectum 2014 Mar;57(3):396-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24509466.
4. ↑ Weren RD, Ligtenberg MJ, Kets CM, de Voer RM, Verwiel ET, Spruijt L, et al. *A germline homozygous mutation in the base-excision repair gene NTHL1 causes adenomatous polyposis and colorectal cancer.* Nat Genet 2015 Jun;47(6):668-71 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25938944.
5. ↑ Barrow P, Khan M, Lalloo F, Evans DG, Hill J. *Systematic review of the impact of registration and screening on colorectal cancer incidence and mortality in familial adenomatous polyposis and Lynch syndrome.* Br J Surg 2013 Dec;100(13):1719-31 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24227356.

Back to top

9.1 Introduction: high-risk familial syndromes

Contents

9.1.1 Background

Approximately 5% of all colorectal cancers and 10–15% of colorectal cancers diagnosed before age 50 years are caused by high-risk germline mutations.[1][2] Genetic knowledge is rapidly expanding and new discoveries are likely to explain cases of heritable predisposition for which a mutation cannot currently be identified. For example, polymerase proofreading-associated polyposis (PPAP) has recently been described and accounts for a small number of families with polyposis.[3] Similarly, mutations in NTHL1 have been found to cause a rare autosomal recessive form of polyposis.[4]

Genetic testing for familial cancer syndromes is under going rapid change as technology improves and costs for more extensive testing strategies drop. Testing strategies are moving towards testing a panel of genes covering all polyposis conditions, or a non-polyposis Lynch panel, or both where the phenotype is unclear. Some centres offer whole exome sequencing but with analysis only of those genes which are appropriate to the clinical presentation. Large deletions, which are common causes some syndromes are not reliably detected by sequencing either in panels or examone sequencing and still need gene specific testing using the technique of MLPA. These *next gen* strategies are now cheaper than traditional Sanger sequencing of individual genes chosen to match the phenotype, with the likelihood that multiple genes will need to be tested sequentially.

9.1.1.1 Table 6.1 Familial syndromes associated with increased risk of colorectal cancer

Syndrome	Gene responsible	Inheritance	Typical phenotype	Extracolonic manifestations
Lynch syndrome*	*MSH2, MLH1, MSH6* or *PMS2*, *EPCAM*	Autosomal dominant	Early onset colorectal cancer, particularly in the proximal colon. The incidence of adenomas is not high but those that do arise have a high risk of rapidly progressing to malignancy. Cancers display microsatellite instability	Endometrial, ovarian, gastric, pancreatic, urothelial, renal pelvic, small intestine, biliary tract, brain, sebaceous gland adenomas and keratoacanthomas
Familial adenomatous polyposis (FAP)*	*APC*	Autosomal dominant	> 100 adenomas	Duodenal, gastric, desmoid, brain, thyroid, hepatoblastoma
Attenuated FAP (AFAP)	*APC*	Autosomal dominant	> 10 adenomas before age 30 years or 20–100 adenomas	Duodenal, gastric
MUTYH-associated polyposis	*MUTYH*	Autosomal recessive	Usually 20–100 adenomas but may have > 100	Duodenal, gastric
Polymerase proofreading-associated polyposis (PPAP)	*POLD1* or *POLE*	Autosomal dominant	10–100 adenomas and variable number of serrated polyps	Endometrial
NTHL1-associated polyposis (NAP)	*NTHL1*	Autosomal recessive	8–50 adenomatous polyps	Endometrial

Syndrome	Gene responsible	Inheritance	Typical phenotype	Extracolonic manifestations
Peutz-Jeghers syndrome	*STK11*	Autosomal dominant	Histologically characteristic hamartomatous polyps throughout gastrointestinal tract and mucocutaneous pigmentation	Upper gastrointestinal and small intestine, breast, gynaecological, pancreas
Juvenile polyposis syndrome	*SMAD4* or *BMPR1A*	Autosomal dominant	Histologically characteristic hamartomatous polyps throughout gastrointestinal tract; polyps of mixed histology may also be present	Upper gastrointestinal and small intestine but no evidence of excess risk for extra-gastrointestinal cancers
Serrated polyposis syndrome	Unknown	Unclear and low penetrance	At least 5 serrated polyps proximal to the sigmoid with ≥ 2 of these > 10 mm or > 20 serrated polyps of any size but distributed throughout the colon	Nil known
Cowden syndrome	*PTEN*	Autosomal dominant	Some patients develop adenomas and hyperplastic polyps in addition to colonic hamartomas. There is no evidence that all families with PTEN are at high risk of bowel cancer. Families with a history of colorectal cancer should follow screening guidelines based on their family history.	Breast, endometrial, thyroid, renal, skin lesions (trichilemmoma, papilloma): A sensitive indicator of Cowden's Syndrome is head circumference, representing macrocephaly.

*Note on nomenclature Historically, eponymous names were used to refer to specific clinical phenotypes in an individual patient, but now that the genetic basis of FAP and LS is known they should be avoided.

- Gardner Syndrome refers to classic FAP where intestinal polyposis is associated with extra-intestinal manifestations including osteomas (typically of the skull), fibromas, epidermoid cysts and desmoid tumours.
- Muir-Torre syndrome refers to Lynch syndrome associated with sebaceous gland tumours such as sebaceous epitheliomas, sebaceous adenomas, sebaceous carcinomas and keratoacanthomas.
- Turcot syndrome (brain tumour – polyposis syndrome) refers to the occurrence of multiple colorectal adenomas and a primary brain tumour. It can also be associated with cafe-au-lait spots. Turcot syndrome is associated with at least 2 distinct types of germline defects:
    - Type I is associated with a mutation in one of the mismatch repair genes and gliomas (predominantly astrocytomas) and accounts for about one third of cases.

- Type 2, which accounts for two thirds of cases, is associated with a mutation in the APC gene (FAP variant) and medulloblastoma is the most common type of brain tumour.

Back to top

9.1.1.2 Principles of management

The optimal management of individuals with, or at risk of, a familial colorectal cancer syndrome is dependent upon determining which syndrome is present. The provisional diagnosis should be based on well verified clinical and pathological data concerning the index patient and other affected members of the family. The diagnosis may ultimately be confirmed by the demonstration of a causative germline mutation.

Care is focused on the family as well as individual patients. It aims to reduce cancer morbidity and mortality by offering information about the risk of colorectal and other cancers and evidenced-based interventions to reduce this risk. There is evidence that participation in regular surveillance programs reduces cancer mortality in individuals carrying mutations causing familial adenomatous polyposis and Lynch syndrome.[5] Screening has not been shown to be beneficial for other rarer familial colorectal cancer syndromes. This is likely a result of small numbers in studied cohorts.

Back to top

9.1.1.3 Multidisciplinary approach

Patients with these syndromes benefit from management through familial cancer clinics that include geneticists, genetic counsellors, family based databases and multidisciplinary collaboration with gastroenterologists, colorectal surgeons and pathologists. The personal history of cancer and polyps in the index patient needs to be established and, if necessary, pathology review arranged. A detailed family history (pedigree) is collected and confirmed, where possible, by obtaining histological reports, clinical records, cancer registry information and/or death certificates. A provisional diagnosis is then reached and germline genetic testing arranged with pre- and post-test genetic counselling. Based on this, the diagnosis is refined and management recommendations made.

The index patient is supported in advising family members of the diagnosis and, where available, the benefits of predictive testing and surveillance. Communication is of utmost importance in the clinic with pre- and post-test counselling of patients and clear lines of communication with treating health professionals outside the familial cancer clinic.

Family registries have been associated with reduced cancer incidence within families. State-based familial cancer registries have been established in Australia (see Supplement. State- and territory-based familial cancer registries).

9.1.1.4 Contents

Subsections:

- Familial adenomatous polyposis
- MUTYH associated polyposis
- Lynch syndrome
- Peutz-Jeghers syndrome
- Juvenile polyposis syndrome
- Serrated polyposis syndrome
- Supplement. State- and territory-based familial cancer registries

Back to top

9.1.2 References

1. ↑ Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW, et al. *ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes.* Am J Gastroenterol 2015 Feb; 110(2):223-62; quiz 263 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25645574.
2. ↑ Stoffel EM, Mangu PB, Gruber SB, Hamilton SR, Kalady MF, Lau MW, et al, 2015. *Hereditary colorectal cancer syndromes: American Society of Clinical Oncology Clinical Practice Guideline endorsement of the familial risk-colorectal cancer: European Society for Medical Oncology Clinical Practice Guidelines.* Journal of Clinical Oncology 2015;33: 209-17 Available from: http://jco.ascopubs.org/content/early/2014/12/01/JCO.2014.58.1322.full.pdf.
3. ↑ Church JM. *Polymerase proofreading-associated polyposis: a new, dominantly inherited syndrome of hereditary colorectal cancer predisposition.* Dis Colon Rectum 2014 Mar;57(3):396-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24509466.
4. ↑ Weren RD, Ligtenberg MJ, Kets CM, de Voer RM, Verwiel ET, Spruijt L, et al. *A germline homozygous mutation in the base-excision repair gene NTHL1 causes adenomatous polyposis and colorectal cancer.* Nat Genet 2015 Jun;47(6):668-71 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25938944.
5. ↑ Barrow P, Khan M, Lalloo F, Evans DG, Hill J. *Systematic review of the impact of registration and screening on colorectal cancer incidence and mortality in familial adenomatous polyposis and Lynch syndrome.* Br J Surg 2013 Dec;100(13):1719-31 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24227356.

Back to top

9.2 Familial adenomatous polyposis

Contents

9.2.1 Background

FAP is an autosomal dominant disorder due to heritable germline mutations of the APC gene and causes the development of large numbers of colorectal adenomas at a young age. Classical FAP is defined by the presence of > 100 adenomas and young age of onset of polyposis; often thousands of adenomas are present. It is associated with a lifetime risk of CRC approaching 100% but accounts for ≤ 1% of all CRC cases. Common extra-colonic manifestations include gastric and duodenal polyps, desmoid tumours, osteomas and multiple congenital hypertrophy of the retinal pigment epithelium (pigmented ocular lesions).[1] Up to 30% of cases occur without a family history of FAP and represent either de novo germline mutations or mosaicism.[2]

Attenuated FAP (AFAP) is also due to autosomal dominant mutations in the APC gene but there are fewer adenomas and a later onset of disease. The diagnosis should be considered in patients with a cumulative count of ≥ 10 adenomas before age 30 years or 20–99 adenomas at any age.[2][3][1] In AFAP, adenomas may be predominantly in the proximal colon and there is often marked phenotypic variability within a family.

People with FAP also have an increased risk of extra-colonic malignancy, including malignancies of the upper gastrointestinal tract (most commonly duodenum), brain, thyroid and liver (hepatoblastoma). There is also an increased risk of desmoid tumours.

Back to top

9.2.2 Management

No systematic reviews on this topic were undertaken in the development of this section. The guidance on FAP is based on recent international guidelines.[2][3][4][1][5][6] See Guidelines Development for more information.

Back to top

9.2.2.1 Genetic testing

Referral to a genetics service for germline genetic testing for mutations in APC is indicated for persons with a cumulative count of ≥ 10 colorectal adenomas before 30 years of age or ≥ 20 colorectal adenomas at any age.[1] It is also indicated when a known pathogenic APC mutation is identified in a relative.

Over 70% of patients with a classical FAP phenotype have an APC mutation identified. Approximately 25% of patients with an attenuated FAP phenotype have an APC mutation identified.[1] Finding a pathogenic mutation confirms the diagnosis and allows relatives to be tested with a very high degree of accuracy. Absence of a mutation in the proband does not definitively rule out the diagnosis though it does in the context of predictive testing of relatives where there is a known family specific mutation.[2]

Back to top

9.2.2.2 Surveillance

Practice point

- Colonic surveillance should be offered to:
  - individuals found on genetic testing to carry a pathogenic APC mutation
  - first-degree relatives of patients with FAP or AFAP in whom genetic testing has been declined or is not possible because the family mutation has not been identified.

Surveillance should commence from age 10 to 15 years or earlier if there are gastrointestinal symptoms (Robays and Poppe, 2014). In families with classical FAP, flexible sigmoidoscopy is adequate since adenomas occur simultaneously throughout the colorectum (Syngal et al., 2015; Stoffel et al., 2015; Robays and Poppe, 2014). Once an adenoma is identified, annual colonoscopy should be performed until colectomy is undertaken. In AFAP, surveillance should be by colonoscopy since the first adenomas may only be present in the proximal colon but surveillance can be delayed until 18 years of age (Syngal et al., 2015; Cancer Institute NSW 2016; Robays and Poppe, 2014).

Back to top

9.2.2.3 Surgical management

In classical FAP, colectomy is required to prevent colorectal cancer and is usually performed between the ages of 15 and 25, once adenomas have been observed.[1][6] The exact timing of surgery and the choice between a total colectomy with an ileorectal anastomosis or a proctocolectomy with an ileal pouch-anal anastomosis (IPAA) depends on many factors including severity of polyposis in the rectum, risk of desmoid tumours and the desire to preserve fecundity and urinary, sexual and bowel function.[2][6]

Practice point

- Total colectomy and ileorectal anastomosis should be reserved for patients with rectal adenomas considered easily controllable by endoscopy and < 1000 colonic adenomas. Proctocolectomy with a permanent ileostomy is rarely needed (Syngal et al., 2015). Annual surveillance of the residual rectum or ileal pouch is required following colectomy (Cancer Institute NSW 2016).
- Some patients with AFAP can be managed with colonoscopic polypectomy at one- to two-yearly intervals (Syngal et al., 2015; Balmaña et al., 2013). If surgery is required due to a high number of adenomas, colectomy with ileorectal anastomosis can nearly always be performed, because of the small number of adenomas in the rectum (Syngal et al., 2015; Balmaña et al., 2013)

Back to top

9.2.2.4 Chemoprevention

There is no evidence that risk reducing medication such as non-steroidal anti-inflammatory drugs (NSAIDs) prevent colorectal cancer in FAP.[1] However, NSAIDs are well documented to reduce adenoma numbers in FAP, and all CRCs in FAP arise from adenomas. Where surgery is inappropriate (e.g. presenting also with complex intra-abdominal desmoid disease or adenomas in pouches) an NSAID (e.g. sulindac) is recommended. Refer to the Primary Prevention Part 2: Chemopreventive candidate agents chapter.

Back to top

9.2.3 References

1. ↑ 1.0 1.1 1.2 1.3 1.4 1.5 1.6 Cancer Institute NSW. *eviQ Cancer Genetics Referral Guidelines for Colorectal Cancer or Polyposis Risk Assessment and Consideration of Genetic Testing.* [homepage on the internet] Sydney; 2016 [cited 2016 Sep 6]. Available from: https://www.eviq.org.au/Category/tabid/65/categoryid/6/Default.aspx.
2. ↑ 2.0 2.1 2.2 2.3 2.4 Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW, et al. *ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes.* Am J Gastroenterol 2015 Feb;110(2):223-62; quiz 263 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25645574.
3. ↑ 3.0 3.1 Stoffel EM, Mangu PB, Gruber SB, Hamilton SR, Kalady MF, Lau MW, et al 2015. *Hereditary colorectal cancer syndromes: American Society of Clinical Oncology Clinical Practice Guideline endorsement of the familial risk-colorectal cancer: European Society for Medical Oncology Clinical Practice Guidelines.* Journal of Clinical Oncology 2015;33: 209-17 Available from: http://jco.ascopubs.org/content/early/2014/12/01/JCO.2014.58.1322.full.pdf.

4. ↑ Barrow P, Khan M, Lalloo F, Evans DG, Hill J. *Systematic review of the impact of registration and screening on colorectal cancer incidence and mortality in familial adenomatous polyposis and Lynch syndrome.* Br J Surg 2013 Dec;100(13):1719-31 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24227356.
5. ↑ Robays J, Poppe B. *Oncogenetic testing for Lynch syndrome and familial adenomatous polyposis.* Brussels: Belgian Health Care Knowledge Centre (KCE); 2014.
6. ↑ [6.0] [6.1] [6.2] Balmaña J, Balaguer F, Cervantes A, Arnold D, ESMO Guidelines Working Group.. *Familial risk-colorectal cancer: ESMO Clinical Practice Guidelines.* Ann Oncol 2013 Oct;24 Suppl 6:vi73-80 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23813931.

Back to top

9.3 MUTYH associated polyposis

Contents

9.3.1 Background

MUTYH-associated polyposis is a recessively inherited predisposition to colorectal polyps and early onset colorectal cancer due to biallelic mutations in the MUTYH gene. Germline MUTYH mutations predispose to developing somatic APC mutations and the KRAS Gly12Cys 'hotspot' mutation in the gastrointestinal tract. Affected individuals commonly have between 20 and 100 adenomas but may have > 100.[1][2]

Back to top

9.3.2 Management

No systematic reviews on this topic were undertaken in the development of this section. The guidance on MUTH-associated polyposis is based on recent international guidelines.[1][3][4][2] (See Guidelines Development for more information).

Back to top

9.3.2.1 Genetic testing

Practice point

- Referral to a genetics service for germline genetic testing for mutations in MUTYH is indicated for persons with a cumulative count of ≥ 20 colorectal adenomas at any age (Syngal et al., 2015). It is also indicated for siblings of a MUTYH biallelic mutation carrier (Syngal et al., 2015).

Testing may also be considered in patients with ≥ 10 adenomas and any of the following (Syngal et al., 2015) :

- age under 50
- synchronous colorectal cancer
- serrated polyposis
- family history suggestive of recessive inheritance (e.g. consanguinity in parents or siblings with documented adenomatous polyposis or colorectal cancer).

Back to top

9.3.2.2 Surveillance and management

Practice point

Biallelic mutation carriers should have colonoscopy every 2 years starting at age 18 to 20 years(Cancer Institute NSW, 2016; Robays and Poppe, 2014; Balmaña et al., 2013). If polyps are detected, annual colonoscopy may be required to control the polyp burden (Cancer Institute NSW, 2016). If polyps cannot be easily managed colonoscopically, a colectomy with ileorectal anastomosis should be considered and discussed with the patient (Cancer Institute NSW, 2016; Balmaña et al., 2013) The residual rectum requires annual surveillance.

Monoallelic *MUTYH* mutations are present in 1 to 2% of the population and may confer, on average, a 1.5- to 2-fold increase in the risk of colorectal cancer.[1] There is currently no consensus regarding surveillance and management, but an option may be to offer colonoscopy 5 yearly from 10 years younger than the earliest cancer diagnosis in the family.[1][2]

Back to top

9.3.3 References

1. ↑ [1.0] [1.1] [1.2] [1.3] Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW, et al. *ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes.* Am J Gastroenterol 2015 Feb;110(2):223-62; quiz 263 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25645574.
2. ↑ [2.0] [2.1] [2.2] Balmaña J, Balaguer F, Cervantes A, Arnold D, ESMO Guidelines Working Group.. *Familial risk-colorectal cancer: ESMO Clinical Practice Guidelines.* Ann Oncol 2013 Oct;24 Suppl 6:vi73-80 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23813931.
3. ↑ Cancer Institute NSW. *eviQ Cancer Genetics Referral Guidelines for Colorectal Cancer or Polyposis Risk Assessment and Consideration of Genetic Testing.* [homepage on the internet] Sydney; 2016 [cited 2016 Sep 6]. Available from: https://www.eviq.org.au/Category/tabid/65/categoryid/6/Default.aspx.
4. ↑ Robays J, Poppe B. *Oncogenetic testing for Lynch syndrome and familial adenomatous polyposis.* Brussels: Belgian Health Care Knowledge Centre (KCE); 2014.

Back to top

9.4 Lynch syndrome

Contents

9.4.1 Background

Lynch syndrome (LS), previously called hereditary nonpolyposis colorectal cancer (HNPCC), is an autosomal dominant condition caused by germline mutations in any one of the mismatch repair genes (MSH2, MLH1, MSH6, PMS2) or loss of expression of MSH2 due to deletion in the nearby EPCAM gene. It is associated with a high risk of early onset colorectal cancer, particularly in the proximal colon. The lifetime risk of some extracolonic cancers is also elevated and is estimated to be 33% for endometrial cancer, 9% for ovarian cancer, 6% for gastric cancer and < 3% for urothelial and small intestinal cancer.[1]

LS is relatively common and is thought to account for approximately 2–3% of all colorectal cancers.[2][3] The risk estimates for colorectal cancer by age 70 years are 31–47% for MLH1 and MSH2 mutation carriers.[4] The risk of colorectal cancer is less in carriers of other mutations and risk estimates range from 10 to 22% for MSH6 mutation carriers and 15 to 20% for PMS2 mutation carriers.[1]

The incidence of adenomas is not high but those that do arise have a high risk of rapidly progressing to malignancy due to loss of the remaining wild type allele of the mutated mismatch repair gene. The cancers thus have mismatch repair deficiency leading to characteristic microsatellite instability (MSI) in the DNA of the cancer cells. The mutated protein degrades and shows loss of expression of one or more of the mismatch repair protein on immunohistochemistry (IHC). The case of MSH2 protein expression loss is usually associated with the loss of expression of the binding partner MSH6 protein as the unbound protein degrades. Similarly, MLH1 protein expression loss usually leads to loss of expression of the PMS2 protein. Isolated loss of MSH6 or PMS2 protein expression suggests the defect is in the affected gene.

Results of IHC and MSI testing need to be interpreted with the knowledge that MLH1 can be silenced by somatic methylation in the MLH1 promoter region in sporadic colorectal cancers. These cancers show high levels of MSI and loss of MLH1 and PMS2 expression on IHC. They typically occur in the proximal colon of older females without a family history of colorectal cancer. They commonly have a V600E mutation of the BRAF oncogene whereas BRAF mutation is rare in LS cancers.

Back to top

9.4.2 Identification of Lynch Syndrome

Identification of LS has traditionally relied on multiple factors, including recognition of typical features and appropriate testing and/or referral to a genetics provider. Although there are some histological features within individual tumours that can indicate a likelihood of MMR deficit, and other clues, such as location of the tumour (e.g. proximal colon cancer), Lynch syndrome-associated colon cancers are not necessarily distinguishable from sporadic colon cancers.[5] Systematic collection and assessment of family history are highly variable among health care providers, and rarely is this information readily available to pathologists who may recognize histological features of LS. Given these limitations and compelling reasons to identify these individuals and their at-risk family members, universal screening has been proposed as a way to adequately identify individuals with LS.

Back to top

9.4.2.1 Universal testing of colorectal cancers

Practice point

- To increase the rate of diagnosis, universal testing of all colorectal cancers (or at least all colorectal cancers diagnosed before age 70 years) is recommended, regardless of family history (Robays and Poppe, 2014; Ladabaum et al., 2015; Giardiello et al., 2014; Rubenstein et al., 2015).

There is no recommendation whether universal testing be done by IHC or MSI testing as the sensitivity and specificity of the tests are very similar. IHC is more widely available and has the advantage of indicating which gene is abnormal. However, appropriate training and experience of pathologists is required for accurate results. [6]

Implementation of universal testing requires an effective multidisciplinary programme with sufficient resources to follow-up positive results.[3] Most cancers demonstrating MSI or loss of *MLH1* and *PMS2* on IHC, will be sporadic cancers with somatic methylation and silencing of *MLH1*. It is recommended that cancers with loss of *MLH1* be tested for *BRAF* mutation or *MLH1* promoter hypermethylation before considering germline mutation testing.[7][2][3][6] This makes testing more cost effective and reduces unnecessary anxiety amongst affected individuals. However, neither test is completely sensitive or specific and the result of methylation testing can depend on the technique used. A recent study reported *MLH1* hypermethylation in 16% of patients with LS and 92% of patients with *BRAF* mutant cancer presumed to be sporadic. [2]

IHC in adenomas is of limited benefit to identify LS as a normal IHC result does not exclude LS.

Practice point

- All colorectal cancers diagnosed before age 70 years should be tested for Lynch syndrome.
- Testing adenomas should probably be restricted to individuals in a clinically suspected Lynch syndrome family where there is no appropriate cancer tissue available for IHC testing. IHC in serrated polyps has no role to identify Lynch syndrome.

Back to top

9.4.2.2 Use of risk prediction models

In individuals without a personal history of colorectal cancer but with a family history suggestive of LS, it is recommended that a risk prediction model be used to guide referral for further assessment. [7][2][3][6] Currently available appropriate risk prediction models are PREMM or MMRpro. The initial approach to further assessment would to perform IHC or MSI testing on the cancer of an affected relative if this is possible to arrange.

Back to top

9.4.3 Management

A systematic review of aspirin in the prevention of colorectal cancer, including Lynch syndrome-associated cancers, was undertaken in the preparation of this guideline. The results are summarised in Primary prevention (Part 2): Chemopreventive candidate agents.

No systematic reviews on testing or surgical management of LS were undertaken in the development of this section. The guidance on LS is based on recent international guidelines.[1][7][2][3][4][6][8]

Back to top

9.4.3.1 Genetic testing

IHC of cancer tissue from an affected family member can be used to guide germline genetic testing of mismatch repair genes. The probability of identifying a pathogenic germline mutation is shown in Table 6.2.[1]

Back to top

9.4.3.1.1 Table 6.2 Probability of identifying a pathogenic germline mutation

Finding	Probability
Loss of *MSH2* and *MSH6*	*MSH2* 67%
Loss of *MLH1* and *PMS2* with no *BRAF* mutation and/or no *MLH1* hypermethylation	*MLH1* 33%
Loss of *MSH6* only	*MSH6* 24%
Loss of *PMS2* only	*PMS2* 62%

Source: eviQ Cancer Genetics Referral Guidelines for Colorectal Cancer or Polyposis Risk Assessment and Consideration of Genetic Testing (2016).[1]

If no germline mutation or a variant of unknown significance is found, LS cannot be excluded.[3] These cases are sometimes referred to as Lynch-like syndrome. Some may be due to biallelic somatic mutations and in future these may be identified on tumour testing and used to exclude LS.[9] However others, particularly those with a suggestive family history, are most likely due to germline mutations not yet detectable by currently available techniques. These families should be managed clinically according to LS guidelines and re-investigated as genetic techniques advance.

Finding a pathogenic germline mutation confirms the diagnosis and allows relatives to be tested with a very high degree of accuracy.

Back to top

9.4.3.2 Surveillance

Surveillance colonoscopy every 1 to 2 years is recommended for individuals carrying a germline mutation or clinically at risk of carrying a mutation but in whom definitive testing is not possible.[1][7][2][3][6] It should commence at age 25 or 5 years younger than the youngest affected family member if < 30 years.[1] Annual surveillance is preferred in known mutation carriers.[3] The risk of colorectal cancer is lower and the age of diagnosis is later in carriers of MSH6 or PMS2 mutations and surveillance starting at age 30 years could be considered,[1][3] although there is no data to directly guide this.[2][6]

Back to top

9.4.3.3 Surgical management

In patients with colorectal cancer and known LS the choice of procedure should be individualised according to the site and number of tumour(s), age at diagnosis, risk of surgical morbidity, patient comorbidities and their wishes. If a segmental (partial) colectomy is performed there is a high (16–19%) 10-year cumulative risk of metachronous colorectal cancer, even with colonoscopic surveillance.[3][8] This risk is substantially reduced by performing an extended resection (either a subtotal colectomy with an ileosigmoid anastomosis or a total colectomy with an ileorectal anastomosis) and is generally favoured.[3][8] Functional outcome is however better after segmental colectomy and this procedure can still be considered in older patients.[3][8] Annual surveillance is required for the residual colorectum.

For patients with LS and rectal cancer, either a proctectomy and coloanal anastomosis or a total proctocolectomy and IPAA can be performed. A restorative proctocolectomy and IPAA will reduce the risk of metachronous cancer however is associated with more functional problems.[3][8] Ongoing surveillance of the pouch-anal anastomosis is required.

In order to plan best surgical management it is important to perform IHC on pre-operative biopsy specimens from patients likely to have LS. [3]

Back to top

9.4.3.4 Chemoprevention

Systematic review evidence on the effectiveness of aspirin in the prevention of colorectal cancer in people with LS is summarised in Primary prevention (Part 2): Chemopreventive candidate agents.

The considerations in making the LS recommendation, and health system implications, are described in Primary prevention (Part 2): Chemopreventive candidate agents.

Regular colonoscopy must continue for patients taking aspirin.

Back to top

9.4.4 References

1. ↑ 1.0 1.1 1.2 1.3 1.4 1.5 1.6 1.7 Cancer Institute NSW. *eviQ Cancer Genetics Referral Guidelines for Colorectal Cancer or Polyposis Risk Assessment and Consideration of Genetic Testing.* [homepage on the internet] Sydney; 2016 [cited 2016 Sep 6]. Available from: https://www.eviq.org.au/Category/tabid/65/categoryid/6/Default.aspx.
2. ↑ 2.0 2.1 2.2 2.3 2.4 2.5 2.6 Ladabaum U, Ford JM, Martel M, Barkun AN. *American Gastroenterological Association Technical Review on the Diagnosis and Management of Lynch Syndrome.* Gastroenterology 2015 Sep;149(3):783-813.e20 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26226576.
3. ↑ 3.00 3.01 3.02 3.03 3.04 3.05 3.06 3.07 3.08 3.09 3.10 3.11 3.12 3.13 Giardiello FM, Allen JI, Axilbund JE, Boland CR, Burke CA, Burt RW, et al. *Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-Society Task Force on Colorectal Cancer.* Dis Colon Rectum 2014 Aug;57(8):1025-48 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25003300.
4. ↑ 4.0 4.1 Jenkins MA, Dowty JG, Ait Ouakrim D, Mathews JD, Hopper JL, Drouet Y et al. *Short-term risk of colorectal cancer in individuals with lynch syndrome: a meta-analysis.* Journal of Clinical Oncology 2015;; 33: 326-31. Available from: http://jco.ascopubs.org/content/early/2014/12/22/JCO.2014.55.8536.short.
5. ↑ Hampel H, Frankel WL, Martin E, Arnold M, Khanduja K, Kuebler P, et al. *Feasibility of screening for Lynch syndrome among patients with colorectal cancer.* J Clin Oncol 2008 Dec 10;26(35):5783-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18809606.
6. ↑ 6.0 6.1 6.2 6.3 6.4 6.5 Rubenstein JH, Enns R, Heidelbaugh J, Barkun A, Clinical Guidelines Committee. *American Gastroenterological Association Institute Guideline on the Diagnosis and Management of Lynch Syndrome.* Gastroenterology 2015 Sep;149(3):777-82; quiz e16-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26226577.
7. ↑ 7.0 7.1 7.2 7.3 Robays J, Poppe B. *Oncogenetic testing for Lynch syndrome and familial adenomatous polyposis.* Brussels: Belgian Health Care Knowledge Centre (KCE); 2014.
8. ↑ 8.0 8.1 8.2 8.3 8.4 Rodriguez-Bigas MA, Möeslein G. *Surgical treatment of hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome).* Fam Cancer 2013 Jun;12(2):295-300 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23508345.

9. ↑ Haraldsdottir S, Hampel H, Tomsic J, Frankel WL, Pearlman R, de la Chapelle A, et al. *Colon and endometrial cancers with mismatch repair deficiency can arise from somatic, rather than germline, mutations.* Gastroenterology 2014 Dec;147(6):1308-1316.e1 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25194673.

Back to top

9.5 Peutz-Jeghers syndrome

Contents

9.5.1 Background

Peutz-Jeghers syndrome is an autosomal dominant disorder in which hamartomatous polyps can occur throughout the gastrointestinal tract. These polyps are histologically distinctive for Peutz-Jeghers syndrome and most patients also have characteristic mucocutaneous pigmentation. There is an elevated risk of many cancers including a 39% lifetime risk of colorectal cancer.[1][2] In addition, there is a risk of small bowel intussusception.

The lifetime risk of all gastrointestinal cancers is estimated to be 57% with a 39% risk of colorectal cancer included in this. The risk of breast cancer is 45% and gynaecological cancer 18% and surveillance for these cancers is recommended. There is also a 11–26% lifetime risk of pancreatic cancer. [2]

Back to top

9.5.2 Management

No systematic reviews on this topic were undertaken in the development of this section. The guidance on Peutz-Jeghers syndrome is based on recent international guidelines.[1][2] See Guidelines Development for more information.

Back to top

9.5.2.1 Screening

Video capsule endoscopy or magnetic resonance enterography should be used to screen for small intestinal polyps from age 8–10 years or earlier if there are symptoms.[1][2] It should be repeated at least 3 times yearly.

Back to top

9.5.2.2 Genetic testing

Genetic testing is indicated to confirm the diagnosis and in relatives of known mutation carriers. Over 90% of patients meeting the clinical criteria for Peutz-Jeghers syndrome have an identifiable pathogenic mutation in the *STK11* gene[2] In 38–50% of cases pathogenic mutations are de novo rather than inherited.[2]. Many are deletions which are not picked up on sequencing, this requiring MLPA.

Back to top

9.5.2.3 Surveillance

Colonoscopy should be performed at age 8 years and then 3 yearly from age 18.[1]

Back to top

9.5.3 References

1. ↑ 1.0 1.1 1.2 1.3 Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW, et al. *ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes.* Am J Gastroenterol 2015 Feb;110(2):223-62; quiz 263 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25645574.
2. ↑ 2.0 2.1 2.2 2.3 2.4 2.5 Cancer Institute NSW. *eviQ Cancer Genetics Referral Guidelines for Colorectal Cancer or Polyposis Risk Assessment and Consideration of Genetic Testing.* [homepage on the internet] Sydney; 2016 [cited 2016 Sep 6]. Available from: https://www.eviq.org.au/Category/tabid/65/categoryid/6/Default.aspx.

Back to top

9.6 Juvenile polyposis syndrome

Contents

9.6.1 Background

Juvenile polyposis syndrome is an autosomal dominant disorder in which multiple hamartomatous polyps with histology characteristic of juvenile polyps occur in the gastrointestinal tract. In distinction from isolated sporadic juvenile polyps, the generally accepted clinical criteria are at least 5 juvenile polyps in the colorectum or juvenile polyps elsewhere in the gastrointestinal tract.[1] There is a 30–40% lifetime risk of colorectal cancer and an increased risk of other gastrointestinal cancers[2]. There is no excess risk of extra-gastrointestinal cancers.

Back to top

9.6.2 Management

No systematic reviews on this topic were undertaken in the development of this section. The guidance on juvenile polyposis syndrome is based on recent international guidelines.[1][2] See Guidelines Development for more information.

Back to top

9.6.2.1 Genetic testing

Genetic testing is indicated to confirm the diagnosis and in relatives of known mutation carriers. Up to 60% of individuals with clinical juvenile polyposis syndrome have identifiable pathogenic mutations in *SMAD4* or *BMPR1A*.[1] In individuals with BMPR1A mutations polyps of mixed morphology can be present in addition to juvenile polyps.

Back to top

9.6.2.2 Surveillance

Practice point

- In patients with a diagnosis of juvenile polyposis syndrome, colonoscopy should commence at age 12–15 or earlier if symptoms occur (Syngal et al., 2015; Cancer Institute NSW, 2016). It should be repeated every 1 to 3 years depending on polyp burden. Colectomy is indicated if polyps cannot be managed endoscopically (Syngal et al., 2015; Cancer Institute NSW, 2016).

Back to top

9.6.3 References

1. ↑ [1.0] [1.1] [1.2] Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW, et al. *ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes.* Am J Gastroenterol 2015 Feb;110(2):223-62; quiz 263 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25645574.
2. ↑ [2.0] [2.1] Cancer Institute NSW. *eviQ Cancer Genetics Referral Guidelines for Colorectal Cancer or Polyposis Risk Assessment and Consideration of Genetic Testing.* [homepage on the internet] Sydney; 2016 [cited 2016 Sep 6]. Available from: https://www.eviq.org.au/Category/tabid/65/categoryid/6/Default.aspx.

Back to top

9.7 Serrated polyposis syndrome

Contents

9.7.1 Background

The World Health Organization (WHO) defines serrated polyposis syndrome as the presence of any of the following:[1][2]

1. at least 5 serrated polyps proximal to the sigmoid colon, with ≥ 2 of these being > 10 mm
2. any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis syndrome
3. > 20 serrated polyps of any size, but distributed throughout the colon.

The polyp count is usually interpreted as being cumulative. This definition is based on expert opinion and may be revised in future when the aetiology is better understood. Serrated polyposis syndrome was originally considered rare but with improved endoscopic detection of serrated polyps, it is becoming more common for an individual to meet this definition.[1] Often some conventional adenomas are also present. The prevalence of colorectal cancer at the time of diagnosis is high with estimates between 25% and 40%.[2] However, once a diagnosis is made and appropriate colonoscopic surveillance is being undertaken, the risk is lower with an estimate of 1.9% over 5 years.[3]

Back to top

9.7.2 Management

No systematic reviews on this topic were undertaken in the development of this section. The guidance on serrated polyposis syndrome is based on recent international guidelines.[1][2][4][3] See Guidelines Development for more information.

Back to top

9.7.2.1 Genetic testing

Although there is often a family history of colorectal cancer, it is uncommon for serrated polyposis syndrome to occur in more than one family member.[2] The genetic cause of serrated polyposis syndrome has not been established and genetic testing is not available.

Back to top

9.7.2.2 Surveillance and surgical management

Practice point

- Expert opinion is that colonoscopy should be performed every 1 to 3 years with the aim to remove all polyps ≥ 5mm. If the number and size of polyps make it impossible to achieve this, colectomy and ileorectal anastomosis should be considered.(Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW, et al 2015)(Cancer Institute NSW 2016)

The type of surgical procedure should be individualised according to the distribution of polyps and patient factors, but most patients will be adequately managed by either a segmental (partial) resection or extended resection (total colectomy with an ileorectal anastomosis). It is reasonable to offer colonoscopic surveillance every 5 years to first degree relatives of serrated polyposis syndrome patients, given their increased risk of colorectal cancer.[1]

Back to top

9.7.3 References

1. ↑ 1.0 1.1 1.2 1.3 Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW, et al. *ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes.* Am J Gastroenterol 2015 Feb;110(2):223-62; quiz 263 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25645574.
2. ↑ 2.0 2.1 2.2 2.3 Cancer Institute NSW. *eviQ Cancer Genetics Referral Guidelines for Colorectal Cancer or Polyposis Risk Assessment and Consideration of Genetic Testing.* [homepage on the internet] Sydney; 2016 [cited 2016 Sep 6]. Available from: https://www.eviq.org.au/Category/tabid/65/categoryid/6/Default.aspx.
3. ↑ 3.0 3.1 Carballal S, Rodríguez-Alcalde D, Moreira L, Hernández L, Rodríguez L, Rodríguez-Moranta F, et al. *Colorectal cancer risk factors in patients with serrated polyposis syndrome: a large multicentre study.* Gut 2015 Aug 11 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26264224.
4. ↑ Robays J, Poppe B. *Oncogenetic testing for Lynch syndrome and familial adenomatous polyposis.* Brussels: Belgian Health Care Knowledge Centre (KCE); 2014.

Back to top

9.8 Supplement. State- and territory-based familial cancer registries

Supplement\. state\- and territory\-based familial cancer registers

State/Territory	Registry details
Australian Capital Territory and New South Wales	NSW & ACT Hereditary Cancer Registry (Cancer Institute NSW) Website: https://www.cancerinstitute.org.au/data-research/data-held-by-cinsw/nsw-and-act-hereditary-cancer-registry Email: HCR@cancerinstitute.org.au Phone: 02 8374 3698 or 1800 505 644 Fax: 02 8374 3644
Northern Territory	Unknown
	Queensland Familial Cancer Registry (QFCR) Website: https://www.health.qld.gov.au/ghq/qfbcr/default.asp

State/Territory	Registry details
Queensland	Phone: 07 3646 1686 Fax: 07 3646 1987
South Australia	Unknown
Tasmania	Tasmanian Cancer Registry Website: https://secure.utas.edu.au/menzies/research/research-centres/tasmanian-cancer-registry Email: TCR@menzies.utas.edu.au Telephone: +61 3 6226 7757 Fax: 03 6226 7755
Victoria	The Victorian Family Cancer Register ceased to operate after 30 June 2016. Services are now provided through family cancer centres.
Western Australia	Familial Cancer Registry (Genetic Services of Western Australia) Email: gswa@health.wa.gov.au Phone: 08 9340 1525 King Edward Memorial Hospital Level 4, Agnes Walsh House, 374 Bagot Road, Subiaco WA 6008

Back to top

10 Imaging a patient with a diagnosis of CRC

Contents

Subsections:

10.1 Colon cancer

No systematic review has been performed on this topic. The guidance below is based on current international guidelines and consensus statements considered to be relevant to Australian practice.

Contents

10.1.1 Background

Imaging is an important part of staging patients with colon cancer.

Staging investigations should preferentially be performed pre-operatively in patients diagnosed with a colon cancer at colonoscopy or computed tomography (CT) colonography. Some patients may have a colon cancer diagnosed by CT scan if they present emergently with obstruction. Others may require postoperative staging investigations after an emergency operation.

Imaging should be reported in conjunction with the patient's clinical circumstances and previous imaging, to prevent incorrect attribution of lesions as metastases. Imaging should be reviewed at the colorectal multidisciplinary team meeting.[1][2]

Back to top

10.1.2 Initial staging investigations

CT of the chest, abdomen and pelvis is the recommended imaging investigation to stage colon cancer.[1][3][4]

10.1.2.1 CT of chest, abdomen and pelvis

10.1.2.1.1 Protocol

The protocol should involve a post-intravenous contrast-enhanced CT of the chest, abdomen and pelvis, with oral contrast.[1][3][4]

10.1.2.1.2 Report

The report should identify and describe all of the following:

- location, size and local extent of the primary lesion
- invasion into adjacent structures which may affect surgical planning
- complications such as local perforation and bowel obstruction
- locoregional lymph nodes (pericolic and local drainage)
- metastatic lymph nodes (retroperitoneal, pelvic and inguinal)
- visceral (lung and liver) and peritoneal metastatic disease.

10.1.2.2 Alternative modalities

If a patient cannot have intravenous contrast, any of the following staging investigations may be used:

- non-contrast CT of the chest, abdomen and pelvis, plus ultrasound of the liver
- non-contrast CT chest, abdomen and pelvis, plus magnetic resonance imaging (MRI) of the liver
- MRI of the abdomen and pelvis.

Back to top

10.1.3 Further staging investigations

Practice point
CT colonoscopy should be considered for a patient with colon cancer if it has not been possible to view the entire colon by colonoscopy due to the risk of synchronous tumours. (New Zealand Guidelines Group 2011.)

MRI of the liver is not part of routine pre-operative staging of colorectal cancer and is not funded by the Medicare Benefits Scheme (MBS). If there is metastatic disease confined to the liver on CT scan, an MRI of the liver can be considered to assess suitability for surgical resection.[4] Many Australian hepatobiliary surgeons will order a post-contrast MRI of the liver, due to its proven increased sensitivity for small liver metastases, compared with CT and positron emission tomography-CT (PET-CT).[5][6] This is particularly important in cases where the background liver parenchyma is abnormal, the patient has recently received chemotherapy, or when a patient cannot have iodinated contrast.

PET-CT imaging is not routinely indicated, nor MBS funded, for pre-operative staging of colorectal cancer. It is recommended to detect additional metastases in patients with colorectal cancer who have potentially resectable lung and liver metastases[3] and is MBS funded for suspected residual, metastatic or recurrent colorectal cancer in a patient for whom active therapy is being considered.

Practice point

If CT shows metastatic disease confined to the liver, MRI of the liver can be considered to assess for resectability, particularly if the background liver parenchyma is abnormal, the patient has recently received chemotherapy, or when a patient cannot have iodinated contrast.

Practice point

For patients with colorectal cancer who have potentially resectable metastatic disease, PET-CT is recommended to detect additional metastases.

Back to top

10.1.4 Surveillance imaging

There is no standardised protocol in Australia for surveillance imaging. There is significant evidence from clinical trials to support integration of imaging into routine follow-up, in addition to clinical follow-up including liver function tests and carcinoembryonic antigen (CEA) measurement. Any follow up imaging should be compared with previous imaging.

International recommendations for surveillance protocols vary. The most frequently followed guidelines in Australia are the American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO) guidelines.[7][8]

ASCO guidelines recommend that, for those colon and rectal cancer patients at higher risk of recurrence and where curative intent was an option, CT imaging of the chest and abdomen should be undertaken annually for 3 years. A pelvic CT should be considered for rectal cancer surveillance, especially for those who had not received radiotherapy.[7]

ESMO guidelines recommend that a CT scan of chest and abdomen every 6–12 months for the first 3 years be considered in patients who are at higher risk of recurrence. Contrast-enhanced ultrasound (CEUS) could substitute for abdominal CT scan. Other radiological examinations are of unproven benefit and must be restricted to patients with suspicious symptoms.[8]

Table 7.1 shows the surveillance schedule proposed by an ESMO consensus conference,[9] based on ASCO and European guidelines. Twelve-monthly scanning would be more typical in stage II and III surveillance, and 6-monthly scanning for resected stage IV disease based on higher risk of recurrence.

10.1.4.1 Table 7.1 CAP surveillance schedule for high-risk colorectal cancer proposed by ESMO

Stage	Time after surgery or adjuvant treatment (months)					
	6	12	18	24	30	36
Stage II–III		x		x		x
Stage IV	x	x	x	x	x	x

Adapted from Schmoll et al 2012[9]

CAP: CT of chest, abdomen and pelvis

Practice point

For patients with stage II and III disease who have undergone initial surgery or adjuvant treatment, a suitable approach to imaging surveillance might involve 12-monthly CT of chest, abdomen and pelvis.

Practice point

For patients with stage IV disease who have undergone a resection procedure with curative intent, a suitable approach to imaging surveillance might involve CT of chest, abdomen and pelvis every 6 months.

Back to top

10.1.5 References

1. ↑ [1.0] [1.1] [1.2] National Institute for Health and Care Excellence. *Colorectal cancer: The Diagnosis and Management of colorectal cancer.* United Kingdom: National Institute for Health and Care Excellence; 2014.

2. ↑ New Zealand Guidelines Group. *Colorectal cancer: Management of Early Colorectal Cancer.* Wellington: Ministry of Health; 2011.
3. ↑ [3.0] [3.1] [3.2] National Comprehensive Cancer Network. *NCCN Guidelines: Colon Cancer.* National Comprehensive Cancer Network; 2016.
4. ↑ [4.0] [4.1] [4.2] Radiologists TRCo. *Recommendations for cross-sectional imaging in cancer management - colon, rectum and anal cancer.* Radiologists TRCo; 2014.
5. ↑ Vreugdenburg TD, Ma N, Duncan JK, Riitano D, Cameron AL, Maddern GJ. *Comparative diagnostic accuracy of hepatocyte-specific gadoxetic acid (Gd-EOB-DTPA) enhanced MR imaging and contrast enhanced CT for the detection of liver metastases: a systematic review and meta-analysis.* Int J Colorectal Dis 2016 Nov;31(11):1739-1749 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27682648.
6. ↑ National Collaborating Centre for Cancer. *The Diagnosis and Management of Colorectal Cancer - Evidence review United Kingdom: National Institute for Health and Care Excellence; 2011.*;.
7. ↑ [7.0] [7.1] Meyerhardt JA, Mangu PB, Flynn PJ, Korde L, Loprinzi CL, Minsky BD, et al. *Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: American Society of Clinical Oncology clinical practice guideline endorsement.* J Clin Oncol 2013 Dec 10;31(35): 4465-70 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24220554.
8. ↑ [8.0] [8.1] Labianca R, Nordlinger B, Beretta GD, Mosconi S, Mandalà M, Cervantes A, et al. *Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.* Ann Oncol 2013 Oct;24 Suppl 6:vi64-72 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24078664.
9. ↑ [9.0] [9.1] Schmoll HJ, Van Cutsem E, Stein A, Valentini V, Glimelius B, Haustermans K, et al. *ESMO Consensus Guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making.* Ann Oncol 2012 Oct;23(10):2479-516 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23012255.

Back to top

10.2 Rectal cancer

No systematic review has been performed for this section. The guidance below is based on current international guidelines and consensus statements considered to be relevant to Australian practice.

Contents

10.2.1 Background

Patients with a new diagnosis of rectal cancer are stratified into different treatment pathways, based upon patient factors and imaging findings after each case is discussed at a multidisciplinary team meeting. Adequate local staging with high-resolution magnetic resonance imaging (MRI) requires the scan to meet internationally recognised minimum standards for spatial resolution and scan technique.[1] A suboptimal MRI scan may compromise reporting accuracy and appropriate patient management.[2]

Back to top

10.2.2 Initial staging investigations

10.2.2.1 High-resolution MRI

High-resolution MRI of the rectum is the recommended primary staging imaging investigation.[3][4][5][6][1][7]

10.2.2.1.1 Protocol

Coverage: L5/S1 to anal verge

The tumour and all mesorectal lymph nodes at and above the level of the tumour should be covered by high-resolution (HR) sequences.

Low tumours within 5 cm of the anal verge need imaging angled to the anal canal to assess the relationship of tumour to the levator ani muscles and anal sphincter complex.

The protocol is set out in Table 7.2.

Notes:

- Anterior saturation bands should be used. Phase L-R can be useful in the axial images to reduce breathing artefact.
- An antiperistaltic agent (e.g hyoscine butylbromide) can be given to reduce artefact from adjacent bowel motion.
- Patients may fast, but there is no other bowel preparation required. The use of per-rectal fluid or gel is not recommended, as it can distort the rectal wall.[1]

10.2.2.1.1.1 Table 7.2. Rectal cancer MRI protocol

	Sequence	Notes
All tumours	Axial large FOV	To cover whole pelvis
	Sagittal T2	Preferably a HR sequence (as defined in the row below)
	Axial oblique T2 HR	Angled to the centre of the tumour Acquired voxel < 1.3 mm [5] 16–18 cm FOV, 3 mm slice thickness 0.6 mm x 0.6 mm in plane resolution^
	Coronal oblique T2 HR†	
	Optional HR T2 oblique	Parallel to sacrum to cover mesorectum up to 5 cm above upper border of tumour if needed
Low tumours‡	Coronal oblique T2 HR	Angled to the anal canal HR parameters as above
	Axial oblique T2 HR†	

FOV: field of view; HR: high resolution

† optional but recommended

‡ within 5cm of anal verge

^ calculated using acquired matrix measurements. Interpolated or zipped measurements do not give the required spatial resolution.

Back to top

10.2.2.1.2 Report

Radiologists are expected to provide a quality report that includes all of:

- distance from anal verge (and distance from puborectalis sling for low tumours within 5 cm of anal verge)
- relationship to the peritoneal reflection

- T stage of the tumour, including the distance of spread in millimetres in the axial plane if it has spread beyond the muscularis propria
- any involvement of the peritoneal reflection or adjacent organs
- N stage of the tumour, using morphological criteria (irregularity of border and/or internal signal heterogeneity)
- presence or absence of extramural venous invasion (EMVI) and whether it is contiguous or non-contiguous
- tumour involving the potential circumferential resection margin (CRM), defined as tumour within 1 mm of the mesorectal fascia or inferior total mesorectal excision (TME) plane
- presence of involved pelvic sidewall lymph nodes outside the mesorectum.

A structured report template is preferred (see Appendix 1 for a recommended pro forma).[8] If free text is used, it should include all of the above information.

Back to top

Practice point

MRI of the rectum is the recommended staging investigation for rectal cancer.

Practice point

High-resolution sequences must be performed and must meet accepted criteria.

Practice point

Additional sequences coronal to the anal canal are required for low tumours (Table 12.2).

Practice point

Template reports are recommended, which include all of:

- Distance from anal verge (and puborectalis sling for low tumours)

Practice point
Relationship to the peritoneal reflection T stage including spread in mm beyond muscularis N stage and pelvic lymph nodes using morphological criteria EMVI status CRM status using 1mm as a cut-off distance.

Back to top

10.2.2.2 CT of chest, abdomen and pelvis

CT of the chest, abdomen and pelvis should be performed as part of pre-operative staging, to assess for more distant nodal and metastatic disease. This should not replace the MRI scan of the pelvis for local staging, unless MRI is contraindicated.[3]

10.2.2.2.1 Protocol

Post intravenous contrast enhanced CT chest abdomen and pelvis with oral contrast.[3][6][7]

10.2.2.2.2 Report

The staging report should identify and describe:

- the primary tumour (within limits of CT)
- metastatic lymph nodes
- visceral (lung, liver) and peritoneal metastatic disease.

10.2.2.2.3 Alternative modalities

If a patient cannot have CT intravenous contrast, staging may be completed by either of the following:

- non-contrast CT of the chest and ultrasound of liver
- non-contrast CT of the chest and MRI of the liver.

Back to top

10.2.2.2.4 Endorectal ultrasound

Endorectal ultrasound (ERUS) may be used to assess T1 and early T2 tumours in patients who may be appropriate for local resection techniques. However, it is not as accurate as MRI in detection of potential CRM involvement and should be performed in addition to a staging rectal MRI scan.[3][4][6]

10.2.2.3 Further staging investigations

As per colon cancer.

10.2.2.4 Restaging MRI following neoadjuvant therapy

The use of MRI scans following neoadjuvant treatment is limited in Australia, and is not funded by the Medicare Benefits Scheme (MBS). There is only minimal evidence that MRI scanning influences pre-treatment management plans, and it is more frequently used for assessing treatment response.[9]

10.2.2.4.1 Protocol

Protocol parameters for MRI of the pelvis undertaken for the purpose of restaging are the same as for primary staging. Some groups recommend the addition of diffusion imaging,[1] and some also use post contrast sequences.

10.2.2.4.2 Report

Reports should include all the same details as the staging report to give MRI (mr) findings post-neoadjuvant treatment (y) for T stage (ymrT), N stage (ymrN), EMVI status (ymrEMVI) and CRM status (ymrCRM). An additional MRI tumour regression grading system (mrTRG) score, obtained from the high-resolution T2 sequences, can be given to define the amount of residual tumour compared to fibrosis to stratify patient response (Table 7.3).[10]

10.2.2.4.2.1 Table 7.3. Definition of MRI tumour regression grading system scores

Score	Definition
mrTRG1	No/minimal fibrosis visible (tiny linear scar) and no tumour signal
mrTRG2	Dense fibrotic scar (low signal) but no tumour signal
mrTRG3	Fibrosis predominates but obvious measureable areas of tumour signal visible
mrTRG4	Tumour signal predominates with little / minimal fibrosis
mrTRG5	Tumour signal only – no fibrosis. Includes tumour progression

Source: Patel et al 2012[10]

Back to top

10.2.2.5 Surveillance imaging

As per colon cancer.

10.2.2.6 Staging of recurrence

Detection or suspicion of recurrence on clinical follow up, colonoscopy or CT may be further evaluated with PET-CT to assess local and systemic spread. If distant disease is absent or resectable and pelvic exenteration is planned for local recurrence, a pelvic MRI should be performed to define the extent of local disease.

10.2.3 References

1. ↑ [1.0] [1.1] [1.2] [1.3] Spada C, Stoker J, Alarcon O, Barbaro F, Bellini D, Bretthauer M, et al. *Clinical indications for computed tomographic colonography: European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastrointestinal and Abdominal Radiology (ESGAR) Guideline.* Eur Radiol 2015 Feb;25 (2):331-45 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25278245.
2. ↑ Suzuki C, Torkzad MR, Tanaka S, Palmer G, Lindholm J, Holm T, et al. *The importance of rectal cancer MRI protocols on interpretation accuracy.* World J Surg Oncol 2008 Aug 20;6:89 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18715510.
3. ↑ [3.0] [3.1] [3.2] [3.3] National Institute for Health and Care Excellence. *Colorectal cancer: The Diagnosis and Management of colorectal cancer.* United Kingdom: National Institute for Health and Care Excellence; 2014.
4. ↑ [4.0] [4.1] New Zealand Guidelines Group. *Colorectal cancer: Management of Early Colorectal Cancer.* Wellington: Ministry of Health; 2011.
5. ↑ [5.0] [5.1] National Comprehensive Cancer Network. *NCCN Guidelines: Colon Cancer.* National Comprehensive Cancer Network; 2016.
6. ↑ [6.0] [6.1] [6.2] Radiologists TRCo. *Recommendations for cross-sectional imaging in cancer management - colon, rectum and anal cancer.* Radiologists TRCo; 2014.
7. ↑ [7.0] [7.1] National Comprehensive Cancer Network. *NCCN Guidelines for Rectal Cancer Version 2.*; 2016 Available from: https://www.tri-kobe.org/nccn/guideline/colorectal/english/rectal.pdf.
8. ↑ Goergen, S. *Radiology Written Report Guideline.* Sydney: The Royal Australian and New Zealand College of Radiologists; 2011 [cited 2016 Dec 24] Available from: http://www.ranzcr.edu.au/component/docman/?task=doc_download&gid=355.
9. ↑ McBrearty A, McCallion K, Moorehead RJ, McAllister I, Mulholland K, Gilliland R, et al. *Re-Staging Following Long-Course Chemoradiotherapy For Rectal Cancer: Does It Influence Management?* Ulster Med J 2016 Sep;85(3):178-181 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27698520.
10. ↑ [10.0] [10.1] Patel UB, Brown G, Rutten H, West N, Sebag-Montefiore D, Glynne-Jones R, et al. *Comparison of magnetic resonance imaging and histopathological response to chemoradiotherapy in locally advanced rectal cancer.* Ann Surg Oncol 2012 Sep;19(9):2842-52 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22526897.

Back to top

10.3 Addenda: rectal MRI cancer report

Rectal MRI report template

MRI Rectum

Clinical details:

REPORT:

PRIMARY TUMOUR

Distance from anal verge:

Craniocaudal length:

Relationship to peritoneal reflection:

Morphology:

Site of invasive edge:

Muscularis propria invasion^:

Extramural venous invasion^^:

Low tumours

- Distance from puborectalis sling:
- Anal sphincter complex invasion: (intersphincteric plane / external sphincter)

LYMPH NODES

Mesorectal: *(N1 / N2 / N1C)*

Pelvic sidewall:

MESORECTAL FASCIA/TME plane: (clear / involved)

OTHER:

CONCLUSION:
(T stage, EMVI status, N stage and CRM status)

^ include maximum distance of T3 extension in millimetres, adjacent organ or peritoneal reflection involvement
^^noting continuous and discontinuous EMVI

Back to top

11 Pathology and staging

No systematic review has been performed for this section. The guidance below is based on current international guidelines and consensus statements considered to be relevant to Australian practice.

Contents

11.1 Background

Patients with a new diagnosis of rectal cancer are stratified into different treatment pathways, based upon patient factors and imaging findings after each case is discussed at a multidisciplinary team meeting. Adequate local staging with high-resolution magnetic resonance imaging (MRI) requires the scan to meet internationally recognised minimum standards for spatial resolution and scan technique.[1] A suboptimal MRI scan may compromise reporting accuracy and appropriate patient management.[2]

Back to top

11.2 Initial staging investigations

11.2.1 High-resolution MRI

High-resolution MRI of the rectum is the recommended primary staging imaging investigation[3][4][5][6][1][5].

11.2.1.1 Protocol

Coverage: L5/S1 to anal verge All mesorectal lymph nodes should be covered by high-resolution (HR) sequences.

Low tumours within 5 cm of the anal verge need imaging angled to the anal canal to assess the relationship of tumour to the levator ani muscles and anal sphincter complex.

The protocol is set out in Table 12.2.

Notes:

- Anterior saturation bands should be used. Phase L-R can be useful in the axial images to reduce breathing artefact.
- An antiperistaltic agent (e.g hyoscine butylbromide) can be given to reduce artefact from adjacent bowel motion.
- Patients may fast, but there is no other bowel preparation required. The use of per-rectal fluid or gel is not recommended, as it can distort the rectal wall [1].

11.2.1.1.1 Table 12.2. Rectal cancer MRI protocol

	Sequence	Notes
All tumours	Axial large FOV	To cover whole pelvis
	Sagittal T2	Preferably a HR sequence (as shown in the row below)
	Axial oblique T2 HR	Angled to the centre of the tumour Acquired voxel < 1.3 mm^3
	Coronal oblique T2 HR†	16–18 cm FOV, 3 mm slice thickness 0.6 mm x 0.6 mm in plane resolution^
	Optional HR T2 oblique	Parallel to sacrum to cover mesorectum up to 5 cm above upper border of tumour if needed
Low tumours‡	Coronal oblique T2 HR	Angled to the anal canal
	Axial oblique T2 HR†	HR parameters as above

FOV: field of view; HR: high resolution

† optional but recommended

‡ within 5cm of anal verge

^ calculated using acquired matrix measurements. Interpolated or zipped measurements do not give the required spatial resolution.

Back to top

11.2.1.2 Report

The staging report should include:

- distance from anal verge (distance from puborectalis sling for low tumours within 5 cm of anal verge)
- T stage of the tumour, including the distance of spread in millimetres in the axial plane if it has spread beyond the muscularis propria
- any involvement of the peritoneal reflection or adjacent organs
- N stage of the tumour, using morphological criteria (irregularity of border and/or internal signal heterogeneity)
- presence or absence of extramural venous invasion (EMVI) and whether it is contiguous or non-contiguous
- tumour involving the potential circumferential resection margin (CRM), defined as tumour within 1 mm of the mesorectal fascia or inferior total mesorectal excision (TME) plane

- presence of involved pelvic sidewall lymph nodes outside the mesorectum.

A structured report template is preferred (see Appendix 1 for a recommended pro forma).13 If free text is used, it should include all of the above information.

Radiologists who do not feel competent in reporting all the above criteria should seek further training or mentorship.

Back to top

Practice point

MRI of the rectum is the recommended staging investigation for rectal cancer.

Practice point

High-resolution sequences must be performed and must meet accepted criteria.

Practice point

Additional sequences coronal to the anal canal are required for low tumours (Table12.2).

Practice point

Reports must include all of:

- T stage including spread in mm from muscularis
- N stage using morphological criteria and pelvic lymph nodes
- EMVI status
- CRM status using 1mm as a cut-off distance
- distance from the puborectalis sling for low tumours.

Back to top

11.2.2 CT of chest, abdomen and pelvis

CT of the chest, abdomen and pelvis should be performed as part of pre-operative staging, to assess for more distant nodal and metastatic disease. This should not replace the MRI scan of the pelvis for local staging, unless MRI is contraindicated.[3]

11.2.2.1 Protocol

Post intravenous contrast enhanced CT chest abdomen and pelvis with oral contrast.[3][6][5]

11.2.2.2 Report

The staging report should identify and describe:

- the primary tumour (within limits of CT)
- metastatic lymph nodes
- visceral (lung, liver) and peritoneal metastatic disease.

11.2.2.3 Alternative modalities

If a patient cannot have intravenous contrast, staging may be completed by either of the following:

- non-contrast CT of the chest and ultrasound of liver
- non-contrast CT of the chest and MRI of the liver.

Back to top

11.2.2.4 Endoscopic ultrasound

Endoscopic ultrasound (EUS) may be used to assess T1 and early T2 tumours. It is able to differentiate SM1, SM2 and SM3 T1 tumours in patients who may be appropriate for local resection techniques. However, it is not as accurate as MRI in detection of mesorectal/pelvic lymph nodes and potential CRM involvement.[3][4][5]

EUS should only be performed by an operator who is appropriately trained.

11.2.3 Further staging investigations

As per colon cancer.

11.2.4 Restaging MRI following neoadjuvant therapy

The use of MRI scans following neoadjuvant treatment is limited in Australia, and is not funded by the Medicare Benefits Scheme (MBS). There is only minimal evidence that MRI scanning influences pre-treatment management plans, and it is more frequently used for confirming treatment response.[7] This may lead to a 'watch and wait' approach, where patients with a clinical complete response may choose not to proceed to surgery. The appropriate timing of MRI scans for post-treatment imaging and surveillance is yet to be established.

11.2.4.1 Protocol

Protocol parameters for MRI of the pelvis undertaken for the purpose of restaging are the same as for primary staging. Some groups recommend the addition of diffusion imaging,[1] and some also use post contrast imaging for post treatment imaging.

11.2.4.2 Report

Reports should include all the same details as the staging report to give MRI (mr) findings post-neoadjuvant treatment (y) for T stage (ymrT), N stage (ymrN), EMVI status (ymrEMVI) and CRM status (ymrCRM). An additional MRI tumour regression grading system (mrTRG) score, obtained from the high-resolution T2 sequences, can be given to define the amount of residual tumour compared to fibrosis to stratify patient response (Table 12.3).[8]

11.2.4.2.1 Table 12.3. Definition of MRI tumour regression grading system scores

Score	Definition
mrTRG1	No/minimal fibrosis visible (tiny linear scar) and no tumour signal
mrTRG2	Dense fibrotic scar (low signal) but no tumour signal
mrTRG3	Fibrosis predominates but obvious measureable areas of tumour signal visible
mrTRG4	Tumour signal predominates with little / minimal fibrosis
mrTRG5	Tumour signal only – no fibrosis. Includes tumour progression

Source: Patel et al 2012[8]

Back to top

11.2.5 Surveillance imaging

As per colon cancer.

11.2.6 Staging of recurrence

Detection or suspicion of recurrence on clinical follow up, colonoscopy or CT may be further evaluated with PET-CT to assess local and systemic spread. If distant disease is absent or resectable and pelvic exenteration is planned for local recurrence, a pelvic MRI should be performed to define the extent of local disease.

11.2.7 Subsections:

- Development of post-surgical staging
- Post-surgical staging following neoadjuvant therapy
- Notable differences between available clinicopathological staging systems
- Selection of a clinicopathological staging system
- Clinical input
- Additional information on pathology reporting
- What is the optimal molecular profiling of colorectal cancer? PTH1

11.3 References

1. ↑ 1.0 1.1 1.2 1.3 Spada C, Stoker J, Alarcon O, Barbaro F, Bellini D, Bretthauer M, et al. *Clinical indications for computed tomographic colonography: European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastrointestinal and Abdominal Radiology (ESGAR) Guideline.* Eur Radiol 2015 Feb;25 (2):331-45 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25278245.
2. ↑ Suzuki C, Torkzad MR, Tanaka S, Palmer G, Lindholm J, Holm T, et al. *The importance of rectal cancer MRI protocols on interpretation accuracy.* World J Surg Oncol 2008 Aug 20;6:89 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18715510.
3. ↑ 3.0 3.1 3.2 3.3 National Institute for Health and Care Excellence. *Colorectal cancer: The Diagnosis and Management of colorectal cancer.* United Kingdom: National Institute for Health and Care Excellence; 2014.
4. ↑ 4.0 4.1 New Zealand Guidelines Group. *Colorectal cancer: Management of Early Colorectal Cancer.* Wellington: Ministry of Health; 2011.
5. ↑ 5.0 5.1 5.2 5.3 National Comprehensive Cancer Network. *NCCN Guidelines: Colon Cancer.* National Comprehensive Cancer Network; 2016.
6. ↑ 6.0 6.1 Radiologists TRCo. *Recommendations for cross-sectional imaging in cancer management - colon, rectum and anal cancer.* Radiologists TRCo; 2014.

7. ↑ McBrearty A, McCallion K, Moorehead RJ, McAllister I, Mulholland K, Gilliland R, et al. *Re-Staging Following Long-Course Chemoradiotherapy For Rectal Cancer: Does It Influence Management?* Ulster Med J 2016 Sep;85(3):178-181 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27698520.
8. ↑ [8.0] [8.1] Patel UB, Brown G, Rutten H, West N, Sebag-Montefiore D, Glynne-Jones R, et al. *Comparison of magnetic resonance imaging and histopathological response to chemoradiotherapy in locally advanced rectal cancer.* Ann Surg Oncol 2012 Sep;19(9):2842-52 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22526897.

Back to top

11.1 Introduction: pathology and staging

No systematic review has been performed for this section. The guidance below is based on current international guidelines and consensus statements considered to be relevant to Australian practice.

Contents

11.1.1 Background

Patients with a new diagnosis of rectal cancer are stratified into different treatment pathways, based upon patient factors and imaging findings after each case is discussed at a multidisciplinary team meeting. Adequate local staging with high-resolution magnetic resonance imaging (MRI) requires the scan to meet internationally recognised minimum standards for spatial resolution and scan technique.[1] A suboptimal MRI scan may compromise reporting accuracy and appropriate patient management.[2]

Back to top

11.1.2 Initial staging investigations

11.1.2.1 High-resolution MRI

High-resolution MRI of the rectum is the recommended primary staging imaging investigation[3][4][5][6][1][5].

11.1.2.1.1 Protocol

Coverage: L5/S1 to anal verge All mesorectal lymph nodes should be covered by high-resolution (HR) sequences.

Low tumours within 5 cm of the anal verge need imaging angled to the anal canal to assess the relationship of tumour to the levator ani muscles and anal sphincter complex.

The protocol is set out in Table 12.2.

Notes:

- Anterior saturation bands should be used. Phase L-R can be useful in the axial images to reduce breathing artefact.
- An antiperistaltic agent (e.g hyoscine butylbromide) can be given to reduce artefact from adjacent bowel motion.
- Patients may fast, but there is no other bowel preparation required. The use of per-rectal fluid or gel is not recommended, as it can distort the rectal wall [1].

11.1.2.1.1.1 Table 12.2. Rectal cancer MRI protocol

	Sequence	Notes
All tumours	Axial large FOV	To cover whole pelvis
	Sagittal T2	Preferably a HR sequence (as shown in the row below)
	Axial oblique T2 HR	Angled to the centre of the tumour Acquired voxel < 1.3 mm^3
	Coronal oblique T2 HR†	16–18 cm FOV, 3 mm slice thickness 0.6 mm x 0.6 mm in plane resolution^
	Optional HR T2 oblique	Parallel to sacrum to cover mesorectum up to 5 cm above upper border of tumour if needed
Low tumours‡	Coronal oblique T2 HR	Angled to the anal canal
	Axial oblique T2 HR†	HR parameters as above

FOV: field of view; HR: high resolution

† optional but recommended

‡ within 5cm of anal verge

^ calculated using acquired matrix measurements. Interpolated or zipped measurements do not give the required spatial resolution.

Back to top

11.1.2.1.2 Report

The staging report should include:

- distance from anal verge (distance from puborectalis sling for low tumours within 5 cm of anal verge)
- T stage of the tumour, including the distance of spread in millimetres in the axial plane if it has spread beyond the muscularis propria
- any involvement of the peritoneal reflection or adjacent organs
- N stage of the tumour, using morphological criteria (irregularity of border and/or internal signal heterogeneity)
- presence or absence of extramural venous invasion (EMVI) and whether it is contiguous or non-contiguous
- tumour involving the potential circumferential resection margin (CRM), defined as tumour within 1 mm of the mesorectal fascia or inferior total mesorectal excision (TME) plane

- presence of involved pelvic sidewall lymph nodes outside the mesorectum.

A structured report template is preferred (see Appendix 1 for a recommended pro forma).13 If free text is used, it should include all of the above information.

Radiologists who do not feel competent in reporting all the above criteria should seek further training or mentorship.

Back to top

Practice point

MRI of the rectum is the recommended staging investigation for rectal cancer.

Practice point

High-resolution sequences must be performed and must meet accepted criteria.

Practice point

Additional sequences coronal to the anal canal are required for low tumours (Table12.2).

Practice point

Reports must include all of:

- T stage including spread in mm from muscularis
- N stage using morphological criteria and pelvic lymph nodes
- EMVI status
- CRM status using 1mm as a cut-off distance
- distance from the puborectalis sling for low tumours.

Back to top

11.1.2.2 CT of chest, abdomen and pelvis

CT of the chest, abdomen and pelvis should be performed as part of pre-operative staging, to assess for more distant nodal and metastatic disease. This should not replace the MRI scan of the pelvis for local staging, unless MRI is contraindicated.[3]

11.1.2.2.1 Protocol

Post intravenous contrast enhanced CT chest abdomen and pelvis with oral contrast.[3][6][5]

11.1.2.2.2 Report

The staging report should identify and describe:

- the primary tumour (within limits of CT)
- metastatic lymph nodes
- visceral (lung, liver) and peritoneal metastatic disease.

11.1.2.2.3 Alternative modalities

If a patient cannot have intravenous contrast, staging may be completed by either of the following:

- non-contrast CT of the chest and ultrasound of liver
- non-contrast CT of the chest and MRI of the liver.

Back to top

11.1.2.2.4 Endoscopic ultrasound

Endoscopic ultrasound (EUS) may be used to assess T1 and early T2 tumours. It is able to differentiate SM1, SM2 and SM3 T1 tumours in patients who may be appropriate for local resection techniques. However, it is not as accurate as MRI in detection of mesorectal/pelvic lymph nodes and potential CRM involvement.[3][4][5]

EUS should only be performed by an operator who is appropriately trained.

11.1.2.3 Further staging investigations

As per colon cancer.

11.1.2.4 Restaging MRI following neoadjuvant therapy

The use of MRI scans following neoadjuvant treatment is limited in Australia, and is not funded by the Medicare Benefits Scheme (MBS). There is only minimal evidence that MRI scanning influences pre-treatment management plans, and it is more frequently used for confirming treatment response.[7] This may lead to a 'watch and wait' approach, where patients with a clinical complete response may choose not to proceed to surgery. The appropriate timing of MRI scans for post-treatment imaging and surveillance is yet to be established.

11.1.2.4.1 Protocol

Protocol parameters for MRI of the pelvis undertaken for the purpose of restaging are the same as for primary staging. Some groups recommend the addition of diffusion imaging,[1] and some also use post contrast imaging for post treatment imaging.

11.1.2.4.2 Report

Reports should include all the same details as the staging report to give MRI (mr) findings post-neoadjuvant treatment (y) for T stage (ymrT), N stage (ymrN), EMVI status (ymrEMVI) and CRM status (ymrCRM). An additional MRI tumour regression grading system (mrTRG) score, obtained from the high-resolution T2 sequences, can be given to define the amount of residual tumour compared to fibrosis to stratify patient response (Table 12.3).[8]

11.1.2.4.2.1 Table 12.3. Definition of MRI tumour regression grading system scores

Score	Definition
mrTRG1	No/minimal fibrosis visible (tiny linear scar) and no tumour signal
mrTRG2	Dense fibrotic scar (low signal) but no tumour signal
mrTRG3	Fibrosis predominates but obvious measureable areas of tumour signal visible
mrTRG4	Tumour signal predominates with little / minimal fibrosis
mrTRG5	Tumour signal only – no fibrosis. Includes tumour progression

Source: Patel et al 2012[8]

Back to top

11.1.2.5 Surveillance imaging

As per colon cancer.

11.1.2.6 Staging of recurrence

Detection or suspicion of recurrence on clinical follow up, colonoscopy or CT may be further evaluated with PET-CT to assess local and systemic spread. If distant disease is absent or resectable and pelvic exenteration is planned for local recurrence, a pelvic MRI should be performed to define the extent of local disease.

11.1.2.7 Subsections:

- Development of post-surgical staging
- Post-surgical staging following neoadjuvant therapy
- Notable differences between available clinicopathological staging systems
- Selection of a clinicopathological staging system
- Clinical input
- Additional information on pathology reporting
- What is the optimal molecular profiling of colorectal cancer? PTH1

11.1.3 References

1. ↑ [1.0] [1.1] [1.2] [1.3] Spada C, Stoker J, Alarcon O, Barbaro F, Bellini D, Bretthauer M, et al. *Clinical indications for computed tomographic colonography: European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastrointestinal and Abdominal Radiology (ESGAR) Guideline.* Eur Radiol 2015 Feb;25 (2):331-45 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25278245.
2. ↑ Suzuki C, Torkzad MR, Tanaka S, Palmer G, Lindholm J, Holm T, et al. *The importance of rectal cancer MRI protocols on interpretation accuracy.* World J Surg Oncol 2008 Aug 20;6:89 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18715510.
3. ↑ [3.0] [3.1] [3.2] [3.3] National Institute for Health and Care Excellence. *Colorectal cancer: The Diagnosis and Management of colorectal cancer.* United Kingdom: National Institute for Health and Care Excellence; 2014.
4. ↑ [4.0] [4.1] New Zealand Guidelines Group. *Colorectal cancer: Management of Early Colorectal Cancer.* Wellington: Ministry of Health; 2011.
5. ↑ [5.0] [5.1] [5.2] [5.3] National Comprehensive Cancer Network. *NCCN Guidelines: Colon Cancer.* National Comprehensive Cancer Network; 2016.
6. ↑ [6.0] [6.1] Radiologists TRCo. *Recommendations for cross-sectional imaging in cancer management - colon, rectum and anal cancer.* Radiologists TRCo; 2014.

7. ↑ McBrearty A, McCallion K, Moorehead RJ, McAllister I, Mulholland K, Gilliland R, et al. *Re-Staging Following Long-Course Chemoradiotherapy For Rectal Cancer: Does It Influence Management?* Ulster Med J 2016 Sep;85(3):178-181 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27698520.
8. ↑ [8.0] [8.1] Patel UB, Brown G, Rutten H, West N, Sebag-Montefiore D, Glynne-Jones R, et al. *Comparison of magnetic resonance imaging and histopathological response to chemoradiotherapy in locally advanced rectal cancer.* Ann Surg Oncol 2012 Sep;19(9):2842-52 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22526897.

Back to top

11.2 Development of post-surgical staging

Contents

11.2.1 Development of post-surgical staging

The first well-documented and tested staging system was that of Dukes[1]. This system was based entirely on the extent of direct tumour spread and the presence or absence of lymph node metastases in the resected specimen of bowel. Although Dukes staging was originally described for rectal cancer, it has also been applied to colonic cancer. Dukes stages A, B and C correlated well with patient survival, and they were easy to recall and apply. For these reasons the system was widely adopted. However, the Dukes system did not seek to address the issue of residual tumour, either local, due to tumour transection, or due to known distant metastases.

The Dukes A, B, C system was broadened by Turnbull, who added a stage D for cases with known distant metastases and locally unresectable tumour[2]. Thus, Turnbull introduced the concept of clinicopathological staging in which residual tumour, found by the surgeon at the time of bowel resection, could determine the assigned stage. Clinicopathological staging has now gained wide acceptance as the preferred method of staging.

The ACPS system was recommended for use in Australia following two workshops on staging held in Brisbane in 1981[3]. The system was validated using prospectively collected data from the Concord Hospital Colorectal Cancer Project. The ACPS is essentially a simplified version of the system used at Concord Hospital since 1971[4] [5]. The ACPS and Concord systems are shown in Table 8.1.

11.2.1.1 Table 8.1. ACPS/Concord substaging definitions

ACPS	Concord substage	Maximum spread
A0	A1	Mucosa
A	A2	Submucosa
	A3	Muscularis propria
B	B1	Beyond muscularis propria
	B2	Free serosal surface
C	C1	Local nodes involved
	C2	Apical nodes involved
D	D1	Tumour transected (histological)
	D2	Distant metastases (clinical or histological)

Source: Davis and Newland[3]

A TNM system acceptable to both the Union Internationale Contre Le Cancer and the American Joint Committee for Cancer[6] was agreed in 1986 with the aim of attempting to achieve uniformity in staging of Colorectal Cancer(Tables 8.2 and 8.3)[7][8]. The ‘p’ prefix is used to indicate postsurgical pathological staging. This system is currently in its 7th edition and has undergone several significant revisions to the numerical coding with successive editions, including interpretation of mesenteric lymph node and non-lymph node associated tumour deposits. Between the 6th and 7th editions of the AJCC cancer staging manual, the definitions of T4a and T4b were reversed. A code was added to indicate the presence of extramural tumour deposits in the absence of lymph node metastasis (N1c). The MX code has been deleted.

11.2.1.2 Table 8.2. Pathological TNM staging nomenclature

T — primary tumour	
X	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
T1	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades through muscularis propria into pericolic tissues
T4a	Tumour penetrates to the surface of the visceral peritoneum
T4b	Tumour directly invades or is adherent to other organs or structures
N - regional lymph node	

T — primary tumour	
NX	Regional lymph nodes cannot be assessed
NO	No regional lymph nodes metastases
N1	Metastasis in 1–3 regional nodes
N1a	Metastasis in 1 regional lymph node
N1b	Metastasis in 2-3 regional lymph nodes
N1c	Tumour deposit(s) in the subserosa, mesentery, or non-peritonised pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in 4 or more regional lymph nodes
N2a	Metastasis in 4-6 regional lymph nodes
N2b	Metastasis in 7 or more regional lymph nodes
M — distant metastasis	
MO	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ or site (e.g.liver, lung, ovary, non-regional node)
M1b	Metastases to more than one organ/site or the peritoneum

Source: AJCC 2010**(AJCC, 2002)**

11.2.1.3 Table 8.3. AJCC/UICC stage groupings

Stage	T	N	MAC
0	Tis	N0	M0
I	T1	N0	M0
	T2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-T2	N1/N1c	M0
	T1	N2a	M0
IIIB	T3-T4a	N1/N1c	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0
	T4a	N2a	M0

Stage	T	N	MAC
IIIC	T3-T4a T4b	N2b N1-N2	M0 M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b

Back to top

11.2.2 References

1. ↑ Dukes, CE. *The classification of cancer of the rectum.* J. Pathol. 1932 [cited 2012 Dec 16];35(3); 323-332 Available from: http://onlinelibrary.wiley.com/doi/10.1002/path.1700350303/abstract.
2. ↑ Turnbull RB Jr, Kyle K, Watson FR, Spratt J. *Cancer of the colon: the influence of the no-touch isolation technic on survival rates.* Ann Surg 1967 Sep;166(3):420-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/6039601.
3. ↑ [3.0] [3.1] Davis NC, Newland RC. *The reporting of colorectal cancer: The Australian clinico-pathological staging system.* Aust N Z J Surg 1982 Aug;52(4):395-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/6180723.
4. ↑ Newland RC, Chapuis PH, Pheils MT, MacPherson JG. *The relationship of survival to staging and grading of colorectal carcinoma: a prospective study of 503 cases.* Cancer 1981 Mar 15;47(6):1424-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/7226068.
5. ↑ Newland RC, Chapuis PH, Smyth EJ. *The prognostic value of substaging colorectal carcinoma. A prospective study of 1117 cases with standardized pathology.* Cancer 1987 Aug 15;60(4):852-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/3594403.
6. ↑ Davis NC, Newland RC. *Terminology and classification of colorectal adenocarcinoma: the Australian clinico-pathological staging system.* Aust N Z J Surg 1983 Jun;53(3):211-21 Available from: http://www.ncbi.nlm.nih.gov/pubmed/6309132.
7. ↑ Hermanek, P.. *The TNM/p TNM classification of colorectal carcinomas — what has changed and why?* 1986 [cited 2016 Dec 16];10, p 6-12.
8. ↑ Beahrs OH, American Cancer S, American Joint Committee on C. *Manual for staging of cancer.* Philadelphia, USA: Lippincott; 1992 [cited 2016 Dec 16].

Back to top

11.3 Post-surgical staging following neoadjuvant therapy

Post\-surgical staging following neoadjuvant therapy

A subset of patients with rectal cancer may be treated with neoadjuvant radiotherapy or chemoradiotherapy prior to surgical resection of the tumour. The stage given in this situation is an indication of the extent of tumour actually present at the time of examination of the surgical specimen, and is not an estimate of tumour prior to neoadjuvant therapy. Tumour spread is defined by the extent of tumour cells. The presence of fibrosis, necrosis or acellular mucin pools should be reported but is not counted in the assessment of extent of tumour spread for staging purposes. The ‘yp’ prefix is used to denote postsurgical TMN stage following neoadjuvant therapy.

Back to top

11.4 Clinicopathological staging systems

Contents

11.4.1 Notable differences between available clinicopathological staging systems

The two main clinicopathological staging systems currently used in Australia, the Australian clinicopathological staging (ACPS) system and pathological staging (pTNM — tumour, node, metastasis), may both be seen as extensions of the original Dukes staging method.

Apart from the symbols used to designate the stages, the two clinicopathological systems have some notable differences.

11.4.1.1 Serosal surface involvement

In the ACPS/Concord system, a “free” serosal surface is defined as a surface that is not adherent to another structure, and the involvement of such a surface by direct spread defines substage B2. A tumour that invades beyond the muscularis propria and into an adjacent structure may still be regarded as substage B1 if involvement of a free serosal surface is not demonstrated. In the pTNM system, a tumour that has infiltrated another structure is classified as T4b regardless of whether or not a free serosal surface is involved.

11.4.1.2 Apical lymph node involvement

An apical lymph node is defined as a node within 1cm of the point of highest vascular pedicle ligation. Apical lymph node metastasis is associated with a worse prognosis than local lymph node metastasis, approaching that of distant metastasis. The presence apical lymph node defines ACPS/Concord substage C2, but is not specified in the N classification of TNM staging.

11.4.1.3 Residual tumour

The ACPS stage D classifies the presence of tumour residual following surgical resection of the primary tumour, whether it is in a line of resection (D1 - histological), and/or distant metastases (D2 - clinical or histological). pTNM stage IV applies only to cases with known distant metastases (clinical or histological). While the pTNM includes an optional R classification (table 8.4) for residual tumour, it is not used to assign a stage for such cases.

Data have been published supporting the inclusion of tumour in a line of resection in ACP stage D, and others have also documented the importance of this histological parameter[1]. Should the histological assessment of lines of resection be incorporated into pTNM staging and involvement [2] by tumour be a criterion for stage IV classification, then the two systems would be identical. In lieu of this, the use of the R code for residual tumour under the pTMM system would provide the necessary information to allow for closer correlation between the two staging systems (see table 8.4).

11.4.1.3.1 Table 8.4. Residual Tumour ® Classification

R — residual tumour	
RX	Presence of residual tumour cannot be assessed
R0	No residual tumour
R1	Microscopic residual tumour
R2	Macroscopic residual tumour

The presence of both loco-regional residual tumour (involved line of resection) and distant residual tumour (unresected metastasis) is taken into account. Source: AJCC[3] .

11.4.2 References

1. ↑ Fielding LP, Arsenault PA, Chapuis PH, Dent O, Gathright B, Hardcastle JD, et al. *Clinicopathological staging for colorectal cancer: an International Documentation System (IDS) and an International Comprehensive Anatomical Terminology (ICAT).* J Gastroenterol Hepatol 1991 Jul;6(4):325-44 Available from: http://www.ncbi.nlm.nih.gov/pubmed/1912440.
2. ↑ Newland RC, Dent OF, Lyttle MN, Chapuis PH, Bokey EL. *Pathologic determinants of survival associated with colorectal cancer with lymph node metastases. A multivariate analysis of 579 patients.* Cancer 1994 Apr 15;73(8):2076-82 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8156513.
3. ↑ (AJCCC) AJCoC. *Cancer staging manual.* Philadelphia, USA: Lippincott-Raven; 2002 [cited 2016 Dec 16].

Back to top

11.5 Selection of staging system

11.5.1 Selection of a clinicopathological staging system

The use of either one or both of the above staging systems has been variously advocated by Pathologist organisations in the USA, UK and Australasia. The College of American Pathologists has published a protocol based on the AJCC/UICC TNM 7th edition. The Royal College of Pathologists of Australasia recommends the use of TMN 7th edition while also recognising the use of the ACPS and Dukes' systems in Australia and recommends that all variables required for staging under these systems be recorded in pathology reports. The Royal College of Pathologists (UK) mandates the use of modified Dukes' staging in addition to TMN, specifically the 5th edition, to preserve the integrity of staging data for longitudinal analyses.

When using the TMN staging, it is essential that the specific edition of the system be recorded in the pathology report, as significant variations in the numerical coding have occurred between successive editions of the AJCC staging manual.

The ACPS system embodies the simplicity of Dukes staging. It comprehensively defines known residual tumour, it is based on a small number of key variables (direct spread, lymph node metastases and known residual tumour) and it has been validated by a large prospective series.

Whichever staging system is chosen, all parameters used to derive tumour stage should be recorded individually and explicitly in the pathology report to ensure effective communication and comparability between centres and over time. Table 8.5 shows a comparison between the ACPS/Concord and AJCC/UICC staging systems.

11.5.1.1 Table 8.5. Translation between ACPS/Concord and AJCC/UICC staging system

ACPS	Concord substage	AJCC/UICC				
		Stage grouping	T	N	M	R
A0	A1	0	Tis	N0	M0	R0
A	A2	I	T1	N0	M0	R0
A	A2	I	T1	N0	M0	R0
	A3	I	T2	N0	M0	R0
B	B1	IIA IIC	T3 T4b	N0	M0	R0
	B2	IIB	T4a	N0	M0	R0
C	C1	IIIA-IIIC	Any T	N1-N2	M0	R0
	C2	IIIA-IIIC	Any T	N1-N2	M0	R0
D	D1		Any T	Any N	M0	R1-R2
	D2	IVA-IVB	Any T	Any N	M1a-M1b	R2

Practice point

TNM staging, ACPS staging and the data required to stage the patient should all be recorded to allow national and international comparisons. (ACPS staging embodies the simplicity of Dukes.)

Back to top

11.6 Clinical input

11.6.1 Clinical input staging

Close collaboration between surgeon and pathologist is essential. The use of a clinicopathological staging system requires that the surgeon make the operative findings known to the pathologist. A convenient proforma for conveying this information is attached as Figure 8.1. Should this information be unavailable to the pathologist, the report should indicate that the stage has been assigned on the assumption that there were no known distant metastases present at the time of the resection.

11.6.1.1 Figure 8.1. Cancer of the colon and rectum — information for the pathologist

Back to top

11.7 Additional information on pathology reporting

Contents

11.7.1 Additional information on pathology reporting

The pathology report provides a histological confirmation of the diagnosis of colorectal cancer together with additional prognostic information that is used to guide further postsurgical clinical management of the patient. Apart from tumour stage, the importance of including information on a range of other variables in the histopathology report is recognised, (refer to Table 8.6). These variables include the components of stage and some other factors that have been shown to have a bearing on prognosis. The independent prognostic effects of many of these variables have been assessed within the ACPS system and have been demonstrated to be stage dependent[1][2][3].

Each variable should be recorded individually and explicitly in pathology reports. The use of structured reporting in synoptic format has been shown to improve the quality and completeness of data. The Royal College of Pathologists of Australasia has published a comprehensive protocol for structured reporting of colorectal cancer that outlines a number of standards (mandatory elements) and guidelines (optional elements), the details of which are summarised in table 8.6.

11.7.1.1 Table 8.6. Reporting on Colorectal Cancer specimens

Pre-analytical	
Demographic information provided on the request form	Name, date of birth, sex, identification and contact details of requesting doctor, date of request, medical record number
Clinical information documented on the request form	Operating surgeon name and contact details Perforation, clinical obstruction, tumour location, synchronous tumours, distance from anal verge, type of operation, preoperative radiotherapy, surgeon's opinion on the existence of residual cancer postsurgery , involvement of adjacent organs, new primary cancer or recurrence
Pathology accession number of the specimen	
^Any other clinical information received in other communications from the requestor or other clinician	
Macroscopic findings	
Specimen length	
Site of the tumour	Caecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon, rectosigmoid junction, rectum
Maximal tumour diameter	
Distance of tumour to nearer proximal or distal resection margin	
Distance of the tumour to the circumferential margin	
Presence or absence of tumour perforation	
Relationship of the tumour to the anterior peritoneal	

reflection (for rectal tumours)	Entirely above, astride, entirely below
Intactness of the mesorectum (for rectal tumours)	Incomplete (grade 1), nearly complete (grade 2), complete (grade 3)
^Any involvement of the peritoneum	By direct spread , tumour nodule(s) discrete from the tumour mass
^Any involvement of the peritoneum	
^Number of lymph nodes placed in each cassette	
^Number, diameter and gross configuration of polyps	
^Any other relevant macroscopic information	
Nature and sites of all blocks	
Microscopic findings	
Tumour type	Adenocarcinoma, mucinous adenocarcinoma, signet-ring cell carcinoma, medullary carcinoma, neuroendocrine carcinoma, squamous carcinoma, adenosquamous carcinoma, undifferentiated carcinoma, other (see WHO classification, 2014)
Histological grade	High grade (well and moderately differentiated) Low grade (poorly and undifferentiated)
Maximal degree of local invasion into or through the bowel wall	Submucosa, muscularis propria, beyond muscularis propria, serosal surface, involves other organs/structures
Involvement of proximal or distal resection margins	Involved margin(s), microscopic clearance (specify in mm if less than 10mm)
Status of nonperitonealised circumferential margin in rectal tumours	
Results of lymph node histopathology	Site(s) and numbers of lymph nodes (number of positive nodes/total number of nodes from this site) Isolated extramural tumour deposits
^Apical lymph node	

involvement if required where staging systems additional to TNM staging are in use	Required for ACPS, Dukes
Venous and small vessel invasion	Intramural vein invasion, extramural vein invasion, small vessel invasion
^Perineural invasion	
Histologically confirmed distant metastases	Sites
Relevant coexistent pathological abnormalities	Polyps, ulcerative colitis, Crohn's disease, dysplasia, other
Microscopic residual tumour status (completeness of resection)	
Response to neoadjuvant therapy	Grade 0 (complete response): No viable cancer cells Grade 1 (moderate response): Single cells or small groups of cancer cells Grade 2 (minimal response): Residual cancer outgrown by fibrosis Grade 3: (poor response): Minimal or no tumour kill; extensive residual cancer
Ancillary test findings	
^Mismatch repair enzymes	MLH1, PMS2, MSH2, MSH6 immunohistochemistry Microsatellite instability (MSI) BRAF (V600E mutation)
^KRAS gene mutation	
Synthesis and summary	
Tumour stage	pTNM and Stage grouping +/ - ACPS
Year and/or edition of staging system	AJCC 2010, 7th edition
Residual tumour status	R
^Diagnostic summary	Specimen type, tumour site, type, stage, completeness of excision
New primary cancer or recurrence	New primary, regional (local) recurrence, distant metastases, indeterminate
Overarching comment	

^Guidelines – recommendations optional, where relevant

11.7.1.2 Figure 8.2. A sample proforma for macroscopic examination

11.7.1.3 Figure 8.3. Sample Pathology Report

_ NEOPLASM (_ resection): Primary adenocarcinoma (_ grade malignancy, substage _ [ACP stage _]).

Differentiation: _. **Advancing edge**: Pushing_Infiltrative. **Direct spread**: _. **Contiguous adenoma**: Absent_ present. **Serosal surface involvement**: Yes_No. _ mm from serosal surface. **Non-peritonealised /Circumferential resection margin involvement**: Yes_No. _ mm from anterior_lateral_posterior margin. **Proximal or distal margin involvement**: Yes_No. _ [specify if less than 10mm] mm from proximal_distal margin.

Peritumoural inflammatory mantle: Prominent_Inconspicuous. **Tumour infiltrating lymphocytes**: Prominent_Inconspicuous.

Lymphatic infiltration: _. **Vascular infiltration**: _Intramural_Extramural arterial_venous invasion. **Perineural infiltration**: _.

Lymph node metastasis: _/_ local nodes. _/_ apical nodes. **Discontinuous extramural tumour deposits**: _.

_[Delete if not applicable] Response to neoadjuvant therapy: _Grade 0 (complete response) No viable cancer cells. _Grade 1 (moderate response) Single cells or small groups of cancer cells. _Grade 2 (minimal response) Residual cancer outgrown by fibrosis. _Grade 3 (poor response) Minimal or no tumour kill; extensive residual cancer.

Immunohistochemistry: DNA mismatch repair proteins: MSH2 _, MLH1 _, MSH6 _, PMS2 _. This is an abnormal_ normal pattern. **BRAF V600E**: _.

Other pathology: _.

AJCC (2010) [4]

11.7.2 References

1. ↑ Fielding LP, Arsenault PA, Chapuis PH, Dent O, Gathright B, Hardcastle JD, et al. *Clinicopathological staging for colorectal cancer: an International Documentation System (IDS) and an International Comprehensive Anatomical Terminology (ICAT).* J Gastroenterol Hepatol 1991 Jul;6(4):325-44 Available from: http://www.ncbi.nlm.nih.gov/pubmed/1912440.
2. ↑ Newland RC, Dent OF, Lyttle MN, Chapuis PH, Bokey EL. *Pathologic determinants of survival associated with colorectal cancer with lymph node metastases. A multivariate analysis of 579 patients.* Cancer 1994 Apr 15;73(8):2076-82 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8156513.
3. ↑ Newland RC, Dent OF, Chapuis PH, Bokey L. *Survival after curative resection of lymph node negative colorectal carcinoma. A prospective study of 910 patients.* Cancer 1995 Aug 15;76(4):564-71 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8625148.
4. ↑ Edge SB, Compton CC. *The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM.* Ann Surg Oncol 2010 Jun;17(6):1471-4 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20180029.

Back to top

11.8 Optimal molecular profiling of CRC

Contents

Pending from systematic review.

11.8.1 Evidence summary and recommendations

11.8.2 References

Back to top

11.8.3 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search

View PICO	NHMRC Evidence statement form PTH1	Systematic review report PTH1

Back to top

12 Preparation for surgery and perioperative optimisation

Contents

12.1 Background

Most patients diagnosed with colorectal carcinoma will undergo an operation. This may occur soon after diagnosis or may occur after neoadjuvant therapy in the case of rectal carcinoma, or after chemotherapy in patients with metastatic disease.

The decision to operate on an individual patient is based on an assessment of the patient's cancer burden, but also on patient factors including pre-existing comorbidities and patient's wishes.

Adequate pre-operative assessment will vary between patients, but in addition to pre-operative cancer staging, it should incorporate blood tests (including anaemia screening, electrolytes and CEA levels)[1][2][3][4] cardiopulmonary testing in selected patients, and referral to specialist services including a perioperative physician if necessary.[5][6]

Patients having elective colorectal cancer surgery should ideally be seen in a pre-admission clinic if available, and/or by an anaesthetist if possible.

A variety of measures and interventions can be used in the perioperative period to improve patient outcomes in the short and long term.

12.1.1 Contents

Subsections:

- Multidisciplinary meetings
- Perioperative anaemia management
- Thromboembolic prophylaxis
- Nutritional interventions
- Stomal therapy
- Body temperature
- Enhanced recovery after surgery
- Mechanical bowel preparation with or without antibiotic prophylaxis (PRP2-5,7)

12.2 References

1. ↑ Harrison LE, Guillem JG, Paty P, Cohen AM. *Preoperative carcinoembryonic antigen predicts outcomes in node-negative colon cancer patients: a multivariate analysis of 572 patients.* J Am Coll Surg 1997 Jul;185 (1):55-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/9208961.
2. ↑ Yang KM, Park IJ, Kim CW, Roh SA, Cho DH, Kim JC. *The prognostic significance and treatment modality for elevated pre- and postoperative serum CEA in colorectal cancer patients.* Ann Surg Treat Res 2016 Oct; 91(4):165-171 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27757393.
3. ↑ Kotzé A, Harris A, Baker C, Iqbal T, Lavies N, Richards T, et al. *British Committee for Standards in Haematology Guidelines on the Identification and Management of Pre-Operative Anaemia.* Br J Haematol 2015 Nov;171(3):322-31 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26343392.
4. ↑ Amato A, Pescatori M. *Perioperative blood transfusions for the recurrence of colorectal cancer.* Cochrane Database Syst Rev 2006 Jan 25;(1):CD005033 Available from: http://www.ncbi.nlm.nih.gov /pubmed/16437512.
5. ↑ Cheema FN, Abraham NS, Berger DH, Albo D, Taffet GE, Naik AD. *Novel approaches to perioperative assessment and intervention may improve long-term outcomes after colorectal cancer resection in older adults.* Ann Surg 2011 May;253(5):867-74 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21183846.
6. ↑ O'Neill F, Carter E, Pink N, Smith I. *Routine preoperative tests for elective surgery: summary of updated NICE guidance.* BMJ 2016 Jul 14;354:i3292 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27418436.

12.3 References

Back to top

12.1 Introduction: preparation for surgery and perioperative optimisation

Contents

12.1.1 Background

Most patients diagnosed with colorectal carcinoma will undergo an operation. This may occur soon after diagnosis or may occur after neoadjuvant therapy in the case of rectal carcinoma, or after chemotherapy in patients with metastatic disease.

The decision to operate on an individual patient is based on an assessment of the patient's cancer burden, but also on patient factors including pre-existing comorbidities and patient's wishes.

Adequate pre-operative assessment will vary between patients, but in addition to pre-operative cancer staging, it should incorporate blood tests (including anaemia screening, electrolytes and CEA levels)[1][2][3][4] cardiopulmonary testing in selected patients, and referral to specialist services including a perioperative physician if necessary.[5][6]

Patients having elective colorectal cancer surgery should ideally be seen in a pre-admission clinic if available, and/or by an anaesthetist if possible.

A variety of measures and interventions can be used in the perioperative period to improve patient outcomes in the short and long term.

12.1.1.1 Contents

Subsections:

- Multidisciplinary meetings
- Perioperative anaemia management
- Thromboembolic prophylaxis
- Nutritional interventions
- Stomal therapy
- Body temperature
- Enhanced recovery after surgery
- Mechanical bowel preparation with or without antibiotic prophylaxis (PRP2-5,7)

12.1.2 References

1. ↑ Harrison LE, Guillem JG, Paty P, Cohen AM. *Preoperative carcinoembryonic antigen predicts outcomes in node-negative colon cancer patients: a multivariate analysis of 572 patients.* J Am Coll Surg 1997 Jul;185 (1):55-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/9208961.
2. ↑ Yang KM, Park IJ, Kim CW, Roh SA, Cho DH, Kim JC. *The prognostic significance and treatment modality for elevated pre- and postoperative serum CEA in colorectal cancer patients.* Ann Surg Treat Res 2016 Oct; 91(4):165-171 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27757393.
3. ↑ Kotzé A, Harris A, Baker C, Iqbal T, Lavies N, Richards T, et al. *British Committee for Standards in Haematology Guidelines on the Identification and Management of Pre-Operative Anaemia.* Br J Haematol 2015 Nov;171(3):322-31 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26343392.
4. ↑ Amato A, Pescatori M. *Perioperative blood transfusions for the recurrence of colorectal cancer.* Cochrane Database Syst Rev 2006 Jan 25;(1):CD005033 Available from: http://www.ncbi.nlm.nih.gov /pubmed/16437512.
5. ↑ Cheema FN, Abraham NS, Berger DH, Albo D, Taffet GE, Naik AD. *Novel approaches to perioperative assessment and intervention may improve long-term outcomes after colorectal cancer resection in older adults.* Ann Surg 2011 May;253(5):867-74 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21183846.
6. ↑ O'Neill F, Carter E, Pink N, Smith I. *Routine preoperative tests for elective surgery: summary of updated NICE guidance.* BMJ 2016 Jul 14;354:i3292 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27418436.

12.1.3 References

Back to top

12.2 MDT meetings

12.2.1 Background

Multidisciplinary team meetings, or tumour boards, where initiated in the mid-to-late 1990s in response to perceptions of inadequate and inequitable cancer treatment.[1] Most national and regional guidelines now suggest that all new colorectal cancer cases should be discussed at a multidisciplinary team meeting, with rectal cancers being discussed pre-operatively.[2][3][4][5][6][7][8]

12.2.2 Overview of evidence (non-systematic literature review)

No systematic reviews were undertaken for this topic. Practice points were based on selected published evidence. See Guidelines development process.

There are no randomised controlled trials (RCTs) examining the effect of multidisciplinary team meetings on patient outcomes in colorectal cancer. However, many studies have concluded that multidisciplinary team meetings are beneficial, sometimes with limited evidence.[9] Eight papers have examined the effect of multidisciplinary team meetings on patient survival[10][11][12][13][14][15][16][17] in colorectal cancer and have reported an association with improved survival in patients discussed at a multidisciplinary team meeting. Many of these studies compared historical cohorts before and after introduction of a multidisciplinary team meeting. Thus, improved outcomes could possibly reflect other improvements in patient care such as better staging, more extensive surgery particularly of liver metastases and more effective chemotherapy.[17]

A recent Australian study[18] has suggested that their multidisciplinary team meeting rarely changed management in routine colon cancer cases, but management did change in 50% of complex cases. These included pre-operative assessments of rectal cancer, recurrence of colorectal cancer, metastatic disease and malignant polyps. The authors suggest a two-tier system for colorectal multidisciplinary team meetings, where all patients are listed, but only complex cases are discussed in detail. This is supported by a recent New Zealand study, which suggested that patients with stage 1 and 2 colorectal cancers rarely had their management impacted after discussion at an multidisciplinary team meeting.[19]

Multidisciplinary team meetings certainly have other benefits, including better communication among clinicians, [20], provision of most up-to-date treatments,[21] education and training, and improved coordination of care. They are an important part of care for colorectal cancer patients, although the resources required to run them are significant and need to be factored into service planning.[22]

Back to top

Practice point

Ideally, all patients with newly diagnosed colorectal cancer should be discussed at a multidisciplinary team meeting.

Practice point

Discussion at a multidisciplinary team meeting is mandatory for high-risk and complex cases such as patients with preoperative rectal cancers, metastatic disease or recurrent disease.

Back to top

12.2.3 References

1. ↑ Expert Advisory Group on Cancer,. *A policy framework for commissioning cancer services – the Calman–Hine Report. A Report by the Expert Advisory Group on Cancer to the Chief Medical Officers of England and Wales.* London, UK: Department of Health; 1995.
2. ↑ Association of Coloproctology of Great Britain and Ireland,. *Guidelines for the Management of Colorectal Cancer.* London: Association of Coloproctology of Great Britain and Ireland; 2007.
3. ↑ Department of Health WA. *Colorectal Model of Care.* Western Australia, Australia: WA Cancer & Palliative Care Network, Department of Health; 2008 [cited 2016 Dec 16].
4. ↑ Cancer Council Victoria. *Optimal care pathway for people with colorectal cancer.*; 2014 Available from: www.cancer.org.au/ocp.
5. ↑ Oncology GGPi. *Evidence-based Guideline for Colorectal Cancer.* Berlin, Germany; 2014.
6. ↑ Chang GJ, Kaiser AM, Mills S, Rafferty JF, Buie WD, Standards Practice Task Force of the American Society of Colon and Rectal Surgeons.. *Practice parameters for the management of colon cancer.* Dis Colon Rectum 2012 Aug;55(8):831-43 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22810468.
7. ↑ Monson JR, Weiser MR, Buie WD, Chang GJ, Rafferty JF, Buie WD, et al. *Practice parameters for the management of rectal cancer (revised).* Dis Colon Rectum 2013 May;56(5):535-50 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23575392.

8. ↑ National Collaborating Centre for Cancer. *The Diagnosis and Management of Colorectal Cancer - Evidence review United Kingdom: National Institute for Health and Care Excellence; 2011.*;.
9. ↑ Meagher AP. *Colorectal cancer: are multidisciplinary team meetings a waste of time?* ANZ J Surg 2013 Mar;83(3):101-3 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23586096.
10. ↑ MacDermid E, Hooton G, MacDonald M, McKay G, Grose D, Mohammed N, et al. *Improving patient survival with the colorectal cancer multi-disciplinary team.* Colorectal Dis 2009 Mar;11(3):291-5 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18477019.
11. ↑ Lordan JT, Karanjia ND, Quiney N, Fawcett WJ, Worthington TR. *A 10-year study of outcome following hepatic resection for colorectal liver metastases - The effect of evaluation in a multidisciplinary team setting.* Eur J Surg Oncol 2009 Mar;35(3):302-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18328668.
12. ↑ Du CZ, Li J, Cai Y, Sun YS, Xue WC, Gu J. *Effect of multidisciplinary team treatment on outcomes of patients with gastrointestinal malignancy.* World J Gastroenterol 2011 Apr 21;17(15):2013-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21528081.
13. ↑ Palmer G, Martling A, Cedermark B, Holm T. *Preoperative tumour staging with multidisciplinary team assessment improves the outcome in locally advanced primary rectal cancer.* Colorectal Dis 2011 Dec;13(12):1361-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20958913.
14. ↑ Ye YJ, Shen ZL, Sun XT, Wang ZF, Shen DH, Liu HJ, et al. *Impact of multidisciplinary team working on the management of colorectal cancer.* Chin Med J (Engl) 2012 Jan;125(2):172-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22340540.
15. ↑ Wille-Jørgensen P, Sparre P, Glenthøj A, Holck S, Nørgaard Petersen L, Harling H, et al. *Result of the implementation of multidisciplinary teams in rectal cancer.* Colorectal Dis 2013 Apr;15(4):410-3 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22958614.
16. ↑ Munro A, Brown M, Niblock P, Steele R, Carey F. *Do Multidisciplinary Team (MDT) processes influence survival in patients with colorectal cancer? A population-based experience.* BMC Cancer 2015 Oct 13;15:686 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26463599.
17. ↑ [17.0] [17.1] Lan YT, Jiang JK, Chang SC, Yang SH, Lin CC, Lin HH, et al. *Improved outcomes of colorectal cancer patients with liver metastases in the era of the multidisciplinary teams.* Int J Colorectal Dis 2016 Feb;31(2):403-11 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26662193.
18. ↑ Ryan J, Faragher I. *Not all patients need to be discussed in a colorectal cancer MDT meeting.* Colorectal Dis 2014 Jul;16(7):520-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24617857.
19. ↑ Fernando C, Frizelle F, Wakeman C, Frampton C, Robinson B. *Colorectal multidisciplinary meeting audit to determine patient benefit.* ANZ J Surg 2015 Nov 3 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26525919.
20. ↑ Segelman J, Singnomklao T, Hellborg H, Martling A. *Differences in multidisciplinary team assessment and treatment between patients with stage IV colon and rectal cancer.* Colorectal Dis 2009 Sep;11(7):768-74 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18662241.
21. ↑ Scott NA, Susnerwala S, Gollins S, Myint AS, Levine E. *Preoperative neo-adjuvant therapy for curable rectal cancer--reaching a consensus 2008.* Colorectal Dis 2009 Mar;11(3):245-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18637934.
22. ↑ Prades J, Remue E, van Hoof E, Borras JM. *Is it worth reorganising cancer services on the basis of multidisciplinary teams (MDTs)? A systematic review of the objectives and organisation of MDTs and their impact on patient outcomes.* Health Policy 2015 Apr;119(4):464-74 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25271171.

Back to top

12.3 Perioperative anaemia management

Contents

12.3.1 Background

Anaemia is common in patients with colorectal cancer, with 30-76% of patients variably reported as anaemic at diagnosis, depending on the level of haemoglobin used to define anaemia.[1][2][3][4][5][6][7] Iron deficiency is also common in colorectal cancer and associated with poor performance and advanced disease.[8][6]

Anaemia is associated with adverse perioperative outcomes including increased morbidity, prolonged length of hospital stay, excessive health resource utilisation, as well as reduced disease free survival.[6][9][10][11][12][13]

Comprehensive patient blood management programs focus on preoperative correction of anaemia, in addition to other methods of minimising blood loss and improving patient care.[14][15]

12.3.2 Overview of evidence (non-systematic literature review)

No systematic reviews were undertaken for this topic. Practice points were based on selected published evidence. See Guidelines development process.

12.3.2.1 Perioperative treatment options for patients with anaemia

Options for correcting perioperative anemia include allogenic blood transfusion, erythropoiesis stimulating agents (ESAs) and iron supplementation in the setting of demonstrable deficiency.

Blood transfusions in the immediate perioperative period have been utilised to rectify the physiological impact of anaemia during surgery. However, the link between blood transfusion and adverse surgical outcomes, as well as increased colorectal cancer recurrence, is now well documented.[16][6][17][18]

Given the association of erythropoiesis stimulating agents with adverse outcomes, including increased thrombosis and decreased survival in cancer patients, and current prescribing restrictions, their use has been limited in colorectal cancer.[19]

12.3.2.2 Testing

Patients undergoing colorectal cancer surgery should be assessed for anaemia and iron deficiency as early as possible prior to surgery, to allow a window to correct reversible causes, in particular haematinic deficiencies, and to enable restoration of erythropoiesis.[20][21][22]

Routine blood tests should include haemoglobin, full blood count, ferritin, transferrin, transferrin saturation, B12, folate, and C-reactive protein (CRP).

The Australian National Blood Authority has easily accessible guidelines on perioperative haemoglobin assessment and optimisation, which are based on a 2010 Australian review with recommendations.[23]

12.3.2.3 Preoperative management of iron-deficiency anaemia

Therapy to correct iron deficiency anaemia should be instituted as soon as possible pre-operatively.[20][21][22]

Oral and intravenous (IV) iron have both been shown to correct iron deficiency anaemia. Four studies have evaluated the efficacy of preoperative oral iron prior to colorectal cancer surgery and have shown it to achieve reduced transfusion rates, but not a consistent increase in haemoglobin preoperatively.[24][25][26][27]

Intravenously administered iron is preferential, given the time it takes to restore iron levels orally.[28][29] IV iron also appears more effective than oral iron in correcting anaemia in gastrointestinal diseases, such as inflammatory bowel disease,[29], as well as prior to most types of surgery.[30] TThere is emerging evidence for its use in colorectal cancer patients.[31]

A randomised controlled trial (RCT) trial of patients undergoing resectional surgery with a preoperative diagnosis of colorectal cancer randomised 60 patients presenting with colorectal cancer to two doses of iron sucrose or placebo.[32]. Less than a third of these patients were anaemic, and the dose of intravenous iron was suboptimal, but there was a trend towards decreased transfusion among the treatment group.[32]

However, two cohort studies in anaemic colorectal cancer patients have shown an increase in haemoglobin prior to surgery and a reduced transfusion rate among patients who received IV iron.[33][34]

One RCT[35] has been recently published which randomised abdominal surgery patients with iron deficiency anaemia to standard care or IV iron carboxymaltose. Seventy per cent of these patients had colorectal cancer. Those in the IV iron group had significantly fewer transfusions, increased haemoglobin at surgery and 4 weeks post surgery, and a decreased length of stay, further supporting the role of IV iron.[35]

12.3.2.4 Postoperative management of iron-deficiency anaemia

If iron deficiency anaemia is not addressed preoperatively and/or the patients lose substantial amounts of blood during surgery, IV iron therapy should be considered after surgery.

A recent Australian study has demonstrated a pragmatic and effective approach to the management of post-operative functional iron deficiency anaemia with intravenous iron carboxymaltose in such patients.[36]

New formulations such as iron carboxymaltose can be given quickly in an outpatient or GP setting and have rare adverse reactions, which improve their acceptability and should increase their use.[30]

Practice point

Patients undergoing elective surgery for colorectal cancer should be assessed for anaemia and iron deficiency and any deficiencies should be addressed preoperatively.

Practice point

Intravenous iron should be considered in preference to oral iron preoperatively given its quicker therapeutic effect.

Practice point

Consideration should also be given to treating postoperative functional iron deficiency anaemia with intravenous iron.

Back to top

12.3.3 References

1. ↑ Ludwig H, Van Belle S, Barrett-Lee P, Birgegård G, Bokemeyer C, Gascón P, et al. *The European Cancer Anaemia Survey (ECAS): a large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients.* Eur J Cancer 2004 Oct;40(15):2293-306 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15454256.

2. ↑ Beale AL, Penney MD, Allison MC. *The prevalence of iron deficiency among patients presenting with colorectal cancer.* Colorectal Dis 2005 Jul;7(4):398-402 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15932566.
3. ↑ Prutki M, Poljak-Blazi M, Jakopovic M, Tomas D, Stipancic I, Zarkovic N. *Altered iron metabolism, transferrin receptor 1 and ferritin in patients with colon cancer.* Cancer Lett 2006 Jul 18;238(2):188-96 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16111806.
4. ↑ Kim J, Konyalian V, Huynh R, Mittal R, Stamos M, Kumar R. *Identification of predictive factors for perioperative blood transfusion in colorectal resection patients.* Int J Colorectal Dis 2007 Dec;22(12):1493-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17768632.
5. ↑ Hamilton W, Lancashire R, Sharp D, Peters TJ, Cheng KK, Marshall T. *The importance of anaemia in diagnosing colorectal cancer: a case-control study using electronic primary care records.* Br J Cancer 2008 Jan 29;98(2):323-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18219289.
6. ↑ [6.0] [6.1] [6.2] [6.3] Acheson AG, Brookes MJ, Spahn DR. *Effects of allogeneic red blood cell transfusions on clinical outcomes in patients undergoing colorectal cancer surgery: a systematic review and meta-analysis.* Ann Surg 2012 Aug;256(2):235-44 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22791100.
7. ↑ Edna TH, Karlsen V, Jullumstrø E, Lydersen S. *Prevalence of anaemia at diagnosis of colorectal cancer: assessment of associated risk factors.* Hepatogastroenterology 2012 May;59(115):713-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22469713.
8. ↑ Prades J, Remue E, van Hoof E, Borras JM. *Is it worth reorganising cancer services on the basis of multidisciplinary teams (MDTs)? A systematic review of the objectives and organisation of MDTs and their impact on patient outcomes.* Health Policy 2015 Apr;119(4):464-74 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25271171.
9. ↑ Ludwig H, Müldür E, Endler G, Hübl W. *Prevalence of iron deficiency across different tumors and its association with poor performance status, disease status and anemia.* Ann Oncol 2013 Jul;24(7):1886-92 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23567147.
10. ↑ Leichtle SW, Mouawad NJ, Lampman R, Singal B, Cleary RK. *Does preoperative anemia adversely affect colon and rectal surgery outcomes?* J Am Coll Surg 2011 Feb;212(2):187-94 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21276532.
11. ↑ Musallam KM, Tamim HM, Richards T, Spahn DR, Rosendaal FR, Habbal A, et al. *Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study.* Lancet 2011 Oct 15;378(9800):1396-407 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21982521.
12. ↑ Kang CY, Chaudhry OO, Halabi WJ, Nguyen V, Carmichael JC, Mills S, et al. *Risk factors for postoperative urinary tract infection and urinary retention in patients undergoing surgery for colorectal cancer.* Am Surg 2012 Oct;78(10):1100-4 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23025950.
13. ↑ Zhen L, Zhe S, Zhenning W, Zhifeng M, Zhidong L, Xiaoxia L, et al. *Iron-deficiency anemia: a predictor of diminished disease-free survival of T3N0M0 stage colon cancer.* J Surg Oncol 2012 Mar 15;105(4):371-5 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21761412.
14. ↑ National Blood Authority. *Patient Blood Management Guidelines: Module 2 Perioperative.* Canberra, Australia; 2016 [cited 2016 Dec 16] Available from: https://www.blood.gov.au/pbm-module-2.
15. ↑ Clevenger B, Mallett SV, Klein AA, Richards T. *Patient blood management to reduce surgical risk.* Br J Surg 2015 Oct;102(11):1325-37; discussion 1324 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26313653.

16. ↑ Amato A, Pescatori M. *Perioperative blood transfusions for the recurrence of colorectal cancer.* Cochrane Database Syst Rev 2006 Jan 25;(1):CD005033 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16437512.
17. ↑ von Bormann B, Suksompong S, Schleinzer W. *Blood transfusions and prognosis in colorectal cancer: long-term results of a randomized controlled trial.* Ann Surg 2015 May;261(5):e136 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24378922.
18. ↑ Busch OR, Hop WC, Hoynck van Papendrecht MA, Marquet RL, Jeekel J. *Blood transfusions and prognosis in colorectal cancer.* N Engl J Med 1993 May 13;328(19):1372-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8292113.
19. ↑ Bohlius J, Schmidlin K, Brillant C, Schwarzer G, Trelle S, Seidenfeld J, et al. *Erythropoietin or Darbepoetin for patients with cancer--meta-analysis based on individual patient data.* Cochrane Database Syst Rev 2009 Jul 8;(3):CD007303 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19588423.
20. ↑ [20.0] [20.1] Froessler B, Papendorf D. *Intravenous iron sucrose--an effective and attractive modality for perioperative anaemia management.* Anaesth Intensive Care 2010 Sep;38(5):960-2 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20865896.
21. ↑ [21.0] [21.1] Muñoz M, Gómez-Ramírez S, Martín-Montañez E, Auerbach M. *Perioperative anemia management in colorectal cancer patients: a pragmatic approach.* World J Gastroenterol 2014 Feb 28;20(8):1972-85 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24587673.
22. ↑ [22.0] [22.1] Muñoz M, Gómez-Ramírez S, Campos A, Ruiz J, Liumbruno GM. *Pre-operative anaemia: prevalence, consequences and approaches to management.* Blood Transfus 2015 Jul;13(3):370-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26192787.
23. ↑ Pasricha SR, Flecknoe-Brown SC, Allen KJ, Gibson PR, McMahon LP, Olynyk JK, et al. *Diagnosis and management of iron deficiency anaemia: a clinical update.* Med J Aust 2010 Nov 1;193(9):525-32 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21034387.
24. ↑ Okuyama M, Ikeda K, Shibata T, Tsukahara Y, Kitada M, Shimano T. *Preoperative iron supplementation and intraoperative transfusion during colorectal cancer surgery.* Surg Today 2005;35(1):36-40 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15622462.
25. ↑ Lidder PG, Sanders G, Whitehead E, Douie WJ, Mellor N, Lewis SJ, et al. *Pre-operative oral iron supplementation reduces blood transfusion in colorectal surgery - a prospective, randomised, controlled trial.* Ann R Coll Surg Engl 2007 May;89(4):418-21 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17535624.
26. ↑ Quinn M, Drummond RJ, Ross F, Murray J, Murphy J, Macdonald A. *Short course pre-operative ferrous sulphate supplementation--is it worthwhile in patients with colorectal cancer?* Ann R Coll Surg Engl 2010 Oct;92(7):569-72 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20573311.
27. ↑ Ferrari P, Nicolini A, Manca ML, Rossi G, Anselmi L, Conte M, et al. *Treatment of mild non-chemotherapy-induced iron deficiency anemia in cancer patients: comparison between oral ferrous bisglycinate chelate and ferrous sulfate.* Biomed Pharmacother 2012 Sep;66(6):414-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22795809.
28. ↑ Evstatiev R, Marteau P, Iqbal T, Khalif IL, Stein J, Bokemeyer B, et al. *FERGIcor, a randomized controlled trial on ferric carboxymaltose for iron deficiency anemia in inflammatory bowel disease.* Gastroenterology 2011 Sep;141(3):846-853.e1-2 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21699794.
29. ↑ [29.0] [29.1] Koduru P, Abraham BP. *The role of ferric carboxymaltose in the treatment of iron deficiency anemia in patients with gastrointestinal disease.* Therap Adv Gastroenterol 2016 Jan;9(1):76-85 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26770269.

30. ↑ 30.0 30.1 Auerbach M. *New intravenous iron replacement therapies.* Clin Adv Hematol Oncol 2010 Oct;8 (10):688-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21317865.
31. ↑ Ng O, Keeler BD, Mishra A, Simpson A, Neal K, Brookes MJ, et al. *Iron therapy for pre-operative anaemia.* Cochrane Database Syst Rev 2015 Dec 22;(12):CD011588 Available from: http://www.ncbi.nlm.nih.gov /pubmed/26694949.
32. ↑ 32.0 32.1 Edwards TJ, Noble EJ, Durran A, Mellor N, Hosie KB. *Randomized clinical trial of preoperative intravenous iron sucrose to reduce blood transfusion in anaemic patients after colorectal cancer surgery.* Br J Surg 2009;96: 1122-8.
33. ↑ Bisbe E, García-Erce JA, Díez-Lobo AI, Muñoz M, Anaemia Working Group España.. *A multicentre comparative study on the efficacy of intravenous ferric carboxymaltose and iron sucrose for correcting preoperative anaemia in patients undergoing major elective surgery.* Br J Anaesth 2011 Sep;107(3):477-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21841061.
34. ↑ Keeler BD, Simpson JA, Ng S, Tselepis C, Iqbal T, Brookes MJ, et al. *The feasibility and clinical efficacy of intravenous iron administration for preoperative anaemia in patients with colorectal cancer.* Colorectal Dis 2014 Oct;16(10):794-800 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24916374.
35. ↑ 35.0 35.1 Froessler B, Palm P, Weber I, Hodyl NA, Singh R, Murphy EM. *The Important Role for Intravenous Iron in Perioperative Patient Blood Management in Major Abdominal Surgery: A Randomized Controlled Trial.* Ann Surg 2016 Jul;264(1):41-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed /26817624.
36. ↑ Khalafallah AA, Yan C, Al-Badri R, Robinson E, Kirkby BE, Ingram E, et al. *Intravenous ferric carboxymaltose versus standard care in the management of postoperative anaemia: a prospective, open-label, randomised controlled trial.* Lancet Haematol 2016 Sep;3(9):e415-25 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27570088.

Back to top

12.4 Thromboembolic prophylaxis

12.4.1 Background

Despite the availability of safe and efficacious antithrombotic agents, as well as the vast clinical experience justifying their use, thromboembolism remains a frequent complication among cancer patients, with substantial adverse health and economic consequences.[1]

Cancer-associated thrombosis remains an important negative predictor of survival as well as a leading cause of death, and is associated with higher (2- to 3-fold) thromboembolism recurrence rates, higher (2- to 6-fold) bleeding complications on anticoagulant therapy, increased hospitalisation and impaired quality of life.[2]

Moreover, an incident thromboembolic event, once a cancer has been diagnosed and treatment started, often denotes a significant clinical hurdle, not only related to the morbidity and mortality associated to the thromboembolic event, but also the potential detrimental effect of an interruption or modification in therapy, attributable to the event and/or delivery of therapeutic anticoagulation.[3][4]

Appropriate risk-adapted primary thromboprophylaxis can have a substantial impact not only on reduction of thromboembolism, but also disease response, survival, quality of life and healthcare resources.[5]

Surgical intervention at any given site, for any malignancy, is associated with a high thromboembolic risk, in particular major abdominopelvic surgery for colorectal cancer.[6] Thromboembolism remains an important and preventable complication of cancer surgery.

12.4.2 Overview of evidence (non-systematic literature review)

No systematic reviews were undertaken for this topic. Practice points were based on selected published evidence. See Guidelines development process.

Pharmacological thromboprophylaxis can reduce the rates of thromboembolism in up to 80% of high risk surgical patients and therefore should be considered for all patients with colorectal cancer undergoing major surgery, unless contraindicated.[7] The use of in-hospital thromboprophylaxis strategies, including low molecular-weight heparin or unfractionated heparin, in conjunction with graduated compression stockings and intermittent pneumatic compression, has been demonstrated to significantly reduce in-hospital rates of thromboembolism.[5][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24][25][26] Two recent Australian studies[27][28] have demonstrated that with good compliance to thromboembolic prophylaxis guidelines, the clinically diagnosed thromboembolism rate is very low in Australia with a 0.79% in-hospital venous thromboembolism (VTE) rate and an out of hospital VTE rate of 0.39% in the first 28 days[27] in one study, and a 4% 90 day VTE rate in a second study[28].

There are data suggesting that the risk of thromboembolism extends beyond the in-hospital stay after major abdominopelvic surgery. A Cochrane review[29] analysing data from four Scandinavian studies published in 2009, suggested a 60% reduction in venography detected thromboembolism rates in patients undergoing abdominal or pelvic surgery who received extended prophylaxis compared to standard prophylaxis. The symptomatic thromboembolism rate was also significantly reduced, from 0.7% in the standard group to 0.2 % in the extended prophylaxis group.[29] Given this finding, recent expert guidelines have suggested extended prophylaxis for 28 days post surgery should be considered, particularly in high-risk patients.[30][31][32][33]. High-risk patients include patients aged over 60 years, those with operation times longer than two hours, patients with reduced mobility post procedure, and those with a past history of thromboembolism. The UK National Institute for Health and Care Excellence Guidelines go further and recommend extended prophylaxis for all patients having major cancer surgery in the abdomen and pelvis.[34] None of these guidelines are specific to colorectal cancer patients.

One RCT (the PROLAPS study) evaluated extended VTE prophylaxis in colorectal cancer patients undergoing laparoscopic surgery, the trial.[35] PROLAPS randomised 225 patients to either short or extended prophylaxis with a composite primary outcome measure combining clinical VTE and ultrasound-detected VTE 1 month postoperatively.[35] It reported a significantly lower rate of VTE in the extended group compared with the standard group at 3 months (0.9% versus 9.7%, p = 0.005). However, there was no difference in the clinically detected rate of VTE.

Four more RCTs have compared standard in hospital and extended VTE prophylaxis and included colorectal cancer patients, but also included patients with other conditions. The ENOXACAN II and FAME trials showed a reduced rate of VTE in the extended groups[36][37] but, as with the PROLAPS trial, there was no difference in the rate of clinically detected VTE. The CANBESURE triall[38] and a Danish RCT[39] were unable to detect any difference in VTE rate between standard and extended prophylaxis.

Given these findings, a clinical review of major clinical guidelines and published clinical data evaluating extended venous thromboprophylaxis after elective colorectal cancer surgery suggested that routine extended VTE prophylaxis should not be standard practice, and that it should be reserved for high risk patients.[40]

Back to top

Practice point

All patients undergoing surgery for colorectal cancer should have standard thromboprophylaxis in hospital with compression stockings, unfractionated or low molecular-weight heparin and sequential compression devices. Extended prophylaxis for 28 days can be considered in high risk patients following colorectal cancer surgery.

Back to top

12.4.3 References

1. ↑ Ay C, Pabinger I, Cohen AT. *Cancer-associated venous thromboembolism: Burden, mechanisms, and management.* Thromb Haemost 2016 Nov 24 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27882374.
2. ↑ Walker AJ, Card TR, West J, Crooks C, Grainge MJ. *Incidence of venous thromboembolism in patients with cancer - a cohort study using linked United Kingdom databases.* Eur J Cancer 2013 Apr;49(6):1404-13 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23146958.
3. ↑ Alcalay A, Wun T, Khatri V, Chew HK, Harvey D, Zhou H, et al. *Venous thromboembolism in patients with colorectal cancer: incidence and effect on survival.* J Clin Oncol 2006 Mar 1;24(7):1112-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16505431.

4. ↑ Devani K, Patil N, Simons-Linares CR, Patel N, Jaiswal P, Patel P, et al. *Trends in Hospitalization and Mortality of Venous Thromboembolism in Hospitalized Patients With Colon Cancer and Their Outcomes: US Perspective.* Clin Colorectal Cancer 2016 Sep 20 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27777043.
5. ↑ [5.0] [5.1] Kakkos SK, Caprini JA, Geroulakos G, Nicolaides AN, Stansby G, Reddy DJ, et al. *Combined intermittent pneumatic leg compression and pharmacological prophylaxis for prevention of venous thromboembolism.* Cochrane Database Syst Rev 2016 Sep 7;9:CD005258 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27600864.
6. ↑ Bergqvist D. *Venous thromboembolism: a review of risk and prevention in colorectal surgery patients.* Dis Colon Rectum 2006 Oct;49(10):1620-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17019655.
7. ↑ Nelson DW, Simianu VV, Bastawrous AL, Billingham RP, Fichera A, Florence MG, et al. *Thromboembolic Complications and Prophylaxis Patterns in Colorectal Surgery.* JAMA Surg 2015 Aug;150(8):712-20 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26060977.
8. ↑ Collins R, Scrimgeour A, Yusuf S, Peto R. *Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery.* N Engl J Med 1988 May 5;318(18):1162-73 Available from: http://www.ncbi.nlm.nih.gov/pubmed/3283548.
9. ↑ Barbui T, Cassinelli G, Cortelazzo S. *Comparison of low molecular weight heparin cy 216 and unfractionated heparin in preventing post operative venous thromboembolism in general surgery a preliminary results of a cooperative study.* Fibrinolysis Proteolysis 1990;4(79).
10. ↑ Boneu B. *An international multicentre study: Clivarin in the prevention of venous thromboembolism in patients undergoing general surgery. Report of the International Clivarin Assessment Group.* Blood Coagul Fibrinolysis 1993 Dec;4 Suppl 1:S21-2 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8180325.
11. ↑ Creperio G, Marabini M, Ciocia G, Bergonzi M, Fincato M. *[Evaluation of the effectiveness and safety of Fragmin (Kabi 2165) versus calcium heparin in the prevention of deep venous thrombosis in general surgery].* Minerva Chir 1990 Sep 15;45(17):1101-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/2177861.
12. ↑ Kakkar VV, Murray WJ. *Efficacy and safety of low-molecular-weight heparin (CY216) in preventing postoperative venous thrombo-embolism: a co-operative study.* Br J Surg 1985 Oct;72(10):786-91 Available from: http://www.ncbi.nlm.nih.gov/pubmed/3899240.
13. ↑ Limmer J, Ellbrück D, Müller H, Eisele E, Rist J, Schütze F, et al. *Prospective randomized clinical study in general surgery comparing a new low molecular weight heparin with unfractionated heparin in the prevention of thrombosis.* Clin Investig 1994 Nov;72(11):913-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/7894222.
14. ↑ McLeod RS, Geerts WH, Sniderman KW, Greenwood C, Gregoire RC, Taylor BM, et al. *Subcutaneous heparin versus low-molecular-weight heparin as thromboprophylaxis in patients undergoing colorectal surgery: results of the canadian colorectal DVT prophylaxis trial: a randomized, double-blind trial.* Ann Surg 2001 Mar;233(3):438-44 Available from: http://www.ncbi.nlm.nih.gov/pubmed/11224634.
15. ↑ Nurmohamed MT, Verhaeghe R, Haas S, Iriarte JA, Vogel G, van Rij AM, et al. *A comparative trial of a low molecular weight heparin (enoxaparin) versus standard heparin for the prophylaxis of postoperative deep vein thrombosis in general surgery.* Am J Surg 1995 Jun;169(6):567-71 Available from: http://www.ncbi.nlm.nih.gov/pubmed/7771617.

16. ↑ Samama M, Bernard P, Bonnardot JP, Combe-Tamzali S, Lanson Y, Tissot E. *Low molecular weight heparin compared with unfractionated heparin in prevention of postoperative thrombosis.* Br J Surg 1988 Feb;75(2):128-31 Available from: http://www.ncbi.nlm.nih.gov/pubmed/2832030.
17. ↑ Allan A, Williams JT, Bolton JP, Le Quesne LP. *The use of graduated compression stockings in the prevention of postoperative deep vein thrombosis.* Br J Surg 1983;70: 172-4.
18. ↑ Holford, CP. *Graded compression for preventing deep venous thrombosis.* Br Med J 1976;2, p. 969-70.
19. ↑ Mellbring G, Palmér K. *Prophylaxis of deep vein thrombosis after major abdominal surgery. Comparison between dihydroergotamine-heparin and intermittent pneumatic calf compression and evaluation of added graduated static compression.* Acta Chir Scand 1986 Oct;152:597-600 Available from: http://www.ncbi.nlm.nih.gov/pubmed/3544626.
20. ↑ Scurr JH, Coleridge-Smith PD, Hasty JH. *Regimen for improved effectiveness of intermittent pneumatic compression in deep venous thrombosis prophylaxis.* Surgery 1987;102, p. 816-20.
21. ↑ Wille-Jørgensen P, Thorup J, Fischer A, Holst-Christensen J, Flamsholt R. *Heparin with and without graded compression stockings in the prevention of thromboembolic complications of major abdominal surgery: a randomized trial.* Br J Surg 1985 Jul;72(7):579-81 Available from: http://www.ncbi.nlm.nih.gov/pubmed/4016545.
22. ↑ Wille-Jørgensen P, Hauch O, Dimo B, Christensen SW, Jensen R, Hansen B. *Prophylaxis of deep venous thrombosis after acute abdominal operation.* Surg Gynecol Obstet 1991 Jan;172(1):44-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/1702235.
23. ↑ Bergqvist D, Lindblad B. *The thromboprophylactic effect of graded elastic compression stockings in combination with dextran 70.* Arch Surg 1984 Nov;119(11):1329-31 Available from: http://www.ncbi.nlm.nih.gov/pubmed/6208877.
24. ↑ Inada K, Shirai N, Hayashi M, Matsumoto K, Hirose M. *Postoperative deep venous thrombosis in Japan. Incidence and prophylaxis.* Am J Surg 1983 Jun;145(6):775-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/6859416.
25. ↑ Rasmussen A, Hansen PT, Lindholt J, Poulsen TD, Toftdahl DB, Gram J, et al. *Venous thrombosis after abdominal surgery. A comparison between subcutaneous heparin and antithrombotic stockings, or both.* J Med 1988;19(3-4):193-201 Available from: http://www.ncbi.nlm.nih.gov/pubmed/2972790.
26. ↑ Wille-Jørgensen P, Rasmussen MS, Andersen BR, Borly L. *Heparins and mechanical methods for thromboprophylaxis in colorectal surgery.* Cochrane Database Syst Rev 2003;(4):CD001217 Available from: http://www.ncbi.nlm.nih.gov/pubmed/14583929.
27. ↑ [27.0] [27.1] Chandra R, Melino G, Thomas M, Lawrence MJ, Hunter RA, Moore J. *Is extended thromboprophylaxis necessary in elective colorectal cancer surgery?* ANZ J Surg 2013 Dec;83(12):968-72 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23802729.
28. ↑ [28.0] [28.1] Holwell A, McKenzie JL, Holmes M, Woods R, Nandurkar H, Tam CS, et al. *Venous thromboembolism prevention in patients undergoing colorectal surgery for cancer.* ANZ J Surg 2014 Apr;84(4):284-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23782713.
29. ↑ [29.0] [29.1] Rasmussen MS, Jørgensen LN, Wille-Jørgensen P. *Prolonged thromboprophylaxis with low molecular weight heparin for abdominal or pelvic surgery.* Cochrane Database Syst Rev 2009 Jan 21;(1):CD004318 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19160234.
30. ↑ Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, et al. *Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.* Chest 2012 Feb;141(2 Suppl):e278S-325S Available from: http://www.ncbi.nlm.nih.gov/pubmed/22315265.

31. ↑ Lyman GH, Bohlke K, Khorana AA, Kuderer NM, Lee AY, Arcelus JI, et al. *Venous thromboembolism prophylaxis and treatment in patients with cancer: american society of clinical oncology clinical practice guideline update 2014.* J Clin Oncol 2015 Feb 20;33(6):654-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25605844.
32. ↑ National Comprehensive Cancer Network. Cancer-associated Venous Thromboembolic Disease. Washington2014.. *Cancer-associated venous thromboembolic disease.* Washington: NCCN.org; 2014 [cited 2016 Dec 16] Available from: http://williams.medicine.wisc.edu/vtecancer.pdf.
33. ↑ Gould MK, Garcia DA, Wren SM, Karanicolas PJ, Arcelus JI, Heit JA, et al. *Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.* Chest 2012 Feb;141(2 Suppl): e227S-77S Available from: http://www.ncbi.nlm.nih.gov/pubmed/22315263.
34. ↑ National Institute for Health and Care Excellence (NICE). *Venous thromboembolism: reducing the risk. Reducing the risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to hospital.* London, UK: Royal College of Physicians; 2010 Available from: https://www.ncbi.nlm.nih.gov/pubmed/23346611.
35. ↑ [35.0] [35.1] Vedovati MC, Becattini C, Rondelli F, Boncompagni M, Camporese G, Balzarotti R, et al. *A randomized study on 1-week versus 4-week prophylaxis for venous thromboembolism after laparoscopic surgery for colorectal cancer.* Ann Surg 2014 Apr;259(4):665-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24253138.
36. ↑ Pai A, Hurtuk MG, Park JJ, Marecik SJ, Prasad LM. *A Randomized Study on 1-Week Versus 4-Week Prophylaxis for Venous Thromboembolism After Laparoscopic Surgery for Colorectal Cancer.* Ann Surg 2016 Apr;263(4):e62 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25211266.
37. ↑ Rasmussen MS, Jorgensen LN, Wille-Jørgensen P, Nielsen JD, Horn A, Mohn AC, et al. *Prolonged prophylaxis with dalteparin to prevent late thromboembolic complications in patients undergoing major abdominal surgery: a multicenter randomized open-label study.* J Thromb Haemost 2006 Nov;4(11):2384-90 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16881934.
38. ↑ Kakkar VV, Balibrea JL, Martínez-González J, Prandoni P, CANBESURE Study Group.. *Extended prophylaxis with bemiparin for the prevention of venous thromboembolism after abdominal or pelvic surgery for cancer: the CANBESURE randomized study.* J Thromb Haemost 2010 Jun;8(6):1223-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20456751.
39. ↑ Lausen I, Jensen R, Jorgensen LN, Rasmussen MS, Lyng KM, Andersen M, et al. *Incidence and prevention of deep venous thrombosis occurring late after general surgery: randomised controlled study of prolonged thromboprophylaxis.* Eur J Surg 1998 Sep;164(9):657-63 Available from: http://www.ncbi.nlm.nih.gov/pubmed/9728784.
40. ↑ Sammour T, Chandra R, Moore JW. *Extended venous thromboembolism prophylaxis after colorectal cancer surgery: the current state of the evidence.* J Thromb Thrombolysis 2016 Jul;42(1):27-32 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26590997.

Back to top

12.5 Nutritional interventions

Contents

12.5.1 Background

Malnutrition is common in patients with cancer due to a combination of the disease process, host response to tumour and anticancer treatments.[1]

Patients with colorectal cancer are more prone to malnutrition than non-GI cancers due to the direct effects of bowel obstruction and malabsorption.

12.5.2 Overview of evidence (non-systematic literature review)

No systematic reviews were undertaken for this topic. Practice points were based on selected published evidence. See Guidelines development process.

12.5.2.1 Assessment of nutrition

Formal preoperative assessment of nutritional status in colorectal cancer patients has not been well investigated.

The measures commonly used to assess nutrition are hypoalbuminaemia, body weight loss and body mass index (BMI).

In a large study reporting on The American College of Surgeons – National Surgical Quality Improvement Program (ACS-NSQIP) database, malnutrition, was most prevalent in colorectal cancer patients, compared with patients with other common types of cancer.[1] This was particularly evident when hypoalbuminaemia was used as a marker for malnutrition, with 27.3% of colorectal cancer patients demonstrating a low albumin.

The risk of malnutrition appears to be further compounded when combined with preoperative chemoradiation in rectal cancer patients. One study reported that 51% of their patients demonstrated malnutrition, as measured by body weight loss, at the completion of chemoradiation and 29% at the time of surgery.[2]

There appears to be a strong association between markers of malnutrition such as hypoalbuminaemia, body weight loss and BMI, and increased postoperative mortality, with hypoalbuminaemia being associated strongly even after multiple regression analysis with all postoperative complications.[1] In rectal cancer patients, malnutrition, as measured by body weight loss, was also associated with increased rates of anastomotic leakage.[2]

There are more effective and precise tools for assessing the nutritional status of patients including the subjective global assessment, malnutrition universal screening tool (MUST) and nutritional risk index (NRI).[3]. The MUST tool appears to be the cheapest and easiest tool to use in colorectal cancer patients.

12.5.2.2 Nutritional support

In patients undergoing elective colorectal cancer surgery, nutritional support with supplements in the immediate preoperative period is a key component of enhanced recovery programs, with postoperative nutritional supplements also used in many programs.[4][5]

Preoperative correction of malnutrition in colorectal cancer patients has not been well studied. Similarly the medium and long term effects of nutritional interventions in colorectal cancer patients have not been evaluated systematically. One Portuguese study randomized 111 patients with colorectal cancer into three groups: a group receiving dietary counselling, a group receiving protein supplements, and those receiving standard care, whilst having preoperative radiotherapy for rectal carcinoma.[6] Both nutritional intervention groups had better intake, improved quality of life and fewer gastrointestinal symptoms than standard treatment patients at the completion of radiotherapy. With dietary counselling these changes were sustained at three months.[6] A more recent study with long term follow-up of this same group of patients demonstrated improved survival in the patients receiving nutritional counselling.[7]

Practice point
Patients undergoing elective surgery for colorectal cancer should be screened for malnutrition.

Practice point
If patients are found to be malnourished, nutritional interventions should be put in place.

Back to top

12.5.3 References

1. ↑ 1.0 1.1 1.2 Hu WH, Cajas-Monson LC, Eisenstein S, Parry L, Cosman B, Ramamoorthy S. *Preoperative malnutrition assessments as predictors of postoperative mortality and morbidity in colorectal cancer: an analysis of ACS-NSQIP.* Nutr J 2015 Sep 7;14:91 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26345703.

2. ↑ [2.0] [2.1] Yamano T, Yoshimura M, Kobayashi M, Beppu N, Hamanaka M, Babaya A, et al. *Malnutrition in rectal cancer patients receiving preoperative chemoradiotherapy is common and associated with treatment tolerability and anastomotic leakage.* Int J Colorectal Dis 2016 Apr;31(4):877-84 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26888783.
3. ↑ Håkonsen SJ, Pedersen PU, Bath-Hextall F, Kirkpatrick P. *Diagnostic test accuracy of nutritional tools used to identify undernutrition in patients with colorectal cancer: a systematic review.* JBI Database System Rev Implement Rep 2015 May 15;13(4):141-87 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26447079.
4. ↑ Gustafsson UO, Tiefenthal M, Thorell A, Ljungqvist O, Nygrens J. *Laparoscopic-assisted and open high anterior resection within an ERAS protocol.* World J Surg 2012 May;36(5):1154-61 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22395344.
5. ↑ Nygren J, Thacker J, Carli F, Fearon KC, Norderval S, Lobo DN, et al. *Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations.* Clin Nutr 2012 Dec;31(6):801-16 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23062720.
6. ↑ [6.0] [6.1] Ravasco P, Monteiro-Grillo I, Vidal PM, Camilo ME. *Dietary counseling improves patient outcomes: a prospective, randomized, controlled trial in colorectal cancer patients undergoing radiotherapy.* J Clin Oncol 2005 Mar 1;23(7):1431-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15684319.
7. ↑ Ravasco P, Monteiro-Grillo I, Camilo M. *Individualized nutrition intervention is of major benefit to colorectal cancer patients: long-term follow-up of a randomized controlled trial of nutritional therapy.* Am J Clin Nutr 2012 Dec;96(6):1346-53 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23134880.

Back to top

12.6 Stomal therapy

12.6.1 Background

Patients undergoing surgery for colorectal cancer, both in elective and emergency settings, may require a stoma. This includes formation of a permanent colostomy in patients with low rectal cancers; construction of ileostomies or colostomies in patients with an obstructing cancer, where an anastomosis is not appropriate; and formation of a temporary diverting loop stoma proximal to an anastomosis.

12.6.2 Overview of evidence (non-systematic literature review)

No systematic reviews were undertaken for this topic. Practice points were based on selected published evidence. See Guidelines development process.

Patients having surgery for colorectal cancer who definitely require a stoma, or who may require a stoma, should be seen by a stomal therapy nurse prior to surgery, and have the appropriate possible site/s for a stoma marked on their abdomen.[1]

There is evidence that patients have a better quality of life postoperatively if their stoma is sited preoperatively by a stomal therapist,[2] aand that these patients will have fewer stoma-related complications.[3][4]

Stomal therapists are able to provide counselling, education and support, and can even facilitate patients talking to other patients with stomas.[5]

Practice point

Patients undergoing colorectal cancer surgery who may, or will, require a stoma should be seen prior to surgery by a stomal therapist.

Practice point

Patients with stomas should be given postoperative education.

Back to top

12.6.3 References

1. ↑ Bass EM, Del Pino A, Tan A, Pearl RK, Orsay CP, Abcarian H. *Does preoperative stoma marking and education by the enterostomal therapist affect outcome?* Dis Colon Rectum 1997 Apr;40(4):440-2 Available from: http://www.ncbi.nlm.nih.gov/pubmed/9106693.
2. ↑ McKenna LS, Taggart E, Stoelting J, Kirkbride G, Forbes GB. *The Impact of Preoperative Stoma Marking on Health-Related Quality of Life: A Comparison Cohort Study.* J Wound Ostomy Continence Nurs 2016 Jan;43(1):57-61 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26727684.
3. ↑ Baykara ZG, Demir SG, Karadag A, Harputlu D, Kahraman A, Karadag S, et al. *A multicenter, retrospective study to evaluate the effect of preoperative stoma site marking on stomal and peristomal complications.* Ostomy Wound Manage 2014 May;60(5):16-26 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24807019.
4. ↑ Person B, Ifargan R, Lachter J, Duek SD, Kluger Y, Assalia A. *The impact of preoperative stoma site marking on the incidence of complications, quality of life, and patient's independence.* Dis Colon Rectum 2012 Jul;55(7):783-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22706131.
5. ↑ Nugent KP, Daniels P, Stewart B, Patankar R, Johnson CD. *Quality of life in stoma patients.* Dis Colon Rectum 1999;42: 1569-74.

Back to top

12.7 Body temperature

Contents

12.7.1 Background

Normal thermoregulation is disrupted during anaesthesia and surgery due to multiple factors.[1] Unintended perioperative hypothermia is common in surgical patients, and has been reported to be associated with platelet dysfunction, bleeding, wound infection, alterations of pharmacotherapeutic effects and shivering.[2]

12.7.2 Overview of evidence (non-systematic literature review)

No systematic reviews were undertaken for this topic. Practice points were based on selected published evidence. See Guidelines development process.

12.7.2.1 Effects of perioperative body temperature on wound site

One randomised controlled trial of 200 patients undergoing colorectal surgery reported that maintenance of a normal body temperature (near 36.5°C) during colorectal surgery using forced-air warming combined with fluid warming decreased the rate of surgical site infectionand reduced length of stay, compared with allowing body temperature to decrease to approximately 34.5°C.[3]

Subsequent observational cohort studies have not always supported the three-fold reduction in surgical site infection seen in the original study.[4][5]

Avoidance of hypothermia should be encouraged for its other benefits, which may include improved wound healing associated with a reduction in hospital stay.[3]

12.7.2.2 Strategies for maintaining perioperative body temperature

Strategies for maintaining perioperative body temperature include warming intravenous (IV) and irrigation fluids, the use of reflective blankets or clothing, and forced air warming, and prewarming.[6][7]

The use of warmed IV fluids has been shown to be effective in maintaining body temperature in adults.[7] Pre-warming for a minimum of 30 minutes may also reduce the risk of subsequent hypothermia.[6] There is no clear evidence that the use of reflective blankets or clothing increases body temperature, compared with usual care.[7]

Practice point
Perioperative normothermia should ideally be maintained at or above 36.0˚C.

Practice point
The use of warmed IV fluids and forced-air warming can be used to minimise perioperative hypothermia.

12.7.3 References

1. ↑ Sessler, DI. *Temperature monitoring and perioperative thermoregulation.* Anesthesiology ;2008 Aug; 109(2): 318–338. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2614355/.
2. ↑ Joanna Briggs Institute. *Strategies for the management and prevention of hypothermia within the adult perioperative environment Best Practice: evidence-based information sheets for health professionals. 2010; 14(13):1-4.*;.
3. ↑ [3.0] [3.1] Kurz A, Sessler DI, Lenhardt R. *Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infection and Temperature Group.* N Engl J Med 1996 May 9;334(19):1209-15 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8606715.
4. ↑ Baucom RB, Phillips SE, Ehrenfeld JM, Muldoon RL, Poulose BK, Herline AJ, et al. *Association of Perioperative Hypothermia During Colectomy With Surgical Site Infection.* JAMA Surg 2015 Jun;150(6):570-5 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25902410.
5. ↑ Lehtinen SJ, Onicescu G, Kuhn KM, Cole DJ, Esnaola NF. *Normothermia to prevent surgical site infections after gastrointestinal surgery: holy grail or false idol?* Ann Surg 2010 Oct;252(4):696-704 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20881777.
6. ↑ [6.0] [6.1] Hart, SR; Bordes, B; Hart, J; Corsino, D; Harmon, D;. *Unintended perioperative hypothermia.* The Ochsner Journal ;2011;11(3):259-270.

7. ↑ 7.0 7.1 7.2 National Collaborating Centre for Nursing and Supportive Care. National Institute for Health and Clinical Excellence (commissioner). *The management of inadvertent perioperative hypothermia in adults. (NICE CG65).* London: National Institute for Health and Clinical Excellence; 2008 Available from: https://www.nice.org.uk/guidance/cg65/evidence/cg65-perioperative-hypothermia-inadvertent-full-guideline2.

Back to top

12.8 Enhanced recovery after surgery

12.8.1 Background

Enhanced recovery after surgery (ERAS) (fast-track) programs are comprehensive multimodal perioperative pathways, which aim to reduce surgical stress, maintain postoperative physiological function, and enhance mobilisation after surgery.[1][2]

12.8.2 Overview of evidence (non-systematic literature review)

No systematic reviews were undertaken for this topic. Practice points were based on selected published evidence. See Guidelines development process.

ERAS programs have multiple components, which vary between programs. Broadly these include:[1][2]

- preoperative education and counselling
- preoperative optimisation
- perioperative nutritional supplements
- antimicrobial and prophylaxis
- venous thromboembolism prophylaxis
- multimodal antiemetics and analgesia
- avoidance of bowel preparation, nasogastric tubes and drains.

ERAS has resulted in reduced morbidity, faster recovery and shorter length of stay in series from dedicated centres.[3][4][5][6]

A meta-analysis of six randomised controlled trials (RCTs) on ERAS compared with standard care in patients undergoing open colorectal surgery has demonstrated that length of stay is reduced and postoperative morbidity almost halved.[7][8][9] The benefits of ERAS programs are still demonstrated in laparoscopic surgery as in open surgery, with a recent systematic review and meta-analysis of three RCTs[10][11][12] and six nonrandomised and observational studies and six clinical trials[13][14][15][16][17][18] showing reduced morbidity and particularly reduced length of stay with the addition of ERAS to minimally invasive surgery.[19]

Successful ERAS programs appear to have multiple components, but need to be multidisciplinary, have ongoing education, regular audit, and be adequately resourced.[20]

Practice point

Patients having elective surgery for colorectal cancer should be managed within an appropriately resourced enhanced recovery after surgery (ERAS) program.

Back to top

12.8.3 References

1. ↑ 1.0 1.1 Gustafsson UO, Tiefenthal M, Thorell A, Ljungqvist O, Nygrens J. *Laparoscopic-assisted and open high anterior resection within an ERAS protocol.* World J Surg 2012 May;36(5):1154-61 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22395344.
2. ↑ 2.0 2.1 Nygren J, Thacker J, Carli F, Fearon KC, Norderval S, Lobo DN, et al. *Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations.* Clin Nutr 2012 Dec;31(6):801-16 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23062720.
3. ↑ Basse L, Hjort Jakobsen D, Billesbølle P, Werner M, Kehlet H. *A clinical pathway to accelerate recovery after colonic resection.* Ann Surg 2000 Jul;232(1):51-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/10862195.
4. ↑ Basse L, Raskov HH, Hjort Jakobsen D, Sonne E, Billesbølle P, Hendel HW, et al. *Accelerated postoperative recovery programme after colonic resection improves physical performance, pulmonary function and body composition.* Br J Surg 2002 Apr;89(4):446-53 Available from: http://www.ncbi.nlm.nih.gov/pubmed/11952586.
5. ↑ Wind J, Hofland J, Preckel B, Hollmann MW, Bossuyt PM, Gouma DJ, et al. *Perioperative strategy in colonic surgery; LAparoscopy and/or FAst track multimodal management versus standard care (LAFA trial).* BMC Surg 2006 Nov 29;6:16 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17134506.
6. ↑ Khoo CK, Vickery CJ, Forsyth N, Vinall NS, Eyre-Brook IA. *A prospective randomized controlled trial of multimodal perioperative management protocol in patients undergoing elective colorectal resection for cancer.* Ann Surg 2007 Jun;245(6):867-72 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17522511.

7. ↑ Varadhan KK, Neal KR, Dejong CH, Fearon KC, Ljungqvist O, Lobo DN. *The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: a meta-analysis of randomized controlled trials.* Clin Nutr 2010 Aug;29(4):434-40 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20116145.
8. ↑ Serclová Z, Dytrych P, Marvan J, Nová K, Hankeová Z, Ryska O, et al. *Fast-track in open intestinal surgery: prospective randomized study (Clinical Trials Gov Identifier no. NCT00123456).* Clin Nutr 2009 Dec;28(6):618-24 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19535182.
9. ↑ Muller S, Zalunardo MP, Hubner M, Clavien PA, Demartines N, Zurich Fast Track Study Group.. *A fast-track program reduces complications and length of hospital stay after open colonic surgery.* Gastroenterology 2009 Mar;136(3):842-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19135997.
10. ↑ Basse L, Jakobsen DH, Bardram L, Billesbølle P, Lund C, Mogensen T, et al. *Functional recovery after open versus laparoscopic colonic resection: a randomized, blinded study.* Ann Surg 2005 Mar;241(3):416-23 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15729063.
11. ↑ King PM, Blazeby JM, Ewings P, Franks PJ, Longman RJ, Kendrick AH, et al. *Randomized clinical trial comparing laparoscopic and open surgery for colorectal cancer within an enhanced recovery programme.* Br J Surg 2006 Mar;93(3):300-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16363014.
12. ↑ Vlug MS, Wind J, Hollmann MW, Ubbink DT, Cense HA, Engel AF, et al. *Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: a randomized clinical trial (LAFA-study).* Ann Surg 2011 Dec;254(6):868-75 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21597360.
13. ↑ Al Chalabi H, Kavanagh DO, Hassan L, Donnell KO, Nugent E, Andrews E, et al. *The benefit of an enhanced recovery programme following elective laparoscopic sigmoid colectomy.* Int J Colorectal Dis 2010 Jun;25(6):761-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20177688.
14. ↑ Junghans T, Raue W, Haase O, Neudecker J, Schwenk W. *[Value of laparoscopic surgery in elective colorectal surgery with "fast-track"-rehabilitation].* Zentralbl Chir 2006 Aug;131(4):298-303 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17004188.
15. ↑ Lloyd GM, Kirby R, Hemingway DM, Keane FB, Miller AS, Neary P. *The RAPID protocol enhances patient recovery after both laparoscopic and open colorectal resections.* Surg Endosc 2010 Jun;24(6):1434-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20035353.
16. ↑ MacKay G, Ihedioha U, McConnachie A, Serpell M, Molloy RG, O'Dwyer PJ. *Laparoscopic colonic resection in fast-track patients does not enhance short-term recovery after elective surgery.* Colorectal Dis 2007 May;9(4):368-72 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17432992.
17. ↑ Raue W, Haase O, Junghans T, Scharfenberg M, Müller JM, Schwenk W. *'Fast-track' multimodal rehabilitation program improves outcome after laparoscopic sigmoidectomy: a controlled prospective evaluation.* Surg Endosc 2004 Oct;18(10):1463-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15791370.
18. ↑ Reurings JC, Spanjersberg WR, Oostvogel HJ, Buskens E, Maring J, Kruijt F, et al. *A prospective cohort study to investigate cost-minimisation, of Traditional open, open fAst track recovery and laParoscopic fASt track multimodal management, for surgical patients with colon carcinomas (TAPAS study).* BMC Surg 2010 Jun 14;10:18 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20546569.
19. ↑ Spanjersberg WR, van Sambeeck JD, Bremers A, Rosman C, van Laarhoven CJ. *Systematic review and meta-analysis for laparoscopic versus open colon surgery with or without an ERAS programme.* Surg Endosc 2015 Dec;29(12):3443-53 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25801106.

20. ↑ Pearsall EA, Meghji Z, Pitzul KB, Aarts MA, McKenzie M, McLeod RS, et al. *A qualitative study to understand the barriers and enablers in implementing an enhanced recovery after surgery program.* Ann Surg 2015 Jan;261(1):92-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24646564.

Back to top

12.9 Mechanical bowel prep and antibiotic prophylaxis

Contents

12.9.1 Background

Patients undergoing surgery for colorectal cancer have a significant risk of surgical site infections, with their associated health care costs and poor outcomes. In the last 100 years many interventions have been used in attempts to modify this risk.[1][2] Surgical site infection rates and anastomotic leak rates have become important clinical indicators used to measure hospital and unit outcomes, and even guide reimbursement, particularly in the USA. Surgical site infection reduction programs or 'bundles' are increasingly a focus for policy makers.

Mechanical bowel preparation (MBP) involves an oral laxative solution to cleanse the colon of faecal contents, and has been thought to reduce the number of bacteria in the bowel, and thus lower the risk of infective complications such as wound infection and anastomotic leak after colorectal surgery including cancer surgery.[1] Three main types of MBP are used currently, including sodium picosulfate, polyethylene glycol (PEG) and sodium phosphate, with no clear evidence to suggest one format is better than the others, although PEG may be better in patients who cannot tolerate electrolyte imbalances.[1]

MBP has been used routinely throughout the 21st century. However, in the last four decades, a number of publications have published results suggesting that MBP may not be necessary and in fact may even have a deleterious effect on patient outcomes.[3][4][5] A Cochrane review was originally published on this issue in 2004, and has subsequently been reviewed twice with additional papers included.[6] The most recent review published in 2011, included 18 studies with 5805 patients, comparing patients receiving MBP with those receiving no MBP.[7] It also included a small group where patients receiving MBP were compared to those only receiving an enema. The authors were unable to show any difference in anastomotic leak rates or wound infection rates between the groups.[7] This led to guidelines from a number of colorectal groups suggesting that MBP should be abandoned for most cases, particularly in colonic surgery.[8][9][7] Despite this, many surgeons still use MBP, particularly for rectal resections.

Antibiotics in one form or another have been used in colorectal surgery since the 1930s, and prophylactic administration of antibiotics has been well documented to decrease morbidity, shorten hospital stay and reduce infection-related costs.[10][11][12] There appears to be no advantage with multiple doses of intravenous antibiotics compared to a single dose of antibiotic.[13] However, cover should be provided against aerobic and anaerobic bacteria.[12]

In the early 1970s, Nichols and Condon popularised a combination of oral and intravenous antibiotics,[2] which was particularly popular in the USA.[14] However, for a variety of reasons, including poor compliance and increased day of surgery admission, this has been replaced in many regions in the last two decades by intravenous antibiotics given prophylactically at operation.[15]

Some centres, particularly in the USA, have continued to use routine preoperative oral antibiotics, with neomycin and erythromycin most commonly used, although metronidazole, ciprofloxacin and aminoglycosides are also employed. Interestingly, in the last 2 years a number of retrospective studies, some including very large data sets from North America, have published results, which suggest a clear benefit with reduced rates of surgical site infections in patients given preoperative oral antibiotics and intravenous antibiotics in combination with mechanical bowel preparation, in comparison to those patients not given oral antibiotics regardless of whether they took MBP or not.[16][17][18][19][20][21]

Analysis of a large cohort of patients from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) reported that patients receiving oral antibiotics in addition to intravenous antibiotics and MBP, also had improved outcomes in other areas in addition to a lower surgical site infection rate, with reduced rates of anastomotic leakage and postoperative ileus on multivariate analysis.[17] The improvements in outcomes were not seen in patients taking preoperative oral antibiotics and intravenous antibiotics if they did not receive MBP.

One recently published Japanese study randomised 515 patients receiving laparoscopic surgery for colorectal cancer, comparing 255 patients receiving preoperative oral antibiotics and intravenous antibiotics to 256 patients only receiving intravenous antibiotics.[22] They found no difference in any of the outcomes studied particularly SSI rates, which were 7.8% in each group, however not all patients in this study received MBP.[22]

Back to top

12.9.2 Systematic review evidence

In patients diagnosed with colorectal cancer and undergoing surgical tumour resection, does mechanical bowel preparation with or without antibiotic prophylaxis, when compared to usual care, achieve better outcomes in terms of anastomotic leakage, surgical site infection, length of hospital stay and ileus?

Fourteen level II randomised controlled trials (RCTs) were analysed examining the effect of MBP (with antibiotic prophylaxis) compared with no MBP (with or without antibiotic prophylaxis) in colorectal cancer.[23][24][25][26][27][28][29][30][31][32][33][34][35][36][37][38]

All of the RCTs were at high risk of bias, and they were from a variety of different countries in Europe and Asia, where quality of colorectal cancer treatment may be comparable to the Australian population.[23][24][25][26][27][28][29][30][31][32][33][34][35][36][37][38] One study performed in Western Australia was directly applicable to Australian colorectal cancer patients.[32]

Outcomes of interest analysed included anastomotic leakage/dehiscence, surgical site/wound infection (including abscess), postoperative ileus and length of hospital stay.

Back to top

12.9.2.1 Anastomotic leakage/dehiscence

Ten RCTs and one subgroup analysis reported overall anastomotic leak rates when comparing MBP (with antibiotic prophylaxis) to no MBP (with or without antibiotic prophylaxis) with postoperative follow up ranging from 24 days to 3 months.[23][24][25][26][28][29][30][32][33][35][38] No trial showed a statistically significant difference in anastomotic leak rate.

One trial[23] marginally favoured no mechanical bowel preparation, while two further trials}}[24][35] favoured mechanical bowel preparation, however these were trends and not statistically significant. The trials that did report small differences between groups were for the outcome of overall anastomotic leakage and tended to have lower participant numbers than those reporting none to negligible differences between groups. Subgroup analysis looking at low anterior resection, stapled and hand sewn anastomoses showed no difference between groups.[36]

Four RCTs looked at the rate of clinically significant anastomotic leakage/dehiscence, and showed no statistically different difference between the groups with and without MBP.[24][25][26][32]

One trial found a trend favouring mechanical MBP (with antibiotic prophylaxis) with patients experiencing lower rates of clinical anastomotic leak in the MBP group than the no-MBP group (0.7% versus 4.1%): odds ratio (OR) 1.75; 95% confidence interval (CI) 0.02 to 1.35, p = 0.06).[32]

Similarly, another group reported a trend to lower rates of clinically significant anastomotic leakage for those undergoing MPB than no MPB (7.0% versus 16.0%). However, the statistical significance was not reported.[25] There was a non-significant trend for reduced anastomotic leakage/dehiscence rates in a subgroup of patients with diverting loop ileostomies receiving MBP than those receiving no MBP (0.0% versus 4.8%; p-value NS).[36]

Three RCTs[24][25][26] and one subgroup analysis[36] reported asymptomatic or minor anastomotic leakage and found no statistically significant differences between patients receiving MBP (with antibiotic prophylaxis) compared with no MBP (with or without antibiotic prophylaxis).

12.9.2.2 Surgical site infection

12.9.2.2.1 Overall wound infection rates

Seven RCTs[32][33][34][25][38][26][34][30] and one subgroup analysis[36] examined overall wound infection rates, and found no statistically significant difference in overall wound infection rates comparing patients taking MBP (with antibiotic prophylaxis) with those taking no MBP (with or without antibiotic prophylaxis).

There were some non-significant trends to better outcomes with MBP in one study with four arms when patients added synbiotics to MBP and oral antibiotics[31], and in another study in patients who had a diverting loop ileostomy.[36] In contrast, another study showed a non-significant trend to lower overall surgical site infection rate in patients with no MBP compared with MPB (29.2% versus 17.2%, p-value NS).[30]

Back to top

12.9.2.2.2 Deeper abdominal, intra-abdominal or wound abscess

Six RCTs[23][24][25][28][32][38] and one subgroup analysis[36] reported deeper abdominal, intra-abdominal or wound abscess rates. Six studies consistently reported minimal to no difference between mechanical bowel preparation (with antibiotic prophylaxis) compared with no mechanical bowel preparation (with or without antibiotic prophylaxis).[24][25][28][32][38] One trial[23]{{ reported a small, non-significant difference in favour of no MBP (with antibiotic prophylaxis) (7.9% versus 3.0%, p = 0.62).

In contrast to the aforementioned trials, one RCT reported significantly lower rates of abscess in the MBP group than the no-MBP group MBP (with antibiotic prophylaxis),including for overall intra-abdominal abscess (2.2% versus 4.7%; difference 2.4; 95% CI 0.5 to 4.4; p = 0.02) and abdominal abscess with anastomotic leak (0.3% versus2.5%; difference 2.2; 95% CI 0.9 to 3.4; p = 0.001).[25]

Back to top

12.9.2.2.3 Organ/space surgical site infection

Two RCTs[37][30] reported organ/space surgical site infection rates and one RCT[33] reported intra-abdominal infection rates. There was no significant difference between groups taking MBP and not taking MBP.

12.9.2.2.4 Mild or superficial surgical site/wound infection

Seven RCTs[30][37][23][35][28][27][25] and one subgroup analysis[36] reported mild or superficial surgical site /wound infection. No study showed a statistically significant difference in mild surgical site infection rates associated with use of MBP.

Three RCTs[23][30][37] reported lower rates of surgical site infections among those that did not have MBP (with antibiotic prophylaxis), with reductions ranging from 4.8% to 10.7%. However, none of these differences were statistically significant.

Back to top

12.9.2.2.5 Severe wound infection/ subcutaneous wound disruption

One RCT[25] and one subgroup analysis of low anterior resection and diverting ileostomy[36] patients reported severe wound infection. Both were consistent in finding no statistically significant differences between MBP (with antibiotic prophylaxis) compared with no MBP (with antibiotic prophylaxis).

A further RCT reported subcutaneous wound disruption rates and also found no significant differences between groups.[28]

12.9.2.2.6 Wound dehiscence

One RCT[33] that reported wound dehiscence within 6 weeks post operation and one subgroup analysis[36] of low anterior resection reporting fascia dehiscence were consistent in reporting minimal between group differences.

In contrast, the subgroup analysis of diverting ileostomy reported fascial dehiscence to be higher for the MBP (with antibiotic prophylaxis) group than the no MBP group, but this was not statistically significant (7.4% versus 0.0%; p-value reported as NS).[36]

Back to top

12.9.2.3 Ileus

Five RCTs reported on post-operative ileus when comparing groups of patients taking MBP (with antibiotic prophylaxis) with those not taking MBP (with or without antibiotic prophylaxis).[26][28][33][35][37] There was no statistically significant difference in the incidence or duration of ileus between the groups.

12.9.2.4 Length of hospital stay

Eleven RCTs reported length of hospital stay as an outcome for MBP (with antibiotic prophylaxis) compared to no MBP (with or without antibiotic prophylaxis).[24][25][26][27][28][29][32][33][35][37]

Five trials reported less than a day difference between arms with no statistically significant differences (p-values ranging from 0.4 to 0.73).[25][28][32][33][38] Four trials reported one day difference between arms but were not statistically significant.[24][26][27][29] One further trial[35] reported a 4.4 median day difference between arms, which favoured no MBP and similarly another trial[37] also favoured no MBP with a 2 day mean difference between arms. However, differences between groups in both trials were not statistically significant (p-values 0.28 and 0.17, respectively). These latter two trials also contained low patient numbers such that results should be interpreted cautiously.[37][35]

Back to top

12.9.3 Evidence summary and recommendations

Evidence summary	Level	References
There is no significant difference in anastomotic leak rate when comparing patients who received MBP to no MBP, regardless of antibiotics administered.	II	[23], [24], [25], [26], [28], [30], [32], [33], [35], [38]
Overall surgical site infection rates are not significantly altered by the use of MBP, regardless of antibiotics taken.	II	[24], [25], [28], [32],

Evidence summary	Level	References
One study (Contant 2007) did show a significant reduction in the intra-abdominal abscess rate in patients who received MBP.		[33], [34], [36], [38]
Incidence and duration of postoperative ileus is not impacted by usage of MBP.	II	[29], [31], [36], [37]
There is no statistically significant difference in hospital stay associated with usage of MBP.	II	[25], [28], [32], [33], [38], [24], [26], [27], [29], [35], [37]

Evidence-based recommendation	Grade
Mechanical bowel preparation should not be used routinely in colonic surgery. It can be used in selectively according to individual patient and tumour characteristics, at the surgeon's discretion.	**D**

12.9.3.1 Considerations in making this recommendation

Mechanical bowel preparation has not been shown to consistently alter outcomes in patients undergoing surgery for colorectal cancer.

12.9.4 Health system implications

12.9.4.1 Clinical practice

The recommendation to consider mechanical bowel preparation on a case-by-case basis does not represent a significant departure from current practice. A 2011 survey of Australian and New Zealand colorectal surgeons found that routine oral mechanical bowel preparation was preferred by 28% for colon resection and 63% for rectal resection.[39]

12.9.4.2 Resourcing

The recommendation has no implications for resourcing.

12.9.4.3 Barriers to implementation

Surgeons who prefer routine mechanical bowel preparation may continue this practice.

12.9.5 Discussion

12.9.5.1 Unresolved issues

It is not clear if mechanical bowel preparation used in combination with preoperative oral antibiotics and intravenous antibiotics is associated with reduced rates of surgical site infection and anastomotic leak.

12.9.5.2 Studies currently underway

There is a Finnish MOBILE trial currently recruiting which is randomizing patients undergoing elective colectomies to receive either mechanical and oral antibiotic bowel preparation or no bowel preparation, which will hopefully help answer this question.[40]

12.9.5.3 Future research priorities

There is some emerging evidence that MBP when used in combination with preoperative oral antibiotics and intravenous antibiotics is associated with reduced rates of surgical site infection and anastomotic leak. This issue will need to be the focus of future RCTs to establish the true role of MBP in patients undergoing surgery for colorectal cancer.

12.9.6 References

1. ↑ 1.0 1.1 1.2 Kumar AS, Kelleher DC, Sigle GW. *Bowel Preparation before Elective Surgery.* Clin Colon Rectal Surg 2013 Sep;26(3):146-52 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24436665.
2. ↑ 2.0 2.1 Nichols RL, Condon RE. *Preoperative preparation of the colon.* Surg Gynecol Obstet 1971 Feb;132 (2):323-37 Available from: http://www.ncbi.nlm.nih.gov/pubmed/4929735.
3. ↑ Hughes ES, McDermott FT, Polglase AL, Johnson WR, Pihl EA. *Sepsis and asepsis in large bowel cancer surgery.* World J Surg 1982 Mar;6(2):160-5 Available from: http://www.ncbi.nlm.nih.gov/pubmed/7090401.
4. ↑ Zmora O, Mahajna A, Bar-Zakai B, Rosin D, Hershko D, Shabtai M, et al. *Colon and rectal surgery without mechanical bowel preparation: a randomized prospective trial.* Ann Surg 2003 Mar;237(3):363-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/12616120.
5. ↑ Burke P, Mealy K, Gillen P, Joyce W, Traynor O, Hyland J. *Requirement for bowel preparation in colorectal surgery.* Br J Surg 1994 Jun;81(6):907-10 Available from: http://www.ncbi.nlm.nih.gov/pubmed /8044619.
6. ↑ Slim K, Vicaut E, Panis Y, Chipponi J. *Meta-analysis of randomized clinical trials of colorectal surgery with or without mechanical bowel preparation.* Br J Surg 2004 Sep;91(9):1125-30 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15449262.
7. ↑ 7.0 7.1 7.2 Güenaga KF, Matos D, Wille-Jørgensen P. *Mechanical bowel preparation for elective colorectal surgery.* Cochrane Database Syst Rev 2011 Sep 7;(9):CD001544 Available from: http://www.ncbi.nlm.nih. gov/pubmed/21901677.

8. ↑ Gustafsson UO, Scott MJ, Schwenk W, Demartines N, Roulin D, Francis N, et al. *Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations.* Clin Nutr 2012 Dec;31(6):783-800 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23099039.
9. ↑ Eskicioglu C, Forbes SS, Fenech DS, McLeod RS, Best Practice in General Surgery Committee.. *Preoperative bowel preparation for patients undergoing elective colorectal surgery: a clinical practice guideline endorsed by the Canadian Society of Colon and Rectal Surgeons.* Can J Surg 2010 Dec;53(6):385-95 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21092431.
10. ↑ Baum ML, Anish DS, Chalmers TC, Sacks HS, Smith H Jr, Fagerstrom RM. *A survey of clinical trials of antibiotic prophylaxis in colon surgery: evidence against further use of no-treatment controls.* N Engl J Med 1981 Oct 1;305(14):795-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/7266633.
11. ↑ Song F, Glenny AM. *Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomized controlled trials.* Br J Surg 1998 Sep;85(9):1232-41 Available from: http://www.ncbi.nlm.nih.gov/pubmed/9752867.
12. ↑ [12.0] [12.1] Nelson RL, Gladman E, Barbateskovic M. *Antimicrobial prophylaxis for colorectal surgery.* Cochrane Database Syst Rev 2014 May 9;(5):CD001181 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24817514.
13. ↑ Rowe-Jones DC, Peel AL, Kingston RD, Shaw JF, Teasdale C, Cole DS. *Single dose cefotaxime plus metronidazole versus three dose cefuroxime plus metronidazole as prophylaxis against wound infection in colorectal surgery: multicentre prospective randomised study.* BMJ 1990 Jan 6;300(6716):18-22 Available from: http://www.ncbi.nlm.nih.gov/pubmed/2105115.
14. ↑ Solla JA, Rothenberger DA. *Preoperative bowel preparation. A survey of colon and rectal surgeons.* Dis Colon Rectum 1990 Feb;33(2):154-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/2105194.
15. ↑ Markell KW, Hunt BM, Charron PD, Kratz RJ, Nelson J, Isler JT, et al. *Prophylaxis and management of wound infections after elective colorectal surgery: a survey of the American Society of Colon and Rectal Surgeons membership.* J Gastrointest Surg 2010 Jul;14(7):1090-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20473578.
16. ↑ Althumairi AA, Canner JK, Pawlik TM, Schneider E, Nagarajan N, Safar B, et al. *Benefits of Bowel Preparation Beyond Surgical Site Infection: A Retrospective Study.* Ann Surg 2016 Dec;264(6):1051-1057 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26727098.
17. ↑ [17.0] [17.1] Kiran RP, Murray AC, Chiuzan C, Estrada D, Forde K. *Combined preoperative mechanical bowel preparation with oral antibiotics significantly reduces surgical site infection, anastomotic leak, and ileus after colorectal surgery.* Ann Surg 2015 Sep;262(3):416-25; discussion 423-5 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26258310.
18. ↑ Kim EK, Sheetz KH, Bonn J, DeRoo S, Lee C, Stein I, et al. *A statewide colectomy experience: the role of full bowel preparation in preventing surgical site infection.* Ann Surg 2014 Feb;259(2):310-4 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23979289.
19. ↑ Moghadamyeghaneh Z, Hanna MH, Carmichael JC, Mills SD, Pigazzi A, Nguyen NT, et al. *Nationwide analysis of outcomes of bowel preparation in colon surgery.* J Am Coll Surg 2015 May;220(5):912-20 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25907871.
20. ↑ Morris MS, Graham LA, Chu DI, Cannon JA, Hawn MT. *Oral Antibiotic Bowel Preparation Significantly Reduces Surgical Site Infection Rates and Readmission Rates in Elective Colorectal Surgery.* Ann Surg 2015 Jun;261(6):1034-40 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25607761.

21. ↑ Scarborough JE, Mantyh CR, Sun Z, Migaly J. *Combined Mechanical and Oral Antibiotic Bowel Preparation Reduces Incisional Surgical Site Infection and Anastomotic Leak Rates After Elective Colorectal Resection: An Analysis of Colectomy-Targeted ACS NSQIP.* Ann Surg 2015 Aug;262(2):331-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26083870.
22. ↑ 22.0 22.1 Ikeda A, Konishi T, Ueno M, Fukunaga Y, Nagayama S, Fujimoto Y, et al. *Randomized clinical trial of oral and intravenous versus intravenous antibiotic prophylaxis for laparoscopic colorectal resection.* Br J Surg 2016 Aug 23 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27550722.
23. ↑ 23.0 23.1 23.2 23.3 23.4 23.5 23.6 23.7 23.8 Bhattacharjee PK, Chakraborty S. *An Open-Label Prospective Randomized Controlled Trial of Mechanical Bowel Preparation vs Nonmechanical Bowel Preparation in Elective Colorectal Surgery: Personal Experience.* Indian J Surg 2015 Dec;77(Suppl 3):1233-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27011543.
24. ↑ 24.00 24.01 24.02 24.03 24.04 24.05 24.06 24.07 24.08 24.09 24.10 24.11 24.12 Bretagnol F, Panis Y, Rullier E, Rouanet P, Berdah S, Dousset B, et al. *Rectal cancer surgery with or without bowel preparation: The French GRECCAR III multicenter single-blinded randomized trial.* Ann Surg 2010 Nov;252(5):863-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21037443.
25. ↑ 25.00 25.01 25.02 25.03 25.04 25.05 25.06 25.07 25.08 25.09 25.10 25.11 25.12 25.13 25.14 25.15 25.16 Contant CM, Hop WC, van't Sant HP, Oostvogel HJ, Smeets HJ, Stassen LP, et al. *Mechanical bowel preparation for elective colorectal surgery: a multicentre randomised trial.* Lancet 2007 Dec 22;370(9605):2112-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18156032.
26. ↑ 26.00 26.01 26.02 26.03 26.04 26.05 26.06 26.07 26.08 26.09 26.10 Fa-Si-Oen P, Roumen R, Buitenweg J, van de Velde C, van Geldere D, Putter H, et al. *Mechanical bowel preparation or not? Outcome of a multicenter, randomized trial in elective open colon surgery.* Dis Colon Rectum 2005 Aug;48(8):1509-16 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15981065.
27. ↑ 27.0 27.1 27.2 27.3 27.4 27.5 Horvat M, Krebs B, Potrc S, Ivanecz A, Kompan L. *Preoperative synbiotic bowel conditioning for elective colorectal surgery.* Wien Klin Wochenschr 2010 May;122 Suppl 2:26-30 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20517667.
28. ↑ 28.00 28.01 28.02 28.03 28.04 28.05 28.06 28.07 28.08 28.09 28.10 28.11 28.12 Jung B, Påhlman L, Nyström PO, Nilsson E, Mechanical Bowel Preparation Study Group.. *Multicentre randomized clinical trial of mechanical bowel preparation in elective colonic resection.* Br J Surg 2007 Jun;94(6):689-95 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17514668.
29. ↑ 29.0 29.1 29.2 29.3 29.4 29.5 29.6 Krebs B. *Prebiotic and Synbiotic Treatment before Colorectal Surgery--Randomised Double Blind Trial.* Coll Antropol 2016 Apr;40(1):35-40 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27301235.
30. ↑ 30.0 30.1 30.2 30.3 30.4 30.5 30.6 30.7 30.8 Pena-Soria MJ, Mayol JM, Anula R, Arbeo-Escolar A, Fernandez-Represa JA. *Single-blinded randomized trial of mechanical bowel preparation for colon surgery with primary intraperitoneal anastomosis.* J Gastrointest Surg 2008 Dec;12(12):2103-8; discussion 2108-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18820977.
31. ↑ 31.0 31.1 31.2 31.3 Pena-Soria MJ, Mayol JM, Anula-Fernandez R, Arbeo-Escolar A, Fernandez-Represa JA. *Mechanical bowel preparation for elective colorectal surgery with primary intraperitoneal anastomosis by a single surgeon: interim analysis of a prospective single-blinded randomized trial.* J Gastrointest Surg 2007 May;11(5):562-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17394048.

32. ↑ 32.00 32.01 32.02 32.03 32.04 32.05 32.06 32.07 32.08 32.09 32.10 32.11 32.12 32.13 Platell C, Barwood N, Makin G. *Randomized clinical trial of bowel preparation with a single phosphate enema or polyethylene glycol before elective colorectal surgery.* Br J Surg 2006 Apr;93(4):427-33 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16491463.
33. ↑ 33.00 33.01 33.02 33.03 33.04 33.05 33.06 33.07 33.08 33.09 33.10 33.11 Ram E, Sherman Y, Weil R, Vishne T, Kravarusic D, Dreznik Z. *Is mechanical bowel preparation mandatory for elective colon surgery? A prospective randomized study.* Arch Surg 2005 Mar;140(3):285-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15781794.
34. ↑ 34.0 34.1 34.2 34.3 34.4 Reddy BS, Macfie J, Gatt M, Larsen CN, Jensen SS, Leser TD. *Randomized clinical trial of effect of synbiotics, neomycin and mechanical bowel preparation on intestinal barrier function in patients undergoing colectomy.* Br J Surg 2007 May;94(5):546-54 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17443852.
35. ↑ 35.00 35.01 35.02 35.03 35.04 35.05 35.06 35.07 35.08 35.09 35.10 Sasaki J, Matsumoto S, Kan H, Yamada T, Koizumi M, Mizuguchi Y, et al. *Objective assessment of postoperative gastrointestinal motility in elective colonic resection using a radiopaque marker provides an evidence for the abandonment of preoperative mechanical bowel preparation.* J Nippon Med Sch 2012;79(4):259-66 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22976604.
36. ↑ 36.00 36.01 36.02 36.03 36.04 36.05 36.06 36.07 36.08 36.09 36.10 36.11 36.12 36.13 Van't Sant HP, Weidema WF, Hop WC, Oostvogel HJ, Contant CM. *The influence of mechanical bowel preparation in elective lower colorectal surgery.* Ann Surg 2010 Jan;251(1):59-63 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20009750.
37. ↑ 37.00 37.01 37.02 37.03 37.04 37.05 37.06 37.07 37.08 37.09 37.10 Watanabe M, Murakami M, Nakao K, Asahara T, Nomoto K, Tsunoda A. *Randomized clinical trial of the influence of mechanical bowel preparation on faecal microflora in patients undergoing colonic cancer resection.* Br J Surg 2010 Dec;97(12):1791-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20799286.
38. ↑ 38.0 38.1 38.2 38.3 38.4 38.5 38.6 38.7 38.8 38.9 Zmora O, Mahajna A, Bar-Zakai B, Hershko D, Shabtai M, Krausz MM, et al. *Is mechanical bowel preparation mandatory for left-sided colonic anastomosis? Results of a prospective randomized trial.* Tech Coloproctol 2006 Jul;10(2):131-5 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16773286.
39. ↑ Kahokehr A, Robertson P, Sammour T, Soop M, Hill AG. *Perioperative care: a survey of New Zealand and Australian colorectal surgeons.* Colorectal Dis 2011 Nov;13(11):1308-13 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20958906.
40. ↑ Clinicaltrial.gov. *MOBILE Trial. Mechanical and Oral Antibiotic Bowel Preparation Versus no Bowel preparatIon for eLEctive Colectomy - a Multicenter, Prospective, Randomized, Controlled Trial. NCT02652637.* [homepage on the internet] U.S. National Institutes of Health; Available from: https://clinicaltrials.gov/ct2/show/NCT02652637.

Back to top

12.9.7 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search

View PICO	NHMRC Evidence statement form PRP2-5,7	Systematic review report PRP2-5,7

Back to top

13 Elective and emergency surgery for colon and rectal cancer

Contents

Subsections:

13.1 Optimal approach to elective resection for colon cancers (COL1-2a)

Contents

13.1.1 Background

The surgical management of adenocarcinoma of the colon is achieved by resection of the primary tumour and anastomosis of the bowel. Until recent decades, this procedure required a laparotomy, usually entailing a long midline abdominal incision. With the advent of laparoscopic surgery in the late 1980s, techniques have been developed that allow a minimally invasive approach to the surgical management of colon cancer. In the last 15 years there have been several large multicentre randomised controlled trials (RCTs), as well as many smaller RCTs and meta-analyses, comparing open and laparoscopic approaches to the elective resection of colon cancer.

13.1.2 Systematic review evidence

In patients diagnosed with colon cancer, what is the optimal resection strategy to achieve the best outcomes in terms of length and quality of life?

A systematic review was undertaken to ascertain the optimal surgical approach for resection of adenocarcinoma of the colon. The review focused on RCTs comparing open and laparoscopic colon resection, with particular reference to the outcomes of colon cancer mortality, disease free survival, colorectal cancer recurrence, lymph node harvest and perioperative mortality and morbidity, as well as surgery-related outcomes including postoperative pain levels, length of hospital stay, return of postoperative bowel function and operative time.

One systematic review and meta-analysis[1] and 17 RCTs reported across 40 articles[2][3][4][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24][25][26][27][28][29][30][31][32][33][34][35][36][37][38][39][40][41][42] were identified that compared open and laparoscopic approaches to the resection of colon cancer. The systematic review and meta-analysis had a low risk of bias.[1] All the RCTs were considered to be at unclear or high risk of bias.[2][3][4][5][6][7][8][9][10][11][12][13][14][15][16][19][17][18][20][21][22][23][24][25][26][27][28][29][30][31][32][33][34][35][36][37][38][39][40][41][42]

The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

13.1.2.1 Oncological outcomes

13.1.2.1.1 Colorectal cancer-specific mortality

Thirteen RCTs reported colorectal cancer mortality rates.[7][10][11][15][21][25][29][31][33][38][39][41][42] The RCT with the longest follow-up reported a nonsignificant difference in cancer-specific mortality between the laparoscopic and open surgery groups at 95 months' follow-up (16% versus 27%; p = 0.07).[21] However, there was an overall cancer-specific survival benefit in favour of the laparoscopic group at 10-year follow up (83% versus 65%; p = 0.02).[21]

13.1.2.1.2 Disease-free survival

Six RCTs[7][8][10][17][18][25] reported 3-year, 5-year and/or 10-year disease-free survival outcomes for patients who underwent laparoscopic or open surgery. All trials were consistent in reporting no difference in disease-free survival between the different surgical approaches at any of these follow up intervals.

13.1.2.1.3 Colorectal cancer recurrence

Eleven RCTs[5][7][8][10][12][17][21][25][26][31][42] reported either overall, local and/or distant colorectal cancer recurrence outcomes for laparoscopic versus open surgery, with follow up periods ranging from 2 to 10 years. One RCT[21] reported a statistically significant difference in colorectal cancer recurrence favouring the laparoscopic group at 10-year follow up (78% versus 64%; p = 0.05). All other RCTs and one meta-analysis[1] reported no difference in rates of colorectal cancer recurrence between groups who underwent open and laparoscopic colon cancer resection.

13.1.2.1.4 Lymph node harvest

The number of lymph nodes removed at colon cancer surgery is considered to be a surrogate marker of the quality of the resection.[43][44] Some authors have reported that removal of fewer than 12 lymph nodes is associated with poor prognosis.

Ten RCTs reported the mean or median number of lymph nodes retrieved.[6][7][8][10][15][25][26][31][41][42] There was no evidence of a significant difference between the two techniques in the number of lymph nodes retrieved.

Back to top

13.1.2.2 Perioperative mortality and morbidity

13.1.2.2.1 Perioperative mortality

Thirteen RCTs reported either operative mortality, perioperative mortality or postoperative mortality.[7][10][11][15][21][25][29][31][33][38][39][41][42] No differences between open and laparoscopic techniques were reported for these outcomes.

13.1.2.2.2 Perioperative morbidity

Five RCTs reported intraoperative complication rates.[11][13][15][29][37] Only one RCT, the Australasian Randomized Clinical Study Comparing Laparoscopic and Conventional Open Surgical Treatments for Colon Cancer (ALCCaS trial),[15] reported that the proportion of patients with one or more intraoperative complication was significantly lower among the open surgery group than the laparoscopic surgery group (3.7% versus 10.5%; p = 0.001). All other RCTs found no statistically significant difference in intraoperative complication rates between the operative techniques.[11][13][29][37]

Ten RCTs reported overall postoperative complication rates.[3][11][13][15][26][29][32][35][37][38] Most found no difference between open and laparoscopic surgery, although two RCTs[11][32] reported that laparoscopic surgery was associated with significantly lower rates of complications in the first 30 days postoperatively, compared with open surgery (15–21.1% versus 30–39.4%; p = 0.01–0.02). In addition, the ALCCaS trial[15] reported that, among patients aged over 70 years, there was a lower rate of postoperative complications (first 59 days) in the laparoscopic group, compared with the open surgery group (37.8% versus 50.7%; p = 0.02).

13.1.2.2.3 Intraoperative blood loss

Of the 10 RCTs that reported median or mean intraoperative blood loss,[11][15][25][26][31][37][38][39][41][42] six reported significantly reduced blood loss in the laparoscopic surgery group, compared with the open surgery group, with a weighted mean difference of 108.39 mL (98.02 mL versus 206.42 mL) for those that reported mean.[11][26][37][38][41] Each of the two trials that reported median blood loss also observed significantly less blood loss in the laparoscopic group, with differences in medians of 75 mL[38] and 55 mL.[41]

The clinical significance of these differences is unclear. Seven RCTs compared intraoperative, perioperative or postoperative blood transfusion rates between open and laparoscopic colon cancer surgery.[15][25][29][31][39][41][42] No differences were found between the groups in any of these trials.

13.1.2.2.4 Injury to other organs

In introducing new techniques to surgery, there is appropriate concern that hitherto-unreported complications may occur. Damage to organs out of the view of the laparoscope during laparoscopic colon cancer surgery is an example of this concern. Four RCTs[13][15][29][41] reported the incidence of intraoperative injury to small bowel, colon, splenic, ureteric, blood vessel and/or bladder in colon cancer surgery. None observed a difference between laparoscopic and open surgery in any of these parameters, with one exception: the ALCCaS trial[15] reported a higher rate of colonic serosal tear in the laparoscopic group, compared with the open surgery group (2.7% versus 0.3%; p = 0.02). This finding is of questionable clinical significance.

13.1.2.2.5 Reoperation

Four RCTs[15][25][38][41] reported reoperation rates in the postoperative period. All of the trials reported trends, with one trial[41] favouring the laparoscopic group and the other three trials favouring the open group. However, none of these differences reached statistical significance (p values ranged from 0.13 to 0.54).

Back to top

13.1.2.2.6 Anastomotic complications

Eleven RCTs[11][13][16][25][26][29][31][32][33][38][39] reported the rate or the cumulative incidence of anastomotic complication rates. None of the studies observed a difference in anastomotic complication rate between laparoscopic and open colon cancer surgery.

13.1.2.2.7 Postoperative small bowel obstruction

Three RCTs reported reoperation rates for bowel obstruction in the early postoperative period.[25][29][34] Two of these trials[25][34] reported no significant difference between open and laparoscopic surgery, whereas one[29] found reported a higher obstruction rate in the laparoscopic group than the open surgery group (2.8% versus 0%; p = 0.02).

Six trials reported rate or cumulative incidence of bowel obstruction up to 5 years after surgery.[29][32][34][36][38][41] None observed a difference in the rate of bowel obstruction between open and laparoscopic surgery, although the CLASSIC trial[36] found a marginally lower rate of bowel obstruction in the 3 years following randomisation in the laparoscopic group than the open surgery group (1.3% versus 4.0%; p value not reported).

13.1.2.2.8 Wound complications

Eight RCTs reported rates of postoperative wound infection[11][13][15][25][26][31][38][41] for laparoscopic versus open surgery. There was no statistically significant difference between the groups in any of these trials.

Several studies reported either postoperative incisional hernia rates or non-infectious wound complication rates. All observed numerical differences favouring the laparoscopic group, but in only one RCT[41] did this difference reach statistical significance (2.1% versus 7.4%; p < 0.001).

13.1.2.2.9 Respiratory complications

Six RCTs reported postoperative pneumonia rates for open versus laparoscopic colon surgery.[15][16][26][29][31][41] Three trials[15][31][26] observed a non-significant trend in favour of the laparoscopic group (0.47–8.5% versus 2.2–10%; p = 0.11–0.41), while the other three trials (LAPKON II 2009, JCOG 2014, COLOR 2007) observed no difference.[16][29][41]

Several studies reported rates of atelectasis or respiratory failure and found there to be no difference between the groups.[11][25][42]

13.1.2.2.10 Other surgery-related outcomes

Minimally invasive surgery has been developed to improve surgery related outcomes for the patient in the immediate postoperative period. Expected outcomes include less postoperative pain, more rapid return of postoperative bowel function, and a shortened hospital stay.

It should be noted that many of the RCTs used to analyse these outcomes were from the era prior to the widespread use of enhanced recovery after surgery (ERAS) protocols, which aim to improve postoperative outcomes with a combination of multimodal analgesic options (and minimal narcotic analgesia), early feeding with diet on the first postoperative day, minimal preoperative bowel preparation and early mobilisation.[45][46][47][48] It can only be speculated whether the following findings would be replicated if both open and laparoscopic surgery patients were exposed to such protocols in a RCT, or whether differences between open and laparoscopic surgery would be less apparent

Back to top

13.1.2.2.11 Postoperative pain

A decrease in pain levels in the postoperative period is an expected outcome from minimally invasive surgery, including laparoscopic colon cancer surgery. Five RCTs[10][25][38][41][42] reported postoperative analgesic requirement for laparoscopic and open surgery groups and two RCTs[25][26] reported pain on the first postoperative day using a visual analogue pain scale.

Pain after laparoscopic colon surgery was consistently less than after open surgery, whether measured by overall postoperative analgesic requirement, days of postoperative narcotic analgesia use or number of postoperative narcotic injections. For example, in one study the laparoscopic group required fewer median days of narcotic use than open surgery group (3 days versus 4 days; $p < 0.001$),[10] while another reported a lower rate of postoperative narcotic use in the laparoscopic group than the open surgery group (32.8% versus 46%; $p < 0.001$).[41] One study[26] reported that mean visual analogue pain scores on the first postoperative day were lower among the laparoscopic surgery group than the open surgery group (3.5 versus 8.6; $p < 0.001$).

13.1.2.2.12 Length of hospital stay

Sixteen RCTs[3][10][11][13][15][19][25][26][29][31][33][37][38][39][41][42] reported the postoperative length of hospital stay for patients undergoing laparoscopic or open resection. Fourteen found that patients having laparoscopic colectomy were discharged earlier,[3][10][11][15][19][25][26][31][33][37][38][39][41][42] with a statistically significant difference in 10 of the RCTs.[3][10][11][19][25][26][31][37][38][41] The ALCCaS trial,[15] which reported findings by age, observed a significantly lower length of stay in the laparoscopic group than the open surgery group in both the under-70 years group (median 7 [range 1–30] versus 8 [range 4–49]; $p = 0.01$) and the over-70 years group (8 [range 2–55] versus 10 [5–59]; $p < 0.001$). The weighted mean difference across nine studies was 1.9 days in favour of laparoscopic surgery (weighted mean 9.7 days versus 11.6 days).

13.1.2.2.13 Return of bowel function

Eight RCTs[13][15][19][25][33][38][41][42] reported return of bowel function outcomes for open versus laparoscopic colon resection. Five trials reported time to first flatus[15][19][25][33][41] with three showing a statistically significant shorter period in favour of the laparoscopic group (mean difference 1.8–3.2 days; p values ranged from < 0.001 to 0.03).[15][19][41]

Four trials[13][15][33][38] reported time to first bowel action. All of these trials showed a shorter time to bowel action in the laparoscopic group, with two trials reaching statistical significance (mean 3.6 versus 4.4 days; $p < 0.0001$–0.01).[15][38]

Several trials reported the time to resuming normal diet, with most showing a shorter time for the laparoscopic group.[13][19][25][42] With most major centres adopting ERAS protocols that include the provision of solid food on the first postoperative day for both open and laparoscopic surgery, the time to resuming diet is no longer a useful outcome in open versus laparoscopic colon resection analysis.

13.1.2.2.14 Operative time

Thirteen RCTs reported operative time for open versus laparoscopic colon resection.[10][11][15][19][25][26][29][31][33][37][38][41][42] Nine RCTs reported mean operative time, with open colon cancer surgery being faster than laparoscopic colon cancer surgery by a weighted mean difference of 44.51 minutes (weighted mean 146.61 minutes versus 191.16 minutes).[11][19][25][26][29][31][33][37][42] A further four RCTs used median operative times for their analysis, reporting a similar trend.[10][15][38][41]

Back to top

13.1.3 Evidence summary and recommendations

Evidence Summary	Level	References
There is no difference in oncological results, as measured by cancer mortality, disease free survival, cancer recurrence and lymph node harvest between open and laparoscopic colon cancer surgery.	II	[5][6][7][8][10][11][15][17][18][21][25][26][29][31][33][38][39][41][42]
Open and laparoscopic colon cancer surgery can be performed with equivalent safety, with no significant difference in perioperative mortality or morbidity between the two techniques.	II	[7][10][11][13][15][21][25][29][31][33][37][38][39][41][42]
Laparoscopic colon cancer surgery provides improved short-term postoperative outcomes, compared with open colon cancer surgery, with less postoperative pain, a shortened time to return of bowel function and a shorter hospital stay..	II	[3][10][11][13][15][19][25][26][31][33][37][38][39][41][42]

Back to top

Evidence-based recommendation	Grade
Either an open approach or a laparoscopic approach can be used for the resection of colon cancer	**D**

Evidence-based recommendation	Grade
Laparoscopic colectomy should be performed when the surgical expertise and hospital infrastructure are available	**D**

Practice point
Laparoscopic colectomy requires significant additional skills. Surgeons should ensure that they have mastered the necessary techniques before performing laparoscopic colectomy as an independent operator.

Practice point
Laparoscopic colorectal surgery is complex minimally invasive surgery that requires high-resolution video imaging and up-to-date equipment, including instrumentation and energy sources. It should only be undertaken in facilities that provide this infrastructure.

Back to top

13.1.3.1 Health system implications

13.1.3.1.1 Clinical practice

Surgeons in tertiary hospitals perform both laparoscopic and open colectomy as is appropriate for an individual patients. Smaller hospitals may not have access to the equipment necessary for safe laparoscopic colectomy.

13.1.3.1.2 Resourcing

The recommendation to use a laparoscopic approach, where the requisite the surgical expertise and hospital infrastructure are available, is unlikely to have any resource issues for larger hospitals. Smaller hospitals may need resources to properly equip operating theatres for laparoscopic colectomy.

13.1.3.1.3 Barriers to implementation

No barriers to the implementation of these recommendations are envisaged.

13.1.3.2 Discussion

13.1.3.2.1 Unresolved issues

There are no significant unresolved issues.

13.1.3.2.2 Studies currently underway

There are no significant ongoing studies.

13.1.3.2.3 Future research priorities

A research focus is techniques for resection in patients with rectal cancer, including total mesocolic excision.

Back to top

13.1.4 References

1. ↑ 1.0 1.1 1.2 Di B, Li Y, Wei K, Xiao X, Shi J, Zhang Y, et al. *Laparoscopic versus open surgery for colon cancer: a meta-analysis of 5-year follow-up outcomes.* Surg Oncol 2013 Sep;22(3):e39-43 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23643698.
2. ↑ 2.0 2.1 COLOR Study Group. *COLOR: a randomized clinical trial comparing laparoscopic and open resection for colon cancer.* Dig Surg 2000;17(6):617-622 Available from: http://www.ncbi.nlm.nih.gov/pubmed/11155008.
3. ↑ 3.0 3.1 3.2 3.3 3.4 3.5 3.6 Allardyce RA, Bagshaw PF, Frampton CM, Frizelle FA, Hewett PJ, Rieger NA, et al. *Australasian Laparoscopic Colon Cancer Study shows that elderly patients may benefit from lower postoperative complication rates following laparoscopic versus open resection.* Br J Surg 2010 Jan;97(1):86-91 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19937975.
4. ↑ 4.0 4.1 Allardyce RA, Bagshaw PF, Frampton CM, Frizelle FA, Hewett PJ, Rieger NA, et al. *Australian and New Zealand study comparing laparoscopic and open surgeries for colon cancer in adults: organization and conduct.* ANZ J Surg 2008 Oct;78(10):840-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18959634.
5. ↑ 5.0 5.1 5.2 5.3 Bagshaw PF, Allardyce RA, Frampton CM, Frizelle FA, Hewett PJ, McMurrick PJ, et al. *Long-term outcomes of the australasian randomized clinical trial comparing laparoscopic and conventional open surgical treatments for colon cancer: the Australasian Laparoscopic Colon Cancer Study trial.* Ann Surg 2012 Dec;256(6):915-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23154392.

6. ↑ 6.0 6.1 6.2 6.3 Braga M, Frasson M, Vignali A, Zuliani W, Di Carlo V. *Open right colectomy is still effective compared to laparoscopy: results of a randomized trial.* Ann Surg 2007 Dec;246(6):1010-4; discussion 1014-5 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18043103.
7. ↑ 7.0 7.1 7.2 7.3 7.4 7.5 7.6 7.7 7.8 Braga M, Frasson M, Zuliani W, Vignali A, Pecorelli N, Di Carlo V. *Randomized clinical trial of laparoscopic versus open left colonic resection.* Br J Surg 2010 Aug;97(8):1180-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20602506.
8. ↑ 8.0 8.1 8.2 8.3 8.4 8.5 Buunen M, Veldkamp R, Hop WC, Kuhry E, Jeekel J, Haglind E, et al. *Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial.* Lancet Oncol 2009 Jan;10(1):44-52 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19071061.
9. ↑ 9.0 9.1 Delgado S, Lacy AM, García Valdecasas JC, Balagué C, Pera M, Salvador L, et al. *Could age be an indication for laparoscopic colectomy in colorectal cancer?* Surg Endosc 2000 Jan;14(1):22-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/10653230.
10. ↑ 10.00 10.01 10.02 10.03 10.04 10.05 10.06 10.07 10.08 10.09 10.10 10.11 10.12 10.13 10.14 10.15 10.16 Fleshman J, Sargent DJ, Green E, Anvari M, Stryker SJ, Beart RW Jr, et al. *Laparoscopic colectomy for cancer is not inferior to open surgery based on 5-year data from the COST Study Group trial.* Ann Surg 2007 Oct;246(4):655-62; discussion 662-4 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17893502.
11. ↑ 11.00 11.01 11.02 11.03 11.04 11.05 11.06 11.07 11.08 11.09 11.10 11.11 11.12 11.13 11.14 11.15 11.16 11.17 11.18 11.19 11.20 Fujii S, Ishibe A, Ota M, Yamagishi S, Watanabe K, Watanabe J, et al. *Short-term results of a randomized study between laparoscopic and open surgery in elderly colorectal cancer patients.* Surg Endosc 2014 Feb;28(2):466-76 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24122242.
12. ↑ 12.0 12.1 12.2 Green BL, Marshall HC, Collinson F, Quirke P, Guillou P, Jayne DG, et al. *Long-term follow-up of the Medical Research Council CLASICC trial of conventional versus laparoscopically assisted resection in colorectal cancer.* Br J Surg 2013 Jan;100(1):75-82 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23132548.
13. ↑ 13.00 13.01 13.02 13.03 13.04 13.05 13.06 13.07 13.08 13.09 13.10 13.11 13.12 13.13 Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, et al. *Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial.* Lancet 2005 May;365(9472):1718-26 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15894098.
14. ↑ 14.0 14.1 Hazebroek EJ, Color Study Group. *COLOR: a randomized clinical trial comparing laparoscopic and open resection for colon cancer.* Surg Endosc 2002 Jun;16(6):949-53 Available from: http://www.ncbi.nlm.nih.gov/pubmed/12163961.
15. ↑ 15.00 15.01 15.02 15.03 15.04 15.05 15.06 15.07 15.08 15.09 15.10 15.11 15.12 15.13 15.14 15.15 15.16 15.17 15.18 15.19 15.20 15.21 15.22 15.23 15.24 15.25 15.26 15.27 15.28 15.29 Hewett PJ, Allardyce RA, Bagshaw PF, Frampton CM, Frizelle FA, Rieger NA, et al. *Short-term outcomes of the Australasian randomized clinical study comparing laparoscopic and conventional open surgical treatments for colon cancer: the ALCCaS trial.* Ann Surg 2008 Nov;248(5):728-38 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18948799.
16. ↑ 16.0 16.1 16.2 16.3 16.4 Janson M, Lindholm E, Anderberg B, Haglind E. *Randomized trial of health-related quality of life after open and laparoscopic surgery for colon cancer.* Surg Endosc 2007 May;21(5):747-53 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17342556.

17. ↑ 17.0 17.1 17.2 17.3 17.4 Jayne DG, Guillou PJ, Thorpe H, Quirke P, Copeland J, Smith AM, et al. *Randomized trial of laparoscopic-assisted resection of colorectal carcinoma: 3-year results of the UK MRC CLASICC Trial Group.* J Clin Oncol 2007 Jul 20;25(21):3061-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17634484.
18. ↑ 18.0 18.1 18.2 18.3 Jayne DG, Thorpe HC, Copeland J, Quirke P, Brown JM, Guillou PJ. *Five-year follow-up of the Medical Research Council CLASICC trial of laparoscopically assisted versus open surgery for colorectal cancer.* Br J Surg 2010 Nov;97(11):1638-45 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20629110.
19. ↑ 19.00 19.01 19.02 19.03 19.04 19.05 19.06 19.07 19.08 19.09 19.10 19.11 Kim JS, Hur H, Min BS, Lee KY, Chung HC, Kim NK. *Inflammatory and tumor stimulating responses after laparoscopic sigmoidectomy.* Yonsei Med J 2011 Jul;52(4):635-42 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21623607.
20. ↑ 20.0 20.1 Kitano S, Inomata M, Sato A, Yoshimura K, Moriya Y, Japan Clinical Oncology Group Study. *Randomized controlled trial to evaluate laparoscopic surgery for colorectal cancer: Japan Clinical Oncology Group Study JCOG 0404.* Jpn J Clin Oncol 2005 Aug;35(8):475-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16006574.
21. ↑ 21.0 21.1 21.2 21.3 21.4 21.5 21.6 21.7 21.8 21.9 Lacy AM, Delgado S, Castells A, Prins HA, Arroyo V, Ibarzabal A, et al. *The long-term results of a randomized clinical trial of laparoscopy-assisted versus open surgery for colon cancer.* Ann Surg 2008 Jul;248(1):1-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18580199.
22. ↑ 22.0 22.1 Lacy AM, Delgado S, García-Valdecasas JC, Castells A, Piqué JM, Grande L, et al. *Port site metastases and recurrence after laparoscopic colectomy. A randomized trial.* Surg Endosc 1998 Aug;12(8):1039-42 Available from: http://www.ncbi.nlm.nih.gov/pubmed/9685538.
23. ↑ 23.0 23.1 Lacy AM, García-Valdecasas JC, Delgado S, Castells A, Taurá P, Piqué JM, et al. *Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial.* Lancet 2002 Jun 29;359(9325):2224-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/12103285.
24. ↑ 24.0 24.1 Lacy AM, García-Valdecasas JC, Piqué JM, Delgado S, Campo E, Bordas JM, et al. *Short-term outcome analysis of a randomized study comparing laparoscopic vs open colectomy for colon cancer.* Surg Endosc 1995 Oct;9(10):1101-5 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8553212.
25. ↑ 25.00 25.01 25.02 25.03 25.04 25.05 25.06 25.07 25.08 25.09 25.10 25.11 25.12 25.13 25.14 25.15 25.16 25.17 25.18 25.19 25.20 25.21 25.22 25.23 25.24 25.25 25.26 25.27 Li JC, Leung KL, Ng SS, Liu SY, Lee JF, Hon SS. *Laparoscopic-assisted versus open resection of right-sided colonic cancer--a prospective randomized controlled trial.* Int J Colorectal Dis 2012 Jan;27(1):95-102 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21861071.
26. ↑ 26.00 26.01 26.02 26.03 26.04 26.05 26.06 26.07 26.08 26.09 26.10 26.11 26.12 26.13 26.14 26.15 26.16 26.17 26.18 26.19 Liang JT, Huang KC, Lai HS, Lee PH, Jeng YM. *Oncologic results of laparoscopic versus conventional open surgery for stage II or III left-sided colon cancers: a randomized controlled trial.* Ann Surg Oncol 2007 Jan;14(1):109-17 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17066227.
27. ↑ 27.0 27.1 Clinical Outcomes of Surgical Therapy Study Group. *A comparison of laparoscopically assisted and open colectomy for colon cancer.* N Engl J Med 2004 May 13;350(20):2050-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15141043.

28. ↑ 28.0 28.1 Nelson H, Weeks JC, Wieand HS. *Proposed phase III trial comparing laparoscopic-assisted colectomy versus open colectomy for colon cancer.* J Natl Cancer Inst Monogr 1995;(19):51-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/7577206.

29. ↑ 29.00 29.01 29.02 29.03 29.04 29.05 29.06 29.07 29.08 29.09 29.10 29.11 29.12 29.13 29.14 29.15 29.16 29.17 29.18 29.19 Neudecker J, Klein F, Bittner R, Carus T, Stroux A, Schwenk W, et al. *Short-term outcomes from a prospective randomized trial comparing laparoscopic and open surgery for colorectal cancer.* Br J Surg 2009 Dec;96(12):1458-67 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19918852.

30. ↑ 30.0 30.1 Ohtani H, Tamamori Y, Arimoto Y, Nishiguchi Y, Maeda K, Hirakawa K. *A meta-analysis of the short- and long-term results of randomized controlled trials that compared laparoscopy-assisted and open colectomy for colon cancer.* J Cancer 2012;3:49-57 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22315650.

31. ↑ 31.00 31.01 31.02 31.03 31.04 31.05 31.06 31.07 31.08 31.09 31.10 31.11 31.12 31.13 31.14 31.15 31.16 31.17 31.18 31.19 Pascual M, Alonso S, Parés D, Courtier R, Gil MJ, Grande L, et al. *Randomized clinical trial comparing inflammatory and angiogenic response after open versus laparoscopic curative resection for colonic cancer.* Br J Surg 2011 Jan;98(1):50-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20799296.

32. ↑ 32.0 32.1 32.2 32.3 32.4 32.5 Pecorelli N, Amodeo S, Frasson M, Vignali A, Zuliani W, Braga M. *Ten-year outcomes following laparoscopic colorectal resection: results of a randomized controlled trial.* Int J Colorectal Dis 2016 Jul;31(7):1283-90 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27090804.

33. ↑ 33.00 33.01 33.02 33.03 33.04 33.05 33.06 33.07 33.08 33.09 33.10 33.11 33.12 33.13 33.14 Procacciante F, De Luca M, Abilaliaj V, Chiaretti M, Diamantini G. *Post-operative ileus in hemicolectomy for cancer: open versus laparoscopic approach.* Ann Ital Chir 2013 Sep;84(5):557-62 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24140940.

34. ↑ 34.0 34.1 34.2 34.3 34.4 Schölin J, Buunen M, Hop W, Bonjer J, Anderberg B, Cuesta M, et al. *Bowel obstruction after laparoscopic and open colon resection for cancer: results of 5 years of follow-up in a randomized trial.* Surg Endosc 2011 Dec;25(12):3755-60 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21667207.

35. ↑ 35.0 35.1 35.2 Stucky CC, Pockaj BA, Novotny PJ, Sloan JA, Sargent DJ, O'Connell MJ, et al. *Long-term follow-up and individual item analysis of quality of life assessments related to laparoscopic-assisted colectomy in the COST trial 93-46-53 (INT 0146).* Ann Surg Oncol 2011 Sep;18(9):2422-31 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21452066.

36. ↑ 36.0 36.1 36.2 36.3 Taylor GW, Jayne DG, Brown SR, Thorpe H, Brown JM, Dewberry SC, et al. *Adhesions and incisional hernias following laparoscopic versus open surgery for colorectal cancer in the CLASICC trial.* Br J Surg 2010 Jan;97(1):70-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20013936.

37. ↑ 37.00 37.01 37.02 37.03 37.04 37.05 37.06 37.07 37.08 37.09 37.10 37.11 37.12 37.13 Tsimogiannis KE, Telis K, Tselepis A, Pappas-Gogos GK, Tsimoyiannis EC, Basdanis G. *A-defensin expression of inflammatory response in open and laparoscopic colectomy for colorectal cancer.* World J Surg 2011 Aug;35(8):1911-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21567262.

38. ↑ 38.00 38.01 38.02 38.03 38.04 38.05 38.06 38.07 38.08 38.09 38.10 38.11 38.12 38.13 38.14 38.15 38.16 38.17 38.18 38.19 38.20 38.21 38.22 38.23 Veldkamp R, Kuhry E, Hop WC, Jeekel J, Kazemier G, Bonjer HJ, et al. *Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial.* Lancet Oncol 2005 Jul;6(7):477-84 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15992696.

39. ↑ 39.00 39.01 39.02 39.03 39.04 39.05 39.06 39.07 39.08 39.09 39.10 39.11 Vignali A, Di Palo S, Orsenigo E, Ghirardelli L, Radaelli G, Staudacher C. *Effect of prednisolone on local and systemic response in laparoscopic vs. open colon surgery: a randomized, double-blind, placebo-controlled trial.* Dis Colon Rectum 2009 Jun;52(6):1080-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19581850.
40. ↑ 40.0 40.1 Weeks JC, Nelson H, Gelber S, Sargent D, Schroeder G, Clinical Outcomes of Surgical Therapy (COST) Study Group. *Short-term quality-of-life outcomes following laparoscopic-assisted colectomy vs open colectomy for colon cancer: a randomized trial.* JAMA 2002 Jan 16;287(3):321-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/11790211.
41. ↑ 41.00 41.01 41.02 41.03 41.04 41.05 41.06 41.07 41.08 41.09 41.10 41.11 41.12 41.13 41.14 41.15 41.16 41.17 41.18 41.19 41.20 41.21 41.22 41.23 41.24 41.25 41.26 41.27 41.28 41.29 Yamamoto S, Inomata M, Katayama H, Mizusawa J, Etoh T, Konishi F, et al. *Short-term surgical outcomes from a randomized controlled trial to evaluate laparoscopic and open D3 dissection for stage II/III colon cancer: Japan Clinical Oncology Group Study JCOG 0404.* Ann Surg 2014 Jul;260(1):23-30 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24509190.
42. ↑ 42.00 42.01 42.02 42.03 42.04 42.05 42.06 42.07 42.08 42.09 42.10 42.11 42.12 42.13 42.14 42.15 42.16 42.17 42.18 Kaiser AM, Kang JC, Chan LS, Vukasin P, Beart RW Jr. *Laparoscopic-assisted vs. open colectomy for colon cancer: a prospective randomized trial.* J Laparoendosc Adv Surg Tech A 2004 Dec;14(6):329-34 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15684776.
43. ↑ Nelson H, Petrelli N, Carlin A, Couture J, Fleshman J, Guillem J, et al. *Guidelines 2000 for colon and rectal cancer surgery.* J Natl Cancer Inst 2001 Apr 18;93(8):583-96 Available from: http://www.ncbi.nlm.nih.gov/pubmed/11309435.
44. ↑ Scott KW, Grace RH. *Detection of lymph node metastases in colorectal carcinoma before and after fat clearance.* Br J Surg 1989 Nov;76(11):1165-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/2688803.
45. ↑ Pritts TA, Nussbaum MS, Flesch LV, Fegelman EJ, Parikh AA, Fischer JE. *Implementation of a clinical pathway decreases length of stay and cost for bowel resection.* Ann Surg 1999 Nov;230(5):728-33 Available from: http://www.ncbi.nlm.nih.gov/pubmed/10561099.
46. ↑ Zargar-Shoshtari K, Connolly AB, Israel LH, Hill AG. *Fast-track surgery may reduce complications following major colonic surgery.* Dis Colon Rectum 2008 Nov;51(11):1633-40 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18536962.
47. ↑ Kahokehr A, Sammour T, Zargar-Shoshtari K, Thompson L, Hill AG. *Implementation of ERAS and how to overcome the barriers.* Int J Surg 2009 Feb;7(1):16-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19110478.
48. ↑ Fearon KC, Ljungqvist O, Von Meyenfeldt M, Revhaug A, Dejong CH, Lassen K, et al. *Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection.* Clin Nutr 2005 Jun;24(3):466-77 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15896435.

Back to top

13.1.5 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search

View PICO	NHMRC Evidence statement form COL1-2a	Systematic review report COL1-2a

Back to top

13.2 Optimal approach to elective resection for rectal cancers

Background

Surgical resection of the tumour remains the primary modality to treat rectal cancer. Technological advances have broadened the range of approaches that can be taken to facilitate curative resection of abdominal tumours, and improved understanding of pelvic anatomy has influenced the extent of resection for rectal cancer. These developments have resulted in a number of randomised controlled trials (RCTs) to determine the optimal approach to the elective resection of rectal cancer.

See the following sections:

- Optimal approach to elective resection for rectal cancers (COL1-2b)
- Local versus radical resection for stage T1-T2 rectal cancer (REC3)

13.2.1 Introduction: elective resection for rectal cancers

Background

Surgical resection of the tumour remains the primary modality to treat rectal cancer. Technological advances have broadened the range of approaches that can be taken to facilitate curative resection of abdominal tumours, and improved understanding of pelvic anatomy has influenced the extent of resection for rectal cancer. These developments have resulted in a number of randomised controlled trials (RCTs) to determine the optimal approach to the elective resection of rectal cancer.

See the following sections:

- Optimal approach to elective resection for rectal cancers (COL1-2b)
- Local versus radical resection for stage T1-T2 rectal cancer (REC3)

13.2.2 Optimal approach to elective resection for rectal cancers (COL1-2b)

Contents

13.2.2.1 Systematic review evidence

In patients diagnosed with rectal cancer, what is the optimal resection strategy to achieve the best outcomes in terms of length and quality of life?

A systematic review was undertaken to determine the optimal resection strategy for rectal cancer to maximise survival and quality of life. The review identified studies that examined the effect of rectal cancer resection type on cancer-related outcomes including mortality, cancer-specific survival, disease-free survival, local recurrence and metastases, morbidity, complications, and other adverse events including quality of life, pain and sexual dysfunction.

Three meta-analyses comparing laparoscopic with open resection surgery[1][2][3] were identified. All of these studies had a low risk of bias. One pooled analysis of data comparing laparoscopic with open resection surgery, [4] with a moderate risk of bias, was also identified.

Twenty-eight level II RCTs were reported across 36 papers.[4][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24][25][26][27][28][29][30][31][32][33][34][35][36][37] Of these, 20 trials[4][5][6][7][8][9][10][11][12][13][14][16][17][18][19][20][21][22][23][24][25][26][27][28][29][33] compared laparoscopic with open rectal cancer resection, and seven trials compared the following surgical interventions:

- single-port laparoscopic rectal surgery versus conventional laparoscopic surgery[34]
- endoscopic mucosal resection with circumferential incision (CIEMR) against endoscopic mucosal resection (EMR)[36]
- cylindrical abdominoperineal resection versus conventional abdominoperineal resection[35]
- transanal endoscopic microsurgery versus low anterior resection[30]
- transanal endoscopic microsurgery versus laparoscopic total mesorectal excision[32][33]
- endoluminal locoregional resection versus total mesorectal excision[31]
- laparoscopic anterior resection versus transanal endoscopic microsurgery anterior resection[37]

Of these RCTs, one[15] was assessed as having a low risk of bias. The remainder had an unclear or high overall risk of bias.

The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

13.2.2.1.1 Survival

Overall survival outcomes, including 15-, 10-, 8-, 5-, 3-, and 1-year survival rates and probability, were reported in 11 RCTs in studies comparing laparoscopic with open rectal cancer resection[5][7][11][12][13][15][16][17][18][28][35] and one meta-analysis of eight studies.[3] Evidence consistently showed no difference between any rectal cancer resection method for these outcomes at any time point.

Three RCTs comparing laparoscopic and open resection reported disease-free survival or recurrence-free survival for stage 1–3 patients.[5][7][15] No statistically significant differences in disease-free survival between open and laparoscopic resection groups were reported.

13.2.2.1.2 Perioperative/30-day/overall mortality

Differences between laparoscopic and open surgery were non-significant for all reported mortality outcomes, including 30-day mortality, perioperative mortality, and overall (> 30 day) mortality.[4][5][6][8][12][13][14][16][17][23][25][26][28][38]

Four RCTs[31][32][33][34] reported mortality outcomes for other surgical interventions. All differences were not statistically significant.

Back to top

13.2.2.1.3 Recurrence and distant metastasis

Nine RCTs compared 3-year, 5-year, and overall local recurrence rates between groups of patients who underwent laparoscopic and open resection.[5][7][13][15][17][18][23][28][38][39]

Only one of these studies showed significant differences between groups:[7]

- In patients with middle rectal cancer (intention-to-treat analysis) 3-year local recurrence was higher for laparoscopic resection than open resection (difference 4.1 percentage points; 90% CI 0.7 to 7.5).
- In patients with lower rectal cancer (as-treated analysis), 3-year local recurrence was lower for laparoscopic resection than open resection (difference 8.9 percentage points; 90% CI –15.6 to –2.2).

However, significance was determined through observation of 90% confidence intervals, and it is questionable whether this difference would be significant at $\alpha = 0.05$.

One study comparing conventional abdominoperineal resection and cylindrical abdominoperineal resection reported no significant difference in local recurrence rates.[35] However, numerically lower local recurrence rates were observed among patients who underwent cylindrical abdominoperineal resection.[35]

Seven RCTs that compared laparoscopic and open resection reported 1-year, 5-year, and overall distant metastases.[4][11][13][17][18][38][39]

Back to top

13.2.2.1.4 Complications and morbidity-related outcomes

A wide range of complication and morbidity related outcomes were reported across the studies. Very few significant differences were observed between laparoscopic and open resection patients, and these differences were not consistent overall.

13.2.2.1.4.1 Port site/wound metastases

Seven RCTs[11][13][16][17][18][23][38] that compared laparoscopic and open resection reported wound/port site metastases as an outcome. No significant differences were observed, with five studies reporting 0% recurrence in both groups.[11][13][16][17][38]

13.2.2.1.4.2 Blood loss and transfusion

Twelve RCTs comparing laparoscopic and open surgery reported significantly lower blood loss in the laparoscopic group, with significant differences ranging from 17.5 mL to 220.3 mL ($p < 0.001$ to $p = 0.036$).[6][8][12][13][14][17][24][25][26][27][28][38]

Similarly, the rate of blood transfusions and amount of blood required were lower among patients who underwent laparoscopic resection in studies reporting these outcomes, including one meta-analysis.[1][4][11][14][16][24]

13.2.2.1.4.3 Length of hospital stay

Of the RCTs that compared laparoscopic and open resection, five reported significantly shorter postoperative hospital stay in the laparoscopic group, with differences ranging from 1.6 to 3.4 days ($p < 0.001$ to $p = 0.036$).[11][12][23][28][38] Findings reported by studies that did not report statistical significance were inconsistent, with a trend towards shorter hospital stays in the laparoscopic group in five studies.[8][11][13][14][17][25][26]

13.2.2.1.4.4 Circumferential resection margin positivity

Nine RCTs that compared laparoscopic and open resection reported rates of positive circumferential resection margins.[7][11][12][14][17][25][27][28] Six of these studies observed numerically higher rates of positive circumferential resection margins in groups who underwent open resection,[7][11][14][27][28] while the remaining three studies[12][17][25] observed numerically higher rates in groups who underwent laparoscopic resection. However, none of these differences were statistically significant.

13.2.2.1.4.5 Number of lymph nodes retrieved

Of the 13 RCTs that compared open and laparoscopic resection,[4][7][8][11][12][13][14][16][17][24][25][28][38] only one study[17] found a significant difference in the number of lymph nodes retrieved. The remaining studies showed mixed not statistically significant differences between groups.

Back to top

13.2.2.1.4.6 Sexual function

Sexual function outcomes were reported in three RCTs that compared laparoscopic resection with open resection [9][14][20] and one RCT that compared cylindrical abdominoperineal resection with conventional abdominoperineal resection.[35] Although sexual function was negatively affected by any type of resection procedure, none of these studies observed significant differences between types of resection.

13.2.2.1.4.7 Conversion

Fifteen RCTs that compared laparoscopic resection with open resection reported rates of conversion from laparoscopic to open surgery.[4][5][6][11][12][13][14][16][17][24][25][26][27][28][38] Conversion rates ranged from 0 to 30.3%, with a median rate of 7.9%.

For other interventions, including transanal endoscopic microsurgery, endoluminal locoregional resection and single-port approaches, reported rates of conversion to laparoscopic anterior resection, open total mesorectal excision, and conventional laparoscopic surgery were between 5 and 11.4%.[30][31][32][33][34]

13.2.2.1.4.8 Morbidity/complications

Although a wide array of short-term and long-term complications and morbidities were reported, only two significant differences were observed:

- Open resection was associated with a higher rate of nerve injury than laparoscopic resection[6]
- Higher rates of major postoperative complications were observed among patients undergoing total mesorectal excision, compared with those receiving endoluminal locoregional resection[31]

13.2.2.1.4.9 Postoperative pain

Postoperative pain was reported by only two RCTs: one that compared laparoscopic resection with open resection[14] and one that compared single-port resection with conventional laparoscopic resection.[34]

The second study reported significantly lower pain scores within 3-4 days after surgery among patients who underwent single-port laparoscopic resection than among those who underwent conventional laparoscopic resection.[34]

The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

Back to top

13.2.2.2 Evidence summary and recommendations

Evidence summary	Level	References
Laparoscopic versus open resection		
For overall survival and mortality, there was no difference between patients undergoing laparoscopic resection and patients undergoing open resection for rectal cancer.	I, II	[1], [3], [4], [5], [6], [7], [8], [11], [12], [13], [14], [15], [16], [17], [18], [23], [25], [26], [28], [38]
There was no statistically significant difference in rates of local recurrence, distant metastases and disease-free survival between patients having an open approach and a laparoscopic approach to rectal cancer surgery.	I, II	[3], [4], [5], [7], [11], [12], [13], [15], [16], [17], [18], [23], [28], [29], [38], [39]
Rates of blood transfusion and the amount of perioperative blood loss were consistently and significantly lower for patients undergoing laparoscopic resection, compared with patients undergoing open rectal cancer resection.	I, II	[1], [4], [6], [8], [11], [12], [13], [14], [16], [17], [23], [24], [25], [26], [27], [28], [38]
Length of hospital stay was significantly shorter for laparoscopic patients, compared with open resection patients.	I, II	[1], [4], [11], [12], [13], [14], [17], [23], [24], [28], [38]
Rates of positive circumferential resection margins did not differ significantly between patients who underwent laparoscopic resection and those who underwent open resection, and reported differences did not consistently favour either approach.	II	[7], [14], [17], [25], [27], [28]

Evidence summary	Level	References
Two recent large multicentre RCTs did not demonstrate pathological oncological equivalence of laparoscopic to open rectal resection. However, data on local recurrence and survival is not yet available.		
Differences in the number of lymph nodes retrieved between patients who underwent laparoscopic resection and those who underwent open resection were mostly not statistically significant. One study observed that significantly more lymph nodes were retrieved among the laparoscopic group.	II	[7], [8], [14], [16], [17], [24], [25], [28]
Although sexual function was negatively affected by all surgery, no difference between patients receiving laparoscopic and open rectal cancer resection for colorectal cancer was observed.	II	[9], [10], [14], [20], [35]
Comparisons between other surgical approaches		
Transanal endoscopic microsurgery was associated with reductions in blood loss and length of hospital stay, compared with laparoscopic total mesorectal excision and low anterior resection. No consistent significant differences between groups in were observed for survival or quality-of-life outcomes in RCTs comparing the following: ■ transanal endoscopic microsurgery versus laparoscopic lower anterior resection ■ endoluminal locoregional resection versus laparoscopic total mesorectal excision ■ transanal endoscopic versus total mesorectal laparoscopic resection.	II	[30], [31], [32], [33], [37]
Postoperative pain		
Of two studies that reported postoperative pain, one found that single-port laparoscopic resection was associated with significantly less pain within 3 days of surgery than conventional laparoscopic resection.	II	[14], [34]

Back to top

Evidence-based recommendation	Grade
Open surgery is appropriate for resection of rectal cancer.	**C**

Evidence-based recommendation	Grade
Laparoscopic surgery for rectal cancer is appropriate in a subset of patients when performed by surgeons with advanced laparoscopic skills. However, it is a technique that has yet to be proven safe and efficacious in all patients for rectal cancer.	

Practice point
Regardless of the approach utilised, rectal cancer resection must be undertaken by surgeons who have been appropriately trained in surgical resection of rectal cancer, utilising the principles of total mesorectal resection as proposed by Heald. This should include sharp dissection undertaken along the mesorectal plane. Surgical resection undertaken by inadequately trained surgeons is likely to result in inferior oncological outcomes.

Practice point
Case selection is important, as it is suboptimal to generalise the surgical approach for rectal cancer to all patients. Factors such as patient body mass index, tumour stage, and surgeon experience are important considerations when determining whether a laparoscopic or open approach is optimal for the patient. Long-term local recurrence and survival data are awaited from recent large multicentre randomised controlled trials.

Back to top

13.2.2.3 Considerations in making these recommendations

Laparoscopic resection of rectal cancer would be considered preferable in terms of reduced length of stay and blood loss, however case selection is important when considering whether a laparoscopic or open approach is optimal. Overall pathological equivalence has yet to be proven and in the decision over which approach is optimal for a particular case, oncological principles must not be compromised.

Long-term local recurrence and survival data for the recent large randomised control trials for laparoscopic rectal resection are awaited. Whilst laparoscopic resection appears equivalent to open resection, when undertaken by surgeons who have had appropriate training and experience, it is likely that there are some case where a laparoscopic approach is not optimal with due consideration of patient, tumour and surgeon factors.

Back to top

13.2.2.4 Health system implications

13.2.2.4.1 Clinical practice

This review included RCTs from a wide range of countries, including Australia and New Zealand. Although about half of the studies were conducted in Asian populations, the evidence may be generalisable to an Australian population. However, there may be some important differences in the practice of rectal cancer resection.

Whilst laparoscopic resection of rectal cancer appears to have equivalent oncological outcomes to open surgery and some potential benefits to the patient over open surgery, it is essential that surgeons have been formally trained in laparoscopic rectal resection prior to undertaking this procedure.

13.2.2.4.2 Resourcing

There are no resource implications associated with implementing the recommendations.

13.2.2.4.3 Barriers to implementation

No barriers to the implementation of these recommendations are envisaged.

Back to top

13.2.2.5 Discussion

13.2.2.5.1 Unresolved issues

More longer-term evidence is needed from RCTs comparing survival data for laparoscopic versus open resection, especially from recent multicentre RCT trials.

RCT evidence regarding the role of alternative approaches, such robotic resection or transanal total mesorectal excision, is required before conclusions can be made on their role.

13.2.2.5.2 Studies currently underway

Results are awaited on the ROLARR trial comparing laparoscopic versus robotic resection of rectal cancer. However no data have yet been published.

COLOR III, a RCT comparing laparoscopic resection versus transanal total mesorectal excision, is currently recruiting.

13.2.2.5.3 Future research priorities

Evidence comparing longer-term survival data and alternative approaches would be valuable.

Back to top

13.2.2.6 References

1. ↑ 1.0 1.1 1.2 1.3 1.4 Arezzo A, Passera R, Scozzari G, Verra M, Morino M. *Laparoscopy for rectal cancer reduces short-term mortality and morbidity: results of a systematic review and meta-analysis.* Surg Endosc 2013 May;27(5):1485-502 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23183871.
2. ↑ Vennix S, Pelzers L, Bouvy N, Beets GL, Pierie JP, Wiggers T, et al. *Laparoscopic versus open total mesorectal excision for rectal cancer.* Cochrane Database Syst Rev 2014 Apr 15;(4):CD005200 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24737031.
3. ↑ 3.0 3.1 3.2 3.3 Zhao D, Li Y, Wang S, Huang Z. *Laparoscopic versus open surgery for rectal cancer: a meta-analysis of 3-year follow-up outcomes.* Int J Colorectal Dis 2016 Apr;31(4):805-11 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26847617.
4. ↑ 4.00 4.01 4.02 4.03 4.04 4.05 4.06 4.07 4.08 4.09 4.10 4.11 Ng SS, Lee JF, Yiu RY, Li JC, Hon SS, Mak TW, et al. *Long-term oncologic outcomes of laparoscopic versus open surgery for rectal cancer: a pooled analysis of 3 randomized controlled trials.* Ann Surg 2014 Jan;259(1):139-47 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23598381.
5. ↑ 5.0 5.1 5.2 5.3 5.4 5.5 5.6 5.7 5.8 Braga M, Frasson M, Vignali A, Zuliani W, Capretti G, Di Carlo V. *Laparoscopic resection in rectal cancer patients: outcome and cost-benefit analysis.* Dis Colon Rectum 2007 Apr;50(4):464-71 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17195085.
6. ↑ 6.0 6.1 6.2 6.3 6.4 6.5 6.6 6.7 van der Pas MH, Haglind E, Cuesta MA, Fürst A, Lacy AM, Hop WC, et al. *Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial.* Lancet Oncol 2013 Mar;14(3):210-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23395398.
7. ↑ 7.00 7.01 7.02 7.03 7.04 7.05 7.06 7.07 7.08 7.09 7.10 7.11 7.12 Bonjer HJ, Deijen CL, Haglind E, COLOR II Study Group. *A Randomized Trial of Laparoscopic versus Open Surgery for Rectal Cancer.* N Engl J Med 2015 Jul 9;373(2):194 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26154803.
8. ↑ 8.0 8.1 8.2 8.3 8.4 8.5 8.6 8.7 8.8 Veenhof AA, Sietses C, von Blomberg BM, van Hoogstraten IM, vd Pas MH, Meijerink WJ, et al. *The surgical stress response and postoperative immune function after laparoscopic or conventional total mesorectal excision in rectal cancer: a randomized trial.* Int J Colorectal Dis 2011 Jan;26(1):53-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20922542.
9. ↑ 9.0 9.1 9.2 9.3 Andersson J, Abis G, Gellerstedt M, Angenete E, Angerås U, Cuesta MA, et al. *Patient-reported genitourinary dysfunction after laparoscopic and open rectal cancer surgery in a randomized trial (COLOR II).* Br J Surg 2014 Sep;101(10):1272-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24924798.
10. ↑ 10.0 10.1 10.2 Andersson J, Angenete E, Gellerstedt M, Angerås U, Jess P, Rosenberg J, et al. *Health-related quality of life after laparoscopic and open surgery for rectal cancer in a randomized trial.* Br J Surg 2013 Jun;100(7):941-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23640671.
11. ↑ 11.00 11.01 11.02 11.03 11.04 11.05 11.06 11.07 11.08 11.09 11.10 11.11 11.12 11.13 11.14 11.15 11.16 Ng SS, Lee JF, Yiu RY, Li JC, Hon SS, Mak TW, et al. *Laparoscopic-assisted versus open total mesorectal excision with anal sphincter preservation for mid and low rectal cancer: a prospective, randomized trial.* Surg Endosc 2014 Jan;28(1):297-306 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24013470.

12. ↑ 12.00 12.01 12.02 12.03 12.04 12.05 12.06 12.07 12.08 12.09 12.10 12.11 12.12 12.13 Ng SS, Leung KL, Lee JF, Yiu RY, Li JC, Hon SS. *Long-term morbidity and oncologic outcomes of laparoscopic-assisted anterior resection for upper rectal cancer: ten-year results of a prospective, randomized trial.* Dis Colon Rectum 2009 Apr;52 (4):558-66 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19404053.
13. ↑ 13.00 13.01 13.02 13.03 13.04 13.05 13.06 13.07 13.08 13.09 13.10 13.11 13.12 13.13 13.14 13.15 Ng SS, Leung KL, Lee JF, Yiu RY, Li JC, Teoh AY, et al. *Laparoscopic-assisted versus open abdominoperineal resection for low rectal cancer: a prospective randomized trial.* Ann Surg Oncol 2008 Sep;15(9):2418-25 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18392659.
14. ↑ 14.00 14.01 14.02 14.03 14.04 14.05 14.06 14.07 14.08 14.09 14.10 14.11 14.12 14.13 14.14 14.15 14.16 14.17 14.18 Kang SB, Park JW, Jeong SY, Nam BH, Choi HS, Kim DW, et al. *Open versus laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): short-term outcomes of an open-label randomised controlled trial.* Lancet Oncol 2010 Jul;11(7):637-45 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20610322.
15. ↑ 15.0 15.1 15.2 15.3 15.4 15.5 15.6 Jeong SY, Park JW, Nam BH, Kim S, Kang SB, Lim SB, et al. *Open versus laparoscopic surgery for mid-rectal or low-rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): survival outcomes of an open-label, non-inferiority, randomised controlled trial.* Lancet Oncol 2014 Jun;15(7):767-74 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24837215.
16. ↑ 16.00 16.01 16.02 16.03 16.04 16.05 16.06 16.07 16.08 16.09 16.10 16.11 16.12 Liang X, Hou S, Liu H, Li Y, Jiang B, Bai W, et al. *Effectiveness and safety of laparoscopic resection versus open surgery in patients with rectal cancer: a randomized, controlled trial from China.* J Laparoendosc Adv Surg Tech A 2011 Jun;21(5): 381-5 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21395453.
17. ↑ 17.00 17.01 17.02 17.03 17.04 17.05 17.06 17.07 17.08 17.09 17.10 17.11 17.12 17.13 17.14 17.15 17.16 17.17 17.18 17.19 17.20 Lujan J, Valero G, Hernandez Q, Sanchez A, Frutos MD, Parrilla P. *Randomized clinical trial comparing laparoscopic and open surgery in patients with rectal cancer.* Br J Surg 2009 Sep;96(9):982-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19644973.
18. ↑ 18.0 18.1 18.2 18.3 18.4 18.5 18.6 18.7 Green BL, Marshall HC, Collinson F, Quirke P, Guillou P, Jayne DG, et al. *Long-term follow-up of the Medical Research Council CLASICC trial of conventional versus laparoscopically assisted resection in colorectal cancer.* Br J Surg 2013 Jan;100(1):75-82 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23132548.
19. ↑ 19.0 19.1 Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, et al. *Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial.* Lancet 2005 May;365(9472):1718-26 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15894098.
20. ↑ 20.0 20.1 20.2 20.3 Jayne DG, Brown JM, Thorpe H, Walker J, Quirke P, Guillou PJ. *Bladder and sexual function following resection for rectal cancer in a randomized clinical trial of laparoscopic versus open technique.* Br J Surg 2005 Sep;92(9):1124-32 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15997446.
21. ↑ 21.0 21.1 Jayne DG, Guillou PJ, Thorpe H, Quirke P, Copeland J, Smith AM, et al. *Randomized trial of laparoscopic-assisted resection of colorectal carcinoma: 3-year results of the UK MRC CLASICC Trial Group.* J Clin Oncol 2007 Jul 20;25(21):3061-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17634484.

22. ↑ 22.0 22.1 Taylor GW, Jayne DG, Brown SR, Thorpe H, Brown JM, Dewberry SC, et al. *Adhesions and incisional hernias following laparoscopic versus open surgery for colorectal cancer in the CLASICC trial.* Br J Surg 2010 Jan;97(1):70-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20013936.
23. ↑ 23.0 23.1 23.2 23.3 23.4 23.5 23.6 23.7 23.8 23.9 Zhou ZG, Hu M, Li Y, Lei WZ, Yu YY, Cheng Z, et al. *Laparoscopic versus open total mesorectal excision with anal sphincter preservation for low rectal cancer.* Surg Endosc 2004 Aug;18(8):1211-5 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15457380.
24. ↑ 24.0 24.1 24.2 24.3 24.4 24.5 24.6 24.7 24.8 Arteaga González I, Díaz Luis H, Martín Malagón A, López-Tomassetti Fernández EM, Arranz Duran J, Carrillo Pallares A. *A comparative clinical study of short-term results of laparoscopic surgery for rectal cancer during the learning curve.* Int J Colorectal Dis 2006 Sep;21 (6):590-5 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16292517.
25. ↑ 25.00 25.01 25.02 25.03 25.04 25.05 25.06 25.07 25.08 25.09 25.10 25.11 25.12 Fleshman J, Branda M, Sargent DJ, Boller AM, George V, Abbas M, et al. *Effect of Laparoscopic-Assisted Resection vs Open Resection of Stage II or III Rectal Cancer on Pathologic Outcomes: The ACOSOG Z6051 Randomized Clinical Trial.* JAMA 2015 Oct 6;314(13):1346-55 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26441179.
26. ↑ 26.0 26.1 26.2 26.3 26.4 26.5 26.6 26.7 Fujii S, Ishibe A, Ota M, Yamagishi S, Watanabe K, Watanabe J, et al. *Short-term results of a randomized study between laparoscopic and open surgery in elderly colorectal cancer patients.* Surg Endosc 2014 Feb;28(2):466-76 Available from: http://www.ncbi.nlm.nih.gov/pubmed /24122242.
27. ↑ 27.0 27.1 27.2 27.3 27.4 27.5 27.6 27.7 Stevenson AR, Solomon MJ, Lumley JW, Hewett P, Clouston AD, Gebski VJ, et al. *Effect of Laparoscopic-Assisted Resection vs Open Resection on Pathological Outcomes in Rectal Cancer: The ALaCaRT Randomized Clinical Trial.* JAMA 2015 Oct 6;314(13):1356-63 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26441180.
28. ↑ 28.00 28.01 28.02 28.03 28.04 28.05 28.06 28.07 28.08 28.09 28.10 28.11 28.12 28.13 28.14 28.15 28.16 Gong J, Shi DB, Li XX, Cai SJ, Guan ZQ, Xu Y. *Short-term outcomes of laparoscopic total mesorectal excision compared to open surgery.* World J Gastroenterol 2012 Dec 28;18(48):7308-13 Available from: http://www. ncbi.nlm.nih.gov/pubmed/23326138.
29. ↑ 29.0 29.1 29.2 Pecorelli N, Amodeo S, Frasson M, Vignali A, Zuliani W, Braga M. *Ten-year outcomes following laparoscopic colorectal resection: results of a randomized controlled trial.* Int J Colorectal Dis 2016 Jul;31(7):1283-90 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27090804.
30. ↑ 30.0 30.1 30.2 30.3 Chen YY, Liu ZH, Zhu K, Shi PD, Yin L. *Transanal endoscopic microsurgery versus laparoscopic lower anterior resection for the treatment of T1-2 rectal cancers.* Hepatogastroenterology 2013 Jun;60(124):727-32 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23159393.
31. ↑ 31.0 31.1 31.2 31.3 31.4 31.5 Lezoche E, Baldarelli M, Lezoche G, Paganini AM, Gesuita R, Guerrieri M. *Randomized clinical trial of endoluminal locoregional resection versus laparoscopic total mesorectal excision for T2 rectal cancer after neoadjuvant therapy.* Br J Surg 2012 Sep;99(9):1211-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22864880.
32. ↑ 32.0 32.1 32.2 32.3 32.4 Lezoche E, Guerrieri M, Paganini AM, D'Ambrosio G, Baldarelli M, Lezoche G, et al. *Transanal endoscopic versus total mesorectal laparoscopic resections of T2-N0 low rectal cancers after neoadjuvant treatment: a prospective randomized trial with a 3-years minimum follow-up period.* Surg Endosc 2005 Jun;19(6):751-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15868260.

33. ↑ 33.0 33.1 33.2 33.3 33.4 33.5 Lezoche G, Baldarelli M, Guerrieri M, Paganini AM, De Sanctis A, Bartolacci S, et al. *A prospective randomized study with a 5-year minimum follow-up evaluation of transanal endoscopic microsurgery versus laparoscopic total mesorectal excision after neoadjuvant therapy.* Surg Endosc 2008 Feb;22(2):352-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17943364.
34. ↑ 34.0 34.1 34.2 34.3 34.4 34.5 34.6 Bulut O, Aslak KK, Levic K, Nielsen CB, Rømer E, Sørensen S, et al. *A randomized pilot study on single-port versus conventional laparoscopic rectal surgery: effects on postoperative pain and the stress response to surgery.* Tech Coloproctol 2015 Jan;19(1):11-22 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25380743.
35. ↑ 35.0 35.1 35.2 35.3 35.4 35.5 35.6 Han JG, Wang ZJ, Wei GH, Gao ZG, Yang Y, Zhao BC. *Randomized clinical trial of conventional versus cylindrical abdominoperineal resection for locally advanced lower rectal cancer.* Am J Surg 2012 Sep;204(3):274-82 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22920402.
36. ↑ 36.0 36.1 Huang J, Lu ZS, Yang YS, Yuan J, Wang XD, Meng JY, et al. *Endoscopic mucosal resection with circumferential incision for treatment of rectal carcinoid tumours.* World J Surg Oncol 2014 Jan 28;12:23 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24472342.
37. ↑ 37.0 37.1 37.2 Chen Y, Guo R, Xie J, Liu Z, Shi P, Ming Q. *Laparoscopy Combined With Transanal Endoscopic Microsurgery for Rectal Cancer: A Prospective, Single-blinded, Randomized Clinical Trial.* Surg Laparosc Endosc Percutan Tech 2015 Oct;25(5):399-402 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26429049.
38. ↑ 38.00 38.01 38.02 38.03 38.04 38.05 38.06 38.07 38.08 38.09 38.10 38.11 38.12 Liu FL, Lin JJ, Ye F, Teng LS. *Hand-assisted laparoscopic surgery versus the open approach in curative resection of rectal cancer.* J Int Med Res 2010 May;38(3):916-22 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20819427.
39. ↑ 39.0 39.1 39.2 Jayne DG, Thorpe HC, Copeland J, Quirke P, Brown JM, Guillou PJ. *Five-year follow-up of the Medical Research Council CLASICC trial of laparoscopically assisted versus open surgery for colorectal cancer.* Br J Surg 2010 Nov;97(11):1638-45 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20629110.

Back to top

13.2.2.7 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search

View PICO	NHMRC Evidence statement form COL1-2b	Systematic review report COL1-2b

Back to top

13.2.3 Local versus radical resection for T1-T2 rectal tumours (REC3)

Contents

13.2.3.1 Systematic review evidence

In patients diagnosed with stage I-II rectal cancer, what is the most effective treatment strategy to achieve the best outcomes in terms of length and quality of life?

A systematic review was performed to compare the effects of local resection (with or without radiotherapy or chemotherapy) and radical resection (with or without radiotherapy or chemotherapy) on outcomes including survival, local recurrence rates, quality of life, adverse events and stoma rates.

The search identified two relevant guidelines for which systematic reviews were conducted, published by the Belgian Health Care Knowledge Centre (KCE)[1] and the United Kingdom National Institute for Health and Care Excellence (NICE).[2] A systematic review was performed to update the search results with relevant literature published after the cut-off dates.

The KCE guideline[1] reported systematic reviews and meta-analyses of level III-1 evidence, each with a low risk of bias, examining the effects of local versus radical resections on early stage colorectal cancer related outcomes:[3][4]

- a systematic review and meta-analysis comparing local resection with radical resection for patients with T1N0M0 rectal adenocarcinoma,[3] which included results (n = 2855) from twelve level III 2 observational studies and one level II randomised controlled trial (RCT)
- a systematic review and meta-analysis comparing local excision with radical surgery after neoadjuvant chemoradiotherapy for rectal cancer,[4] which included six level III-2 observational studies and one level II RCT.

Both these systematic reviews were reported as having a low risk of bias, with scores of 8,[3] and 9,[4] out of 11 on the AMSTAR risk of bias checklist.

Three level II RCTs[5][6][7] were also included in the KCE guideline review. One of these studies[5] was reported to be at high overall risk of bias. Assessment of bias was not reported for the other two RCTs.

The NICE guideline[2] reported four level III-1 observational studies comparing local versus radical resection strategies.[8][9][10][11] Two of these studies were reported as having a serious risk of bias,[8][9] one had a very serious risk of bias,[11] and one had no serious risk of bias.[10]

The updated systematic review of those undertaken for the KCE and NICE guidelines identified one additional systematic review and meta-analysis,[12] which included one RCT and six observational studies. This review had a low risk of bias.

The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

Back to top

13.2.3.1.1 Overall survival

Two systematic reviews and meta-analyses included in the KCE guideline[1] reported the effects of resection type on mortality and survival outcomes. A meta-analysis of 12 observational studies (n = 2,855) reported that 5-year overall survival was significantly higher for local resection patients, compared with radical resection patients (relative risk [RR] 1.46; 95% CI 1.19 to 1.77, p = 0.0002), with RRs ranging from 0.11 to 2.87 reported by each included study for the comparison of local vs radical resections.[3]

In an analysis of seven pooled observational studies conducted in T1 patients, transanal endoscopic microsurgery was associated with a nonsignificant reduction in overall survival, compared with total mesorectal excision (odds ratio [OR] 0.87; 95% CI 0.55 to 1.38).[12]

A retrospective observational study in patients with T1 or T2 N0M0 rectal adenocarcinoma (n = 153),[13] reported that 3-year overall survival among T1 patients did not differ between local excision and total mesorectal excision groups (100%). Among T2 patients, there was a nonsignificant increase in 3-year overall survival in the total mesorectal excision group (90%), compared with the local excision group (76.9%).[13]

Overall, evidence showed mixed and mostly nonsignificant differences in survival and mortality rates between local and radical resection patients.

Back to top

13.2.3.1.2 Disease-free survival

One meta-analysis study[3] observed the radical resection as group having a significantly higher 5 year disease free survival in comparison to local resection group, (RR 1.54; CI 1.15-2.05, p=0.003). However, this effect may be explained by the increased use of local resection on tumours in the lower third of the rectum, which have poorer prognosis. One retrospective observational study[13] reported that, among T1 patients, local excision was associated with a nonsignificant reduction in 3-year disease-free survival, compared with total mesorectal excision (84.21% versus 94.9%). Among T2 patients, 3-year disease-free survival was significantly lower in the local excision group, compared with the total mesorectal excision group (61.5% versus 87.5%; p = 0.44).[13]

Other studies that reported disease-free survival[4][12] found only negligible differences between local and radical resection groups.

Back to top

13.2.3.1.3 Local recurrence

The majority of studies reported higher rates of local recurrence in the local resection group. One systematic review and meta-analysis[3] reported that local resection was associated with significantly higher rates of local recurrence than radical resection (RR 2.36; 95% CI 1.64 to 3.39). Another systematic review and meta-analysis [4] reported that local excision was associated with a nonsignificant increase in local recurrence, compared with radical excision (10.1% versus 8%; OR 1.29; 95% CI 0.72 to 2.31).

A RCT found that 5-year local recurrence rate did not differ significantly between transanal endoscopic microsurgery and total mesorectal excision groups for T1 stage patients (p = 0.94), but local recurrence was significantly higher in the transanal endoscopic microsurgery group than the total mesorectal excision (96.1% versus 94.7%; p = 0.035) for T2 patients.[8]

Both the KCE and NICE guidelines stated that there was no good evidence to suggest that local resection does not harm by leading to increased local recurrence or metastases.[1][2] Across the studies, there was generally no clear difference in recurrence rate between treatment groups, and local recurrence rates were low in both groups. The only exception was a large observational study of data from a cancer registry which reported that, among the subgroup of patients with T2 tumours, transanal endoscopic microsurgery was associated with a higher local recurrence rate than total mesorectal excision.[11]

Back to top

13.2.3.1.4 Postoperative complications

The KCE guideline states that major post-operative complications and peri-operative deaths are less frequent following local resection than radical resection.[1] Only one systematic review and one RCT examined postoperative complications as an outcome, revealing two different findings.[3][6] The systematic review and meta-analysis reported that the risk of post-operative complications was significantly lower for the local resection group, compared with the radical resection group, both for the total number of all postoperative complications (RR 0.16; 95% CI 0.08 to 0.30) and for major postoperative complications (RR 0.20; 95% CI 0.10 to 0.41).[3] In contrast, a small (n=35) comparative study observed an equal percentage of minor and major postoperative complications in both endoluminal locoregional resection and total mesorectal excision groups.[6]

13.2.3.1.5 Stoma formation and quality of life

The KCE guideline states that the benefits of local resection are less blood loss, a lower rate of permanent stoma, and shorter hospital stay. A systematic review and meta-analysis reported that the rate of lower stoma formation was lower for local resection, compared with radical resection (RR 0.17: 95% CI 0.09 to 0.30).[3]

Back to top

13.2.3.2 Evidence summary and recommendations

Evidence summary	Level	References
There is limited evidence comparing local versus radical excision for early-stage (T1 to T2) rectal cancer in the Australasian population.	II, III-1	[3], [4], [5], [7], [8], [10], [11], [12], [13]
Evidence for overall survival showed inconsistent and mostly nonsignificant differences in relation to survival and mortality rates between local and radical resection patients.	II, III-1	[3], [4], [5], [7], [8], [10], [11], [12], [13]
There were negligible differences in disease-free survival rates between local and radical resection groups.	II, III-1	[3], [4], [5], [7], [8], [10], [11], [12], [13]
Local recurrence rates were higher for patients undergoing local excision, compared with radical resection, particularly among those with T2 stage tumours. Local recurrence rates did not differ between patients undergoing transanal endoscopic microsurgery and those undergoing transanal local excision.	II, III-1	[3], [4], [5], [7], [8], [10], [11], [12], [13]

Evidence summary	Level	References
The rate of distant metastases was similar between local excision and radical resection.	II, III-1	[3], [4], [5], [7], [8], [10], [11], [12], [13]
Major postoperative complications and peri-operative mortality were less frequent following local resection than radical excision. Operative blood loss, permanent stoma rate and hospital stay were all reduced with local excision, compared with radical resection.	II, III-1	[3], [4], [5], [7], [8], [10], [11], [12], [13]

Back to top

Evidence-based recommendation	Grade
For patients with stage 1 rectal cancer (T1/2, N0, M0), cases should be discussed by a multidisciplinary team to determine optimal management with respect to risk of local recurrence, avoidance of a permanent stoma, and fitness for surgery.	**C**

Evidence-based recommendation	Grade
Local excision may be considered for T1 tumours, provided they can be removed with clear margins. However, patients should be counselled that the risk of local recurrence increases as the T1 tumour stage progresses from T1sm1 to T1sm2 to T1sm3, respectively. The treating clinician should also explain to the patient that radical resection may be required after histopathological review of the local excision specimen.	**D**

Evidence-based recommendation	Grade
Radical resection should be recommended for patients with T2 tumours if they are fit for surgery.	**C**

Practice point

When determining the optimal management strategy for each patient, the multidisciplinary team, treating clinician and patient should discuss the balance of risks (e.g. local recurrence) and benefits (e.g. avoidance of a permanent stoma), with consideration of the individual's fitness for surgery. The treating clinician should explain to the patient that local excision carries a lower risk of perioperative mortality and a lower permanent stoma rate, but is associated with a higher local recurrence rate, which increases as the depth of tumour invasion increases from T1sm1 to T1sm2 to T1sm3 to T2.

Practice point

Radical resection is recommended for patients with T1sm3 tumours, and for those with T2 tumours who are considered fit for radical surgery.

Practice point

The use of transanal endoscopic microsurgery or transanal minimally invasive surgery has not shown any significant advantages over transanal local excision, however it is essential to obtain clear resection margins and the choice of approach to local resection should be determined by the individual surgeon with this factor in mind.

Practice point

Application of radiotherapy before or after local excision of rectal cancer may reduce the risk of local recurrence. However, it may have an adverse effect on bowel function.

13.2.3.2.1 Considerations in making these recommendations

For local excision, the rate of local recurrence increases as the depth of tumour invasion increases from T1sm1 to T1sm2 to T1sm3 to T2. T1sm3 tumours are associated with a significant increase in local recurrence, so this tumour stage may be considered the tipping point for radical resection.

Back to top

13.2.3.3 Health system implications

13.2.3.3.1 Clinical practice

The guidance will not change the way that care is currently organised.

13.2.3.3.2 Resourcing

Implementation of this recommendation would have no significant resource implications.

13.2.3.3.3 Barriers to implementation

No barriers to the implementation of this recommendation are foreseen.

Back to top

13.2.3.4 Discussion

13.2.3.4.1 Unresolved issues

The role of neoadjuvant or neoadjuvant radiotherapy, with or without chemotherapy, as an adjunct to local excision of early rectal cancer, remains undetermined.

Determination and individualisation of approach also remains uncertain and there is a lack of evidence to make a definitive decision.

13.2.3.4.2 Studies currently underway

No relevant current studies have been identified that would be expected to provide more evidence on this topic.

13.2.3.4.3 Future research priorities

Further high-level studies comparing local versus radical excision for early-stage rectal cancer could provide evidence about long-term survival and recurrence.

Back to top

13.2.3.5 References

1. ↑ [1.0] [1.1] [1.2] [1.3] [1.4] Peeters MVC, E.; Bielen, D. et al.. *Guideline on the management of rectal cancer: update of capita selecta – Part 3: Local vs Radical resection for stage 1 tumours. Good Clinical Practice (GCP). KCE Reports 260. D/2016/10.273/11. Brussels: Belgian Health Care Knowledge Centre (KCE); 2016.* ;.

2. ↑ 2.0 2.1 2.2 National Institute for Health and Care Excellence. *Colorectal cancer: The Diagnosis and Management of colorectal cancer.* United Kingdom: National Institute for Health and Care Excellence; 2014.
3. ↑ 3.00 3.01 3.02 3.03 3.04 3.05 3.06 3.07 3.08 3.09 3.10 3.11 3.12 3.13 3.14 Kidane B, Chadi SA, Kanters S, Colquhoun PH, Ott MC. *Local resection compared with radical resection in the treatment of T1N0M0 rectal adenocarcinoma: a systematic review and meta-analysis.* Dis Colon Rectum 2015 Jan;58(1):122-40 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25489704.
4. ↑ 4.00 4.01 4.02 4.03 4.04 4.05 4.06 4.07 4.08 4.09 4.10 Shaikh I, Askari A, Ourû S, Warusavitarne J, Athanasiou T, Faiz O. *Oncological outcomes of local excision compared with radical surgery after neoadjuvant chemoradiotherapy for rectal cancer: a systematic review and meta-analysis.* Int J Colorectal Dis 2015 Jan; 30(1):19-29 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25367179.
5. ↑ 5.0 5.1 5.2 5.3 5.4 5.5 5.6 5.7 Chen YY, Liu ZH, Zhu K, Shi PD, Yin L. *Transanal endoscopic microsurgery versus laparoscopic lower anterior resection for the treatment of T1-2 rectal cancers.* Hepatogastroenterology 2013 Jun;60(124):727-32 Available from: http://www.ncbi.nlm.nih.gov/pubmed /23159393.
6. ↑ 6.0 6.1 6.2 Lezoche E, Baldarelli M, Lezoche G, Paganini AM, Gesuita R, Guerrieri M. *Randomized clinical trial of endoluminal locoregional resection versus laparoscopic total mesorectal excision for T2 rectal cancer after neoadjuvant therapy.* Br J Surg 2012 Sep;99(9):1211-8 Available from: http://www.ncbi.nlm. nih.gov/pubmed/22864880.
7. ↑ 7.0 7.1 7.2 7.3 7.4 7.5 7.6 Winde G, Nottberg H, Keller R, Schmid KW, Bünte H. *Surgical cure for early rectal carcinomas (T1). Transanal endoscopic microsurgery vs. anterior resection.* Dis Colon Rectum 1996 Sep;39 (9):969-76 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8797643.
8. ↑ 8.0 8.1 8.2 8.3 8.4 8.5 8.6 8.7 8.8 Lee W, Lee D, Choi S, Chun H. *Transanal endoscopic microsurgery and radical surgery for T1 and T2 rectal cancer.* Surg Endosc 2003 Aug;17(8):1283-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/12739119.
9. ↑ 9.0 9.1 Lezoche E, Paganini AM, Fabiani B, Balla A, Vestri A, Pescatori L, et al. *Quality-of-life impairment after endoluminal locoregional resection and laparoscopic total mesorectal excision.* Surg Endosc 2014 Jan;28(1):227-34 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24002918.
10. ↑ 10.0 10.1 10.2 10.3 10.4 10.5 10.6 10.7 Palma P, Horisberger K, Joos A, Rothenhoefer S, Willeke F, Post S. *Local excision of early rectal cancer: is transanal endoscopic microsurgery an alternative to radical surgery?* Rev Esp Enferm Dig 2009 Mar;101(3):172-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed /19388797.
11. ↑ 11.0 11.1 11.2 11.3 11.4 11.5 11.6 11.7 11.8 Saraste D, Gunnarsson U, Janson M. *Local excision in early rectal cancer-outcome worse than expected: a population based study.* Eur J Surg Oncol 2013 Jun;39(6):634-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23414776.
12. ↑ 12.0 12.1 12.2 12.3 12.4 12.5 12.6 12.7 12.8 Lu JY, Lin GL, Qiu HZ, Xiao Y, Wu B, Zhou JL. *Comparison of Transanal Endoscopic Microsurgery and Total Mesorectal Excision in the Treatment of T1 Rectal Cancer: A Meta-Analysis.* PLoS One 2015;10(10):e0141427 Available from: http://www.ncbi.nlm.nih.gov/pubmed /26505895.
13. ↑ 13.0 13.1 13.2 13.3 13.4 13.5 13.6 13.7 13.8 13.9 Elmessiry MM, Van Koughnett JA, Maya A, DaSilva G, Wexner SD, Bejarano P, et al. *Local excision of T1 and T2 rectal cancer: proceed with caution.* Colorectal Dis 2014 Sep;16(9):703-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24787457.

Back to top

13.2.3.6 Appendices

View recommendation components | View pending evidence | View body of evidence | View all comments | View literature search

View PICO | NHMRC Evidence statement form REC3 | Systematic review report REC3

Back to top

13.3 Emergency management of malignant large bowel obstruction (COLMNG5)

Contents

Back to top

13.3.1 Background

Malignant large bowel obstruction occurs in up to 20% of patients with colorectal cancer.[1] It is a significant cause of mortality among patients with colorectal cancer; up to 25% of all postoperative deaths are associated with malignant bowel obstruction.[2] It is also associated with significant morbidity, including a high probability of receiving a stoma.

Patients with malignant large bowel obstruction may be candidates for curative treatment or palliative treatment. Due to the increased availability of computed tomography (CT), patients' status is often known prior to therapeutic intervention.

Given that this malignant large bowel obstruction is common, patients with this problem can present to any hospital that has emergency admissions. There has been a long debate over the best approach to left-sided malignant large bowel obstruction, predominantly focused on restorative procedures, versus non-restorative procedures which result in an end colostomy. The advent of self-expanding metallic stents (SEMS) has added a further management option to the mix.

Back to top

13.3.2 Systematic review evidence

In patients diagnosed with colorectal cancer and acute obstruction, does stenting or colostomy achieve equivalent or better outcomes, compared to acute resection with primary anastomosis?

A systematic review was undertaken to evaluate outcomes following stenting or colostomy in patients with acute large bowel obstruction, compared with acute resection plus primary anastomosis. Two randomised controlled trials (RCTs) were identified that compared (1) the use of temporary stents, followed by an elective surgery with (2) acute resection with primary anastomosis.[3][4] All participants were patients who presented with left-sided colonic cancer as confirmed by CT. Acute resections consisted of either a colectomy[4] or a left hemicolectomy, sigmoid colectomy or a high anterior resection.[3] The median follow-up period in these RCTs ranged from 18 months[4] to 37.6 months.[3]

Both trials were at high risk of bias, as the blinding processes were not reported.[3][4] The first[3] provided minimal description of the randomisation process, and the trial was terminated early due to a high rate of complications in the comparator group.

The studies are heterogeneous, small in sample size and empirical results vary in significance. Outcomes reported varied between trials. Overall, RCT evidence on which to evaluate the use of stents in curative obstructive colorectal patients is limited.[3][4]

Two RCTs comparing preoperative stenting versus emergency surgery for acute left sided obstruction were prematurely closed because of adverse outcomes in the stenting group, namely tumour perforation, in the stent group.[5][6] These RCTs were therefore excluded from the systematic review.

The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

Back to top

13.3.2.1 Perioperative morbidity and adverse events

13.3.2.1.1 Overall morbidity

A Spanish RCT (n = 28) reported that stenting was associated with a significant (p=0.042) benefit for overall morbidity.[3]

An Egyptian RCT (n = 60) also reported that stenting was associated with a significant reduction in morbidity. Stenting patients lost less blood (p = 0.010) and required fewer blood transfusions (p = 0.035) and fewer fresh frozen plasma infusions (p = 0.010) intraoperatively.[4] The stenting group also showed significantly fewer median bowel motions per day (p = 0.013) at 3 months' follow-up,[4] but this was no longer significant at 6 months' follow-up.

13.3.2.1.2 Anastomotic leakage

In both studies, patients who received stents did not experience any anastomotic leakage within the trial period.[3][4] In the smaller study, the rate of anastomotic dehiscence was significantly lower (p=0.035) in the stenting group than the emergency primary anastomosis group,[3] but in the larger study there was no statistically significant difference in the rate of anastomotic leakage between groups.[4]

Back to top

13.3.2.1.3 Wound infections

The larger study reported that significantly fewer patients presented with wound infections in the stenting group, compared with the acute resection group (10% versus 30%; p = 0.022).[4] The smaller study reported a numerically lower rate of surgical space infections in the stenting group than the resection and anastomosis group, but the difference was not statistically significant overall.[3] The variation of significance may be due to small sample sizes.

13.3.2.1.4 Other morbidity

Neither study reported stent-related technical complications such as perforation, bleeding or stent migration. The clinical implications of this is unknown, as it was not analysed further in either trial.

The larger study reported that chest infections occurred less frequently in those with stents than those with acute resection and anastomosis, but this difference was not statistically significant ($p = 0.098$).[4] The smaller study reported a significantly higher rate of reoperations within the overall follow-up period among those who underwent acute resection, compared with those who received stents (approximately 31% versus zero; $p = 0.035$).[3]

Back to top

13.3.2.1.5 Length of hospital stay

Both trials reported longer hospital stays for those in the stenting group than the acute resection and anastomosis group, although this difference was not statistically significant.[3][4] The smaller study reported that mean postoperative stay was significantly shorter for the stenting group.[3]

13.3.2.1.6 Perioperative mortality

Both trials reported no mortality as a result of the stenting procedure.[3][4] However, the statistical significance of this was either not reported on[4] or found to be not statistically significant.[3]

13.3.2.1.7 Overall survival

The smaller study reported that approximately 58% of patients who received stents, and approximately 70% of those who received acute resections, survived at the end of 59 months of follow up.[3] However, this difference was not statistically significant ($p = 0.843$).

Back to top

13.3.3 Evidence summary and recommendations

Evidence summary	Level	References
Patients who received stents before an elective surgery showed reduced perioperative morbidity than those who underwent emergency resection and anastomosis.	II	[3], [4]
Two RCTs were prematurely closed because of adverse outcomes, namely tumour perforation, in the stent group.	N/A	[5], [6]

Evidence summary	Level	References
The benefits of stenting on perioperative mortality rates and length of hospital stays were inconclusive.	II	[3], [4]
There is weak evidence that the use of stents may reduce the risk of adverse events in colorectal cancer patients with cases of curative obstruction.	II	[3], [4]
The trials did not report complications of stent migration, perforation or bleeding.	N/A	[3], [4]
The studies did not report 5-year survival, cancer-specific survival, stoma rate or quality of life as outcomes.	N/A	[3], [4]

Back to top

Evidence-based recommendation	Grade
In patients with acute obstruction due to left-sided colorectal cancer who are potentially curative, the use of stenting as a bridge to surgery is not recommended as standard treatment, due to the potential risk of tumour perforation and conversion of a curative case to a palliative case.	**D**

Consensus-based recommendation

The insertion of an intraluminal colonic stent can be considered in large bowel obstruction secondary to colorectal cancer as palliation to relieve large bowel obstruction in patients with incurable metastatic colorectal cancer.

Consensus-based recommendation

For patients with potentially curable left-sided obstructing colonic cancer who are considered to be at increased risk of post-operative mortality, stent placement may be considered as an alternative to emergency surgery.

Consensus-based recommendation

If stenting is considered, it should be discussed by the multidisciplinary team and implications for anti-VEGF systemic therapy should be assessed.

Back to top

13.3.4 Considerations in making these recommendations

Randomised controlled trials demonstrate no specific benefit from stenting as compared to primary surgery. There is a recognised incidence of local tumour perforation from stenting, which may convert a curative case to a potentially palliative case. Whilst this has not demonstrated reduced long-term survival, two large randomised controlled trials were closed early as a result of this.[5][6] Hence, insertion of a stent as a bridge to surgery cannot be recommended in curative cases unless the patient is considered unfit for major surgery.

There does appear to be a role for insertion of a stent to relieve obstruction as a palliative procedure, if the technical skill is available. This approach might reduce the incidence of stoma formation and avoid the requirement of surgery in a proportion of cases in which metastatic colorectal cancer is incurable or where patients considered unfit for major surgery. However, the use of anti-VEGF systemic therapy may be contraindicated in the presence of a stent, as there is evidence that the risk of perforation is increased.[7][8] Balancing the potential long term benefits on survival of anti-VEGF agents versus stenting or surgery, the later removing the risk of perforation and allowing anti-VEGF therapy to subsequently proceed, should therefore be discussed in this situation.

Back to top

13.3.5 Health system implications

13.3.5.1 Clinical practice

These recommendations would potentially necessitate the increased availability of the expertise to insert SEMS. However, this expertise is already established in clinical practice, so the recommendation would not require a change to the way that care is currently organised.

13.3.5.2 Resourcing

Increased application of stenting will require increased availability of personnel with the technical ability to insert a colonic stent, particularly if it is to be used out of routine hours. This could be colorectal surgeons or gastroenterologists. However, it may be challenging in smaller centres.

13.3.5.3 Barriers to implementation

No barriers to the implementation of these recommendations are envisaged.

Back to top

13.3.6 Discussion

13.3.6.1 Unresolved issues

Currently, there are no RCTs comparing outcomes of colostomies or Hartmann's Procedure with those of resections, or comparing colectomies with anastomosis.

In patients with curative obstructive colorectal cancer, the use of stents as an alternative to primary resection remains undecided. More evidence is required to demonstrate a concrete benefit over acute resection with primary anastomosis.

13.3.6.2 Studies currently underway

No relevant major RCTs are awaited. Publication of findings from the CReST study,[9] the largest multicentre cohort study yet completed, may address endpoints other than survival, such as avoidance of a permanent stoma.

13.3.6.3 Future research priorities

Further evidence is required to determine the role of stenting in palliative cases.

Back to top

13.3.7 References

1. ↑ Irvin TT, Greaney MG. *The treatment of colonic cancer presenting with intestinal obstruction.* Br J Surg 1977 Oct;64(10):741-4 Available from: http://www.ncbi.nlm.nih.gov/pubmed/922296.
2. ↑ Mella J, Biffin A, Radcliffe AG, Stamatakis JD, Steele RJ. *Population-based audit of colorectal cancer management in two UK health regions. Colorectal Cancer Working Group, Royal College of Surgeons of England Clinical Epidemiology and Audit Unit.* Br J Surg 1997 Dec;84(12):1731-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/9448628.
3. ↑ 3.00 3.01 3.02 3.03 3.04 3.05 3.06 3.07 3.08 3.09 3.10 3.11 3.12 3.13 3.14 3.15 3.16 3.17 3.18 3.19 3.20 Alcántara M, Serra-Aracil X, Falcó J, Mora L, Bombardó J, Navarro S. *Prospective, controlled, randomized study of intraoperative colonic lavage versus stent placement in obstructive left-sided colonic cancer.* World J Surg 2011 Aug;35(8):1904-10 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21559998.
4. ↑ 4.00 4.01 4.02 4.03 4.04 4.05 4.06 4.07 4.08 4.09 4.10 4.11 4.12 4.13 4.14 4.15 4.16 4.17 4.18 Ghazal AH, El-Shazly WG, Bessa SS, El-Riwini MT, Hussein AM. *Colonic endolumenal stenting devices and elective surgery versus emergency subtotal/total colectomy in the management of malignant obstructed left colon carcinoma.* J Gastrointest Surg 2013 Jun;17(6):1123-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23358847.

5. ↑ 5.0 5.1 5.2 Pirlet IA, Slim K, Kwiatkowski F, Michot F, Millat BL. *Emergency preoperative stenting versus surgery for acute left-sided malignant colonic obstruction: a multicenter randomized controlled trial.* Surg Endosc 2011 Jun;25(6):1814-21 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21170659.
6. ↑ 6.0 6.1 6.2 van Hooft JE, Bemelman WA, Oldenburg B, Marinelli AW, Lutke Holzik MF, Grubben MJ, et al. *Colonic stenting versus emergency surgery for acute left-sided malignant colonic obstruction: a multicentre randomised trial.* Lancet Oncol 2011 Apr;12(4):344-52 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21398178.
7. ↑ van Halsema EE, van Hooft JE, Small AJ, Baron TH, García-Cano J, Cheon JH, et al. *Perforation in colorectal stenting: a meta-analysis and a search for risk factors.* Gastrointest Endosc 2014 Jun;79(6):970-82.e7; quiz 983.e2, 983.e5 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24650852.
8. ↑ Imbulgoda A, MacLean A, Heine J, Drolet S, Vickers MM. *Colonic perforation with intraluminal stents and bevacizumab in advanced colorectal cancer: retrospective case series and literature review.* Can J Surg 2015 Jun;58(3):167-71 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25799132.
9. ↑ Hill J KC, Morton D, Magill L, Handley K, Gray RG, et al. *CREST: Randomised phase III study of stenting as a bridge to surgery in obstructing colorectal cancer—Results of the UK ColoRectal Endoscopic Stenting Trial (CREST). Proceedings of the American Society of Clinical Oncology Annual Meeting; 2016 Jun 3-7. Chicago (IL).*;.

Back to top

13.3.8 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search

View PICO	NHMRC Evidence statement form COLMNG5	Systematic review report COLMNG5

Back to top

13.4 Peritonectomy with hyperthermic intraperitoneal chemotherapy (COLMNG3)

Contents

13.4.1 Background

Peritoneal metastases are present synchronously in 5–10% of patients at the time of diagnosis of primary colorectal cancer. They may also occur metachronously following treatment of the primary colorectal cancer. Because peritoneal carcinomatosis is associated with a poor prognosis, a conservative surgical approach has traditionally been adopted, consisting of limited resection (with or without the formation of a defunctioning stoma) followed by palliative chemotherapy.

In recent years, there has been emerging evidence that cytoreductive surgery followed by intraperitoneal chemotherapy may improve survival. However, cytoreductive surgery and intraperitoneal chemotherapy can be associated with considerable perioperative mortality and morbidity, and are highly specialised procedures that are currently only available at selected centres with the requisite expertise.

Back to top

13.4.2 Systematic review evidence

For patients diagnosed with colorectal cancer and peritoneal involvement or isolated peritoneal recurrence of colorectal cancer, does peritonectomy, with or without perioperative intraperitoneal chemotherapy (PIC), achieve better outcomes in terms of length and quality of life than usual care?

A systematic review was undertaken to determine the role of cytoreductive surgery, with or without perioperative intraperitoneal chemotherapy, by comparing it with usual care (limited resection or no resection with or without stoma and/or palliative chemotherapy) in patients with synchronous or metachronous peritoneal metastases from primary colorectal cancer.

The systematic review identified four studies comparing the combination of cytoreductive surgery and perioperative intraperitoneal chemotherapy with usual care.[1][2][3][4] All patients had histologically proven peritoneal carcinomatosis from a primary colorectal cancer. All studies included both patients with primary peritoneal carcinomatosis and patients with metachronous peritoneal carcinomatosis. Two of the four studies[2][4] also included patients with adenocarcinoma of the appendix, for which the role of cytoreductive surgery and perioperative intraperitoneal chemotherapy is well established. However, appendiceal cancers comprised only 15% and 17.5% of these study cohorts[2][4] and inclusion of these studies did not alter the outcomes of the systematic review.

All studies were at high risk of bias.[1][2][3][4] All studies were also heterogeneous with a variable number of patients with synchronous and metachronous peritoneal metastases. Different disease staging systems were used across the studies, which made comparisons of outcomes across studies more difficult.[1][2][3][4] Intraperitoneal chemotherapy regimens vary considerably in their timing and the chemotherapy agents used. Variations in regimens both within and between studies further complicated comparisons of outcomes between studies. Median follow up ranged from 17 months to 94 months.

Two randomised controlled trials (RCTs) were identified:

- The Swedish peritoneal study[2] (n = 48) compared cytoreduction plus sequential postoperative intraperitoneal chemotherapy (n = 24) with systemic chemotherapy (n = 24). In the cytoreduction group, 21 patients also received intraperitoneal chemotherapy, while the other three patients only underwent cytoreductive surgery. Complete cytoreduction was achieved in 14 (58%) of patients. Five patients (21%) had no residual nodules greater than 2.5 mm (completeness of cytoreduction [CCR] score of 1), two patients (8%) had residual disease with nodules less than 25 mm (CCR2), and three patients (13%) had residual disease with nodules greater than 25 mm (CCR3). Patients in the chemotherapy arm received 5-FU, leucovorin and oxaliplatin. Although the authors had planned for a sample size of 100, the study was terminated prematurely after 7 years because of slow accrual.

- A Dutch RCT[4] (n = 105) compared the combination of cytoreduction surgery, HIPEC and postoperative adjuvant chemotherapy (n = 54) with systemic chemotherapy using 5-FU and leucovorin (n = 51). Of the cytoreduction group, 41% achieved complete cytoreduction but 41% and 18% respectively had what the authors described as R2-a and R2-b resection (macroscopic residual disease).

Two cohort studies were identified:

- A multicentre retrospective cohort study[3] (n = 294) compared cytoreductive surgery plus perioperative intraperitoneal chemotherapy with limited resection (with or without palliative chemotherapy). The sample included 18 patients (6.1%) with stage I disease, 111 (37.8%) with stage II disease, 46 (15.6%) with stage III disease, and 119 (40.5%) with stage IV disease, graded according to peritoneal surface disease severity score. Complete cytoreduction was achieved in 65% of patients, while 25% of patients had CCR1 and 10% had CCR2 or CCR3. Of the 110 patients in the cytoreduction group, 55 (45%) received HIPEC, 19 (17%) received early postoperative intraperitoneal chemotherapy, and 36 (33%) received both HIPEC and early post-operative chemotherapy (5-fluorouracil 650–800 mg/m2).

- A retrospective cohort study[1] (n = 151) compared patients who underwent cytoreductive surgery (with or without intraperitoneal chemotherapy) with patients who underwent only an 'open-and-close' procedure. The sample included 49 patients (32.7%) with a peritoneal carcinomatosis index score (PCI) of 1–10, 45 (30%) with a PCI of 11–20 and 56 (37.3%) with a PCI of 21–39. Of the 128 patients in the cytoreduction group, 57 (44.5%) received sequential postoperative intraperitoneal chemotherapy, 69 (53.9%) received HIPEC and two patients (1.5%) underwent cytoreductive surgery alone. Complete cytoreduction was achieved in 97 (64.7%) of patients. Chemotherapy regimens used for the HIPEC included mitomycin C (n = 2), oxaliplatin in combination with 5-FU and folinic acid (n = 44) and the combination of oxaliplatin, irinotecan, 5-FU and folinic acid (n = 23). Forty-seven patients (37.3%) received neoadjuvant chemotherapy and 27 (21.4%) also received adjuvant systemic chemotherapy.

Back to top

13.4.2.1 Perioperative mortality, morbidity and adverse events

Three studies reported treatment-related mortality.[1][2][4] One retrospective cohort study[1] reported five deaths among 126 patients (8%) in the cytoreduction group within 90 days of treatment. The Dutch RCT reported seven deaths among 105 patients (6.7%) in the cytoreduction group.[4] The Swedish peritoneal study reported no 30-day surgical mortality or treatment-related mortality from grade III or IV toxicity.[2]

High rates of treatment-related morbidity were reported. One retrospective cohort study reported an overall 90-day grade III or IV morbidity rate of 71%.[1] In a subsequent RCT, 30-day morbidity rate was 33% in patients who underwent cytoreduction.[2] The same RCT also reported that 6-month treatment-related grade III or IV morbidity was comparable between patients undergoing cytoreduction and intraperitoneal cavity chemotherapy and patients receiving systemic adjuvant therapy (42% versus 50%, p value not reported).[2] In addition to these complications, seven (29%) of the surgical patients also required an unplanned re-operation for major intra-abdominal complications.[2]

The other RCT[4] only briefly reported early surgical and postoperative complications because this was a follow-up study that focused on longer-term outcomes. The investigators reported a mortality rate of 8% (four patients in each of the cytoreduction surgery and intraperitoneal chemotherapy groups). Morbidity rates were not reported quantitatively but the authors stated that treatment related toxicities were high. The initial 2003 publication of this study reported that the most significant complications were small bowel leakage (15%) and post-operative intraabdominal sepsis.[5] Grade III and IV bone marrow toxicity as a result of mitomycin C within intraperitoneal chemotherapy was noted in 14% and 5% of patients, respectively.

Treatment termination because of disease progression was also reported in the two RCTs.[2][4] In both studies, this was less likely in the cytoreduction and intraperitoneal chemotherapy group (21% versus 50% in the Swedish peritoneal study,[2] and 25% versus 86% in the Dutch study).[4]

Back to top

13.4.2.2 Survival outcomes

In all four studies, the patients who received cytoreduction with or without intra-peritoneal chemotherapy group showed improved survival, compared with the palliative group.[1][2][3][4] Of the four studies, one reported overall median survival,[3] one reported overall survival, median survival and disease free survival,[1] one reported overall survival,[2] and one reported disease-specific survival.[4]

In the Swedish peritoneal study[2] 5-year overall survival was significantly higher for patients who underwent cytoreduction and intraperitoneal cavity chemotherapy, compared with those who only received systemic adjuvant therapy (33% versus 4%; $p = 0.02$). The Dutch RCT[4] reported disease-specific survival of 22.2 months for patients who underwent cytoreduction, compared with 12.6 months for patients who received systemic chemotherapy ($p = 0.028$). Among patients who had complete cytoreduction ($n = 21$), median survival was 48 months and 5-year overall survival was 45%.[4]

In the multicentre retrospective cohort study[3] the overall median survival for the palliative surgery group was 9 months, compared with 36 months for cytoreduction and HIPEC, 38 months for cytoreduction and early postoperative intraperitoneal chemotherapy, and 43 months for the combination of cytoreduction, HIPEC and early postoperative intraperitoneal chemotherapy after 17 months median follow up ($p < 0.001$). The other retrospective cohort study[1] reported that overall median survival was 6.5 months for patients who underwent an ‘open-and-close’ procedure only, compared with 25–34 months for those who underwent cytoreduction and intraperitoneal chemotherapy.[1] This study also reported overall survival rates of 40% for the cytoreduction and HIPEC group, 18% for the cytoreduction and sequential postoperative intraperitoneal chemotherapy group and 0% for the ‘open-and-close’ group after 49 months median follow up ($p < 0.001$).[1] The same study also reported a 5-year disease-free survival rate of 32% for patients who underwent cytoreduction and HIPEC.[1]

Overall, there is some limited evidence that cytoreductive surgery and intraperitoneal chemotherapy improves survival, but this must be balanced against perioperative mortality and morbidity.

13.4.2.3 Quality-of-life outcomes

Quality-of-life outcomes were not reported in any of the studies included in the systematic review. There is no evidence to determine differences in quality of life outcomes.

Back to top

13.4.3 Evidence summary and recommendations

Evidence summary	Level	References
In patients with peritoneal metastases from colorectal cancer (synchronous or metachronous), cytoreduction surgery with intraperitoneal chemotherapy is associated with improved survival, compared with palliative surgery and systemic chemotherapy.	II, III-1	[1], [2], [3], [4]
Cytoreduction surgery with perioperative intraperitoneal chemotherapy is associated with significant treatment morbidity.	II, III-1	[2], [3], [4]

Evidence-based recommendation	Grade
Cytoreduction with perioperative intraperitoneal chemotherapy should be considered for patients with colorectal peritoneal metastases (either synchronous or metachronous to the primary). Where this procedure is suitable, the patient should be offered referral to a centre with the necessary expertise and infrastructure to perform this procedure.	**D**

Evidence-based recommendation	Grade
Cytoreduction surgery and perioperative intraperitoneal chemotherapy should only be offered after due consideration of, and discussion with the patient about, the potential treatment-related mortality and morbidity.	**D**

Practice point

Patients with peritoneal carcinomatosis should be referred to a centre with expertise in the management of peritoneal surface malignancies and should be offered enrolment in a prospective trial, so as to allow further evaluation of cytoreduction and intraperitoneal chemotherapy.

Practice point

Prior to referral, treating clinicians should have an in-depth discussion with every patient about the potential survival advantage and potential treatment-related mortality or morbidity.

Practice point

All patients' cases should be discussed at a multidisciplinary team meeting with clinicians who have expertise in the management of peritoneal metastases, to review the relevant clinical information, previous histology (if applicable) and relevant imaging prior to offering patients cytoreductive surgery and intraperitoneal chemotherapy.

Practice point

All patients offered this procedure in established cytoreduction centres should be asked to give their consent for their patient records to be available for ongoing auditing of clinical outcomes. Patients should also be invited and encouraged to participate in research to enable collection of prospective longitudinal data for clinical and quality-of-life outcomes.

Back to top

13.4.3.1 Considerations in making these recommendations

Although available evidence is encouraging, there is currently insufficient evidence to recommend the widespread adoption of cytoreduction surgery and intraperitoneal chemotherapy for patients with colorectal peritoneal metastases. Further studies, with appropriate patient selection and outcomes, are needed before cytoreduction and intraperitoneal chemotherapy can be recommended.

Back to top

13.4.3.2 Health system implications

13.4.3.2.1 Clinical practice

Cytoreduction surgery with perioperative intraperitoneal chemotherapy is a highly specialised treatment that is currently only offered at highly selected centres with the requisite expertise. The management of patients with peritoneal metastases requires a multidisciplinary team approach where the expertise is not restricted to surgical and medical oncology expertise alone.

With increasing evidence for the potential survival benefit of cytoreduction surgery and perioperative intraperitoneal chemotherapy, referrals to centres with the necessary expertise may increase.

13.4.3.2.2 Resourcing

The present recommendations would have only a minor effect on resourcing, because they would affect only referral centres with the necessary expertise and infrastructure to perform this procedure.

It is possible that there may be increased demand for cytoreduction surgery and perioperative intraperitoneal chemotherapy in the future, which may necessitate the development and establishment of more expert centres. The development and establishment of more expert centres should be undertaken in a consultative manner, taking into consideration the expertise and infrastructure available as well as commitment to ongoing audit and research. However, it is still envisaged that these expert centres are likely to be located in large tertiary referral centres, which would require patients from rural and regional areas of Australia to travel large distances for treatment.

13.4.3.2.3 Barriers to implementation

No barriers to the implementation of these recommendations are envisaged.

Back to top

13.4.4 Discussion

13.4.4.1 Unresolved issues

Prognosis for patients with peritoneal carcinomatosis is poor. There is some suggestion that an elective relook may allow early diagnosis of peritoneal carcinomatosis, resulting in earlier treatment, and therefore lead to improved survival. However, it is unclear whether this is simply the result of lead time bias or whether this represents more effective treatment early in the diagnosis of peritoneal carcinomatosis. Data from long-term prospective RCTs are not currently available.

Cytoreduction surgery, with or without intraperitoneal chemotherapy, requires further prospective evaluation. At present, it is not clear if intraperitoneal chemotherapy is a necessary part of treatment in addition to cytoreduction. Furthermore, even if intraperitoneal chemotherapy is a necessary component of treatment, there is insufficient evidence to conclude which intraperitoneal chemotherapy regimen is most effective in terms of timing and mode of delivery as well as the chemotherapy agent used.

Quality-of-life outcomes have not been included in studies reporting outcomes in patients undergoing cytoreduction with or without intraperitoneal chemotherapy. These need to be evaluated as part of a prospective study.

13.4.4.2 Studies currently underway

No large multicentre randomised trials are currently underway comparing cytoreduction and perioperative intraperitoneal chemotherapy with standard care. However, results are awaited from a RCT recently completed in France, which evaluated the role of HIPEC after cytoreduction surgery.[6]

Further large RCTs investigating the role of cytoreduction surgery and perioperative intraperitoneal chemotherapy are unlikely. This is partly because variations in practice between expert centres prevent investigators easily reaching consensus on the protocol for a multicentre trial.

Several randomised trials are currently ongoing evaluating the merit of elective relook in patients at high risk of developing peritoneal disease. These may inform the benefit of early treatment of peritoneal metastases.

13.4.4.3 Future research priorities

The role of cytoreduction surgery and intra-peritoneal chemotherapy requires further evaluation. Future prospective trials should be sufficiently powered to assess the trade-off between increased survival with cytoreductive surgery and perioperative intraperitoneal chemotherapy and the treatment related mortality and morbidity.

These studies should include quality-of-life outcomes and cost-effectiveness outcomes. Reporting of outcomes should be standardised to enable results to be compared between studies.

Back to top

13.4.5 References

1. ↑ 1.00 1.01 1.02 1.03 1.04 1.05 1.06 1.07 1.08 1.09 1.10 1.11 1.12 1.13 Cashin PH, Graf W, Nygren P, Mahteme H. *Cytoreductive surgery and intraperitoneal chemotherapy for colorectal peritoneal carcinomatosis: prognosis and treatment of recurrences in a cohort study.* Eur J Surg Oncol 2012 Jun;38(6):509-15 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22475555.
2. ↑ 2.00 2.01 2.02 2.03 2.04 2.05 2.06 2.07 2.08 2.09 2.10 2.11 2.12 2.13 2.14 2.15 2.16 2.17 Cashin PH, Mahteme H, Spång N, Syk I, Frödin JE, Torkzad M, et al. *Cytoreductive surgery and intraperitoneal chemotherapy versus systemic chemotherapy for colorectal peritoneal metastases: A randomised trial.* Eur J Cancer 2016 Jan;53:155-62 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26751236.

3. ↑ 3.0 3.1 3.2 3.3 3.4 3.5 3.6 3.7 3.8 Chua TC, Morris DL, Saxena A, Esquivel J, Liauw W, Doerfer J, et al. *Influence of modern systemic therapies as adjunct to cytoreduction and perioperative intraperitoneal chemotherapy for patients with colorectal peritoneal carcinomatosis: a multicenter study.* Ann Surg Oncol 2011 Jun;18(6):1560-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21203904.
4. ↑ 4.00 4.01 4.02 4.03 4.04 4.05 4.06 4.07 4.08 4.09 4.10 4.11 4.12 4.13 4.14 4.15 4.16 Verwaal VJ, Bruin S, Boot H, van Slooten G, van Tinteren H. *8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer.* Ann Surg Oncol 2008 Sep;15(9):2426-32 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18521686.
5. ↑ Verwaal VJ, van Ruth S, de Bree E, van Sloothen GW, van Tinteren H, Boot H, et al. *Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer.* J Clin Oncol 2003 Oct 15;21(20):3737-43 Available from: http://www.ncbi.nlm.nih.gov/pubmed/14551293.
6. ↑ U.S. National Institutes of Health. *Clinical trial: Systemic chemotherapy with or without intraperitoneal chemohyperthermia in treating patients undergoing surgery for peritoneal carcinomatosis from colorectal cancer. Accessed from: https://clinicaltrials.gov/ct2/show/NCT00769405. August 2016.*;.

Back to top

13.4.6 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search

View PICO	NHMRC Evidence statement form COLMNG3	Systematic review report COLMNG3

Back to top

14 Adjuvant therapy for colon cancer

Approximately 70–80% of patients with newly diagnosed cases of colorectal cancer undergo curative resection. However 40% of these develop incurable recurrent disease due to undetected micrometastases.[1]

In particular, patients with stage III (T1 to T4, N1-2) or Dukes C colon cancer have a 5-year survival rate of 42–92%, varying substantially depending on the T and N stage.[2] Those with stage II (T3 or T4, N0) or Dukes B colon cancer have a 5-year survival rate of 62–88%.2 The poorest outcomes being seen in those with high risk clinic-pathologic features.[3]

The inability to cure all such patients is a direct consequence of residual disease left behind after surgery. Over the last two decades, adjuvant chemotherapy has been offered to such high-risk patients with the aim to decrease relapse and improve overall survival, by attempting to eliminate this microscopic residual disease.

As the median age of diagnosis for colon cancer is just over 70 years, older patients constitute a large proportion of the stage II and III population.

14.1 Definitions

Adjuvant therapy is any treatment that is given in addition to a standard curative cancer treatment such as surgery. By convention, the term ‘adjuvant’ is reserved for postoperative treatment, while ‘neoadjuvant’ refers to treatment given prior to the definitive surgery.

Chemotherapy is cytotoxic drug treatment. Systemic chemotherapy affects the entire body, and is given with the intent of killing residual cancer cells that may lodge and grow in distant organs such as the liver and lungs.

Back to top

14.1.1 Contents

Subsections:

14.2 References

1. ↑ Lombardi L, Gebbia V, Silvestris N, Testa A, Colucci G, Maiello E. *Adjuvant therapy in colon cancer.* Oncology 2009;77 Suppl 1:50-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20130432.
2. ↑ Zhang ZY, Luo QF, Yin XW, Dai ZL, Basnet S, Ge HY. *Nomograms to predict survival after colorectal cancer resection without preoperative therapy.* BMC Cancer 2016 Aug 19;16(1):658 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27553083.

3. ↑ Böckelman C, Engelmann BE, Kaprio T, Hansen TF, Glimelius B. *Risk of recurrence in patients with colon cancer stage II and III: a systematic review and meta-analysis of recent literature.* Acta Oncol 2015 Jan;54 (1):5-16 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25430983.

Back to top

14.1 Introduction: adjuvant therapy for colon cancer

Approximately 70–80% of patients with newly diagnosed cases of colorectal cancer undergo curative resection. However 40% of these develop incurable recurrent disease due to undetected micrometastases.[1]

In particular, patients with stage III (T1 to T4, N1-2) or Dukes C colon cancer have a 5-year survival rate of 42–92%, varying substantially depending on the T and N stage.[2] Those with stage II (T3 or T4, N0) or Dukes B colon cancer have a 5-year survival rate of 62–88%.2 The poorest outcomes being seen in those with high risk clinic-pathologic features.[3]

The inability to cure all such patients is a direct consequence of residual disease left behind after surgery. Over the last two decades, adjuvant chemotherapy has been offered to such high-risk patients with the aim to decrease relapse and improve overall survival, by attempting to eliminate this microscopic residual disease.

As the median age of diagnosis for colon cancer is just over 70 years, older patients constitute a large proportion of the stage II and III population.

14.1.1 Definitions

Adjuvant therapy is any treatment that is given in addition to a standard curative cancer treatment such as surgery. By convention, the term ‘adjuvant’ is reserved for postoperative treatment, while ‘neoadjuvant’ refers to treatment given prior to the definitive surgery.

Chemotherapy is cytotoxic drug treatment. Systemic chemotherapy affects the entire body, and is given with the intent of killing residual cancer cells that may lodge and grow in distant organs such as the liver and lungs.

Back to top

14.1.1.1 Contents

Subsections:

- Adjuvant therapy for stage III colon cancer
  - What is the efficacy of adjuvant therapy in elderly CRC patients? ADJ1
- Adjuvant therapy for stage II colon cancer
- Irinotecan and targeted (biological) agents in adjuvant therapy for Stage II and Stage III colon cancer
- Discussion: adjuvant therapy for colon cancer

14.1.2 References

1. ↑ Lombardi L, Gebbia V, Silvestris N, Testa A, Colucci G, Maiello E. *Adjuvant therapy in colon cancer.* Oncology 2009;77 Suppl 1:50-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20130432.
2. ↑ Zhang ZY, Luo QF, Yin XW, Dai ZL, Basnet S, Ge HY. *Nomograms to predict survival after colorectal cancer resection without preoperative therapy.* BMC Cancer 2016 Aug 19;16(1):658 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27553083.
3. ↑ Böckelman C, Engelmann BE, Kaprio T, Hansen TF, Glimelius B. *Risk of recurrence in patients with colon cancer stage II and III: a systematic review and meta-analysis of recent literature.* Acta Oncol 2015 Jan;54 (1):5-16 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25430983.

Back to top

14.2 Adjuvant therapy for stage III colon

Contents

14.2.1 Background

Patients with stage III (T1 to T4, N1-2) or Dukes C colon cancer have 5-year disease-free survival of around 49%, improving to 64% with the addition of adjuvant chemotherapy.[1] The benefit of adjuvant treatment has been demonstrated,[2] meaning 6 months of adjuvant chemotherapy should be offered to patients with stage III colon cancer, unless medically unfit, with the aim of improving relapse free and overall survival.[3]

Back to top

14.2.2 Overview of evidence (non-systematic literature review)

No systematic reviews were undertaken for this topic. Practice points were based on selected published evidence. See Guidelines development process.

14.2.2.1 Addition of oxaliplatin to 5FU-based regimens

The efficacy of oxaliplatin plus 5-fluorouracil (5FU) as adjuvant therapy for stage III disease was demonstrated in two pivotal randomised controlled trials (RCTs): the MOSAIC study[4] and the NSABP C07 study.[5] Both studies included stage II and III patients.

In the MOSAIC trial,[4] 2246 patients were randomised to receive a combined bolus/infusional leucovorin (LV) plus 5FU regimen (LV5FU2) alone, or with oxaliplatin (FOLFOX4), for 6 months. On final analysis, the 10-year overall survival rates for patients with stage III disease were 59.0% and 67.1%, respectively (hazard ratio [HR] 0.80; p = .016).[4]

The NSABP C07 trial[5] randomised 2492 patients to either 5FU 500 mg/m^2, plus LV 500 mg/m2 both IV weekly for 6 weeks during each 8-week cycle (Roswell Park regimen) for three cycles, or the same 5FU-LV regimen with oxaliplatin 85 mg/m2 IV administered on weeks one, three and five of each 8-week cycle for three cycles. This study confirmed the additional disease-free survival benefit provided by oxaliplatin, as observed in the MOSAIC trial.[5]

Back to top

14.2.2.2 Addition of oxaliplatin plus capecitabine (XELOX) to 5FU-based regimens

A subsequent RCT, the NO1968 study, compared capecitabine plus oxaliplatin (XELOX; oxaliplatin 130 mg/m^2 on day one plus capecitabine 1000 mg/m^2 b.i.d on days one to 14, every 3 weeks for 24 weeks) with bolus 5FU-LV (Mayo Clinic for 24 weeks or Roswell Park for 32 weeks) in patients with stage III colon cancer.[6] The 3-year disease-free survival rate was 70.9% with XELOX and 66.5% with 5FU-LV (HR 0.80, p < 0.005).5 XELOX is thus considered an additional adjuvant treatment option for patients with stage III colon cancer.

Practice point

Oxaliplatin in combination with a fluoropyrimidine is standard therapy for young patients (< 70 years) with stage III colon cancer.

Practice point

Capecitabine plus oxaliplatin (XELOX) can be considered as an option for adjuvant treatment for patients with stage III colon cancer.

14.2.3 References

1. ↑ Böckelman C, Engelmann BE, Kaprio T, Hansen TF, Glimelius B. *Risk of recurrence in patients with colon cancer stage II and III: a systematic review and meta-analysis of recent literature.* Acta Oncol 2015 Jan;54 (1):5-16 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25430983.
2. ↑ Lombardi L, Gebbia V, Silvestris N, Testa A, Colucci G, Maiello E. *Adjuvant therapy in colon cancer.* Oncology 2009;77 Suppl 1:50-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20130432.
3. ↑ National Comprehensive Cancer Network. *NCCN Guidelines: Colon Cancer.* National Comprehensive Cancer Network; 2016.
4. ↑ [4.0] [4.1] [4.2] André T, de Gramont A, Vernerey D, Chibaudel B, Bonnetain F, Tijeras-Raballand A, et al. *Adjuvant Fluorouracil, Leucovorin, and Oxaliplatin in Stage II to III Colon Cancer: Updated 10-Year Survival and Outcomes According to BRAF Mutation and Mismatch Repair Status of the MOSAIC Study.* J Clin Oncol 2015 Dec 10;33(35):4176-87 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26527776.
5. ↑ [5.0] [5.1] [5.2] Yothers G, O'Connell MJ, Allegra CJ, Kuebler JP, Colangelo LH, Petrelli NJ, et al. *Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses.* J Clin Oncol 2011 Oct 1;29(28):3768-74 Available from: http://www.ncbi.nlm.nih.gov/pubmed /21859995.
6. ↑ Haller DG, Tabernero J, Maroun J, de Braud F, Price T, Van Cutsem E, et al. *Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer.* J Clin Oncol 2011 Apr 10;29(11):1465-71 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21383294.

Back to top

14.2.1 Adjuvant therapy for stage III colon

Contents

14.2.1.1 Background

Patients with stage III (T1 to T4, N1-2) or Dukes C colon cancer have 5-year disease-free survival of around 49%, improving to 64% with the addition of adjuvant chemotherapy.[1] The benefit of adjuvant treatment has been demonstrated,[2] meaning 6 months of adjuvant chemotherapy should be offered to patients with stage III colon cancer, unless medically unfit, with the aim of improving relapse free and overall survival.[3]

Back to top

14.2.1.2 Overview of evidence (non-systematic literature review)

No systematic reviews were undertaken for this topic. Practice points were based on selected published evidence. See Guidelines development process.

14.2.1.2.1 Addition of oxaliplatin to 5FU-based regimens

The efficacy of oxaliplatin plus 5-fluorouracil (5FU) as adjuvant therapy for stage III disease was demonstrated in two pivotal randomised controlled trials (RCTs): the MOSAIC study[4] and the NSABP C07 study.[5] Both studies included stage II and III patients.

In the MOSAIC trial,[4] 2246 patients were randomised to receive a combined bolus/infusional leucovorin (LV) plus 5FU regimen (LV5FU2) alone, or with oxaliplatin (FOLFOX4), for 6 months. On final analysis, the 10-year overall survival rates for patients with stage III disease were 59.0% and 67.1%, respectively (hazard ratio [HR] 0.80; p = .016).[4]

The NSABP C07 trial[5] randomised 2492 patients to either 5FU 500 mg/m^2, plus LV 500 mg/m2 both IV weekly for 6 weeks during each 8-week cycle (Roswell Park regimen) for three cycles, or the same 5FU-LV regimen with oxaliplatin 85 mg/m2 IV administered on weeks one, three and five of each 8-week cycle for three cycles. This study confirmed the additional disease-free survival benefit provided by oxaliplatin, as observed in the MOSAIC trial.[5]

Back to top

14.2.1.2.2 Addition of oxaliplatin plus capecitabine (XELOX) to 5FU-based regimens

A subsequent RCT, the NO1968 study, compared capecitabine plus oxaliplatin (XELOX; oxaliplatin 130 mg/m^2 on day one plus capecitabine 1000 mg/m^2 b.i.d on days one to 14, every 3 weeks for 24 weeks) with bolus 5FU-LV (Mayo Clinic for 24 weeks or Roswell Park for 32 weeks) in patients with stage III colon cancer.[6] The 3-year disease-free survival rate was 70.9% with XELOX and 66.5% with 5FU-LV (HR 0.80, $p < 0.005$).5 XELOX is thus considered an additional adjuvant treatment option for patients with stage III colon cancer.

Practice point

Oxaliplatin in combination with a fluoropyrimidine is standard therapy for young patients (< 70 years) with stage III colon cancer.

Practice point

Capecitabine plus oxaliplatin (XELOX) can be considered as an option for adjuvant treatment for patients with stage III colon cancer.

14.2.1.3 References

1. ↑ Böckelman C, Engelmann BE, Kaprio T, Hansen TF, Glimelius B. *Risk of recurrence in patients with colon cancer stage II and III: a systematic review and meta-analysis of recent literature.* Acta Oncol 2015 Jan;54 (1):5-16 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25430983.
2. ↑ Lombardi L, Gebbia V, Silvestris N, Testa A, Colucci G, Maiello E. *Adjuvant therapy in colon cancer.* Oncology 2009;77 Suppl 1:50-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20130432.
3. ↑ National Comprehensive Cancer Network. *NCCN Guidelines: Colon Cancer.* National Comprehensive Cancer Network; 2016.
4. ↑ [4.0] [4.1] [4.2] André T, de Gramont A, Vernerey D, Chibaudel B, Bonnetain F, Tijeras-Raballand A, et al. *Adjuvant Fluorouracil, Leucovorin, and Oxaliplatin in Stage II to III Colon Cancer: Updated 10-Year Survival and Outcomes According to BRAF Mutation and Mismatch Repair Status of the MOSAIC Study.* J Clin Oncol 2015 Dec 10;33(35):4176-87 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26527776.
5. ↑ [5.0] [5.1] [5.2] Yothers G, O'Connell MJ, Allegra CJ, Kuebler JP, Colangelo LH, Petrelli NJ, et al. *Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses.* J Clin Oncol 2011 Oct 1;29(28):3768-74 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21859995.

6. ↑ Haller DG, Tabernero J, Maroun J, de Braud F, Price T, Van Cutsem E, et al. *Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer.* J Clin Oncol 2011 Apr 10;29(11):1465-71 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21383294.

Back to top

14.2.2 Adjuvant therapy for elderly stage III CRC (ADJ1)

Contents

14.2.2.1 Background

Adjuvant chemotherapy is standard treatment for elderly patients with stage III colon cancer.

The use of single-agent fluoropyrimidines is supported by a pooled analysis[1] of individual patient data from seven phase III randomised controlled trials (RCTs) involving a total of 3351 patients. Included were studies comparing postoperative fluorouracil plus leucovorin (five trials) or fluorouracil plus levamisole (two trials) with surgery alone in patients with stage II or III colon cancer.[1] The study reported a significant positive effect on both overall survival (hazard ratio [HR] 0.76, $p < 0.001$) and time to tumour recurrence (HR 0.68, $p < 0.001$), with no significant interaction observed between age and the efficacy of treatment. The incidence of toxic effects was not increased among patients aged over 70 years, except for leukopenia in one study.[1]

The roles of additional agents in adjuvant therapy in the elderly have not been well defined.

Back to top

14.2.2.2 Systematic review evidence

In elderly patients (≥70 years) diagnosed with colon cancer, what is the efficacy of surgery and adjuvant combination chemotherapy (involving either 5-fluorouracil or capecitabine combined with oxaliplatin), compared to surgery with a single chemotherapeutic agent (fluoropyrimidine), in achieving the best outcomes in terms of colorectal cancer mortality, recurrence, quality of life and adverse effects? (ADJ1)

A systematic review was undertaken to evaluate outcomes (cancer-related outcomes, quality of life outcomes and adverse events) for patients with colorectal cancer aged 70 years and over undergoing surgery in combination with either single-agent chemotherapy or combination chemotherapy (oxaliplatin plus either 5-fluoruracil [5FU] or capecitabine).

Three randomised controlled trials (RCTs) were identified that compared adjuvant combination chemotherapy with single chemotherapy in the treatment of Stage II or Stage III colorectal cancer and included elderly patients:

- The XELOXA study[2][3] compared the combination of oxaliplatin and capecitabine (XELOX) with the combination of leucovorin fluorouracil (FULV) given as either of two regimens. Sub-group analysis was performed for Stage III patients aged 70 years and older (n = 409).[3]
- The MOSAIC study[4][5][6][7][8] compared the combination of FULV plus oxaliplatin (FOLFOX4) with FULV. Sub-group analysis was performed for Stage II or Stage III patients aged 70 years and older (n = 315).[4][8]
- The US National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 study4,10,12,13 compared the combination of FULV plus oxaliplatin (FLOX) with FULV. It included sub-group analysis for Stage II or Stage III patients aged 70 years and older (n = 299).[9][7][10]

The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

Back to top

14.2.2.2.1 Addition of oxaliplatin to 5FU-based regimens

In contrast with the efficacy of single-agent fluoropyrimidines as adjuvant treatment in older patients, subset analyses of all three studies combining oxaliplatin with a fluoropyrimidine have not demonstrated any survival advantage from adding oxaliplatin in older patients:

- In an analysis of 396 patients aged ≥70 enrolled in the NSABP CO7 study[9] there was no advantage from the addition of oxaliplatin for disease free survival at median follow-up of 96 months: HR 1.03 (95% CI 0.77 to 1.36). Similarly, overall survival was not improved: HR 1.18 (95% CI 0.68 to 1.62).
- The latest analysis of data from 315 patients aged 70 and older from the MOSAIC study[4] show that the addition of oxaliplatin did not improve overall survival at median follow-up of 9.46 years: HR 1.19 (95% CI 0.83 to 1.7).
- In an analysis of data for 409 patients aged 70 years and older from the XELOXA study,[3] there was no improvement in disease free survival (HR 0.86, 95% CI 0.64 to 1.16) or overall survival (HR 0.98, 95% CI 0.62 to 1.56) at a median follow-up of 74 months.

In a pooled analysis of all three studies[7] (n = 1119) there was no improvement in disease free survival (HR 0.94, 95% CI 0.78 to 1.12) or overall survival (HR 1.04, 95% CI 0.85 to 1.27) in the elderly patients receiving oxaliplatin.

Back to top

14.2.2.2.2 Understanding the lack of benefit from the addition of oxaliplatin in stage III colon cancer

Oxaliplatin, fluorouracil, and leucovorin are commonly used to treat patients with advanced colorectal cancer. An analysis of the safety and efficacy of oxaliplatin plus fluorouracil/leucovorin administered bimonthly (FOLFOX4) in patients age younger than and at least 70 years[11] reported no impact of age on oxaliplatin benefit. This retrospective analysis of 3742 colorectal cancer patients from four clinical trials, 614 of whom were aged ≥ 70 years, found the relative benefit of FOLFOX4 versus control did not differ by age for response rate, progression free-survival or overall survival.

The discordance between the outcome data for the addition of oxaliplatin for the treatment of elderly patients in the adjuvant setting, versus the metastatic setting, remains largely unexplained. In the MOSAIC trial, the incidence of second cancers was significantly different between the elderly and the younger patients (11.0% versus 4.0%; p = 0.001) but not in the 5FU-alone arm (6.3% versus 5.3%; p = 0.16).[8] In elderly patients treated with FOLFOX4, the median overall survival after recurrence was 3.6 months, compared with 13.7 months in patients treated with 5FU. However, no excess of second cancers or shorter post recurrence survival was reported in the other studies, and the observations from the MOSAIC trial could not fully explain a failure of oxaliplatin to improve outcomes in older patients.

Back to top

14.2.2.3 Evidence summary and recommendations

Evidence summary	Level	References
In elderly patients (≥ 70 years) following surgery for stage III colon cancer, subset analyses of three randomised controlled trials found no survival benefit from the addition of oxaliplatin to a fluoropyrimidine containing adjuvant chemotherapy (involving either 5-fluorouracil or capecitabine), compared to adjuvant chemotherapy with a fluoropyrimidine alone.	I, II	[7], [9], [2], [4]

Consensus-based recommendation

Elderly patients (≥ 70 years) with stage III colon cancer who are fit for adjuvant chemotherapy should receive 6 months of a single-agent fluoropyrimidine (either 5FU or capecitabine).

Practice point

The addition of oxaliplatin to adjuvant fluoropyrimidine-based therapy in elderly patients (≥ 70 years) with stage III colon cancer did not improve survival outcomes.

Practice point

The combination of oxaliplatin and fluoropyrimidine-based therapy in the metastatic setting provides a similar benefit in elderly patients and younger patients. The discordance between the adjuvant and metastatic setting remain unexplained.

14.2.2.3.1 Considerations in making these recommendations

While oxaliplatin-based treatment provides a similar advantage for older and younger patients with metastatic disease, the data do not support this approach in older patients in the adjuvant setting. Therefore, oxaliplatin-based therapy cannot be recommended for older patients.

Back to top

14.2.2.3.2 Health system implications

14.2.2.3.2.1 Clinical practice

The recommendation would not change current practice.

14.2.2.3.2.2 Resourcing

The recommendation has no implications for resourcing.

14.2.2.3.2.3 Barriers to implementation

No barriers to the implementation of this recommendation are envisaged.

Back to top

14.2.2.4 References

1. ↑ 1.0 1.1 1.2 Sargent DJ, Goldberg RM, Jacobson SD, Macdonald JS, Labianca R, Haller DG, et al. *A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients.* N Engl J Med 2001 Oct 11;345(15):1091-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/11596588.
2. ↑ 2.0 2.1 Haller DG, Tabernero J, Maroun J, de Braud F, Price T, Van Cutsem E, et al. *Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer.* J Clin Oncol 2011 Apr 10;29(11):1465-71 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21383294.
3. ↑ 3.0 3.1 3.2 Schmoll HJ, Tabernero J, Maroun J, de Braud F, Price T, Van Cutsem E, et al. *Capecitabine Plus Oxaliplatin Compared With Fluorouracil/Folinic Acid As Adjuvant Therapy for Stage III Colon Cancer: Final Results of the NO16968 Randomized Controlled Phase III Trial.* J Clin Oncol 2015 Nov 10;33(32):3733-40 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26324362.
4. ↑ 4.0 4.1 4.2 4.3 André T, de Gramont A, Vernerey D, Chibaudel B, Bonnetain F, Tijeras-Raballand A, et al. *Adjuvant Fluorouracil, Leucovorin, and Oxaliplatin in Stage II to III Colon Cancer: Updated 10-Year Survival and Outcomes According to BRAF Mutation and Mismatch Repair Status of the MOSAIC Study.* J Clin Oncol 2015 Dec 10;33(35):4176-87 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26527776.
5. ↑ André T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, et al. *Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer.* N Engl J Med 2004 Jun 3;350(23):2343-51 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15175436.
6. ↑ André T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, et al. *Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial.* J Clin Oncol 2009 Jul 1;27(19):3109-16 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19451431.
7. ↑ 7.0 7.1 7.2 7.3 McCleary NJ, Meyerhardt JA, Green E, Yothers G, de Gramont A, Van Cutsem E, et al. *Impact of age on the efficacy of newer adjuvant therapies in patients with stage II/III colon cancer: findings from the ACCENT database.* J Clin Oncol 2013 Jul 10;31(20):2600-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23733765.

8. ↑ 8.0 8.1 8.2 Tournigand C, André T, Bonnetain F, Chibaudel B, Lledo G, Hickish T, et al. *Adjuvant therapy with fluorouracil and oxaliplatin in stage II and elderly patients (between ages 70 and 75 years) with colon cancer: subgroup analyses of the Multicenter International Study of Oxaliplatin, Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer trial.* J Clin Oncol 2012 Sep 20;30(27):3353-60 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22915656.
9. ↑ 9.0 9.1 9.2 Yothers G, O'Connell MJ, Allegra CJ, Kuebler JP, Colangelo LH, Petrelli NJ, et al. *Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses.* J Clin Oncol 2011 Oct 1;29(28):3768-74 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21859995.
10. ↑ Kuebler JP, Colangelo L, O'Connell MJ, Smith RE, Yothers G, Begovic M, et al. *Severe enteropathy among patients with stage II/III colon cancer treated on a randomized trial of bolus 5-fluorouracil/leucovorin plus or minus oxaliplatin: a prospective analysis.* Cancer 2007 Nov 1;110(9):1945-50 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17853393.
11. ↑ Goldberg RM, Tabah-Fisch I, Bleiberg H, de Gramont A, Tournigand C, Andre T, et al. *Pooled analysis of safety and efficacy of oxaliplatin plus fluorouracil/leucovorin administered bimonthly in elderly patients with colorectal cancer.* J Clin Oncol 2006 Sep 1;24(25):4085-91 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16943526.

Back to top

14.2.2.5 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search

View PICO	NHMRC Evidence statement form ADJ1	Systematic review report ADJ1

Back to top

14.3 Adjuvant therapy for stage II colon

14.3.1 Background

Patients with stage II (T3 or T4, N0) or Dukes B colon cancer have a 5-year disease free survival rate of around 80% when all groups are combined, with minimal or no impact from adjuvant chemotherapy.[1]

14.3.2 Overview of evidence (non-systematic literature review)

No systematic reviews were undertaken for this topic. Practice points were based on selected published evidence. See Guidelines development process.

Controversy still exists regarding the role of standard adjuvant therapy for Stage II disease. The addition of oxaliplatin to fluorouracil does not appear to offer benefit in patients with stage II colon cancer.[2][3]

Furthermore, the prognosis is often underestimated, with 5-year overall survivals of 87–90% for 'high risk' disease and 89–91% for 'low/medium risk' disease being reported in a recent clinical trial.[2] Multiple clinical and pathologic factors define a subset of patients at increased risk of recurrence (including T4, perforation at presentation and inadequate node sampling)[1] but whether these 'high-risk' patients benefit more from chemotherapy remains to be conclusively demonstrated.

Adjuvant chemotherapy for stage II cancers can be considered on a case-by-case basis but cannot be considered a standard of care.

Practice point

The optimal approach to adjuvant therapy in stage II colon cancer remains uncertain. Adjuvant therapy can be considered in high-risk patients on a case-by-case basis.

Back to top

14.3.3 References

1. ↑ [1.0] [1.1] Böckelman C, Engelmann BE, Kaprio T, Hansen TF, Glimelius B. *Risk of recurrence in patients with colon cancer stage II and III: a systematic review and meta-analysis of recent literature.* Acta Oncol 2015 Jan;54(1):5-16 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25430983.
2. ↑ [2.0] [2.1] Yothers G, O'Connell MJ, Allegra CJ, Kuebler JP, Colangelo LH, Petrelli NJ, et al. *Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses.* J Clin Oncol 2011 Oct 1;29(28):3768-74 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21859995.

3. ↑ Haller DG, Tabernero J, Maroun J, de Braud F, Price T, Van Cutsem E, et al. *Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer.* J Clin Oncol 2011 Apr 10;29(11):1465-71 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21383294.

Back to top

14.3.1 Adjuvant therapy for stage II colon

14.3.1.1 Background

Patients with stage II (T3 or T4, N0) or Dukes B colon cancer have a 5-year disease free survival rate of around 80% when all groups are combined, with minimal or no impact from adjuvant chemotherapy.[1]

14.3.1.2 Overview of evidence (non-systematic literature review)

No systematic reviews were undertaken for this topic. Practice points were based on selected published evidence. See Guidelines development process.

Controversy still exists regarding the role of standard adjuvant therapy for Stage II disease. The addition of oxaliplatin to fluorouracil does not appear to offer benefit in patients with stage II colon cancer.[2][3]

Furthermore, the prognosis is often underestimated, with 5-year overall survivals of 87–90% for 'high risk' disease and 89–91% for 'low/medium risk' disease being reported in a recent clinical trial.[2] Multiple clinical and pathologic factors define a subset of patients at increased risk of recurrence (including T4, perforation at presentation and inadequate node sampling)[1] but whether these 'high-risk' patients benefit more from chemotherapy remains to be conclusively demonstrated.

Adjuvant chemotherapy for stage II cancers can be considered on a case-by-case basis but cannot be considered a standard of care.

Practice point
The optimal approach to adjuvant therapy in stage II colon cancer remains uncertain. Adjuvant therapy can be considered in high-risk patients on a case-by-case basis.

Back to top

14.3.1.3 References

1. ↑ 1.0 1.1 Böckelman C, Engelmann BE, Kaprio T, Hansen TF, Glimelius B. *Risk of recurrence in patients with colon cancer stage II and III: a systematic review and meta-analysis of recent literature.* Acta Oncol 2015 Jan;54(1):5-16 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25430983.
2. ↑ 2.0 2.1 Yothers G, O'Connell MJ, Allegra CJ, Kuebler JP, Colangelo LH, Petrelli NJ, et al. *Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses.* J Clin Oncol 2011 Oct 1;29(28):3768-74 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21859995.
3. ↑ Haller DG, Tabernero J, Maroun J, de Braud F, Price T, Van Cutsem E, et al. *Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer.* J Clin Oncol 2011 Apr 10;29(11):1465-71 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21383294.

Back to top

14.4 Irinotecan and targeted agents (Stage II-III colon)

Contents

14.4.1 Background

14.4.1.1 Overview of evidence (non-systematic literature review)

No systematic reviews were undertaken for this topic. Practice points were based on selected published evidence. See Guidelines development process.

14.4.1.1.1 Irinotecan

Three prospective randomised trials[1][2][3] failed to demonstrate a benefit from the addition of irinotecan to fluorouracil in patients with stage II or III colon cancer.

14.4.1.1.2 Targeted (biological) therapies

The addition of biologic agents to conventional adjuvant therapy has not led to any patient benefit.

The addition of the anti-angiogenic targeted therapy bevacizumab to FOLFOX failed to benefit patients with stage II or III colon cancer in two large phase III trials[4][5] and a similar lack of benefit was seen with the addition of bevacizumab to capecitabine[6]. These findings prompted the early closure of the Eastern Cooperative Oncology Group (ECOG) E5202 trial of adjuvant FOLFOX with and without bevacizumab in high-risk Stage II patients. No data from this study has been presented or published.

The pivotal phase III trial of adjuvant chemotherapy incorporating the anti-EGFR targeted therapy cetuximab (NCCTG-NO147) was also negative.[7] The trial had been modified to include patients with wild-type KRAS only when data regarding the predictive value of KRAS testing for response to the anti-EGFR antibodies became available, however in the wild-type KRAS subgroup the addition of cetuximab in the adjuvant setting did not confer benefit and analysis of the mutant KRAS population (enrolled prior to the amendment) showed a detrimental effect for the addition of cetuximab. The Pan-European PETACC-8 study with a similar randomisation to FOLFOX with or without cetuximab[8] has completed recruitment and again saw no impact on progression free survival in patients with wild-type *KRAS*.

Practice point

Neither Irinotecan or a biological agent (either bevacizumab or cetuximab) should be used as adjuvant therapy for patients with stage II or III colon cancer.

Back to top

14.4.2 References

1. ↑ Saltz LB, Niedzwiecki D, Hollis D, Goldberg RM, Hantel A, Thomas JP, et al. *Irinotecan fluorouracil plus leucovorin is not superior to fluorouracil plus leucovorin alone as adjuvant treatment for stage III colon cancer: results of CALGB 89803.* J Clin Oncol 2007 Aug 10;25(23):3456-61 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17687149.
2. ↑ Van Cutsem E, Labianca R, Bodoky G, Barone C, Aranda E, Nordlinger B, et al. *Randomized phase III trial comparing biweekly infusional fluorouracil/leucovorin alone or with irinotecan in the adjuvant treatment of stage III colon cancer: PETACC-3.* J Clin Oncol 2009 Jul 1;27(19):3117-25 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19451425.
3. ↑ Ychou M, Raoul JL, Douillard JY, Gourgou-Bourgade S, Bugat R, Mineur L, et al. *A phase III randomised trial of LV5FU2 + irinotecan versus LV5FU2 alone in adjuvant high-risk colon cancer (FNCLCC Accord02 /FFCD9802).* Ann Oncol 2009 Apr;20(4):674-80 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19179549.

4. ↑ Allegra CJ, Yothers G, O'Connell MJ, Sharif S, Petrelli NJ, Lopa SH, et al. *Bevacizumab in stage II-III colon cancer: 5-year update of the National Surgical Adjuvant Breast and Bowel Project C-08 trial.* J Clin Oncol 2013 Jan 20;31(3):359-64 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23233715.
5. ↑ de Gramont A, Van Cutsem E, Schmoll HJ, Tabernero J, Clarke S, Moore MJ, et al. *Bevacizumab plus oxaliplatin-based chemotherapy as adjuvant treatment for colon cancer (AVANT): a phase 3 randomised controlled trial.* Lancet Oncol 2012 Dec;13(12):1225-33 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23168362.
6. ↑ Kerr RS, Love S, Segelov E, Johnstone E, Falcon B, Hewett P, et al. *Adjuvant capecitabine plus bevacizumab versus capecitabine alone in patients with colorectal cancer (QUASAR 2): an open-label, randomised phase 3 trial.* Lancet Oncol 2016 Nov;17(11):1543-1557 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27660192.
7. ↑ Alberts SR, Sargent DJ, Nair S, Mahoney MR, Mooney M, Thibodeau SN, et al. *Effect of oxaliplatin, fluorouracil, and leucovorin with or without cetuximab on survival among patients with resected stage III colon cancer: a randomized trial.* JAMA 2012 Apr 4;307(13):1383-93 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22474202.
8. ↑ Taieb J, Tabernero J, Mini E, Subtil F, Folprecht G, Van Laethem JL, et al. *Oxaliplatin, fluorouracil, and leucovorin with or without cetuximab in patients with resected stage III colon cancer (PETACC-8): an open-label, randomised phase 3 trial.* Lancet Oncol 2014 Jul;15(8):862-73 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24928083.

Back to top

14.5 Discussion

14.5.1 Unresolved issues

The failure of oxaliplatin to show a benefit in adjuvant therapy for elderly patients is not well understood. The discordance between clinical trial outcomes for oxaliplatin treatment in elderly patients when given in adjuvant therapy, and when given in the treatment of metastatic disease, cannot be explained based on current data.

The role of adjuvant therapy for patients with stage II colon cancer has not been well defined.

14.5.2 Studies currently underway

ECOG E5202, comparing adjuvant FOLFOX alone with FOLFOX plus bevacizumab in patients with high-risk Stage II colon cancer, was closed prematurely due to the lack of benefit from the addition of oxaliplatin in other studies. No outcome data has yet been reported.

14.5.3 Future research priorities

Future research priorities include:

- improved risk stratification for patients based on existing and emerging tumour tissue and blood prognostic markers
- real time markers of adjuvant therapy benefit.

Back to top

15 Neoadjuvant & adjuvant therapy for rectal cancer

The aim of neoadjuvant and adjuvant therapy for rectal cancer is to reduce the risk of local and distant recurrence (metastatic disease). Locally recurrent rectal cancer is often incurable and is associated with high morbidity and deterioration in quality of life. Distant recurrence, if unresectable, is virtually always fatal.

Adjuvant therapy is any treatment that is given in addition to a standard curative cancer treatment such as surgery. By convention, the term ‘adjuvant’ is reserved for postoperative treatment, while ‘neoadjuvant’ refers to treatment given prior to the definitive treatment.

15.1 Radiation treatment

Radiation treatment uses ionising radiation to kill cancer cells. Only tissues within the treatment portals are affected. Radiation treatment prevents or reduces the incidence of recurrent rectal cancer within the pelvis.[1]

The value of radiation treatment (preferably given preoperatively) in the management of rectal cancer is well established. Several meta-analyses that included multiple trials have demonstrated a significant improvement in local disease control.[2]

15.2 Chemotherapy

Chemotherapy is cytotoxic drug treatment. Systemic chemotherapy affects the entire body, and is given with the intent of killing circulating cancer cells that may lodge and grow in distant organs such as the liver and lungs.[3]

The addition of fluoropyrimidine-based chemotherapy to radiation treatment in the treatment of rectal cancer is primarily for its effect as a radiosensitiser, enhancing the effect of radiation. Adjuvant chemotherapy cycles are given with the aim of eradicating systemic micro-metastatic disease.

15.2.1 Contents

Sections:

1. ↑ Barton, M. *Oncology for Medical Students: Principles of radiotherapy.* [homepage on the internet] Cancer Council Australia 2014; [cited 2016 Dec 28]. Available from: http://wiki.cancer.org.au/oncologyformedicalstudents_mw/index.php?oldid=1680.
2. ↑ Colorectal Cancer Collaborative Group.. *Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials.* Lancet 2001 Oct 20;358(9290):1291-304 Available from: http://www.ncbi.nlm.nih.gov/pubmed/11684209.
3. ↑ George, M; Schwarz, M; McKinnon, R. *Clinical Oncology for Medical Students: Principles of medical therapy.* [homepage on the internet] Cancer Council Australia 2014; [cited 2016 Dec 26]. Available from: http://wiki.cancer.org.au/oncologyformedicalstudents_mw/index.php?oldid=1683.

15.1 Introduction: neoadjuvant & adjuvant therapy for rectal cancer

The aim of neoadjuvant and adjuvant therapy for rectal cancer is to reduce the risk of local and distant recurrence (metastatic disease). Locally recurrent rectal cancer is often incurable and is associated with high morbidity and deterioration in quality of life. Distant recurrence, if unresectable, is virtually always fatal.

Adjuvant therapy is any treatment that is given in addition to a standard curative cancer treatment such as surgery. By convention, the term ‘adjuvant’ is reserved for postoperative treatment, while ‘neoadjuvant’ refers to treatment given prior to the definitive treatment.

15.1.1 Radiation treatment

Radiation treatment uses ionising radiation to kill cancer cells. Only tissues within the treatment portals are affected. Radiation treatment prevents or reduces the incidence of recurrent rectal cancer within the pelvis.[1]

The value of radiation treatment (preferably given preoperatively) in the management of rectal cancer is well established. Several meta-analyses that included multiple trials have demonstrated a significant improvement in local disease control.[2]

15.1.2 Chemotherapy

Chemotherapy is cytotoxic drug treatment. Systemic chemotherapy affects the entire body, and is given with the intent of killing circulating cancer cells that may lodge and grow in distant organs such as the liver and lungs.[3]

The addition of fluoropyrimidine-based chemotherapy to radiation treatment in the treatment of rectal cancer is primarily for its effect as a radiosensitiser, enhancing the effect of radiation. Adjuvant chemotherapy cycles are given with the aim of eradicating systemic micro-metastatic disease.

15.1.2.1 Contents

Sections:

1. ↑ Barton, M. *Oncology for Medical Students: Principles of radiotherapy.* [homepage on the internet] Cancer Council Australia 2014; [cited 2016 Dec 28]. Available from: http://wiki.cancer.org.au /oncologyformedicalstudents_mw/index.php?oldid=1680.
2. ↑ Colorectal Cancer Collaborative Group.. *Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials.* Lancet 2001 Oct 20;358(9290):1291-304 Available from: http://www.ncbi.nlm.nih.gov/pubmed/11684209.
3. ↑ George, M; Schwarz, M; McKinnon, R. *Clinical Oncology for Medical Students: Principles of medical therapy.* [homepage on the internet] Cancer Council Australia 2014; [cited 2016 Dec 26]. Available from: http://wiki.cancer.org.au/oncologyformedicalstudents_mw/index.php?oldid=1683.

15.2 Neoadjuvant therapy for rectal cancer

15.2.1 Background

Neoadjuvant treatment with radiation (with or without chemotherapy), followed by surgery, is current practice for managing most mid-low rectal cancers that are staged preoperatively as at least T3 and/or at least N1 (i.e. Stage II or III), in individuals well enough to tolerate it.

The timing of treatment preoperatively rather than postoperatively is based on the results of the CAO/ARO/AIO-94 study, a seminal 2004 phase III randomised controlled trial (RCT) comparing preoperative (neoadjuvant) with postoperative (adjuvant) chemoradiation, which reported a significant improvement in local control in favour of neoadjuvant chemoradiation.[1] This finding changed practice at the time.[1]

Both neoadjuvant long-course chemoradiation and short-course radiation treatment alone are delivered with the primary aim of reducing the risk of local recurrence. Neoadjuvant therapy can also achieve downsizing of the tumour, attain pathological complete response, and enable sphincter preservation surgery. However, there is not enough time for tumour downsizing with short-course radiation treatment followed by immediate surgery.

Both short-course radiation treatment and long-course chemoradiation emerged as recommended management options following trials investigating either strategy that recruited simultaneously and were conducted in parallel over several years during the 1980s and 1990s. Geographic preferences have emerged: for chemoradiation in the USA and Mediterranean Europe, and for radiation treatment in Scandinavia and Northern Europe. Recent RCTs comparing chemoradiation and radiation treatment have not shown any clear advantage for one strategy over the other.

15.2.2 Determining suitability for neoadjuvant therapy

It is important to make the distinction between upper (high) rectal cancers and/or rectosigmoid cancers, and the mid–low cancers that lie within the true pelvis. This is crucial as upper cancers do not require treatment with neoadjuvant therapy, and overall management (including adjuvant therapy) should follow that of colon cancers. The somewhat common approximation of upper versus lower rectal cancer being situated above or below the

peritoneal reflection is not accurate for each and every patient, and should not be used alone to distinguish between upper and lower rectal cancers for the purposes of deciding management.[2] The key neoadjuvant rectal cancer trials defined rectal cancer by the number of centimetres from the anal verge; but the studies included a variety of upper limits, usually ranging between 15-16cm; and most participants' tumours were in fact situated <10cm from the anal verge.[3][4] The decision regarding whether a rectal cancer – based on its location – requires neoadjuvant treatment relies on expert and accurate multidisciplinary input in particular from the radiologist and surgical endoscopist.

It is also important to acknowledge the heterogeneity in rectal cancers staged as Stage II (T3-4 N0). Patients with T4 tumours (AJCC/UICC stage IIB and IIC disease) should always undergo neoadjuvant treatment where feasible. Within the Stage IIA (T3N0) T3 MRI staging, a tumour may be considered 'early T3' or 'late T3', or somewhere in between, depending on the distance of extension in millimetres in the axial plane beyond the muscularis propria.[5][6] On this basis, T3 disease has been subdivided into T3a-d disease in some literature, T3a being <1mm, T3b 1-5mm, T3c 5-15mm and T3d >15mm extension.[5] A simpler subdivision has used T3a as ≤5mm and T3b as >5mm extension.[6] Notably, although the depth of T3 extension has been shown to be a prognostic factor for recurrence,[6][5] the current American Joint Committee on Cancer (AJCC) 8th Edition TNM staging system[7] does not include subdivisions of T3 disease. The Royal College of Pathologists of Australasia Structured Pathology Reporting of Colorectal Cancer Protocol[8] notes that in lieu of providing a formal T3a-d classification, the distance of invasion in millimetres may be provided in the pathology report as an alternative; although this is not prescriptive.

Within radiological (MRI) reporting, considerable variability has been documented as to whether T3 distance in millimetres is routinely formally reported.[9] Accurate MRI staging is critical determining T2 versus T3 disease, and depth of extension through muscularis propria for T3 disease. It is acknowledged that accuracy, especially when distinguishing between T2 and early T3 disease, is challenging.[10]

European ESMO guidelines note that 'early cT3' (<1mm extension) rectal cancers could be appropriate for primary TME surgery without neoadjuvant therapy.[11] The St Gallen EORTC conference consensus recommendations in 2016 also indicated primary TME surgery without neoadjuvant therapy as an option for early low-risk rectal cancers, including cT3a (<1mm extension) disease.[12] However, the US NCCN guidelines do not distinguish between T3 tumours and recommend neoadjuvant therapy for all T3 disease.[13] Ultimately a high level of confidence in the MRI staging is crucial as this directly influences management strategy. As millimetres can mean the difference between primary surgery or neoadjuvant therapy, careful multidisciplinary review and discussion is essential.

For clinical stage I (cT1-2, N0, M0) rectal cancer, if there is a high level of confidence in the preoperative staging evaluation of node negative disease, surgery alone without neoadjuvant treatment is the preferred approach. If subsequent histopathological evaluation unexpectedly results in upstaging (pT3 or N1-2 disease) or there are several high-risk features (such as positive margins or lymphovascular invasion), then adjuvant therapy should be considered on an individual case-by-case basis. An ASTRO 2016 Clinical Practice Statement utilised a systematic review and expert opinion to formulate recommendations for appropriate customisation of radiation treatment for stage II and III rectal cancer. It noted several acceptable options for medically inoperable patients or those who refused surgery, including definitive radiation treatment or chemoradiation.[14] This guidance could be extended to patients with stage I disease.

In patients who refuse or who are unable to tolerate surgery, definitive radiation treatment with or without chemotherapy may be considered as a potentially curative approach. There are no randomised controlled trial data to support this. See 'Watch and wait' approach after clinical complete response to neoadjuvant chemoradiation.

Practice point

Accurate determination of suitability for neoadjuvant therapy is based on careful preoperative location and staging assessments, and requires optimal quality of care from each aspect of the multidisciplinary team's assessment.

Practice point

'Early' cT3N0 rectal cancer (<1mm extension) is considered potentially suitable for surgery without neoadjuvant treatment in some international guidelines; but requires a high level of confidence in staging investigations and interpretation.

See:

- Short course radiation treatment
- Neoadjuvant long-course chemoradiation NEO1b

15.2.3 References

1. ↑ [1.0] [1.1] Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al. *Preoperative versus postoperative chemoradiotherapy for rectal cancer.* N Engl J Med 2004 Oct 21;351(17):1731-40 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15496622.
2. ↑ Salerno G, Sinnatamby C, Branagan G, Daniels IR, Heald RJ, Moran BJ. *Defining the rectum: surgically, radiologically and anatomically.* Colorectal Dis 2006 Sep;8 Suppl 3:5-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16813584.
3. ↑ Mulcahy, MF. *Radiotherapy for Cancer of the Rectum: Which Patients Stand to Benefit?* Gastrointestinal Cancer Research. 3(2):81-83. ;2009;3(2):81-83 Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2684722/.
4. ↑ Joshi, N; Woody, NM; Abdel-Wahab M. *Pre-operative chemoradiation for rectosigmoid cancers: Where do we draw the line?* Appl Rad Oncol 2014 Sep Available from: http://cdn.agilitycms.com/applied-radiation-oncology/ARO_09-14_JoshiROC.pdf.

5. ↑ [5.0] [5.1] [5.2] Shin R, Jeong SY, Yoo HY, Park KJ, Heo SC, Kang GH, et al. *Depth of mesorectal extension has prognostic significance in patients with T3 rectal cancer.* Dis Colon Rectum 2012 Dec;55(12):1220-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23135579.
6. ↑ [6.0] [6.1] [6.2] Merkel S, Mansmann U, Siassi M, Papadopoulos T, Hohenberger W, Hermanek P. *The prognostic inhomogeneity in pT3 rectal carcinomas.* Int J Colorectal Dis 2001 Sep;16(5):298-304 Available from: http://www.ncbi.nlm.nih.gov/pubmed/11686527.
7. ↑ Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, et al. (Eds.). *AJCC Cancer Staging Manual (8th edition).* Springer International Publishing: American Joint Commission on Cancer; 2017 [cited 2016 Dec 28].
8. ↑ Royal College of Pathologists of Australasia. *Colorectal Cancer Structured Reporting Protocol (3rd edition).* Royal College of Pathologists of Australasia; 2016 Available from: https://www.rcpa.edu.au/Library/Practising-Pathology/Structured-Pathology-Reporting-of-Cancer/Cancer-Protocols/Gastrointestinal/Protocol-colorectal-cancer.
9. ↑ Gormly K; Coscia C; Wells T, et al. *MRI rectal cancer in Australia and New Zealand: an audit from the PETACC-6 trial. Cancer Imaging. 2015;15(Suppl 1):P44. doi:10.1186/1470-7330-15-S1-P44.*; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4601852/.
10. ↑ Beets-Tan RG, Beets GL, Vliegen RF, Kessels AG, Van Boven H, De Bruine A, et al. *Accuracy of magnetic resonance imaging in prediction of tumour-free resection margin in rectal cancer surgery.* Lancet 2001 Feb 17;357(9255):497-504 Available from: http://www.ncbi.nlm.nih.gov/pubmed/11229667.
11. ↑ Glimelius B, Tiret E, Cervantes A, Arnold D, ESMO Guidelines Working Group.. *Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.* Ann Oncol 2013 Oct;24 Suppl 6:vi81-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24078665.
12. ↑ Lutz MP, Zalcberg JR, Glynne-Jones R, Ruers T, Ducreux M, Arnold D, et al. *Second St. Gallen European Organisation for Research and Treatment of Cancer Gastrointestinal Cancer Conference: consensus recommendations on controversial issues in the primary treatment of rectal cancer.* Eur J Cancer 2016 May 30;63:11-24 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27254838.
13. ↑ National Comprehensive Cancer Network. *NCCN Guidelines for Rectal Cancer Version 2.*; 2016 Available from: https://www.tri-kobe.org/nccn/guideline/colorectal/english/rectal.pdf.
14. ↑ Goodman KA, Patton CE, Fisher GA, Hoffe SE, Haddock MG, Parikh PJ, et al. *Appropriate customization of radiation therapy for stage II and III rectal cancer: Executive summary of an ASTRO Clinical Practice Statement using the RAND/UCLA Appropriateness Method.* Pract Radiat Oncol 2015 Nov 24 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26922700.

Back to top

15.2.1 Neoadjuvant therapy for rectal cancer

15.2.1.1 Background

Neoadjuvant treatment with radiation (with or without chemotherapy), followed by surgery, is current practice for managing most mid-low rectal cancers that are staged preoperatively as at least T3 and/or at least N1 (i.e. Stage II or III), in individuals well enough to tolerate it.

The timing of treatment preoperatively rather than postoperatively is based on the results of the CAO/ARO/AIO-94 study, a seminal 2004 phase III randomised controlled trial (RCT) comparing preoperative (neoadjuvant) with postoperative (adjuvant) chemoradiation, which reported a significant improvement in local control in favour of neoadjuvant chemoradiation.[1] This finding changed practice at the time.[1]

Both neoadjuvant long-course chemoradiation and short-course radiation treatment alone are delivered with the primary aim of reducing the risk of local recurrence. Neoadjuvant therapy can also achieve downsizing of the tumour, attain pathological complete response, and enable sphincter preservation surgery. However, there is not enough time for tumour downsizing with short-course radiation treatment followed by immediate surgery.

Both short-course radiation treatment and long-course chemoradiation emerged as recommended management options following trials investigating either strategy that recruited simultaneously and were conducted in parallel over several years during the 1980s and 1990s. Geographic preferences have emerged: for chemoradiation in the USA and Mediterranean Europe, and for radiation treatment in Scandinavia and Northern Europe. Recent RCTs comparing chemoradiation and radiation treatment have not shown any clear advantage for one strategy over the other.

15.2.1.2 Determining suitability for neoadjuvant therapy

It is important to make the distinction between upper (high) rectal cancers and/or rectosigmoid cancers, and the mid–low cancers that lie within the true pelvis. This is crucial as upper cancers do not require treatment with neoadjuvant therapy, and overall management (including adjuvant therapy) should follow that of colon cancers. The somewhat common approximation of upper versus lower rectal cancer being situated above or below the peritoneal reflection is not accurate for each and every patient, and should not be used alone to distinguish between upper and lower rectal cancers for the purposes of deciding management.[2] The key neoadjuvant rectal cancer trials defined rectal cancer by the number of centimetres from the anal verge; but the studies included a variety of upper limits, usually ranging between 15-16cm; and most participants' tumours were in fact situated <10cm from the anal verge.[3][4] The decision regarding whether a rectal cancer – based on its location – requires neoadjuvant treatment relies on expert and accurate multidisciplinary input in particular from the radiologist and surgical endoscopist.

It is also important to acknowledge the heterogeneity in rectal cancers staged as Stage II (T3-4 N0). Patients with T4 tumours (AJCC/UICC stage IIB and IIC disease) should always undergo neoadjuvant treatment where feasible. Within the Stage IIA (T3N0) T3 MRI staging, a tumour may be considered 'early T3' or 'late T3', or somewhere in between, depending on the distance of extension in millimetres in the axial plane beyond the muscularis propria.[5][6] On this basis, T3 disease has been subdivided into T3a-d disease in some literature, T3a being <1mm, T3b 1-5mm, T3c 5-15mm and T3d >15mm extension.[5] A simpler subdivision has used T3a as ≤5mm and T3b as >5mm extension.[6] Notably, although the depth of T3 extension has been shown to be a

prognostic factor for recurrence,[6][5] the current American Joint Committee on Cancer (AJCC) 8th Edition TNM staging system[7] does not include subdivisions of T3 disease. The Royal College of Pathologists of Australasia Structured Pathology Reporting of Colorectal Cancer Protocol[8] notes that in lieu of providing a formal T3a-d classification, the distance of invasion in millimetres may be provided in the pathology report as an alternative; although this is not prescriptive.

Within radiological (MRI) reporting, considerable variability has been documented as to whether T3 distance in millimetres is routinely formally reported.[9] Accurate MRI staging is critical determining T2 versus T3 disease, and depth of extension through muscularis propria for T3 disease. It is acknowledged that accuracy, especially when distinguishing between T2 and early T3 disease, is challenging.[10]

European ESMO guidelines note that 'early cT3' (<1mm extension) rectal cancers could be appropriate for primary TME surgery without neoadjuvant therapy.[11] The St Gallen EORTC conference consensus recommendations in 2016 also indicated primary TME surgery without neoadjuvant therapy as an option for early low-risk rectal cancers, including cT3a (<1mm extension) disease.[12] However, the US NCCN guidelines do not distinguish between T3 tumours and recommend neoadjuvant therapy for all T3 disease.[13] Ultimately a high level of confidence in the MRI staging is crucial as this directly influences management strategy. As millimetres can mean the difference between primary surgery or neoadjuvant therapy, careful multidisciplinary review and discussion is essential.

For clinical stage I (cT1-2, N0, M0) rectal cancer, if there is a high level of confidence in the preoperative staging evaluation of node negative disease, surgery alone without neoadjuvant treatment is the preferred approach. If subsequent histopathological evaluation unexpectedly results in upstaging (pT3 or N1-2 disease) or there are several high-risk features (such as positive margins or lymphovascular invasion), then adjuvant therapy should be considered on an individual case-by-case basis. An ASTRO 2016 Clinical Practice Statement utilised a systematic review and expert opinion to formulate recommendations for appropriate customisation of radiation treatment for stage II and III rectal cancer. It noted several acceptable options for medically inoperable patients or those who refused surgery, including definitive radiation treatment or chemoradiation.[14] This guidance could be extended to patients with stage I disease.

In patients who refuse or who are unable to tolerate surgery, definitive radiation treatment with or without chemotherapy may be considered as a potentially curative approach. There are no randomised controlled trial data to support this. See 'Watch and wait' approach after clinical complete response to neoadjuvant chemoradiation.

Practice point

Accurate determination of suitability for neoadjuvant therapy is based on careful preoperative location and staging assessments, and requires optimal quality of care from each aspect of the multidisciplinary team's assessment.

Practice point

'Early' cT3N0 rectal cancer (<1mm extension) is considered potentially suitable for surgery without neoadjuvant treatment in some international guidelines; but requires a high level of confidence in staging investigations and interpretation.

See:

- Short course radiation treatment
- Neoadjuvant long-course chemoradiation NEO1b

15.2.1.3 References

1. ↑ [1.0] [1.1] Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al. *Preoperative versus postoperative chemoradiotherapy for rectal cancer.* N Engl J Med 2004 Oct 21;351(17):1731-40 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15496622.
2. ↑ Salerno G, Sinnatamby C, Branagan G, Daniels IR, Heald RJ, Moran BJ. *Defining the rectum: surgically, radiologically and anatomically.* Colorectal Dis 2006 Sep;8 Suppl 3:5-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16813584.
3. ↑ Mulcahy, MF. *Radiotherapy for Cancer of the Rectum: Which Patients Stand to Benefit?* Gastrointestinal Cancer Research. 3(2):81-83. ;2009;3(2):81-83 Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2684722/.
4. ↑ Joshi, N; Woody, NM; Abdel-Wahab M. *Pre-operative chemoradiation for rectosigmoid cancers: Where do we draw the line?* Appl Rad Oncol 2014 Sep Available from: http://cdn.agilitycms.com/applied-radiation-oncology/ARO_09-14_JoshiROC.pdf.
5. ↑ [5.0] [5.1] [5.2] Shin R, Jeong SY, Yoo HY, Park KJ, Heo SC, Kang GH, et al. *Depth of mesorectal extension has prognostic significance in patients with T3 rectal cancer.* Dis Colon Rectum 2012 Dec;55(12):1220-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23135579.
6. ↑ [6.0] [6.1] [6.2] Merkel S, Mansmann U, Siassi M, Papadopoulos T, Hohenberger W, Hermanek P. *The prognostic inhomogeneity in pT3 rectal carcinomas.* Int J Colorectal Dis 2001 Sep;16(5):298-304 Available from: http://www.ncbi.nlm.nih.gov/pubmed/11686527.
7. ↑ Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, et al. (Eds.). *AJCC Cancer Staging Manual (8th edition).* Springer International Publishing: American Joint Commission on Cancer; 2017 [cited 2016 Dec 28].
8. ↑ Royal College of Pathologists of Australasia. *Colorectal Cancer Structured Reporting Protocol (3rd edition).* Royal College of Pathologists of Australasia; 2016 Available from: https://www.rcpa.edu.au/Library/Practising-Pathology/Structured-Pathology-Reporting-of-Cancer/Cancer-Protocols/Gastrointestinal/Protocol-colorectal-cancer.
9. ↑ Gormly K; Coscia C; Wells T, et al. *MRI rectal cancer in Australia and New Zealand: an audit from the PETACC-6 trial. Cancer Imaging. 2015;15(Suppl 1):P44. doi:10.1186/1470-7330-15-S1-P44.*; Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4601852/.

10. ↑ Beets-Tan RG, Beets GL, Vliegen RF, Kessels AG, Van Boven H, De Bruine A, et al. *Accuracy of magnetic resonance imaging in prediction of tumour-free resection margin in rectal cancer surgery.* Lancet 2001 Feb 17;357(9255):497-504 Available from: http://www.ncbi.nlm.nih.gov/pubmed/11229667.
11. ↑ Glimelius B, Tiret E, Cervantes A, Arnold D, ESMO Guidelines Working Group.. *Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.* Ann Oncol 2013 Oct;24 Suppl 6:vi81-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24078665.
12. ↑ Lutz MP, Zalcberg JR, Glynne-Jones R, Ruers T, Ducreux M, Arnold D, et al. *Second St. Gallen European Organisation for Research and Treatment of Cancer Gastrointestinal Cancer Conference: consensus recommendations on controversial issues in the primary treatment of rectal cancer.* Eur J Cancer 2016 May 30;63:11-24 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27254838.
13. ↑ National Comprehensive Cancer Network. *NCCN Guidelines for Rectal Cancer Version 2.*; 2016 Available from: https://www.tri-kobe.org/nccn/guideline/colorectal/english/rectal.pdf.
14. ↑ Goodman KA, Patton CE, Fisher GA, Hoffe SE, Haddock MG, Parikh PJ, et al. *Appropriate customization of radiation therapy for stage II and III rectal cancer: Executive summary of an ASTRO Clinical Practice Statement using the RAND/UCLA Appropriateness Method.* Pract Radiat Oncol 2015 Nov 24 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26922700.

Back to top

15.2.2 Short course radiation treatment

Contents

15.2.2.1 Background

Short-course radiation treatment (usually as 5 Gy delivered in five daily fractions over 5 days) has been the subject of multiple randomised controlled trials (RCTs), either compared with long-course chemoradiation, or with surgery alone (with or without adjuvant chemotherapy).

A 2015 systematic review and meta-analysis, which included eight RCTs, reported:

- a reduction in the risk of local recurrence with short-course radiation treatment, compared with surgery alone or postoperative therapy
- borderline improvement in overall survival with radiation treatment, compared with surgery alone

- no statistically significant differences in local recurrence or overall survival rates when comparing short-course radiation treatment with conventional long-course chemoradiation.

15.2.2.2 Overview of evidence (non-systematic literature review)

No systematic reviews were undertaken for this topic. Practice points to were based on the findings of major RCTs and consideration of international guidelines. See Guidelines development process.

Back to top

15.2.2.2.1 Short-course radiation treatment versus surgery alone

Several phase III RCTs, including three large well-designed international RCTs[1][2][3][4] have reported that short-course neoadjuvant radiation treatment improves local control, compared with surgery alone, in patients with resectable rectal cancer:

- The Swedish Rectal Cancer Trial compared 25 Gy in five fractions preoperatively, or surgery alone, in 1168 patients. The intervention group showed statistically significantly improved local control (89% versus 73%, p<0.001) and overall 5-year survival (58% versus 48%, p=0.004), compared with the control arm.[1] Increased hospitalisations for complications, mainly gastrointestinal, were noted during the first 6 months among patients randomised to radiation treatment.[5] This trial, which recruited patients between 1987 and 1990, predated total mesorectal excision surgery (see Optimal approach to elective resection for rectal cancers). The fact that surgery was not standardised to include total mesorectal excision (TME), where possible, resulted in a control arm that is difficult to compare with more modern practice.

- The Dutch TME Trial compared quality-controlled total mesorectal excision plus short-course radiation treatment with total mesorectal excision alone in 1861 patients.[4] The short-course radiation treatment group showed lower 5-year local recurrence rates than the surgery group (5.6% versus 10.9%), but there was no difference between groups in 5-year overall survival (64%).4,5 Patients with TNM Stage III cancer and negative circumferential resection margin had improved overall survival. Ten-year survival rates for the irradiated group and non-irradiated group were 50% and 40%, respectively (p = 0·032).[6] There was a significantly higher rate of perineal wound problems after abdominoperineal resection among those who received radiation treatment than those who did not (29% versus 18%).[7] A higher incidence of longer-term toxicities, such as faecal incontinence, dissatisfaction with bowel function and sexual dysfunction, was noted in patients from the radiation treatment arm. However, over time there were no significant differences in reported quality of life.[2][8]

- A multicentre RCT (the MRC CR07 and NCIC-CTG CO16 study) compared preoperative short-course radiation treatment with selective (based on pathological findings) postoperative chemoradiation in 1350 patients.[2] Neoadjuvant short-course radiation treatment decreased local recurrence, compared with selective chemoradiation (hazard ratio [HR] 0.39; 95% confidence interval [CI] 0.27 to 0.58, p < 0.0001), corresponding to an absolute difference at 3 years of 6.2%). Three-year disease-free survival was improved in the neoadjuvant group (HR 0.76, p = 0.013), but there was no difference between groups in overall survival. Quality-of-life data showed no differences between arms for general health, but a higher risk of male sexual dysfunction and faecal incontinence in the neoadjuvant group.[2]

All three of these studies included patients with stage I rectal cancer, who would currently be managed with surgery alone.

Back to top

15.2.2.2.2 Short-course radiation treatment versus long-course chemoradiation

Two phase III RCTs have compared short-course RT (5 x 5 Gy daily fractions) with C-RT (50.4 Gy RT over 5.5 weeks):

- A 2006 Polish RCT compared short-course RT (5 Gy in 5 fractions) with conventional fractionated radiation treatment (2 Gy over 25 or 30 fractions) plus bolus fluoropyrimidine chemotherapy in 316 patients with stage T3-4 rectal cancer within reach of digital examination without infiltration of the anal sphincter.[9] The primary aim of the trial was to verify whether long course preoperative chemoradiotherapy had an advantage in sphincter preservation, in comparison with short-course preoperative radiotherapy. Local staging included endorectal ultrasound or pelvic CT in patients with freely movable tumours not involving the entire circumference of the bowel rectal wall. Despite a higher pathological complete response in the conventional arm (16% versus 1%), there were no differences between groups for sphincter preservation, local recurrence rate or disease-free survival. There were no statistically significant differences in the rate of postoperative complications or late toxicities.[10] In interpreting these findings it must be noted that bolus fluoropyrimidine would not be considered standard today, and that adjuvant chemotherapy was optional in this trial.

- A 2012 phase III RCT conducted in Australia and New Zealand (the TROG 01.04 study) compared short-course RT (5 x 5 Gy fractions) with conventional C RT using infusional fluorouracil (5-FU) in 326 patients with ultrasound-staged or MRI-staged (42%) T3 localised rectal cancer.[11] It was designed to have 80% power to detect a difference in local recurrence rate at 3 years, of 15% (short-course) versus 5% (conventional chemoradiation).[11] Postsurgical treatment differed according to treatment arm; the short-course arm received six cycles of adjuvant fluoropyrimidine chemotherapy whereas the chemoradiation arm received four. The pathological complete response was superior in the conventional chemoradiation arm (15% versus 1%). There was a non-statistically significant reduction in 3-year local recurrence rates favouring conventional chemoradiation over short-course radiation treatment (4.4% versus 7.5% , p = 0.24), but no differences in distant recurrence, relapse-free or overall survival. There were no statistically significant differences in early toxicity[12], late toxicities, or first year quality of life[13]. Subgroup analysis of 79 patients with distal tumours (< 5cm from anal verge) showed a large observed, but not statistically significant, difference favouring chemoradiation for reduction in local recurrence (1 of 31 patients who received conventional C-RT versus 6 of 48 patients who received short course , HR 0.26; 95% CI 0.06 to 1.20; p = 0.26).

Based on these two RCTs, both regimens seem to be equally effective for T3 rectal cancer. The relative merits of either approach for early or late T3 tumours cannot be assessed due to the lack of MRI data and circumferential resection margin data.

A third, smaller RCT in 83 patients with stage II and III disease, published in 2012, similarly reported higher rates of pathological complete response, but no differences in rates of R0 resection[14].

A 2016 Polish phase III RCT compared neoadjuvant short-course RT plus adjuvant FOLFOX4 chemotherapy with or long-course C-RT (50.4 Gy in 28 daily fractions) plus bolus 5FU and weekly oxaliplatin in 515 evaluable patients.[15] The study reported equivalent rates for R0 resection, pathological complete response and disease-free survival, but an improved overall survival rate favouring the short-course arm (73% versus 65%, p = 0.046). The rate of acute toxicity was also lower in the short-course arm, although rates of postoperative and late toxicities were equivalent.[15] It is difficult to interpret the results of this study, given the different chemotherapy regimen used in each arm.

Overall, there are no clear survival (recurrence-free survival or overall survival) benefits when comparing short-course RT and long-course chemoradiation for T3 rectal cancer. Although there is no definitive evidence favouring long-course chemoradiation over short-course radiation treatment, concern over the risk of local recurrence with its high morbidity means that long-course chemoradiation is often favoured over the short-course radiation treatment approach, especially for patients with locally advanced or T4 disease, or when the total mesorectal excision plane is threatened. However, there are regional and international variations in practice.

Internationally, guidelines permit either approach:

- The US National Comprehensive Cancer Network (NCCN) guidelines[16] include both approaches, but recommend long-course chemoradiation for T4 disease.
- The European Society for Medical Oncology (ESMO) Clinical Practice Guidelines[17] also acknowledge that either approach is appropriate.
- The St Gallen European Organisation for Research and Treatment of Cancer (EORTC) rectal guidelines consensus panel[18] recommend long-course chemoradiation over short-course radiation treatment for most clinical situations for stage II and III rectal cancer, but concluded that either modality was appropriate for early T3N0 tumours with clear mesorectal fascia.

Short-course radiation treatment is clearly more convenient for patients. It may have a valuable role in the treatment of selected patients assessed as too frail to undergo long-course chemoradiation, those who have relative contraindications to chemotherapy, or those for whom long travelling distances to a treatment centre would be a barrier to short-course treatment. Such issues should be discussed in a multidisciplinary setting in order to determine the most appropriate individualised therapeutic strategy.

Back to top

Practice point

Preoperative (neoadjuvant) radiation treatment (either short-course radiation treatment alone or long-course chemoradiation) is recommended for most patients with stage II and III rectal cancers, to reduce risk of local recurrence.

Practice point

Short-course radiation treatment should be considered if there are clear concerns regarding a patient's physical or psychosocial ability to tolerate long-course chemoradiation.

Practice point

MRI imaging, patient and clinical factors including comorbidity status should be carefully reviewed by the multidisciplinary team. If clinical T4 primary or nodal disease is seen, or tumour extends close to the mesorectal fascia, then long-course chemoradiation is preferable where possible.

Back to top

15.2.2.3 References

1. ↑ [1.0] [1.1] Påhlman L, Swedish Rectal Cancer Trial Writing Committee. *Improved Survival with Preoperative Radiotherapy in Resectable Rectal Cancer.* N Engl J Med 1997;336: p. 980-87.
2. ↑ [2.0] [2.1] [2.2] [2.3] Peeters, KC, van de Velde CJ, Leer JW, Martijn H, Junggeburt JM, Kranenbarg EK, Steup WH, Wiggers T, Rutten HJ, Marijnen CA.. *Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients--a Dutch colorectal cancer group study.* Journal of clinical oncology : official journal of the American Society of Clinical Oncology [cited 2005];23, p. 6199-206.
3. ↑ Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. *Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer.* N Engl J Med 2001 Aug 30;345(9): 638-46 Available from: http://www.ncbi.nlm.nih.gov/pubmed/11547717.
4. ↑ [4.0] [4.1] Peeters KC, Marijnen CA, Nagtegaal ID, Kranenbarg EK, Putter H, Wiggers T, et al. *The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma.* Ann Surg 2007 Nov;246(5):693-701 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17968156.
5. ↑ Birgisson H, Påhlman L, Gunnarsson U, Glimelius B, Swedish Rectal Cancer Trial Group.. *Adverse effects of preoperative radiation therapy for rectal cancer: long-term follow-up of the Swedish Rectal Cancer Trial.* J Clin Oncol 2005 Dec 1;23(34):8697-705 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16314629.
6. ↑ van Gijn W, Marijnen CA, Nagtegaal ID, Kranenbarg EM, Putter H, Wiggers T, et al. *Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial.* Lancet Oncol 2011 Jun;12(6):575-82 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21596621.

7. ↑ Marijnen CA, Kapiteijn E, van de Velde CJ, Martijn H, Steup WH, Wiggers T, et al. *Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer: report of a multicenter randomized trial.* J Clin Oncol 2002 Feb 1;20(3):817-25 Available from: http://www.ncbi.nlm.nih.gov/pubmed/11821466.
8. ↑ Marijnen CA, van de Velde CJ, Putter H, van den Brink M, Maas CP, Martijn H, et al. *Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: report of a multicenter randomized trial.* J Clin Oncol 2005 Mar 20;23(9):1847-58 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15774778.
9. ↑ Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. *Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer.* Br J Surg 2006 Oct;93(10):1215-23 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16983741.
10. ↑ Bujko K, Nowacki MP, Kepka L, Oledzki J, Bebenek M, Kryj M, et al. *Postoperative complications in patients irradiated pre-operatively for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs chemoradiation.* Colorectal Dis 2005 Jul;7(4):410-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15932569.
11. ↑ [11.0] [11.1] Ngan SY, Burmeister B, Fisher RJ, Solomon M, Goldstein D, Joseph D, et al. *Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04.* J Clin Oncol 2012 Nov 1;30(31):3827-33 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23008301.
12. ↑ Ansari N, Solomon MJ, Fisher RJ, Mackay J, Burmeister B, Ackland S, et al. *Acute Adverse Events and Postoperative Complications in a Randomized Trial of Preoperative Short-course Radiotherapy Versus Long-course Chemoradiotherapy for T3 Adenocarcinoma of the Rectum: Trans-Tasman Radiation Oncology Group Trial (TROG 01.04).* Ann Surg 2016 Sep 14 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27631775.
13. ↑ McLachlan SA, Fisher RJ, Zalcberg J, Solomon M, Burmeister B, Goldstein D, et al. *The impact on health-related quality of life in the first 12 months: A randomised comparison of preoperative short-course radiation versus long-course chemoradiation for T3 rectal cancer (Trans-Tasman Radiation Oncology Group Trial 01.04).* Eur J Cancer 2016 Mar;55:15-26 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26771873.
14. ↑ Latkauskas T, Pauzas H, Gineikiene I, Janciauskiene R, Juozaityte E, Saladzinskas Z, et al. *Initial results of a randomized controlled trial comparing clinical and pathological downstaging of rectal cancer after preoperative short-course radiotherapy or long-term chemoradiotherapy, both with delayed surgery.* Colorectal Dis 2012 Mar;14(3):294-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21899712.
15. ↑ [15.0] [15.1] Bujko K, Wyrwicz L, Rutkowski A, Malinowska M, Pietrzak L, Kryński J, et al. *Long-course oxaliplatin-based preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer: results of a randomized phase III study.* Ann Oncol 2016 May;27(5):834-42 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26884592.
16. ↑ National Comprehensive Cancer Network. *NCCN Guidelines for Rectal Cancer Version 2.*; 2016 Available from: https://www.tri-kobe.org/nccn/guideline/colorectal/english/rectal.pdf.
17. ↑ Glimelius B, Tiret E, Cervantes A, Arnold D, ESMO Guidelines Working Group.. *Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.* Ann Oncol 2013 Oct;24 Suppl 6:vi81-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24078665.

18. ↑ Lutz MP, Zalcberg JR, Glynne-Jones R, Ruers T, Ducreux M, Arnold D, et al. *Second St. Gallen European Organisation for Research and Treatment of Cancer Gastrointestinal Cancer Conference: consensus recommendations on controversial issues in the primary treatment of rectal cancer.* Eur J Cancer 2016 May 30;63:11-24 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27254838.

Back to top

15.2.3 Neoadjuvant long-course chemoradiation

Contents

15.2.3.1 Background

Chemotherapy is routinely added to long-course radiation treatment. A 2012 Cochrane systematic review and meta-analysis of six relevant randomised controlled trials (RCTs) in stage III (node positive) rectal cancer found that chemoradiation was associated with a lower risk of local recurrence and improved disease-free survival, compared with radiation treatment alone.[1] However, no differences in sphincter preservation or overall survival were observed. A similar 2013 Cochrane meta-analysis of five trials (all of which were also included in the 2012 meta-analysis), including both stage II and III rectal cancer, made similar findings of improved pathological complete response rates and lower rates of local recurrence, with no difference in treatment for rates of sphincter preservation or overall survival.[2]

Neoadjuvant therapy is regarded as standard treatment for most stage II and III rectal cancers. The key demonstrated benefits of neoadjuvant therapy are reductions in the risk of local recurrence and its significant associated morbidity and of short-term and long-term toxicities. It has not been shown to improve disease-free survival or overall survival.

Neoadjuvant therapy, rather than surgery followed by adjuvant therapy, has been the preferred approach world-wide since the 2004 publication of the seminal German CAO/ARO/AIO-94 study, which compared preoperative with postoperative chemoradiation in 823 patients.[3] At 5-year follow-up, the study reported equivalent disease-free and overall survival in both treatment groups, but more than halving of the rate of local relapse in the preoperative group (6% versus 13%, p = 0.006), corresponding to a relative risk of recurrence of 0.46 favouring preoperative therapy. The preoperative treatment group also showed a lower risk of grade 3–4 acute toxicity (27% versus 40%, p = 0.001) and grade 3–4 long-term toxicity (14% versus 24%, p = 0.01).[3] There were no differences between groups in the rates of postoperative complications.[3]

Back to top

15.2.3.2 Systematic review evidence

For patients diagnosed with stage II-III rectal cancer, for which patients does neoadjuvant chemoradiation with surgery achieve equivalent or better outcomes than surgery alone? (NEO1b)

A systematic review was undertaken to evaluate three strategies for managing rectal cancer:

- neoadjuvant chemoradiation followed by resection
- resection followed by postoperative chemoradiation
- resection alone (no chemoradiation).

Four level II RCTs were identified that recruited patients with stage II and III rectal cancer:

- The CAO/ARO/AIO-94 study[3] conducted in Germany compared preoperative with postoperative chemoradiation in 823 patients with clinical stage T3 or T4 or node-positive disease. Five-year[3] and 10-year follow-up data[4] have been published.
- The US National Surgical Adjuvant Breast and Bowel Project R-03 (NSABP R-03) study[5] compared preoperative or postoperative chemoradiotherapy in 267 patients with clinical T3 or T4 or node-positive rectal cancer.
- A single-institution trial conducted in Korea randomised 240 patients to chemoradiation (50Gy in 25 daily fractions with concurrent capecitabine) given preoperatively or postoperatively.[6] Adjuvant therapy in both arms was either capecitabine or bolus 5FU (driven by availability).
- A single-institution trial conducted in China randomised patients to either total mesorectal excision surgery alone, or total mesorectal excision preceded by chemoradiation (with capecitabine and oxaliplatin which is not regarded as standard).[7] Both arms received postoperative adjuvant chemotherapy. Interim findings from only 184 randomised patients have been published.

Three of these four studies were underpowered, with patient recruitment substantially lower than anticipated. The NSABP R-03 study[5] accrued only 267 of a planned 900 patients. The Chinese study is an interim analysis of 184 of a planned 500 patients; this trial used a non-inferiority study design.[7] The Korean study did not reach accrual target.[6] Of a planned 432 patients, 240 were enrolled and their data analysed. Only the CAO/ARO/AIO-94 study accrued to target (planned 680, enrolled 823 patients anticipating 15% dropout).[3][4] Therefore, we accorded more weight to the data from this study.

Outcomes reported by these RCTs included local recurrence, disease-free survival, overall survival, distant metastases, and complications including perioperative and postoperative mortality. All of these studies all had an unclear (high) risk of bias, as outcome assessors were not blinded to intervention type and outcomes were not always clearly described in the study protocol.[5][7][4][6]

The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

Back to top

15.2.3.2.1 Local recurrence

Local recurrence was reported in all RCTs as 3-, 5- or 10-year local recurrence rates.

In the CAO/ARO/AIO-94 study[4], the preoperative chemoradiation group showed significantly lower 5-year and 10-year local recurrence, compared with the postoperative chemoradiation group: 5% versus 9.7% at 5 years and 7.1% versus 10.1% at 10 years (hazard ratio [HR] 0.6%, p = 0.048) on intention-to-treat analysis. The benefit of preoperative treatment over postoperative treatment was accentuated when comparing those who actually received their assigned treatments (6.8% versus 10.5%; HR 0.54, p = 0.02).[4]

The other studies reported no significant difference in local recurrence rates:

- The NSABP R-03 study[5] reported similar local-regional recurrence risk (5-year cumulative incidence 10.7%) in the preoperative and postoperative chemoradiation groups (HR 0.86; 95% confidence interval [CI] 0.41 to 1.81, p = 0.693).
- The Korean study[6] reported no significant differences in 5-year local recurrence between the preoperative and postoperative chemoradiation treatment groups (absolute difference 1%, p = 0.393).
- The Chinese study[7] reported no difference in 3-year local recurrence between groups who received preoperative chemoradiation group and surgery alone (absolute difference 0.1%, p = 0.776).

15.2.3.2.2 Disease-free survival

Disease-free survival was reported in all four RCTs.[5][4][6][7]

The NSABP R-03 study[5] reported a higher 5-year disease-free survival rate in the preoperative chemoradiation group, compared with the postoperative chemoradiation group (64.7% versus 53.4%; HR 0.63 (95% CI 0.44 to 0.90, p = 0.011).

The other three studies[3][6][7] reported marginal, but not statistically significant increases in disease-free survival among the preoperative chemoradiation group compared with the postoperative chemoradiation or no chemoradiation (surgery only) group:

- The CAO/ARO/AIO-94 study[4] reported no difference in disease-free survival for preoperative chemoradiation versus postoperative radiation at 10-year follow-up (p = 0.540).
- The Korean study[6] reported no difference in disease-free survival for preoperative chemoradiation versus postoperative radiation at 5-year follow-up (p=0.866).
- The Chinese study[7] reported no difference in disease-free survival for preoperative chemoradiation versus surgery alone (p=0.766).

Back to top

15.2.3.2.3 Overall survival

Overall survival was reported in all four RCTs.[4][5][6][7] None of the RCTs reported a statistically significant difference between groups in overall survival. The NSABP R-03 study[5] reported a nonsignificant overall survival benefit at 5-year follow-up favouring preoperative therapy (74.5% versus 65.5%; HR 0.693, 95% CI 0.468 to 1.026, p = 0.065).

15.2.3.2.4 Distant metastasis

Distant metastases were reported in all RCTs[4][5][6][7], with no significant differences observed.

15.2.3.2.5 Complications

Perioperative and postoperative complications reported in the RCTs included rates of perioperative mortality, anastomotic leakage, obstruction, wound infection, and fistula.

Perioperative mortality rates were reported in two RCTs. The CAO/ARO/AIO-94 study[3] reported in-hospital mortality rates of 0.7% in the preoperative chemoradiation group and 1.3% in the postoperative chemoradiation group (p = 0.41). The Chinese study[7] reported no perioperative mortality in either group.

The CAO/ARO/AIO-94 study 5-year follow-up data[3] showed significantly lower rates of perioperative and postoperative toxicity in the preoperative chemoradiation group, compared with the postoperative chemoradiation group: acute grade 3–4 toxicity 27% versus 40% (p = 0.001) and long-term toxicity 14% versus 24% (p = 0.01). Rates of postoperative complications were similar between groups (36% versus 34%, p = 0.68). There were no differences in rates of delayed wound healing, postoperative bleeding, ileus, or anastomotic leakage.

The other three RCTs reported no significant differences in complication rates between treatment groups. The NSABP R-03 study[5] reported similar rates of postoperative complications in the preoperative and postoperative chemoradiation groups (25% versus 22.6%). Neither the Korean[6] nor the Chinese[7] studies reported significant differences in complication rates, with low rates observed in each group.

Back to top

15.2.3.3 Evidence summary and recommendations

Evidence summary	Level	References
Patients with Stage II–III rectal cancer undergoing neoadjuvant chemoradiation have a reduced risk of local recurrence compared with those underdoing postoperative chemoradiation (evidence from one study).	II	[4], [5], [6], [7]
Preoperative chemoradiation has not been clearly demonstrated to improve disease-free survival, compared with postoperative chemoradiation or with surgery alone, in patients with Stage II–III rectal cancer. A significant improvement in disease-free survival favouring was reported in one study that was underpowered for this outcome.	II	[4], [5], [6], [7]
Preoperative chemoradiation does not reduce the risk of distant metastases, compared with postoperative chemoradiation or with surgery alone, in patients with Stage II–III rectal cancer.	II	[4], [6], [7]
Patients receiving preoperative chemoradiation may have a lower incidence of perioperative and postoperative complications, compared with those receiving postoperative chemoradiation (evidence from one study).	II	[3]

Evidence-based recommendation	Grade
Where possible, neoadjuvant chemoradiation should be recommended to most patients with stage II-III rectal cancer.	**C**

Practice point
The current standard dose of neoadjuvant chemoradiation is 50–50.4 Gy (boost volume after 45 Gy) with either continuous infusional 5FU or capecitabine.

Practice point

'Early' cT3N0 rectal cancer (<1mm extension) is considered potentially suitable for surgery without neoadjuvant treatment in some international guidelines; but requires a high level of confidence in staging investigations and interpretation.

Back to top

15.2.3.4 Considerations in making these recommendations

Neoadjuvant chemoradiation can be recommended for most patients with stage II–III rectal cancer with the aims of reducing the risk of local recurrence and for reducing rates of perioperative and postoperative complications, on the basis of limited evidence from one study.[3][4] However, it has not been shown to improve disease-free survival or overall survival rates.

Some international guidelines suggest that for 'early' T3 (stage II) rectal cancer (<1mm extension beyond muscularis propria) then surgery without neoadjuvant therapy is acceptable. This would need to be agreed upon in multidisciplinary team discussion, with a high level of confidence in MRI staging.

The absolute benefit of neoadjuvant chemoradiation in reducing risk of recurrence is small, compared with adjuvant chemoradiation (3% at 10 year follow up in the CAO/ARO/AIO-94 study[4]). Nevertheless, due to the significant morbidity associated with local recurrence, any modality that can reduce this risk is preferred as long as toxicities are acceptable.

Available evidence suggests that toxicity rates are reduced when using neoadjuvant chemoradiation rather than adjuvant chemoradiation.

15.2.3.5 Health system implications

15.2.3.5.1 Clinical practice

Neoadjuvant chemoradiation is currently standard practice in Australia, so the recommendation does not represent any change to current clinical practice.

15.2.3.5.2 Resourcing

No additional resourcing would be required to implement the recommendation, as neoadjuvant chemoradiation is currently regarded as standard practice in Australia.

15.2.3.5.3 Barriers to implementation

No barriers to implementation are anticipated, as neoadjuvant chemoradiation is currently regarded as standard practice in Australia.

Back to top

15.2.3.6 References

1. ↑ McCarthy K, Pearson K, Fulton R, Hewitt J. *Pre-operative chemoradiation for non-metastatic locally advanced rectal cancer.* Cochrane Database Syst Rev 2012 Dec 12;12:CD008368 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23235660.
2. ↑ De Caluwé L, Van Nieuwenhove Y, Ceelen WP. *Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer.* Cochrane Database Syst Rev 2013 Feb 28;(2):CD006041 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23450565.
3. ↑ 3.00 3.01 3.02 3.03 3.04 3.05 3.06 3.07 3.08 3.09 3.10 Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al. *Preoperative versus postoperative chemoradiotherapy for rectal cancer.* N Engl J Med 2004 Oct 21;351(17):1731-40 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15496622.
4. ↑ 4.00 4.01 4.02 4.03 4.04 4.05 4.06 4.07 4.08 4.09 4.10 4.11 4.12 4.13 Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, et al. *Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years.* J Clin Oncol 2012 Jun 1;30(16):1926-33 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22529255.
5. ↑ 5.00 5.01 5.02 5.03 5.04 5.05 5.06 5.07 5.08 5.09 5.10 5.11 Roh MS, Colangelo LH, O'Connell MJ, Yothers G, Deutsch M, Allegra CJ, et al. *Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03.* J Clin Oncol 2009 Nov 1;27(31):5124-30 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19770376.
6. ↑ 6.00 6.01 6.02 6.03 6.04 6.05 6.06 6.07 6.08 6.09 6.10 6.11 6.12 Park JH, Yoon SM, Yu CS, Kim JH, Kim TW, Kim JC. *Randomized phase 3 trial comparing preoperative and postoperative chemoradiotherapy with capecitabine for locally advanced rectal cancer.* Cancer 2011 Aug 15;117(16):3703-12 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21328328.
7. ↑ 7.00 7.01 7.02 7.03 7.04 7.05 7.06 7.07 7.08 7.09 7.10 7.11 7.12 7.13 Fan WH, Wang FL, Lu ZH, Pan ZZ, Li LR, Gao YH, et al. *Surgery with versus without preoperative concurrent chemoradiotherapy for mid/low rectal cancer: an interim analysis of a prospective, randomized trial.* Chin J Cancer 2015 Jun 10;34(9):394-403 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26111932.

Back to top

15.2.3.7 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search

View PICO	NHMRC Evidence statement form NEO1b	Systematic review report NEO1b

Back to top

15.3 'Watch and wait' approach after clinical complete response to neoadjuvant chemoradiation

Contents

15.3.1 Background

Rectal cancer surgery is associated with risks of significant morbidity, poor functional outcomes and permanent stomas. Patients who have a pathological remission and confirmed by surgery have an excellent oncological outcome. Therefore, a 'watch and wait' alternative has been proposed for patients who achieve a complete response to nonsurgical treatment with chemoradiation. As this approach is still investigational, it should ideally be subject to clearly defined protocols and managed by a multidisciplinary team, rather than applied ad hoc.

Note that this is not the same as non-operative management for other reasons after neoadjuvant CRT (e.g. patient refusal of surgery). The 'watch and wait' approach as described here only applies to patients who achieve a clinical complete response as determined by the treating team.

Approximately 10–20% of patients who receive neoadjuvant chemoradiation have a pathological complete response at the time of surgery.[1] These patients are expected to have an excellent prognosis. However, the critical issue is whether a clinical complete response after neoadjuvant treatment correlates well with a pathological complete response.

Traditionally, determination of response has relied on clinical and endoscopic examination by the surgeon. However, a mucosal clinical complete response may not correlate well with a pathological complete response at the primary site. Regional node status can only be monitored by radiological imaging, which is also imperfect in assessing a complete response in patients with nodal disease.[2]

MRI is not funded in Australia for this indication. Furthermore, even on MRI it may be difficult to distinguish between fibrosis and residual tumour plus micro-metastases may be missed at the nodal level.[3]

A high level of confidence in postoperative staging would be required in order to be confident not to proceed with surgery. Furthermore, careful surveillance would then be required in order to detect early recurrence. See Optimal approach to elective resection for rectal cancers for discussion of alternative, minimally invasive, surgical options for tumours with an excellent clinical response to neoadjuvant therapy.

Back to top

15.3.2 Systematic review evidence

For patients diagnosed with stage II-III rectal cancer, for which patients does neoadjuvant chemoradiation with surgery achieve equivalent or better outcomes than neoadjuvant chemoradiotherapy alone? (NEO1a)

A systematic review was undertaken to evaluate the benefits of definitive chemoradiation (clinical complete response) not followed by resection.

One systematic review and meta-analysis[4] and 12 cohort studies[5][6][7][8][9][10][11][12][13][14][15] were identified that compared outcomes for patients who underwent either surgery or observation after neoadjuvant chemoradiation.

The meta-analysis[4] included pooled data from nine of the cohort studies comparing patients with clinical complete response followed by a 'watch and wait' approach (n = 251), with those who had surgery (n = 334). This meta-analysis had a moderate risk of bias.

There was significant heterogeneity among the comparator characteristics of the cohort studies. Only four[5][12][13][15] of the 12 studies compared all patients with a clinical complete response who then either had a ‘watch and wait’ approach or surgery. For the remainder of the studies, the comparison arm consisted of patients who had a pathological complete response at surgery (five studies),Refs or patients who did not have a clinical complete response and thus proceeded to surgery (three studies).Refs This heterogeneity limits interpretation of results and does not permit easy comparisons between studies.

Seven of the cohort studies[5][6][7][8][9][10][16] had a high risk of bias, one study had a moderate risk of bias[11], and three studies had a low risk of bias}}[12][13][14].

Outcomes reported in observational studies included local recurrence, disease-free survival, overall survival, distant metastases, and perioperative complications including colostomy-free survival and incontinence.

The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

Back to top

15.3.2.1 Local recurrence

The meta-analysis[4] reported that local recurrence risk was significantly higher at 1, 2, 3, and 5 years among patients with clinical complete response to neoadjuvant therapy who underwent ‘watch and wait’ than those who underwent surgery: relative risk (RR) at 5-year follow-up 5.69 (95% confidence interval [CI] 1.99 to 16.25, p = 0.001). Although most of the included individual studies reported non- significant differences in local recurrence favouring the surgical arm, pooled analysis showed a statistically significant difference at all time points analysed.[4]

Three cohort studies that were not included in the meta-analysis[10][8][15] reported local recurrence rates in patients who received chemoradiation with and without surgery.

A Danish prospective observational study compared watch-and-wait with surgical resection in patients with resectable, T2 or T3, N0-N1 rectal adenocarcinoma who underwent high-dose chemoradiation.[10] It reported local recurrence in 9 of 40 patients from the watch and wait (local recurrence risk of 26%) at a median follow-up of 2 years.[10]

A UK study (the OnCoRe project)[8] performed propensity-score matched cohort analysis for patients with rectal adenocarcinoma who received preoperative chemoradiotherapy (45 Gy in 25 daily fractions with concurrent fluoropyrimidine-based chemotherapy). Patients who had a clinical complete response were offered a watch-and-wait approach, while those who did not have a clinical complete response were offered surgical resection if eligible. The study reported a local recurrence rate of 38% in the watch-and-wait arm at 3 years.[8]

A Taiwanese retrospective cohort study of 44 patients with cCR, 18 of whom opted for watch-and-wait, with a mean follow-up time of approximately 4 years, reported two local recurrence in the watch-and-wait group; and none in the surgery group.[15]

Back to top

15.3.2.2 Disease-free survival

The systematic review and meta-analysis[4] reported that there was no significant difference in disease-free survival at 1, 2, 3 and 5 years between patients who underwent watch-and-wait and those who underwent surgery: RR at 5-year follow-up 0.96 (95% CI 0.85 to 1.08).

Only one study[5] included in this systematic review and meta-analysis observed a significantly lower 5-year disease-free survival rate among patients with clinical complete response to neoadjuvant chemoradiation who underwent watch-and-wait than among those who underwent surgery (60.9% versus 82.8%; RR 0.79; 95% CI 0.65 to 0.98, p=0.011). All other cohort studies included in the systematic review and meta-analysis observed non-significant differences rates between groups in disease-free survival ranging from 0.2% to 12.5%.[4]

Of the three cohort studies that were not included in the meta-analysis,[10][8][15] the OnCoRe project}}[8] observed no difference in 3-year non-regrowth disease-free survival, and the Taiwanese retrospective study reported disease-free survival of 69.8 months ('watch and wait') and 89 months (surgery) (p=0.354)[15]. The Danish prospective observational study[10] did not formally report disease-free survival.

Back to top

15.3.2.3 Overall survival

The meta-analysis reported no significant difference in overall survival at 1, 2, 3 and 5 years between patients who underwent watch-and-wait and those who underwent surgery: RR at 5-year follow-up1.01; 95% CI 0.92 to 1.11).[4]

Of the three studies that were not included in the meta-analysis, none reported statistically significant between-group differences in overall survival.[10][8][15]

Back to top

15.3.2.4 Distant metastasis

The meta-analysis reported no significant difference in the rate of distant metastases at 1, 2, 3 or 5 year: RR at 5-year follow-up 0.95; 95% CI 0.47 to 1.91, p=0.88).[4] Included individual studies mostly observed no significant differences between groups.[4]

Of the three studies not included in the meta-analysis,[10][8][15] the Danish prospective observational study[10] reported higher distant metastases rates in the surgery group (18.2%) compared with the definitive chemoradiation group (7.5%) at a median follow-up of 26.7 months. However, no statistical comparison was provided and samples sizes were small (n = 11 for chemoradiation followed by surgery and n = 40 for

chemoradiation followed by observation). The surgery group consisted of all patients who did not have clinical complete response, so their results are not directly comparable with the group who did achieve clinical complete response to neoadjuvant treatment. The Taiwanese retrospective cohort study reported one distant metastasis in the surgery group and none in the watch-and-wait group at a mean follow-up of approximately 4 years.[15]

Back to top

15.3.3 Evidence summary and recommendations

Evidence summary	Level	References
Among patients with rectal cancer who have undergone chemoradiation, there is a higher risk of local recurrence with a 'watch and wait' approach compared with patients who have surgery, as evidenced by a meta-analysis observational of cohort studies. However, there was heterogeneity in the design of individual cohort studies.	III-2	[4], [10], [5], [12], [13], [6], [14], [7], [11], [9], [17], [15]
Observed disease-free survival rates among patients with rectal cancer did not consistently differ between those who received chemoradiation alone and those who received chemoradiation followed by surgery, despite a higher risk of local recurrence when the 'watch and wait' strategy was used.	III-2	[5], [12], [13], [14], [4], [7], [8], [11], [9], [15], [16]
No significant differences in distant metastases or overall survival among patients with rectal cancer were observed between those who received chemoradiation alone and those who received chemoradiation followed by surgery.	III-2	[10], [5], [12], [13], [6], [14], [4], [7], [8], [11], [9], [15], [16]

Evidence-based recommendation	Grade
If a patient with rectal cancer has a clinical complete response to neoadjuvant chemoradiation, and planned resection according to the standard recommendation is either not possible or the patient declines it, a 'watch and wait' approach could be undertaken: ■ 'Watch and wait' should only be undertaken after the risks and benefits have been discussed with the multidisciplinary team and the patient. ■ Patients who have chosen to undergo 'watch and wait' management must be monitored closely for local recurrence. ■ If local recurrence is detected, the patient must be offered an appropriate surgical resection procedure.	**D**

Practice point

A ‘watch and wait’ approach for patients with clinical complete response following chemoradiation is not considered standard practice. Clinicians and patients who select this option must be aware of increased risk of recurrence necessitating surgical intervention, and the importance of close follow-up.

Practice point

Follow-up and surveillance guidelines for a ‘watch and wait’ approach, in particular the frequency of follow-up tests, are not established. Testing may include serial CEA measurements, clinical examination, radiological surveillance, and sigmoidoscopy/colonoscopy.

Back to top

15.3.3.1 Considerations in making these recommendations

RCTs have not evaluated chemoradiation alone, compared with neoadjuvant chemoradiation followed by surgery, in patients with rectal cancer. Available evidence is from retrospective or prospective cohort studies in which patients with a clinical complete response underwent a watch-and-wait approach. These observational studies are challenging to interpret, as those patients who have a clinical complete response to chemoradiation may have an improved prognosis, whether or not they subsequently have surgery.

There is a higher risk of local recurrence with a watch-and-wait strategy. However, salvage surgery is appropriate and, based on available evidence, appears to achieve similar rates of disease-free survival and overall survival as immediate surgery.

Back to top

15.3.3.2 Health system implications

15.3.3.2.1 Clinical practice

Choosing observation alone, without surgery, in patients with clinical complete response after chemoradiation is not currently considered standard practice.

If observation without surgery is undertaken, the patient needs to understand this is not conventional treatment and compliance with close and strict surveillance is mandatory.

15.3.3.2.2 Resourcing

Strict surveillance would require resourcing for timely clinical review, imaging and examination ideally under anaesthetic.

Avoidance of surgery could result in lower costs, but these may be negated by intensive surveillance protocols.

Patients who are being followed with “watch and wait” should ideally be done so with a protocolised regimen of follow-up with prospective data collection.

15.3.3.2.3 Barriers to implementation

Lack of robust evidence may preclude uptake of this strategy.

Concern that patients may not adhere to strict follow up and surveillance, thus potentially rendering a curable early recurrence incurable if detected late.

No definitive recommendations available for optimum follow up strategy in this context.

Back to top

15.3.4 References

1. ↑ Maas M, Nelemans PJ, Valentini V, Das P, Rödel C, Kuo LJ, et al. *Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data.* Lancet Oncol 2010 Sep;11(9):835-44 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20692872.
2. ↑ Smith FM, Wiland H, Mace A, Pai RK, Kalady MF. *Clinical criteria underestimate complete pathological response in rectal cancer treated with neoadjuvant chemoradiotherapy.* Dis Colon Rectum 2014 Mar;57(3):311-5 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24509452.
3. ↑ Hanly AM, Ryan EM, Rogers AC, McNamara DA, Madoff RD, Winter DC, et al. *Multicenter Evaluation of Rectal cancer ReImaging pOst Neoadjuvant (MERRION) Therapy.* Ann Surg 2014 Apr;259(4):723-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23744576.
4. ↑ 4.00 4.01 4.02 4.03 4.04 4.05 4.06 4.07 4.08 4.09 4.10 4.11 Li J, Li L, Yang L, Yuan J, Lv B, Yao Y, et al. *Wait-and-see treatment strategies for rectal cancer patients with clinical complete response after neoadjuvant chemoradiotherapy: a systematic review and meta-analysis.* Oncotarget 2016 Apr 6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27070085.
5. ↑ 5.0 5.1 5.2 5.3 5.4 5.5 5.6 Araujo RO, Valadão M, Borges D, Linhares E, de Jesus JP, Ferreira CG, et al. *Nonoperative management of rectal cancer after chemoradiation opposed to resection after complete clinical response. A comparative study.* Eur J Surg Oncol 2015 Nov;41(11):1456-63 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26362228.
6. ↑ 6.0 6.1 6.2 6.3 Lee SY, Kim CH, Kim YJ, Kim HR. *Oncologic Outcomes according to the Treatment Strategy in Radiologic Complete Responders after Neoadjuvant Chemoradiation for Rectal Cancer.* Oncology 2015;89(6):311-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26426305.

7. ↑ 7.0 7.1 7.2 7.3 7.4 Maas M, Beets-Tan RG, Lambregts DM, Lammering G, Nelemans PJ, Engelen SM, et al. *Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer.* J Clin Oncol 2011 Dec 10;29(35):4633-40 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22067400.
8. ↑ 8.00 8.01 8.02 8.03 8.04 8.05 8.06 8.07 8.08 8.09 8.10 Renehan AG, Malcomson L, Emsley R, Gollins S, Maw A, Myint AS, et al. *Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis.* Lancet Oncol 2016 Feb;17(2):174-83 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26705854.
9. ↑ 9.0 9.1 9.2 9.3 9.4 Smith JD, Ruby JA, Goodman KA, Saltz LB, Guillem JG, Weiser MR, et al. *Nonoperative management of rectal cancer with complete clinical response after neoadjuvant therapy.* Ann Surg 2012 Dec;256(6):965-72 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23154394.
10. ↑ 10.00 10.01 10.02 10.03 10.04 10.05 10.06 10.07 10.08 10.09 10.10 10.11 Appelt AL, Pløen J, Harling H, Jensen FS, Jensen LH, Jørgensen JC, et al. *High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study.* Lancet Oncol 2015 Aug;16(8):919-27 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26156652.
11. ↑ 11.0 11.1 11.2 11.3 11.4 Ayloor Seshadri R, Kondaveeti SS, Jayanand SB, John A, Rajendranath R, Arumugam V, et al. *Complete clinical response to neoadjuvant chemoradiation in rectal cancers: can surgery be avoided?* Hepatogastroenterology 2013 May;60(123):410-4 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23635444.
12. ↑ 12.0 12.1 12.2 12.3 12.4 12.5 Dalton RS, Velineni R, Osborne ME, Thomas R, Harries S, Gee AS, et al. *A single-centre experience of chemoradiotherapy for rectal cancer: is there potential for nonoperative management?* Colorectal Dis 2012 May;14(5):567-71 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21831177.
13. ↑ 13.0 13.1 13.2 13.3 13.4 13.5 Habr-Gama A, Perez RO. *The surgical significance of residual mucosal abnormalities in rectal cancer following neoadjuvant chemoradiotherapy (Br J Surg 2012; 99: 993-1001).* Br J Surg 2012 Nov;99(11):1601; author reply 1601-2 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23027080.
14. ↑ 14.0 14.1 14.2 14.3 14.4 Li J, Liu H, Yin J, Liu S, Hu J, Du F, et al. *Wait-and-see or radical surgery for rectal cancer patients with a clinical complete response after neoadjuvant chemoradiotherapy: a cohort study.* Oncotarget 2015 Dec 8;6(39):42354-61 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26472284.
15. ↑ 15.00 15.01 15.02 15.03 15.04 15.05 15.06 15.07 15.08 15.09 15.10 15.11 Lai CL, Lai MJ, Wu CC, Jao SW, Hsiao CW. *Rectal cancer with complete clinical response after neoadjuvant chemoradiotherapy, surgery, or "watch and wait".* Int J Colorectal Dis 2016 Feb;31(2):413-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26607907.
16. ↑ 16.0 16.1 16.2 Smith RK, Fry RD, Mahmoud NN, Paulson EC. *Surveillance after neoadjuvant therapy in advanced rectal cancer with complete clinical response can have comparable outcomes to total mesorectal excision.* Int J Colorectal Dis 2015 Jun;30(6):769-74 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25787162.
17. ↑ Smith RK, Fry RD, Mahmoud NN, Paulson EC. *Surveillance after neoadjuvant therapy in advanced rectal cancer with complete clinical response can have comparable outcomes to total mesorectal excision.* Int J Colorectal Dis 2015 Jun;30(6):769-74 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25787162.

Back to top

15.3.5 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search

View PICO	NHMRC Evidence statement form NEO1a	Systematic review report NEO1a

Back to top

15.4 Neoadjuvant chemotherapy regimen

Contents

15.4.1 Background

Fluoropyrimidine-based chemotherapy is the standard choice of radiation sensitiser for use in combination with radiation treatment. Intravenous and oral routes of administration are used.

Other approaches that are not currently standard treatment for rectal cancer, but are either under investigation or have been proposed for evaluation, include:

- the addition of oxaliplatin
- neoadjuvant systemic chemotherapy cycles given without radiation
- targeted therapies such as bevacizumab, panitumumab and cetuximab.

Back to top

15.4.2 Overview of evidence (non-systematic literature review)

No systematic reviews were undertaken for this topic. Practice points were based on selected published evidence. See Guidelines development process.

15.4.2.1 Intravenous or oral fluoropyrimidine

Continuous infusional therapy is preferred over bolus injection for fluoropyrimidine-based chemotherapy, based on a 1994 study investigating bolus versus infusional adjuvant chemoradiation in 644 patients with rectal cancer, which reported that infusional 5-fluorouracil (5-FU) increased time to relapse and improved overall survival.[1]

5FU has been the standard backbone of chemotherapy in the management of both colon and rectal cancer. Capecitabine, an oral 5FU analogue, is a prodrug that is converted systemically by the enzyme thymidine phosphorylase to 5FU. Compared with infusional 5FU, it is associated with a higher risk of hand-foot syndrome, but a lower risk of neutropenia.[2]

Two randomised controlled trials (RCTs)[2][3] have shown similar outcomes for capecitabine compared with infusional 5FU when combined with radiation treatment for rectal cancer:

- A 2012 German study in 392 evaluable patients compared capecitabine or infusional 5FU with radiation treatment in the neoadjuvant setting. This was a non-inferiority study and capecitabine was found to be non-inferior for overall survival at 5 years (76% versus 67%, non-inferiority p = 0.0004).)[2]
- The larger US National Surgical Adjuvant Breast and Bowel Project (NSABP) R-04 study randomised 1608 patients to one of four arms: infusional 5FU with or without oxaliplatin, or capecitabine with or without oxaliplatin. Comparing groups receiving the 5FU- and capecitabine-based regimens, there were no statistically significantly differences in rates of sphincter preservation, pathological complete response, locoregional control or 5-year overall survival.[3][4]

Because of the risk of toxicity, and given that capecitabine is an oral cytotoxic agent self-administered at home, patients should be carefully selected, where possible, to ensure appropriate compliance with the drug in order to avoid serious toxicity from inadvertent dosing errors.

Practice point
Infusional fluoropyrimidine is preferable to bolus fluoropyrimidine for use in combination with radiation treatment for rectal cancer.

Practice point

Oral capecitabine or intravenous infusional 5FU are both acceptable agents to combine with radiation treatment for rectal cancer.

Practice point

If capecitabine is considered, patients should be carefully selected to minimise risk of non-compliance or overdosing.

Back to top

15.4.2.2 Neoadjuvant oxaliplatin

Oxaliplatin is a platinum analogue commonly used in metastatic colorectal cancer. Multiple trials have investigated its use combined with neoadjuvant radiation treatment and fluoropyrimidine in rectal cancer. Several large-scale phase III RCTs have produced somewhat conflicting results with respect to efficacy These studies have also demonstrated greater toxicity when adding oxaliplatin to fluoropyrimidine. Oxaliplatin is commonly associated with myelosuppression and peripheral neuropathy.

There have been several negative studies:

- The STAR-01 trial from Italy randomised 747 patients to standard chemoradiation with or without weekly oxaliplatin. Pathological complete response, sphincter preservation, and overall survival were not significantly different between treatment arms.[5][6]
- The ACCORD 12/0405 PRODIGE 2 trial (n=598) compared capecitabine with and without oxaliplatin in combination with radiation treatment. It reported no significant differences in rates of pathological complete response, sphincter preservation, local control or overall survival.[7][8]
- The PETACC-6 trial (n=1094) compared capecitabine with and without oxaliplatin, both before and after surgery. It reported no difference in rates of disease-free survival and overall survival with or without oxaliplatin.[9][10]
- The four-arm NSABP R-04 compared infusional 5FU alone, 5FU with oxaliplatin, capecitabine alone and capecitabine with oxaliplatin. The addition of oxaliplatin was not associated with any differences in rates of locoregional control, disease-free survival or overall survival.[4]
- A Chinese study (n=206) randomised patients to receive preoperative radiotherapy with either capecitabine or capecitabine and oxaliplatin with all patients receiving post-operative adjuvant mFOLFOX. This study found no difference in pathological complete remission, local recurrence, disease free survival and overall survival. Three year distant metastatic rate was improved with the experimental arm (16.5% vs 28.2%, p=0.045).[11]

Other large studies have yielded positive results for the role of oxaliplatin:

- The German CAO/ARO/AIO-04 trial (n=1236 assessable patients)[12] used a non-standard schedule of neoadjuvant infusional 5FU in both arm and gave oxaliplatin both before and after surgery in the experimental arm. The oxaliplatin group showed improved rates of pathological complete response and 3-year disease-free survival (75.9% versus 71.2%, p=0.03), representing an absolute 4.7% gain. It is not known whether this benefit is due to the neoadjuvant, or adjuvant oxaliplatin, or both.
- A three-arm Chinese trial (FOWARC) randomised 495 patients (475 evaluable) to radiotherapy with either infusional 5FU or mFOLFOX6, or to mFOLFOX6 without radiation treatment.[13] All arms received postoperative chemotherapy. The neoadjuvant mFOLFOX6 group showed a higher rates of pathological complete response (27.5% versus 14% for 5FU plus radiation treatment and 6% for chemotherapy alone) and a higher rate of tumour downstaging, but a similar sphincter preservation rate.[13] Survival data are not yet available.

A 2013 meta-analysis assessing short-term outcomes, which included four RCTs, similarly found that the addition of oxaliplatin improved pathological complete response rate and reduced the rate of perioperative metastases, but increased toxicity, with no differences in the rates of R0 resection, sphincter preservation or surgical complications.[14] A subsequent meta-analysis (currently only available in abstract form), which included the same studies and an additional RCT, reported similarly that the addition of oxaliplatin increased the proportion of patients who achieved pathological complete response after neoadjuvant treatment, but was again associated with higher toxicity.[15]

Practice point

Neoadjuvant oxaliplatin with radiation treatment for rectal cancer is not currently regarded as standard therapy. Data for local control or survival benefit are mixed and oxaliplatin is associated with higher toxicity than fluoropyrimidine alone.

Back to top

15.4.2.3 Neoadjuvant systemic chemotherapy

One management strategy currently under investigation is the use of initial systemic chemotherapy in the neoadjuvant setting. This approach facilitates the early delivery of systemic doses of chemotherapy, and may treat potential micrometastatic disease early rather than after radiation treatment and surgery.

Additionally, the role of chemotherapy alone, without radiation treatment, is under question – ideally avoiding short-term and late toxicities related to radiotherapy. A small number of prospective studies have investigated this approach: either neoadjuvant chemotherapy without radiation treatment, or combined with radiation treatment in various sequences. Most are small single-arm studies combining capecitabine or 5FU with oxaliplatin; several of the chemotherapy-alone studies also include bevacizumab (see *Targeted therapies*, below). A retrospective analysis of the US National Cancer Database, which compared patients with stage II/II rectal cancer reported that patients who received neoadjuvant multiagent chemotherapy had an inferior overall survival than those who received neoadjuvant chemoradiotherapy.[16] This strategy cannot be recommended outside of a clinical trial.

Practice point

The role of neoadjuvant systemic chemotherapy is still under investigation and is not regarded as routine.

Back to top

15.4.2.4 Targeted therapies

The use of targeted therapies such as bevacizumab, panitumumab and cetuximab as neoadjuvant therapy in the management of rectal cancer has not been investigated in phase III RCTs.

Bevacizumab is a humanised monoclonal antibody targeting vascular endothelial growth factor. It is routinely used in the treatment of metastatic colorectal cancer. Multiple studies, mostly small single-arm phase II trials have investigated its use in the neoadjuvant setting for rectal cancer. A 2011 systematic review[17] reported good pathological complete response rates with the use of neoadjuvant bevacizumab, but also some concerns regarding perioperative morbidity. Currently bevacizumab is not recommended in the neoadjuvant or adjuvant disease setting for rectal cancer, excepting metastatic disease.

Cetuximab and panitumumab are monoclonal antibodies targeting epidermal growth factor receptor. Efficacy in colorectal cancer is limited to patients with wild-type K-ras. These are also used routinely in the management of metastatic disease. There are several small, largely single-arm phase II studies. The largest study, the EXPERT-C trial, is a phase II RCT including 165 patients who received neoadjuvant CAPOX chemotherapy and chemoradiation, followed by adjuvant CAPOX, with or without cetuximab (both neoadjuvant and adjuvant). Sixty per cent of assessable tumours were K-ras wild-type. The addition of cetuximab improved radiological response but, importantly, not the primary endpoint of pathological complete response, and was associated with increased toxicity. Subsequent analysis did not demonstrate improvement in progression-free survival or overall survival,[18][19]

Practice point

The roles of bevacizumab, panitumumab and cetuximab in the neoadjuvant setting for rectal cancer are uncertain, based on available evidence. These are not currently available for the treatment of non-metastatic rectal cancer, and they are not indicated in this setting.

Back to top

15.4.3 References

1. ↑ O'Connell MJ, Martenson JA, Wieand HS, Krook JE, Macdonald JS, Haller DG, et al. *Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery.* N Engl J Med 1994 Aug 25;331(8):502-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8041415.
2. ↑ 2.0 2.1 2.2 Hofheinz RD, Wenz F, Post S, Matzdorff A, Laechelt S, Hartmann JT, et al. *Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial.* Lancet Oncol 2012 Jun;13(6):579-88 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22503032.

3. ↑ 3.0 3.1 O'Connell MJ, Colangelo LH, Beart RW, Petrelli NJ, Allegra CJ, Sharif S, et al. *Capecitabine and oxaliplatin in the preoperative multimodality treatment of rectal cancer: surgical end points from National Surgical Adjuvant Breast and Bowel Project trial R-04.* J Clin Oncol 2014 Jun 20;32(18):1927-34 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24799484.
4. ↑ 4.0 4.1 Allegra CJ, Yothers G, O'Connell MJ, Beart RW, Wozniak TF, Pitot HC, et al. *Neoadjuvant 5-FU or Capecitabine Plus Radiation With or Without Oxaliplatin in Rectal Cancer Patients: A Phase III Randomized Clinical Trial.* J Natl Cancer Inst 2015 Nov;107(11) Available from: http://www.ncbi.nlm.nih.gov/pubmed/26374429.
5. ↑ Aschele C, Cionini L, Lonardi S, Pinto C, Cordio S, Rosati G, et al. *Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial.* J Clin Oncol 2011 Jul 10;29(20):2773-80 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21606427.
6. ↑ Aschele C, Cionini L, Lonardi S, et al. *Final results of STAR-01: A randomized phase III trial comparing preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer.* J Clin Oncol ; 2011; 29: 2773-80.
7. ↑ Gérard JP, Azria D, Gourgou-Bourgade S, Martel-Laffay I, Hennequin C, Etienne PL, et al. *Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2.* J Clin Oncol 2010 Apr 1;28(10):1638-44 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20194850.
8. ↑ Francois, E; Gourgou-Bourgade, S; Azria, D; Conroy, T; Bouche, O; Doyen, J, et al. *ACCORD12/0405-Prodige 2 phase III trial neoadjuvant treatment in rectal cancer: Results after 5 years of follow-up.* J Clin Oncol 34, 2016 (suppl 4S; abstr 490) ;http://meetinglibrary.asco.org/content/160015-173.
9. ↑ Schmoll, H; Haustermans, K; Price, T; Nordlinger, B; Hofheinz, R; Daisne, J, et al. *Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin versus capecitabine alone in locally advanced rectal cancer: Disease-free survival results at interim analysis.* J Clin Oncol 32:5s, 2014 (suppl; abstr 3501) Available from: http://meetinglibrary.asco.org/content/134502-144.
10. ↑ Schmoll, H; Stein, A; Hofheinz, R; Price, T; Nordlinger, B; Daisne, J, et al. *Preoperative chemoradiotherapy and postoperative chemotherapy with capecitabine and oxaliplatin vs. capecitabine alone in locally advanced rectal cancer: final analyses.* Ann Oncol (2016) 27 (suppl 6): doi: 10.1093/annonc/mdw370.16 Available from: http://annonc.oxfordjournals.org/content/27/suppl_6/467PD.short?rss=1.
11. ↑ Jiao D, Zhang R, Gong Z, Liu F, Chen Y, Yu Q, et al. *Fluorouracil-based preoperative chemoradiotherapy with or without oxaliplatin for stage II/III rectal cancer: a 3-year follow-up study.* Chin J Cancer Res 2015 Dec;27(6):588-96 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26752933.
12. ↑ Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, et al. *Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years.* J Clin Oncol 2012 Jun 1;30(16):1926-33 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22529255.
13. ↑ 13.0 13.1 Deng Y, Chi P, Lan P, Wang L, Chen W, Cui L, et al. *Modified FOLFOX6 With or Without Radiation Versus Fluorouracil and Leucovorin With Radiation in Neoadjuvant Treatment of Locally Advanced Rectal Cancer: Initial Results of the Chinese FOWARC Multicenter, Open-Label, Randomized Three-Arm Phase III Trial.* J Clin Oncol 2016 Sep 20;34(27):3300-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27480145.

14. ↑ An X, Lin X, Wang FH, Goodman K, Cai PQ, Kong LH, et al. *Short term results of neoadjuvant chemoradiotherapy with fluoropyrimidine alone or in combination with oxaliplatin in locally advanced rectal cancer: a meta analysis.* Eur J Cancer 2013 Mar;49(4):843-51 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23063351.
15. ↑ Wyrwicz L, Temnyk M, Spalek M. *The addition of oxaliplatin increases pathological complete response: a meta-analysis of randomized controlled trials on radiochemotherapy in rectal cancer.* Ann Oncol (2016) 27 (suppl 2): ii65 Available from: http://annonc.oxfordjournals.org/content/27/suppl_2/ii65.3.short?rss=1#.
16. ↑ Cassidy RJ, Liu Y, Patel K, Zhong J, Steuer CE, Kooby DA, et al. *Can we eliminate neoadjuvant chemoradiotherapy in favor of neoadjuvant multiagent chemotherapy for select stage II/III rectal adenocarcinomas: Analysis of the National Cancer Database.* Cancer 2016 Oct 25 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27780316.
17. ↑ Fornaro L, Caparello C, Vivaldi C, Rotella V, Musettini G, Falcone A, et al. *Bevacizumab in the pre-operative treatment of locally advanced rectal cancer: a systematic review.* World J Gastroenterol 2014 May 28;20(20):6081-91 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24876730.
18. ↑ Sclafani F, Gonzalez D, Cunningham D, Hulkki Wilson S, Peckitt C, Giralt J, et al. *RAS mutations and cetuximab in locally advanced rectal cancer: results of the EXPERT-C trial.* Eur J Cancer 2014 May;50(8): 1430-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24582914.
19. ↑ Dewdney A, Cunningham D, Tabernero J, Capdevila J, Glimelius B, Cervantes A, et al. *Multicenter randomized phase II clinical trial comparing neoadjuvant oxaliplatin, capecitabine, and preoperative radiotherapy with or without cetuximab followed by total mesorectal excision in patients with high-risk rectal cancer (EXPERT-C).* J Clin Oncol 2012 May 10;30(14):1620-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22473163.

Back to top

15.5 Optimal timing surgery after neoadjuvant therapy

15.5.1 Background

Traditionally, surgery is timed to occur 6-8 weeks after completion of neoadjuvant long-course chemoradiation. This is to allow enough time for pathological downstaging as well as patient recovery from neoadjuvant treatment. On the other hand, waiting too long could possibly increase the risk of tumour regrowth, metastatic potential, or the development of fibrosis making surgery more challenging.

An interval of at least 6 weeks between chemoradiation and surgery is favoured, based on the 1999 Lyon R90-01 study comparing intervals of less than 2 weeks and 68 weeks from radiation treatment completion to surgery. It found that the 6- to 8-week period improved tumour downstaging rates, compared with a shorter period.[1] A 6-week wait was also the schedule used in the seminal German CAO/ARO/AIO-94 study rectal cancer study.[2]

15.5.2 Overview of evidence (non-systematic literature review)

No systematic reviews were undertaken for this topic. Practice points were based on selected published evidence. See Guidelines development process.

A 2016 meta-analysis[3] included 13 prospective or retrospective studies investigating intervals between chemoradiation and surgery that were either longer or shorter than the 'traditional' 6- to 8-week period (over 3500 patients in total). It found that waiting longer than 8 weeks was associated with an increased pathological complete response rate: risk ratio (RR) 1.42 (95% CI 1.19 to 1.68, $p < 0.0001$). There were no differences in survival outcomes, R0 resection or sphincter preservation rates, or complications. However, this meta-analysis did not include any randomised controlled trials (RCT) and is largely based on retrospective data.[3]

Three phase III RCTs have directly addressed this question:

- In the Lyon R90-01 study, 210 patients who received radiation treatment (39Gy in 13 daily fractions) were randomised to surgery within 2 weeks or at 6–8 weeks from completion of radiation treatment.[1] A higher rate of pathological complete response was noted in the longer wait group, but no difference in overall survival was seen. However, the results of this study are difficult to interpret because it used a hypo-fractionated schedule, compared with standard schedules.
- In the GRECCAR-6 study, 265 patients were randomised to undergo surgery 7 versus 11 weeks post completion of chemoradiation.[4] There was no difference in in the rates of pathological complete response or sphincter preservation between arms. Of some concern, the 11-week arm had a non-significantly higher rate of conversion to open surgery (15% versus 10%, $p = 0.26$) and more postoperative complications, including perineal healing complications if abdominoperineal resection was required.
- The UK NCT 01037049 trial, reported in abstract form and not yet published, randomised 237 patients with high risk features to surgery at either 6 weeks or 12 weeks after CRT.[5] Patients in the 12-week arm were more frequently downstaged (58% versus 43%, p=0.019) and had a higher pCR rate (20% versus 9%,P<0. 05). No significant difference was seen in surgical morbidity.

A retrospective cohort study using the National Cancer Database, published in 2016, included 6397 patients who had neoadjuvant therapy followed by surgery.[6] Of those patients who had pathological complete response, 76.2% had surgery within 60 days. Delaying surgery more than 60 days in this cohort study was associated with a higher risk of positive surgical margins and decreased likelihood of sphincter preservation, as well as shorted overall survival (hazard ratio [HR] 1.3; 95% CI 1.19 to 1.45 $p < 0.001$). This is retrospective data and thus should be interpreted with caution.

Interim results from the Stockholm III trial are available.[7] This study randomised 657 patients between 1998 and 2010 to one of three arms: short-course radiation treatment with immediate surgery, short-course radiation treatment with surgery after 4–8 weeks, or long-course radiation treatment with surgery after 4–8 weeks. A pre-

planned interim analysis reported that patients who had short-course radiation treatment with delayed (4–8 weeks) surgery showed better outcomes, compared with those who had immediate surgery, including higher rates of tumour downstaging, pathologic complete regression (11.8% versus 1.7%), and tumour regression. It remains to be seen whether this translates to improved recurrence-free or overall survival. It was also observed that patients receiving short-course radiotherapy followed by surgery in between 11 and 17 days after the start of radiotherapy had the highest complication rate. Surgery should be avoided in this time window.

Practice point

Available data for the optimal timing between completion of neoadjuvant C-RT and surgery indicate that surgery at least 6 weeks but by 12 weeks appears to be appropriate, until results from further studies become available.

Practice point

Waiting longer within the 6-12 week time frame to allow optimal pathological downstaging may be selected preferentially, for example for patients with T4 tumours, where maximal downstaging is desirable.

Back to top

15.5.3 References

1. ↑ [1.0] [1.1] Francois Y, Nemoz CJ, Baulieux J, Vignal J, Grandjean JP, Partensky C, et al. *Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90-01 randomized trial.* J Clin Oncol 1999 Aug;17(8):2396 Available from: http://www.ncbi.nlm.nih.gov/pubmed/10561302.
2. ↑ Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al. *Preoperative versus postoperative chemoradiotherapy for rectal cancer.* N Engl J Med 2004 Oct 21;351(17):1731-40 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15496622.
3. ↑ [3.0] [3.1] Petrelli F, Sgroi G, Sarti E, Barni S. *Increasing the Interval Between Neoadjuvant Chemoradiotherapy and Surgery in Rectal Cancer: A Meta-analysis of Published Studies.* Ann Surg 2016 Mar;263(3):458-64 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24263329.
4. ↑ Lefevre JH, Mineur L, Kotti S, Rullier E, Rouanet P, de Chaisemartin C, et al. *Effect of Interval (7 or 11 weeks) Between Neoadjuvant Radiochemotherapy and Surgery on Complete Pathologic Response in Rectal Cancer: A Multicenter, Randomized, Controlled Trial (GRECCAR-6).* J Clin Oncol 2016 Jul 18 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27432930.

5. ↑ Evans, J; Bhoday, J; Sizer, B; Tekkis, B; Swift, R; Perez, R; et al. *Results of a prospective randomised control 6 vs 12 trial: Is greater tumour downstaging observed on post treatment MRI if surgery is delayed to 12-weeks versus 6-weeks after completion of neoadjuvant chemoradiotherapy?* Ann Oncol (2016) 27 (suppl 6): doi: 10.1093/annonc/mdw370.01 [cited 2016 Dec 28] Available from: http://annonc.oxfordjournals.org/content/27/suppl_6/452O.full.
6. ↑ Huntington CR, Boselli D, Symanowski J, Hill JS, Crimaldi A, Salo JC. *Optimal Timing of Surgical Resection After Radiation in Locally Advanced Rectal Adenocarcinoma: An Analysis of the National Cancer Database.* Ann Surg Oncol 2016 Mar;23(3):877-87 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26514119.
7. ↑ Pettersson D, Lörinc E, Holm T, Iversen H, Cedermark B, Glimelius B, et al. *Tumour regression in the randomized Stockholm III Trial of radiotherapy regimens for rectal cancer.* Br J Surg 2015 Jul;102(8):972-8; discussion 978 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26095256.

Back to top

15.6 Adjuvant therapy for rectal cancer

Contents

See sections:

- Postoperative chemotherapy
- Postoperative radiation treatment|

15.6.1 Adjuvant therapy for rectal cancer

Contents

See sections:

- Postoperative chemotherapy
- Postoperative radiation treatment|

15.6.2 Postoperative chemotherapy

Contents

15.6.2.1 Background

The aim of adjuvant chemotherapy is to eliminate micrometastatic disease, thereby reducing the risk of cancer recurrence and improving recurrence-free and overall survival.

Many studies that had reported benefit for adjuvant chemotherapy in this setting occurred in the era preceding neoadjuvant chemoradiation, before surgical advances became part of standard treatment. Pathological complete response to neoadjuvant therapy occurs in 10–20% of patients and is associated with a good prognosis.[1] As such, the role of postoperative therapy has now been brought into question.

Postoperative adjuvant therapy for cancers above the peritoneal reflection should be decided as per colon cancer recommendations (see Adjuvant treatment for colon cancer).

Oxaliplatin in combination with a fluoropyrimidine has now become standard therapy for stage III colon cancer, based on several trials including the MOSAIC[2] and NSABP C-07[3] studies (see Adjuvant treatment for colon cancer). It has since been investigated for rectal cancer.

Back to top

15.6.2.2 Overview of evidence (non-systematic literature review)

No systematic reviews were undertaken for this topic. Practice points were based on selected published evidence. See Guidelines development process.

15.6.2.2.1 Post-operative adjuvant chemotherapy for rectal cancer following preoperative neoadjuvant therapy

Two recent systematic reviews and meta-analyses were published in 2015 addressing this issue specifically in patients who had received prior neoadjuvant therapy:

- A 2015 systematic review and meta-analysis[4] included four eligible phase III randomised controlled trials (RCTs) in patients with stage II or III rectal cancer with R0 resection (n = 1196). It found no significant differences in overall survival between those patients who received adjuvant chemotherapy compared with observation alone (hazard ratio [HR] 0.97, p=0.775). Disease-free survival and distant recurrences were also similar between arms. Subgroup analysis indicated that those patients with upper rectal tumour (10–15 cm from the anal verge) benefited from chemotherapy, with improved disease-free survival and less distant recurrence. This was based on individual patient data meta-analysis. However, there was no difference in survival outcomes with or without chemotherapy for patients with pathological stage III (node positive) versus stage II disease, or based on pathological nodal status (N0 vs N1 vs N2).

- A 2015 systematic review and meta-analysis[5] included two RCTs, one pooled analysis of five additional RCTs, and 10 retrospective studies, including 5457 patients in total. This analysis found improved 5 year overall survival (OR 0.64, p = 0.0006) and 5-year disease-free survival (odds ratio [OR] 0.71, p < 0.0001) but noted most of this benefit was limited to the retrospective studies. Subgroup analysis of those with node positive disease was not undertaken.

A 2012 Cochrane meta-analysis of adjuvant chemotherapy for rectal cancer, including literature published between 1975 and 2011, included 21 RCTs and nearly 10,000 patients with rectal cancer.[6] Only adjuvant 5FU was used in these trials (i.e. no oxaliplatin or other agents). The Cochrane review found that adjuvant chemotherapy significantly reduced the risk of death and disease recurrence. However, only one of these trials included neoadjuvant chemoradiation for all patients, so the data are hard to interpret in the context of today's conventional neoadjuvant treatment. In the three trials that reported data separately for stage III (node positive) rectal cancer, there was no difference in overall survival for patients with stage III disease who did and did not receive adjuvant chemotherapy.

Overall, the benefit of fluoropyrimidine-based adjuvant chemotherapy for patients is somewhat uncertain in the modern management of rectal cancer, which includes neoadjuvant treatment and more anatomically appropriate surgery (such as total mesorectal excision) than previously. International guidelines vary. The US National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines recommends adjuvant chemotherapy, preferably doublet therapy including oxaliplatin, for any T3-4 or node positive rectal cancer.[7] European Society for Medical Oncology (ESMO) Guidelines note that adjuvant chemotherapy 'can be given' for high risk stage II and stage III rectal cancer but acknowledge that the level of scientific evidence for benefit is much lower than for colon cancer.[8] The St Gallen European Organisation for Research and Treatment of Cancer (EORTC) Consensus Panel agreed that for tumours staged clinically and pathologically as N0, adjuvant chemotherapy was not recommended.[9] However, for cN+ downstaged to pN0 there was no consensus, and most participants preferred to deliver adjuvant therapy for pN+ disease.[9]

Practice point

Strong evidence for benefit of adjuvant chemotherapy for rectal cancer is lacking, even in patients with node positive disease. In disease regarded as high risk, the uncertain benefits of adjuvant chemotherapy should be acknowledged.

Practice point

Patients with upper third rectal tumours (10–15cm from the anal verge) with either cN+ or pN+ findings, are possibly those who may derive any/most benefit from adjuvant chemotherapy.

Back to top

15.6.2.2.2 The role for oxaliplatin as adjuvant therapy in rectal cancer

Several trials have investigated the role of oxaliplatin in the adjuvant setting for rectal cancer:

- The ADORE phase II RCT conducted in Korea, randomised 321 patients with resected stage II/III rectal cancer who had received neoadjuvant CRT, to four cycles of adjuvant bolus 5FU/LV or eight cycles of FOLFOX chemotherapy.[10] At 3-year follow-up, disease-free survival was improved favouring the FOLFOX arm (71.6% versus 62.9%, HR 0.657, p = 0.047). The benefit appeared limited to patients with pathological stage III disease with no benefit observed for those with stage II cancer. Overall survival was also improved for the FOLFOX arm (3-year overall survival 95% versus 85.7%; HR 0.456, p = 0.036). Higher rates of toxicities were observed in the FOLFOX arm, including myelosuppression and neuropathy.

- The CHRONICLE phase III RCT[11] compared either observation alone or six cycles of XELOX (capecitabine and oxaliplatin) therapy in 113 patients with resected rectal cancer following chemoradiation. This study closed prematurely and did not meet its target recruitment of 780 patients so interpretation is limited due to low statistical power. Only 48% of patients assigned to postoperative chemotherapy completed all six cycles, with 39% of these patients having dose reductions and 40% experiencing grade 3–4 toxicities. The 3-year disease-free survival was not significantly different: 78% (chemotherapy) versus 71%, HR 0.8, p = 0.56, and 3-year overall survival was also similar.

A 2016 systematic review and meta-analysis included four RCTs (n = 2793) including both the above trials and also the PETACC-6 and CAO/ARO/AIO-04 studies, both of which included postoperative oxaliplatin in their randomisations.[12] It reported that adjuvant oxaliplatin-based chemotherapy was associated with improved disease-free survival (HR 0.85, p = 0.03) but no difference in overall survival, compared with fluoropyrimidine-based chemotherapy alone.[12] Comparison between stage II and stage III disease was not made. Similar compliance levels, but higher toxicities were noted for oxaliplatin-containing arms. Notably there was significant heterogeneity; in particular regimens differed considerably across the trials and follow up to date is relatively short.[12]

A second review and meta-analysis of five randomized trials (either fluoropyrimidine-only or fluoropyrimidine plus oxaliplatin-based adjuvant chemotherapy) did not find an overall survival or disease-free survival benefit, when comparing adjuvant oxaliplatin-based chemotherapy with fluoropyrimidine alone.[13]

Practice point

For patients with pathological stage II/III rectal cancer, adjuvant oxaliplatin-based chemotherapy is associated with increased toxicities. Benefits, if any, may be confined to those with stage III disease; but not all data concur.

Practice point

The uncertain benefits of oxaliplatin as adjuvant therapy in rectal cancer should be acknowledged.

Back to top

15.6.2.2.3 The role of adjuvant chemotherapy after pathological complete response

A 2012 systematic review and meta-analysis of patient outcomes following pathological complete response, which included 16 studies, demonstrated that those patients with a pathological complete response had fewer local recurrences (OR 0.25, p = 0.002) and lower rates of distant failure (OR 0.23, p < 0.001).[14] It was noted that 61.4% of patients in the pathological complete response cohort received adjuvant chemotherapy.

A 2015 pooled analysis of individual patient data from 13 separate datasets, included 3313 patients, 898 (27%) of whom achieved pathological complete response after neoadjuvant chemoradiation and surgery.[15] These patients had good prognosis, with statistically improved recurrence-free, disease-free and overall survival compared with patients who did not achieve pathological complete response. Of these patients, 290 (32%) subsequently had adjuvant chemotherapy whilst 608 (68%) did not. For those patients with pathological complete response, adjuvant chemotherapy made no impact on rates of recurrence-free survival, disease-free survival, or overall survival.

One prospective Spanish single-institution study included 176 patients with cT3-4 rectal cancer who received neoadjuvant chemoradiation then surgery. Those who had pathological complete response did not receive adjuvant chemotherapy. For 26 patients (15%) who achieved pathological complete response, 5-year disease-free survival was 95% and overall survival was 100%.[16] Follow-up of 210 patients from a single-institution database in China identified 40 patients with pathological complete response following neoadjuvant chemoradiation and surgery, of whom 19 received post-operative chemotherapy and 21 did not (non-randomised). Five-year disease free survival was 90% and 76% ($p = 0.142$). Retrospective studies are however limited by selection bias among other biases.

Data for the role of adjuvant chemotherapy following pathological complete response is otherwise largely limited to retrospective studies. A 2006 retrospective study of 95 patients who had received chemoradiation followed by surgery observed that chemotherapy added no additional 3-year disease-free survival benefit for patients with pathological node-negative disease.[17]

With large studies of adjuvant chemotherapy in rectal cancer (regardless of pathological response) not showing clear benefit for adjuvant chemotherapy, it would seem intuitive that those with pathological complete response, who inherently have better prognosis, could avoid its potential toxicities. Given that a RCT comparing observation with adjuvant therapy in patients with pathological complete response is unlikely, decisions need to be made on the basis of available prospective and retrospective cohort studies. The St Gallen EORTC consensus panel was divided as to whether or not adjuvant chemotherapy should be given in this context.[9]

Practice point

There are no randomised trials for adjuvant chemotherapy for patients with pathological complete response after chemoradiation followed by surgery. Available evidence suggests that these patients have a very good prognosis and any absolute benefits are likely to be small.

Back to top

15.6.2.3 References

1. ↑ Maas M, Nelemans PJ, Valentini V, Das P, Rödel C, Kuo LJ, et al. *Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data.* Lancet Oncol 2010 Sep;11(9):835-44 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20692872.
2. ↑ André T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, et al. *Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial.* J Clin Oncol 2009 Jul 1;27(19):3109-16 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19451431.
3. ↑ Yothers G, O'Connell MJ, Allegra CJ, Kuebler JP, Colangelo LH, Petrelli NJ, et al. *Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses.* J Clin Oncol 2011 Oct 1;29(28):3768-74 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21859995.
4. ↑ Breugom AJ, Swets M, Bosset JF, Collette L, Sainato A, Cionini L, et al. *Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data.* Lancet Oncol 2015 Feb;16(2):200-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25589192.
5. ↑ Petrelli F, Coinu A, Lonati V, Barni S. *A systematic review and meta-analysis of adjuvant chemotherapy after neoadjuvant treatment and surgery for rectal cancer.* Int J Colorectal Dis 2015 Apr;30(4):447-57 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25433820.
6. ↑ Petersen SH, Harling H, Kirkeby LT, Wille-Jørgensen P, Mocellin S. *Postoperative adjuvant chemotherapy in rectal cancer operated for cure.* Cochrane Database Syst Rev 2012 Mar 14;(3):CD004078 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22419291.
7. ↑ National Comprehensive Cancer Network. *NCCN Guidelines for Rectal Cancer Version 2.*; 2016 Available from: https://www.tri-kobe.org/nccn/guideline/colorectal/english/rectal.pdf.
8. ↑ Glimelius B, Tiret E, Cervantes A, Arnold D, ESMO Guidelines Working Group.. *Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.* Ann Oncol 2013 Oct;24 Suppl 6:vi81-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24078665.
9. ↑ [9.0] [9.1] [9.2] Lutz MP, Zalcberg JR, Glynne-Jones R, Ruers T, Ducreux M, Arnold D, et al. *Second St. Gallen European Organisation for Research and Treatment of Cancer Gastrointestinal Cancer Conference: consensus recommendations on controversial issues in the primary treatment of rectal cancer.* Eur J Cancer 2016 May 30;63:11-24 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27254838.
10. ↑ Hong YS, Nam BH, Kim KP, Kim JE, Park SJ, Park YS, et al. *Oxaliplatin, fluorouracil, and leucovorin versus fluorouracil and leucovorin as adjuvant chemotherapy for locally advanced rectal cancer after preoperative chemoradiotherapy (ADORE): an open-label, multicentre, phase 2, randomised controlled trial.* Lancet Oncol 2014 Oct;15(11):1245-53 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25201358.
11. ↑ Glynne-Jones R, Counsell N, Quirke P, Mortensen N, Maraveyas A, Meadows HM, et al. *Chronicle: results of a randomised phase III trial in locally advanced rectal cancer after neoadjuvant chemoradiation randomising postoperative adjuvant capecitabine plus oxaliplatin (XELOX) versus control.* Ann Oncol 2014 Jul;25(7):1356-62 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24718885.

12. ↑ 12.0 12.1 12.2 Zhao L, Liu R, Zhang Z, Li T, Li F, Liu H, et al. *Oxaliplatin/fluorouracil-based adjuvant chemotherapy for locally advanced rectal cancer after neoadjuvant chemoradiotherapy and surgery: a systematic review and meta-analysis of randomized controlled trials.* Colorectal Dis 2016 Aug;18(8):763-72 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27169752.
13. ↑ Boustani J, Caubet M, Bosset JF. *Adjuvant Chemotherapy in Rectal Cancer after Chemoradiotherapy.* Clin Oncol (R Coll Radiol) 2016 Feb;28(2):140-5 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26698026.
14. ↑ Martin ST, Heneghan HM, Winter DC. *Systematic review and meta-analysis of outcomes following pathological complete response to neoadjuvant chemoradiotherapy for rectal cancer.* Br J Surg 2012 Jul;99(7):918-28 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22362002.
15. ↑ Maas M, Nelemans PJ, Valentini V, Crane CH, Capirci C, Rödel C, et al. *Adjuvant chemotherapy in rectal cancer: defining subgroups who may benefit after neoadjuvant chemoradiation and resection: a pooled analysis of 3,313 patients.* Int J Cancer 2015 Jul 1;137(1):212-20 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25418551.
16. ↑ García-Albéniz X, Gallego R, Hofheinz RD, Fernández-Esparrach G, Ayuso-Colella JR, Bombí JA, et al. *Adjuvant therapy sparing in rectal cancer achieving complete response after chemoradiation.* World J Gastroenterol 2014 Nov 14;20(42):15820-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25400468.
17. ↑ Fietkau R, Barten M, Klautke G, Klar E, Ludwig K, Thomas H, et al. *Postoperative chemotherapy may not be necessary for patients with ypN0-category after neoadjuvant chemoradiotherapy of rectal cancer.* Dis Colon Rectum 2006 Sep;49(9):1284-92 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16758130.

Back to top

15.6.3 Postoperative radiation treatment

Where possible, preoperative radiation treatment is favoured over postoperative radiation treatment as several trials discussed previously, including the landmark German CAO/ARO/AIO-94 study,[1][2] have shown that a neoadjuvant approach is more effective (less local recurrence) and less toxic, than postoperative delivery of radiation treatment. This approach would only ever be considered on an individual basis if preoperative radiation treatment (or chemoradiation) had not been delivered and pathological staging revealed unexpectedly higher-risk disease (T3 +/- N1-2, or R1 resection).[3]

In ideal circumstances, preoperative discussion and review of clinical details and MRI imaging in a multidisciplinary setting should reduce the proportion of patients who then require postoperative radiotherapy. However, no test is 100% sensitive, so unexpected upstaging at the time of histopathological assessment does occur.

A meta-analysis of 8 randomised trials of 2157 patients shows that post-operative adjuvant radiotherapy significantly reduces the yearly risk of local recurrence by 37% compared to surgery alone (p=0.002).[3]

The National Institute of Health (NIH) made a clinical announcement in 1991 about the benefits of a sequential regimen of 5-flurouracil based chemotherapy and radiation therapy in reducing overall tumour recurrence rates, local recurrence and prolong survival in patients with resected stage II and III rectal cancer.[4] This was based on the results of the Krook trial[5] in 204 patients demonstrating that a combination of post operative radiation with 5-FU and systemic therapy with a flurouracil based regimen reduced recurrence by 34% (p = 0.0016), local recurrence by 46% (p = 0.036) and distant metastasis by 37%(p = 0.01) and overall death rate by 29% (p = 0.025) compared to radiation alone. The INT0114 study of 1695 patients compared bolus 5FU alone, 5FU plus leucovorin, 5FU plus levamisole and 5FU plus leucovorin all with pelvic radiation post operatively. No difference in disease free survival or overall survival was seen.[6]

INT861751 randomised 660 patients with high risk rectal cancer to post operative 5FU given by bolus or protracted venous infusion (PVI) during radiotherapy. PVI demonstrated an improved disease free survival and overall survival predominantly in reducing distant relapse. The subsequent large INT0144 study of 1917 patients [7] however found no difference in relapse free survival or overall survival at 3 years for patients receiving post-operative pelvic radiotherapy with one of three adjuvant chemotherapy protocols: 1) bolus 5FU in two 5 day cycles before and after radiotherapy plus PVI 5FU during radiation, PVI 5FU 42 days before and 56 days after radiation and concurrent PVI 5FU or 3) bolus 5FU plus leucovorin in two 5 day cycles before and after radiation with bolus 5FU and levamisole. The PVI arm had a much lower haematological toxicity rate than the bolus arms.

Practice point

Patients with higher risk disease post-operatively who did not receive neoadjuvant treatment should be considered for adjuvant pelvic radiotherapy concurrent with 5 fluorouracil chemotherapy.

References

1. ↑ Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al. *Preoperative versus postoperative chemoradiotherapy for rectal cancer.* N Engl J Med 2004 Oct 21;351(17):1731-40 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15496622.
2. ↑ Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, et al. *Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years.* J Clin Oncol 2012 Jun 1;30(16):1926-33 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22529255.
3. ↑ [3.0] [3.1] Colorectal Cancer Collaborative Group.. *Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials.* Lancet 2001 Oct 20;358(9290):1291-304 Available from: http://www.ncbi.nlm.nih.gov/pubmed/11684209.
4. ↑ National Cancer Institute. *Benefits of adjuvant therapy for rectal cancer.* [homepage on the internet] US National Library of Medicine; 1991 Mar 13 [cited 2017 Jan 4]. Available from: https://www.nlm.nih.gov/databases/alerts/rectal_cancer.html.

5. ↑ Krook JE, Moertel CG, Gunderson LL, Wieand HS, Collins RT, Beart RW, et al. *Effective surgical adjuvant therapy for high-risk rectal carcinoma.* N Engl J Med 1991 Mar 14;324(11):709-15 Available from: http://www.ncbi.nlm.nih.gov/pubmed/1997835.
6. ↑ Tepper JE, O'Connell M, Niedzwiecki D, Hollis DR, Benson AB 3rd, Cummings B, et al. *Adjuvant therapy in rectal cancer: analysis of stage, sex, and local control--final report of intergroup 0114.* J Clin Oncol 2002 Apr 1;20(7):1744-50 Available from: http://www.ncbi.nlm.nih.gov/pubmed/11919230.
7. ↑ Smalley SR, Benedetti JK, Williamson SK, Robertson JM, Estes NC, Maher T, et al. *Phase III trial of fluorouracil-based chemotherapy regimens plus radiotherapy in postoperative adjuvant rectal cancer: GI INT 0144.* J Clin Oncol 2006 Aug 1;24(22):3542-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16877719.

Back to top

15.7 Discussion

Contents

15.7.1 Unresolved issues

The optimal protocol for neoadjuvant therapy, including the role of chemotherapy cycles at systemic doses, has not been determined. One observational study reported clinical complete response rates of up to 48% with the administration of extra chemotherapy in the wait period after chemoradiotherapy.[1]

15.7.2 Studies currently underway

Several randomised controlled trials (RCTs) are currently underway that should help to inform management of rectal cancer. In particular, the role of short-course versus long-course neoadjuvant treatment and the role of neoadjuvant chemotherapy cycles are two key areas for which additional prospective trial data will become available. Trials include (but are not limited to):

- The Stockholm III study[2] of short-course versus long-course radiation treatment.. This trial randomised 657 patients between 1998 and 2010 to one of three arms: short-course radiation treatment with immediate surgery (within a week), short-course radiation treatment with delayed surgery (4–8 weeks), or long-course RT with surgery within 4–8 weeks. Survival outcomes are yet to be reported.
- The PROSPECT/N1048 trial, a phase III RCT study assigning patients to standard preoperative chemoradiation treatment followed by total mesorectal excision and then adjuvant FOLFOX versus six cycles of preoperative FOLFOX with risk-adjusted use of preoperative radiation therapy.[3]
- The PRODIGE 23, an RCT comparing neoadjuvant chemoradiation with capecitabine then 6 months of adjuvant chemotherapy, with six cycles of FOLFIRINOX chemotherapy prior to chemoradiation, then 3 months of adjuvant chemotherapy. The adjuvant chemotherapy can be either mFOLFOX6 or capecitabine.[4]
- The phase III RAPIDO trial, which randomises patients with high risk rectal cancer (T4 and/or N2, other high risk features) to neoadjuvant chemoradiation with capecitabine then optional postoperative chemotherapy, or short course radiation treatment plus six cycles of neoadjuvant CAPOX without postoperative chemotherapies.[4]

15.7.3 Future research priorities

Future research priorities should include the validation of biomarkers to help guide management of rectal cancer. These may include both prognostic and predictive biomarkers to help determine the level of intensity of therapy as well as the most appropriate drug selection. In ideal circumstances treatment could be tailored to the individual on the basis of clinical, tumour and biomarker characteristics.

More robust methods to determine clinical complete response after neoadjuvant therapy are needed to help better help to better stratify patients into those who require surgery and those who can possibly be treated with an organ preservation strategy or ‘watch and wait’ protocols.

Multiple developments have occurred over the last two decades with respect to the management of curable rectal cancer resulting in greater locoregional disease control. Ongoing studies will help inform the best anti-cancer agents to use in the neoadjuvant disease setting, and the optimal timing of radiotherapy and surgery.

15.7.4 References

1. ↑ Habr-Gama A, Perez RO, Sabbaga J, Nadalin W, São Julião GP, Gama-Rodrigues J. *Increasing the rates of complete response to neoadjuvant chemoradiotherapy for distal rectal cancer: results of a prospective study using additional chemotherapy during the resting period.* Dis Colon Rectum 2009 Dec;52(12):1927-34 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19934911.
2. ↑ Pettersson D, Lörinc E, Holm T, Iversen H, Cedermark B, Glimelius B, et al. *Tumour regression in the randomized Stockholm III Trial of radiotherapy regimens for rectal cancer.* Br J Surg 2015 Jul;102(8):972-8; discussion 978 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26095256.
3. ↑ ClinicalTrials.gov Identifier: NCT01515787. *PROSPECT: Chemotherapy Alone or Chemotherapy Plus Radiation Therapy in Treating Patients With Locally Advanced Rectal Cancer Undergoing Surgery.* Available from: https://clinicaltrials.gov/ct2/show/NCT01515787.
4. ↑ [4.0] [4.1] Nilsson PJ, van Etten B, Hospers GA, Påhlman L, van de Velde CJ, Beets-Tan RG, et al. *Short-course radiotherapy followed by neo-adjuvant chemotherapy in locally advanced rectal cancer--the RAPIDO trial.* BMC Cancer 2013 Jun 7;13:279 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23742033.

Back to top

16 Management resectable locally recurrent and metastatic disease

Contents

Sections:

16.1 Introduction: management resectable locally recurrent and metastatic disease

Contents

Sections:

16.2 Investigation of recurrent colorectal cancer

Consensus-based recommendation
Insert here.

Back to top

References

16.3 Management of recurrent, resectable CRC (MNG13)

Contents

Insert content here

Back to top

16.3.1 Evidence summary and recommendations

16.3.2 References

Back to top

16.3.3 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search

View PICO	NHMRC Evidence statement form MNG13	Systematic review report MNG13

Back to top

16.4 Management of metastatic resectable CRC (MNG14)

Contents

Insert content here

Back to top

16.4.1 Evidence summary and recommendations

16.4.2 References

Back to top

16.4.3 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search

View PICO	NHMRC Evidence statement form MNG14	Systematic review report MNG14

Back to top

16.5 Introduction: management of non resectable recurrent metastatic CRC

16.5.1 Management of non-resectable locally recurrent disease and metastatic disease

Among patients with metastatic colorectal cancer, curative treatment can only be proposed for those in whom both the primary and distant metastases are resectable. Rates of long-term survival and cure after complete resection are between 20% and 50%.[1][2] The majority of patients with metastatic colorectal cancer will not have disease that can be surgically resected with curative intent. For these patients, the goal of care is generally palliative. Aims may include prolongation of survival, improvement of tumour related symptoms, and maintenance of quality of life.

At the time of diagnosis, up to 25% of patients with colorectal cancer present with synchronous metastases.[3] Initial management of the primary site in patients who present with metastatic disease is controversial. The choice and sequence of treatment is guided by the presence and absence of symptoms from the primary tumour and whether or not the metastases are potentially resectable.

The optimal treatment strategy for patients with non-resectable metastatic colorectal cancer is rapidly evolving. The past 10 years have seen unprecedented advances in the treatment of metastatic colorectal cancer, with a doubling of the average median survival and patients usually living longer than 2 years. When immediate surgical resection of colorectal liver metastases is not possible, treatment modalities include systemic chemotherapy and liver-directed therapies.

Active systemic therapies include the fluoropyrimidines, oxaliplatin, irinotecan, the therapeutic monoclonal antibodies (bevacizumab, cetuximab and panitumumab) and the multikinase inhibitors. The best way to combine and sequence all of these agents is not known. Increasingly, biomarker expression is driving therapeutic decision-making. In a small percentage of patients, primarily non-resectable liver metastases may become resectable after responding to chemotherapy. However, fewer than 10% of patients treated with chemotherapy alone are alive beyond 5 years.

Liver-directed therapies include invasive thermal ablation and techniques for reducing blood supply to the metastases, such as embolisation.

For an individual patient, defining the goal of treatment informs the choice of first-line systemic treatment and the integration and sequencing of multimodal therapies. Palliative chemotherapy and other systemic therapies can significantly improve overall survival and quality of life, and are the mainstay of therapy for patients with non-resectable metastatic colorectal cancer who have adequate performance status to undergo these treatments.

16.5.1.1 Contents

Subsections:

- What is the impact of different liver directed therapies in patients with unresectable metastatic disease? MNG16
- How should a synchronous primary be managed in patients with metastatic disease? MNG17 NARRATIVE

16.5.2 References

1. ↑ Belot A, Grosclaude P, Bossard N, Jougla E, Benhamou E, Delafosse P, et al. *Cancer incidence and mortality in France over the period 1980-2005.* Rev Epidemiol Sante Publique 2008 Jun;56(3):159-75 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18547762.
2. ↑ Cotte E, Villeneuve L, Passot G, Boschetti G, Bin-Dorel S, Francois Y, et al. *GRECCAR 8: impact on survival of the primary tumor resection in rectal cancer with unresectable synchronous metastasis: a randomized multicentre study.* BMC Cancer 2015 Feb 12;15:47 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25849254.
3. ↑ Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier AM. *Epidemiology and management of liver metastases from colorectal cancer.* Ann Surg 2006 Aug;244(2):254-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16858188.

Back to top

16.6 Liver directed therapies, unresectable metastatic CRC (MNG16)

Contents

Insert content here

Back to top

16.6.1 Background

The liver is the most common site for metastases of colorectal cancer.[1] Nearly 50% of metastatic colorectal cancer patients will develop liver metastases during the course of their disease, with half having hepatic metastases at the time of primary diagnosis and the other half developing metachronous disease.[2]

Multiple locoregional strategies have been trialled in an attempt to improve the long-term outcome for patients with non-resectable metastatic colorectal cancer, and to achieve better control of liver metastases.

Current technologies include:

- hepatic arterial infusion of chemotherapy agents
- invasive thermal ablation with distinct size limitations (e.g. radiofrequency ablation
- conformal radiation treatment techniques (e.g. stereotactic body radiotherapy and high-dose rate brachytherapy)
- selective internal radiation treatment
- embolisation techniques:
  - chemoembolisation (e.g. the use of drug-eluting beads to deliver chemotherapy to the site)
  - radioembolisation with yttrium-labelled microspheres.

Embolisation techniques rely on the unique differential blood supply of the liver, in which hepatic metastases are preferentially supplied by the hepatic artery. These techniques are used for more diffuse liver metastases.

The roles of liver-directed therapies have not been well defined. Ablative treatments are sometimes utilised after the cancer has progressed on systemic therapy but remains limited to the liver, or in addition to systemic therapy in earlier stages of metastatic disease, aiming to ablate all sites of disease. Whether this rationale is valid remains uncertain. Although some of these methods can provide local control, it is unclear whether the sequential use of regional treatments followed by systemic therapy at the time of progression provides better long-term benefit, in terms of duration of symptom control or survival, than systemic therapy alone.

European Society for Medical Oncology (ESMO) consensus guidelines for the management of patients with colorectal cancer (2016),[3] that patients whose disease is not amenable to surgical resection, but who have a limited number of metastases and involved sites (oligometastatic disease), may be considered for local liver ablative treatments as part of a 'situation-adapted' treatment strategy following systemic therapy

16.6.2 Systematic review evidence

In patients with incurable metastatic colorectal cancer, what are the effects of liver-directed therapies on survival and quality-of-life outcomes, compared with standard care? (MNG16)

A systematic review was undertaken to evaluate the effects of liver-directed therapies in patients with non-resectable metastatic colorectal cancer. Seven level II studies were identified that compared liver-directed therapies with systemic therapy alone in colorectal cancer patients with incurable metastatic liver disease. Six randomised controlled trials (RCTs) evaluated ablative therapies with or without systemic therapy, compared with to systemic therapy alone:

- A multicentre Australian study (SIRFLOX)[4] compared the combination of selective internal radiation therapy (SIRT) plus modified FOLFOX (mFOLFOX6) with mFOLFOX6 alone in 530 patients.
- A German open-label phase III RCT[5] compared the combination of SIRT plus intravenous fluorouracil (FU) to FU alone in 44 patients.
- An Australian RCT[6] compared the combination of SIRT (SIR-Spheres) plus systemic fluorouracil/leucovorin chemotherapy (FULV) with FULV alone in 21 patients.
- An RCT by the European Organisation for Research and Treatment of Cancer (EORTC), the Chemotherapy + Local Ablation Versus Chemotherapy (CLOCC) study,[7] compared the combination of radiofrequency ablation plus FOLFOX4 with FOLFOX4 alone, and with modified FOLFOX4 with bevacizumab (mFOLFOX4) in 119 patients with metastatic colorectal cancer, mainly pre-treated. The CLOCC study was initially designed as a phase III study, but transitioned to a phase II study because of slow accrual.
- A US phase II multicentre RCT[8] compared the combination of transarterial chemoembolisation using irinotecan drug-eluting beads (DEBIRI) plus mFOLFOX plus bevacizumab, with the combination of mFOLFOX plus bevacizumab in 70 patients.
- An Italian multicentre RCT[9] compared DEBIRI with systemic irinotecan, fluorouracil and leucovorin (FOLFIRI).

One RCT by the US Cancer and Leukemia Group B (CALGB 9481) evaluated hepatic arterial infusion in comparison: this US study[10] compared hepatic arterial infusion with systemic bolus FULV in 135 patients.

Of these studies, one study had low risk of bias[4] two studies had a moderate risk of bias,[6][10] and four studies had a high risk of bias overall.[5][7][8][9]

The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

Outcomes reported included tumour response, progression-free survival, overall survival, quality of life, adverse events, and subsequent hepatic surgery resection rates.

16.6.2.1 Ablative therapies

16.6.2.1.1 Tumour response

Tumour response outcomes were reported by five of the RCTs.[4][5][6][8][9]

The Australian SIRT study reported that the addition of SIRT to FULV a significantly improved both the first integrated and best confirmed tumour responses at 36 months follow-up.[6] Compared with the FULV only group, the SIRT treatment group showed greater complete and partial responses and fewer patients with stable disease ($p < 0.001$).[6] No disease progression was reported in the treatment group.[6]

The SIRFLOX trial reported a nonsignificant improvement in overall tumour response rate in patients who received SIRT plus chemotherapy patients compared with those who received systemic chemotherapy alone (76.4% versus 68.1%; $p = 0.113$).[4] The improvement in complete response rate approached significance (4.5% versus 1.5%; $p = 0.054$). However, the SIRT group showed significantly better outcomes than the control group for liver response rate (78.7% versus 68.8%; $p = 0.042$) and liver complete response (6% versus 1.9%; $p = 0.02$).[4] Similarly, the German trial reported that the rate of partial response after a median follow-up of 24.8 months was greater in SIRT group than the non-SIRT group: 10% versus zero; 95% confidence interval (CI) -0.10 to 0.32.[5] The proportion of patients with stable disease was higher in the SIRT group than the non-SIRT group ($p = 0.001$). Fewer patients in the SIRT group showed progressive disease, but statistical analysis of these data was not reported.[5]

The US DEBIRI study[8] reported that patients who received DEBIRI in addition to systemic chemotherapy showed a significant improvement in overall response rates at follow-up intervals of 2 months ($p = 0.01$), 4 months ($p = 0.03$) and 6 months ($p = 0.05$) using Response Evaluation Criteria In Solid Tumors (RECIST v1.1) instrument. There was also a significantly higher overall response rate in the DEBIRI arm at 2 months ($p = 0.01$) and at 12 months' follow-up using Choi's criteria.[8] However, there was no significant difference in overall response between treatment arms at 4 months ($p = 0.09$) and 6 months ($p = 0.12$) using Choi's Criteria.[8] There was also a significantly higher rate of downsizing to resection in the FOLFOX-DEBIRI group than the FOLFOX/bevacizumab arm (35% versus 16%, $p = 0.05$). Statistical analysis was not reported for the other outcomes measured in this study.[8]

The Italian DEBIRI study did not report significant differences in outcomes between patients who received DEBIRI alone and those who received to systemic chemotherapy.[9] Although the statistical significance cannot be confirmed as these weren't reported, the DEBIRI group showed a higher tumour response rate at 50 months' follow-up, less stable disease and fewer with progressive tumours, compared with the group of patients who did not receive DEBIRI.[9]

Tumour response rates associated with radiofrequency ablation study were not reported in the CLOCC study.10

16.6.2.1.2 Progression-free survival

Progression-free survival was reported by all the included RCTs.

The SIRFLOX trial reported similar median progression-free survival rates in the treatment and control groups at 60 months' follow-up:10.7 months versus 10.2 months, hazard ratio (HR) 0.93 (95% CI 0.77 to 1.12; p = 0.43).[4] However, the SIRT group showed a significantly longer median time to liver progression: 20.5 months versus 12.6 months (p = 0.002); HR of 0.69 (95% CI 0.55 to 0.90).[4]

The German SIRT trial reported significantly greater median time to progression and time to liver progression at 26 months in the SIRT group compared with the non-SIRT group: HRs 0.51 (95% CI 0.28 to 0.94, p=0.03) and 0.38 (95% CI 0.20 to 0.72, p = 0.003) respectively.[5] This remained the same for the censored median time to liver progression (p = 0.002); HR 0.35 (95% CI 0.18 to 0.69).[5]

The earlier Australian SIRT trial reported significantly longer median time to disease progression at 36 months in the SIRT group than the non-SIRT group (18.6 months versus 3.6 months; p < 0.0005).[6] While the study showed an improvement in progression-free survival with the addition of SIRT to FULV, the small numbers limit interpretation, as does the less conventional chemotherapy comparator.

The CLOCC study[7] reported increased median time to progression in the radiofrequency ablation plus chemotherapy group, compared with the chemotherapy only group (16.8 months versus 9.9 months; p=0.025); HR 0.63 (95% CI 0.42 to 0.95). Progression-free survival at a median follow-up of 4.4 years was significantly higher in the treatment than control group (27.6% versus 10.6%; p = 0.025).[7]

The US DEBIRI study reported that the addition of DEBIRI to systemic chemotherapy achieved a small increase in median time to liver progression at 24 months' follow-up (17 months versus 12 months; p=0.05).[8] However, between group differences were nonsignificant for median progression free survival in the 'Liver non-target liver only' (p = 0.68), median progression-free survival overall (p = 0.18) and median progression free survival for overall extra-hepatic disease (p = 0.35).[8]

The Italian DEBIRI study reported that, at 50 months' median follow-up, patients who received DEBIRI had significantly longer progression-free survival than the non-DEBIRI group (7 months versus 5 months; p = 0.006) and longer median time to hepatic progression (7 months versus 4 month, p = 0.006).[9] DEBIRI was also associated with a nonsignificant increase in median time to extra-hepatic progression (p=0.64).[9]

16.6.2.1.3 Overall survival

Overall survival was reported by four of the RCTs.[5][6][7][9]

The Australian SIRT study reported significantly greater overall survival in patients who received both SIRT and FULV, compared with those who received FULV only: HR 0.33 (95% CI 0.12 to 0.91; p=0.025). The difference remained statistically significant but was less pronounced for censored data: (HR 0.39 (95% CI 0.14 to 1.13; p = 0.07).[6] While the study showed an improvement in overall survival with the addition of SIRT to FULV, the small numbers limit interpretation, as does the less conventional chemotherapy comparator. The German SIRT study[5] reported a non-significant increase in median overall survival among patients who received SIRT plus 5FU group, compared with those who received 5FU only (10 months versus 7.3 months, p = 0.8): HR 0.92 (95% CI 0.47 to 1.78).[5]

The CLOCC study reported a small nonsignificant increase in median overall survival at 4.4 years' median follow-up among patients who received radiofrequency ablation than those who did not (45.3 months versus 40.5 months, p = 0.22): HR 0.74 (95% CI 0.46 to 1.19).[7]

However, unpublished 10-year follow-up data from this study showed significant benefits for the radiofrequency ablation group, compared with the control group).[11]: • longer median survival (45.6 versus 40.5 months) • higher rate of overall survival (36% versus 9%; HR 0.58, 95% CI 0.33 to 0.88) • a lower rate of liver recurrence (65% versus 85%) • a lower rate of death due to progressive disease (57% versus 81%). However, the radiofrequency ablation group showed a higher rate of extrahepatic recurrence (35% versus 14%).[11]

The Italian DEBIRI study reported significantly longer overall median survival at 50 months' median follow-up in patients who received DEBIRI, compared with those who received systemic chemotherapy: 22 (95% CI 21 to 23) months versus 15 (95% CI 12 to 18) months (p = 0.031).[9] A difference in median survival favouring DEBIRI was reported at 2 years' follow-up (56% versus 32%) and at 30 months' follow-up (34% versus 9%) and 50 months' follow-up (15% versus 0%), although statistical analyses were not reported.[9]

16.6.2.1.4 Resection rate

Resection rates were reported by two RCTs.[4][8]

The SIRFLOX study reported no significant difference in liver resection rates between the SIRT group and the systemic chemotherapy only group (14.2% versus 13.7%, p = 0.857).[4]

The US DEBRI study reported a substantially higher resection rate in patients who received DEBIRI in addition to systemic chemotherapy, compared with those who received non-DEBIRI regimens, which was of borderline statistical significance (35% versus 6%, p = 0.05).[8]

16.6.2.1.5 Adverse events

Adverse event rates were reported by all the RCTs.

The SIRFLOX study reported that the total rate of adverse events (≥ Grade 3) was higher among the SIRT group than the non-SIRT group at 60 months' follow-up, but this difference was not statistically significant (85.4% versus 73.4%, p = 0.516).[4] The SIRT group showed was a significantly higher incidence of neutropenia (p = 0.004), febrile neutropenia (p = 0.02), thrombocytopenia (p < 0.001), fatigue (p = 0.019) and abdominal pain (p = 0.009).[4] There were no significant differences in the rates of other adverse events.[4]

This finding was supported by those of the German trial.[5] After 24.8 months' median follow up, there were more reports of gastrointestinal events, neurology and other toxicities in the SIRT group than the non-SIRT group. In contrast to the SIRFLOX findings, fewer Grade 3 or 5 toxicities were reported among patients who received SIRT than those who did not, but this difference was not statistically significant (5% versus 27%, p = 0.1).[5]

The other Australian SIRT study reported that more Grade 3 and 4 toxicity events occurred in SIRT patients than non-SIRT patients (13 versus 5).[6] There were greater reports of granulocytopenia, anorexia, cirrhosis, mucositis and diarrhoea. One death out of the entire trial was attributed to SIRT. No significance was reported for any of these outcomes.[6]

In the CLOCC study the addition of radiofrequency ablation to systemic chemotherapy was associated with higher incidences of Grade 3–4 tolerance to systemic treatment than chemotherapy alone, although the impact of this finding cannot be determined as statistical analysis was not reported.[7]

In the US study DEBIRI in addition to systemic chemotherapy was associated with significantly greater incidences of serious adverse events than chemotherapy alone ($p = 0.03$).[8] The DEBIRI group also showed numerically greater incidences of chemotherapy-related adverse events, but this difference was not statistically significant ($p = 0.08$). This pattern was seen across total adverse incidence and specific adverse events, but no statistically significant differences were reported. However, there was a consistent trend toward higher incidences of adverse events among patients who received DEBIRI in addition to their standard chemotherapy.[8]

The Italian DEBIRI study reported significantly fewer grade ≥ 3 neutropenia events among patients who received DEBIRI than among those who received FOLFIRI after 50 months' median follow-up (4% versus 44%, $p < 0.0001$).[9]

16.6.2.1.6 Quality of life

Quality-of-life outcomes were reported by three of the RCTs.[6][7][9]

The Italian DEBIRI study[9] reported differences in quality-of-life outcomes in favour of DEBIRI compared with FOLFIRI: better physical functioning at 3 months and at 8 months ($p = 0.025$ for both comparisons) and a longer time from treatment to the beginning of decline in quality of life (8 months versus 3 months, $p = 0.0002$).[9]

The Australian SIRT study reported no significant differences in patient-rated or clinician-rated quality-of-life scores between patients receiving SIRT in addition to FULV and those receiving FULV only.

The CLOCC study[7] reported no significant differences in quality of life between patients receiving radiofrequency ablation in addition to systemic chemotherapy and those receiving chemotherapy alone.

16.6.2.2 Hepatic arterial infusion

The CALGB 9481 study,13 which compared hepatic arterial infusion with systemic bolus fluorouracil and leucovorin (FULV) in 135 patients, reported tumour response and survival outcomes, adverse events, and quality of life.

16.6.2.2.1 Tumour response

The CALGB 9481 study reported a substantial improvement in overall tumour response rate with hepatic arterial infusion, compared with systemic chemotherapy at 6 years' follow-up (47% versus 24%, p = 0.012).[10] This advantage was observed in the complete and partial response rates. Fewer patients remained with stable disease in the hepatic arterial infusion group than the systemic chemotherapy group, although statistical analysis of these data was not reported.[10]

16.6.2.2.2 Progression-free survival

The CALGB 9481 study reported a significant increase in median time to hepatic progression in the hepatic arterial infusion group, compared with the systemic chemotherapy group, at 3 years' follow-up (p = 0.034).[10] However, a shorter median time to extra-hepatic progression was also observed in the hepatic arterial infusion group than the systemic chemotherapy group (p = 0.029). A nonsignificant difference in median time to progression, favouring the systemic chemotherapy group, was also observed (p = 0.95).[10]

16.6.2.2.3 Overall survival

The CALGB 9481 study reported a significant increase in progression-free survival in the hepatic arterial infusion group, compared with the systemic chemotherapy group, at 6 years' follow-up (24.4 months versus 20 months, p = 0.034).[10] This effect was also seen at 2 years' follow-up (51% versus 25%), although the statistical significance of this finding was not reported.[10]

16.6.2.2.4 Adverse events

The CALGB 9481 study reported lower rates of adverse events among patients who received hepatic arterial infusion, compared with those who received systemic chemotherapy, including significantly reductions in neutropenia grade ≥ 3 (p < 0.0001) and stomatitis (p = 0.00002), and a nonsignificant reduction in diarrhoea (p = 0.075).[10] However, bilirubin elevation ≥ 3 mg/dL was reported in a higher proportion of the hepatic arterial infusion group than the systemic chemotherapy (p = 0.006).[10]

16.6.2.2.5 Quality of life

The CALGB 9481 study assessed quality-of-life (physical functioning domain) using the Rand 26-item Health Status Profile.[10] The hepatic arterial infusion group showed improved quality of life, compared with the systemic chemotherapy group, at 3 months (p = 0.038), 6 months (p = 0.024) and among late dropouts at 12 months (p = 0.001). At 18 months' follow-up, overall physical functioning was superior among the hepatic arterial infusion group (62% versus 58%), but statistical analysis was not reported.[10]

16.6.3 Evidence summary and recommendations

Evidence summary	Level	References
There remains a lack of evidence that SIRT improves survival or quality of life in either treatment naive or chemo-refractory patients with metastatic colorectal cancer.		
[improved?] Response rates within the liver and delayed progression of liver metastases have been reported with SIRT and chemotherapy but the clinical relevance of these endpoints remain unclear.		
Hepatic arterial infusion in patients with metastatic colorectal cancer patients has not been shown to significantly improve overall survival.		
Limitations on the use of hepatic arterial infusion include the requirement of specific technical expertise and careful patient selection. Thus the relative benefit of hepatic arterial infusion chemotherapy in this setting remains uncertain.		
Although recent small randomised studies using using irinotecan drug-eluting beads (DEBIRI) are suggestive of improved outcomes with transarterial chemoembolisation, there is insufficient evidende to determine whether it is superior to standard systemic therapies.		
Overall, liver-directed therapies provide little or no benefit for quality of life in metastatic colorectal cancer patients with non-resectable liver disease. (not sure if we can say this??		
Overall, the evidence suggests some benefit to tumour response rate with the use of DEBIRI, hepatic arterial infusion, or the addition of SIRT for colorectal cancer patients with unresectable liver disease.		
The strength of evidence for liverdirected therapies to extend progression free survival varied from poor to strong across the studies. However, most studies reported a benefit overall.		
While the liver directed therapies radiofrequency ablation, SIRT with chemotherapy and hepatic arterial infusion or DEBIRI alone have been reported to extend the overall survival of colorectal cancer patients with unresectable liver disease, significance varied.		
Among patients receiving SIRT in addition to chemotherapy, improved overall survival was reported, although significance varied in strength.		
There is inconclusive evidence to suggest a definitive benefit given by liver directed		

Evidence summary	Level	References
therapies in improving resection rate in colorectal cancer patients with incurable liver metastases.		
Liver-directed therapies, in combination with systemic chemotherapy, were generally associated with higher incidences of adverse events in treated patients. In particular, there were often more reports of neutropenia, diarrhoea, fatigue, abdominal pain, haemotologic toxicities and gastrointestinal events, but the significance of these were either not known or varied. Generally fewer adverse events were associated with the use of hepatic arterial infusion or DEBIRI alone, but the significance of these varied.		
For patients who received SIRT in addition to systemic chemotherapy, there were also more reports of adverse events than non-SIRT patients.		

Practice point

All patients should be discussed at a multidisciplinary team meeting with clinicians who have expertise in management of metastatic colorectal cancer.

Practice point

All patients should be discussed at a multidisciplinary team meeting with clinicians who have expertise in management of metastatic colorectal cancer.

Practice point

For patients who could be considered surgical candidates if their metastases were smaller, we suggest initial systemic chemotherapy followed by re-evaluation for surgery.

Practice point

Wherever possible, patients considering liver-directed therapies should be enrolled into clinical trials examining these treatments in comparison to standard therapies.

Practice point

In patients with non-resectable liver metastases only (or oligometastatic disease) local ablation techniques can be considered by the MDT based on local experience, patient preference and tumour characteristics. Treating clinicians should have an in-depth discussion with every patient regarding technical complexity, potential outcomes and complications in addition to other therapies available for that patient.

Practice point

For patients with a limited number of metastases who are though unfit for surgery, regional tumour radiofrequency ablation can be considered if the necessary expertise exists at your site. The best results with RFA are in patients with three or fewer lesions, 5 cm or less in diameter, that are not located near the major vascular structures.

16.6.3.1 Considerations in making these recommendations

Non-systematic review evidence outlined below was regarded important for consideration.

16.6.3.1.1 Radiofrequency ablation

The CLOCC study[7] is the only prospectively reported study to date to investigate the benefit of adding radiofrequency ablation to systemic chemotherapy in patients with non-resectable liver metastases from colorectal adenocarcinoma without detectable extrahepatic disease. While this study is suggestive of a long-term benefit from the addition of radiofrequency ablation in patients with liver-dominant metastatic colorectal cancer who are undergoing systemic chemotherapy, additional experience in a larger number of patients is needed before this can be adopted as a standard of care.

Other investigators have reported that radiofrequency ablation is a relatively well-tolerated technique. However, severe and potentially fatal complications can arise. A systematic review of evidence by the American Society of Clinical Oncology[12] reported that radiofrequency ablation was associated with a low mortality rate (zero to 2%), while reported rates of major complications were between 6% and 9%.(not sure if I should describe any of the complication grouping)

16.6.3.1.2 Transarterial chemoembolisation

Limited evidence suggests that hepatic transarterial embolisation and transarterial chemoembolisation can achieve disease stabilisation of liver metastases in treated patients.[13][14] However, prolongation of survival has not been demonstrated conclusively. Most of the studies that have evaluated these techniques have not included a control group. The few available RCTs report conflicting results.references

A Cochrane systematic review[15] included only one RCT, and concluded that the there was insufficient evidence to recommend transarterial chemoembolisation for the treatment of colorectal metastases, except as part of a clinical trial.

While the two DEBIRI studies included in our systematic review[8][9] are suggestive of improved outcomes with transarterial chemoembolisation, larger randomised trials are required to confirm these results before it can be concluded that transarterial embolisation or transarterial chemoembolisation is superior to standard systemic therapies.

16.6.3.1.3 Hepatic arterial infusion

The combined use of intra-arterial plus systemic chemotherapy, which aims to prevent extrahepatic tumour progression while achieving maximum therapeutic effect in the liver, has been extensively reported. Despite optimisation of surgical techniques and the chemotherapy regimen, the benefit of combined hepatic artery infusion and chemotherapy remains uncertain.

Only one study[10] met our systematic review criteria, the US CALGB 9481 study in which 135 treatment-naive patients with metastatic colorectal cancer and unresectable liver metastases occupying less than 70% of the liver were randomly assigned to receive hepatic arterial infusion (floxuridine) or systemic bolus FULV. Data have been published for final follow-up of 15 months.[10]

At least two other trials have compared hepatic arterial infusion with intravenous FULV.[16][17] A meta-analysis [18] included all three RCTs comparing hepatic arterial infusion with intravenous FULV, and seven earlier RCTs that compared hepatic arterial infusion with either systemic chemotherapy or best supportive care. All these studies concluded that hepatic arterial infusion achieved higher response rates than systemic fluorouracil, but no overall survival advantage was seen.

None of these trials included a control group of patients receiving irinotecan or oxaliplatin – agents known to improve survival compared with FULV alone. Thus, the relative benefit of HAI chemotherapy in this setting remains uncertain.

16.6.3.1.4 Stereotactic ablative body radiotherapy

External beam radiotherapy for the treatment of hepatic metastases has been limited by low tolerance of the normal liver parenchyma. Newer approaches using conformal radiation treatment with hypofractionation, such as stereotactic body radiotherapy and high-dose rate brachytherapy, have been reported to achieve high rates of local control of colorectal liver metastases.[19][20]

Advantages include short treatment time and favourable overall toxicity profile.References However, the role of conformal radiation treatment in the management of non-resectable liver metastases is undefined. Prospective studies are needed to identify which patients benefit most from this approach.

16.6.3.2 Health system implications

16.6.3.2.1 Clinical practice

Liver-directed therapies are highly specialised therapies which are carried out in centres with the requisite expertise. The management these patients requires multidisciplinary team approach whereby the likely interactions between any prior, concurrent or planned biological, chemotherapeutic, local or locoregional ablative, surgical, external beam radiation treatment, or radiosurgery should be extensively discussed. It is likely that these expert centres are likely to be located in tertiary referral centres. Consideration would need to be given to equitable access particularly for patients from regional/rural areas.

16.6.3.2.2 Resourcing

The present recommendations would have little effect on current resourcing.

16.6.3.2.3 Barriers to implementation

No barriers to the implementation of these recommendations are envisaged.

16.6.4 Discussion

16.6.4.1 Unresolved issues

To be added

16.6.4.2 Studies currently underway

The overall survival analysis of the three first-line studies planned for 2017 will hopefully give clinicians guidance as to the role of SIRT in chemo-naive patients:

- [Name of study 1][Reference]
- [Name of study 1][Reference]
- [Name of study 1].[Reference]

Two RCTs of primary site resection in patients who present with non-resectable metastatic disease are yet to be reported: (?closed to recruitment – need to check)

- the Dutch Colorectal Cancer Group's CAIRO4 study[21] comparing systemic therapy (fluoropyrimidine-based chemotherapy in combination with bevacizumab) only, with resection of the primary tumour followed by systemic therapy, in patients with synchronous unresectable metastases of colorectal cancer and few or no symptoms of the primary tumour
- the German SYNCHRONOUS study[22] comparing resection of the primary tumour before systemic chemotherapy, with no resection, in patients with synchronous unresectable metastases and no symptoms of the primary tumour.[22][23][24][25]

16.6.4.3 Future research priorities

Quality of life is a critical aspect of palliative treatment. All previous studies evaluating the impact of primary tumour resection for patients with non-resectable metastatic colorectal cancer have focused on survival and morbidity. Quality of life has never been specifically assessed.

16.6.5 References

1. ↑ Clark ME, Smith RR. *Liver-directed therapies in metastatic colorectal cancer.* J Gastrointest Oncol 2014 Oct;5(5):374-87 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25276410.
2. ↑ Weitz J, Koch M, Debus J, Höhler T, Galle PR, Büchler MW. *Colorectal cancer.* Lancet 2005 Jan;365(9454): 153-65 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15639298.
3. ↑ Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, et al. *ESMO consensus guidelines for the management of patients with metastatic colorectal cancer.* Ann Oncol 2016 Aug;27(8): 1386-422 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27380959.
4. ↑ 4.00 4.01 4.02 4.03 4.04 4.05 4.06 4.07 4.08 4.09 4.10 4.11 van Hazel GA, Heinemann V, Sharma NK, Findlay MP, Ricke J, Peeters M, et al. *SIRFLOX: Randomized Phase III Trial Comparing First-Line mFOLFOX6 (Plus or Minus Bevacizumab) Versus mFOLFOX6 (Plus or Minus Bevacizumab) Plus Selective Internal Radiation Therapy in Patients With Metastatic Colorectal Cancer.* J Clin Oncol 2016 May 20;34(15):1723-31 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26903575.
5. ↑ 5.00 5.01 5.02 5.03 5.04 5.05 5.06 5.07 5.08 5.09 5.10 5.11 Hendlisz A, Van den Eynde M, Peeters M, Maleux G, Lambert B, Vannoote J, et al. *Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy.* J Clin Oncol 2010 Aug 10;28(23):3687-94 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20567019.
6. ↑ 6.00 6.01 6.02 6.03 6.04 6.05 6.06 6.07 6.08 6.09 6.10 6.11 Van Hazel G, Blackwell A, Anderson J, Price D, Moroz P, Bower G, et al. *Randomised phase 2 trial of SIR-Spheres plus fluorouracil/leucovorin chemotherapy versus fluorouracil/leucovorin chemotherapy alone in advanced colorectal cancer.* J Surg Oncol 2004 Nov 1;88(2):78-85 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15499601.

7. ↑ 7.0 7.1 7.2 7.3 7.4 7.5 7.6 7.7 7.8 7.9 Ruers T, Punt C, Van Coevorden F, Pierie JP, Borel-Rinkes I, Ledermann JA, et al. *Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: a randomized EORTC Intergroup phase II study (EORTC 40004).* Ann Oncol 2012 Oct;23(10):2619-26 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22431703.
8. ↑ 8.00 8.01 8.02 8.03 8.04 8.05 8.06 8.07 8.08 8.09 8.10 8.11 8.12 8.13 Martin RC 2nd, Scoggins CR, Schreeder M, Rilling WS, Laing CJ, Tatum CM, et al. *Randomized controlled trial of irinotecan drug-eluting beads with simultaneous FOLFOX and bevacizumab for patients with unresectable colorectal liver-limited metastasis.* Cancer 2015 Oct 15;121(20):3649-58 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26149602.
9. ↑ 9.00 9.01 9.02 9.03 9.04 9.05 9.06 9.07 9.08 9.09 9.10 9.11 9.12 9.13 9.14 Fiorentini G, Aliberti C, Tilli M, Mulazzani L, Graziano F, Giordani P, et al. *Intra-arterial infusion of irinotecan-loaded drug-eluting beads (DEBIRI) versus intravenous therapy (FOLFIRI) for hepatic metastases from colorectal cancer: final results of a phase III study.* Anticancer Res 2012 Apr;32(4):1387-95 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22493375.
10. ↑ 10.00 10.01 10.02 10.03 10.04 10.05 10.06 10.07 10.08 10.09 10.10 10.11 10.12 10.13 Kemeny NE, Niedzwiecki D, Hollis DR, Lenz HJ, Warren RS, Naughton MJ, et al. *Hepatic arterial infusion versus systemic therapy for hepatic metastases from colorectal cancer: a randomized trial of efficacy, quality of life, and molecular markers (CALGB 9481).* J Clin Oncol 2006 Mar 20;24(9):1395-403 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16505413.
11. ↑ 11.0 11.1 Ruers T, Punt C, Van Coevorden F, et al. *Radiofrequency ablation (RFA) combined with chemotherapy for unresectable colorectal liver metastases (CRC LM): long-term survival results of a randomized phase II study of the EORTC-NCRI CCSG-ALM Intergroup 40004 (CLOCC).* J Clin Oncol 2015;33:33; 2015.
12. ↑ Wong SL, Mangu PB, Choti MA, Crocenzi TS, Dodd GD 3rd, Dorfman GS, et al. *American Society of Clinical Oncology 2009 clinical evidence review on radiofrequency ablation of hepatic metastases from colorectal cancer.* J Clin Oncol 2010 Jan 20;28(3):493-508 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19841322.
13. ↑ Massmann A, Rodt T, Marquardt S, Seidel R, Thomas K, Wacker F, et al. *Transarterial chemoembolization (TACE) for colorectal liver metastases--current status and critical review.* Langenbecks Arch Surg 2015 Aug;400(6):641-59 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26088872.
14. ↑ Richardson AJ, Laurence JM, Lam VW. *Transarterial chemoembolization with irinotecan beads in the treatment of colorectal liver metastases: systematic review.* J Vasc Interv Radiol 2013 Aug;24(8):1209-17 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23885916.
15. ↑ Riemsma RP, Bala MM, Wolff R, Kleijnen J. *Transarterial (chemo)embolisation versus no intervention or placebo intervention for liver metastases.* Cochrane Database Syst Rev 2013 Apr 30;(4):CD009498 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23633373.
16. ↑ de Gramont A, Bosset JF, Milan C, Rougier P, Bouché O, Etienne PL, et al. *Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French intergroup study.* J Clin Oncol 1997 Feb;15(2):808-15 Available from: http://www.ncbi.nlm.nih.gov/pubmed/9053508.

17. ↑ Lorenz M, Müller HH. *Randomized, multicenter trial of fluorouracil plus leucovorin administered either via hepatic arterial or intravenous infusion versus fluorodeoxyuridine administered via hepatic arterial infusion in patients with nonresectable liver metastases from colorectal carcinoma.* J Clin Oncol 2000 Jan; 18(2):243-54 Available from: http://www.ncbi.nlm.nih.gov/pubmed/10637236.
18. ↑ Mocellin S, Pilati P, Lise M, Nitti D. *Meta-analysis of hepatic arterial infusion for unresectable liver metastases from colorectal cancer: the end of an era?* J Clin Oncol 2007 Dec 10;25(35):5649-54 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18065736.
19. ↑ Collettini F, Lutter A, Schnapauff D, Hildebrandt B, Puhl G, Denecke T, et al. *Unresectable colorectal liver metastases: percutaneous ablation using CT-guided high-dose-rate brachytherapy (CT-HDBRT).* Rofo 2014 Jun;186(6):606-12 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24407711.
20. ↑ Aslam MI, Kelkar A, Sharpe D, Jameson JS. *Ten years experience of managing the primary tumours in patients with stage IV colorectal cancers.* Int J Surg 2010;8(4):305-13 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20380899.
21. ↑ 't Lam-Boer J, Mol L, Verhoef C, de Haan AF, Yilmaz M, Punt CJ, et al. *The CAIRO4 study: the role of surgery of the primary tumour with few or absent symptoms in patients with synchronous unresectable metastases of colorectal cancer--a randomized phase III study of the Dutch Colorectal Cancer Group (DCCG).* BMC Cancer 2014 Oct 2;14:741 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25277170.
22. ↑ [22.0] [22.1] Rahbari NN, Lordick F, Fink C, Bork U, Stange A, Jäger D, et al. *Resection of the primary tumour versus no resection prior to systemic therapy in patients with colon cancer and synchronous unresectable metastases (UICC stage IV): SYNCHRONOUS--a randomised controlled multicentre trial (ISRCTN30964555).* BMC Cancer 2012 Apr 5;12:142 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22480173.
23. ↑ Mathus-Vliegen EM, Tytgat GN. *Analysis of failures and complications of neodymium: YAG laser photocoagulation in gastrointestinal tract tumors. A retrospective survey of 18 years' experience.* Endoscopy 1990 Jan;22(1):17-23 Available from: http://www.ncbi.nlm.nih.gov/pubmed/1689658.
24. ↑ Spinelli P, Mancini A, Dal Fante M. *Endoscopic treatment of gastrointestinal tumors: indications and results of laser photocoagulation and photodynamic therapy.* Semin Surg Oncol 1995 Jul;11(4):307-18 Available from: http://www.ncbi.nlm.nih.gov/pubmed/7481368.
25. ↑ Tan CC, Iftikhar SY, Allan A, Freeman JG. *Local effects of colorectal cancer are well palliated by endoscopic laser therapy.* Eur J Surg Oncol 1995 Dec;21(6):648-52 Available from: http://www.ncbi.nlm.nih.gov/pubmed/8631414.

Back to top

16.6.6 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search

View PICO	NHMRC Evidence statement form MNG16	Systematic review report MNG16

Back to top

16.7 Synchronous primary in metastatic CRC

Contents

Insert content here

Update group - check on subcommittee authorship

Back to top

16.7.1 Background

At the time of diagnosis, up to 25% of patients with colorectal cancer present with synchronous metastases.[1] Most patients (70%–90%) with metastatic disease are unsuitable for curative surgical treatment, and early chemotherapy in association with targeted therapies has been demonstrated to provide optimal palliation in terms of survival and quality of life or tumour down-staging.Reference

Initial management of the primary site in patients who present with metastatic disease is controversial. The choice and sequence of treatment is guided by the presence and absence of symptoms from the primary tumour and whether or not the metastases are potentially resectable.

With the exception of perforated or bleeding primary tumours, where surgical intervention is often indicated, it is still controversial whether either primary tumour resection followed by chemotherapy or immediate chemotherapy without primary tumour resection is the best therapeutic option.

16.7.2 Overview of evidence (non-systematic literature review)

No systematic reviews were undertaken for this topic. Practice points were based on selected published literature. X-ref to guidelines development chapter

16.7.2.1 Impact of palliative resection of primary on survival in patients with non-resectable metastatic colorectal cancer

Several studies have assessed the impact of primary tumour resection for colorectal cancer with non-resectable metastases.[2][3][4][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20] The published studies were predominantly non-randomised, mostly retrospective and reported by single institutions.

A meta-analysis of 21 studies (including 44,226 patients) evaluating the effect of primary tumour resection in patients with non-resectable metastatic colorectal cancer concluded that there was a significantly lower mortality risk compared with no resection: odds ratio (OR) 0.28; 95% confidence interval (CI) 0.165 to 0.474. This translated into a difference in mean survival of approximately 6.4 months in favour of resection.[21] The authors acknowledged significant cross-study heterogeneity and selection biases in the majority of studies.[21] Results of meta-analyses that have taken the effect of chemotherapy into account have been conflicting. A meta-analysis of individual data from randomised controlled trials (RCTs) of first-line chemotherapy for metastatic colorectal cancer (which included patients with non-resectable disease) found that primary tumour resection was independently associated with better overall survival in multivariate analysis: hazard ratio (HR) for death 0.63 (95% CI 0.53 to 0.75).[22]

To the contrary, a Cochrane review of seven non-randomised studies, totalling 1086 patients, concluded that resection of the primary cancer in asymptomatic patients with non-resectable metastatic colorectal cancer managed with chemo/radiotherapy was not associated with consistent improvement in overall survival and did not significantly reduce the risk of primary site complications (i.e. bleeding, perforation, obstruction).[23] Another systematic review and meta-analysis identified five studies that compared open palliative colectomies with laparoscopic palliative colectomies in this setting found laparoscopic procedures were associated with reduced post-operative complications, blood loss and length of hospital stays.{{Cite footnote|Citation:Yang TX, Billah B, Morris DL, Chua TC 2013}6

Australian data suggest that the majority of palliative metastatic colorectal cancer patients in clinical practice have their colorectal primary tumours resected. A retrospective analysis of the prospective Treatment of Recurrent and Advanced Colorectal Cancer registry reported on just over 1000 synchronous metastatic colorectal cancer patients between July 2009 and November 2015.47 Of those patients, 70% were considered palliative at multidisciplinary team meeting.[24] And of those 45% had their colorectal primary tumours resected.[24] Reasons for primary resection in the palliative group were surgeon decision (45%) and obstruction (33%) but 4% achieved curative resection of metastases. In this study, performance status, metastasis resection (R0 versus R1 versus R2 versus no resection), resection of the colorectal primary and treatment intent determined at multidisciplinary team meeting were the most significant factors for progression-free and overall survival.[24] These data, in the setting of modern chemotherapy management, add to the literature supporting routine colorectal primary resection even when the metastases are not resectable.[24]

16.7.2.2 Asymptomatic primary tumour

The decision to surgically resect the primary in asymptomatic patients with non-resectable metastatic colorectal cancer is complex and requires careful consideration of the risk to benefit ratio for the patient. The impact of prophylactic surgery in this setting is uncertain.[17]

Leaving the primary tumour intact may not lead to unacceptable local complications (or significantly compromise survival).[25][26][27]48-50 There is a relatively low risk of bleeding (3%) or obstruction/perforation (7–14%) in patients who present with metastatic colorectal cancer and an intact asymptomatic primary managed at least initially without resection.[23][26][28]

Moreover, this group of patients appear to have higher rates of postoperative morbidity (20–30%) and perioperative mortality (1–6% percent)[9][16][17] which may lead to delays in the initiation of systemic therapies and detrimental effects on survival.

The prospective multicentre phase II NSABP C-10 trial[25] showed that patients with an asymptomatic primary colon tumour and non-resectable metastatic disease who received mFOLFOX with bevacizumab experienced an acceptable level of morbidity without upfront resection of the primary tumour. In this study, survival did not appear to be compromised by leaving the primary tumour intact and improvement in the primary site can be seen within the first 2 weeks of systemic therapy.

Systemic chemotherapy is generally the favoured treatment for patients presenting with synchronous metastatic colorectal cancer with asymptomatic primary. Although with modern chemotherapy regimens there may be a response within the primary tumour, this response may not be as robust as seen in the metastatic

disease sites.[29] Thus, for patients with an intact primary site it is imperative to evaluate the primary site periodically. There are no guidelines for identifying non-resectable metastatic colorectal cancer patients with intact primaries who are more likely to suffer complications and require surgery during systemic therapy. Some have shown that even patients who appear to be at a high risk for subsequent complications based on tumour site or colonoscopic findings (i.e. nearly obstructing lesion or inability to advance the scope beyond the tumour) can avoid palliative surgery and obtain good control with systemic therapy.[30] The current National Comprehensive Cancer Network Guidelines[31] recommend leaving the primary tumour intact and starting systemic therapy first in patients with non-resectable metastatic colorectal cancer and asymptomatic intact primaries.

16.7.2.3 Symptomatic primary tumour

Patients who present with synchronous metastatic disease and a symptomatic primary tumour (obstruction, bleeding, and perforation), surgical resection of the primary tumour or proximal diversion can be considered prior to commencement of systemic therapy. Even patients with incurable metastatic disease may benefit from surgical palliative of obstruction and bleeding from the primary tumour.[Egoslim consensus guidelines 2015]

For bowel perforation, surgery should be considered to either remove the tumour when it is easily resectable (such as a right hemicolectomy for right-side colon lesions or sigmoid colectomy for sigmoid lesions), or to create a stoma (left colon) in cases requiring more technical surgery, such as low anterior resection and total mesorectal excision.[32]

Nonsurgical methods of palliation can be considered for patients not suitable for surgical procedures (endoluminal placement of a self-expanding metal stent or laser ablation for non-obstructing tumours).

Practice point

Until further information is available from randomised clinical trials yet to be reported (the Dutch Colorectal Cancer Group's CAIRO4 study[33] and the German SYNCHRONOUS study[34]), the risks of surgery outweigh the possible benefits of resection of asymptomatic primary tumours in the setting of unresectable metastatic colorectal cancer.

Practice point

Until further information is available from randomised clinical trials yet to be reported (the Dutch Colorectal Cancer Group's CAIRO4 study[33] and the German SYNCHRONOUS study[34]), the risks of surgery outweigh the possible benefits of resection of asymptomatic primary tumours in the setting of unresectable metastatic colorectal cancer.

Practice point

Routine palliative resection of a synchronous primary lesion should therefore only be considered if the patient has an imminent risk of perforation, acute significant bleeding, obstruction or other significant tumour-related symptoms.

Practice point

An intact primary is not a contraindication to the use of Bevacizumab in combination with chemotherapy. (not sure if I need to mention anything about this)

16.7.3 Evidence summary and recommendations

16.7.4 References

1. ↑ Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouvier AM. *Epidemiology and management of liver metastases from colorectal cancer.* Ann Surg 2006 Aug;244(2):254-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16858188.
2. ↑ Aslam MI, Kelkar A, Sharpe D, Jameson JS. *Ten years experience of managing the primary tumours in patients with stage IV colorectal cancers.* Int J Surg 2010;8(4):305-13 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20380899.
3. ↑ Bajwa A, Blunt N, Vyas S, Suliman I, Bridgewater J, Hochhauser D, et al. *Primary tumour resection and survival in the palliative management of metastatic colorectal cancer.* Eur J Surg Oncol 2009 Feb;35(2):164-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18644695.
4. ↑ Benoist, S Pautrat, K Mitry, E Rougier, P Penna, C Nordlinger, B. *Treatment strategy for patients with colorectal cancer and synchronous irresectable liver metastases.* Br J Surg 2005 Sep;92(9), p. 1155-1160 DOI: 10.1002/bjs.5060.
5. ↑ Chan TW, Brown C, Ho CC, Gill S. *Primary tumor resection in patients presenting with metastatic colorectal cancer: analysis of a provincial population-based cohort.* Am J Clin Oncol 2010 Feb;33(1):52-5 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19704367.
6. ↑ Costi R, Mazzeo A, Di Mauro D, Veronesi L, Sansebastiano G, Violi V, et al. *Palliative resection of colorectal cancer: does it prolong survival?* Ann Surg Oncol 2007 Sep;14(9):2567-76 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17541693.
7. ↑ Evans MD, Escofet X, Karandikar SS, Stamatakis JD. *Outcomes of resection and non-resection strategies in management of patients with advanced colorectal cancer.* World J Surg Oncol 2009 Mar 10;7:28 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19284542.

8. ↑ Frago R, Kreisler E, Biondo S, Salazar R, Dominguez J, Escalante E. *Outcomes in the management of obstructive unresectable stage IV colorectal cancer.* Eur J Surg Oncol 2010 Dec;36(12):1187-94 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20864304.
9. ↑ [9.0] [9.1] Galizia G, Lieto E, Orditura M, Castellano P, Imperatore V, Pinto M, et al. *First-line chemotherapy vs bowel tumor resection plus chemotherapy for patients with unresectable synchronous colorectal hepatic metastases.* Arch Surg 2008 Apr;143(4):352-8; discussion 358 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18427022.
10. ↑ Karoui M, Roudot-Thoraval F, Mesli F, Mitry E, Aparicio T, Des Guetz G, et al. *Primary colectomy in patients with stage IV colon cancer and unresectable distant metastases improves overall survival: results of a multicentric study.* Dis Colon Rectum 2011 Aug;54(8):930-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21730780.
11. ↑ Kaufman MS, Radhakrishnan N, Roy R, Gecelter G, Tsang J, Thomas A, et al. *Influence of palliative surgical resection on overall survival in patients with advanced colorectal cancer: a retrospective single institutional study.* Colorectal Dis 2008 Jun;10(5):498-502 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17949445.
12. ↑ Konyalian, V. R. Rosing, D. K. Haukoos, J. S. Dixon, M. R. Sinow, R. Bhaheetharan, S. Stamos, M. J. Kumar, R. R.. *The role of primary tumour resection in patients with stage IV colorectal cancer.* Colorectal Disease 2007 May 10;9(5), p. 430-437 DOI: 10.1111/j.1463-1318.2007.01161.x.
13. ↑ Law WL, Chan WF, Lee YM, Chu KW. *Non-curative surgery for colorectal cancer: critical appraisal of outcomes.* Int J Colorectal Dis 2004 May;19(3):197-202 Available from: http://www.ncbi.nlm.nih.gov/pubmed/14618348.
14. ↑ Michel P, Roque I, Di Fiore F, Langlois S, Scotte M, Tenière P, et al. *Colorectal cancer with non-resectable synchronous metastases: should the primary tumor be resected?* Gastroenterol Clin Biol 2004 May;28(5):434-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15243315.
15. ↑ Mik M, Dziki L, Galbfach P, Trzcinski R, Sygut A, Dziki A. *Resection of the primary tumour or other palliative procedures in incurable stage IV colorectal cancer patients?* Colorectal Dis 2010 Jul;12(7 Online):e61-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19486103.
16. ↑ [16.0] [16.1] Ruo L, Gougoutas C, Paty PB, Guillem JG, Cohen AM, Wong WD. *Elective bowel resection for incurable stage IV colorectal cancer: prognostic variables for asymptomatic patients.* J Am Coll Surg 2003 May;196(5):722-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/12742204.
17. ↑ [17.0] [17.1] [17.2] Scoggins CR, Meszoely IM, Blanke CD, Beauchamp RD, Leach SD. *Nonoperative management of primary colorectal cancer in patients with stage IV disease.* Ann Surg Oncol 1999 Oct;6(7):651-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/10560850.
18. ↑ Stelzner, S Hellmich, G Koch, R Ludwig, K. *Factors predicting survival in stage IV colorectal carcinoma patients after palliative treatment: A multivariate analysis.* Journal of Surgical Oncology 2005 Mar 15;89(4), p. 211-217 DOI: 10.1002/jso.20196.
19. ↑ Tebbutt NC, Norman AR, Cunningham D, Hill ME, Tait D, Oates J, et al. *Intestinal complications after chemotherapy for patients with unresected primary colorectal cancer and synchronous metastases.* Gut 2003 Apr;52(4):568-73 Available from: http://www.ncbi.nlm.nih.gov/pubmed/12631671.
20. ↑ Yun HR, Lee WY, Lee WS, Cho YB, Yun SH, Chun HK. *The prognostic factors of stage IV colorectal cancer and assessment of proper treatment according to the patient's status.* Int J Colorectal Dis 2007 Nov;22(11):1301-10 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17486358.

21. ↑ 21.0 21.1 Clancy C, Burke JP, Barry M, Kalady MF, Calvin Coffey J. *A meta-analysis to determine the effect of primary tumor resection for stage IV colorectal cancer with unresectable metastases on patient survival.* Ann Surg Oncol 2014 Nov;21(12):3900-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24849523.
22. ↑ Faron M, Pignon JP, Malka D, Bourredjem A, Douillard JY, Adenis A, et al. *Is primary tumour resection associated with survival improvement in patients with colorectal cancer and unresectable synchronous metastases? A pooled analysis of individual data from four randomised trials.* Eur J Cancer 2015 Jan;51(2):166-76 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25465185.
23. ↑ 23.0 23.1 Cirocchi R, Trastulli S, Abraha I, Vettoretto N, Boselli C, Montedori A, et al. *Non-resection versus resection for an asymptomatic primary tumour in patients with unresectable stage IV colorectal cancer.* Cochrane Database Syst Rev 2012 Aug 15;(8):CD008997 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22895981.
24. ↑ 24.0 24.1 24.2 24.3 Malouf P, Gibbs P, Shapiro J, Sockler J, Bell S. *Australian contemporary management of synchronous metastatic colorectal cancer.* ANZ J Surg 2016 Apr 28 Available from: http://www.ncbi.nlm.nih.gov/pubmed/27122066.
25. ↑ 25.0 25.1 McCahill LE, Yothers G, Sharif S, Petrelli NJ, Lai LL, Bechar N, et al. *Primary mFOLFOX6 plus bevacizumab without resection of the primary tumor for patients presenting with surgically unresectable metastatic colon cancer and an intact asymptomatic colon cancer: definitive analysis of NSABP trial C-10.* J Clin Oncol 2012 Sep 10;30(26):3223-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22869888.
26. ↑ 26.0 26.1 Poultsides GA, Servais EL, Saltz LB, Patil S, Kemeny NE, Guillem JG, et al. *Outcome of primary tumor in patients with synchronous stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment.* J Clin Oncol 2009 Jul 10;27(20):3379-84 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19487380.
27. ↑ Tsang, W Ziogas, A Lin, B Seery, T Karnes, W Stamos, M Zell, J. *Role of Primary Tumor Resection Among Chemotherapy-Treated Patients with Synchronous Stage IV Colorectal Cancer: A Survival Analysis.* Journal of Gastrointestinal Surgery 2013 Dec 3;18(3), p. 592-598 DOI: 10.1007/s11605-013-2421-0.
28. ↑ Nitzkorski, J Farma, J Watson, J Siripurapu, V Zhu, F Matteotti, R Sigurdson, E. *Outcome and Natural History of Patients with Stage IV Colorectal Cancer Receiving Chemotherapy Without Primary Tumor Resection.* Annals of Surgical Oncology 2011 Aug 23;19(2), p. 379-383 DOI: 10.1245/s10434-011-2028-1.
29. ↑ Gervaz P, Rubbia-Brandt L, Andres A, Majno P, Roth A, Morel P, et al. *Neoadjuvant chemotherapy in patients with stage IV colorectal cancer: a comparison of histological response in liver metastases, primary tumors, and regional lymph nodes.* Ann Surg Oncol 2010 Oct;17(10):2714-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20405223.
30. ↑ Ballian N, Mahvi DM, Kennedy GD. *Colonoscopic findings and tumor site do not predict bowel obstruction during medical treatment of stage IV colorectal cancer.* Oncologist 2009 Jun;14(6):580-5 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19465681.
31. ↑ National Comprehensive Cancer Network. *NCCN Guidelines: Colon Cancer.* National Comprehensive Cancer Network; 2016.
32. ↑ Adam R, de Gramont A, Figueras J, Kokudo N, Kunstlinger F, Loyer E, et al. *Managing synchronous liver metastases from colorectal cancer: a multidisciplinary international consensus.* Cancer Treat Rev 2015 Nov;41(9):729-41 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26417845.

33. ↑ 33.0 33.1 't Lam-Boer J, Mol L, Verhoef C, de Haan AF, Yilmaz M, Punt CJ, et al. *The CAIRO4 study: the role of surgery of the primary tumour with few or absent symptoms in patients with synchronous unresectable metastases of colorectal cancer--a randomized phase III study of the Dutch Colorectal Cancer Group (DCCG).* BMC Cancer 2014 Oct 2;14:741 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25277170.

34. ↑ 34.0 34.1 Rahbari NN, Lordick F, Fink C, Bork U, Stange A, Jäger D, et al. *Resection of the primary tumour versus no resection prior to systemic therapy in patients with colon cancer and synchronous unresectable metastases (UICC stage IV): SYNCHRONOUS--a randomised controlled multicentre trial (ISRCTN30964555).* BMC Cancer 2012 Apr 5;12:142 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22480173.

Back to top

16.7.5 Appendices

View recommendation components | View pending evidence | View body of evidence | View all comments | View PICO

Back to top

16.8 Discussion

17 Role systemic therapies in non-resectable metastatic CRC

References

Back to top

17.1 Introduction: role systemic therapies in non-resectable metastatic CRC

References

Back to top

17.2 Molecular pathology and biomarkers for systemic therapy

xxx

17.3 Systemic chemotherapy first-line treatment

References

Back to top

17.4 Biological agents in first-line tx of metastatic CRC

References

Back to top

17.5 Subsequent treatment & continuum-of-care model

References

Back to top

17.6 Systemic second-line treatment

References

Back to top

17.7 Systemic third-line treatment

References

Back to top

17.8 Supportive care options

18 Follow-up after curative resection for CRC

18.1 Background

The debate regarding the rigour and intensity of follow-up investigations is complex.

Patient surveillance following curative resection for colorectal cancer varies from minimal to intensive follow-up. There is no consensus on the definition of these approaches and, therefore, there are many different protocols for minimal and intensive follow-up.

Minimal follow-up may include clinical assessment with or without carcinoembryonic antigen (CEA) testing and colonoscopy. Alternatively, minimal follow-up can involve performing investigations only when patients become symptomatic.

Intensive follow-up may include, in addition to clinical assessment and CEA, computed tomography (CT) and/or positron emission tomography (PET) at regular intervals.

Intensive follow-up after curative resection for colorectal cancer is common practice, but the evidence to date has been limited and non-conclusive.

18.1.1 Contents

Subsections:

- Rationale for follow-up
- Optimal surveillance protocol (FUR1-2)
- Health professionals performing follow-up and suggested follow-up schedule

18.1 Introduction: follow-up after curative resection for CRC

18.1.1 Background

The debate regarding the rigour and intensity of follow-up investigations is complex.

Patient surveillance following curative resection for colorectal cancer varies from minimal to intensive follow-up. There is no consensus on the definition of these approaches and, therefore, there are many different protocols for minimal and intensive follow-up.

Minimal follow-up may include clinical assessment with or without carcinoembryonic antigen (CEA) testing and colonoscopy. Alternatively, minimal follow-up can involve performing investigations only when patients become symptomatic.

Intensive follow-up may include, in addition to clinical assessment and CEA, computed tomography (CT) and/or positron emission tomography (PET) at regular intervals.

Intensive follow-up after curative resection for colorectal cancer is common practice, but the evidence to date has been limited and non-conclusive.

18.1.1.1 Contents

Subsections:

- Rationale for follow-up
- Optimal surveillance protocol (FUR1-2)
- Health professionals performing follow-up and suggested follow-up schedule

18.2 Rationale for follow-up

The primary aim for surveillance is to promote long-term survival through the early detection of local and distant recurrent disease.

Surveillance is also useful for detecting metachronous colorectal cancers, reassuring patients, and maximising quality of life, and for enabling collection of data for research purposes.

Contents

18.2.1 Overview of evidence (non-systematic literature review)

No systematic reviews were undertaken for this topic. Practice points were based on selected evidence and consensus. See Guidelines development process.

18.2.1.1 Early detection of recurrence

About one in three patients who have curative surgery for colorectal cancer will die as a result of recurrent disease.[1] Follow-up is performed to improve on this outcome by detecting recurrence at an earlier and potentially curable stage. In general, this will mean detecting recurrence in an asymptomatic person. Ideally such recurrence would be early and resectable local or distant disease, for which further treatment is potentially curative and may prolong survival. Proponents of intensive follow-up argue that this approach could lead to earlier detection of recurrent and/or metachronous disease and, by improving resectability rates, may improve survival time.

Chemotherapy and surgical resection for metastatic or recurrent disease have been shown to improve survival. Patients who have complete resection of liver metastases have a 5-year survival rate of approximately 40%.[2] Similar results have been reported for lung metastases.[3] Additionally, advances in pelvic exenteration for locally recurrent rectal cancer have shown improved complete oncological resection rates (R0) and achieved 5-year disease-free survival rates of up to 43%.[4]

Comparably complete cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) for colorectal cancer related peritoneal carcinomatosis is, in highly selected patients, beneficial, resulting in 40-50% five-year survival and 16% ten-year survival.[5][6]

18.2.1.2 Detection of secondary primary tumours

Following curative surgery for colorectal cancer, patients have an increased incidence of metachronous primary colorectal cancers and adenomatous polyps.[7] In one series, the rates of development of new primary cancers and adenomas at 4 years were 7.7% and 62%, respectively.[8]

Colonoscopic surveillance and the removal of any adenomas might reduce the incidence of subsequent primary bowel cancer.

18.2.1.3 Data collection and audit

Follow-up provides information on clinical outcomes for clinicians to evaluate their practice against professional standards.[9] It is essential for participation in clinical trials.[10] Follow-up is also required in order to produce national outcomes data to assess the impact of new guidelines and the introduction of alternative therapies.

Practice point

As there are no reliable indicators of an individual's risk of synchronous or metachronous lesions, nor of treatable recurrence, all patients who have undergone curative surgery should be offered follow-up if they are fit for further intervention should disease be detected.

Practice point

Patients who are unfit for further surgery or who have advanced disease require appropriate follow-up directed at psychological support and symptom relief.

18.2.2 References

1. ↑ Kievit J, Bruinvels DJ. *Detection of recurrence after surgery for colorectal cancer.* Eur J Cancer 1995 Jul; 31A(7-8):1222-5 Available from: http://www.ncbi.nlm.nih.gov/pubmed/7577026.
2. ↑ Kanas GP, Taylor A, Primrose JN, Langeberg WJ, Kelsh MA, Mowat FS, et al. *Survival after liver resection in metastatic colorectal cancer: review and meta-analysis of prognostic factors.* Clin Epidemiol 2012;4: 283-301 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23152705.
3. ↑ Gonzalez M, Poncet A, Combescure C, Robert J, Ris HB, Gervaz P. *Risk factors for survival after lung metastasectomy in colorectal cancer patients: a systematic review and meta-analysis.* Ann Surg Oncol 2013 Feb;20(2):572-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23104709.
4. ↑ Milne T, Solomon MJ, Lee P, Young JM, Stalley P, Harrison JD. *Assessing the impact of a sacral resection on morbidity and survival after extended radical surgery for locally recurrent rectal cancer.* Ann Surg 2013 Dec;258(6):1007-13 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23364701.
5. ↑ Elias D, Lefevre JH, Chevalier J, Brouquet A, Marchal F, Classe JM, et al. *Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin.* J Clin Oncol 2009 Feb 10;27(5):681-5 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19103728.
6. ↑ Quenet F, Goéré D, Mehta SS, Roca L, Dumont F, Hessissen M, et al. *Results of two bi-institutional prospective studies using intraperitoneal oxaliplatin with or without irinotecan during HIPEC after cytoreductive surgery for colorectal carcinomatosis.* Ann Surg 2011 Aug;254(2):294-301 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21772129.
7. ↑ Nava HR, Pagana TJ. *Postoperative surveillance of colorectal carcinoma.* Cancer 1982 Mar 1;49(5):1043-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/7059921.
8. ↑ Beck DE, Opelka FG, Hicks TC, Timmcke AE, Khoury DA, Gathright JB Jr. *Colonoscopic follow-up of adenomas and colorectal cancer.* South Med J 1995 May;88(5):567-70 Available from: http://www.ncbi.nlm.nih.gov/pubmed/7732448.
9. ↑ The Royal College of Surgeons of England: Association of coloproctology of Great Britain and Ireland. *Guidelines for the Management of Colorectal Cancer.*; 1996.

10. ↑ Beart RW Jr, O'Connell MJ. *Postoperative follow-up of patients with carcinoma of the colon.* Mayo Clin Proc 1983 Jun;58(6):361-3 Available from: http://www.ncbi.nlm.nih.gov/pubmed/6855273.

Back to top

18.3 Optimal follow-up surveillance protocol (FUR1-2)

Contents

18.3.1 Systematic review evidence

In patients who have had curative resection of colorectal cancer, what surveillance protocol achieves the best outcomes in terms of detected recurrent disease, 5-year survival, quality of life, and colorectal cancer-related mortality? (FUR1-2a)

A systematic review was performed to compare the outcomes of minimal and intensive follow-up modalities in patients who had undergone curative resection for colorectal cancer. Note: colonoscopy follow-up is covered in the colorectal cancer surveillance guidelines (http://wiki.cancer.org.au/australia/Guidelines:Colorectal_cancer/Colonoscopy_surveillance)

Five prospective randomised controlled trials (RCTs) were identified:[1][2][3][4][5]

- The UK CEA Second-Look (CEASL) trial[5] performed carcinoembryonic antigen (CEA) testing in 1447 patients, and randomised those with significantly elevated CEA to aggressive follow-up (second-look surgery) or conventional follow-up.
- The UK Follow-up After Colorectal Surgery (FACS) trial[1] compared minimal follow-up with three more intensive follow-up protocols that included additional imaging (approximately 300 patients per group): computed tomography (CT), CEA, or CEA plus CT.
- The Italian GILDA trial[3] compared follow-up protocols based on minimal and intensive imaging.
- A Spanish study[2] compared a simple surveillance protocol with an intensive protocol that involved abdominal CT or ultrasonography, chest radiograph, and colonoscopy.
- A French study[4] randomised patients to conventional follow-up or positron emission tomography (PET) to detect tumour recurrence.

Of these RCTs one[1] had a high risk of bias, while the remaining RCTs[2][3][4][5] had unclear risk of bias.

All studies reported on overall survival and rates of tumour recurrence.[1][2][3][4][5] Other reported outcomes included time to recurrence and outcomes of curative surgery following the detection of recurrence.

The search strategy, inclusion and exclusion criteria, and quality assessment are described in detail in the Technical report.

18.3.1.1 Survival and mortality

Survival and mortality data from all five RCTs showed consistent non-significant differences between different follow-up protocols for patients who had undergone curative resection for colorectal cancer.[1][2][3][4][5]

The CEASL trial[5] reported no significant differences in overall mortality the conventional follow-up group and the aggressive follow-up group: risk ratio (RR) 1.16 (95% confidence interval [CI] 0.87 to 1.37).

The FACS trial[1] reported no significant differences between groups for overall mortality ($p = 0.45$) and colorectal cancer-specific mortality ($p = 0.66$) on intention-to-treat (ITT) analysis. Furthermore, no significant differences in mortality rates were observed between protocols with and without CEA ($p > 0.05$), and between protocols with and without CT ($p > 0.05$).

The GILDA trial[3] found no differences in outcomes between patients undergoing less intensive and more intensive follow-up protocols with 82.9% survival observed in the less intensive follow-up group and 81.6% survival observed in the more intensive follow-up group: hazard ratio (HR) 1.14 (95% CI 0.87 to 1.48, $p = 0.34$). Similar 5-year survival rates were also observed in this trial (84% versus 81%), but no statistical comparisons were provided.

The Spanish study[2] also reported a non-significant difference in overall survival between simple and intensive protocols with a median follow-up time of 49 months (79.5%, versus 83.5%, $p = 0.41$).

The French PET study[4] found no significant difference in rates of 2-year overall mortality between the conventional follow-up group and of the PET group (9.2% versus 5%, p = 0.33).

18.3.1.2 Tumour recurrence

Rates of tumour recurrence were reported in five RCTs.[1][2][3][4][5]

Overall, detection of tumour recurrence did not differ significantly according to follow-up modality. However there was a significant difference in the rates detection of resectable recurrence between the conventional and intensive-imaging follow-up groups. CT scans were effective in detecting recurrences.

The CEASL trial[5] reported higher recurrence rates in the conventional follow-up group (82.4%) compared with the second-look group (76.9%), but did not report statistical analysis of these data.

The FACS trial[1] also reported non-significant differences in recurrence rates between the four follow-up groups: "minimum follow-up" 12.3%, CEA 19%, CT 19.1%, and CEA plus CT 15.9%, (p = 0.08). However, significant differences were observed for the rate of recurrence detected by each method: "minimum" 3%, CEA 11%, CT 16.1% and CEA plus CT 13.2% (p < 0.001). When follow-up groups were split into CEA versus no CEA, no significant differences were observed in overall recurrence rates (p=0.41) or the rate of recurrence detected during follow-up (p=0.14). By contrast, when patients receiving CT were compared with those who did not receive CT, a significantly higher rate of detected recurrences was observed in the CT groups than the no-CT group (14.6% versus 7%, p < 0.001). However this effect was not significantly different for rates of overall recurrence (p = 0.39).

Although the GILDA trial[3] did not provide statistical comparisons between groups for recurrence rates, similar overall recurrence rates were observed between less intensive (18.8%) and more intensive (22%) follow-up groups. Comparable rates were also observed when recurrence was stratified by type, including local anastomotic, local extra-anastomotic, liver only, lung only, multiple, and other site recurrence.

The Spanish RCT comparing simple and intense protocols[2] reported several tumour recurrence-related outcomes including overall recurrence, type of recurrence, and the rate of resectable tumour recurrence stratified across stage and location (rectal and colon). The overall recurrence rate was non-significantly higher in the intensive follow-up group compared with the simple follow-up group (27.6% versus 25.8%, p = 0.74), and the type of recurrence (metachronous versus loco-regional versus distant) did not differ significantly between groups (p = 0.81). Overall rates of resectable tumour recurrence were, however, significantly different between groups, with 51% recurrence observed in the intense group and 29% observed in the simple follow-up group: odds ratio (OR) 2.85 (95% CI 1.04 to 7.87, p = 0.04). However, when stratified by tumour stage (II versus III), only patients with stage II tumours showed a significant difference in recurrence, with patients in the intensive follow-up group having higher recurrence (73.3%) than the simple follow-up group (20%): OR 8.88 (95% CI 1.40 to 49.3, p = 0.01). When resectable tumour recurrence was stratified by location, patients with tumour of the colon did not show a significant difference between groups: OR 2.22 (95% CI 0.7 to 6.67, p = 0.89). By comparison, among patients with resectable rectal tumours, a higher proportion was detected by intensive follow-up than simple follow-up (80% versus 20%, p = 0.08). However, this effect was not significant after controlling for age, preoperative CEA levels, tumour stage, tumour location, and risk of metachronous lesions: OR 29.4 (95% CI 0.94 to 916.48, p = 0.054).

The French PET trial[4] reported 2-year survival rates. It reported comparable rates of recurrence in for the conventional and PET groups both on ITT analysis (32.3% versus 38.5%) and per-protocol analysis (32.3% versus 38.3%). However no statistical comparison of these data was provided.

18.3.1.3 Time to recurrence

Time to recurrence was reported as an outcome in three RCTs.[4][1][2]

In the FACS trial[1], Kaplan-Meier curves were used to compare time to recurrence between four different follow-up protocols (minimal, CEA, CT and CEA plus CT). No significant difference was observed between these protocols over 5 years of follow-up ($p = 0.18$).

Similarly, the Spanish study[2] reported comparable mean time to recurrence for simple and intense follow-up protocols (39 months versus 39 months).

By contrast, the French RCT comparing conventional and PET protocols[4] reported a significantly shorter mean time to detected recurrence in the PET follow-up group than the conventional follow-up group (12.1 versus 15.4 months) for patients included in the per-protocol analysis ($p = 0.01$), with similar rates observed on ITT analysis.

18.3.1.4 Curative follow-up surgery

Rates of attempted and successful curative surgery following the identification of local recurrence during follow-up were reported in the FACS trial[1] and the French PET study[4].

The French study[4] reported higher rates of curative resection in the PET group compared with the conventional screening group on per-protocol analysis (65% versus 9.5%, $p < 0.0001$). Similarly, the rate of successful curative resection was higher for patients undergoing PET follow-up than conventional follow-up (43.5% versus 9.5%, $p < 0.01$).

Similarly to the Spanish study[2], the FACS trial[1] also reported higher rates of attempted curative resection in the intensive follow-up group. On ITT analysis, the rate of surgical treatment with curative intent was significantly lower in the minimal follow-up group (2.3%), than the other three groups:

- CEA only (6.7%): OR 3.00 (95% CI 1.23 to 7.33, $p = 0.004$)
- CT only (8%): OR 3.10 (95% CI 1.27 to 7.57, $p = 0.01$)
- combination of CEA plus CT (6.6%): OR 6.71 (95% CI 1.96 to 22.9, $p = 0.005$).[1]

The combination of CEA and CT did not add any benefit when compared with CEA alone or CT alone. The same significant effects were also observed on per-protocol analysis. No significant differences in overall recurrence were observed on ITT analysis when follow-up protocols that included CEA were compared with no CEA ($p = 0.53$), or when protocols that included CT were compared with no CT ($p = 0.59$).[1]

18.3.1.5 Quality of life

Quality of life was reported as an outcome in the GILDA trial.[3] This study observed no significant difference between SF12 mental and physical health scores for patients undergoing less intensive versus more intensive follow-up protocols. Psychological General Well-Being Index questionnaire scores also showed no differences between patients undergoing different follow-up protocols. No statistics were provided for these comparisons.

Back to top

18.3.2 Evidence summary and recommendations

Evidence summary	Level	References
Survival and mortality No difference between intensive and less intensive follow-up groups was observed for both overall survival and mortality.	II	[1], [2], [3], [4], [5]
Tumour recurrence Rates of tumour recurrence and detected tumour recurrence were inconsistent across studies, with the majority reporting no consistent or significant differences between different follow-up schedules. There was a significant increase in the detection of resectable recurrence with intensive follow-up.	II	[1], [2], [3], [4], [5]
Time to recurrence Time to recurrence was not consistently different between follow-up groups and may be dependent on the type, rather than the intensity, of the follow-up.	II	[1], [2], [4]
Curative follow-up surgery More intensive follow-up schedules (including CEA, CT and PET) may result in higher rates of curative follow-up resection and improved survival in those patients in whom resectable colorectal cancer was detected.	II	[1], [4]
Quality of life Quality of life was only reported in one study, which showed negligible difference between follow-up groups.	II	[3]

Evidence-based recommendation	Grade
Intensive follow-up after curative surgery for colorectal cancer should include colonoscopy with CEA and/or CT scan, with the aim of early detection of recurrence or residual disease where there is the possibility for curative resection. PET CT scan can be used as an effective adjunct for detection of recurrence, especially when the CEA and/or CT scans are suggestive of recurrence.	**D**

Practice point
These recommendations apply only to asymptomatic patients. All patients who develop symptoms should be investigated rigorously.

Practice point
Colonoscopy should be included as routine follow-up, primarily as a preventive measure.

Practice point
Intensive follow-up for colorectal cancer should be considered for patients who have had potentially curable disease, although optimal modality and frequency are yet to be firmly established.

Practice point
Intensive follow-up can detect resectable recurrences earlier which may have benefit in survival, albeit a small difference.

Practice point
CEA and CT scans are readily accessible and relatively sensitive investigations.

18.3.2.1 Considerations in making these recommendations

The benefits from follow-up include:

- the detection of potentially curable recurrent disease
- the ability to remove metachronous polyps and to detect early metachronous cancers
- the provision of audit and survival data
- patient support.

The most recent randomised controlled trials[1][2][3][4][5] and meta-analyses[6][7] support a survival advantage, albeit small, for patients who are followed up intensively after curative resection of colorectal cancer.

18.3.2.2 Health system implications

18.3.2.2.1 Clinical practice

Between 12 and 20 patients must undergo intensive investigation for one patient to have a resectable recurrence detected and receive surgery for curative intent.[1]

18.3.2.2.2 Resourcing

CEA is relatively cost-effective when compared with CT scans. However, two-thirds of patients with recurrence were detected on CT scan first in the FACS study.9[1]

18.3.2.2.3 Barriers to implementation

No barriers to the implementation of these recommendations are envisaged.

18.3.3 Discussion

18.3.3.1 Unresolved issues

There are no significant unresolved issues.

18.3.3.2 Studies currently underway

There are no significant ongoing studies.

18.3.3.3 Future research priorities

Although the costs and complications of follow-up investigations can be considerable, the cost-benefit ratio needs to be assessed formally with further trials.

There is research on which to establish an algorithm based on the rate of change in CEA, to improve specificity for the detection of recurrent disease. This approach has been successful using cancer antigen 125 levels in the detection of ovarian cancer.[6] The implementation of such an algorithm may lead to fewer CT scans and would reduce costs to the health system.

There is growing interest in systematic second-look surgery and HIPEC in patients who are high risk for CRC related peritoneal carcinomatosis (T4 lesions, perforation at primary operation and ovarian/low volume peritoneal metastases excised) due to the late onset of symptoms and low sensitivity of imaging techniques and tumour markers. A French multi-centre randomized trial is ongoing (Prophylochip).[8] Patients at high risk after adjuvant treatment with FOLFOX 6 and with a negative follow-up are randomly assigned to surveillance or second-look laparotomy and HIPEC. The aim of the research is to evaluate rate of peritoneal recurrence at three years.).[8]

18.3.4 References

1. ↑ 1.00 1.01 1.02 1.03 1.04 1.05 1.06 1.07 1.08 1.09 1.10 1.11 1.12 1.13 1.14 1.15 1.16 1.17 1.18 1.19 1.20 Primrose JN, Perera R, Gray A, Rose P, Fuller A, Corkhill A, et al. *Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer: the FACS randomized clinical trial.* JAMA 2014 Jan 15;311(3): 263-70 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24430319.
2. ↑ 2.00 2.01 2.02 2.03 2.04 2.05 2.06 2.07 2.08 2.09 2.10 2.11 2.12 2.13 2.14 Rodriguez-Moranta F, Salo J, Arcusa A, Boadas J, Pinol V, Bessa X, et al. *Postoperative surveillance in patients with colorectal cancer who have undergone curative resection: a prospective, multicenter, randomized, controlled trial.* J Clin Oncol 2006 Jan 1;24(3):386-93.
3. ↑ 3.00 3.01 3.02 3.03 3.04 3.05 3.06 3.07 3.08 3.09 3.10 3.11 3.12 Rosati G, Ambrosini G, Barni S, Andreoni B, Corradini G, Luchena G, et al. *A randomized trial of intensive versus minimal surveillance of patients with resected Dukes B2-C colorectal carcinoma.* Ann Oncol 2016 Feb;27(2):274-80 Available from: http://www.ncbi.nlm.nih.gov/pubmed/26578734.
4. ↑ 4.00 4.01 4.02 4.03 4.04 4.05 4.06 4.07 4.08 4.09 4.10 4.11 4.12 4.13 4.14 4.15 4.16 Sobhani I, Tiret E, Lebtahi R, Aparicio T, Itti E, Montravers F, et al. *Early detection of recurrence by 18FDG-PET in the follow-up of patients with colorectal cancer.* Br J Cancer 2008 Mar 11;98(5):875-80 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18301402.
5. ↑ 5.00 5.01 5.02 5.03 5.04 5.05 5.06 5.07 5.08 5.09 5.10 Treasure T, Monson K, Fiorentino F, Russell C. *The CEA Second-Look Trial: a randomised controlled trial of carcinoembryonic antigen prompted reoperation for recurrent colorectal cancer.* BMJ Open 2014 May 13;4(5):e004385 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24823671.
6. ↑ 6.0 6.1 Jeffery GM, Hickey BE, Hider P. *Follow-up strategies for patients treated for non-metastatic colorectal cancer.* Cochrane Database Syst Rev 2002;(1):CD002200 Available from: http://www.ncbi.nlm.nih.gov/pubmed/11869629.

7. ↑ Renehan AG, Egger M, Saunders MP, O'Dwyer ST. *Impact on survival of intensive follow up after curative resection for colorectal cancer: systematic review and meta-analysis of randomised trials.* BMJ 2002 Apr 6;324(7341):813 Available from: http://www.ncbi.nlm.nih.gov/pubmed/11934773.
8. ↑ [8.0] [8.1] ClinicalTrials.gov. *Trial Comparing Simple Follow-up to Exploratory Laparotomy Plus "in Principle" (Hyperthermic Intraperitoneal Chemotherapy) HIPEC in Colorectal Patients (ProphyloCHIP).* [homepage on the internet]; Available from: https://clinicaltrials.gov/ct2/show/study/NCT01226394.

Back to top

18.3.5 Appendices

View recommendation components	View pending evidence	View body of evidence	View all comments	View literature search

View PICO	NHMRC Evidence statement form FUR1-2a	Systematic review report FUR1-2a

Back to top

18.4 Health professionals performing follow-up & suggested schedule

Contents

18.4.1 Overview of evidence (non-systematic literature review)

No systematic reviews were undertaken for this topic. Practice points were based on selected evidence and consensus. See Guidelines development process.

18.4.1.1 Health professionals performing follow-up

It has not been established whether outcomes differ by provider of follow-up care. For example it has not been established whether intensive (hospital-based) follow up is associated with a survival advantage over care provided by a general practitioner or clinical nurse consultant in colorectal cancer. Further studies are needed to determine whether community-based follow up can be adequately performed without decreasing patient survival, and to define the optimal balance between follow-up care provided by the general practitioner or clinical nurse consultant and the specialist.

Practice point
Follow-up can be delivered as a combination of visits to the surgeon or associated gasteroenterologist, with ongoing care by the GP and clinical nurse consultant.

18.4.1.2 Suggested follow-up schedule

After the routine review post discharge, patients should be reviewed at 3- to 6-monthly intervals for the first year (3 monthly in those patients who had poor prognostic factors such a positive margin, patients with stage III disease who decline chemotherapy) , 6-monthly for the next two years and then yearly for a total of 5 years. There is no consensus on these intervals, as evidenced by the variability in follow-up protocols in the published literature, but there are organizations that would support a similar follow-up schedule.[1][2][3] This is a guide for the clinician and further trials will be necessary to establish optimal protocols.

Clinical assessment includes history and physical examination. Regular carcinoembryonic antigen (CEA) measurement and computed tomography (CT) should be considered in follow-up protocols as they may provide useful in early detection of recurrence and the potential for surgery with curative intent. Positron emission tomography (PET)/CT can be an effective alternative to standard CT after detection of a significant rise in CEA.[4][5][6]

The anastomosis should be assessed 12 months after surgery to exclude recurrence. If the patient did not have complete colonoscopy prior to surgery, then this should be performed at least 6 months after surgery.

Future studies should focus on the cost-effectiveness and efficiency of investigations employed.[7]

18.4.2 References

1. ↑ Meyerhardt JA, Mangu PB, Flynn PJ, Korde L, Loprinzi CL, Minsky BD, et al. *Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: American Society of Clinical Oncology clinical practice guideline endorsement.* J Clin Oncol 2013 Dec 10;31(35):4465-70 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24220554.
2. ↑ National Comprehensive Cancer Network. *NCCN Guidelines: Colon Cancer.* National Comprehensive Cancer Network; 2016.
3. ↑ National Comprehensive Cancer Network. *NCCN Guidelines for Rectal Cancer Version 2.*; 2016 Available from: https://www.tri-kobe.org/nccn/guideline/colorectal/english/rectal.pdf.
4. ↑ Yu T, Meng N, Chi D, Zhao Y, Wang K, Luo Y. *Diagnostic Value of (18)F-FDG PET/CT in Detecting Local Recurrent Colorectal Cancer: A Pooled Analysis of 26 Individual Studies.* Cell Biochem Biophys 2015 Jun;72 (2):443-51 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25737131.
5. ↑ Peng NJ, Hu C, King TM, Chiu YL, Wang JH, Liu RS. *Detection of resectable recurrences in colorectal cancer patients with 2-[18F]fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography.* Cancer Biother Radiopharm 2013 Jul;28(6):479-87 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23713869.
6. ↑ Culverwell AD, Chowdhury FU, Scarsbrook AF. *Optimizing the role of FDG PET-CT for potentially operable metastatic colorectal cancer.* Abdom Imaging 2012 Dec;37(6):1021-31 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22371087.
7. ↑ Ohlsson B, Pålsson B. *Follow-up after colorectal cancer surgery.* Acta Oncol 2003;42(8):816-26 Available from: http://www.ncbi.nlm.nih.gov/pubmed/14968942.

Back to top

19 Psychosocial care

Contents

19.1 Background

The diagnosis and treatment of cancer presents a major and stressful life event that can reduce quality of life in the short and long term. Apart from the existential challenge faced by all patients with a life-threatening disease, patients with colorectal cancer have specific challenges.

Before their operation, people with colorectal cancer commonly experience fear, isolation and uncertainty, and have a high need for information and support.[1] Postoperatively, patients may experience physical, social and psychological challenges, especially if they have a new stoma.

Back to top

19.1.1 Physical challenges

Postoperative physical challenges include bowel issues, such as frequent bowel movements, constipation and diarrhoea. Patients with stomas may face leakage, skin and stoma problems, and odour.[2][3]

Sexual dysfunction is also very common among people with colorectal cancer, with sexual dysfunction rates following rectal surgery ranging from 23% to 69% in men and 19% to 62% in women.[4] Problems with erectile function and ejaculation have been reported in men,[5] and women have experienced dyspareunia, vaginal dryness and pain interfering with sexual pleasure after surgery.[6] Some patients experience a disturbed body image,[7] which can lead to low self-esteem and exacerbate sexual dysfunction.

Back to top

19.1.2 Social challenges

Patients who have undergone surgery for colorectal cancer (especially those with stomas) may avoid and fear social interactions, and experience disrupted intimate relationships due to body changes, changes in roles, social restrictions and sexual dysfunction.[7][8]

Back to top

19.1.3 Psychological challenges

19.1.3.1 Cognitive dysfunction

The effects of chemotherapy on cognitive function have been assessed in patients with colorectal cancer, as for those with other cancers. A recent meta-analysis of 13 relevant studies[9] found evidence of impairment in executive function and memory in patients of all ages. Longer treatment duration, but not shorter time since treatment, was associated with worse impairment.[9]

Back to top

19.1.3.2 Anxiety and depression

Many patients with colorectal cancer experience moderate-to-severe anxiety and depression. In a population-based Australian sample of 1966 colorectal cancer survivors assessed at six time points from 5 months to 5 years post diagnosis,[10] the prevalence of high overall distress ranged between 44% and 32%. The study[10] identified four trajectories of distress – some declining, and others (38.5% of the sample) steadily increasing over time. Other studies have reported clinical levels of depression in 8–23% of people with colorectal cancer and anxiety in 16– 39%.[11][12][13][14]

Back to top

19.1.3.3 Distress affects survival rates

Patients' distress is important, not only because of its impact on quality of life, but also its impact on survival. Quality of life has been reported to predict survival in patients with advanced colorectal cancer.[15] Depression has also been found to influence survival in a population-based sample of 1074 colorectal cancer survivors in the Netherlands.[16] In analyses adjusted for metastasis and other potential confounders, depressive symptoms significantly increased the risk of death among 1-year to 10-year colorectal cancer survivors (hazard ratio [HR] 1.88; 95 % CI, 1.24–2.83; $p < 0.01$) and even more in 1-year to 2-year colorectal cancer survivors (HR, 2.55; 95 % CI, 1.44–4.51; $p < 0.001$).[16] Thus depression has the highest negative effect on survival in the first 1-2 years, but this effect extends out to 10 years post-diagnosis.

Back to top

19.1.3.4 Who is more vulnerable to anxiety and depression?

A number of studies have explored predictors of anxiety, depression and distress among people with colorectal cancer. However, a recent systematic review[17] noted that most studies were cross-sectional and psychosocial variables have been poorly studied.

Many of the factors associated with anxiety, depression and distress may be modified with appropriate intervention.

Factors that were associated with an increased risk of developing anxiety include:[14]

- more, or more severe, symptoms such as poor self-reported cognitive functioning, dyspnoea and diarrhoea
- financial difficulties.

Factors that were associated with an increased risk of developing depression include:[14]

- neo-adjuvant radiotherapy
- poor physical, cognitive or social functioning
- difficulties with personal care and communicating with others.

Factors that were associated with an increased risk of developing distress include:[10]

- male sex
- younger age
- lower education
- poor socioeconomic advantage
- poor social support
- late disease stage
- pre-diagnosis anxiety, pessimism and a distressed personality style.[17]

The investigators of an Australian prospective survey of colorectal cancer survivors[10] concluded that, based on their higher levels of distress, men who are younger, and with low education and poor social support, should be a priority for targeted intervention.

Back to top

19.1.4 Family distress

There is also evidence that families of people with colon cancer experience considerable distress, particularly if the person has metastatic disease.[18] In a large Australian study of patients with advanced cancer in the palliative care setting,[19] evidence of substantial psychological distress warranting specific support was identified in up to half of the patients (20% of whom had colorectal cancer), one-third of their spouses and one-quarter of their offspring. For people in palliative care, this distress reverberates through the family in such a way that both patient and family-centred models of care need to be adopted.

Back to top

19.2 Psychological care and treatments

The importance of psychosocial care is recognised in the 2003 national guideline Clinical practice guidelines for the psychosocial care of adults with cancer.[20] This guideline is a useful evidence-based source for practising clinicians.

19.2.1 Persisting unmet need

Despite widespread acceptance that psychosocial care is integral to quality cancer care, psychological morbidity is often undetected and underestimated in busy cancer services,[21] and people with cancer continue to experience high levels of unmet need for psychosocial care.[22] Colorectal cancer patients report many deficiencies in their supportive care.[23]

Back to top

19.2.2 Screening for distress

Because anxiety and depression are often under-detected, international guidelines recommend routine screening of all cancer patients for psychological distress, using validated, reliable, objective measures.[24] The International Psycho-Oncology Society (IPOS) and 68 affiliated organisations have set a standard of care involving monitoring distress as the '6th vital sign'. The authors of an Australian study that measured distress in colorectal cancer survivors[10] recommend that screening should occur not only at diagnosis, but also at key points of the illness trajectory and into survivorship, to ensure that late-onset distress is not missed. Recent Australian clinical guidelines for screening for, and managing, anxiety and depression in cancer patients[10] recommend the following tools to screen for distress: the 1-item "Distress Thermometer" (with 39 problem areas to tick)[24] and the 9-item ESAS (Edmonton Symptom Assessment Schedule).[25]

Back to top

19.2.3 Psychological intervention

There is now a large evidence base, summarised in meta-analyses and systematic reviews, demonstrating that interventions for distress in patients with cancer are effective in the short and long term.[26][27][28][29] A recent review of psychological interventions specifically in colorectal cancer,[30] which identified 11 studies meeting inclusion criteria, found that psychosocial interventions (including educational interventions, cognitive–behavioural therapy, relaxation training and supportive group therapy) for colorectal cancer patients reduced length of hospital stay, days to stoma proficiency, and anxiety and depression, and improved quality of life.

Relaxation-based therapies are greatly beneficial in reducing anxiety, treatment-related phobias, conditioned nausea and vomiting, and insomnias.[31] Both cognitive–behavioural and supportive–expressive therapies are effective in countering existential fears of dying, aloneness, meaninglessness and unrealistic fears about processes of treatment.[26] Early referral for specialist support from a clinical psychologist or liaison psychiatrist is worthwhile when symptoms of distress or high risk become evident. One study has also shown that peer support (face-to-face group or individual by phone) is feasible, acceptable and appreciated by colo-rectal patients, although efficacy of this intervention has not yet been evaluated.[32]

Randomised controlled trials of early versus late referral to palliative care services show strong evidence of the benefits of early referral in reducing time spent in hospital, enhancing symptom control, increasing family satisfaction, and permitting death to occur in the desired location.[33] Early referral to community-based domiciliary palliative care services support and information, where available, may have several benefits and enhance quality of life. Support can be provided by various health disciplines with appropriate training.

Practice point

- patients with colorectal cancer should be screened for psychological distress at diagnosis and key points in their disease trajectory.
- Psychological interventions should be a component of colorectal cancer care, as they can improve the quality of life for patients with cancer.

Back to top

19.2.4 Information needs and decision aids

19.2.4.1 Providing information to patients

Surveys of patients with cancer repeatedly identify information provision as a major unmet need.[21] Research has shown that the provision of adequate information is related to increased psychological wellbeing.[34] Effective communication skills, which can be learned through facilitated communication skills training, ensure that this information is clearly explained and understood.[35]

Six main principles of information provision for cancer patients are relevant to the care of people with colorectal cancer patients:

- Treatment options should be explained clearly, with realistic information about potential effectiveness and adverse effects.
- Patients should be invited to guide the clinician to provide the level of detail they wish to receive and to enable their desired level of active involvement in decision making.[36]
- Clinicians should review both the person’s understanding of the information, and their reactions to it, as a means of increasing integration and providing emotional support.
- Written materials should be provided, and clinicans should consider offering audio recording of key consultations.[33] The involvement of a specialist nurse or counsellor, provision of a follow-up letter, and participation in psychoeducational programs may also assist in recall of information.[37][38]
- Information should be made available over time and, if desired, review appointments that allow time for further integration of information should be scheduled.

- Patients' carers and families should also be kept well informed.

Back to top

19.2.5 The role of decision aids

Some decisions in colorectal cancer are 'preference sensitive'; that is, the optimal decision is one that is consistent with patient values and preferences. Shared decision making is a model that seeks to include both patients and their healthcare providers in the decision making process. It encourages patients to play an active role in decisions concerning their health, which is a goal of patient-centered care.[39]

Shared decision making can be facilitated by patient decision aids, which are defined as interventions designed to help people make specific and deliberative choices among options by providing information on the options and outcomes relevant to the patient's health status.[40] The effectiveness of decision aids has been demonstrated in at least three separate systematic reviews.[35][41][42]

Decision aids have been shown to:[35][41][42]

- improve patient knowledge
- lower decisional conflict related to feeling uninformed and unclear about personal values
- reduce the proportion of people who were passive in decision making post-intervention
- improve agreement between patient values and health care option chosen.

Only a few decision aids have been developed and evaluated for colorectal cancer treatment. In an Australian-US collaboration,[43] a decision aid was developed for patients with advanced colorectal cancer who are considering first-line chemotherapy and reviewing treatment options, prognostic information, and toxicities. In a randomised controlled trial with 207 patients, patients receiving the decision aid demonstrated a greater increase in understanding of prognosis, options, and benefits, with higher overall understanding ($P < .001$), compared with patients who received a standard medical oncology consultation. Anxiety was similar between groups, and decisions were not affected; 74% chose chemotherapy, 7% supportive care alone, and 10% observation.

Another trial evaluating a decision aid for people with colorectal cancer has been registered, but has not yet reported results. The decision aid addresses the two surgical options for rectal cancer patients: low anterior resection with re-establishment of bowel continuity, and abdominoperineal resection with a permanent stoma. The decision aid is currently being piloted and a barriers analysis, exploring factors that might hinder introduction into routine care, is planned to follow. Further work on decision aid development for colorectal cancer treatment is required.

Practice point

- The use of decision aids should be considered for preference-sensitive decisions about treatment for colorectal cancer.

Back to top

1. ↑ Worster B, Holmes S. *The preoperative experience of patients undergoing surgery for colorectal cancer: a phenomenological study.* Eur J Oncol Nurs 2008 Dec;12(5):418-24 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18842456.
2. ↑ Black, P.. *Coping with common stoma problems in care homes.* Nursing & Residential Care 2011;13(3): 126-128.
3. ↑ Burch J. *The pre- and postoperative nursing care for patients with a stoma.* Br J Nurs 2005 Mar;14(6): 310-8 Available from: http://www.ncbi.nlm.nih.gov/pubmed/15902026.
4. ↑ Ho VP, Lee Y, Stein SL, Temple LK. *Sexual function after treatment for rectal cancer: a review.* Dis Colon Rectum 2011 Jan;54(1):113-25 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21160322.
5. ↑ Pietrangeli, A. Bove, L. Innocenti, P. Pace, A. Tirelli, C. Santoro, E. Jandolo, B.. *Neurophysiological evaluation of sexual dysfunction in patients operated for colorectal cancer.* Clin Auton Res 1998;8(6): 353-35.
6. ↑ Bambrick, M. Fazio, V. W. Hull, T. L. Pucel, G.. *Sexual function following restorative proctocolectomy in women.* Dis Colon Rectum 1996;39(6): 610-614.
7. ↑ [7.0] [7.1] Ross L, Abild-Nielsen AG, Thomsen BL, Karlsen RV, Boesen EH, Johansen C. *Quality of life of Danish colorectal cancer patients with and without a stoma.* Support Care Cancer 2007 May;15(5):505-13 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17103196.
8. ↑ Simmons KL, Smith JA, Bobb KA, Liles LL. *Adjustment to colostomy: stoma acceptance, stoma care self-efficacy and interpersonal relationships.* J Adv Nurs 2007 Dec;60(6):627-35 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18039249.
9. ↑ [9.0] [9.1] Hodgson KD, Hutchinson AD, Wilson CJ, Nettelbeck T. *A meta-analysis of the effects of chemotherapy on cognition in patients with cancer.* Cancer Treat Rev 2013 May;39(3):297-304 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23219452.
10. ↑ [10.0] [10.1] [10.2] [10.3] [10.4] [10.5] Dunn J, Ng SK, Holland J, Aitken J, Youl P, Baade PD, et al. *Trajectories of psychological distress after colorectal cancer.* Psychooncology 2013 Aug;22(8):1759-65 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23125004.
11. ↑ Tsunoda A, Nakao K, Hiratsuka K, Yasuda N, Shibusawa M, Kusano M. *Anxiety, depression and quality of life in colorectal cancer patients.* Int J Clin Oncol 2005 Dec;10(6):411-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16369745.
12. ↑ Strong V, Waters R, Hibberd C, Rush R, Cargill A, Storey D, et al. *Emotional distress in cancer patients: the Edinburgh Cancer Centre symptom study.* Br J Cancer 2007 Mar 26;96(6):868-74 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17311020.
13. ↑ Medeiros M, Oshima CT, Forones NM. *Depression and anxiety in colorectal cancer patients.* J Gastrointest Cancer 2010 Sep;41(3):179-84 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20180047.
14. ↑ [14.0] [14.1] [14.2] Gray NM, Hall SJ, Browne S, Johnston M, Lee AJ, Macleod U, et al. *Predictors of anxiety and depression in people with colorectal cancer.* Support Care Cancer 2014 Feb;22(2):307-14 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24077745.
15. ↑ Maisey NR, Norman A, Watson M, Allen MJ, Hill ME, Cunningham D. *Baseline quality of life predicts survival in patients with advanced colorectal cancer.* Eur J Cancer 2002 Jul;38(10):1351-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/12091066.

16. ↑ 16.0 16.1 Mols F, Husson O, Roukema JA, van de Poll-Franse LV. *Depressive symptoms are a risk factor for all-cause mortality: results from a prospective population-based study among 3,080 cancer survivors from the PROFILES registry.* J Cancer Surviv 2013 Sep;7(3):484-92 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23677523.
17. ↑ 17.0 17.1 Sales PM, Carvalho AF, McIntyre RS, Pavlidis N, Hyphantis TN. *Psychosocial predictors of health outcomes in colorectal cancer: a comprehensive review.* Cancer Treat Rev 2014 Jul;40(6):800-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24679516.
18. ↑ Northouse LL, Mood D, Templin T, Mellon S, George T. *Couples' patterns of adjustment to colon cancer.* Soc Sci Med 2000 Jan;50(2):271-84 Available from: http://www.ncbi.nlm.nih.gov/pubmed/10619695.
19. ↑ Kissane, David W. Bloch, Sidney Burns, W. Ivon McKenzie, Dean Posterino, Maria. *Psychological morbidity in the families of patients with cancer.* Psychooncology 1994;3(1): 47-56.
20. ↑ National Breast Cancer Centre, National Cancer Control Initiative. *Clinical practice guidelines for the psychosocial care of adults with cancer.* Camperdown, NSW: National Breast Cancer Centre 2003 Jan 1 Available from: http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/cp90.pdf.
21. ↑ 21.0 21.1 Newell S, Sanson-Fisher RW, Girgis A, Bonaventura A. *How well do medical oncologists' perceptions reflect their patients' reported physical and psychosocial problems? Data from a survey of five oncologists.* Cancer 1998 Oct 15;83(8):1640-51 Available from: http://www.ncbi.nlm.nih.gov/pubmed/9781960.
22. ↑ Sanson-Fisher R, Girgis A, Boyes A, Bonevski B, Burton L, Cook P. *The unmet supportive care needs of patients with cancer. Supportive Care Review Group.* Cancer 2000 Jan 1;88(1):226-37 Available from: http://www.ncbi.nlm.nih.gov/pubmed/10618627.
23. ↑ van Ryn, M. Phelan, S. M. Arora, N. K. Haggstrom, D. A. Jackson, G. L. Zafar, S. Y. Griffin, J. M. Zullig, L. L. Provenzale, D. Yeazel, M. W. Jindal, R. M. Clauser, S. B.. *Patient-reported quality of supportive care among patients with colorectal cancer in the Veterans Affairs Health Care System.* J Clin Oncol 2014;32 (8): 809-815.
24. ↑ 24.0 24.1 Holland JC, Bultz BD, National comprehensive Cancer Network (NCCN). *The NCCN guideline for distress management: a case for making distress the sixth vital sign.* J Natl Compr Canc Netw 2007 Jan;5 (1):3-7 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17323529.
25. ↑ Bruera E, Kuehn N, Miller MJ, Selmser P, Macmillan K. *The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients.* J Palliat Care 1991;7(2):6-9 Available from: http://www.ncbi.nlm.nih.gov/pubmed/1714502.
26. ↑ 26.0 26.1 Osborn RL, Demoncada AC, Feuerstein M. *Psychosocial interventions for depression, anxiety, and quality of life in cancer survivors: meta-analyses.* Int J Psychiatry Med 2006;36(1):13-34 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16927576.
27. ↑ Hart SL, Hoyt MA, Diefenbach M, Anderson DR, Kilbourn KM, Craft LL, et al. *Meta-analysis of efficacy of interventions for elevated depressive symptoms in adults diagnosed with cancer.* J Natl Cancer Inst 2012 Jul 3;104(13):990-1004 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22767203.
28. ↑ Jacobsen PB, Jim HS. *Psychosocial interventions for anxiety and depression in adult cancer patients: achievements and challenges.* CA Cancer J Clin 2008 Jul;58(4):214-30 Available from: http://www.ncbi.nlm.nih.gov/pubmed/18558664.
29. ↑ Subnis UB, Starkweather AR, McCain NL, Brown RF. *Psychosocial therapies for patients with cancer: a current review of interventions using psychoneuroimmunology-based outcome measures.* Integr Cancer Ther 2014 Mar;13(2):85-104 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24105361.

30. ↑ Chien CH, Liu KL, Chien HT, Liu HE. *The effects of psychosocial strategies on anxiety and depression of patients diagnosed with prostate cancer: a systematic review.* Int J Nurs Stud 2014 Jan;51(1):28-38 Available from: http://www.ncbi.nlm.nih.gov/pubmed/23398917.
31. ↑ Hoon, L. S. Chi Sally, C. W. Hong-Gu, H.. *Effect of psychosocial interventions on outcomes of patients with colorectal cancer: a review of the literature.* Eur J Oncol Nurs 2013;17(6): 883-891.
32. ↑ Ieropoli SC, White VM, Jefford M, Akkerman D. *What models of peer support do people with colorectal cancer prefer?* Eur J Cancer Care (Engl) 2011 Jul;20(4):455-65 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20738390.
33. ↑ 33.0 33.1 Cheung YL, Molassiotis A, Chang AM. *The effect of progressive muscle relaxation training on anxiety and quality of life after stoma surgery in colorectal cancer patients.* Psychooncology 2003 Apr;12(3):254-66 Available from: http://www.ncbi.nlm.nih.gov/pubmed/12673809.
34. ↑ Higginson IJ, Wade AM, McCarthy M. *Effectiveness of two palliative support teams.* J Public Health Med 1992 Mar;14(1):50-6 Available from: http://www.ncbi.nlm.nih.gov/pubmed/1376133.
35. ↑ 35.0 35.1 35.2 Stacey D, Bennett CL, Barry MJ, Col NF, Eden KB, Holmes-Rovner M, et al. *Decision aids for people facing health treatment or screening decisions.* Cochrane Database Syst Rev 2011 Oct 5;(10):CD001431 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21975733.
36. ↑ De Vries AM, de Roten Y, Meystre C, Passchier J, Despland JN, Stiefel F. *Clinician characteristics, communication, and patient outcome in oncology: a systematic review.* Psychooncology 2014 Apr;23(4):375-81 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24243790.
37. ↑ Singh S, Butow P, Charles M, Tattersall MH. *Shared decision making in oncology: assessing oncologist behaviour in consultations in which adjuvant therapy is considered after primary surgical treatment.* Health Expect 2010 Sep;13(3):244-57 Available from: http://www.ncbi.nlm.nih.gov/pubmed/20579121.
38. ↑ Waller A, Forshaw K, Bryant J, Mair S. *Interventions for preparing patients for chemotherapy and radiotherapy: a systematic review.* Support Care Cancer 2014 Aug;22(8):2297-308 Available from: http://www.ncbi.nlm.nih.gov/pubmed/24906837.
39. ↑ Damian D, Tattersall MH. *Letters to patients: improving communication in cancer care.* Lancet 1991 Oct 12;338(8772):923-5 Available from: http://www.ncbi.nlm.nih.gov/pubmed/1681275.
40. ↑ Barry MJ, Edgman-Levitan S. *Shared decision making--pinnacle of patient-centered care.* N Engl J Med 2012 Mar 1;366(9):780-1 Available from: http://www.ncbi.nlm.nih.gov/pubmed/22375967.
41. ↑ 41.0 41.1 O'Connor AM, Bennett C, Stacey D, Barry MJ, Col NF, Eden KB, et al. *Do patient decision aids meet effectiveness criteria of the international patient decision aid standards collaboration? A systematic review and meta-analysis.* Med Decis Making 2007 Sep;27(5):554-74 Available from: http://www.ncbi.nlm.nih.gov/pubmed/17873255.
42. ↑ 42.0 42.1 O'Brien MA, Whelan TJ, Villasis-Keever M, Gafni A, Charles C, Roberts R, et al. *Are cancer-related decision aids effective? A systematic review and meta-analysis.* J Clin Oncol 2009 Feb 20;27(6):974-85 Available from: http://www.ncbi.nlm.nih.gov/pubmed/19124808.
43. ↑ Leighl NB, Shepherd HL, Butow PN, Clarke SJ, McJannett M, Beale PJ, et al. *Supporting treatment decision making in advanced cancer: a randomized trial of a decision aid for patients with advanced colorectal cancer considering chemotherapy.* J Clin Oncol 2011 May 20;29(15):2077-84 Available from: http://www.ncbi.nlm.nih.gov/pubmed/21483008.

20 Appendices

20.1 Guideline development process

Contents

20.1.1 Introduction

These draft clinical practice guidelines are a revision and update of the 2005 *Clinical Practice Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer*. The guidelines were originally developed in 1999.

This current revision and update was commissioned and funded by the Department of Health Commonwealth of Australia.

The guidelines project commenced in December 2014, and in June 2015 the National Health and Medical Research Council (NHMRC) agreed to consider approving the guideline, provided it was developed according to NHMRC procedures and requirements.

Back to top

20.1.2 Guidelines development group

Cancer Council Australia approached key stakeholders from Working Party members who were involved in the development of the 2005 colorectal cancer (CRC) guidelines. From this group, Cancer Council Australia appointed a designated Management Committee responsible for the overall management and strategic leadership of the guideline development process. This group acted as a steering committee to ensure that all deliverables agreed in the project plan were delivered to acceptable standards in accordance with NHMRC requirements, within agreed timeframes and within the approved budget.

A wider multidisciplinary Working Party of relevant experts was then convened to develop the revised guidelines and author specific sections. This was to ensure that representatives from all specialities and disciplines involved in the diagnosis and treatment of CRC were represented. Two consumer representatives were invited to be part of the Working Party.

A project team based at Cancer Council Australia conducted the systematic reviews, comprising of systematic literature searches, literature screening against pre-determined inclusion and exclusion criteria and critical evaluation and data extraction of the included literature. The project team was responsible for liaising with the Working Party members in regards to content development, content review and compiling the document. The clinical practice guideline was developed according to the procedures and requirements for meeting the 2011 NHMRC standard for clinical practice guidelines.[1] The development program was designed to meet the scientific rigour required by the standard for developing high quality, evidence-based clinical practice guidelines. A series of NHMRC resources and handbooks[2][3][4][5][6][7][8][9][10] guided the process and outlined the major steps and expectations involved in developing guidelines. These documents provided the definitions and protocols for developing research questions and search strategies, conducting systematic literature reviews, summarising and assessing the relevant literature and finally, formulating and grading the recommendations. They also included checklists and templates created to satisfy designated standards of quality and process.

The questions were allocated to specific Guidelines Working Party members to act as lead authors according to their areas of expertise. Each lead author team was able to co-opt additional experts as co-authors for their allocated questions. The Management Committee assessed the suggestion of any additional co-authors including their declaration of interest (see link).

Back to top

20.1.3 Steps in preparing clinical practice guidelines to NHMRC criteria

For every question the below steps were followed:
1. Develop a structured clinical question (PICO question)
2. Search for existing relevant guidelines and systematic reviews
3. Process if relevant clinical practice guideline was identified or not

3a If no relevant clinical practice guideline was found	**3b If a relevant clinical practice guideline was found and assessed as suitable for adaption**
Check if an existing systematic review of high quality exists and can be used to inform the systematic review process	Conduct systematic literature review update for the question of the existing clinical practice guideline
Developing the systematic review protocol and systematic literature search strategy for each PICO question	Screening of literature update results against pre-defined inclusion and exclusion criteria
Conducting the systematic literature search according to protocol	Critical appraisal and data extraction of each new included article
Screening of literature results against pre-defined inclusion and exclusion criteria	Update evidence table of evidence review of existing guideline with new literature update results
Critical appraisal and data extraction of each included article	

4. Summarise the relevant data
5. Assess the body of evidence and formulate recommendations
6. Write the content narrative

Back to top

20.1.3.1 Developing a structured clinical question

A wide range of questions were proposed for inclusion in the revised guidelines. In 2015, the Management Committee discussed the clinical questions that would be answered by systematic review. A shortlisting and voting process was undertaken to determine the final questions.

The questions focused on chemoprevention, screening, diagnosis, treatment and follow up. All proposed questions were reviewed on the basis of their purpose, scope and clinical importance to the target audience and were structured according to the PICO (populations, interventions, comparisons, outcomes) framework (see the clinical question list). The lead author and subcommittee members provided the systematic review team with feedback to refine the PICO questions.

Search for existing relevant guidelines and systematic reviews For each PICO question, the National Guideline Clearinghouse, the [www.cancerview.ca Guidelines Resource Centre] as well as the scoping search for the PICO question were scanned for relevant clinical practice guidelines that could potentially be suitable for adaption.

If an existing guideline was identified, the guideline was assessed for adaption according to the AGREEII assessment tool.

Relevant guidelines that did not meet the criteria for adaption were checked for systematic reviews that could be used as a source of relevant references to inform the systematic review process for the PICO question. Full systematic reviews were then performed as outlined in the following sections.

Back to top

20.1.3.2 Developing a systematic search strategy

For each PICO question, systematic literature search strategies were developed by the technical team. Most searches were directed to CRC as a generic base. Searches were limited or widened as necessary according to the PICO structure using keywords or MESH and subject terms. Systematic search strategies were derived from these terms for each included electronic databases. The included standard databases searched were PubMed, Embase, Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects and Health Technology Assessment for all questions. The psychosocial questions also included CINAHL and PsycINFO databases to retrieve relevant literature.

Back to top

20.1.3.3 Conducting the systematic literature search according to protocol

Clinical practice guidelines should be based on systematic identification and synthesis of the best available scientific evidence.[2] For each clinical question, that required a systematic literature review, literature searches were conducted systematically with the literature cut-off date of 31 August 2016. The following electronic databases were part of the systematic literature search strategy:

- **PubMed (U.S. National Library of Medicine):** bibliographic references and abstracts to articles in a range of languages on topics such as clinical medical information and biomedicine, and including the allied health fields, biological and physical sciences
- **EMBASE**: major pharmacological and biomedical database indexing drug information from 4550 journals published in 70 countries
- **Database of Abstracts of Reviews of Effects and Health Technology Assessment:** contains details of systematic reviews that evaluate the effects of healthcare interventions and the delivery and organisation of health services
- **The Cochrane Database of Systematic Reviews:** contains systematic reviews of primary research in human health care and health policy, and are internationally recognised as the highest standard in evidence-based health care
- **CINAHL:** bibliographic references and abstracts to journal articles, book chapters, pamphlets, audiovisual materials, software, dissertations, critical paths, and research instruments on topics including nursing and allied health, biomedicine, consumer health, health sciences librarianship, behavioural sciences, management, and education
- **Psychinfo:** Bibliographic references and abstracts to journal articles, book chapters, dissertations and technical reports on psychology; social, clinical, cognitive and neuropsychology; psychiatry, sociology, anthropology and education, with source material from a wide range of languages.

A search filter to retrieve relevant literature considering Aboriginal and Torres Strait Islander peoples was added to each question.

Additional relevant papers from reference lists and, where appropriate, clinical trial registries, were also identified for retrieval as part of the snowballing process.

The full detailed systematic literature search strategy for every clinical question is fully documented in the technical report of the question (see Technical report).

20.1.3.4 Screening of literature results against pre-defined inclusion and exclusion criteria

Part of the systematic review process is to screen all retrieved literature results against the pre-defined inclusion and exclusion criteria in two stages.

a) First screen
During the first screening round, the titles and abstracts of all retrieved literature were screened by one or two reviewers. All irrelevant, incorrect and duplicates were removed.

b) Second screen
A second screen was undertaken based on the full article. A reviewer assessed each article for inclusion against the pre-defined inclusion and exclusion criteria for each question. In the case of a disagreement between the reviewers, a third independent reviewer assessed the article against the inclusion and exclusion criteria. Articles that met the inclusion criteria were forwarded for quality assessment and data extraction.

20.1.3.5 Critical appraisal and data extraction of each included article

Two assessors independently assessed the risk of bias of each of the included studies using a study design specific assessment tool and where necessary pre-specified criteria (see Technical report for all quality assessment tools). Any disagreements were adjudicated by a third reviewer.

For all included articles, the relevant data was extracted and summarised in study characteristics and evidence tables. Each data extraction was checked by a second assessor. These tables are included in the technical report for each question (see Technical report).

20.1.3.6 Summary of the relevant data

For each outcome examined, the results, level of the evidence, the risk of bias due to study design, and the relevance of the evidence for each included study were documented a body of evidence table.

Each question was addressed by a systematic review resulting in a systematic review report. All systematic review reports are published in the technical report of the guidelines. Levels of evidence are shown below.

20.1.3.6.1 Table A1. Designations of levels of evidence according to type of research question (NHMRC, 2009)

Level	Intervention	Diagnosis	Prognosis	Aetiology	Screening
I	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive patients with a defined	A prospective cohort study	A prospective cohort study	A randomised controlled trial

		clinical presentation			
III-1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive patients with a defined clinical presentation	All or none	All or none	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study
III-3	A comparative study without concurrent controls: Historical control study Two or more single arm study	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: Historical control study

	Interrupted time series without a parallel control group				Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of patients at different stages of disease	A cross-sectional study	Case series

Source: National Health and Medical Research Council. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009. (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

Back to top

20.1.3.7 Assess the body of evidence and formulate recommendations

The technical report for each question was forwarded to each lead author. The authors, in collaboration with their subcommittee members and systematic review team (who conducted the systematic reviews and provided the technical reports), assessed the body of evidence and completed the NHMRC Evidence Statement form to record the volume of the evidence, its consistency, clinical impact, generalisability and applicability and developed evidence statements (see Technical report). The process is described in NHMRC additional levels of evidence and grades for recommendations for developers of guidelines (2009).[10]

Following grading of the body of evidence and development of evidence statements, expert authors were asked to formulate evidence-based recommendations that related to the summarised body of evidence. The method of grading recommendations is shown in Table A2.

20.1.3.7.1 Table A2. Grading of recommendations

Component of Recommendation	**Recommendation Grade**			
	A **Excellent**	**B** **Good**	**C** **Satisfactory**	**D** **Poor**
	one or more level I studies with a low risk of	one or two level II studies with a low risk of bias or a systematic	one or two level III studies with a low risk	level IV studies, or level I to III studies

Volume of evidence [1**]	bias or several level II studies with a low risk of bias	review/several level III studies with a low risk of bias	of bias, or level I or II studies with a moderate risk of bias	/systematic reviews with a high risk of bias
Consistency [2**]	all studies consistent	most studies consistent and inconsistency may be explained	some inconsistency reflecting genuine uncertainty around clinical question	evidence is inconsistent
Clinical impact	very large	substantial	moderate	slight or restricted
Generalisability	population/s studied in body of evidence are the same as the target population for the guideline	population/s studied in the body of evidence are similar to the target population for the guideline	population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population[3]	population/s studied in body of evidence different to target population and hard to judge whether it is sensible to generalise to target population
Applicability	directly applicable to Australian healthcare context	applicable to Australian healthcare context with few caveats	probably applicable to Australian healthcare context with some caveats	not applicable to Australian healthcare context

[1] Level of evidence determined from level of evidence criteria

[2] If there is only one study, rank this component as 'not applicable'

[3] For example results in adults that are clinically sensible to apply children OR psychosocial outcomes for one cancer that may be applicable to patients with another cancer.

[**]For a recommendation to be graded A or B, the volume and consistency of evidence must also be graded either A or B. *Source: National Health and Medical Research Council. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009. (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)*

The overall recommendations grade are shown in Table A3.

20.1.3.7.2 Table A3. Overall recommendation grades

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

Source: National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendations for developers of guidelines. Canberra: NHMRC; 2009. (https://www.nhmrc.gov.au/_files_nhmrc/file/guidelines/developers/nhmrc_levels_grades_evidence_120423.pdf)

In addition to developing evidence-based recommendations as a result of the systematic review for a question, expert authors could also draft consensus-based recommendations in the absence of evidence after having performed a systematic review, or practice points, when a matter was outside the scope of the search strategy for the systematic review. The NHMRC approved recommendation types and definitions are shown in Table A4.

20.1.3.7.3 Table A4. NHMRC approved recommendation types and definitions

Type of recommendation	Definition
Evidence-based recommendation	A recommendation formulated after a systematic review of the evidence, indicating supporting references
Consensus-based recommendation	A recommendation formulated in the absence of quality evidence, after a systematic review of the evidence was conducted and failed to identify admissible evidence on the clinical question
Practice point	A recommendation on a subject that is outside the scope of the search strategy for the systematic review, based on expert opinion and formulated by a consensus process

Source: National Health and Medical Research Council. Procedures and requirements for meeting the NHMRC standard for clinical practice guidelines. Melbourne: National Health and Medical Research Council, 2011

Back to top

20.1.3.8 Writing the content

For each question, the assigned lead authors were asked to draft their guideline chapter using the following format:

- general introduction to the clinical question

- background to the clinical question, including its clinical importance and historical evidence, where relevant
- review of the evidence, including the number, quality and findings of studies identified by the systematic review
- evidence summary in tabular form including evidence statements, levels of evidence of included studies, and reference citations
- evidence-based recommendation(s) and corresponding grade(s), consensus-based recommendations and practice points
- implications for implementation of the recommendations, including possible effects on usual care, organisation of care, and any resource implications
- discussion, including unresolved issues, relevant studies currently underway, and future research priorities
- references.

The content draft was then reviewed by subcommittee members who were available. The draft documents often underwent several iterations.

Back to top

20.1.3.9 Review of the draft chapters

The draft guidelines sections were circulated to the Working Party members and posted on Cancer Council's wiki platform. The group was asked to review the content and submit feedback. Members were asked to submit further suggestions on consensus-based recommendation and practice points.

A face-to-face meeting with all available Working Party members was held in December 2016 to review and finalise the draft guidelines for public consultation. Prior to this meeting, the latest iteration draft guidelines were circulated as soon as they were available. All members were asked to review the content, individual recommendations and practice points in detail, and to identify and note any controversies and points to be discussed at the group meeting.

During the meeting, each chapter/section was tabled as an agenda point and recommendations and practice points were discussed in detail. All clinical guidance was reviewed and approved by consensus, which was reached by voting. In some cases, the authors agreed on specific actions for the content or discussed further sections or amendments to be added. These were actioned by the authors.

Each recommendation and practice point was approved once the eligible panellists (excluding representatives of the funding bodies and panellists who cannot vote due to conflict of interest) have reached consensus.

Back to top

20.1.4 Public consultation

A complete draft of the guideline was sent out for public consultation from DATE TO DATE. Submissions were invited from the general public and professional societies and groups and other relevant stakeholders. The consultation was publicised by email to key stakeholders, including contacting professional societies and groups, consumer groups and other relevant parties.

All feedback on the draft received during the consultation period will be compiled and sent to the relevant author and subcommittee to review their draft content, assessing and considering the submitted comments. Each additional submitted paper during public consultation was be assessed by the methodologist team against the systematic review protocol.

Another face-to-face Working Party meeting will be convened to review all public consultation comments and the amended content. Subsequent changes to the draft will be agreed by consensus, based on consideration of the evidence. The same consensus process that was followed prior to public consultation would be followed again. All changes resulting from the public consultation submission reviews will be documented and made accessible once the guidelines are published.

A final independent review of experts in their fields is also planned to be conducted before the final draft is submitted to NHMRC Council. Any further suggestions by the independent expert reviewers will be integrated in the final draft and then submitted to NHMRC Council for approval.

Back to top

20.1.5 Organisations formally endorsing the guidelines

The following medical colleges and professional bodies will be approached to endorse the guideline:

- Australian College of Rural and Remote Medicine (ACRRM)
- Medical Oncology Group of Australia Incorporated (MOGA)
- Royal College of Pathologists of Australia (RCPA)
- Royal Australasian College of Physicians (RACP) – Adult Medicine Division
- Royal Australian College of Physicians – Australian Chapter of Palliative Medicine (AChPM, RACP)
- Royal Australian College of Physicians – Australian Faculty of Public Health Medicine (AFPHM, RACP)
- Royal Australian College of Surgeons (RACS)
- Royal Australian College of General Practitioners (RACGP)
- add others.

Back to top

20.1.6 Dissemination and implementation

Cancer Council Australia will create a plan regarding the dissemination of the guideline in Australia.

The guidelines will also be made available online via the Cancer Council Australia Cancer Guidelines wiki. The online guideline version increases availability as well as accessibility, and usage will be tracked and analysed with a web analytics solution. Interlinking and listing the guidelines on national and international guideline portal is an important part of the digital dissemination strategy. Important Australian health websites, such as EviQ and healthdirect Australia will be approached to link to the online guideline. The guideline will also to be listed on national and international guideline portals such as Australia’s Clinical Practice Guidelines Portal,

Guidelines International Network guidelines library and National Guidelines Clearinghouse. The Cancer Guidelines wiki is a responsive website that is optimised for mobile and desktop access. When accessing the guidelines with a mobile and tablet device, an icon can be easily added to the homescreen of mobile devices, offering easy mobile access. In addition, the final guideline document will be launched via email alert to professional organisations, interested groups and clinical experts in the field, directing them via URL link to the online guideline and all associated resources.

The Cancer Guidelines wiki is based on semantic web technology, so the guidelines are available in a machine-readable format, which offers the possibility to easily integrate the guideline content with systems and web applications used in the Australian healthcare context.

Use of the guidelines as part of core curriculum in specialty exams will be encouraged. It is recognised that a planned approach is necessary to overcome specific barriers to implementation in particular settings and to identify appropriate incentives to encourage uptake of guideline recommendations. Implementation of the guidelines will require a combination of effective strategies and may include further CME initiatives and interactive learning, the development and promotion of computer-assisted decision aids and electronic decision-support systems, and the creation of audit and other clinical tools.

Back to top

20.1.7 Future updates

The incoming literature updates will continue to be monitored for each systematic review question. If there is strong evidence emerging in a specific area of colorectal cancer management, the Management Committee will be reconvened to assess if this warrants a guideline update (full or partly). It is recommended that these guidelines be updated after 5 years. [confirm timing with MC]

20.1.8 References

1. ↑ National Health and Medical Research Council. *Procedures and requirements for meeting the NHMRC standard for clinical practice guidelines.* Melbourne; 2011.
2. ↑ [2.0] [2.1] National Health and Medical Research Council. *A guide to the development, evaluation and implementation of clinical practice guidelines.* Commonwealth of Australia: National Health and Medical Research Council; 1999 Jan 1 Available from: http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cp30.pdf.
3. ↑ National Health and Medical Research Council. *How to review the evidence: Systematic identification and review of scientific literature.* Canberra: National Health and Medical Research Council; 1999 Available from: http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cp65.pdf.
4. ↑ National Health and Medical Research Council. *How to prepare and present evidence-based information for consumers of health services: A literature review.* Commonwealth of Australia: National Health and Medical Research Council; 1999 Jan 1 Available from: http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cp72.pdf.
5. ↑ National Health and Medical Research Council. *How to present evidence for consumers: Preparation of consumer publications.* Canberra: Commonwealth of Australia; 1999.

6. ↑ National Health and Medical Research Council. *How to put evidence into practice: Implementation and dissemination strategies.* Commonwealth of Australia: National Health and Medical Research Council; 2000 Jan 1 Available from: http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cp71.pdf.
7. ↑ National Health and Medical Research Council. *How to use the evidence: assessment and application of scientific evidence.* Commonwealth of Australia: National Health and Medical Research Council; 2000 Jan 1 Available from: http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cp69.pdf.
8. ↑ National Health and Medical Research Council. *How to compare the costs and benefits: evaluation of the economic evidence.* Commonwealth of Australia: National Health and Medical Research Council; 2001 Jan 1 Available from: http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cp73.pdf.
9. ↑ National Health and Medical Research Council. *Using socioeconomic evidence in clinical practice guidelines.* NHMRC 2002 Available from: http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cp89.pdf.
10. ↑ [10.0] [10.1] National Health and Medical Research Council. *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines.* Canberra; 2009 Available from: www.mja.com.au/sites/default/files/NHMRC.levels.of.evidence.2008-09.pdf.

Back to top

20.2 Clinical question list

Contents

20.2.1 Primary Prevention (section lead: Finlay Macrae) Clinical Question PPR1:

Clinical Question PPR1:

What is the risk-benefit ratio for use of aspirin for prevention of colorectal cancer stratified by risk of colorectal cancer itself? (What is the optimal dose and frequency of administration?)

PICO Question PPR1:

In an asymptomatic population at average risk or increased risk of colorectal cancer, what is the cost-benefit ratio of prophylactic Aspirin use in reducing the mortality and incidence of colorectal cancer?

Population	Intervention	Comparator	Outcomes	Study Design
■ Asymptomatic western population at average risk of colorectal cancer, or ■ Populations at increased risk of colorectal cancer	Prophylactic aspirin use	Placebo or no Aspirin use	■ Colorectal cancer incidence ■ Colorectal cancer mortality ■ Adverse effects	Systematic reviews of Level II evidence or randomised controlled trials.

Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Intervention studies	
Study design	Systematic reviews of Level II evidence or randomised controlled trials.	In vitro studies or preclinical trials
Population	■ Asymptomatic western population at average risk of colorectal cancer, or ■ Populations at increased risk of colorectal cancer due to either: ■ Family history of colorectal cancer, or ■ Previous colorectal cancer or adenomas, or ■ Familial adenomatous polyposis, or ■ Lynch Syndrome	■ Diagnosis of FAP or suspected FAP without genetic testing ■ genetic or clinical diagnosis of HNPCC, or increased risk ■ A non-syndromic family history of colorectal cancer ■ Inflammatory bowel disease, chronic ulcerative colitis, or Crohn disease ■ other hereditary polyposis syndromes ■ Studies in children (<25 yrs)

Selection criteria	Inclusion criteria	Exclusion criteria
Intervention	Prophylactic use of Aspirin for the primary prevention of colorectal cancer, with any of the following: ■ Aspirin at ≤100mg, 100-325mg, or >325mg/day ■ Aspirin at alternate days (any dosage) ■ Duration of ≤2 yrs, >2-4 yrs, or >4 yrs ■ Exposure commencing <50yrs, 50-70yrs, >70yrs	■ Aspirin in combination therapy (where separate placebo and aspirin only groups were not reported separately ■ Studies of aspirin with only cardiovascular endpoint analysis
Comparator	Placebo or no Aspirin use	Long term use of Aspirin or NSAID
Outcomes	■ Colorectal cancer incidence ■ Colorectal cancer mortality ■ Adverse effects, including either: ■ Incidence of peptic ulcers ■ Incidence of GI bleeding ■ Incidence of intracranial haemorrhage ■ Incidence of stroke (haemorrhagic or thrombotic) ■ Incidence of Aspirin hypersensitivity ■ Incidence of renal impairment ■ Death due to side effects	
Language	English	
Publication period	From 1/01/2004 to 31/08/2016	

Back to top

20.2.2 Population screening for colorectal cancer (section leads: James St. John and Hooi Ee)

Clinical Question PPR1:

1. Is population screening based on testing with
(a) immunochemical FOBT (iFOBT),
(b) flexible sigmoidoscopy,
(c) colonoscopy,

(d) faecal biomarkers such as DNA
(e) plasma biomarkers such as DNA
(f) any combination of the above screening tests effective in reducing bowel cancer mortality rates, feasible, acceptable and a cost-effective method of screening for the target population?

2. Is population screening starting at an earlier age more effective, feasible, acceptable and cost-effective, compared with starting at age 50 yr?

3. In population screening, do the harms outweigh the benefits if routine screening by any method is continued beyond the age of 75yr?

PICO Question PSC1a (Intervention studies):

In persons without a colorectal cancer diagnosis or symptoms that might indicate colorectal cancer, which screening modality (immunochemical FOBT, flexible sigmoidoscopy, colonoscopy, faecal or blood biomarkers, or any combinations) compared with no screening, reduce colorectal cancer mortality, or the incidence of metastases at diagnosis?

Population	Intervention	Comparator	Outcomes
Persons without a colorectal cancer diagnosis or symptoms that might indicate colorectal cancer	■ Immunochemical FOBT, or ■ Flexible sigmoidoscopy, or ■ Colonoscopy, or ■ Faecal biomarkers, or ■ Blood biomarkers, or ■ Any combinations.	No screening test	■ Colorectal cancer specific mortality ■ Metastatic colorectal cancer diagnosis

Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Intervention	Diagnostic performance
Study design	Systematic reviews of Level II evidence or randomised controlled trials	Level III-2 evidence or lower
Population	Persons without a colorectal cancer diagnosis or symptoms that might indicate colorectal cancer	
	■ Immunochemical FOBT, or	

Selection criteria	Inclusion criteria	Exclusion criteria
Intervention	■ Flexible sigmoidoscopy, or ■ Colonoscopy, or ■ Faecal biomarkers, or ■ Blood biomarkers, or ■ any combinations.	
Comparator	No screening test	
Outcomes	■ Colorectal cancer specific mortality, or ■ Metastatic colorectal cancer diagnosis, with ■ Subgroup analysis for population that started screen prior to age 50, or ■ Subgroup analysis for population screening beyond the age of 75 years	
Language	English	
Publication period	From 1/01/2004 to 31/08/2016	

Back to top

Clinical Question PSC1:

1. Is population screening based on testing with (a) immunochemical FOBT (iFOBT), (b) flexible sigmoidoscopy, (c) colonoscopy, (d) faecal biomarkers such as DNA (e) plasma biomarkers such as DNA (f) any combination of the above screening tests effective in reducing bowel cancer mortality rates, feasible, acceptable and a cost-effective method of screening for the target population?

2. Is population screening starting at an earlier age more effective, feasible, acceptable and cost-effective, compared with starting at age 50 yr?

3. In population screening, do the harms outweigh the benefits if routine screening by any method is continued beyond the age of 75yr?

PICO Question PSC1b (Diagnostic accuracy):

For persons without a colorectal cancer diagnosis or symptoms that might indicate colorectal cancer, which screening modality (immunochemical FOBT, flexible sigmoidoscopy, colonoscopy, faecal or blood biomarkers, or any combinations) performs best in detecting colorectal cancer, and how does the diagnostic performance change with family history, age, or gender?

Population	Index Test 1	Index Test 2	Reference standard	Outcomes
Persons without a colorectal cancer diagnosis or symptoms that might indicate colorectal cancer (with a family history of colorectal cancer or no family history of colorectal cancer)	Screening for CRC with: ■ Immunochemical FOBT, or ■ Flexible sigmoidoscopy, ■ Colonoscopy, or ■ Faecal biomarkers, or ■ Blood biomarkers, or ■ Any combinations	An alternative screening test or no screening	Colonoscopy or long-term follow up	Diagnostic performance related to advanced adenoma and colorectal cancer

Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Diagnostic accuracy	
Study design	■ Systematic reviews of Level II evidence, randomised controlled trials, or ■ Fully paired diagnostic study, or paired randomised cohort study	Diagnostic case-control studies or studies of diagnostic yield
Population	Persons without a colorectal cancer diagnosis or symptoms that might indicate colorectal cancer (with a family history of colorectal cancer or no family history of colorectal cancer)	
Index Test 1	Screening test for colorectal cancer: ■ Immunochemical FOBT, or ■ Flexible sigmoidoscopy, or ■ Colonoscopy, or ■ Faecal biomarkers, or ■ Blood biomarkers, or ■ Any combinations.	
Index Test		

Selection criteria	Inclusion criteria	Exclusion criteria
2	An alternative screening test or no screening.	
Reference standard	Colonoscopy or long-term follow up	
Outcomes	■ Advanced adenoma detection rate, or ■ Colorectal cancer detection rate, or ■ Sensitivity and/or specificity for advanced adenomas, or ■ Sensitivity and/or specificity for colorectal cancers ■ Subgroup analysis of above outcomes for family history, age, gender	
Language	English	
Publication period	From 1/01/2004 to 31/08/2016	

Back to top

Clinical Question PSC1:

1. Is population screening based on testing with (a) immunochemical FOBT (iFOBT), (b) flexible sigmoidoscopy, (c) colonoscopy, (d) faecal biomarkers such as DNA (e) plasma biomarkers such as DNA (f) any combination of the above screening tests effective in reducing bowel cancer mortality rates, feasible, acceptable and a cost-effective method of screening for the target population?

2. Is population screening starting at an earlier age more effective, feasible, acceptable and cost-effective, compared with starting at age 50 yr?

3. In population screening, do the harms outweigh the benefits if routine screening by any method is continued beyond the age of 75yr?

PICO Question PSC1c (Feasibility studies):

In persons without a bowel cancer diagnosis or symptoms that might indicate bowel cancer, is population based screening using any of the following modalities (immunochemical FOBT, flexible sigmoidoscopy, colonoscopy, CT colonography, faecal or blood biomarkers, or combinations) feasible or acceptable?

Population	Intervention	Comparator	Outcomes
	■ Immunochemical FOBT, or		Feasibility outcomes: ■ Acceptability, or ■ Demand, or

Population	Intervention	Comparator	Outcomes
Persons without a colorectal cancer diagnosis or symptoms that might indicate colorectal cancer	■ Flexible sigmoidoscopy, or ■ Colonoscopy, or ■ Faecal biomarkers, or ■ Blood biomarkers, or ■ Any combinations	■ An alternative screen modality, or ■ No screening test	■ Implementation, or ■ Practicality, or ■ Adaptation, or ■ Integration, or ■ Expansion, or ■ Limited-efficacy testing, ■ Age-specific subgroup analysis

Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Intervention studies	
Study design	Cohort studies	
Population	Persons without a colorectal cancer diagnosis or symptoms that might indicate colorectal cancer	
Intervention	■ Immunochemical FOBT, or ■ Flexible sigmoidoscopy, or ■ Colonoscopy, or ■ Faecal biomarkers, or ■ Blood biomarkers, or ■ Any combinations	
Comparator	■ An alternative screen modality, or ■ No screening test	
Outcomes	Feasibility outcomes: ■ Acceptability, or ■ Demand, or ■ Implementation, or ■ Practicality, or ■ Adaptation, or ■ Integration, or	

Selection criteria	Inclusion criteria	Exclusion criteria
	■ Expansion, or ■ Limited-efficacy testing, ■ Age-specific subgroup analysis	
Language	English	
Publication period	From 1/01/2004 to 31/08/2016	

Back to top

Clinical Question PSC1:

1. Is population screening based on testing with (a) immunochemical FOBT (iFOBT), (b) flexible sigmoidoscopy, (c) colonoscopy, (d) faecal biomarkers such as DNA (e) plasma biomarkers such as DNA (f) any combination of the above screening tests effective in reducing bowel cancer mortality rates, feasible, acceptable and a cost-effective method of screening for the target population?

2. Is population screening starting at an earlier age more effective, feasible, acceptable and cost-effective, compared with starting at age 50 yr?

3. In population screening, do the harms outweigh the benefits if routine screening by any method is continued beyond the age of 75yr?

PICO Question PSC1d (Cost effectiveness):

In persons without a bowel cancer diagnosis or symptoms that might indicate bowel cancer, what is the most cost-effective screening modality (immunochemical FOBT, flexible sigmoidoscopy, colonoscopy, CT colonography, faecal or blood biomarkers, or any combinations) compared with no screening?

Population	Intervention	Comparator	Outcomes
Persons without a colorectal cancer diagnosis or symptoms that might indicate colorectal cancer	■ Immunochemical FOBT, or ■ Flexible sigmoidoscopy, or ■ Colonoscopy, or ■ Faecal biomarkers, or ■ Blood biomarkers, or ■ Any combinations	■ An alternative screen modality, or ■ No screening test	Quality-adjusted life-years

Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Intervention	
Study design	Cohort studies	
Population	Persons without a colorectal cancer diagnosis or symptoms that might indicate colorectal cancer	
Intervention	■ Immunochemical FOBT, or ■ Flexible sigmoidoscopy, or ■ Colonoscopy, or ■ Faecal biomarkers, or ■ Blood biomarkers, or ■ Any combinations	
Comparator	■ An alternative screen modality, or ■ No screening test	
Outcomes	■ Cost effectiveness outcomes: ■ Cost/quality-adjusted life-years	
Language	English	
Publication period	From 1/01/2004 to 31/08/2016	

Back to top

20.2.3 The symptomatic patient (section lead: Jon Emery)

Clinical Question SPT1-2:
What signs/symptoms alone or in combination are most predictive of colorectal cancer?

PICO SPT1-2a (signs/symptoms):
In symptomatic patients without a colorectal cancer diagnosis, what signs or symptoms (persistent changed bowel movements, persistent diarrhoea or constipation, unexplained rectal bleeding, general or localised abdominal pain, unexplained palpable abdominal or rectal mass, unexplained weight loss, iron deficient anaemia, tiredness, fatigue, or any combination) correlate best with a diagnosis of colorectal cancer?

Population	Signs/Symptoms	Outcomes
Patients without colorectal cancer diagnosis presenting with symptoms of colorectal cancer	Signs or symptoms alone or in combination: ■ persistent changed bowel movements ■ persistent diarrhoea or constipation ■ unexplained rectal bleeding ■ general or localised abdominal pain ■ unexplained palpable abdominal or rectal mass ■ unexplained weight loss ■ iron-deficient anaemia ■ tiredness or fatigue ■ rectal or anal pain	■ Diagnosis of colorectal cancer ■ Specificity ■ Sensitivity ■ Positive predictive value ■ Negative predictive value ■ AUC of ROC

Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Prognostic studies or Diagnostic accuracy studies	
Study design	Cohort studies, or systematic reviews thereof	
Population	Patients without colorectal cancer diagnosis presenting with symptoms of colorectal cancer	■ Patients not recruited in the primary care setting (i.e. patients in hospitals). ■ Patients diagnosed with colorectal cancer, or ■ Asymptomatic patients
	■ Persistent changed bowel movements, or ■ Persistent diarrhoea or constipation, or	

Selection criteria	Inclusion criteria	Exclusion criteria
Prognostic factor/Index test	■ Unexplained rectal bleeding, or ■ General or localised abdominal pain, or ■ Unexplained palpable abdominal or rectal mass, or ■ Unexplained weight loss, or ■ Iron-deficient anaemia, or ■ Tiredness or fatigue, or ■ Rectal or anal pain, or ■ Combinations of any above	
Comparator	Asymptomatic patients at the same risk of colorectal cancer	
Reference Standard	■ Colonoscopy ■ Sigmoidoscopy ■ Double-contrast barium enema ■ Follow-up	
Outcomes	Diagnosis of colorectal cancer ■ Specificity ■ Sensitivity ■ PPV and/or NPV, ■ AUC of ROC	
Language	English	
Publication period	From 1/01/2004 to 31/08/2016	

Back to top

Clinical Question - SPT1-2:
What is the optimal maximum time from referral to diagnosis and treatment (diagnostic interval)? **PICO Question SPT1-2b (diagnostic interval):**
In symptomatic patients without a colorectal cancer diagnosis, what is the optimal maximum diagnostic interval that achieves better
FIX

Population	Intervention	Comparator	Outcomes
Symptomatic patients without a colorectal cancer diagnosis	The time delay between presentation with symptoms associated with colorectal cancer and treatment for colorectal cancer	An alternative delay, or immediate treatment	■ 3-year survival, or ■ 5-year survival, or ■ Colorectal cancer mortality ■ Metastatic disease at diagnosis

Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Intervention	
Study design	Prospective and retrospective studies	Modelling studies
Population	Symptomatic patients without a colorectal cancer diagnosis	Patients diagnosed with colorectal cancer
Intervention	The time delay between presentation with symptoms associated with colorectal cancer and treatment for colorectal cancer	
Comparator	An alternative delay, or immediate treatment	
Outcomes	■ 3-year survival, or ■ 5-year survival, or ■ Colorectal cancer mortality ■ Metastatic disease at diagnosis	
Language	English	
Publication period	From 1/01/2004 to 31/08/2016	

Back to top

20.2.4 Risk and screening based on family history (section lead: Mark Jenkins)

Clinical Question FHS2:
What is the strength of association between family history and colorectal cancer risk and how do these associations vary by, number of affected relatives and degree of relatedness and age and sex of affected relatives and by the age and sex of the at-risk person?

PICO Question FSH2:
Has a family history of colorectal cancer been shown to be reliably associated with a greater increase in risk of occurrence of or death from colorectal cancer when compared to persons who do not have a family history of colorectal cancer?

Population	Exposure	Comparator/ Reference group	Outcomes
Persons without a colorectal cancer diagnosis or symptoms that might indicate colorectal cancer	Presence of a family history of colorectal cancer	No known family history of colorectal cancer	■ Colorectal cancer mortality ■ Colorectal cancer diagnosis

Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Aetiology/risk factor	
Study design	Systematic reviews of cohort studies, prospective cohort studies, retrospective cohort studies.	Case-control studies
Population	Persons without a colorectal cancer diagnosis or symptoms that might indicate colorectal cancer	
Exposure	Independently confirmed family history of colorectal cancer including first-degree, second-degree relative, sibling or parent diagnosed with colorectal cancer.	Does not describe family history
Comparator/ Reference group	No known family history of colorectal cancer	Known genetic abnormalities

Selection criteria	Inclusion criteria	Exclusion criteria

Outcomes	■ Colorectal cancer mortality
	■ Colorectal cancer diagnosis
	■ with subgroup analysis of:
	  ■ affected relative(s) by age or gender
	  ■ at risk person by age or gender	

Language	English	
Publication Period	From 1/01/2004 to 31/08/2016	

Back to top

20.2.5 Pathology and staging (section leads: Pierre Chapuis and Charles Chan)

Clinical Question PTH1:
What is the optimal molecular profiling of colorectal cancer?

PICO Question PTH1:
In patients diagnosed with colorectal cancer and have undergone surgical resection of the primary colorectal tumour, which molecular marker (BRAF/KRAS/NRAS/MMRD/MSI) best predicts response to surgery, or adjuvant therapy or radiotherapy (disease-free survival, overall survival, disease-specific mortality, overall mortality, or relapse incidence)?

Population	Prognostic factor	Outcomes
Patients diagnosed with colorectal cancer and have had resection of the primary tumour (any age, with or without a family history of CRC, or any stage of CRC including M1)	Any single prognostic marker (or any combination) examined in the primary resected colorectal cancer tumour tissue: Immunohistochemical markers: BRAF Mismatch repair enzymes (MLH1, MSH2, PMS2, MSH6)	Response to surgery, or adjuvant therapy or radiotherapy, including: ■ disease-free survival ■ overall survival ■ disease-specific mortality ■ overall mortality

Population	Prognostic factor	Outcomes
	PCR markers: BRAF Microsatellite instability (which loci?) KRAS NRAS	■ relapse incidence

Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Prognostic studies	Interventions studies or diagnostic accuracy studies
Study design	Prospective and retrospective cohort studies (level I-III evidence)	Case series, or cohort study of persons at different stages of disease
Population	Patients diagnosed with colorectal cancer and have had resection of the primary tumour (any age, with/without family history of CRC, or any stage of CRC including M1)	
Prognostic Factors	Any single prognostic marker (or any combination) examined in the primary resected colorectal cancer tumour tissue: Immunohistochemical markers: ■ BRAF ■ Mismatch repair enzymes (MLH1, MSH2, PMS2, MSH6) PCR markers: ■ BRAF ■ Microsatellite instability (MSI) (which loci?) ■ KRAS ■ NRAS	
Outcomes	Response to surgery, or adjuvant therapy or radiotherapy, including: ■ disease-free survival ■ overall survival ■ disease-specific mortality ■ overall mortality	

Selection criteria	Inclusion criteria	Exclusion criteria
	■ relapse incidence	
Language	English	
Publication period	From 1/01/2004 to 31/08/2016	

Back to top

20.2.6 Preparation for surgery and colonoscopy (section lead: Elizabeth Murphy)

Clinical Question PRP2-5, 7:
Can peri operative management be optimised?
PICO Question PRP2-5, 7:
In patients diagnosed with colorectal cancer and undergoing surgical tumour resection, does mechanical bowel preparation with or without antibiotic prophylaxis, when compared to usual care, achieve better outcomes in terms of anastomotic leakage, surgical site infection, length of hospital stay and ileus?

Population	Intervention	Comparator	Outcomes
Patients diagnosed with colorectal cancer and undergoing surgical tumour resection of curative intent	Either: 1. Mechanical bowel preparation with oral and intravenous antibiotic prophylaxis or 2. Mechanical bowel preparation and intravenous antibiotic prophylaxis or 3. Mechanical bowel preparation and oral antibiotic prophylaxis	No mechanical bowel preparation	■ Anastomotic leakage /dehiscence rates ■ Rate of surgical site/wound infection ■ Length of hospital stay ■ Ileus

Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Intervention	
Study design	Systematic reviews of Level II evidence, randomised controlled trials	
Population	Patients diagnosed with colorectal cancer and undergoing surgical tumour resection of curative intent	Palliative patients, emergent surgery, >33% non- colorectal cancer patients
Intervention	1. Mechanical bowel preparation with oral and intravenous antibiotic prophylaxis or 2. Mechanical bowel preparation and intravenous antibiotic prophylaxis or 3. Mechanical bowel preparation and oral antibiotic prophylaxis or 4. No mechanical bowel preparation and intravenous antibiotic prophylaxis	
Comparator	No mechanical bowel preparation	
Outcomes	■ Anastomotic leakage/dehiscence rates ■ Rate of surgical site/wound infection ■ Length of hospital stay ■ Ileus	Outcomes related to colonoscopy
Language	English	
Publication period	From 1/01/2004 to 31/08/2016	

Other perioperative techniques to be covered narratively

- Perioperative anaemia management
- Thromboembolism prophylaxis
- Perioperative normothermia
- Enhanced recovery programs
- Oral vs. IV antiobiotic prophylaxis

Back to top

20.2.7 Elective and emergency surgery for colon and rectal cancer

Clinical Question COL1-2a:(section lead: Andrew Luck)
What is the optimal approach to resection of colorectal cancers?
PICO Question COL1-2a:(section lead: Andrew Luck)
In patients diagnosed with colon cancer, what is the optimal resection strategy to achieve the best outcomes in terms of length and quality of life?

Population	Intervention	Comparator	Outcomes
Patients diagnosed with colon cancer and undergoing tumour resection	Laparoscopic colon resection	Open colon resection	■ Colorectal cancer mortality ■ Disease free survival ■ Colorectal cancer recurrence ■ Perioperative morbidity /complications/adverse events ■ Complications/adverse events ■ Length of hospital stay ■ Post-op time to return of bowel function ■ Length of operation ■ Quality of life ■ Lymph node number ■ Blood loss ■ Blood transfusion

Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Intervention	
Study design	Systematic reviews of Level II evidence, randomised controlled trials	
Population	Patients diagnosed with colon cancer (including rectosigmoid cancer) and undergoing tumour resection	

Selection criteria	Inclusion criteria	Exclusion criteria
Intervention	Laparoscopic colon resection	Robotic-assisted laparoscopic surgery, single-incision laparoscopic surgery (SILS), hand-assisted laparoscopic surgery (HALS) Fast track/Enhanced recovery after surgery (ERAS) Subtotal colectomy only, total colectomy only, proctocolectomy only; emergent surgery
Comparator	Open colon resection (colectomy)	Fast track/Enhanced recovery after surgery (ERAS) Subtotal colectomy only, total colectomy only, proctocolectomy only; emergent surgery

Outcomes	■ Colorectal cancer mortality
	  ■ operative
	  ■ perioperative
	  ■ postoperative
	■ Disease free survival
	■ Colorectal cancer recurrence
	  ■ proximal
	  ■ distal
	  ■ wound site/port site/peritoneal seeding
	■ Perioperative morbidity/complications /adverse events including:
	  ■ intra/post/peri-operative
	  ■ reoperation
	  ■ anastomotic complications /reoperation (including leakage)
	  ■ bowel obstruction complications /reoperation
	  ■ wound complications
	  ■ Ileus complications
	  ■ haemorrhage/gastrointestinal bleeding/haemoperitoneum
	  ■ respiratory complications
	  ■ organ injury
	  ■ faecal incontinence	

Selection criteria	Inclusion criteria	Exclusion criteria
	▪ stomal stenosis ▪ intraoperative neuropraxia ▪ in-hospital pyrexia ▪ postoperative gastroenterogical disorder ▪ small bowel infection ▪ perioperative fistula for colon, caecum or appendix ▪ Length of hospital stay ▪ Post-op time to return of bowel function ▪ Length of operation ▪ Quality of life ▪ General ▪ Cancer focused ▪ Pain ▪ Re-operation ▪ Lymph node number	
Language	English	
Publication	From 1/01/2004 to 31/08/2016	

Back to top

Clinical Question COL1-2b:(section lead: Andrew Luck)

What is the optimal approach to resection of colorectal cancers?

PICO Question COL1-2b:(section lead: Andrew Luck)

In patients diagnosed with rectal cancer, what is the optimal resection strategy to achieve the best outcomes in terms of length and quality of life?

Population	Intervention	Comparator	Outcomes
			▪ Colorectal cancer mortality ▪ 30-day mortality rate ▪ Perioperative mortality ▪ 3-year survival

Population	Intervention	Comparator	Outcomes
Patients diagnosed with rectal cancer and undergoing tumour resection	■ Polypectomy ■ Local transanal resection ■ Transanal endoscopic microsurgery ■ Total mesorectal excision ■ Abdominoperineal resection ■ Anterior resection ■ Laparoscopic resection ■ Open resection	An alternative resection strategy	■ 5-year survival ■ 10-year survival ■ Disease free survival ■ Local recurrence rate ■ Distant metastases ■ Wound/port site metastases ■ Perioperative morbidity ■ Postoperative complications ■ Permanent stoma rate ■ Quality of life ■ Sexual dysfunction ■ Postoperative pain

Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Intervention	
Study design	Systematic reviews of Level II evidence, randomised controlled trials	
Population	Patients diagnosed with rectal cancer and undergoing tumour resection	
Intervention	■ Polypectomy ■ Local transanal resection ■ Transanal endoscopic microsurgery ■ Total mesorectal excision ■ Abdominoperineal resection ■ Anterior resection ■ Laparoscopic resection	
Comparator	An alternative resection strategy	

Selection criteria	Inclusion criteria	Exclusion criteria
Outcomes	■ Colorectal cancer mortality ■ 30-day mortality rate ■ Perioperative mortality ■ 3-year survival ■ 5-year survival ■ 10-year survival ■ Disease free survival ■ Local recurrence rate ■ Distant metastases ■ Wound/port site metastases ■ Perioperative morbidity ■ Postoperative complications ■ Permanent stoma rate ■ Quality of life ■ Sexual dysfunction ■ Postoperative pain	
Language	English	
Publication period	From 1/01/2004 to 31/08/2016	

Back to top

Clinical Question REC3: (section lead: Alexander (Sandy) Heriot)

What is the most effective treatment for early rectal cancer?

PICO Question REC3:

In patients diagnosed with stage I-II rectal cancer, what is the most effective treatment strategy to achieve the best outcomes in terms of length and quality of life?

Population	Intervention	Comparator	Outcomes
Patients diagnosed with localised stage I-II potential resectable rectal cancer (nodal status unknown)	Local resection with or without radiotherapy or chemotherapy	Radical resection with or without radiotherapy or chemotherapy	■ Overall survival ■ 30-day survival ■ Local recurrence (positive nodes or margins) ■ Rectal cancer mortality ■ Quality of life

Population	Intervention	Comparator	Outcomes
			■ Adverse events ■ Stoma rates

Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Intervention	
Study design	Systematic reviews of Level II evidence, randomised controlled trials, or Level III-2 comparative studies	
Population	Patients diagnosed with localised stage I-II potential resectable rectal cancer (nodal status unknown)	
Intervention	Local resection with or without radiotherapy or chemotherapy	
Comparator	Radical resection with or without radiotherapy or chemotherapy	
Outcomes	■ Overall survival ■ 30-day survival ■ Local recurrence (positive nodes or margins) ■ Rectal cancer mortality ■ Quality of life ■ Adverse events ■ Stoma rates	
Language	English	
Publication period	From 1/01/2004 to 31/08/2016	

Back to top

Clinical Question COLMNG 5: (section leads: Andrew Luck and Alexander (Sandy) Heriot)
What are the benefits of stenting or colostomy vs. acute resection with primary anastomosis in acute obstruction due to left-sided colon or rectal carcinoma?

PICO Question COLMNG 5:
In patients diagnosed with colorectal cancer and acute obstruction, does stenting or colostomy achieve equivalent or better outcomes compared to acute resection with primary anastomosis?

Population	Intervention	Comparator	Outcomes
			■ Perioperative mortality

Population	Intervention	Comparator	Outcomes
Patients diagnosed with colorectal cancer and acute obstruction (due to left-side colon cancer or rectal cancer)	■ Stenting, or ■ Colostomy, or ■ Hartmann's procedure	Acute surgical resection with primary anastomosis	■ Perioperative morbidity ■ 5 year survival ■ Cancer specific survival ■ Length of hospital stay ■ Stoma rate (temporary or permanent) ■ Quality of life ■ Adverse events

Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Intervention	
Study design	Systematic reviews of Level II evidence or randomised controlled trials	
Population	Patients diagnosed with colorectal cancer and acute obstruction (due to left-side colon cancer or rectal cancer)	Colorectal cancer patients without acute obstruction, metastatic and palliative patients
Intervention	■ Stenting, or ■ Colostomy, or ■ Hartmann's procedure	
Comparator	Acute surgical resection with primary anastomosis	
Outcomes	■ Perioperative mortality ■ Perioperative morbidity ■ 5 year survival ■ Cancer specific survival ■ Length of hospital stay ■ Stoma rate (temporary or permanent) ■ Quality of life	

Selection criteria	Inclusion criteria	Exclusion criteria
	■ Adverse events	
Language	English	
Publication period	From 1/01/2004 to 31/08/2016	

Back to top

Clinical Question COLMNG 3: (Section leads: Cherry Koh and Andrew Luck)

What is the role for peritonectomy with or without perioperative intraperitoneal chemotherapy in the treatment recurrent as well as primary colorectal cancer with peritoneal involvement (not including appendiceal neoplasia)?

PICO Question COLMNG 3:

For patients diagnosed with colorectal cancer and peritoneal involvement or isolated peritoneal recurrence of colorectal cancer, does peritonectomy, with or without perioperative intraperitoneal chemotherapy (PIC), achieve better outcomes in terms of length and quality of life than usual care?

Population	Intervention	Comparator	Outcomes
Patients diagnosed with colorectal cancer and peritoneal involvement or isolated peritoneal recurrence of colorectal cancer	Peritonectomy with or without HIPEC	Usual care (systemic chemotherapy)	■ Colorectal cancer specific mortality ■ 30-day mortality ■ 5-year survival ■ Quality of life ■ Adverse events

Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Intervention	
Study design	Systematic reviews of Level II evidence, randomised controlled trials, pseudorandomised controlled trials, or cohort studies	
Population	Patients diagnosed with colorectal cancer and peritoneal involvement or isolated peritoneal recurrence of colorectal cancer	

Selection criteria	Inclusion criteria	Exclusion criteria
Intervention	Peritonectomy with or without intraperitoneal chemotherapy	
Comparator	Usual care (systemic chemotherapy)	
Outcomes	■ Colorectal cancer specific mortality ■ 30-day mortality ■ 5-year survival ■ Quality of life ■ Adverse events	
Language	English	
Publication period	From 1/01/2004 to 31/08/2016	

Back to top

20.2.8 Adjuvant therapy for colon cancer (section lead: Peter Gibbs)

Clinical Question ADJ1:
What is the efficacy of adjuvant combination chemotherapy in elderly patients with colon cancer?
PICO Question ADJ1:
In elderly patients (≥70 years) diagnosed with colon cancer, what is the efficacy of surgery and adjuvant combination chemotherapy (involving either 5-flurouracil or capecitabine combined with oxaliplatin), compared to surgery with a single chemotherapeutic agent (Fluoropyrimidine) in achieving the best outcomes in terms of colorectal cancer mortality, recurrence, quality of life and adverse effects?

Population	Intervention	Comparator	Outcomes
Elderly patients diagnosed with colon cancer (≥70 years)	Surgery in combination with one of the following: ■ Chemotherapy (either 5-Fluoruracil, Capecitabine, or	Surgery with a single chemotherapeutic agent (Fluoropyrimidine based).	■ Colorectal cancer mortality ■ Colorectal recurrence

Population	Intervention	Comparator	Outcomes
	■ Oxaliplatin) AND an additional adjuvant chemotherapy drug (either 5-fluoruracil, capecitabine, or oxaliplatin)		■ Quality of life ■ Adverse events

Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Intervention	
Study design	Systematic reviews of Level II evidence or randomised controlled trials	
Population	Elderly patients diagnosed with colon cancer (≥70 years)	
Intervention	Surgery in combination with one of the following chemotherapies (5-Fluoruracil, Capecitabine, or Oxaliplatin) and an additional adjuvant chemotherapy drug (either 5-fluoruracil, capecitabine, or oxaliplatin)	
Comparator	Surgery with a single chemotherapeutic agent (Fluoropyrimidine based)	
Outcomes	■ Colorectal cancer mortality ■ Colorectal recurrence ■ Quality of life ■ Adverse events	
Language	English	
Publication period	From 1/01/2004 to 31/08/2016	

Back to top

20.2.9 Neo-adjuvant and adjuvant therapy for rectal cancer (section leads: Desmond Yip and Kathryn Field)

Clinical Question NEO1,5,6:

RENAME TO 1a/1b Which patients with rectal cancer stage I-II could be considered for definitive chemoradiotherapy (no surgery), neo-adjuvant chemoradiotherapy or surgery alone?

a) What is the optimal timing for surgery after neoadjuvant therapy?
b) Should they be restaged?

PICO Question NEO1,5,6-a:

RENAME TO 1a/1b *For patients diagnosed with stage I-III rectal cancer, for which patients does neo-adjuvant treatment (short or long course chemoradiotherapy) with surgery achieve equivalent or better outcomes in terms of length and quality of life than neoadjuvant chemoradiotherapy alone?*

Population	Intervention	Comparator	Outcomes
Patients diagnosed with stage I-III rectal cancer	Definitive neoadjuvant chemoradiotherapy	Neoadjuvant chemoradiotherapy with surgery	■ Rectal cancer mortality ■ 30-day mortality ■ Distant metastases ■ Disease-free survival ■ Overall survival ■ Local recurrence ■ Quality of life ■ Sexual dysfunction ■ Adverse events ■ Rehospitalisation ■ Permanent stoma formation ■ Return to normal bowel function

Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Intervention	
Study design	Level III-2 cohort studies and non-randomised trials	
Population	Patients diagnosed with stage I-III rectal cancer	■ Patients with distant metastases M1 ■ Patients diagnosed with rectosigmoid cancer ■ Palliative treatment studies
Intervention	Definitive neoadjuvant chemoradiotherapy	Adjuvant/postoperative chemoradiotherapy
Comparator	Neoadjuvant chemoradiotherapy with surgery	

Selection criteria	Inclusion criteria	Exclusion criteria
Outcomes	■ Rectal cancer mortality ■ 30-day mortality ■ Distant metastases ■ Disease-free survival ■ Overall survival ■ Local recurrence ■ Quality of life ■ Sexual dysfunction ■ Adverse events ■ Rehospitalisation ■ Permanent stoma formation ■ Return to normal bowel function	
Language	English	
Publication period	From 1/01/2004 to 31/08/2016	

Back to top

Clinical Question NEO1,5,6: (Yip, Field)

Which patients with rectal cancer stage I-II could be considered for definitive chemoradiotherapy (no surgery), neo-adjuvant chemoradiotherapy or surgery alone?

a) What is the optimal timing for surgery after neoadjuvant therapy?

b) Should they be restaged?

PICO Question NEO1,5,6-b:

For patients diagnosed with stage I-III rectal cancer, for which patients does neoadjuvant treatment (short or long course chemoradiotherapy) with surgery achieve equivalent or better outcomes in terms of length and quality of life than surgery alone?

Population	Intervention	Comparator	Outcomes
		Short/long course	■ Rectal cancer mortality ■ 30-day mortality ■ Distant metastases ■ Disease-free survival ■ Overall survival ■ Local recurrence

Population	Intervention	Comparator	Outcomes
Patients diagnosed with stage I-III rectal cancer	Surgery without neoadjuvant therapy	chemoradiotherapy with surgery	■ Quality of life ■ Sexual dysfunction ■ Adverse events ■ Rehospitalisation ■ Permanent stoma formation ■ Return to normal bowel function

Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Intervention	
Study design	Systematic reviews of level II evidence or randomised controlled trials	
Population	Patients diagnosed with stage I-III rectal cancer	■ Patients with distant metastases M1 ■ Patients diagnosed with rectosigmoid cancer ■ Palliative treatment studies
Intervention	Surgery without neoadjuvant therapy	
Comparator	Short/long course chemoradiotherapy with surgery	
Outcomes	■ Rectal cancer mortality ■ 30-day mortality ■ Distant metastases ■ Disease-free survival ■ Overall survival ■ Local recurrence ■ Quality of life ■ Sexual dysfunction ■ Adverse events ■ Rehospitalisation ■ Permanent stoma formation ■ Return to normal bowel function	
Language	English	

Selection criteria	Inclusion criteria	Exclusion criteria
Publication period	From 1/01/2004 to 31/08/2016	

Back to top

20.2.10 Management of resectable locally recurrent disease and metastatic disease (section lead: Cherry Koh)

Clinical Question MNG13:
Which patients with locally recurrent colon or rectal cancer are more suitable for curative surgery?
PICO Question MNG13:
In patients with locally recurrent colon or rectal cancer, what is the role of curative surgery (+/- chemotherapy, +/- radiotherapy) when compared to surgical palliation +/- palliative chemotherapy +/- palliative radiotherapy or other palliative interventions in terms of outcomes (overall survival, disease free survival, quality of life and complications)?

Population	Intervention	Comparator	Outcomes
Patients diagnosed with locally recurrent colon or rectal cancer	Curative surgery with or without chemotherapy, with or without radiotherapy	Surgical palliation with or without palliative chemotherapy or radiotherapy and/or palliative care	■ Overall survival ■ Disease-free survival ■ Quality of life ■ Complications

Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Intervention	
Study design	Randomised, or pseudo-randomised controlled trial, or cohort study	Studies with relatively low case numbers collected over long periods of time.
Population	Persons diagnosed with locally recurrent colon or rectal cancer and any nodal status	■ Non-locally recurrent colon or rectal cancer ■ Non-resectable disease ■ Metastatic disease

Selection criteria	Inclusion criteria	Exclusion criteria
Intervention	Curative surgery with or without chemotherapy, with or without radiotherapy	Without curative surgery
Comparator	Non-surgical (chemotherapy, radiotherapy, etc) and/or palliative care	
Outcomes	■ Overall survival ■ Disease-free survival ■ Quality of life ■ Complications	
Language	English	
Publication period	From 1/01/2004 to 31/08/2016	

Back to top

Clinical Question MNG14:

What is the role of curative surgery in treating patients with synchronous or metachronous metastatic colon or rectal cancer?

PICO Question MNG14:

In patients with resectable synchronous or metachronous metastatic colorectal cancer, what is the role of surgical resection +/- chemotherapy when compared to non-surgical /palliative interventions in terms of outcomes (overall survival, disease free survival, quality of life and complications)?

Population	Intervention	Comparator	Outcomes
Patients diagnosed with metastatic colon or rectal cancer and synchronous or metachronous resectable metastases	■ Curative surgery ■ With or without chemotherapy ■ With or without radiotherapy	Non-surgical (chemotherapy, radiotherapy, etc) and/or palliative care	■ Overall survival ■ Disease-free survival ■ Quality of life ■ Complications

Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Intervention	

Selection criteria	Inclusion criteria	Exclusion criteria
Study design	Systematic reviews of Level II evidence or randomised controlled trials, or cohort study	
Population	With metastatic colorectal cancer and resectable synchronous or metachronous metastases	■ Non-metastatic colon or rectal cancer ■ Unresectable disease
Intervention	Curative surgery with or without chemotherapy with or without radiotherapy	
Comparator	Non-surgical (chemotherapy, radiotherapy, etc) and/or palliative care	
Outcomes	■ Overall survival ■ Disease-free survival ■ Quality of life ■ Complications	
Language	English	
Publication period	From 1/01/2004 to 31/08/2016	

Back to top

20.2.11 Management of non-resectable locally recurrent disease and metastatic disease (section lead: Louise Nott)

Clinical Question MNG16:
What is the impact of different liver directed therapies in patients with incurable metastatic colorectal cancer?
PICO Question MNG16:
In patients diagnosed with incurable metastatic colorectal cancer, what impact does different liver directed therapies compared with standard care, have on the best outcomes in terms of length and quality of life?

Population	Intervention	Comparator	Outcomes
	■ Liver directed therapies involving: ■ Trans-arterial (chemo) embolization, or		■ Colorectal cancer mortality, or

Population	Intervention	Comparator	Outcomes
Patients with metastatic incurable colorectal cancer	■ Hepatic intra-arterial infusion, or ■ Stereotactic radiotherapy, or ■ Radiofrequency ablation ■ Radioembolization in particular SIR-Spheres	Standard care (no therapy or, systemic chemotherapy with or without biologic surgery)	■ Survival (progression free or overall), or ■ Quality of life, or ■ Adverse events, or ■ Surgical resection rate

Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Intervention	
Study design	Systematic reviews of Level II evidence, randomised controlled trials	
Population	Patients with metastatic incurable colorectal cancer	Patients diagnosed with metastatic resectable colorectal cancer
Intervention	Liver directed therapies with or without standard therapy, including: ■ Trans-arterial (chemo) embolization, or ■ Hepatic intra-arterial infusion, or ■ Stereotactic radiotherapy, or ■ Radiofrequency ablation, or ■ Radioembolization in particular SIR Spheres	
Comparator	Standard care (no therapy or, systemic chemotherapy with or without biologic therapy)	
Outcomes	■ Colorectal cancer mortality, or ■ Survival (progression free or overall), or ■ Quality of life, or ■ Adverse events, or ■ Surgical resection rate	
Language	English	
Publication		

Selection criteria	Inclusion criteria	Exclusion criteria
period	From 1/01/2004 to 31/08/2016	

Back to top

20.2.12 Follow up after curative resection for colorectal cancer (section lead: Peter Lee)

Clinical Question FUR1-2:
What is the optimal follow up protocol for post-curative resection of colorectal cancer?
PICO Question FUR1-2a (Surveillance frequency):
In patients who have had curative resection of colorectal cancer, what surveillance frequency achieves the best outcomes in terms of detected recurrent disease, 5-year survival, quality of life, and colorectal cancer related mortality?

Population	Intervention	Comparator	Outcomes
Patient who have had curative resection of colorectal cancer	Follow-up including: ■ Sigmoidoscopy, or ■ Serum CEA test, or ■ Imaging (CT scan), or ■ Chest X-ray, or ■ FOBT, or ■ Ultrasonographic screening	An alternative follow-up modality	■ Colorectal cancer mortality, or ■ Recurrence rates, or ■ Rate of curative resection following recurrence, or ■ Time to recurrence, or- 5 year survival, or ■ Quality of life

Inclusion and Exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Intervention	
Study design	Systematic reviews of Level II evidence or randomised controlled trials	Modelling studies
Population	Patient who have had curative resection of colorectal cancer	
	Follow-up including: ■ Sigmoidoscopy, or ■ Serum CEA test, or ■ Imaging (CT scan), or	

Selection criteria	Inclusion criteria	Exclusion criteria
Intervention	■ Chest X-ray, or ■ FOBT, or ■ Ultrasonographic screening	
Comparator	An alternative follow-up modality	
Outcomes	■ Colorectal cancer mortality, or ■ Recurrence rates, or ■ Rate of curative resection following recurrence, or ■ Time to recurrence, or- 5 year survival, or ■ Quality of life	
Language	English	
Publication period	From 1/01/2004 to 31/08/2016	

20.3 Journal articles

Contents

20.3.1 Bowel cancer

Journal articles developed out of the Australian *Clinical practice guidelines for the prevention, early detection and management of colorectal cancer* and *Clinical practice guidelines for surveillance colonoscopy*.

As part of the dissemination and implementation plans for these guidelines, lead authors were encouraged to develop articles to submit to journals for publication in order to further promote the updated Australian guidance on surveillance colonoscopy and the prevention, early detection and management of colorectal cancer.

Dissemination and implementation plans:

- Clinical practice guidelines for the prevention, early detection and management of colorectal cancer

- Clinical practice guidelines for surveillance colonoscopy.

20.3.1.1 Colorectal cancer

Journal articles published or accepted for publication:

Revised Australian national guidelines for colorectal cancer screening: family history *Mark A Jenkins, Driss Ait Ouakrim, Alex Boussioutas, John L Hopper, Hooi C Ee, Jon D Emery, Finlay A Macrae, Albert Chetcuti, Laura Wuellner and James B St John* (29 October 2018)

The National Bowel Cancer Screening Program: time to achieve its potential to save lives *Hooi C Ee, James St John* (31 July 2019)

20.3.1.2 Surveillance colonoscopy

Journal articles published or accepted for publication:

TBC

20.3.2 Skin cancer

20.3.2.1 Keratinocyte cancer

Journal articles published or accepted for publication:

TBC

20.3.2.2 Melanoma

Journal articles developed out of the Australian *Clinical practice guidelines for the diagnosis and management of melanoma*.

As part of the dissemination and implementation plan for the guideline, lead authors were encouraged to develop articles to submit to journals for publication in order to further promote the updated Australian guidance on the diagnosis and management of melanoma.

Journal articles published or accepted for publication:

When is a sentinel node biopsy indicated for patients with primary melanoma? An update of the 'Australian guidelines for the management of cutaneous melanoma' *David E Gyorki, Andrew Barbour, Mark Hanikeri, Victoria Mar, Shahneen Sandhu and John F Thompson*

Clinical practice guidelines for the diagnosis and management of melanoma: melanomas that lack classical clinical features *Victoria J Mar, Alex J Chamberlain, John W Kelly, William K Murray and John F Thompson*

Updated evidence-based clinical practice guidelines for the diagnosis and management of melanoma: definitive excision margins for primary cutaneous melanoma *Michael J Sladden, Omgo E Nieweg, Julie Howle, Brendon J Coventry and John F Thompson*

Methods of melanoma detection and of skin monitoring for individuals at high risk of melanoma: new Australian clinical practice *Nikki R Adler, John W Kelly, Pascale Guitera, Scott W Menzies, Alex J Chamberlain, Paul Fishburn, Alison E Button-Sloan, Clinton Heal, H Peter Soyer and John F Thompson*

Multidisciplinary care of cancer patients – a passing fad or here to stay? *John F Thompson and Gabrielle J Williams*

Improving diagnostic accuracy for suspicious melanocytic skin lesions: new Australian melanoma clinical practice guidelines stress the importance of clinician/pathologist communication *Richard A Scolyer, H Peter Soyer, John W Kelly, Craig James, Catriona A McLean, Brendon J Coventry, Peter M Ferguson, Robert V Rawson, Victoria J Mar, Sara L de Menezes, Paul Fishburn, Jonathan R Stretch, Stephen Lee and John F Thompson*

New treatment paradigms for clinically-apparent metastatic melanoma in regional lymph nodes *Michael A. Henderson, John Spillane, T. Michael Hughes, Andrew J. Spillane, B. Mark Smithers and John F. Thompson*

Evidence-based clinical practice guidelines for the management of patients with lentigo maligna *Mitchell Robinson, Clare Primiero, Pascale Guitera, Angela Hong, Richard A. Scolyer, Jonathan R. Stretch, Geoffrey Strutton, John F. Thompson and H. Peter Soyer*

Diagnosis and Management of Cutaneous Melanoma *Victoria Mar (20-4-2020: accepted for publication AJGP)*

New Australian melanoma management guidelines – the patient perspective *J F Thompson & Alison Button-Sloan (27-May-2020: accepted for publication MJA)*

Last updated: 6 July 2020

20.4 Technical report

This Technical Report accompanies the *Clinical practice guidelines for the prevention, early detection and management of colorectal cancer*, developed by Cancer Council Australia.

It outlines the guideline development process and methodology, lists the clinical questions, provides all accompanying NHMRC Statement Forms, the detailed technical documentation for each question and the risk of bias assessment tools used to assess the included literature as a result of a systematic review.

Contents

20.4.1 Guideline development process

20.4.2 Clinical question list

20.4.3 Evidence statement forms, systematic review reports and modelling reports

The following reports are for questions that were answered by a new systematic literature review or modelling.

The questions were given alphanumeric codes when they were developed, please refer to the codes below.

PPR1: *In an asymptomatic population at average risk or increased risk of colorectal cancer, what is the cost-benefit ratio of prophylactic Aspirin use in reducing the mortality and incidence of colorectal cancer?*
Evidence statement form PPR1
Systematic review report PPR1

PSC1a: *In persons without a colorectal cancer diagnosis or symptoms that might indicate colorectal cancer, which screening modality (immunochemical FOBT, flexible sigmoidoscopy, colonoscopy, faecal or blood biomarkers, or any combinations) compared with no screening, reduce colorectal cancer mortality, or the incidence of metastases at diagnosis?*
Albert to check
Evidence statement form PSC1a
Systematic review report PSC1a

PSC1b: *For persons without a colorectal cancer diagnosis or symptoms that might indicate colorectal cancer, which screening modality (immunochemical FOBT, flexible sigmoidoscopy, colonoscopy, faecal or blood biomarkers, or any combinations) performs best in detecting colorectal cancer, and how does the diagnostic performance change with family history, age, or gender?*
Evidence statement form PSC1b
Systematic review report PSC1b

PSC1c: *In persons without a bowel cancer diagnosis or symptoms that might indicate bowel cancer, is population based screening using any of the following modalities (immunochemical FOBT, flexible*

sigmoidoscopy, colonoscopy, CT colonography, faecal or blood biomarkers, or combinations) feasible or acceptable?
Modelling report PSC1c

PSC1d: *In persons without a bowel cancer diagnosis or symptoms that might indicate bowel cancer, what is the most cost-effective screening modality (immunochemical FOBT, flexible sigmoidoscopy, colonoscopy, CT colonography, faecal or blood biomarkers, or any combinations) compared with no screening?*
Modelling report PSC1d

SPT1-2a: *In symptomatic patients without a colorectal cancer diagnosis, what signs or symptoms (persistent changed bowel movements, persistent diarrhoea or constipation, unexplained rectal bleeding, general or localised abdominal pain, unexplained palpable abdominal or rectal mass, unexplained weight loss, iron deficient anaemia, tiredness, fatigue, or any combination) correlate best with a diagnosis of colorectal cancer?*
Evidence statement form SPT1-2a
Systematic review report SPT1-2a

SPT1-2b: In symptomatic patients without a colorectal cancer diagnosis, what is the optimal maximum diagnostic interval that achieves better.....TO FIX
Evidence statement form SPT1-2b
Systematic review report SPT1-2b

FHS2: *Has a family history of colorectal cancer been shown to be reliably associated with a greater increase in risk of occurrence of or death from colorectal cancer when compared to persons who do not have a family history of colorectal cancer?*
Evidence statement form FHS2
Systematic review report FSH2

PTH1: *In patients diagnosed with colorectal cancer and have undergone surgical resection or biopsy of the primary colorectal tumour, which molecular marker (BRAF/KRAS/NRAS/MMRD/MSI) best predicts response to surgery, or adjuvant therapy or radiotherapy (disease-free survival, overall survival, disease-specific mortality, overall mortality, or relapse incidence)?*
Evidence statement form PTH1
Systematic review report PTH1

PRP2-5,7: *In patients diagnosed with colorectal cancer and undergoing surgical tumour resection, does mechanical bowel preparation with or without antibiotic prophylaxis, when compared to usual care, achieve better outcomes in terms of anastomotic leakage, surgical site infection, length of hospital stay and ileus?*
Evidence statement form PRP2-5,7
Systematic review report PRP2-5,7

COL1-2a: *In patients diagnosed with colon cancer, what is the optimal resection strategy to achieve the best outcomes in terms of length and quality of life?*
Evidence statement form COL1-2a
Systematic review report COL1-2a

COL1-2b: *In patients diagnosed with rectal cancer, what is the optimal resection strategy to achieve the best outcomes in terms of length and quality of life?*
Evidence statement form COL1-2b
Systematic review report COL1-2b

REC3: *In patients diagnosed with stage I-II rectal cancer, what is the most effective treatment strategy to achieve the best outcomes in terms of length and quality of life?*
Evidence statement form REC3
Systematic review report REC3

COLMNG5: *In patients diagnosed with colorectal cancer and acute obstruction, does stenting or colostomy achieve equivalent or better outcomes compared to acute resection with primary anastomosis?*
Evidence statement form COLMNG5
Systematic review report COLMNG5

COLMNG3: *For patients diagnosed with colorectal cancer and peritoneal involvement or isolated peritoneal recurrence of colorectal cancer, does peritonectomy, with or without perioperative intraperitoneal chemotherapy (PIC), achieve better outcomes in terms of length and quality of life than usual care?*
Evidence statement form COLMNG3
Systematic review report COLMNG3

ADJ1: *In elderly patients (≥70 years) diagnosed with colon cancer, what is the efficacy of surgery and adjuvant combination chemotherapy (involving either 5-flurouracil or capecitabine combined with oxaliplatin), compared to surgery with a single chemotherapeutic agent (Fluoropyrimidine) in achieving the best outcomes in terms of colorectal cancer mortality, recurrence, quality of life and adverse effects?*
Evidence statement form ADJ1
Systematic review report ADJ1

NEO1b: INSERT
Evidence statement form NEO1b
Systematic review report NEO1b

NEO1a: INSERT
Evidence statement form NEO1a
Systematic review report NEO1a

MNG13: *In patients with locally recurrent colon or rectal cancer, what is the role of curative surgery (+/- chemotherapy, +/- radiotherapy) when compared to surgical palliation +/- palliative chemotherapy +/- palliative radiotherapy or other palliative interventions in terms of outcomes (overall survival, disease free survival, quality of life and complications)?*
Evidence statement form MNG13
Systematic review report MNG13

MNG14: *In patients with resectable synchronous or metachronous metastatic colorectal cancer, what is the role of surgical resection +/- chemotherapy when compared to non-surgical /palliative interventions in terms of outcomes (overall survival, disease free survival, quality of life and complications)?*
Evidence statement form MNG14
Systematic review report MNG14

MNG16: *In patients diagnosed with incurable metastatic colorectal cancer, what impact does different liver directed therapies compared with standard care, have on the best outcomes in terms of length and quality of life?*
Evidence statement form MNG16
Systematic review report MNG16

FUR1-2a: *In patients who have had curative resection of colorectal cancer, what surveillance frequency achieves the best outcomes in terms of detected recurrent disease, 5-year survival, quality of life, and colorectal cancer related mortality?*
Evidence statement form FUR1-2a
Systematic review report FUR1-2a

20.4.3.1 Cohort studies (risk factors) risk of bias assessment tool

'''CHECK WITH ALBERT'''

- Cohort studies risk of bias assessment form
- Cohort studies risk of bias assessment help sheet

Back to top

20.5 Additional resources

20.6 Glossary and abbreviations

20.7 Working party members & contributors

Contents

20.7.1 Colorectal Cancer Guidelines Working Party members and contributors

20.7.1.1 Management Committee

Name	Affiliation
Professor Timothy Price (Chair)	"Chair, Management Committee and Colorectal Cancer Guidelines Revision Working Party Medical Oncologist, The Queen Elizabeth Hospital, Adelaide"
Professor Sanchia Aranda	CEO, Cancer Council Australia
Dr Cameron Bell	Gastroenterologist, Royal North Shore Hospital, Sydney
Professor Alexander (Sandy) Heriot	Consultant Colorectal Surgeon Director Cancer Surgery, Peter MacCallum Cancer Centre Director, Lower GI Tumour Stream, Victorian Comprehensive Cancer Centre
Professor Finlay Macrae	Gastroenterologist, Royal Melbourne Hospital, Melbourne
Dr Elizabeth Murphy	Head, Colorectal Surgical Unit, Lyell McEwin Hospital Adelaide
Professor Michael Solomon	Colorectal Surgeon, Royal Prince Alfred Hospital, Sydney
Professor James St John	Gastroenterologist, Honorary Senior Associate, Cancer Council Victoria, Melbourne
Dr Bernie Towler	Chief Medical Adviser, Population Health Division, Department of Health, Canberra
Ms Jutta von Dincklage & Laura Wuellner	Head, Clinical Guidelines Network
Professor John R Zalcberg	Head of Cancer at the School of Public Health and Preventive Medicine, Monash University, Melbourne

20.7.1.2 Guideline section leaders

Name	Specialty	Section
Professor Finlay Macrae	Gastroenterology	Primary prevention
Professor James St John	Gastroenterology	Population screening for colorectal cancer (co-lead)
Dr Hooi Ee	Gastroenterology	Population screening for colorectal cancer (co-lead)

Name	Specialty	Section
Professor Mark Jenkins	Genetic epidemiology, cancer epidemiology (colorectal cancer, Lynch syndrome, genetic epidemiology)	Risk and screening based on family history
Professor Phyllis Butow	Psycho-oncology	Psychosocial care
Professor Barbara Leggett	Gastroenterology	High-risk familial syndromes
Dr Kirsten Gormly	Radiology	Imaging a patient with a diagnosis of colon/rectal adenocarcinoma
Dr Andrew Luck	Colorectal surgery	Elective and emergency surgery colon
Professor Alexander (Sandy) Heriot	Colorectal surgery	Elective and emergency surgery for colon and rectal cancer
Dr Elizabeth Murphy	Colorectal surgery	Preparation for surgery and peri-operative optimisation
Professor Pierre Chapuis	Colorectal surgery	Pathology and staging (co-lead)
A/Professor Charles Chan	Pathology	Pathology and staging (co-lead)
A/Professor Peter Gibbs	Medical oncology	Adjuvant therapy for colon cancer
Professor Desmond Yip	Medical oncology	Neoadjuvant and adjuvant therapy for rectal cancer (co-lead)
Dr Kathryn Field	Medical oncology	Neoadjuvant and adjuvant therapy for rectal cancer (co-lead)
Dr Peter J. Lee	Colorectal surgery	Follow up after curative resection for colorectal cancer
Dr Cherry Koh	Colorectal surgery	Management of resectable locally recurrent disease and metastatic disease
Dr Louise Nott	Medical oncology	Management of non-resectable locally recurrent disease and metastatic disease

20.7.1.3 Additional working party members

Name	Specialty
Jeff Cuff	Consumer representative
Jillian Arnott	Consumer representative
Professor Karen Canfell	Director, Cancer Research Division, Cancer Council NSW (Epidemiology expert)
Professor Dianne O'Connell	Senior Epidemiologist, Manager, Cancer Research Division, Cancer Council NSW (Epidemiology expert)

20.7.2 Chapter details

20.7.2.1 Colorectal cancer in Australia

Name	Affiliation
Dr Prema Thavaneswaran*	Manager Public Health Policy
Professor Jane Young	Executive Director, Research, Institute of Academic Surgery, Executive Director, Surgical Outcomes Research Centre (SOuRCe) Royal Prince Alfred Hospital and University of Sydney, Professor in Cancer Epidemiology, School of Public Health, University of Sydney
Professor Michael Solomon	Colorectal Surgeon, Royal Prince Alfred Hospital, Sydney

*Section lead author

20.7.2.2 Primary prevention

Name	Affiliation
Professor Finlay Macrae*	Gastroenterologist, Royal Melbourne Hospital, VIC
Ms Julie Clarke	Senior Research Scientist, CSIRO
Professor Jon Emery	General Practitioner
Dr Trevor Lockett	Theme Leader, Commonwealth Scientific and Industrial Research Organisation (CSIRO)
Professor John McNeil	Head of Department of Epidemiology & Preventive Medicine, Head of School of Public Health & Preventive Medicine, Monash University, Melbourne

Name	Affiliation
Professor Allan Spigelman	Head of School, St Vincent's Clinical School
Dr Aung Ko Win	Genetic Epidemiologist, Centre for Epidemiology & Biostatistics, Melbourne School of Population and Global Health
A/Professor Robyn Woods	Associate Professor, Monash University
Professor Graeme Young	Professor of Global Gastrointestinal Health, Faculty of Medicine, Nursing and Health Sciences, Flinders University
Professor John R Zalcberg	Head of Cancer at the School of Public Health and Preventive Medicine, Monash University, Melbourne

*Section lead author

20.7.2.3 Population screening for colorectal cancer

Name	Affiliation
Professor James St John*	Gastroenterologist, Honorary Senior Associate, Cancer Council Victoria, Melbourne
Dr Hooi Ee*	Gastroenterologist, Sir Charles Gairdner Hospital, Perth
Professor Jon Emery	Honorary Senior Visiting Research Fellow, Winthrop Professor of General Practice at the Western University of Australia and Professor of Primary Care Cancer Research at the University of Melbourne (also practising GP)
Professor Finlay Macrae	Gastroenterologist, Royal Melbourne Hospital, Melbourne
Ms Rachel Mulqueeney	Cancer Screening Project Coordinator Prevention Division Cancer Council Victoria

*Section lead author

20.7.2.4 The symptomatic patient

Name	Affiliation
Professor Jon Emery*	General Practitioner
Dr Cameron Bell	Gastroenterologist – Royal North Shore Hospital, Sydney
A/Professor Gregor	

Name	Affiliation
Brown	Head of Endoscopy, The Alfred Hospital, Melbourne
Professor Finlay Macrae AO	Gastroenterologist, Royal Melbourne Hospital, VIC
Dr Iain Skinner	Colorectal surgeon
A/Professor Justin Tse	Director of Medical Student Education (Clinical Dean) St Vincent's Clinical School, The University of Melbourne

*Section lead author

20.7.2.5 Risk and screening based on family history

Name	Speciality	Affiliation
Professor Mark Jenkins*	Genetic epidemiology, cancer epidemiology	Director of the Centre for Epidemiology & Biostatistics, University of Melbourne, Melbourne.
Professor Alex Boussioutas	Gastroenterology	GE at University of Melbourne, Pter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne
Dr Driss Ait Quakrim	Epidemiology	Research Fellow – Epidemiologist, Centre for Epidemiology and Biostatistics, University of Melbourne, Melbourne

*Section lead author

20.7.2.6 High-risk familial syndromes

Name	Speciality	Affiliation
Professor/Dr Barbara Leggett*	Gastroenterology	Laboratory Head, Conjoint Gastroenterology, QIMR Berghofer Medical Research Institute, QLD
Dr Nicola Poplawski	Clinical Genetics	Clinical Geneticist, SA Pathology, South Australia
Dr Nicholas Pachter	Paediatrics	Clinical Senior Lecturer, School of Paediatrics and Child Health, The University of Western Australia, Perth
Dr Christophe Rosty	Pathology	Envoi Pathology and University of Queensland School of Medicine. QLD
Dr Ian Norton	Gastroenterology & Hepatology	Director of Endoscopy, Royal North Shore Hospital, Endoscopist, Sydney Adventist Hospital, Sydney
Dr Caroline Wright	Colorectal Surgery	Colorectal surgeon, Royal Prince Alfred Hospital, Senior Lecturer in Surgery, The University of Sydney
Dr Aung Ko	Genetic Epidemiology	Centre for Epidemiology & Biostatistics, Melbourne School of Population and Global Health, Melbourne

*Section lead author

20.7.2.7 Imaging a patient with a diagnosis of colon/rectal adenocarcinoma

Name	Speciality	Affiliation
Dr Kirsten Gormly*	Radiology	Radiologist, Dr Jones and Partners, SA
Dr Wendy Brown	Radiology	Senior Staff Specialist, Radiology Department, Royal Prince Alfred Hospital, Camperdown, NSW
Dr Damien Stella	Paediatrics	Radiologist, Royal Melbourne Hospital
Dr Elizabeth (Liz) Murphy*	Colorectal Surgery	Head, Colorectal Surgical Unit, Lyell McEwin Hospital Adelaide, SA
Professor Timothy (Tim) Price	-	Chair, Management Committee and Colorectal Cancer Guidelines Revision Working Party. Medical Oncologist, The Queen Elizabeth Hospital, Adelaide

*Section lead author

20.7.2.8 Pathology and staging

Name	Speciality	Affiliation
Professor Pierre Chapuis*	Colorectal Surgery	Clinical Professor, Surgery, Concord Clinical School & Director of Postgraduate Surgical Education for the Discipline of Surgery, The University of Sydney (Head of Academic Surgery), NSW
Associate Professor Charles Chan*	Pathology	Clinical Associate Professor Medicine, Concord Clinical School, Sydney, NSW
Professor Soon Lee	Pathology	Professor and Chair of Pathology, University of Western Sydney; Head, Cancer Pathology and Cell Biology, Ingham Institute for Applied Medical Research; Senior Pathologist, Liverpool Hospital and Royal Prince Alfred Hospital; Clinical Professor and Head, Cancer Pathology, Bosch Institute, University of Sydney; Conjoint Professor, University of New South Wales, NSW
Emeritus Professor Ron Newland	Anatomical Pathology	Department of Anatomical Pathology at Concord Repatriation General Hospital, Sydney, NSW

Name	Speciality	Affiliation
Dr Christine Hemmings	Anatomical Pathology, Colorectal Disease	Surgical Pathologist and Head of Molecular Oncology Division at St John of God Subiaco Hospital, Perth, WA
Associate Professor Anthony Gill	Surgical Pathology	Associate Professor Medicine, Northern Clinical School University of Sydney
Associate Professor Neil Walker	Gastrointestinal Pathology	TBC
Dr Jeanne Tie	Medical oncology /Translational oncology	Medical Oncologist at the Royal Melbourne Hospital and Western Hospital, and a Clinical Research Fellow at the Walter and Eliza Hall Institute of Medical Research, Melbourne, VIC
Associate Professor Lara Lipton	Medical oncology /Translational oncology	Consultant Haemotologist at Cabrini Medical Centre and Medical Oncologist at the Cancer Clinic at Royal Melbourne Hospital
Dr Christophe Rosty	Anatomical Pathology, Colorectal disease	Director of Surgical Pathology at Royal Brisbane and Women's Hospital and Associate Professor of Molecular and Cellular Pathology, University of Queensland

*Section lead author

20.7.2.9 Preparation for surgery and peri-operative optimisation

Name	Speciality	Affiliation
Dr Elizabeth (Liz) Murphy*	Colorectal Surgery	Head, Colorectal Surgical Unit, Lyell McEwin Hospital Adelaide, SA
Professor Kathryn Robinson	Haemotology	Transfusion medicine specialist, Australian Red Cross Blood Service, Haematologist, The Queen Elizabeth Hospital, Adelaide, SA
Dr Bernd Froessler	Anaesthesia	Staff Specialist, Anaesthesia, Lyell McEwin Hospital; Clinical Senior Lecturer, University of Adelaide
Dr Simon McRae	Haematology	Clinical Trial Program Coordinator, Venous Thrombosis, Queen Elizabeth Hospital, Haemophilia Treatment Centre, Royal Adelaide Hospital, SA

Name	Speciality	Affiliation
Dr Kate Burbury	Haematology	Lead Haematologist for Haemostasis and Thrombosis, Peter MacCallum Cancer Centre, Melbourne, VIC
Professor Peter Collignon	Pathology	Director, Microbiology and Infectious Diseases, The Canberra Hospital, Clinical Associate Professor in Infectious Diseases, Canberra Clinical School of The University of Sydney, NSW
Dr Karen Barclay	Colorectal Surgery	Colorectal Surgeon and Senior Lecturer in Surgery, Acting Head of the Academic Surgical Unit, NCHER, The Northern Hospital and the University of Melbourne, VIC
Dr Glenn Guest	Colorectal Surgery	Colorectal Surgeon (Bowel), St John of God Geelong Hospital, Melbourne, VIC
Dr Cherry Koh	Colorectal Surgery	Colorectal surgeon, Royal Prince Alfred Hospital, Sydney
Professor Timothy (Tim) Price	Medical Oncologist	Medical Oncologist, The Queen Elizabeth Hospital, Adelaide, SA
Dr Nabila Ansari	Colorectal Surgery	Colorectal Surgeon, Royal Prince Alfred Hospital, Sydney
Professor Alexander (Sandy) Heriot*	Colorectal Surgery	Colorectal Surgeon, Peter MacCallum Cancer Centre, Melbourne, VIC
Professor Joanne Perry	Colorectal Nursing	Colorectal Cancer Support Nurse, Royal Adelaide Hospital, SA

*Section lead author

20.7.2.10 Elective and emergency surgery for colon and rectal cancer

Name	Speciality	Affiliation
Dr Andrew Luck*	Colorectal Surgery	Colorectal Surgeon, Lyell McEwin Hospital, Adelaide, SA
Dr Carina Chow	Colorectal surgery	Colorectal Surgeon , Royal Brisbane Hospital, QLD
Dr Chip Farmer	Colorectal surgery	Colorectal Surgeon, The Alfred Hospital, Melbourne, VIC
Dr Henry Hicks	Colorectal Surgery	General Surgeon, Wagga Wagga Specialist Medical Centre, NSW
Associate Professor Marina Wallace	Colorectal Surgery	Professor of Surgery, University of Western Australia, WA

*Section lead author

20.7.2.11 Adjuvant therapy for colon cancer

Name	Speciality	Affiliation
Associate Professor Peter Gibbs*	Medical Oncology	Laboratory Head, Walter & Eliza Hall, Institute of Medical Research, Melbourne, VIC

*Section lead Author

20.7.2.12 Neoadjuvant and adjuvant therapy for rectal cancer

Name	Speciality	Affiliation
Professor Desmond Yip*	Medical Oncology	Medical Oncologist and Clinical Director, The Canberra Hospital, Australian National University; Honorary Associate, Sydney Medical School, The University of Sydney, ACT
Professor Les Bokey	Colorectal Surgery	Colorectal Surgeon, Liverpool Hospital, Sydney, NSW
Associate Professor George Hruby	Radiation oncology	Radiation Oncologist, Chris O'Brien Lifehouse, Sydney, NSW
Professor Ian Jones	Colorectal Surgery	Colorectal Surgeon, Royal Melbourne Hospital, VIC
Dr Kathryn Field*	TBD	Royal Melbourne Hospital, VIC
Associate Professor Christos Karapetis	Medical Oncologist	Medical Oncologist, Flinders Medical Centre, Adelaide, SA
Dr Elizabeth (Liz) Murphy	Colorectal Surgery	Head, Colorectal Surgical Unit, Lyell McEwin Hospital, Adelaide, SA
Associate Professor Sam Ngan	Radiation Oncology	Head of the GI Unit of the Department of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC
Dr Kirsten Gormly*	Radiology	Radiologist, Dr Jones and Partners Medical Imaging, Adelaide, SA
Professor Alexander (Sandy) Heriot	Colorectal surgery	Colorectal Surgeon, Peter MacCallum Cancer Centre, Melbourne, VIC

*Section lead author

20.7.2.13 Management of resectable locally recurrent disease and metastatic disease

Name	Speciality	Affiliation
Dr Cherry Koh*	Colorectal surgery	Surgical Outcomes Research Centre (SOuRCe), Sydney, NSW
Professor Timothy (Tim) Price	Medical oncology	Medical Oncologist,The Queen Elizabeth Hospital, Adelaide, SA
Professor Alexander (Sandy) Heriot	Colorectal surgery	Colorectal Surgeon, Peter MacCallum Cancer Centre, Melbourne
Professor Peter Hewett	Colorectal surgery	Head of Colorecal Surgery Unit, The Queen Elizabeth Hospital, Adelaide, SA
Dr Sarat Chander	Radiation oncology	Radiation Oncologist, Peter MacCallum Cancer Centre, Melbourne, VIC
Dr Nicholas O'Rourke	Bariatric Surgery, General Surgery, Hepatobiliary Surgery	Syrgeon (laparoscopic and hepatobiliary), Wesley Hospital, Brisbane, QLD
Dr Kirsten Gormly	Radiology	Radiologist, Dr Jones and Partners Medical Imaging, Adelaide
Associate Professor Tristan Van	Cardiothoracic Surgery, Aortic Surgery, Minimally Invasive Cardiac Surgery, Minimally Invasive Thoracic Surgery	Consultant Cardiothoracic Surgeon, Professor of Cardiovascular and Thoracic Surgery at the Macquarie University Hospital and Associate Clinical Professor at the University of Sydney, Department of Cardiothoracic Surgery, Royal Prince Alfred Hospital, Sydney, NSW
Peter Lee	TBD	TBD

*Section lead author

20.7.2.14 Management of non-resectable locally recurrent disease and metastatic disease

Name	Speciality	Affiliation
	Medical	Medical Oncologist, Royal Hobart Hospital and St John's Hospital,

Name	Speciality	Affiliation
Louise Nott*	oncology	TAS
Dr Muhammad Khattak	Medical Oncology	Medical Oncologist, Royal Perth Hospital, Perth, WA
Dr Thomas (Tom) Ferguson	Medical Oncology	Medical Oncologist, Royal Perth Hospital, Perth

* Section lead author

20.7.2.15 Follow Up After Curative Resection for Colorectal Cancer

Name	Speciality	Affiliation
Dr Peter J. Lee*	Colorectal surgery	Colorectal surgeon (visiting), Colorectal, Royal Prince Alfred Hospital, Chris O'Brien Lifehouse, St Luke's Hospital, Sydney, NSW
Dr Andrew Gilmour	Colorectal Surgery	TBD
Professor Phillip Beale	Medical oncology	TBD

*Section lead author

20.7.2.16 Psychosocial care

Name	Affiliation
Professor Phyllis Butow*	Chair Psycho-Oncology Co-operative Research Group (PoCoG), and Co Director of the Centre for Medical Psychology and Evidence-based Medicine (CeMPED) and of the Surgical Outcomes Research Centre (SoURCe), University of Sydney
Professor Afaf Girgis	Director, Psycho-Oncology Research Group, Centre for Oncology Education and Research Translation, Ingham Institute for Applied Medical Research, South Western Sydney Clinical School, University of NSW
Dr Jannelle Lavesque	Psycho-oncology Research Group, Centre for Oncology Education and Research Translation (CONCERT), Ingham Institute for Applied Medical Research, South Western Sydney Clinical School, UNSW Medicine
Professor Penny Schofield	Professor, Department of Psychological Sciences, Swinburne University; Honorary Principal Research Fellow, Department of Cancer Experiences Research, Peter MacCallum Cancer Centre
Dr Heather Shepherd	ADAPT Research Fellow and Program Manager, Psycho-oncology Co-operative Research Group (PoCoG), The University of Sydney

*Section lead author

20.8 Project team contributions

Cancer Council Australia project team contributions

}

Name	Affiliation
Jutta von Dincklage	Head, Clinical Guidelines Network, Cancer Council Australia (until November 2016)
Laura Wuellner	Project Manager, Clinical Guidelines Network (until November 2016), Acting Head, Clinical Guidelines Network, Cancer Council Australia (from November 2016)
Katrina Anderson	Project Manager, Clinical Guidelines Network (from November 2016)
Katrina Anderson	Project Manager, Clinical Guidelines Network (from November 2016)
Dr Albert Chetcuti	Project Officer, Systematic Literature Reviews, Colorectal Cancer Guidelines
Ben Lee-Bates	Research Assistant, Colorectal Cancer Guidelines
Victoria Freeman	Research Assistant, Colorectal Cancer Guidelines
Melissa Chow	Research Assistant, Colorectal Cancer Guidelines
Cecilia Taing	Research Assistant, Colorectal Cancer Guidelines

20.9 Conflict of interest register