Cancer Council Australia

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

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

The guideline recommendations were approved by the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) on 27 October 2017 under section 14A of the *National Health and Medical Research Council Act 1992*.

Please also see the following files:

- administrative report
- dissemination report.

This is a wiki-based guideline. To request a PDF version of the recommendations in the guideline (short-form guideline), please contact the Project Manager, Clinical Guidelines Network at guidelines(at)cancer.org.au.

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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 in its prevention, detection and management.

1.1.1 Purpose and scope

These 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.

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.[2] Australian guidelines 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.

These guidelines do not cover surveillance colonoscopy in adenoma follow-up, surveillance colonoscopy following curative resection of colorectal cancer, or colonoscopic surveillance in inflammatory bowel disease. An update of the 2011 Clinical Practice Guidelines for Surveillance Colonoscopy[3] is currently underway.

1.1.2 Intended users

These guidelines are intended for health professionals caring for people with colorectal cancer.

They may also be of interest to policy makers and people with training in medicine or other health sciences.

They are not intended as health information for the general public.

1.1.3 Target populations

These guidelines cover a range of Australian populations, including:

- people without symptoms or signs of colorectal cancer to whom prevention and screening apply
- people with a family history of colorectal cancer or known familial syndromes
- people with symptoms and signs that may suggest colorectal cancer
- people with a positive faecal occult blood test
- people with precancerous lesions detected on colonoscopy
- people with a diagnosis of colorectal cancer at any disease stage.

Clinicians should consider the specific needs of diverse patients, including younger people, Aboriginal and Torres Strait Islanders and culturally and linguistically diverse people diagnosed with colorectal cancer. Please note: for each systematic review, the search strategies specifically included terms relevant to Aboriginal and Torres Strait Islander peoples. However, the literature searches did not identify any studies specifically relevant to Aboriginal and Torres Strait Islander populations that met the inclusion criteria.

1.1.4 Healthcare settings in which the guideline will be applied

These guidelines apply to the range of public and private healthcare settings in which services are provided for the target populations. These include:

- general practice
- screening services
- hospitals
- specialist clinics
- imaging services
- pathology services
- allied health care services.

1.1.5 Funding

The Australian Government Department of Health commissioned and funded Cancer Council Australia to undertake the current revision and update of this guideline.

1.1.6 Scheduled review of these guidelines

It is inevitable that parts of this guideline will become out of date as further literature is published. Newly published evidence relevant to each systematic review question will be monitored. If strong evidence supporting a change in the guideline is published, the Working Party will consider if an update is required for a specific section.

We recommend that the guideline as a whole should be reviewed and updated every 5 years.

1.1.7 Acknowledgement

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;.
2. ↑ Australian Cancer Network Colorectal Cancer Working Party. *Clinical practice guidelines for the prevention, early detection and management of colorectal cancer.* The Cancer Council Australia and Australian Cancer Network 1999.
3. ↑ Cancer Council Australia Colonoscopy Surveillance Working Party. *Clinical Practice Guidelines for Surveillance Colonoscopy – in adenoma follow-up; following curative resection of colorectal cancer; and for cancer surveillance in inflammatory bowel disease.* Sydney: Cancer Council Australia; 2011 Dec.

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2 Summary of recommendations

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

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.

The guideline recommendations were approved by the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) on 27 October 2017 under section 14A of the *National Health and Medical Research Council Act 1992*.

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 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

2.2 Recommendations

2.2.1 Primary prevention

2.2.2 Dietary and lifestyle strategies

Practice point
Folic acid intake outside pregnancy should not exceed 1mg per day and those with a history of colorectal adenomas should not take more than 200mcg as a supplement.

Practice point
It is recommended to follow the primary prevention messages from the World Cancer Research Fund /American Institute for Cancer Research on tobacco smoking, alcohol, diet, body fatness, physical activity (see Table 2.3).

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2.2.3 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.	**B**

Evidence-based recommendation	Grade
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.	

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.

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2.2.4 Population screening for colorectal cancer

2.2.5 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 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.	**N/A**

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	

Evidence-based recommendation	Grade
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.

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2.2.6 The symptomatic patient

2.2.7 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.

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2.2.8 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.

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2.2.9 Risk and screening based on family history

2.2.10 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.

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2.2.11 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**

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2.2.12 High-risk familial syndromes

2.2.13 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)

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2.2.14 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.

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2.2.15 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).

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2.2.16 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).

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2.2.17 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)

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

2.2.19 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.

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2.2.20 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.

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2.2.21 Pathlogy and staging

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2.2.22 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.

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2.2.23 Additional information on pathology reporting

Practice point

DNA mismatch repair status studies should be performed on all cases of colorectal cancer for the detection of Lynch syndrome.

Practice point

BRAF mutation studies should be performed in conjunction with DNA mismatch repair status studies to differentiate between sporadic and familial (Lynch syndrome) cases of DNA mismatch repair status-deficient colorectal cancer.

Practice point

Extended RAS mutation testing should be carried out on all patients at the time of diagnosis of metastatic colorectal cancer. Note: RAS testing is not currently pathologist-determinable and therefore can only be performed for metastatic colorectal cancer following a request from a specialist (surgeon or oncologist).

Practice point

Synoptic reporting is strongly recommended to capture the key variables to enable translation between major internationally recognised staging systems and facilitate multidisciplinary patient management.

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2.2.24 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**

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2.2.25 Preparation for surgery and peri-operative optimisation

2.2.26 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.

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2.2.27 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.

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2.2.28 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.

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2.2.29 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.

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2.2.30 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.

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2.2.31 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.

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2.2.32 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.

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2.2.33 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**

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2.2.34 Elective and emergency surgery for colon and rectal cancer

2.2.35 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.

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2.2.36 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.

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2.2.37 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.

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2.2.38 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	**D**

Evidence-based recommendation	Grade
case to a palliative case.	

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.

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2.2.39 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 intraperitoneal chemotherapy. Where this procedure is suitable, offer 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	**D**

Evidence-based recommendation	Grade
offered after due consideration of, and discussion with the patient about, the potential treatment-related mortality and morbidity.	

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.

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2.2.40 Adjuvant therapy for colon cancer

2.2.41 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.

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2.2.42 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.

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2.2.43 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.

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2.2.44 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.

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2.2.45 Neoadjuvant and adjuvant therapy for rectal cancer

2.2.46 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.

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2.2.47 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.

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2.2.48 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.

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

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.	**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.

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2.2.50 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.

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2.2.51 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.

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2.2.52 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.

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2.2.53 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.

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2.2.54 Management of resectable locally recurrent disease and metastatic disease

2.2.55 Investigation of recurrent cancer

Practice point

Initial assessment of patients with suspected local or systematic recurrence should include serum CEA, contrast CT scan of the chest, abdomen and pelvis (unless contraindicated) and PET.

Practice point

Depending on the type of recurrence, additional investigations are likely to be necessary. A high-quality pelvic MRI is recommended for patients with locally recurrent rectal cancer. Additional local investigations may also need to be considered depending on patient and disease factors such as CT or MRA if mesenteric or iliac vessel involvement is suspected, or cystoscopy if bladder involvement is suspected.

Practice point

If possible, local recurrence should be histologically confirmed before surgery. If this is not possible because of the extraluminal location of the disease, a transvaginal biopsy may be feasible where the recurrence abuts the vagina. Alternatively, CT-guided percutaneous biopsies can be considered after assessing the need for biopsy at a multidisciplinary team meeting.

Practice point

In patients with liver metastases, an MRI of the liver is usually also necessary if surgery is being considered. The use of disodium gadoxetate (*Primovist*) contrast can increase the sensitivity and specificity of MRI for detecting liver metastases. Colonoscopy may be needed if further resection is planned.

Practice point

In patients with suspected lung metastases, CT chest and PET are usually sufficient to confirm diagnosis. In patients where there is diagnostic uncertainty or concerns for mediastinal nodal involvement, an endobronchial ultrasound or bronchoscopy may be needed.

Practice point

All patients with locally recurrent disease or metastatic disease should be discussed in a multidisciplinary team meeting taking into consideration patient's previous surgical history, current imaging, fitness and desire for further treatment.

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2.2.56 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.

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2.2.57 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.

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

2.2.59 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.

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2.2.60 Management of synchronous primary colorectal cancer with unresectable metastatic disease

Practice point

Routine palliative resection of asymptomatic synchronous primary lesion in patients with unresectable metastatic colorectal cancer remains controversial and there are no prospective randomised studies to guide treatment. Recruitment into such trials has been difficult.

Practice point

All patients with an asymptomatic primary and unresectable metastatic colorectal cancer should be discussed in a multi-disciplinary team meeting and the risks and benefits of a palliative resection for an individual patient be carefully discussed bearing in mind the volume of metastatic disease, degree of stenosis/risk of impending obstruction, comorbidities and patient preferences.

Practice point

Patients with an asymptomatic primary and good medium to long term disease control after initial systemic therapy could be re-evaluated for potential resection of both the primary tumour and metastases in the absence of widespread disease progression.

Practice point

For patients with a symptomatic primary tumour (obstruction, bleeding or perforation) and synchronous metastatic disease, resection of the primary tumour should be considered before initiation of systemic therapy. For candidates not suitable for primary tumour resection other palliative options to control symptoms including surgical bypass, radiotherapy, stents, laser ablation in addition to systemic treatment should be considered.

Practice point

For patients with unresectable metastatic rectal cancer with symptomatic primary tumour, irradiation (+/- chemotherapy) of the primary tumour should be considered after multidisciplinary discussion in order to obtain optimal symptom control and reduce patient morbidity.

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2.2.61 The role of systemic therapies in non-resectable metastatic disease

2.2.62 Molecular pathology and biomarkers – implications for systemic therapy

Practice point

RAS testing should be carried out on all patients at the time of diagnosis of metastatic colorectal cancer.

Practice point

RAS mutational status is a negative predictive biomarker for therapeutic choices involving EGFR antibody therapies in metastatic colorectal cancer.

Practice point

Cetuximab and panitumumab should only be considered for the treatment of patients with RAS wild-type metastatic colorectal cancer.

Practice point

The BRAF mutation status should ideally be performed at the time of diagnosis of metastatic colorectal cancer, as this represents a distinct biologic subtype.

Practice point

The presence of a BRAF mutation in metastatic colorectal cancer is considered a poor prognostic marker.

Practice point

BRAF mutation status in combination with testing for DNA mismatch repair deficiency can assist in the identification of a germline versus somatic cause of DNA mismatch repair deficiency.

Practice point

The preponderance of the available evidence is that response to EGFR-targeted agents is less likely in patients whose tumours harbour a BRAF mutation.

Practice point

Metastatic colorectal cancer patients with a BRAF mutation should be considered for a clinical trial where available or triplet chemotherapy if suitable.

Practice point

MSI testing in the metastatic setting can be useful to help identify patients who require referral for further genetic testing and counselling.

Practice point

BRAF V600 mutational analysis should be done in conjunction with MSI testing for prognostic stratification.

Practice point

MSI testing may be a predictive marker for the use of immune checkpoint inhibitors in the treatment of patients with metastatic colorectal cancer.

Practice point

Emerging biomarkers are not recommended for routine patient management outside of the clinical trial setting.

Practice point

The location of the primary tumour is a strong prognostic factor. Patients with left sided primary tumours have a favourable outcome compared with those with right sided tumours regardless of treatment type received.

Practice point

Left sided colorectal cancer should be considered for initial doublet chemotherapy and anti-EGFR therapy where appropriate. Alternate options remain appropriate based on patient preference and comorbidity.

Practice point

Right sided colorectal cancer should be considered for initial doublet chemotherapy plus or minus anti-VEGF. There may be a role for initial chemotherapy with anti-EGFR in right sided colon cancer where the aim of treatment is down staging for resection given the improved response with anti-EGFR. However, this should be done with caution given the lack of benefit on overall survival or progression free survival.

Practice point

Sequential use of all available therapies should continue to be utilised in patients with colorectal cancer regardless of the side of the primary tumour, provided it is appropriate for the individual patient.

Practice point

Future trials for colon cancer should stratify patients by 'sidedness,' to better understand this issue.

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2.2.63 Systemic chemotherapy treatment options for first-line treatment

Practice point

For patients who are able to tolerate it, combination chemotherapy with a doublet (FOLFOX, XELOX [CAPOX], or FOLFIRI) rather than a single agent sequential therapy for initial treatment of metastatic colorectal cancer, is preferred.

Practice point

Patients with potentially resectable metastatic disease should be discussed at a multidisciplinary meeting, and treatment plans should consider patient comorbidity and suitability for an aggressive treatment strategy

Practice point

Monotherapy is not appropriate and combination chemotherapy with a doublet (FOLFOX, XELOX [CAPOX], or FOLRIR) should be used where the aim of therapy is significant cytoreduction. For those with RAS wild-type tumours, an anti-EGFR antibody in conjunction with combination chemotherapy can be considered especially in those with left sided primaries.

Practice point

For those with good performance status and without significant comorbidities intensive triplet chemotherapy with FOLFIRINOX can be considered.

Practice point

Patient comorbidities, ECOG performance status, and location and burden of metastatic disease should be considered in treatment decisions.

Practice point

For patients who are medically unfit with poor performance status, a supportive care approach may be appropriate.

Practice point

In patients with poor performance status or significant comorbidities palliative treatment with single agent fluoropyrimidine (with or without bevacizumab) may be preferred to doublet chemotherapy. Fluoropyrimidine-based therapy alone (or in combination with bevacizumab) can be considered in patients with low-volume unresectable disease.

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2.2.64 Role of biological agents in first-line treatment of metastatic colorectal cancer

Practice point

Biological agents targeting EGFR or VEGF in combination with chemotherapy are recommended in the first-line treatment of most patients unless contraindicated.

Practice point

EGFR antibodies should:

- be used in patients with RAS wild-type tumours
- be used in combination with FOLFIRI or FOLFOX
- not be combined with capecitabine-based and bolus 5FU-based regimen.

Practice point

Patients with left sided colorectal cancer should be considered for initial doublet chemotherapy and anti-EGFR therapy where appropriate. Alternate options remain appropriate based on patient preference and comorbidity.See left vs. right section

Practice point

EGFR antibodies may be less efficacious in patients with BRAF mutations.

Practice point

VEGF antibody (bevacizumab):

- should be used in combination with cytotoxic doublets including FOLFOX, XELOX and FOLFIRI
- can be used in combination with the triplet cytotoxic regimen FOLFOXIRI in select fit patients where tumour shrinkage is the goal, and potentially in fit patients with a BRAF mutation
- can be used in combination with fluoropyrimidine monotherapy in less fit patients unlikely to be suitable for a doublet cytotoxic regimen.

Practice point

Patients with right sided colorectal cancer should be considered for initial doublet chemotherapy plus or minus anti-VEGF. See left vs. right section

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2.2.65 Subsequent treatment and the continuum-of-care model

Practice point

Individualisation and discussion with the patient is essential when planning treatment breaks and or de-escalation/maintenance schedules.

Practice point

When the combination of leucovorin calcium (folinic acid), 5-fluorouracil (5FU) and oxaliplatin (FOLFOX), with or without bevacizumab, is used for first-line therapy, the available data suggest that it is reasonable to discontinue oxaliplatin temporarily while maintaining a fluoropyrimidine with or without bevacizumab.

Practice point

When the combination of folinic acid, 5FU and irinotecan hydrochloride (FOLFIRI), with or without bevacizumab, is used for first- line therapy, patients can continue on induction therapy for as long as tumour shrinkage continues and the treatment is tolerable.

Practice point

For patients receiving initial therapy with folinic acid, 5FU, oxaliplatin and irinotecan hydrochloride (FOLFOXIRI), with or without bevacizumab, a fluoropyrimidine plus bevacizumab may be considered as maintenance therapy (as was done in the pivotal trials examining FOLFOXIRI).

Practice point

For patients receiving initial therapy with a single-agent fluoropyrimidine (plus bevacizumab), induction therapy should be maintained.

Practice point

Initial induction therapy or a second-line therapy should be reintroduced at radiological or first signs of symptomatic progression.

Practice point

If a second-line therapy is chosen, re introduction of the initial induction treatment should be a part of the entire treatment strategy as long as no relevant residual toxicity is present.

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2.2.66 Systemic options for second-line treatment

Practice point

Patients who did not receive bevacizumab as part of first-line therapy should be considered for bevacizumab in second-line therapy, in combination with a second-line cytotoxic regimen.

Practice point

Patients who received bevacizumab as part of the first-line regimen and have RAS wild-type (BRAF wild-type) metastatic colorectal cancer should be considered for combination EGFR monoclonal antibodies with FOLFIRI/irinotecan.

Practice point

Patients who received a first-line oxaliplatin-containing regimen should be switched to an irinotecan-containing regimen, and vice versa.

Practice point

Patients who experience disease progression during first-line 5FU monotherapy should be offered an irinotecan or oxaliplatin-containing regimen if they have adequate performance status.

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2.2.67 Systemic options for third-line treatment

Practice point

Patients with mCRC considering treatment in the third-line setting have limited therapeutic options and typically have reduced quality of life; therefore physicians must carefully balance any efficacy benefit associated with therapy with its toxicity profile.

Practice point

Cetuximab or panitumumab treatment should be considered in patients with RAS wild-type and BRAF wild-type metastatic colorectal cancer not previously treated with these agents, taking into account the following:

- Cetuximab and Panitumumab are equally effective as single agents.
- Cetuximab in combination with irinotecan is more active than cetuximab alone in patients refractory to irinotecan with adequate performance status to receive combination therapy.

Practice point

If available, regorafenib or trifluridine/tipiracil can be considered for patients with metastatic colorectal cancer refractory to all standard available therapies.

Practice point

Patients receiving third-line therapy should be offered participation in clinical trials, wherever available.

Practice point

Symptom burden is often high in patients with mCRC especially as the disease progresses. Early palliative care intervention should be considered for all patients with mCRC as they can improve the quality of life of patients with cancer.

2.2.68 Follow-up after curative resection for colorectal cancer

2.2.69 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.

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2.2.70 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.

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2.2.71 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.

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2.2.72 Pyschosocial care

2.2.73 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.

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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

Contents

3.1 Introduction

Colorectal cancer (also called bowel cancer) means cancer in the large bowel (the colon) or in the section at the end of the bowel just before the anus (the rectum). It starts in the inner lining of the bowel and typically begins as growths on the inside of the bowel (polyps), which can become cancerous and spread if they are not detected and removed.

Bowel cancer is the second most common cancer diagnosed in both men and women. Australia has one of the highest rates of bowel cancer in the world. Approximately 9% of cancer deaths in Australia are due to bowel cancer.

Bowel cancer is more common in people aged over 50 years than in younger adults. The chance of developing bowel cancer before age 85 is about one in 11 for men and one in 15 for women.

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3.2 What increases a person’s risk of bowel cancer?

The risk of bowel cancer is increased by smoking, eating a high amount of red meat (especially when cooked until blackened), eating a high amount of processed meats (e.g. smoked, cured, salted or preserved meats), drinking alcohol, and being overweight or obese. The risk is reduced by regular physical activity and eating plenty of foods that contain fibre.

Bowel cancer runs in some families due to changes in the building blocks of cells that are passed through families (inherited genetic mutations). Some of these cause specific conditions, such as Lynch syndrome, familial adenomatous polyposis (FAP), and attenuated FAP. Doctors use a system of three categories to work out an individual’s level of risk. A person’s risk category depends on how many close relatives have bowel cancer and their age at diagnosis. Someone with several close relatives with bowel cancer, especially if they were diagnosed at a young age, has much higher risk of bowel cancer than someone with no close relatives with bowel cancer.

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3.3 How is bowel cancer diagnosed?

Signs and symptoms of bowel cancer may include bleeding from the bowel, abdominal pain, changes in regular bowel habits to more frequent looser stools (poo) or constipation, weight loss, or a reduction in the number of blood cells that carry oxygen to body tissues (anaemia). These symptoms are not always caused by cancer and can also be linked to less serious health conditions.

Bowel cancer may also be detected before any symptoms develop. In the National Bowel Cancer Screening Program, most screen-detected cancers are asymptomatic.

Most people with signs and symptoms, which may reflect a bowel cancer, go to their general practitioner (GP) first. If a GP thinks a person's symptoms or physical findings could be due to bowel cancer, they will usually arrange further investigation with referral to a gastroenterologist or colorectal surgeon.

The next step is to have a colonoscopy. During this procedure, the health professional is able to view the entire large bowel using a colonoscope to inspect the lining of the bowel. This guideline recommends that people with symptoms of bowel cancer should have a colonoscopy as soon as it can be arranged, but no more than 120 days from first seeing a doctor about those symptoms.

If a colonoscopy shows that a person could have bowel cancer, a piece of the abnormal-looking bowel (biopsy) will be taken to be tested by a pathologist. The person may also need to have imaging, such as abdominal scans, before deciding the best type of treatment for the bowel cancer. Sometimes the first sign of bowel cancer is sudden blockage of the bowel. When this happens, bowel cancer is diagnosed by x-ray or computed tomography (CT) scan and usually requires an emergency operation. After bowel cancer is diagnosed, doctors work out how far it has spread (cancer stage). This may be done by checking findings of the scans. Tissue taken at the time of colonoscopy may be tested for genetic changes in the cancer cells, which can help determine the best treatment. The health professionals treating the person will work closely together to get an accurate understanding of the cancer.

There are several different systems for recording cancer stage. All these systems use codes based on letters and numbers, to indicate how far the cancer has spread through different tissues and organs, and how much cancer is still in the body after surgery. Australian doctors use a combination of these staging systems. Being diagnosed with bowel cancer can be stressful and frightening. Supportive care to help cope with these feelings is an important part of treatment for bowel cancer. Doctors should check whether people are distressed and provide psychological support, if needed. This may include referral to a health professional or organisation such as Cancer Council.

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3.4 How can we reduce bowel cancer in Australia?

Testing healthy people for early signs of bowel cancer (screening) can reduce the number of deaths due to bowel cancer. Australia has a National Bowel Cancer Screening Program, which involves mailing faecal occult blood test (FOBT) kits to people in the target age groups. The person collects tiny samples of their stools (poo) at home and sends them to a testing centre, where the sample is examined for invisible traces of blood. If the test finds some blood (i.e. the result of the test is positive), the person is advised to have more tests, in particular, colonoscopy. In Australia, the screening strategy with the best balance of effectiveness, avoiding unnecessary tests, safety and value for money, is to offer a FOBT every 2 years to people aged 50–74, provided they do not have symptoms of bowel cancer or are not from a high-risk family.

There are a lot of studies indicating that regular aspirin taken by people older than 50 years can reduce the risk of developing bowel cancer. Although there are some risks of taking aspirin, everyone should consider taking a low dose (e.g. 100 mg) of aspirin every day for at least 2.5 years, starting between the ages of 50 and 70 years, unless there are reasons not to such as previous ulcer symptoms. People genetically at risk for bowel cancer or with a strong family history of bowel cancer should particularly consider taking aspirin. Individuals should talk to their GP about whether it would be suitable for them to take aspirin to prevent bowel cancer.

People from high-risk families need extra screening tests to find bowel cancer early. This includes having a colonoscopy every 5 years or more frequently in some circumstances. The age at which a person should start regular bowel screening tests depends on their risk category. They may also be advised to start taking low-dose aspirin regularly from age 25.

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3.5 How is bowel cancer treated?

Treatments for bowel cancer include surgery, chemotherapy and radiation treatment.

3.5.1 Surgery

Most people with bowel cancer have an operation to remove as much of the cancer as possible. This may happen straight after getting the diagnosis, or after having chemotherapy and/or radiation treatment for a few months first (for example, if the cancer is in the rectum). Whether an operation is best for the person, and the type of operation, depends on the size of the cancer and how far it has spread, their general health, and their personal choice.

Surgery can either be a traditional operation through a long incision in the abdomen, or by ‘keyhole surgery’ (laparoscopy). Laparoscopy should only be done in hospitals with special expertise in this technique and by surgeons with the right training and skill.

Before the operation, the person will have a medical assessment, including blood tests, so that any problems such as anaemia, iron deficiency or malnutrition can be treated before the operation. Blood clots in people having surgery for bowel cancer should be prevented by using compression stockings, machines to keep the blood flowing to the legs (sequential compression devices), and blood-thinners such as low molecular-weight heparin. These preventive measures may need to be continued for 4 weeks after surgery.

Infections in the surgical wound are common after bowel cancer surgery. Some surgeons try to reduce the risk of infection by using laxatives to empty the bowel before surgery (mechanical bowel preparation).

Sometimes the low part of the bowel close to the anus needs to be removed, but this is uncommon. If this is necessary, the person can no longer pass bowel motions (stool, poo) through their rectum and anus. When this happens, the surgeon makes a new opening (stoma) in the abdominal wall, which can be attached to a colostomy bag to collect faeces, instead of going to the toilet the normal way. Anyone who needs (or might need) a stoma should see a stomal therapist before their operation, and should be given education and support afterwards to take care of their stoma.

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3.5.2 Chemotherapy and radiation treatment

Chemotherapy uses drugs to kill cancer cells in the body. There are many different chemotherapy drugs and several different standard combinations. The best combination for a person with bowel cancer depends on how far the cancer has spread, the type of cancer, their age, and their general health. The oncologist and pathologist will look at the genetic mutations in the cancer to decide which chemotherapy drugs will work best. Radiation uses x-rays to kill cancer cells and is a common treatment for rectal cancer. Whether or not it is suitable for someone with bowel cancer depends on how far the cancer has spread, as well as other factors. If radiation is used, it is usually done before surgery.

When chemotherapy or radiation treatment is given before surgery for rectal cancer, the aim is to reduce the size of the cancer before it is operated on and minimse the risk of leaving any microscopic cells behind. This is called neoadjuvant therapy. In some cases the cancer may completely respond to this treatment. This is not common and can never be confirmed without surgery and examination of the specimen that has been removed. When chemotherapy and/or radiation treatment is given after surgery, it is called adjuvant treatment.

Chemotherapy after surgery is the standard treatment for people with colon cancer that has spread beyond the bowel, especially where it has spread to the lymph nodes but has not spread further. For people with colon cancer that has not spread to the lymph nodes, chemotherapy after surgery has not been proven to improve outlook, but there may be specific groups of people who this could help.

For people with rectal cancer, both chemotherapy and radiation are common treatments. Chemotherapy is often given alongside radiation treatment to boost the effect of the radiation, and both treatments are given together over a course of several weeks. The combination of chemotherapy and radiation (chemoradiation) is recommended before surgery for most people with rectal cancer, to reduce the risk of the cancer returning. Surgery should be planned for 6–12 weeks after chemoradiation. Radiation treatment might be given on its own if the person is too unwell to cope with the combination of chemotherapy and radiation, or for people having shorter radiation treatment (‘short-course’ radiation).

Chemotherapy after surgery for rectal cancer aims to kill any remaining cancer cells that are invisible to the surgeon but could spread afterwards. However, the benefits are not as well proven for rectal cancer. For people with rectal cancer, their team of health professionals will assess various factors before recommending a treatment plan. Chemoradiation after surgery should be considered if a person has a high risk of rectal cancer returning and they did not have chemoradiation before their surgery.

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3.6 Follow-up after surgery

After surgery for bowel cancer, there is a chance that the cancer could come back (recurrence) due to microscopic cells undetectable to the surgeon and radiologist. The chance of recurrence depends on how advanced the cancer is and if the cancer was removed completely at surgery. As treatment for cancer gets better and better, recurrence rates are getting lower.

Recurring bowel cancer may or may not cause symptoms. The purpose of follow-up after surgery is to find new or regrowing cancer early so they can be treated. Check-ups should be done at regular intervals for 5 years after surgery. Surgeons, gastroenterologists, GPs and nurses can work together to provide thorough check-ups. Tests may include physical examination, regular colonoscopy, CT scans, and blood tests, including measuring the amount of carcinoembryonic antigen (CEA), which can indicate that there is a cancer.

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3.7 What happens if bowel cancer returns or spreads?

If cancer comes back after surgery, it can be confined to the bowel or bowel area, or it could be discovered after it has already spread (metastasised) in the blood or lymph vessels. The liver and lungs are the most common places to find these bowel cancer growths (metastases).

If the results of a person’s routine check-ups make their doctor suspect the bowel cancer has returned, more tests will be done. These tests could include another CEA blood test, CT scan of the chest, abdomen and pelvis, and positron emission tomography (PET scan). Other tests, such as magnetic resonance imaging (MRI scans), may also be needed.

If rectal cancer returns and is confined to the area around the rectum, the person will have the best chance of long-term survival if they have surgery to completely remove the cancer (pelvic exenteration), at a hospital that has the skills to do this operation. Chemoradiation before surgery should also be considered if not given previously. The risks and benefits should be carefully explained to the person before choosing surgery. If bowel cancer has spread to the liver or lungs, there is still a chance that it could be treated. Liver surgery to remove as much cancer as possible is the best option to improve the person’s chance of survival if there is cancer in the liver. If possible, chemotherapy may be given after liver surgery. If surgery is not possible because the cancer has spread too far in the liver, other treatments are available to destroy colon cancer cells in the liver. These include using radiation inside the liver, using chemotherapy and blocking blood vessels in the liver, using heat to kill cancer cells, injecting chemotherapy drugs into the liver artery, and special radiation treatment techniques. These techniques may be offered in some hospitals.

For people with bowel cancer that is not curable by surgery, treatment aims to prolong life and improve or maintain quality of life. Treatment can include surgery to prevent other problems like bleeding and blockage of the bowel, chemotherapy, radiation treatment, or a combination of these. Many different medicines and chemotherapy combinations are used to treat people with bowel cancer that has spread throughout the body (metastatic bowel cancer). The timing and combinations of drugs will vary between individuals, based on the patient and the results of pathology tests and genetic tests. Doctors should always discuss the side effects and the likely results of various treatments with the patient.

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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 16 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]

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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 14,962 new cases of colorectal cancer were diagnosed in Australia in 2013 (8,214 males and 6,748 females). In comparison, there were 6,986 new cases diagnosed in 1982.[2]

The age-standardised incidence rate for colorectal cancer has remained stable from 58.2 per 100,000 persons in 1982 to 57.7 cases per 100,000 persons in 2013 (67.6 for males and 48.8 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 2014, 4,071 deaths from colorectal cancer in Australia (2,236 males and 1,835 females) were recorded.[10] In comparison, there were 2500 deaths recorded in 1968.[10] The age-standardised mortality rate for colorectal cancer decreased from 31 deaths per 100,000 persons in 1968 to 14.9 deaths per 100,000 in 2014 (18.1 for males and 12.1 for females).[10]

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 for national statistics 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]

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4.2.2 Age and sex

The trend in age-specific incidence rates for colorectal cancer in 2013 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 49 years and under (with only 9% of cases diagnosed in those aged under 49 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, 2013

Source: Australian Institute of Health and Welfare (2017).[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 (0.7% per year).[2] However, over the same period the number of newly diagnosed cases of colorectal cancer increased by 20% in males, and 23% 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, 1982–2013

Source: Australian Institute of Health and Welfare (2017).[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 2014 were observed in the oldest age groups, with those aged 80–84 demonstrating a rate of 132.7 deaths per 100,000 population, and those aged 85 years and over demonstrating a rate of 212.5 deaths per 100,000 (Figure 1.3).[2] Approximately 30% of all colorectal cancer deaths occurred in those aged between 50 and 69 years (1218 deaths). While death from colorectal cancer was relatively uncommon among those aged less than 50 years (213 deaths; 5%).[2]

Figure 1.4 shows the time trends in mortality from colorectal cancer in Australian men and women.[2] Between 1995 and 2014 there was a decline in the age-standardised mortality rate, which fell by an average of 2.5% per year overall.[2]

4.2.2.3 Figure 1.3 Age-specific mortality rates for colorectal cancer, Australia, 2014

Source: Australian Institute of Health and Welfare (2017)[2]

4.2.2.4 Figure 1.4 Age-standardised mortality rates for colorectal cancer, Australia, 1968–2014

Source: Australian Institute of Health and Welfare (2017).[2] The incidence (or mortality) rate has been age-standardised to the Australian population (ASR) at 30 June 2001.

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4.2.3 Socioeconomic status

In the 5 years from 2008 to 2012, those living in the most disadvantaged areas of Australia accounted for the highest age-standardised incidence rate for colorectal cancer (65 per 100,000).[11]

In the 5 years from 2010 to 2014, 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).[11]

[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.

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4.2.4 Remoteness area

In the 5 years from 2008 to 2012, people living in outer regional areas of Australia had the highest age-standardised incidence rate for colorectal cancer (67.9 per 100,000).[11]

Between 2010 and 2014, age-standardised mortality rates[ii] for colorectal cancer were highest in Outer regional areas of Australia, with 16 deaths per 100,000. Age-standardised mortality rates were lowest in Very remote areas (10.9 deaths per 100,000).[11]

[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.

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4.2.5 State and territory

The incidence of colorectal cancer varied between jurisdictions in the period between 2008 and 2012. Tasmania (74 cases per 100,000 persons) and Queensland (63 cases per 100,000 persons) had the highest age-standardised incidence rates, while Western Australia (58 cases per 100,000 persons) and the Northern Territory (51 cases per 100,000 persons) had the lowest.[11]

Between 2010 and 2014, Tasmania had the highest age-standardised mortality rate[ii] for colorectal cancer (19 deaths per 100,000 population), while Western Australia had the lowest (13 deaths per 100,000 population).[11]

[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.

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4.2.6 Aboriginal and Torres Strait Islander peoples

Between 2008 and 2012, 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 an average of 116 new cases per year, based on National Mortality Database data from New South Wales, Victoria, Queensland, Western Australia, and the Northern Territory.[11]

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 0.9.[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 2010–2014, the age-standardised mortality rate for colorectal cancer was lower for Aboriginal and Torres Strait Islander people (11.5 deaths per 100,000) than for non-Indigenous Australians (15.5 deaths per 100,000), based on National Mortality Database data from New South Wales, Queensland, Western Australia, South Australia and the Northern Territory.[11]

[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.

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4.3 Colorectal cancer screening

The early detection of colorectal cancer through population screening programs is associated with earlier stage at diagnosis, better treatment options. 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.[16] The program has been phased in gradually, and by 2020, will offer free biennial screening to everyone aged between 50 and 74 years.

In addition to the NBCSP, there are, currently, other ways that Australians can participate in screening for colorectal cancer, although these programs don't provide a reminder service for follow-up of positive screening tests. In conjunction with their general practitioner, individuals can purchase FOBT kits from many pharmacies without prescription, or obtain a kit from non-government organisations such as some Cancer Councils[17] or from community or consumer organisations such as Rotary or Bowel Cancer Australia.

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4.3.1 Screening participation rates in the general population

Of the 2,607,502 FOBT invitation kits that were sent out to eligible individuals (50-74 years) between 2014 /2015, a total of 1,013,040 people participated in the program by returning a completed FOBT for analysis.[18] Therefore, the overall Australia-wide crude participation rate was 38.9 %.[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.[17]

The national participation rate of 38.9 % for 2014–2015 was slightly higher when compared with the previous rolling 2-year period (2013–2014), which had a participation rate of 37%.[11]11 In addition, the participation rate was highest for individuals receiving their second or later (subsequent) screening invitation ((42% 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).[19] 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.[19] 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.[19] 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.[19]

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4.3.2 Screening participation rates by population subgroups

Data regarding NBCSP participation in certain population subgroups are incomplete or unavailable. Some participants, such as Aboriginal and/or Torres Strait Islanders, people with a disability or people who speak a language other than English at home must self-identify this on the participant details form. It is not possible to accurately report NBCSP participation rates for these subgroups.[16]

4.3.3 Screening participation rates by state and territory

In 2013–2014, NBCSP participation rates[iii] did vary by state and territory.[16] 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.[16]

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.[16] 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.

[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.

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4.3.4 Screening participation rates by age and sex

Participation rates[iii] 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).[16]

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.[20]

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).[16] Participation rates were lowest in 50 year-old men.[16]

[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.

4.3.4.1 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)[16]

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4.3.5 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[iii], when compared with those living in all other areas rated according to level of socioeconomic status (Figure 1.6).[16]

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.[21] 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.[21] Similarly, a study in South Australia demonstrated a general pattern of lower screening participation in more disadvantaged socioeconomic groups.[20] 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.[20]

[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.

4.3.5.1 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)[16]

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4.3.6 Screening participation rates by remoteness area

Over 66% of all participants came from Major cities (with a 36.6% crude participation rate[iii]).[16] 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).

[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.

4.3.6.1 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)[16]

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

4.4.1 Survival

In 2009-2013, the 5-year relative survival for colorectal cancer in the Australian population was 68.7% (68.1% for males and 69.4% for females) (Figure 7.8).[11] Five-year relative survival has improved between 1984-1988 and 2009-2013; increasing by 19% from 49.7% to 68.7%.[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 [22] as well as the availability of new chemotherapeutic and biologic treatment agents.[23] 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).[16]

4.4.1.1 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]

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4.4.2 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]

4.4.2.1 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]

4.4.2.2 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]

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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 are 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 Chapter subsections

Please see:

- Dietary and lifestyle strategies
- Chemopreventive candidate agents (PPR1)

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;.
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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]

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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.

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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]
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

Strength of association	Decreases risk	Increases risk
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.

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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]

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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]

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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]

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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]

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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]

5.2.1.5.4 Folic acid

A joint position statement between Cancer Council Australia and the Cancer Society of New Zealand[43] on folate and cancer risk, including folic acid supplementation, was published in August 2010 and updated in March 2014. The statement included evidence from a review of recommendations for folic acid supplementation by the Scientific Advisory Committee on Nutrition of the British Food Standards Agency.[44] The British review included publications from the Aspirin/Folate Polyp Prevention Study[45][46] and an ecological study highlighting a temporal association between folic acid fortification and an increase in bowel cancer incidence in the USA and Canada.[47]

The position statement included the following recommendation in relation to folic acid fortification:

Based on current evidence, the benefits of folic acid fortification for reducing the incidence of neural tube defects outweigh any potential increased risk of cancer. Therefore the Cancer Society of New Zealand and Cancer Council Australia are not opposed to mandatory fortification of foods with folic acid. However careful monitoring of emerging evidence on any adverse effects of folic acid fortification, particularly cancer incidence, is required.

The Cancer Society of New Zealand and Cancer Council Australia support the respective government guidelines for food and nutrition (New Zealand Food and Nutrition Guidelines and Australian Dietary Guidelines[48]) and recommend people obtain their nutritional requirements from whole foods, such as fruits, vegetables, breads and cereals rather than individual nutrients in a supplement form.

People with existing bowel adenomas and those with an increased risk of developing bowel adenomas should avoid taking high-dose (above the upper limit of 1mg per day[49]) supplements that contain folic acid".[43]

Practice point

Folic acid intake outside pregnancy should not exceed 1mg per day and those with a history of colorectal adenomas should not take more than 200mcg as a supplement.

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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.[50] 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.[51] 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.[52]

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.

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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][53][54] 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.[55] Another meta-analysis found a similar inverse relationship between colonic adenoma risk and physical activity.[53][54]

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.[53][19][56]

Increasing exercise after non-metastatic colorectal cancer treatment was associated with reduced risk of colorectal cancer-specific and overall mortality for women and men[57][58] 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.[59]

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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.
Diet	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.
	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.

Factor	Key message
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.

Practice point

It is recommended to follow the primary prevention messages from the World Cancer Research Fund /American Institute for Cancer Research on tobacco smoking, alcohol, diet, body fatness, physical activity (see Table 2.3).

Next section: Aspirin for prevention of colorectal cancer

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5.2.3 References

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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? (PPR1)

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.

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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.

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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]

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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.

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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.

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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]

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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]

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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]

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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 and clinical evidence that gastric mucosal injury is attenuated with repeated administration of aspirin over time.[22][23][24]
- 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.[25]

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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], [26], [5], [6], [7], [8], [27], [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], [26], [5], [6], [7], [8], [27], [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]
Potential harms of aspirin Aspirin was shown to be associated with increased incidence of the following adverse events: ■ dyspepsia ■ peptic ulcer ■ bleeding diathesis	I, II	[3], [26], [5], [18], [10], [11]

Evidence summary	Level	References
■ gastrointestinal haemorrhage (such as associated with use of oral anticoagulants or antiplatelet agents). Aspirin should be avoided in those with: ■ aspirin allergy ■ renal impairment.		
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 predominantly 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], [26], [5], [6], [7], [8], [27], [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	II	[1], [2]

Evidence summary	Level	References
The dose demonstrated in the pivotal CAPP2 trial was 600 mg daily taken for at least 2 years.		
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 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**

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5.3.2.2.3.1 Considerations in making these recommendations

There was robust discussion within the chapter subcommittee regarding the clinical background of the participants in the reported randomised controlled trials; the gender imbalance across these trials; and the potential harms and benefits of taking aspirin, both in the context of colorectal cancer prevention, prevention of other cancers, and the role of aspirin in preventing cardiovascular events. However the group was able to come to a decision about the guidance in this chapter, based on the interpretation of the systematic review evidence.

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.

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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[28] 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.

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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).

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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.

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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 colorectal cancer (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.

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5.3.2.4.2 Studies currently underway

CAPP3[25] 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.[29]

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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. Potential future research questions include:

- Is there evidence of differential benefit of aspirin on preventing sessile serrated versus pedunculated polyps?
- Is there benefit if people start taking aspirin at 40 years of age, to prevent the increase in CRC that is currently seen after age 50 years? (Current evidence suggests a 10 year lag time before CRC prevention is evident.)

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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)[30]
- the Continuous Update Project (CUP) review of food, nutrition and physical activity in the prevention of colorectal cancer (2011).[31]

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.

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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)

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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.[32] 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.[33] Despite these inconsistent and findings, the accumulating clinical evidence still suggests a significant association between statin usage and reduced colorectal cancer risk.[33]

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.[34]

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).[35] 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.[36]

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.

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5.3.3.1.3 Metformin

Patients with diabetes mellitus have an increased risk of colorectal cancer.[37] 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.[38] 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.[39][40] 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, $p = 0.154$).[41]

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.

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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.[42] 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.[42]

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.[43][44][45] 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.[43] 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).[44] 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).[45]

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.[46] [47] 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),[48] 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).[49]

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

Bisphosphonates cannot be recommended for chemoprevention.

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5.3.3.3 Appendices

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6 Population screening for colorectal cancer

Contents

6.1 Background

Colorectal cancer is an exemplar disease for population screening. It is one of only three cancers – the others being cancers of the female breast and the cervix – which satisfies all 10 of the World Health Organization's principles of screening:[1]

1. It is an important health problem.[2]
2. There is a recognisable latent or early symptomatic stage.
3. Its biology is generally well understood.
4. There should be an accepted treatment for patients with recognised disease.
5. Effective and accurate screening tests are available.
6. The screening test is considered acceptable to the population.
7. There is agreement on who should be screened.
8. Facilities for diagnosis and treatment are available.
9. There is an economically balanced case for screening in relation to expenditure on healthcare as a whole.[3]
10. Screening is a continuous process.[1]

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 invitees with colorectal cancer symptoms to consult a GP rather than undergo a screening test.

Ideally, centrally organised population programs should 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, and evaluation of outcomes and cost-effectiveness, as well as assessment of the quality of each step in the screening pathway.[4][5][6][7] Screening for colorectal cancer now has widespread acceptance at an international level, although local circumstances affect program design and choice of screening test.[8] Many national programs, especially those in Europe, Canada and Australasia, utilise organised population screening rather than opportunistic approaches.[9]

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6.1.1 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 years).[10] 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 recommended screening cohort.[11]

The Australian Government introduced the National Bowel Cancer Screening Program (NBCSP) in 2006, with a mail-out of immunochemical faecal occult blood test (iFOBT, also known as faecal immunochemical tests or FITs) kits to Australians turning 55 and 65 from August that year. This marked the commencement of an incremental roll-out, expanding the program as capacity increased and working towards coverage of the 50–74 years age group by 2020 (see Table 3.1).[12]

The key elements of the NBCSP are:[12]

- the use of 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 collation of data and reporting of NBCSP outcomes via regular reports.

See the NBCSP participant's screening pathway.

6.1.1.1 Table 3.1 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

Source: Australian Institute of Health and Welfare[12]

Extensive published research has shown that the NBCSP, even in its incomplete form, is having a significant impact on reducing colorectal cancer burden. Key findings include:

- a favourable shift in pathological stage in screen-detected cancers [13][14][15]
- modelling studies supporting both marked cost-effectiveness[16] and a considerable impact on colorectal cancer mortality[17]
- data linkage studies demonstrating that NBCSP invitees, especially those who participated in the program, have a lower risk of dying from colorectal cancer.[15][18]

Screening infrastructure in the NBCSP is being progressively strengthened to improve its efficiency and effectiveness. Recent initiatives include the development of a new, interactive central register (the National Cancer Screening Register [NCSR]), public awareness campaigns and measures to boost training and quality of colonoscopy. On current evidence, the most significant barrier to improved program effectiveness is the relatively low participation rate (37% of all invitees at December 2014).[19]

There is, as a matter of course, a requirement to continually review screening policy (screening test, interval, pathway, cohort, etc.) for optimal population benefit as new evidence is published. In 2015 the Australian Commonwealth Department of Health commissioned a review of national guidelines for population screening for colorectal cancer, as part of the revision of the 2005 NHMRC-approved Clinical practice guidelines for the prevention, early detection and management of colorectal cancer.[20]

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. In addition to systematic reviews of published clinical evidence, modelling studies were commissioned to evaluate the cost-effectiveness of alternate technology options for screening and the optimal target age range.

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6.1.2 Screening benefit

The primary aims of colorectal cancer screening are to reduce the morbidity and mortality of the disease through (1) earlier detection of cancer and (2) prevention of cancer through detection and removal of pre-malignant adenomas.[20] Such screening can be provided on an individual basis (opportunistic screening) or for populations through centrally organised programs.

Opportunistic screening has been adopted as the preferred approach in some health settings, particularly in the USA.[21][22] 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.[4] This potentially increases the impact on colorectal 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.

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6.1.3 Screening test accuracy

There are a number of tests designed to detect signs of colorectal cancer in asymptomatic patients, with differing performance, costs, acceptability and risks.[10] These include:

- faecal tests – faecal occult blood tests (FOBTs) to detect bleeding arising from cancers or adenomas, or newer technologies involving detection of DNA mutations shed by cancer (faecal DNA test)
- endoscopic tests to directly visualise mucosal abnormalities (flexible sigmoidoscopy, colonoscopy)

- computed tomography (CT) colonography to detect anatomical abnormalities with x-ray
- plasma tests to detect cancer biomarkers.

There are two types of FOBTs:[23][24]

- immunochemical FOBTs (iFOBTs), which directly detect haemoglobin, using antibodies specific for the globin moiety of human haemoglobin (used by the NBCSP since its onset)
- guaiac FOBTs (gFOBTs) detect peroxidase activity, an indirect method for identification of haemoglobin.

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 cancer.[25][26][27][28][29] Subsequent meta-analyses provided Level I evidence for a 15–30% reduction in mortality.[30][31] High-level evidence for effectiveness has now become available for one-time flexible sigmoidoscopy,[32][33][34][35] with reductions in colorectal cancer-related mortality. However, the other modalities have yet to undergo comparable trials and thus the evidence base to support effectiveness relies primarily on observational data. Three RCTs to evaluate colonoscopy are currently in progress.[36][37][38]

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6.1.4 The balance of benefits, harms and 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.

A recent comparative modelling evaluation conducted on behalf of the US Preventive Services Task Force used life–years gained as a measurement of effectiveness and the estimated number of colonoscopies as a measurement of burden to compare colorectal cancer screening strategies using eight different screening test technologies.[21] Under the assumption of 100% screening adherence in each case, the evaluation found that, in the US context, the strategies providing the best balance of benefits to harms would be 10-yearly colonoscopy screening, 10-yearly flexible sigmoidoscopy screening combined with annual iFOBT, 5-yearly CTC screening, and yearly iFOBT alone for screening for ages 50–74 years. However, the study did not report on the impact of more realistic adherence assumptions (which could be expected to differ by screening modality and frequency) on either benefits or harms. Furthermore, the cost-effectiveness of the alternative strategies was not considered.

The comparative benefits, harms and cost-effectiveness of the NBCSP in Australia have recently been estimated compared to other potential future alternative or adjunctive options for screening in Australia.[39] 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.

The modelling is described in detail in the Technical report.

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6.1.5 Screening age

The early RCTs on gFOBT-based screening showed benefit for people aged 45–50 years and older.[40][41][42][43][25][28][29][26][27] Cost-effectiveness studies also demonstrate that the age range for screening influences cost-effectiveness. [12] The risk of colorectal cancer increases with age, as shown in Table 3.2. The observation that 10-year risk increases 4-fold between ages of 40 and 50 years has 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.[12][13][14][15][16][17]

The recently published US Preventive Services Task Force 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.[22] They observed a diminishing benefit and a greater risk of adverse events after age 75.

When complete in 2020, the NBCSP will invite the general population aged 50 to 74 to screen. The starting age was based on the low age-specific incidence of colorectal cancer in those below 50 years of age and concern that the risk with follow-up colonoscopy (including the small risk of death from colonoscopy) is much closer to the low risk of colorectal cancer and its mortality in those less than 50.[44]

This review re-examines evidence on the appropriate age range for screening, prompted by suggestions of an increase in risk for colorectal cancer in younger people and the longer life expectancy for the elderly.

A detailed modelled analysis has also been undertaken to quantify the benefits, harms and cost-effectiveness of extending the age range for screening in the Australian context. This analysis concluded that continuing to screen at a population level was no longer cost-effective in people over the age of 74 years (due to the competing mortality risk). For younger people, the analysis found that starting screening at age 45 years could be cost-effective, but the ratio of benefits to harms, expressed as the number-needed-to-colonoscope (NNC) for each death prevented, was far less favourable than when screening people aged 50–74 years. For the existing NBCSP, the estimated NNC is 56 colonoscopies for each death prevented in the program (in a perfectly adherent cohort); thus this is the existing benchmark. For a program starting screening at age 45 years (but still finishing at 74 years), the NNC for each death prevented would be increased to 71 colonoscopies per death prevented (in a perfectly adherent cohort). This is a substantial increase in the NNC over the entire lifetime of those eligible for, and participating in, screening, given that the difference in the period of eligibility is only 5 years.

6.1.5.1 Table 3.2. Absolute risk of colorectal cancer

If a person is aged	Risk of colorectal cancer over the next 10 years			
Men		**Women**		
30	0.074%	1 in 1350	0.072%	1 in 1390
40	0.32%	1 in 313	0.27%	1 in 370
50	1.15%	1 in 87	0.80%	1 in 125
60	2.79%	1 in 36	1.74%	1 in 57

If a person is aged	Risk of colorectal cancer over the next 10 years			
70	4.57%	1 in 22	2.90%	1 in 34

Absolute risk is the observed or calculated probability of the occurrence of colorectal cancer in a population. These risks were calculated from the Australian Institute of Health and Welfare[44] national colorectal cancer incidence data for the year 2000, which included some of the highest incidence in recent years and was prior to roll-out of the National Bowel Cancer Screening Program (NBCSP).

6.1.6 Chapter subsections

Please see:

- Evidence: population screening for CRC
- Evidence summary, recommendations and considerations
- Discussion

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6.3 Appendices

NHMRC Evidence statement form PSC1a

	NHMRC Evidence statement form PSC1b		
Systematic review report PSC1a	Systematic review report PSC1b	Modelling report PSC1c	Modelling report PSC1d

6.1 Introduction: population screening for colorectal cancer

Contents

6.1.1 Background

Colorectal cancer is an exemplar disease for population screening. It is one of only three cancers – the others being cancers of the female breast and the cervix – which satisfies all 10 of the World Health Organization's principles of screening:[1]

1. It is an important health problem.[2]
2. There is a recognisable latent or early symptomatic stage.
3. Its biology is generally well understood.
4. There should be an accepted treatment for patients with recognised disease.
5. Effective and accurate screening tests are available.
6. The screening test is considered acceptable to the population.
7. There is agreement on who should be screened.
8. Facilities for diagnosis and treatment are available.
9. There is an economically balanced case for screening in relation to expenditure on healthcare as a whole.[3]
10. Screening is a continuous process.[1]

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 invitees with colorectal cancer symptoms to consult a GP rather than undergo a screening test.

Ideally, centrally organised population programs should 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, and evaluation of outcomes and cost-effectiveness, as well as assessment of the quality of each step in the screening pathway.[4][5][6][7] Screening for colorectal cancer now has widespread acceptance at an international level, although local circumstances affect program design and choice of screening test.[8] Many national programs, especially those in Europe, Canada and Australasia, utilise organised population screening rather than opportunistic approaches.[9]

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6.1.1.1 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 years).[10] 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 recommended screening cohort.[11]

The Australian Government introduced the National Bowel Cancer Screening Program (NBCSP) in 2006, with a mail-out of immunochemical faecal occult blood test (iFOBT, also known as faecal immunochemical tests or FITs) kits to Australians turning 55 and 65 from August that year. This marked the commencement of an incremental roll-out, expanding the program as capacity increased and working towards coverage of the 50–74 years age group by 2020 (see Table 3.1).[12]

The key elements of the NBCSP are:[12]

- the use of 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 collation of data and reporting of NBCSP outcomes via regular reports.

See the NBCSP participant’s screening pathway.

6.1.1.1.1 Table 3.1 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

Period	Target ages
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

Source: Australian Institute of Health and Welfare[12]

Extensive published research has shown that the NBCSP, even in its incomplete form, is having a significant impact on reducing colorectal cancer burden. Key findings include:

- a favourable shift in pathological stage in screen-detected cancers [13][14][15]
- modelling studies supporting both marked cost-effectiveness[16] and a considerable impact on colorectal cancer mortality[17]
- data linkage studies demonstrating that NBCSP invitees, especially those who participated in the program, have a lower risk of dying from colorectal cancer.[15][18]

Screening infrastructure in the NBCSP is being progressively strengthened to improve its efficiency and effectiveness. Recent initiatives include the development of a new, interactive central register (the National Cancer Screening Register [NCSR]), public awareness campaigns and measures to boost training and quality of colonoscopy. On current evidence, the most significant barrier to improved program effectiveness is the relatively low participation rate (37% of all invitees at December 2014).[19]

There is, as a matter of course, a requirement to continually review screening policy (screening test, interval, pathway, cohort, etc.) for optimal population benefit as new evidence is published. In 2015 the Australian Commonwealth Department of Health commissioned a review of national guidelines for population screening for colorectal cancer, as part of the revision of the 2005 NHMRC-approved Clinical practice guidelines for the prevention, early detection and management of colorectal cancer.[20]

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. In addition to systematic reviews of published clinical evidence, modelling studies were commissioned to evaluate the cost-effectiveness of alternate technology options for screening and the optimal target age range.

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6.1.1.2 Screening benefit

The primary aims of colorectal cancer screening are to reduce the morbidity and mortality of the disease through (1) earlier detection of cancer and (2) prevention of cancer through detection and removal of pre-malignant adenomas.[20] Such screening can be provided on an individual basis (opportunistic screening) or for populations through centrally organised programs.

Opportunistic screening has been adopted as the preferred approach in some health settings, particularly in the USA.[21][22] 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.[4] This potentially increases the impact on colorectal 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.

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6.1.1.3 Screening test accuracy

There are a number of tests designed to detect signs of colorectal cancer in asymptomatic patients, with differing performance, costs, acceptability and risks.[10] These include:

- faecal tests – faecal occult blood tests (FOBTs) to detect bleeding arising from cancers or adenomas, or newer technologies involving detection of DNA mutations shed by cancer (faecal DNA test)
- endoscopic tests to directly visualise mucosal abnormalities (flexible sigmoidoscopy, colonoscopy)
- computed tomography (CT) colonography to detect anatomical abnormalities with x-ray
- plasma tests to detect cancer biomarkers.

There are two types of FOBTs:[23][24]

- immunochemical FOBTs (iFOBTs), which directly detect haemoglobin, using antibodies specific for the globin moiety of human haemoglobin (used by the NBCSP since its onset)
- guaiac FOBTs (gFOBTs) detect peroxidase activity, an indirect method for identification of haemoglobin.

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 cancer.[25][26][27][28][29] Subsequent meta-analyses provided Level I evidence for a 15–30% reduction in mortality.[30][31] High-level evidence for effectiveness has now become available for one-time flexible sigmoidoscopy,[32][33][34][35] with reductions in colorectal cancer-related mortality. However, the other modalities have yet to undergo comparable trials and thus the evidence base to support effectiveness relies primarily on observational data. Three RCTs to evaluate colonoscopy are currently in progress.[36][37][38]

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6.1.1.4 The balance of benefits, harms and 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.

A recent comparative modelling evaluation conducted on behalf of the US Preventive Services Task Force used life–years gained as a measurement of effectiveness and the estimated number of colonoscopies as a measurement of burden to compare colorectal cancer screening strategies using eight different screening test technologies.[21] Under the assumption of 100% screening adherence in each case, the evaluation found that, in the US context, the strategies providing the best balance of benefits to harms would be 10-yearly colonoscopy screening, 10-yearly flexible sigmoidoscopy screening combined with annual iFOBT, 5-yearly CTC screening, and yearly iFOBT alone for screening for ages 50–74 years. However, the study did not report on the impact of more realistic adherence assumptions (which could be expected to differ by screening modality and frequency) on either benefits or harms. Furthermore, the cost-effectiveness of the alternative strategies was not considered.

The comparative benefits, harms and cost-effectiveness of the NBCSP in Australia have recently been estimated compared to other potential future alternative or adjunctive options for screening in Australia.[39] 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.

The modelling is described in detail in the Technical report.

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6.1.1.5 Screening age

The early RCTs on gFOBT-based screening showed benefit for people aged 45–50 years and older.[40][41][42][43][25][28][29][26][27] Cost-effectiveness studies also demonstrate that the age range for screening influences cost-effectiveness. [12] The risk of colorectal cancer increases with age, as shown in Table 3.2. The observation that 10-year risk increases 4-fold between ages of 40 and 50 years has 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.[12][13][14][15][16][17]

The recently published US Preventive Services Task Force 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.[22] They observed a diminishing benefit and a greater risk of adverse events after age 75.

When complete in 2020, the NBCSP will invite the general population aged 50 to 74 to screen. The starting age was based on the low age-specific incidence of colorectal cancer in those below 50 years of age and concern that the risk with follow-up colonoscopy (including the small risk of death from colonoscopy) is much closer to the low risk of colorectal cancer and its mortality in those less than 50.[44]

This review re-examines evidence on the appropriate age range for screening, prompted by suggestions of an increase in risk for colorectal cancer in younger people and the longer life expectancy for the elderly.

A detailed modelled analysis has also been undertaken to quantify the benefits, harms and cost-effectiveness of extending the age range for screening in the Australian context. This analysis concluded that continuing to screen at a population level was no longer cost-effective in people over the age of 74 years (due to the competing mortality risk). For younger people, the analysis found that starting screening at age 45 years could be cost-effective, but the ratio of benefits to harms, expressed as the number-needed-to-colonoscope (NNC) for each death prevented, was far less favourable than when screening people aged 50–74 years. For the existing NBCSP, the estimated NNC is 56 colonoscopies for each death prevented in the program (in a perfectly adherent cohort); thus this is the existing benchmark. For a program starting screening at age 45 years (but still finishing at 74 years), the NNC for each death prevented would be increased to 71 colonoscopies per death prevented (in a perfectly adherent cohort). This is a substantial increase in the NNC over the entire lifetime of those eligible for, and participating in, screening, given that the difference in the period of eligibility is only 5 years.

6.1.1.5.1 Table 3.2. Absolute risk of colorectal cancer

If a person is aged	Risk of colorectal cancer over the next 10 years			
Men		**Women**		
30	0.074%	1 in 1350	0.072%	1 in 1390
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6.1.1.6 Chapter subsections

Please see:

- Evidence: population screening for CRC
- Evidence summary, recommendations and considerations
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6.1.2 References

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6.1.3 Appendices

NHMRC Evidence statement form PSC1a

Systematic review report PSC1a	NHMRC Evidence statement form PSC1b		
	Systematic review report PSC1b	Modelling report PSC1c	Modelling report PSC1d

6.2 Evidence: Population screening for CRC

Systematic reviews and modelling were performed to determine:

- the benefit of screening with various modalities (PSC1a)
- test accuracy (PSC1b)
- the cost-effectiveness of population screening using various strategies (PSC1c)
- the optimal target age range for population screening (PSC1d).

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6.2.1 Evidence: Screening benefit (PSC1a)

Contents

6.2.1.1 Systematic review evidence

In persons without a colorectal cancer diagnosis or symptoms that might indicate colorectal cancer, which screening modality (immunochemical faecal occult blood test [iFOBT], flexible sigmoidoscopy, colonoscopy, CT colonography, faecal or blood biomarkers, or any combinations) compared with no screening, reduces colorectal cancer mortality, or the incidence of metastases at diagnosis? (PSC1a)

A systematic review was performed to update the 2005 Australian guidelines for the prevention, early detection and management of colorectal cancer.[1]

We identified later relevant evidence-based guidelines which conducted systematic reviews of the literature for the period 2004–2010:

- the International Agency for Research on Cancer's *European guidelines for quality assurance in colorectal cancer screening and diagnosis* (2010)[2]
- the Ontario Ministry of Health and Long-term Care's *Fecal occult blood test for colorectal cancer screening: evidence-based analysis* (2009).[3]
- the Ontario Ministry of Health and Long-term Care's *Flexible sigmoidoscopy for colorectal cancer screening: an evidence-based analysis* (2009).[4]

We chose to adapt these three guidelines, updating the systematic literature review 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 published the 2016 update[5] of its 2008 colorectal cancer screening guidelines.[6] The literature described in the 2016 edition[5] is also covered in this review.

At the time of publication of the 2005 Australian Guidelines[1] the only high level evidence of screening benefit was from three randomised controlled trials (RCTs).[7][8][9][10][11][12] All three RCTs used Hemoccult, a guaiac faecal occult blood test (gFOBT). 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% (noting that the trials

involved differing numbers of rounds of screening and differing follow-up periods). These findings are further supported by a 2012 update from the Nottingham trial of faecal occult blood testing for colorectal cancer [13] which, after a median of 19.5 years' follow-up, reported a colorectal cancer-specific mortality reduction of 13%. To date, only one published RCT[14] has compared immunochemical faecal occult blood test (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.

The update systematic review identified four level II RCTs reported in 5 articles comparing outcomes for an asymptomatic population receiving flexible sigmoidoscopy with no screening (no contact). [15][16][17][18][19] No RCTs conducted in an asymptomatic population were found which compared any other screening methodology to no screening.

A meta-analysis of pooled data from the United Kingdom Flexible Sigmoidoscopy Screening (UKFSS), Norwegian Colorectal Cancer Prevention (NORCCAP), Italian '**SC**reening for **CO**lon**RE**ctum' (SCORE) and US Prostate, Lung, Colorectal and Ovarian (PLCO) trials was also identified.[20] This meta-analysis was at low risk of bias, and reported colorectal cancer-specific mortality, with subgroup analysis for distal and proximal disease.

6.2.1.1.1 Overall (all-cause) mortality

None of the screening RCTs,[7][8][9][15][16][14][18] whether based on screening by FOBT or flexible sigmoidoscopy, reported any significant difference in overall (all-cause) mortality.

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6.2.1.1.2 Colorectal cancer-specific mortality

As reported in the review supporting the 2005 Colorectal Cancer guidelines,[1] three level II RCTs reported colorectal cancer-specific mortality in gFOBT screening trials.[7][8][9] These trials, which involved 1–11 rounds of screening, collectively reported that screening for faecal occult blood reduced overall colorectal cancer-specific mortality on the basis of intention-to-screen by 15–33%. The 2012 update from the Nottingham trial[13] reported a colorectal cancer-specific mortality reduction of 13% at approximately 20 years follow-up. A 2003 Chinese RCT [14] 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. Colonoscopy was only performed in those participants with a positive iFOBT when flexible sigmoidoscopy failed to reveal a distal lesion and then only if a second round iFOBT proved to be positive (0.16%).[14]

In this update review of the flexible sigmoidoscopy trials, the UKFSS,[17] and PLCO[16] trials both reported a statistically significant reduction in colorectal cancer specific mortality in the screened group compared with the control (no screening) group after a single round of sigmoidoscopy screening and screening with follow-up durations from 7–12 years. The relative reduction in colorectal cancer-specific mortality varied from hazard ratio

(HR) 0.57[17] to relative risk (RR) 0.74.[16] In the final NORCCAP trial report[18] 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 sigmoidoscopy.[18] In sub-analysis according to the screening modality, the overall reduction in colorectal cancer-specific mortality was statistically significant only for those who had both flexible sigmoidoscopy and iFOBT (HR = 0.62, p = 0.01) and not for flexible sigmoidoscopy alone (HR = 0.84, p = 0.30).

The meta-analysis[20] of pooled data from the UKFSS,[17] NORCCAP,[19] SCORE,[15] and PLCO[16] trials included data from a population of 337,905 participants with an average weighted median follow-up period of 10.8 years. It showed a statistically significant reduction in colorectal cancer-specific mortality in flexible sigmoidoscopy screened group, compared with the non-screened group: 28% relative risk reduction (RR = 0.72; 95% confidence interval (CI) 0.65 to 0.80).

All populations included in this update systematic review[15][16][17][14][18][19][20], were asymptomatic and from Western countries (UK, Sweden, Norway, USA, Italy), except for one RCT conducted in a Chinese population.[14] The early gFOBT screening trials[10][11][12] included participants from USA, UK, and Denmark.

In three flexible sigmoidoscopy trials,[15][16][17] those involved were volunteers who expressed willingness to accept flexible sigmoidoscopy if randomised to the screening arm. Reported participation rates may therefore over-estimate participation rates achievable in the general population.

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6.2.1.1.3 Application of the evidence on screening benefit

To date, the only RCT level evidence comparing screening with an unscreened control group comes from three large gFOBT trials[7][8][9] first reported in the 1990s, one iFOBT trial,[14] and the recent flexible sigmoidoscopy trials.[15][16][17][18][19][20]

Currently, many countries around the world, including Australia, New Zealand, Canada, and a number of European countries, have established national population-based colorectal cancer screening programs that 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 diagnosis,[2] 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 brands of iFOBT 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.

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

Next section: screening test accuracy

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6.2.2 Evidence: Screening test accuracy (PSC1b)

Contents

6.2.2.1 Systematic review evidence

For persons without a colorectal cancer diagnosis or symptoms that might indicate colorectal cancer, which screening modality (immunochemical faecal occult blood test [iFOBT], flexible sigmoidoscopy, colonoscopy, faecal or blood biomarkers, or any combination) performs best in detecting colorectal cancer, and does the diagnostic performance change with family history, age, or sex? (PSC1b)

A systematic review was performed to update the 2005 Australian guidelines for the prevention, early detection and management of colorectal cancer.[1]

We identified later relevant evidence-based guidelines which conducted systematic reviews of the literature for the period 2004–2010:

- the International Agency for Research on Cancer's *European guidelines for quality assurance in colorectal cancer screening and diagnosis* (2010)[2]
- the Ontario Ministry of Health and Long-term Care's *Fecal occult blood test for colorectal cancer screening: evidence-based analysis* (2009).[3]
- the Ontario Ministry of Health and Long-term Care's *Flexible sigmoidoscopy for colorectal cancer screening: an evidence-based analysis* (2009).[4]

We chose to adapt these guidelines, updating the systematic literature review 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 published the 2016 update[5] of its 2008 colorectal cancer screening guidelines.[6] The literature described in the 2016 edition[5] is also covered in this review.

Our update systematic review identified 29 diagnosis accuracy studies[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] reporting the performance of colorectal cancer screening modalities, including immunochemical FOBT (iFOBT) and faecal or plasma 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 studies[8][9][10] (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 iFOBTs of various brands. Very few studies reported blood/plasma cancer-specific biomarkers, or faecal cancer-specific biomarkers. Only three studies[11][12][34] reported the performance of multi-target faecal DNA tests. One study[13] reported the diagnostic performance of the faecal cancer-specific biomarker MMP-9 protein, and another[14] reported the diagnostic performance of plasma cancer-specific biomarker SEPT9 methylated DNA. Several studies reported the diagnostic performance of iFOBT [15][16] or the SEPT9[14] cancer-specific biomarker depending on participant age, and a few studies reported the diagnostic performance for iFOBT[15][17] or the SEPT9 cancer-specific biomarker[14] by sex. All participants had a colonoscopy as the reference standard.

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6.2.2.1.1 Immunochemical faecal occult blood test (iFOBT)

The diagnostic performance for detection of colorectal cancer using iFOBT was reported across 20 studies,[7][8][10][12][16][18][19][20][21][22][23][24][25][26][27][28][29][30][34][35] most of which used an Eiken branded test kit. Colorectal cancer prevalence determined by reference colonoscopy was 0.48% in a combined population of 100,093 participants in these 20 studies. All studies consistently reported a sensitivity of greater than 50%, with most studies reporting sensitivities in the 60–85% range. Specificity was consistently high across all 20 studies and ranged from 85% to 100%. The positive predictive value ranged from 1% to 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 studies. [7][12][15][19][20][26][28][29][30][31][32][34][35] The prevalence of advanced adenomas was 4.5% in a combined population of 60,671 participants included in these 13 studies. 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 for adenoma 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.[8][10][16][17][18][22][23][25][27][33] The prevalence of colorectal cancer and/or advanced adenomas was 3.6% in a combined population of 40,272 participants included in these 10 studies. Sensitivities reported ranged from 5% to 75%, but was commonly reported in the range 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 studies[8][9][10] reported the diagnostic performance of iFOBT for the detection of colorectal cancer and/or advanced adenoma in above-average risk populations with known family history of colorectal cancer. These studies reported inconsistent results. No studies reported the use of biomarker assays in this above average risk population.

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6.2.2.1.2 Faecal cancer-specific biomarker (DNA)

One study reported the diagnostic performance of two faecal DNA tests[11] for the detection of colorectal cancer. In addition, two studies[12][34] reported different multi-target faecal DNA assays to detect colorectal cancer.

Both multi-target faecal DNA tests outperformed other faecal DNA tests. One study reported sensitivities above 90%,[12] and the other reported sensitivities ranging from 25% to 58%.[34]

Specificities were above 84% for all tests reported.[11]

Two studies reported the diagnostic performance of faecal DNA tests[11][34] at detecting advanced adenomas. Reported sensitivities ranged from 17% to 46% and specificities ranged from 84% to 96%.

One study[12] reported the diagnostic performance of a multi-target faecal DNA in combination with an iFOBT for detection of colorectal cancer and/or advanced adenomas. Sensitivity and specificity were 42.4% and 86.6% respectively.[12]

No studies reported the use of faecal biomarker assays in an above-average risk population.

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6.2.2.1.3 Blood cancer-specific biomarkers

A single study[14] reported the diagnostic performance of a plasma methylated SEPT9 DNA assay for the detection of colorectal cancer or advanced adenomas. Sensitivities ranged from 48% to 56% and specificity ranged from 89% to 92%, depending on age (< 65 versus ≥ 65 years) or sex analysis for detection of colorectal cancer. Sensitivities ranged from 4.6% to 13% and specificity ranged from 88.6% to 92.6%, depending on age (< 65 versus ≥ 65 years) or sex analysis for detection of advanced adenomas.

No studies specifically reported the diagnostic performance of blood cancer-specific biomarker assays for advance neoplasms (i.e. the combination of cancer and advanced adenomas) or in participants with above-average risk of colorectal cancer.

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

Next section: screening cost effectiveness

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6.2.3 Evidence: Screening cost effectiveness (PSC1c)

Contents

6.2.3.1 Background

The literature review found high-level evidence supporting effectiveness (mortality reduction) of immunochemical faecal occult blood testing (iFOBT) and flexible sigmoidoscopy in population screening for colorectal cancer, compared with no screening. However, there was no high-level evidence evaluating colonoscopy, computed tomography (CT) colonography, or cancer-specific faecal or blood biomarkers.

Future large-scale trials to further evaluate screening strategies are unlikely, due to the cost and necessary duration. When RCT evidence cannot be obtained, modelling studies based on sophisticated understanding of colorectal cancer natural history are an acceptable source of data to guide public health planning decisions.[1][2][3][4][5]

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6.2.3.2 Modelling study findings

In persons without a colorectal cancer diagnosis or symptoms that might indicate colorectal cancer, what is the most cost-effective, feasible and acceptable screening modality (iFOBT, flexible sigmoidoscopy, colonoscopy, CT colonography, faecal or blood biomarkers test, or any combinations) compared with no screening? (PSC1c)

A comprehensive validated model of colorectal cancer development and bowel screening ('Policy1-Bowel') was used to simulate the National Bowel Cancer Screening Program (NBCSP) and alternative screening approaches (Table 3.3). Details of the methods and result can be found in the Technical Report.

The term 'adherence' applies to compliance with recommendations for screening, follow-up and surveillance.

The strategies were evaluated in context of three scenarios:

- Scenario 1 assumes perfect adherence to screening, follow-up and surveillance recommendations.
- Scenario 2 assumes high (but imperfect) participation (participation after first invitation was 57% for screening strategies using iFOBT and faecal/ blood biomarkers test, and was 35% for screening strategies using colonoscopy, sigmoidoscopy and CT colonography).
- Scenario 3 assumes lower participation (participation after first invitation was 27% for screening strategies using iFOBT and faecal/ blood biomarkers test, and was 15% for screening strategies using colonoscopy, sigmoidoscopy and CT colonography).

Specific participation assumptions differed according to screening modality and an individual's screening history and were derived based on currently observed screening participation in Australia and expert opinion for new modalities (see Appendix for details of participation assumptions for each modality).

6.2.3.2.1 Table 3.3 Screening strategies evaluated

Strategy name	Description
No screening (comparator)	No screening
iFOBT2y	iFOBT screening every 2 years at age 50–74 years (NBCSP from 2020)
iFOBT1y	iFOBT screening every year at age 50–74 years
plasmaDNA2y (exploratory modelling based on limited data from a small number of cross-sectional studies; no data on longitudinal outcomes for this technology available)	pDNA screening every 2 years at 50–74 years (pDNA assuming test for methylated SEPT9 DNA, as reported in Church et al 2014).[6]

Strategy name	Description
fDNA2y (exploratory modelling based on limited data from a small number of cross-sectional studies; no data on longitudinal outcomes for this technology available)	fDNA screening every 2 years at age 50–74 years (multi-target faecal testing including iFOBT, assuming test characteristics reported in Imperiale et al (2014).[7]
fDNA5y (exploratory modelling based on limited data from a small number of cross-sectional studies; no data on longitudinal outcomes for this technology available)	fDNA screening every 5 years at age 50–74 years
COL10y	COL screening every 10 years at ages 55, 65 and 75 years
SIG10y	SIG screening every 10 years at ages 55, 65 and 75 years
CTC10y (exploratory modelling based on limited data from a small number of cross-sectional studies; no data on longitudinal outcomes for this technology available)	CTC screening every 10 years at ages 55, 65 and 75 years
SIG@60	Once-off SIG screening at age 60 years
SIG@55_iFOBT2y @60To74	Once-off SIG screening at age 55 years combined with iFOBT every 2 years at age 60–74 years
COL@50_iFOBT2y @52To74	Once-off COL screening at age 50 years combined with iFOBT every 2 years at age 52–74 years^
iFOBT2y+SIG@50	iFOBT screening every 2 years at age 50–74 years (NBCSP from 2020) combined with SIG at age 50 years for negative iFOBT
iFOBT2y+SIG@54_64_74	iFOBT screening every 2 years at age 50–74 years (NBCSP from 2020) combined with SIG at ages 54, 64 and 74 years for negative iFOBT
iFOBT2y+plasmaDNA	iFOBT screening every 2 years at age 50–74 years (NBCSP from 2020) combined with pDNA testing in under-screened individuals^^

COL: colonoscopy; CTC: computed tomographic colonography; iFOBT: immunochemical faecal occult blood test; fDNA: faecal DNA test; pDNA: plasma DNA test; SIG: flexible sigmoidoscopy

Notes:

^: Individuals aged 50 years who do not participate in colonoscopy screening will be invited to have an iFOBT.

^^: Under-screened individuals are those who are not under colonoscopy surveillance and have not had an iFOBT test in the past 4 years (including those who are eligible for screening but have never have a screening test).

No leakage (drop in participation) from main program is assumed after pDNA is offered (a favourable scenario).

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6.2.3.3 Health outcomes (benefits)

6.2.3.3.1 Perfect adherence

When assuming perfect adherence to screening, follow-up and surveillance recommendations (Scenario 1), colorectal cancer screening was predicted to reduce age-standardised risk (in 0-89 years) of colorectal cancer incidence by 23–67% and colorectal cancer mortality by 30–82% (encompassing a range of results, depending on screening technology and screening interval and age range), compared to no screening.

For seven screening strategies, a reduction in age-standardised colorectal cancer mortality risk (in 0-89 years) of greater than 75% was predicted in perfectly adherent cohorts. These strategies were:

- faecal DNA test (fDNA) screening every 2 years at age 50–74 years (82% reduction)
- colonoscopy screening every 10 years at age 55, 65 and 75 years (77% reduction)
- once-only colonoscopy screening at age 50 years combined with iFOBT screening every 2 years at age 52–74 years (80% reduction)
- iFOBT screening every year at age 50–74 years (81% reduction)
- iFOBT screening every 2 years at age 50–74 years (75% reduction)
- iFOBT screening every 2 years at age 50–74 years , with adjunctive flexible sigmoidoscopy at age 50 years for individuals with negative iFOBT results (77% reduction)
- iFOBT screening every 2 years at age 50–74 years, with adjunctive flexible sigmoidoscopy screening at age 54, 64 and 74 years for individuals with negative iFOBT (79% reduction).

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6.2.3.3.2 Imperfect adherence

After accounting for realistic adherence to screening, follow-up and surveillance recommendations:

- When assuming high participation (Scenario 2), colorectal cancer screening was predicted to reduce age-standardised risk (in 0-89 years) of colorectal cancer incidence by 6–48% and colorectal cancer mortality by 7–69%, compared to no screening.

- When assuming low participation (Scenario 3), colorectal cancer screening was predicted to reduce age-standardised risk (in 0-89 years) of colorectal cancer incidence by 3–38% and colorectal cancer mortality by 3–56%, compared to no screening.

Seven strategies predicted a greater than 50% mortality reduction in Scenario 2 (high participation) and greater than 35% reduction in Scenario 3 (low participation):

- fDNA screening every 2 years (63% in Scenario 2; 44% in Scenario 3)
- once-off colonoscopy screening at age 50 years combined with 2-yearly iFOBT screening at 52–74 years (57% in Scenario 2; 40% in Scenario 3)
- iFOBT screening every year at age 50–74 years (69% in Scenario 2; 56% in Scenario 3)
- iFOBT screening every 2 years at age 50–74 years (53% in Scenario 2; 36% in Scenario 3)

- iFOBT screening every 2 years at age 50–74 years, with adjunctive flexible sigmoidoscopy screening at age 50 years for individuals with negative iFOBT (53% in Scenario 2; 37% in Scenario 3)
- iFOBT screening every 2 years at age 50–74 years, with adjunctive flexible sigmoidoscopy screening at age 54, 64 and 74 years for individuals with negative iFOBT (55% in Scenario 2; 37% in Scenario 3)
- iFOBT screening every 2 years, with plasma DNA testing (pDNA) for under-screened individuals, assuming that the offer of pDNA does not induce any 'leakage' (participation drop) in iFOBT screening – a favourable assumption (54% in Scenario 2; 39% in Scenario 3).

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6.2.3.4 Cost-effectiveness

Of the strategies examined, only computed tomography colonography (CTC) screening every 10 years and iFOBT screening every 2 years remained cost-effective in all screening participation scenarios considered, in context of an indicative willingness-to-pay threshold of A$50,000 per life–year saved in Australia. Of these two strategies, iFOBT was the most effective, with an incremental cost-effectiveness ratio of A$6,412–33,535 per life–year saved, compared with CTC screening every 10 years (depending on participation).

Therefore, the current NBCSP is the most effective strategy for colorectal cancer screening in Australia that is also cost-effective.

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6.2.3.5 Resource utilisation

Modelling was used to estimate the number of iFOBT test, pDNA tests, fDNA tests, colonoscopy, flexible sigmoidoscopy and CTC tests in the lifetime of 100,000 persons alive at 40 years for each strategy.

In all participation scenarios, colonoscopy screening every 10 years, once-off colonoscopy screening at age 50 years combined with iFOBT screening every 2 years, iFOBT screening every year and fDNA screening every 2 years were predicted to lead to the highest number of colonoscopy procedures. Screening with once-off flexible sigmoidoscopy at 60 years, with sigmoidoscopy every 10 years, or with CTC screening every 10 years, were estimated to lead to the lowest number of colonoscopies.

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6.2.3.6 Balance of benefits to harms

In all participation scenarios, strategies assuming pDNA screening every 2 years, colonoscopy screening every 10 years, and once-off colonoscopy screening at age 50 years combined with iFOBT every 2 years, were estimated to be associated with the highest number-needed-to-colonoscope (NNC) per colorectal cancer case or colorectal cancer death prevented, compared with the other strategies (i.e. these strategies had the least favourable ratio of benefits to harms).

When compared with iFOBT screening every 2 years, five strategies were found to be associated with greater reductions in colorectal cancer deaths but also resulted in higher numbers of colonoscopies in all scenarios (details in Table 9.3):

- fDNA screening every 2 years at age 50–74 years (fDNA2y)
- Once-off COL screening at age 50 years, combined with iFOBT every 2 years at age 52–74 years (COL@50_iFOBT2y)
- iFOBT screening every year at age 50–74 (iFOBT1y)
- iFOBT screening every 2 years at age 50–74 years (NBCSP from 2020) combined with flexible sigmoidoscopy at age 50 for negative iFOBT (iFOBT2y+SIG@50)
- iFOBT screening every 2 years at age 50–74 years (NBCSP from 2020) combined with SIG at 54, 64 and 74 years for negative iFOBT (iFOBT2y+SIG@54_64_74).

These five strategies were estimated to be associated with a higher NNC per colorectal cancer death prevented compared with iFOBT every 2 years (278–1150 in Scenario 1, 106–381 in Scenario 2, and 65–190 in Scenario 3).

No strategy was predicted to result in both fewer colorectal cancer deaths and fewer colonoscopies than iFOBT every 2 years. This finding implies that the strategy adopted in the current NBCSP has an optimal balance of benefits and harms, given the strategies considered in this evaluation.

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

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6.2.3.7 References

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6.2.4 Evidence: Screening age (PSC1d)

Is population screening starting at an earlier age more effective and as feasible, acceptable and cost-effective as screening starting at age 50 years? In population screening, do the harms outweigh the benefits if routine screening is continued beyond the age of 75 years? (PSC1d)

Contents

6.2.4.1 Background

Randomised clinical trials[1][2][3][4][5][6][7][8] 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 under 50 years, or older than 75 years.

When RCT evidence cannot be obtained, modelling studies based on sophisticated understanding of colorectal cancer natural history are an acceptable source of data to guide public health planning decisions.[9][10][11][12][13]

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6.2.4.2 Modelling study findings

A modelled evaluation was undertaken to assess the benefit, harms and cost-effectiveness of colorectal cancer screening in people aged 50–74 years with iFOBT every 2 years (the strategy adopted by the current NBCSP program), in comparison with potential alternatives for the target age for colorectal cancer screening in Australia:

- inviting people from age 40 or 45 years (versus 50 years)
- continuing screening to age 79 or 84 years (versus 74 years)
- a combination of these age ranges.

All strategies were evaluated for three scenarios with different screening adherence assumptions:

- Scenario 1 assumed perfect adherence to recommendations for screening, follow-up and surveillance.
- Scenario 2 assumed ‘high’ adherence (approximately 66–69% screening participation).
- Scenario 3 assumed ‘low’ adherence (approximately 49% screening participation, derived from currently observed rate[14]).

Although Scenario 1 is not achievable in practice, this analysis allows direct comparison of the outcomes and costs of screening approaches independent of the differing (and uncertain) adherence assumptions for each new strategy. Scenarios 2 and 3 were selected in order to test the robustness of the study findings by evaluating strategies under realistic participation assumptions of imperfect adherence.

When the two realistic (imperfect) participation scenarios were considered, favourable assumptions were made with respect to screening participation in 40–49 year-olds and 75–84 year-olds (i.e. the screening participation rate among the 40–49 and 75–84 years age groups was assumed to be the same as the rate modelled for 50-year-olds and 74-year-olds, respectively, with no impact on screening behaviour at 50–74 years. As a result, strategies assuming an alternative screening age range were associated with a higher proportion of individuals

being screened at least once in a lifetime compared to the current NBCSP, which may not be the case in practice (i.e. people screened in their forties may be, in practice, less likely to screen at older ages). These participation assumptions must therefore be considered in interpreting the result for realistic (imperfect) adherence), whereas the findings for perfectly adherent cohorts reflect the direct effects of screening age range *per se*.

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6.2.4.3 Health outcomes

With perfect adherence, the current NBCSP would reduce age-standardised risk (in 0-89 years) of colorectal cancer incidence by 52% and mortality by 74%, compared with no screening. Extending the target age group would result in additional, relatively modest benefits; extending screening to a younger age group (starting at 40 or 45 years) would result in additional reductions in incidence (4–6 percentage points) and mortality (4–8 percentage points). Similarly, extending screening to an older age-group (ending at 79 or 84 years) would result in an additional reductions in incidence (2 percentage points) and mortality (4–5 percentage points).

Compared with no screening, iFOBT screening every 2 years at age 50–74 years (the current NBCSP) was predicted to:

- reduce colorectal cancer incidence by 52% and reduce colorectal cancer mortality by 74% in Scenario 1 (perfect adherence)
- reduce colorectal cancer incidence by 33% and reduce colorectal cancer mortality by 53% under Scenario 2 (‘high’ adherence)
- reduce colorectal cancer incidence by 23% and reduce colorectal cancer mortality by 37% under Scenario 3 (‘low’ adherence).

Extending the target age group would result in additional reduction in colorectal cancer incidence and mortality:

- lowering the screening start age to 40 or 45 years would result in additional reductions of 2-6 percentage points in colorectal cancer incidence and 2–9 percentage points in colorectal cancer mortality in all scenarios
- extending the age of ceasing screening to 79 years or 84 years would result in an additional reduction of 1–2 percentage points in colorectal cancer incidence and 2–5 percentage points in colorectal cancer mortality in all scenarios
- extending the screening age from the current 50–74 years to 40–84 years would result an additional overall reduction of 7–8 percentage points in cancer incidence and 12–14 percentage points in cancer mortality in all scenarios.

If the screening age range was widened from the current 50–74 years to 40–84 years, an overall reduction of 7–8 percentage points in cancer incidence and 12–14 percentage points in cancer mortality was estimated.

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6.2.4.4 Cost-effectiveness

With an indicative willingness-to-pay threshold of A$50,000 per life–year saved in Australia, only two strategies were found to be cost-effective in all scenarios after calculating the incremental cost-effective ratio (ICER):

- the current NBCSP (ICER A$4,264–8,075 per life–year saved, depending on participation)
- screening at 45–74 years (ICER A$19,451–40,813 per life–year saved, depending on participation).

Extending screening to older ages was not cost-effective in any participation scenario.

Starting screening at age 40 years was not found to be cost-effective in all participation scenarios, but starting at 45 years was found to be potentially cost-effective in all participation scenarios.

The cost-effectiveness modelling is described in detail in the Technical report.

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6.2.4.5 Resource utilisation

Predicted resource requirements in the lifetime of 100,000 persons alive at 40 years within the current NBCSP strategy (iFOBT screening every 2 years in people aged 50–74 years) were:

- 1 million iFOBT tests and 127,300 colonoscopies in Scenario 1 (perfect screening adherence)
- 720,200 iFOBT tests and 66,700 colonoscopies in Scenario 2 (high screening adherence)
- 472,000 iFOBT tests and 44,700 colonoscopies in Scenario 3 (low screening adherence).

Extending the screening age-range resulted in predicted increases in resource utilisation, compared with the current NBCSP strategy:

- Screening at 50–79 years would result in a 21–30% increase in colonoscopies in all scenarios.
- Screening at 50–84 years would result in a 42–64% increase in colonoscopies in all scenarios.
- Screening at 45–74 years would result in a 7–14% increase in colonoscopies in all scenarios.
- Screening at 40–74 years would result in a 27-38% increase in colonoscopies in all scenarios.
- Screening at 40–84 years would result in a 66–91% increase in iFOBT tests and a 72–109% increase in colonoscopies in all scenarios.

This modelling is described in detail in the Technical report.

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6.2.4.6 Balance of benefits to harms

For the current NBCSP, the model predicted the following NNCs compared with no screening:

- (Scenario 1) 28 colonoscopies per case prevented and 56 colonoscopies per death prevented
- (Scenarios 2 and 3) 22 colonoscopies per case prevented and 39–41 colonoscopies per death prevented.

For details, see the Modelling report.

The 'benefit–harms frontier' (showing strategies with the favourable balance between benefit and harm, compared with strategies of similar effectiveness considered in the evaluation) and the incremental benefits to harms ratio (IBHR) of the 'dominating' strategies are shown in the modelling report. We thus estimated the number of *additional* colonoscopies required to prevent one *additional* colorectal cancer case/colorectal death for each strategy, compared with the next most effective strategy on the frontier. These NNCs for the *additional* deaths prevented for age-extensions of the NBCSP are up to 2–14 times higher than that the baseline NNC for the existing NBCSP.

For example, at current levels of participation, starting screening from age 45 years would be associated with an *additional* 67 colonoscopies for each *additional* death prevented, compared with an NNC of 39 colonoscopies per death prevented by the existing program.

For more information about the balance of benefits to harms, see the Modelling report.

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

Next section: evidence summary, recommendations and considerations

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6.2.4.7 References

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6.2.4.8 Appendices

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6.3 Evidence summary, recommendations and considerations

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6.3.1 Evidence summary table

Evidence summary	Level	References
Screening benefit (PSC1a)		
Several RCTs evaluating guaiac faecal occult blood test -based screening demonstrated a significant reduction in colorectal cancer-specific mortality, compared with no screening.	I, II	[1], [2], [3], [4], [5], [6], [7], [8], [9], [10], [11]
A large study evaluating the combination of once-only immunochemical faecal occult blood testing, with flexible sigmoidoscopy (but not colonoscopy) for those with a positive test, showed a 32% reduction in rectal cancer mortality, but no reduction in overall mortality or colon cancer-specific mortality, at 8-year follow-up.	II	[12]
A total of 4 Level II RCTs compared flexible sigmoidoscopy as a screening modality	I, II	

Evidence summary	Level	References
with no screening, and reported a combined 28% reduction in colorectal cancer-specific mortality in those randomised to screening after nearly 11 years of follow-up. This benefit in colorectal cancer-specific mortality was attributed only to a reduction in distal colorectal cancer-specific mortality and not proximal colorectal cancer-specific mortality. Most trials provided a once-only flexible sigmoidoscopy as the screening test.		[1], [2], [3], [4], [5], [6], [7]
No high-level RCTs were found that compared screening with colonoscopy, CT colonography, faecal DNA biomarkers, or blood or plasma cancer-specific biomarkers such as DNA, with no screening.	N/A	
Only one RCT (NORCCAP) reported the combination of two screening modalities, flexible sigmoidoscopy and immunochemical faecal occult blood testing (iFOBT). 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).	II	[13]
Screening test accuracy (PSC1b)		
iFOBT performed best at detection of colorectal cancer (when compared to a colonoscopy reference standard), and was also able to detect a proportion of advanced adenomas.	II, III-1	[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]
There is insufficient evidence to fully assess the diagnostic performance (including longitudinal outcomes) of non-FOBT faecal or blood-based cancer-specific biomarker assays.	II, III-1	[39], [40], [41], [19]
There is insufficient evidence to determine how the diagnostic performance of iFOBT or biomarker assays may alter with participant age, sex, or risk of colorectal cancer.	II, III-1	[41], [19], [42], [20]
Screening cost effectiveness (PSC1c)		
	N/A	

Assuming 100% adherence to screening recommendations, modelling predicted the most effective screening strategies would be: ■ iFOBT every year in people aged 50–74 years ■ once-only colonoscopy screening at age 50 years combined with iFOBT every 2 years in people aged 52–74 ■ colonoscopy screening every 10 years at ages 55, 65 and 75 years ■ iFOBT screening every 2 years at age 50–74 years, with or without adjunct flexible sigmoidoscopy (either at age 50 years or at ages 54, 64 and 74 years) for individuals with negative iFOBT. Analysis based on early data from cross-sectional studies also suggested that screening with a faecal DNA assay every 2 years may be effective if emerging evidence supports the assumed test characteristics.		
The current National Bowel Cancer Screening Program (NBCSP) strategy (iFOBT every 2 years at age 50–74 years) is associated with predicted reductions of 52% in colorectal cancer incidence and 75% in colorectal cancer-specific mortality in perfectly adherent people. Overall, the most effective strategies (as noted above) were associated with a 52–67% reduction in colorectal cancer incidence and 75–82% reduction in colorectal cancer mortality, compared with no screening, given perfect adherence.	N/A	
The incremental cost-effectiveness (ICER) analysis identified five strategies that represented the best value for money of all the available strategies assessed (i.e. strategies found to cost the least among all strategies with similar or higher effectiveness), but only two of these would be cost-effective in Australia under all scenarios, given the indicative willingness-to-pay threshold of A$50,000 per life–year saved: ■ CT colonography every 10 years ■ iFOBT every 2 years at age 50–74 years (the current program). However, analysis for CT colonography screening was based on more limited evidence for cross-sectional accuracy and there is a lack of evidence for longitudinal outcomes (long-term benefit). In the modelled analysis, the current NBCSP was the most effective of these two strategies. iFOBT screening every year was not found to be cost-effective, with an ICER of > $100,000 per life–year saved.	N/A	
	N/A	

Evidence summary	Level	References
The ICER for the current NBCSP (iFOBT screening every 2 years), compared with the next most effective strategy (CT colonography) on the cost-effectiveness frontier, was A$6,412-33,535 per life–year saved (depending on participation), taking into account all the other strategies included in the analysis. This is not the same as the cost-effectiveness ratio (CER) of the current NBCSP compared with no screening (estimated at approximately $2,000–3,000 per life–year saved). Each of these estimates provides a measure of the cost-effectiveness of the current NBCSP, but the ICER considers a range of other, theoretically possible, options. Whichever measure is used, the current NBCSP was found to be cost-effective.		
The current NBCSP (iFOBT screening every 2 years) requires 56 colonoscopies to prevent one colorectal cancer death, assuming 100% adherence to screening recommendations. No other strategy was found to have both fewer colorectal cancer deaths and fewer colonoscopies than iFOBT every 2 years, implying that the current NBCSP has an optimal balance of benefits and harms.	N/A	
Screening age (PSC1d)		
To date, no published RCTs have reported outcomes related to colorectal cancer screening-specific outcomes in those less than 50 years of age, or greater than 75 years of age.	N/A	
Screening with iFOBT once every two years between 50 and 74 years (the current NBCSP) was predicted to reduce colorectal cancer incidence by 52% and reduce colorectal cancer mortality by 74%, compared to no screening (assuming perfect adherence).	N/A	
Compared to the current NBCSP, lowering the screening start age to 40 or 45 years would result in additional reductions of 2–6 percentage points in colorectal cancer incidence and 2–9 percentage points in colorectal cancer-specific mortality, in all participation scenarios considered.	N/A	
Extending the age of ceasing screening to 79 or 84 years would result an additional reduction of 1–2 percentage points in colorectal cancer incidence and 2–5 percentage points in colorectal cancer mortality.	N/A	
When considering cost-effectiveness only for those strategies involving iFOBT every 2 years, but with different age ranges, four strategies were found to have the best value for money of all the available strategies assessed (i.e. strategies found to cost the least among all strategies with similar or higher effectiveness).	N/A	

Evidence summary	Level	References
In context of an indicative willingness-to-pay threshold of A$50,000 per life–year saved in Australia, only two were found to be cost-effective in all participation scenarios: the current program (ICER $4,264–8,075 per life–year saved) and screening at 45–74 years (ICER $19,451–40,813 per life–year saved). Extending the screening end age to 79 or 84 years was not found to be cost-effective in this analysis.		
Although potentially cost-effective, lowering the screening start age to 45 years was predicted to be associated with a less favourable ratio of benefits to harms than the current program. The number-needed-to-colonoscope (NNC) for the current program for each death prevented is 39–56, whereas the NNC for each extra death prevented by starting at age 45 years is 67–375 (depending on participation). At current levels of participation, starting from age 45 years would be associated with an additional 67 colonoscopies for each additional death prevented, compared with an NNC of 39 colonoscopies per death prevented for the existing program.	N/A	
Starting at age 45 years would increase the demand for colonoscopy services by 7–14% (depending on participation).	N/A	
The effect of starting screening earlier is amplified in imperfect adherence scenarios because the increase in deaths prevented is primarily due to an overall increase in the number of those screened at least once in a lifetime at any age (i.e. being screened at least once is the major determinant of outcome). Screening from age 50 to age 74 years is more cost effective than screening people in their forties.	N/A	

N/A: not applicable

^NHMRC classification of levels of evidence does not currently encompass modelling studies.

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6.3.2 Recommendations

6.3.2.1 Overall population screening strategy

Evidence-based recommendation	Grade
Overall population screening strategy	**C**

Evidence-based recommendation	Grade
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.	

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6.3.2.2 Primary screening test

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**

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6.3.2.3 Frequency of testing

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

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6.3.2.4 Target age group

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**

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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.

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6.3.3 Considerations in making these recommendations

The recommendation for iFOBT every 2 years, starting at age 50 years and continuing to age 74 years, is based on effectiveness, cost-effectiveness, the balance of benefits to harms and feasibility within the current Australian health care system. A previous analysis with '*Policy1-Bowel*' model found that with current levels of participation, the NBCSP is expected to prevent 92,200 cancer cases and 59,000 deaths over the period 2015-2040; an additional 24,300 and 37,300 cases and 16,800 and 24,800 deaths would be prevented if participation was increased to 50% and 60%, respectively.[43] In 2020, an estimated 101,000 program-related colonoscopies will be performed, associated with approximately 270 adverse events; an additional 32,500 and 49,800 colonoscopies and 88 and 134 adverse events would occur if participation was increased to 50% and 60%, respectively. The overall number-needed-to-screen (NNS) is 647-788 per death prevented, with NNC of 52-59 colonoscopies per death prevented. The program is highly cost-effective due to the cancer treatment costs averted (cost-effectiveness ratio compared to no screening, A$2,000-3,000/life-year saved) and is expected to become cost saving by 2029, with A$1.7, A$2.0 and A$2.1 billion in savings accrued (2015 prices) between 2030–2040, at participation rates of 40%, 50% and 60%, respectively.

We used a comprehensive validated model to simulate the NBCSP. The analysis of 14 screening scenarios showed that only iFOBT every 2 years, and CT colonography every 10 years, were cost-effective at all three levels of participation and that iFOBT every 2 years (as used in the current NBCSP) had a cost-effectiveness ratio of $2,000–$3,000 per life–year saved as well as a favourable profile with respect to the NNC.

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6.3.3.1 Applicability to the Australian setting

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 per life–year saved used in Australia.

These findings relate to population screening in Australia. Their applicability to other countries will depend on similarities to Australia, including level of risk for colorectal cancer and the design and costs of their health services.

6.3.3.2 Balance of benefits and harms

The risks of screening include potential psychological adverse effects, which range from the trauma of identifying disease in symptom-free, healthy individuals, to stress experienced by people in whom cancer is suspected although later discounted, to more subtle concerns of participants during the screening process.[44] Healthcare professionals must recognise the potential adverse psychological effects of screening, although several studies have shown no evidence of long-term harm after screening.[45][46][47] These potential adverse effects are balanced by avoiding the distress associated with diagnosis of an advanced cancer when there has been no opportunity for early detection by screening.

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6.3.3.3 Choice of target age range for population screening

The age range for organised population screening continues to be 50–74 years, based on considerations of effectiveness, cost-effectiveness and the balance of benefits to harms.

When assessing changes to the screening age, reducing the starting age of 45 years was cost-effective, but with a much less favourable ratio of benefits to harms than for 50–74 years and required a substantially higher number of colonoscopies for each extra cancer death prevented.

Since screening from age 50–74 years was both more effective and cost-effective, resources would be better invested in increasing participation in the existing NBCSP target age group rather than in starting screening at the age of 45 years. Screening after 74 years of age was not found to be cost-effective and is not recommended.

6.3.3.4 Choice of testing interval for population screening

The recommendation not to increase the current frequency of testing is based on the modelling study findings that annual testing with iFOBTs would not be a cost-effective screening strategy in the Australian setting.

Modelling indicated that testing with iFOBTs every 2 years is a very cost-effective screening strategy for colorectal cancer in the Australian setting.

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6.3.3.5 Choice of immunochemical occult blood test as preferred screening test for population screening

6.3.3.5.1 Faecal occult blood tests versus flexible sigmoidoscopy or CT colonography

Population-based screening using faecal occult blood tests or flexible sigmoidoscopy can reduce colorectal cancer-specific mortality. While both methods of screening are effective, there are major concerns about feasibility, acceptability, and cost-effectiveness with flexible sigmoidoscopy.

While the literature review demonstrated the effectiveness of flexible sigmoidoscopy for population screening, it has several disadvantages. Its acceptability to health professionals and the target population is unclear in Australia. Participants are likely to request sedation, which substantially increases costs. Requests for flexible sigmoidoscopy may result in complete colonoscopy instead. Population screening based on flexible sigmoidoscopy would not be feasible in Australia because of the lack of dedicated facilities and staff to support such a program, the high capital cost of developing those facilities, problems of access related to travel times for participants living in outer regional, rural and remote areas. Modelling indicated that screening based on flexible sigmoidoscopy would not be cost-effective.

The high level of cost effectiveness for CT colonography should be interpreted in the light of a limited evidence base for long-term outcomes after CT colonography screening. Furthermore, we were unable to fully take into account infrastructure investments and costs that would be required. CT colonography was not considered to be a feasible option for population screening, as a substantial increase in infrastructure, capacity and workforce would be necessary.

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6.3.3.5.2 Immunochemical versus guaiac occult blood tests

There is supporting high-level evidence from one RCT of iFOBT,[12] three large RCTs evaluating screening with guaiac faecal occult blood test (gFOBT)[1][2][3] from the 1990s, as well as three case-control studies[48][49][50] on the effectiveness of FOBT as a population-based screening modality.

The success of iFOBT screening for colorectal cancer in the Australian population was reported in the 2012 Analysis of Bowel Cancer Outcomes for the National Bowel Cancer Screening Program.[51] In this report, colorectal cancer mortality was compared between people in the NBCSP invitee and the never-invited groups in an intention-to-screen colorectal cancer mortality analysis. Of the 10,080 never-invited people with a colorectal cancer diagnosis, 1,973 (19.6%) had died of colorectal cancer before 2012. Of the 2,609 people in the NBCSP invitee group with a colorectal cancer diagnosis, 298 (11.4%) had died of colorectal cancer by the same date: hazard ratio (HR) 1.77; 95% confidence interval (CI) 1.57 to 2.00. When corrected for potential lead-time bias in screen-detected cancers, the risk of death from colorectal cancer was still significantly higher in the never-invited group (hazard ratio 1.15, 95% CI: 1.01–1.31). The mean follow-up time to bowel cancer death for all diagnoses was 18.6 months (range 0–64.3 months, standard deviation 13.9 months).

To date, there has been only one high-level published RCT that compared iFOBT-based screening with no screening.[12] With the widespread availability of evidence-based colorectal cancer screening in many countries including Australia (National Bowel Cancer Screening Program [NBCSP]), it would be unethical to initiate new randomised controlled trials to compare screening by iFOBT with no screening.[52]

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)[53] recommend population screening with iFOBT over gFOBT on the basis of:

- superior performance (e.g. sensitivity and specificity) in detecting cancers and adenomas
- greater acceptability to participants
- comparable complication rates and costs.[54]

iFOBTs used as a screening modality for colorectal cancer will also detect a significant proportion of advanced adenomas in the average-risk population. Removal of advanced adenomas at colonoscopy should reduce the future incidence of colorectal cancer.

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6.3.4 Health system implications of the recommendations

6.3.4.1 Clinical practice

Implementation of the recommendation to continue the current NBCSP strategy for screening in the average-risk population (iFOBT every 2 years, at age 50–74 years) will not result in any change in 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 off 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 are able to promote and substantially boost participation in the NBCSP. Other key roles include explaining the significance of positive screening test results, arranging colonoscopy, discussing any further action that needs to be taken as well as interacting with the central register.

Colonoscopy services urgently need to introduce booking systems within a model of care that give priority to these and other high-risk groups to put this into effect.

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6.3.4.2 Resourcing

Implementation of the screening recommendations will not result in any change from the resource requirements already predicted.

Resourcing considerations for implementation of the recommendations include:

- continued expansion of the NBCSP to complete rollout of screening every two years 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.

It would be 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.

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6.3.4.3 Barriers to implementation

No new barriers to the implementation of the screening recommendations are envisaged.

Existing 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.[55][56] Recent studies have demonstrated that several of these barriers can be at least partially overcome so as to improve participation.[57][58][59]

The 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 GP all lead to a significant improvement in participation.[57][58][59]

Appropriate public education and promotion is usually necessary to enhance participation rates.

In Australia, weather conditions and geographic factors may affect performance of iFOBTs.[60][61] 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 where return of postal items may be slow and throughout Australia during hot summer months.

Next section: discussion

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6.3.5 References

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6.3.6 Appendices

NHMRC Evidence statement form PSC1a

Systematic review report PSC1a	NHMRC Evidence statement form PSC1b		
	Systematic review report PSC1b	Modelling report PSC1c	Modelling report PSC1d

6.4 Discussion

Contents

6.4.1 Unresolved issues

There is currently insufficient evidence from appropriately designed studies to determine the following:

- the diagnostic performance of non-FOBT faecal or blood-based cancer-specific biomarker assays, and whether these are influenced by participant age, sex, or risk of colorectal cancer
- the effectiveness and cost-effectiveness of population screening based on colonoscopy, CT colonography, faecal DNA biomarkers, or blood or plasma cancer-specific biomarkers such as DNA
- the effectiveness and cost-effectiveness of population screening based on combinations of screening modalities
- the effectiveness and cost-effectiveness of population screening in people younger than 50 years or older than 75 years.

Other unresolved issues include:

- whether the inappropriately high rate of colonoscopy in Australia reduces effectiveness of the NBCSP
- how the NBSCP should respond to the changing epidemiology of colorectal cancer, including incidence at younger age and changes in distribution of cancer within the large bowel
- how to maximise participation rates.

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6.4.2 Studies currently underway

No evidence was identified from randomised controlled trials (RCTs) evaluating colonoscopy, computed tomography (CT) colonography, or cancer-specific faecal or blood biomarkers. Three RCTs evaluating colonoscopy-based screening are in progress:

- The Northern-European Initiative on Colorectal Cancer (NordICC)[1]
- Colonoscopy Versus Fecal Immunochemical Test in Reducing Mortality From Colorectal Cancer (CONFIRM)[2]
- Colorectal Cancer Screening in Average-risk Population: Immunochemical Fecal Occult Blood Testing Versus Colonoscopy.[3]

Only one of these RCTs[2] includes a no-screening arm.

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6.4.3 Future research priorities

Future research opportunities include:

- studies assessing the place of combinations of screening tests (e.g. iFOBT every 2 years and flexible sigmoidoscopy every 10 years (at ages 55, 65 and 75 years)

- studies on screening tailored to the presence of special risk factors (e.g. adjusting the starting age of screening, using more sensitive iFOBT conditions or combining screening tests tailored to factors such as sex, BMI, history of cigarette smoking)
- evaluation of the performance characteristics of new versions of tests for faecal and blood-based cancer-specific biomarkers.

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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, Australia, 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 Chapter subsections

Please see sections:

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

7.2 References

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7.1 Introduction: the symptomatic patient

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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, Australia, 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 Chapter subsections

Please see sections:

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

7.1.2 References

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7.2 Signs & symptoms predictive of CRC

Contents

7.2.1 Systematic review 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? (SPT1-2a)

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 31 August 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 immunochemical faecal occult blood test (iFOBT) in the Australian National Bowel Cancer Screening Program. 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 immunochemical faecal occult blood test (iFOBT)
- barium enema
- colonoscopy
- flexible sigmoidoscopy
- CT colonography.

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

For details about this systematic review, please see the Technical report.

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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 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.	II, III-2, III-3	[5], [6], [7], [8], [9], [10], [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]
	II, III-	[5], [20], [21], [22], [14],

Evidence summary	Level	References
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).	2, III-3, IV	[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]

* The available data did not allow clear distinction between iron-deficiency and non-iron deficiency anaemia. 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
	III-2,	[28], [12], [7],

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-3, IV	[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 iFOBT (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, iFOBT 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 iFOBT and calprotectin in patients with bowel symptoms referred from primary care. This demonstrated that a negative iFOBT 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]

The guideline development group also discussed the role of CT colonography as an alternative investigation. CT colonography has high sensitivity for colorectal cancer and could potentially be used therefore to rule out this diagnosis in patients with bowel symptoms.[31][32][33] CT colonography may be considered as an alternative diagnostic test, particularly in the following scenarios:

- Individuals with symptoms of colorectal cancer below the 3% CRC risk threshold.
- Individuals in areas with limited access to colonoscopy services but where there is access to CT.
- Individuals who have contra-indications to colonoscopy.

The New Zealand Society of Gastroenterology recommends CT colonography as an alternative to colonoscopy in: symptomatic patients over 80 years, individuals with an abdominal mass, and in those at higher risk of complications from colonoscopy.[34] It should be noted that in the NICE modelling study of alternative testing strategies in individuals with symptoms of colorectal cancer below the 3% risk threshold, iFOBT was the most cost-effective investigation to support triage of referrals for colonoscopy. This modelling was set in a UK healthcare context and did not consider issues of differential access to colonoscopy and CT colonography.

Under current Medicare eligibility rules, GPs can only request CT colonography if a patient has had an incomplete colonoscopy in the previous 3 months or there is a contraindication to colonoscopy. This creates a significant barrier to its use in Australian primary care as an alternative test to colonoscopy in symptomatic individuals. It can be requested by a specialist ‘for exclusion of colorectal neoplasia in a symptomatic or high risk patient’, and therefore may have a potential role in triage for a colonoscopy triage setting.

7.2.2.5.1 Table 10.1. Colonoscopy triage categories

Category 1	Category 2	Category 3	No colonoscopy indicated
Positive immunochemical faecal occult blood test (iFOBT) (asymptomatic)			
Anaemia and any one of: ■ ≥ 60 years ■ Rectal bleeding	**Anaemia** and all of: ■ No GI symptoms ■ iFOBT –ve ■ No likely non-GI cause identified	**Anaemia** and all of: ■ No GI symptoms ■ iFOBT –ve ■ Likely non-GI cause ■ Age ≥ 50 years	**Anaemia** and all of: ■ No GI symptoms ■ iFOBT –ve ■ Untreated likely non-GI cause (e.g, menorrhagia, diet) ■ Age ≤ 50 years
Rectal bleeding < 12 months and any one of: ■ ≥ 50 years ■ Abdominal pain ■ Altered bowel habit > 6/52 ■ Unexplained weight loss	**Rectal bleeding < 12 months** and all of: ■ No other GI symptoms ■ < 50 years ■ 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 ■ iFOBT or calprotectin +ve*	**Altered bowel habit > 6/52** and all of: ■ 40–60 years ■ iFOBT 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	

Category 1	Category 2	Category 3	No colonoscopy indicated
Unexplained abdominal pain and any one of: ■ Rectal bleeding ■ Unexplained weight loss ■ iFOBT or calprotectin +ve*	**Unexplained abdominal pain** and all of: ■ ≥ 40 years ■ iFOBT 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 ■ iFOBT or calprotectin +ve*	**Unexplained weight loss** and all of: ■ ≥ 40 years ■ iFOBT 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 ■ iFOBT and calprotectin – ve*
Mass palpable on abdominal or rectal examination or on rigid sigmoidoscopy			

Source: Victorian Colonoscopy Categorisation Guidelines[35]

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. There is currently no Medicare Benefits Scheme (MBS) rebate for calprotectin.

**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, 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.

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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.

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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 iFOBT) 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.[36]

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.[37]

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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.

Next section: optimal max time from referral to diagnosis and treatment

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7.2.7 Appendices

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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 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.

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7.3.2 Systematic review 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? (SPT1-2b)

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]

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

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7.3.2.1 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]

7.3.2.2 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, 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.

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7.3.2.3 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]

7.3.2.4 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.

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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 more than 120 days. Diagnostic intervals greater than 120 days are associated with poorer clinical outcomes.	**C**

Evidence-based recommendation	Grade
† First healthcare presentation is defined as the date of presentation in general practice with symptoms suggestive of colorectal cancer or positive iFOBT for screening.	

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.

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 will of course never be Level I evidence to inform these recommendations as RCTs of different diagnostic intervals would be deemed unethical. A maximum diagnostic interval of 120 days from first presentation to healthcare (first healthcare presentation is defined as the date of presentation in general practice with symptoms suggestive of colorectal cancer or positive iFOBT for screening) to diagnosis should be the target to prevent poorer outcomes in those with colorectal cancer. We noted the current recommendation in the Optimal care pathway[15] for colorectal cancer of a maximum of four weeks from referral to colonoscopy for people with symptoms suggestive of colorectal cancer. Recognising that there will be a small proportion of people with colorectal cancer in triage Category 2 (approximately 1-2%), we recommend that all Category 1 and Category 2 colonoscopies (screen positive iFOBT or symptomatic patients) should be performed no later than 120 days from first presentation[i] to healthcare. Ideally colonoscopy should be performed sooner than this to reduce the risk of psychological harm to patients.[16][17]

The Working Party and subcommittee members had robust discussion regarding the maximum optimal time from first healthcare presentation to diagnostic colonoscopy and treatment. Although the group was in agreement about the interpretation of the systematic review evidence, there was concern about de-emphasising the need for prompt evaluation. The Working Party acknowledges that the guideline may be read with the expectation that it will assist in triage of colonoscopy patients. The authors resolved it was appropriate to maintain the evidence-based recommendations, acknowledging the grade and limitations of the available evidence, but also add the practice point about the ideal interval for symptomatic patients. Given the unavoidable delays along the pathway, all people with a positive iFOBT or with symptoms suggestive of colorectal cancer should have a colonoscopy as promptly as possible.

[i] Date of first presentation is defined as the positive screening iFOBT.

7.3.4 Benefits and harms

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. While recognising the current challenges of meeting demand in public health endoscopy services, the guideline development group recommended a target diagnostic interval of a maximum of 120 days from first presentation to healthcare (first healthcare presentation is defined as the date of presentation in general practice with symptoms suggestive of colorectal cancer or positive iFOBT for screening) for all patients meeting either Category 1 or Category 2 criteria.

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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. Meeting a 120 day target from first presentation for all Category 1 and Category 2 will have significant resource implications for some public hospital endoscopy services.

7.3.5.3 Barriers to implementation

These recommendations are made in the context of the roll-out of the NBCSP, due to be fully implemented by 2020 which will place additional demand for colonoscopy. We acknowledge the challenges of measuring this target given that the evidence is based on the diagnostic interval commencing at the time of first presentation to healthcare. In order to monitor the 120 day diagnostic interval target, referrals will need to record the date of first presentation to healthcare with symptoms suggestive of colorectal cancer. We recognise that this may be logistically challenging to collect and recommend that this information is collected within the standardised GP referral proforma[18] (see Resourcing).

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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 colonoscopy in Category 1 and 2 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.

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.

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7.3.8 Appendices

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8 Risk and screening based on family history

Evidence shows that family history of colorectal cancer is an important risk factor for developing the disease. Genes have been identified which, when inherited in a mutated form, substantially increase a person's 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*, biallelic mutation of which causes *MUTYH*-associated 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 cause a very high risk for cancer (see High-risk familial syndromes).

However, mutations in these genes cause fewer than 5% of all colorectal cancer cases and at most, only explain half of the reasons why family history is a risk factor for colorectal cancer.[1] The remainder of the observed increases in familial risk could be due in part to mutations in yet-to-be-discovered colorectal cancer susceptibility genes[2], polygenic factors such as single-nucleotide polymorphisms (SNPs)[3][4] or dietary and other lifestyle factors shared by family members. Many statistical models have been developed for colorectal cancer risk that include family history as well as other risk factors.[5] Due to limited resources, only family history is considered in this chapter.

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

- to prioritise 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 people who have a family history of colorectal cancer, who are not known or suspected to have a genetic syndrome.

For information on screening strategies for specific high-risk familial syndromes, see:

- Familial adenomatous polyposis (FAP)
- MUTYH associated polyposis (MAP)
- Lynch syndrome
- Peutz-Jeghers syndrome
- Juvenile polyposis syndrome

- Serrated polyposis syndrome

8.1 Chapter subsections

Please see sections:

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

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8.1 Introduction: Risk and screening based on family history

Evidence shows that family history of colorectal cancer is an important risk factor for developing the disease. Genes have been identified which, when inherited in a mutated form, substantially increase a person's 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)

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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 cause a very high risk for cancer (see High-risk familial syndromes).

However, mutations in these genes cause fewer than 5% of all colorectal cancer cases and at most, only explain half of the reasons why family history is a risk factor for colorectal cancer.[1] The remainder of the observed increases in familial risk could be due in part to mutations in yet-to-be-discovered colorectal cancer susceptibility genes[2], polygenic factors such as single-nucleotide polymorphisms (SNPs)[3][4] or dietary and other lifestyle factors shared by family members. Many statistical models have been developed for colorectal cancer risk that include family history as well as other risk factors.[5] Due to limited resources, only family history is considered in this chapter.

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

- to prioritise 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 people who have a family history of colorectal cancer, who are not known or suspected to have a genetic syndrome.

For information on screening strategies for specific high-risk familial syndromes, see:

- Familial adenomatous polyposis (FAP)
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- Lynch syndrome
- Peutz-Jeghers syndrome
- Juvenile polyposis syndrome
- Serrated polyposis syndrome

8.1.1 Chapter subsections

Please see sections:

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

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8.2 Colorectal cancer risk according to family history (FHS2)

Contents

8.2.1 Background

The best evidence for the association between colorectal cancer risk and family history of the disease comes from cohort studies that compare the risk of colorectal cancer for people with and without a family history of colorectal cancer. Ideally, these studies should take into account any differences between people with and without a family history for colorectal cancer risk factors.

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 genetic relationship of the relative(s) with colorectal cancer, and the diagnosis age of relative(s) diagnosed with colorectal cancer.

Case control studies and cohort studies which have been well designed including stringent methods for collection of family cancer data in relatives, reported an approximate doubling of lifetime risk.[1][2][3][4] For example:

- A Danish study of parents of colorectal cancer patients diagnosed before age 60 years[1] reported that, compared with the average population, the risk of colorectal cancer was 1.6 times higher among patients' mothers and 1.9 times higher among patients' fathers.
- An Australian study reported that, compared to people with no relative with colorectal cancer, those with one relative with colorectal cancer had 1.8 times the colorectal cancer risk.[2]
- A US study of people reported that the risk of colorectal cancer for men and women of first-degree relatives with colorectal cancer was 1.72 greater than for those without a family history of the disease[3]
- A US study reported that the risk of colon cancer was 2.2 times higher among patients with a first-, second- or third-degree relative with colon cancer than for those with no family history.[4]

In contrast to these modest levels of increased risk, colorectal cancer risk has been found 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 age 55) or when two close relatives have had colorectal cancer, irrespective of the age at diagnosis.[3][4][3]

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

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8.2.2 Update of 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? (FHS2)

A systematic review of cohort studies since 2005 (the publication of the previous guidelines[5]) was undertaken to update the evidence for the estimated 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.

Six studies were identified: one analysis of pooled data from two prospective cohort studies,[6] and five cohort studies[7][8][9][10][11]. 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[12] was also identified.

Of the cohort studies, one[9] was deemed to have a low risk of producing biased estimates, two[7][11] were deemed to have a moderate risk of bias, and three[6][8][10] were deemed to have a high risk of bias.

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8.2.2.1 Increased risk of colorectal cancer by family history

Overall, cohort studies report that people with a family member diagnosed with colorectal cancer have an increased risk of colorectal cancer, compared with the average 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 5.1), 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	Colorectal cancer risk relative to the average population risk
No family history	0.86[11] (14% decrease)
One or more first-degree relative diagnosed at any age	1.4[10] – 2.1[8], 2.05[11] (40–110% increase)

Family history of colorectal cancer	Colorectal cancer risk relative to the average population risk
One first-degree relative diagnosed before age 50	3.3[11] (230% increase)
One first-degree relative diagnosed between ages 50 and 60	2.2[10] to 2.5[11] (120–150% increase)
Two or more first-degree relatives	3.0[11] (200% increase)
No first-degree relative, at least one second-degree relative	1.1-1.5[11] (10–50% increase)

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8.2.2.2 Category 1 — those near average risk

Lifetime risk is to age 75 years: approximately 5% to 10% (assuming no colorectal cancer screening).

Some examples of asymptomatic people who fit into this category are the following (for a full description see Table 5.3 below):[2][4][3][6][8][10][12][13].

- 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.[4][11]

8.2.2.3 Category 2 — those at moderately increased risk

Lifetime risk to age 75 years: approximately 15–30% (assuming no colorectal cancer screening).

Some examples of asymptomatic people who fit into this category if they have none of the high-risk features listed in category 3 **and** have **either** of the following (for a full description see Table 5.3 below):

- one first-degree relative with colorectal cancer diagnosed before the age of 55 years[2][4][11][14][15][16]
- two first-degree relatives or one first-degree relative and at least two second-degree relative diagnosed with colorectal cancer at any age.[11][15][16][17]^

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.

^Note: Previous guidelines specified that relatives with cancer needed to be on the same side of the family in order to meet eligibility of this risk category. Recent data suggests that a similar level of risk occurs if the relatives with cancer are on opposite sides of the family,[11] therefore this restriction has now been omitted.

8.2.2.4 Category 3 — those at high risk

Lifetime risk to age 75: approximately 30–40% (assuming no colorectal cancer screening).

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

- at least three first-degree relatives diagnosed with colorectal cancer at any age[11]
- at least three first-degree or second-degree relative with colorectal cancer with at least one diagnosed before age 55 years.

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.

Category 2 and 3 excludes people known to be, or have a high probability of having a high-risk familial syndrome due a genetic predisposition to colorectal cancer. These people have potentially a much higher risk of colorectal cancer and therefore more intensive screening is recommended. See High-risk familial syndromes.

Therefore these categories excludes people who have:

- a relative confirmed as carrying a pathogenic mutation in a gene associated with a high-risk familial syndrome, who have not themselves been tested
- a relative with multiple colorectal cancers
- a relative with familial adenomatous polyposis
- at least three first-degree or second-degree relatives with a Lynch syndrome-related cancer (endometrial, ovarian, stomach, small bowel, renal pelvis or ureter, biliary tract, brain) with at least one diagnosed before age 55 years).

All the above should be referred to a familial cancer clinic for testing for a high-risk familial syndrome.

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

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

Category	Examples of Family history (full description in Table 5.3)	Risk compared with the average population.
1	No first- or second-degree relative with colorectal cancer	10% decreased risk
	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 increased risk
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 increased risk
3	At least three first-degree or second-degree relatives with colorectal cancer, with at least one diagnosed under 55 years At least three first-degree relatives with colorectal cancer diagnosed at 55 years or older	7- to 10-fold increased risk

Sources: St John et al (1993)[2], Fuchs et al (1994)[3], Slattery et al (1994)[4], Bass et al (2008)[7], Schoen et al (2015)[9], Taylor et al (2011)[11], Lynch et al (2003)[13], Hall et al (1996)[14], Leu et al (2008)[12], Benhamiche-Bouvier et al (2000)[15], Sandhu et al (2001)[16], Aitken et al (1996)[17], Anderson et al (2003)[18]

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.

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8.2.2.4.2 Table 5.3. Colorectal cancer risk categories by family history

Risk category by family history		Number of 1st degree relatives with CRC before age 55								
		0				1			2	
		Number of 1st degree relatives with CRC at 55 or older								
		0	1	2	3	0	1	2	0	1
	0	1	1	2	3	2	2	3	2	3
	1	1	1	2	3	2	3	3	3	3

Number of 2nd degree relatives with CRC before age 55	0	Number of 2nd degree relatives with CRC at 55 or older	2	1	2	3	3	3	3	3	3	3
			3	2	2	3	3	3	3	3	3	3
			4	2	3	3	3	3	3	3	3	3
	1		0	1	2	3	3	2	3	3	3	3
			1	2	3	3	3	3	3	3	3	3
			2	3	3	3	3	3	3	3	3	3
	2		0	2	3	3	3	3	3	3	3	3
			1	3	3	3	3	3	3	3	3	3

8.2.3 Evidence summary and recommendations

Evidence summary	Level	References
Category 1 – Those near average risk Approximately 95–98% of the population are in this category. Those with a weak family history, which is approximately 65% of those with any family history, will also be in this category. For the majority of people, the risk of colorectal cancer ranges from slightly below average to slightly above average. For some people, risk will be increased up to two-fold the average risk. Approximately 10% of people in this group will develop colorectal cancer in their lifetime.	II, III-2	[17], [18], [19], [20], [21], [22], [23], [24]
Category 2 – Those at moderately increase risk Approximately 2–5% of the population 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	[2], [4], [14], [15], [16], [17]
Category 3 – Those at potentially high risk Less than 1% of the population 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	[25], [26], [27], [28]

Important note: These recommendations are in relation to the risk of colorectal cancer for relatives of patients with colorectal cancer. For recommendations about tailored screening categories 1-3, please see Screening strategies for people with a family history of colorectal cancer.

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.

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8.2.3.1 Considerations in making these recommendations

There was robust discussion by the Working Party about the categories of risk outlined in this chapter. For category 3, there was discussion regarding the decision to exclude people known to have, or with a high probability of having, a high-risk familial syndrome due to a genetic predisposition to colorectal cancer. Ultimately the Working Party was in agreement about the three-level risk categorisation and feel this is adequately outlined in the chapter.

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8.2.4 Health system implications

8.2.4.1 Clinical practice

The RACGP recommended use of validated family history screening questionnaire to identify people in general practice with significant family history of cancer.[29]

Under-ascertainment of people with a significant family history to general practice requires the need for more proactive approaches in primary care to identify families at increased risk of CRC.

8.2.4.2 Resourcing

There are no known resourcing implications.

8.2.4.3 Barriers to implementation

Current GP software systems do not support systematic family history collection or risk assessment here.

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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 insufficient 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 and the removal of pre-malignancies, 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. Therefore older studies may be more relevant to estimates of familial risk.

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. These algorithms should also assess the effect on the accuracy of risk stratification of including personal risk factors for colorectal cancer other than family history.

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.

Next section: screening strategies for people with a family history of colorectal cancer

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8.2.7 Appendices

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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 average population. Based on this, the current practice in Australia and in many other countries is to have more intensive or frequent screening for those with stronger family history. The majority of screening guidelines recommend biennial faecal occult blood test (FOBT) or 10-yearly colonoscopy for the lowest risk category, 5-yearly colonoscopy for the middle risk category and annual or biennial (every two years) colonoscopy for the highest risk category which includes those with high risk familial syndromes.[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 colonoscopy for people at moderately increased risk (category 2) and people at 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 a high-risk familial syndrome, and included flexible sigmoidoscopy every 1–2 years for familial adenomatous polyposis (FAP), and annually or at least once every two years beginning at age 25 years or five years earlier than the age at diagnosis of the earliest cancer in the family for Lynch syndrome.[4]

An alternative to recommending an increase in screening modality for people in higher risk categories, is to recommend screening to begin at an earlier age, under the assumption that increased risk due to family history applies to each age category. Screening regimens could be based on absolute risk – following a 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 at lower risk based on family history.

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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 on: the 2005 edition of this guideline[4]; the systematic reviews performed for the Colorectal cancer risk according to family history and the Evidence for benefit from population screening sections; selected subsequent articles and international guidelines; and consensus. Please see Guideline development process for more information.

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]

8.3.2.2 Absolute risk

The 10-year risk of colorectal cancer for: the average risk population along with those at two-fold risk (both category 1); those at three- to six-fold increased risk (category 2); and those at seven- to ten-fold risk, can be calculated from population-based statistics (Table 5.4). 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 in turn 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 5.4. Ten-year absolute risks of colorectal cancer (%) based on age and level of increased risk due to family history

Number of first-degree relatives with colorectal cancer	Multiplication of population risk due to family history (RR)	Age 30	Age 35	Age 40	Age 45	Age 50
0	0.9	0.07%	0.12%	0.25%	0.5%	0.9%
1	2	0.15%	0.29%	0.59%	1.1%	1.9%
2	3-6	0.30%	0.60%	1.20%	2.2%	3.8%
3+	7-10	0.60%	1.2%	2.4%	4.8%	7.6%

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 at least as high as the risk of a 50 year-old at average risk who are recommended to begin 2-yearly iFOBT screening in this chapter.

The red shaded cells represent risks approximately 4% of higher that are recommended 5-yearly colonoscopy in this chapter.

Source: Incidence data from AIHW Australian colorectal cancer incidence for males and females combined for the year 2000.[6]

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8.3.3 Screening by risk category

8.3.3.1 Category 1 — Those near average risk

Category	Family history	Screening recommendation
1	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	iFOBT every 2 years from age 50 to age 74

Sources: St John et al (1993)[7], Fuchs et al (1994)[8], Slattery et al (1994)[9], Bass et al (2008)[10], Schoen et al (2015)[11], Taylor et al (2011)[1], Lynch et al (2003)[12], Hall et al (1996)[13], Leu et al (2008)[14], Benhamiche-Bouvier et al (2000)[15], Sandhu et al (2001)[16], Aitken et al (1996)[17], Anderson et al (2003)[18]

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.

The yield of clinically significant lesions at screening colonoscopy is low (see Colorectal cancer risk according to family history).[17][19][20][21][22] 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 average population.[23][24] 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.[25]

- See the evidence-based recommendation: 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 also the evidence-based recommendation on aspirin use for people aged 50–70 years who are at average risk 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.

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8.3.3.2 Category 2 — Those at moderately increased risk

Category	Family history	Screening recommendation
2	One first-degree relative with colorectal cancer diagnosed under 55 years Two first-degree relatives with colorectal cancer diagnosed at any age One first-degree relative and at least two second-degree relative with colorectal cancer diagnosed at any age	iFOBT every 2 years from age 40 to age 49. Colonoscopy every five years from age 50 to age 74.

Sources: St John et al (1993)[7], Fuchs et al (1994)[8], Slattery et al (1994)[9], Bass et al (2008)[10], Schoen et al (2015)[11], Taylor et al (2011)[1], Lynch et al (2003)[12], Hall et al (1996)[13], Leu et al (2008)[14], Benhamiche-Bouvier et al (2000)[15], Sandhu et al (2001)[16], Aitken et al (1996)[17], Anderson et al (2003)[18]

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.

For people in this category, their risk of colorectal cancer is as high at age 40 as the average population is at age 50 (see Colorectal cancer risk according to family history). Their risk of colorectal cancer at age 40 is approximately 1%, which is equivalent to the risk for people in category 1 at age 50.

Accordingly, 2-yearly screening from age 40 is appropriate. By age 50 their 10-year colorectal cancer risk is approximately 4%, which is sufficiently high to warrant screening by 5-yearly colonoscopy.

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.

Practice point

- 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

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.

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8.3.3.3 Category 3 — those at potentially high risk

Category	Family history	Screening recommendation
3	At least three first-degree or second-degree relatives with colorectal cancer, with at least one diagnosed under 55 years At least three first-degree relatives with colorectal cancer diagnosed at any age	iFOBT every 2 years from age 35 to age 44. Colonoscopy every five years from age 45 to age 74.

Sources: St John et al (1993)[7], Fuchs et al (1994)[8], Slattery et al (1994)[9], Bass et al (2008)[10], Schoen et al (2015)[11], Taylor et al (2011)[1], Lynch et al (2003)[12], Hall et al (1996)[13], Leu et al (2008)[14], Benhamiche-Bouvier et al (2000)[15], Sandhu et al (2001)[16], Aitken et al (1996)[17], Anderson et al (2003)[18]

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.

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.[26] 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.

For people in this category, their risk of colorectal cancer is as high at age 35 as the average population is at age 50 (see Colorectal cancer risk according to family history). Their risk of colorectal cancer at age 35 is approximately 1.2%, which is equivalent to the risk for people in category 1 at age 50.

Accordingly, 2-yearly iFOBT screening from age 35 is appropriate. By age 45 their 10-year colorectal cancer risk ranges from approximately above 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 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.

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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 average population screening is appropriate by biennial iFOBT from age 50 to 74 years. For those with one affected first-degree relative, 10 year risk at age 45 is about 1% so biennial iFOBT could be considered from age 45.	II, III-2	[17], [19], [20], [21], [22]
Category 2 - Those at moderately increase risk The risk of colorectal cancer is as high at age 40 as the average population is at age 50, so population-based screening is appropriate until age 50. The 10-year risk of colorectal cancer from age 50 is approximately 4%, so five-yearly colonoscopy is justified from age 50.	II, III-2	[7], [9], [13], [15], [16], [17]
Category 3 - Those at potentially high risk	II, III-2	[27], [28], [29], [30]

Evidence summary	Level	References
This group excludes those known to be, or suspected to have a cancer genetic syndrome based on tumour or genetic testing of relatives. The risk of colorectal cancer is as high at age 35 as the average 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 4%, so five-yearly colonoscopy is justified from age 45.		

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**

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8.3.5 Health system implications

8.3.5.1 Clinical practice

Since the last guidelines, the National Bowel Cancer Screening Program has been funded with a phased roll-out. By 2019 it will offer all Australians free colorectal cancer screening from age 50-74 by biennial iFOBT. These guidelines recommend that all people in Category 1 avail themselves of this screening program which will be sufficient given their risk of colorectal cancer.

These guidelines differ from the previous guidelines12 in in a number of ways. There have been some 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 for category 2 and category 3, screening begins with iFOBT before age 50, before transitioning to colonoscopy at a later age.

8.3.5.2 Resourcing

Resources must be in place to support the continued expansion of the NBCSP to complete rollout of screening every two years (biennial screening) by 2020.

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.

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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, such as observational studies and 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 is 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][31]

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, evaluate the screening strategies and further examine the relationship between risk and age.

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

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8.3.8 Appendices

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Systematic review report FHS1

9 High-risk familial syndromes

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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 may not be reliably detected by sequencing either in panels or exome sequencing and may still need gene specific testing using the technique of MLPA though detection of these mutations through software algorithms applied to next gen sequencing approaches is quickly improving . These next gen strategies are now a lot 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 when only Sanger sequencing is available.

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

Syndrome	Gene responsible	Inheritance	Typical phenotype	Extracolonic manifestations
	EPCAM deletion leading to		Early onset colorectal cancer, particularly in the proximal colon.	Endometrial, ovarian, gastric, pancreatic, urothelial, renal pelvic,

Syndrome	Gene responsible	Inheritance	Typical phenotype	Extracolonic manifestations
Lynch syndrome*	epigenetic silencing of MSH2 , MLH1, MSH6 or PMS2	Autosomal dominant	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	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
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

Syndrome	Gene responsible	Inheritance	Typical phenotype	Extracolonic manifestations
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). Cowden Syndrome is often associated with 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.

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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. Genetic testing is highly specific for the syndromes in question, and, for most genes, highly sensitive. There remains a small group of patients and families meeting phenotypic diagnostic criteria for the various syndromes where a mutation in the relevant gene is not identified. This could be because of cryptic mutations difficult to uncover, or because another gene, yet to be discovered, is responsible. This means that phenotypic diagnoses need to be respected for management purposes even if a genotype has not been characterised.

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.

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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 Chapter subsections

Please see sections:

- 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

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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 may not be reliably detected by sequencing either in panels or exome sequencing and may still need gene specific testing using the technique of MLPA though detection of these mutations through software algorithms applied to next gen sequencing approaches is quickly improving . These next gen strategies are now a lot 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 when only Sanger sequencing is available.

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*	EPCAM deletion leading to epigenetic silencing of MSH2 , MLH1, MSH6 or PMS2	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				

Syndrome	Gene responsible	Inheritance	Typical phenotype	Extracolonic manifestations
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
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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). Cowden Syndrome is often associated with 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.

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- 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.

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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. Genetic testing is highly specific for the syndromes in question, and, for most genes, highly sensitive. There remains a small group of patients and families meeting phenotypic diagnostic criteria for the various syndromes where a mutation in the relevant gene is not identified. This could be because of cryptic mutations difficult to uncover, or because another gene, yet to be discovered, is responsible. This means that phenotypic diagnoses need to be respected for management purposes even if a genotype has not been characterised.

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.

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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 Chapter subsections

Please see sections:

- 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

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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 lesions known as 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.

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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.

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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]

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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.

Practice point

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).

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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)

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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.

Next section: MUTYH associated polyposis

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9.3 MUTYH associated polyposis

Contents

9.3.1 Background

MUTYH-associated polyposis is a recessively inherited predisposition to adenomatous 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]

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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).

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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
- both adenomatous and serrated polyps where the adenomatous polyps dominate

Practice point

- 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.

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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]

Next section: Lynch syndrome

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9.3.3 References

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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 a deletion of the last few exons of the gene EPCAM that results in epigenetic silencing of MSH2. 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.

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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.[6][7]

It should be noted that evidence to support the cost-effectiveness of universal testing of colorectal cancers in Australia is not yet available, but that this is an area of ongoing active research.[6]

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9.4.2.1 Universal testing of colorectal cancers

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).

There is no recommendation whether universal testing should 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.[8]

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.[9][2][3][8] 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. However, where adenomas are the only neoplastic tissue available (especially if >1cm in size) within a family for mismatch repair expression testing, such testing should be done. An informative test is helpful, though a negative test is not.

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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. [9][2][3][8] Currently available appropriate risk prediction models are PREMM or MMRpro. A simpler algorithm but with less evidence of validity is the Management for Lynch Syndrome protocol on EviQ. 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.

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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][9][2][3][4][8][10]

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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]

Genetic Testing for Hereditary Mutations in the Mismatch Repair Genes (MMR-genes) protocol on eviQ includes the following flow chart

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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, characterized by mismatch repair deficiency with loss of expression of the MMR proteins, 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.[11] 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.

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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][9][2][3][8] 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 are no data to directly guide this.[2][8]

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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][10] 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][10] Functional outcome is however better after segmental colectomy and this procedure can still be considered in older patients.[3][10] 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][10] 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]

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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.

Next section: Peutz-Jeghers syndrome

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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% (similar to BRCA mutation risk women) and gynaecological cancer 18% and surveillance for these cancers is recommended. There is also a 11–26% lifetime risk of pancreatic cancer. [2]

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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.

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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 every 3 years indefinitely.

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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.

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9.5.2.3 Surveillance

Colonoscopy should be performed at age 8 years and then 3 yearly from age 18.[1]

Surveillance for gastrointestinal polyps	■ Starting at age 8 years of age (or earlier with onset of symptoms) ■ annual haemoglobin ■ baseline Video Capsule Endoscopy (VCE) or Magnetic Resonance Endoscopy (MRE) repeated every 3 years ■ baseline gastroduodenoscopy and colonoscopy ■ if no polyps found: recommence at 18 years and repeat every 3 years ■ if polyps are found screening should occur at least every 3 years or more frequently as determined by polyp load

Next section: Juvenile polyposis syndrome
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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. Some patients may also manifest hereditary haemorrhagic telangiectasia.

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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.

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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.

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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).

Next section: serrated polyposis syndrome
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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.

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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]

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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.

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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.

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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] There is not clear evidence regarding the age to commence screening of first degree relatives but reasonable choices would be age 40 or 10 years younger than the youngest age of serrated polyposis syndrome diagnosis in the family, whichever comes first.

Next section: supplement state and territory-based familial cancer registries

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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.

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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	Queensland Familial Cancer Registry (QFCR) Website: https://www.health.qld.gov.au/ghq/qfbcr/default.asp 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.
	Familial Cancer Registry (Genetic Services of Western Australia)

State/Territory	Registry details
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

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10 Imaging a patient with a diagnosis of CRC

Chapter subsections

Please see sections:

- Colon cancer
- Rectal cancer
- Addenda: rectal MRI cancer report

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]

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10.1.2 Overview of evidence (non-systematic literature review)

No systematic reviews were undertaken for this topic. Practice points were based on selected evidence and guidelines. Please see Guidelines Development for more information.

10.1.3 Initial staging investigations

CT of the chest, abdomen and pelvis is the recommended imaging investigation to stage colon cancer.[1][3][4]

10.1.3.1 CT of chest, abdomen and pelvis

10.1.3.1.1 Protocol

The protocol should involve a post-intravenous contrast-enhanced CT of the chest, abdomen and pelvis, with oral contrast.[1][3][4]

10.1.3.1.2 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.

10.1.3.2 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.

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10.1.4 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.

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10.1.5 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.

10.1.5.1 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 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.

See Follow-up after curative resection for colorectal cancer chapter for further information regarding surveillance imaging.

Next section: imaging rectal cancer
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10.1.6 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.

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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]

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10.2.2 Overview of evidence (non-systematic literature review)

No systematic reviews were undertaken for this topic. Practice points were based on selected evidence and guidelines. Please see Guidelines Development for more information.

Many studies, including the MERCURY trial, have demonstrated the ability of MRI to provide important prognostic information about the staging of the tumour and relationship to the mesorectal fascia (MRF) which is the potential circumferential resection margin (CRM). Using high resolution scan technique, MRI has been shown to have good accuracy in assessing the depth of T3 extension, distance of tumour to the CRM, lymph nodes assessment by morphological criteria, and the presence of extramural venous invasion (EMVI).[3][4][5][6][7]

10.2.3 Initial staging investigations

10.2.3.1 High-resolution MRI

High-resolution MRI of the rectum is the recommended primary staging imaging investigation.[8][9][10][11][1][12]

10.2.3.1.1 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]

10.2.3.1.1.1 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 [10] 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.

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10.2.3.1.2 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).[13] If free text is used, it should include all of the above information.

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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)
- 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.

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10.2.3.2 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.[8]

10.2.3.2.1 Protocol

Post intravenous contrast enhanced CT chest abdomen and pelvis with oral contrast.[8][11][12]

10.2.3.2.2 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.

10.2.3.2.3 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.

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10.2.3.2.4 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.[8][9][11]

10.2.3.3 Further staging investigations

As per colon cancer.

10.2.3.4 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.[14]

10.2.3.4.1 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.

10.2.3.4.2 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).[15]

10.2.3.4.2.1 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

Score	Definition
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[15]

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10.2.3.5 Surveillance imaging

As per colon cancer.

10.2.3.6 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.

Next section: rectal MRI cancer report

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10.2.4 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.
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5. ↑ MERCURY Study Group.. *Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study.* BMJ 2006 Oct 14;333(7572):779 Available from: http://www.ncbi.nlm.nih.gov/pubmed/16984925.

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8. ↑ 8.0 8.1 8.2 8.3 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.
9. ↑ 9.0 9.1 New Zealand Guidelines Group. *Colorectal cancer: Management of Early Colorectal Cancer.* Wellington: Ministry of Health; 2011.
10. ↑ 10.0 10.1 National Comprehensive Cancer Network. *NCCN Guidelines: Colon Cancer.* National Comprehensive Cancer Network; 2016.
11. ↑ 11.0 11.1 11.2 Radiologists TRCo. *Recommendations for cross-sectional imaging in cancer management - colon, rectum and anal cancer.* Radiologists TRCo; 2014.
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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

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11 Pathology and staging

Staging of colorectal cancer refers to the classification of the tumour according to the extent of spread in a manner that has a clinically useful correlation with prognosis.

Applications of staging include patient management, quality assurance and research.

A number of imaging techniques, including CT scan, MRI, PET scanning, and endorectal ultrasound, can be used to define the extent of tumour spread before treatment (see Imaging for colon cancer and Imaging for rectal cancer). There is, however, no known, reliable, preoperative staging system that correlates accurately with patient survival.

Chapter subsections

Please see:

- 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
- Molecular profiling of colorectal cancer (PTH1)

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11.1 Introduction: pathology and staging

Staging of colorectal cancer refers to the classification of the tumour according to the extent of spread in a manner that has a clinically useful correlation with prognosis.

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11.2 Development of post-surgical staging

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11.2.1 Development of post-surgical staging

The first well-documented and tested staging system was that of Dukes.[1] This classification system was based entirely on the extent of direct tumour spread through the bowel wall and the presence or absence of lymph node metastases in the resected specimen. Although Dukes staging was originally conceived for rectal cancer, it is also applicable to colon cancer. Dukes stages A, B and C correlate well with patient survival, and are easy to recall and apply. For these reasons the system is widely adopted and remains an objective, unambiguous classification adaptable to multidisciplinary patient care. However, the Dukes system does not address the important issue of ‘residual tumour’ identified by the surgeon at the time of bowel resection, either local due to tumour transection or due to known distant metastases.

The Dukes (A, B, C) system was further modified 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 involvement by direct spread
C	C1	Local nodes involved
	C2	Apical nodes involved
D	D1	Tumour transected (histological)
	D2	Distant metastases (clinical or histological)

Source: Davis and Newland 1983[3]

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A TNM system acceptable to both the Union Internationale Contre Le Cancer (UICC) and the American Joint Committee for Cancer (AJCC)[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 now in its 8th edition (implementation date 1/1/2018) 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.[9] 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), and the MX code was deleted. In the 8th edition, the definitions of carcinoma in situ and lymph node status have been further refined. A separate M code has been introduced for peritoneal carcinomatosis, which has been separated out from M1b into M1c. The prognostic and predictive implications of microsatellite instability (MSI), mutations of KRAS, NRAS and BRAF are also discussed.

11.2.1.2 Table 8.2. Pathological TNM staging nomenclature

T — primary tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ: intramucosal (involvement of lamina propria with no extension through muscularis mucosae)
T1	Tumour invades submucosa (through muscularis mucosae but not into the muscularis propria)
T2	Tumour invades muscularis propria
T3	Tumour invades through muscularis propria into pericolorectalic (subserosal) tissues
T4	Tumour invades the visceral peritoneum or invades or adheres to adjacent organ or structure
T4a	Tumour penetrates to the surface of the visceral peritoneum (including gross perforation of the bowel through areas of inflammation to the surface of the visceral peritoneum)
T4b	Tumour directly invades or adheres to other organs or structures
N - regional lymph node	
NX	Regional lymph nodes cannot be assessed
NO	No regional lymph nodes metastases
N1	One to three regional nodes are positive (tumour in lymph nodes measuring >0.2mm), or any number of tumour deposits are present and all identifiable lymph nodes are negative
N1a	One regional lymph node is positive
N1b	Two or three regional lymph nodes are positive
N1c	No regional lymph nodes are positive, but there are tumour deposits in the ■ subserosa ■ mesentery ■ or non-peritonised pericolic or perirectal/mesorectal tissues
N2	Four or more regional lymph nodes are positive
N2a	Four to six regional lymph nodes are positive
N2b	Seven or more regional lymph nodes are positive
M — distant metastasis	

T — primary tumour	
MO	No distant metastasis by imaging, etc; no evidence of tumour in distant sites or organs (This category is not assigned by pathologists.)
M1	Metastasis to one or more distant sites or organs or peritoneal metastasis is identified
M1a	Metastasis to one site or organ is identified without peritoneal metastasis
M1b	Metastases to two or more sites or organs is identified without peritoneal metastasis
M1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastases

Source: AJCC 2017[9]

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11.2.1.3 Table 8.3. AJCC prognostic stage groups

Stage	T	N	M
0	Tis	N0	M0
I	T1 T2	N0 N0	M0 M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-T2 T1	N1/N1c N2a	M0 M0
IIIB	T3-T4a T2-T3 T1-T2	N1/N1c N2a N2b	M0 M0 M0
IIIC	T4a T3-T4a T4b	N2a N2b N1-N2	M0 M0 M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b
IVC	Any T	Any N	M1c

Source: AJCC 2017[9]

Next section: post-surgical staging following neoadjuvant therapy

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11.2.2 References

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11.3 Post-surgical staging following neoadjuvant therapy

Post\-surgical staging following neoadjuvant therapy

A subset of patients with primary 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 direct spread 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 TNM stage following neoadjuvant therapy.

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11.4 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.

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11.4.1 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.

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11.4.2 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.[1] The presence of an involved apical lymph node defines ACPS/Concord substage C2, but is not specified in the N classification of TNM staging.

11.4.3 Residual tumour

The ACPS/Concord stage D classifies the presence of residual tumour remaining after surgical resection of the primary tumour, at 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[2]. Should the histological assessment of lines of resection be incorporated into pTNM staging and involvement [1] 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). Notably the R classification definitions have changed in the latest edition of the AJCC staging manual. In the 7th edition R2 designated the total burden of residual disease, including the presence of distant residual tumour (e.g. unresected liver metastasis), whereas the 8th edition definition specifically refers only to locoregional residual tumour.[3][4]

11.4.3.1 Table 8.4. Residual Tumour R Classification

R — residual tumour	
RX	Presence of residual tumour cannot be assessed
R0	No residual tumour
R1	Microscopic residual tumour
R2	Macroscopic residual tumour at the primary cancer site or regional nodal sites (This designation is not used to indicate metastatic disease identified but not resected at surgical exploration)

Source: AJCC 2017[4]

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11.4.4 References

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11.5 Selection of staging system

11.5.1 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.

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. At the time of writing the College of American Pathologists' published protocol is based on the AJCC/UICC TNM 7th edition.[1] The Royal College of Pathologists of Australasia's protocol recommends the use of TNM 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.[2] The Royal College of Pathologists (UK) mandates the use of modified Dukes' staging in addition to TNM, specifically the 5th edition, to preserve the integrity of staging data for longitudinal analyses.[3]

When using the TNM 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/Concord 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.[4][5]

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 current AJCC staging systems.

11.5.1.1 Table 8.5. Translation between ACPS/Concord and AJCC staging system

ACPS	Concord substage	AJCC 8th edition (2017)				
		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	0-III	Any T	Any N	M0	R1-R2
	D2	IVA-IVC	Any T	Any N	M1a-M1c	Any R

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.

Next section: clinical input

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1. ↑ College of American Pathologists. *Protocol for Examination of Specimens From Patients With Primary Carcinoma of the Colon and Rectum. Version: ColoRectum 3.4.0.0.* CAP; 2016.
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11.6 Clinical input

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. This is facilitated by completion of a convenient proforma for conveying this information to the pathologist as shown in 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.

Figure 8.1. Cancer of the colon and rectum — information for the pathologist

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11.7 Additional information on pathology reporting

Contents

11.7.1 Prognostic factors independent of stage

The pathology report provides a histological confirmation of the diagnosis of colorectal cancer and summation of additional prognostic information that is used to guide further postsurgical clinical management of the patient.[1][2] Apart from tumour stage, the importance of including information on a range of other variables in the histopathology report is recognised (see Table 8.6). These variables include the components of stage and some other factors that have been shown to have a statistically independent 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.[3][4][5] Those having independent prognostic significance have also been included in current pathology reporting protocols. These include histological tumour type, tumour grade /differentiation, non-peritonealised circumferential margin status, and lymphatic and vascular invasion.[6][7][8] The extent of tumour spread beyond the bowel wall has been shown to have prognostic significance, and while subdivision of pT3 has not been adopted by the AJCC, the maximum distance of tumour extension beyond the muscularis propria may be reported as a measurement in millimetres.[9][10][7] The true significance of other features, such as the presence of perineural invasion, tumour budding, and discontinuous extramural tumour deposits not associated with lymph nodes, is still to be fully resolved.[11]

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11.7.2 Molecular markers

Molecular research has greatly advanced the understanding of colorectal carcinogenesis, but its impact on routine clinical practice has so far been limited.

11.7.2.1 Microsatellite instability (MSI), DNA mismatch repair (MMR) and Lynch syndrome

Up to 15% of colorectal cancers harbour multiple defects in repetitive non-coding regions of DNA known as microsatellites (microsatellite instability, MSI). This is the result of loss of DNA microsatellite mismatch repair (MMR) protein function.[12] MMR deficiency is the genetic defect in Lynch syndrome (hereditary non-polyposis colorectal cancer) which accounts for 2-3% of colorectal cancers. MMR deficient CRCs are more frequently right-sided and show distinctive histological features including prominent tumour-infiltrating lymphocytes, a pushing invasive tumour front, and mucinous or poor differentiation.[13] These tumours have been reported to be associated with higher risk of synchronous and metachronous tumours.[14] Their relationship to prognosis and responsiveness to FU-based chemotherapy remains controversial.[15][16][17]

Tumours that are right-sided, synchronous or metachronous, and/or show histological features described above should raise suspicion for MMR deficiency (sporadic or familial). Those that present under age 50, are associated with a strong family history or the presence of other Lynch syndrome associated cancers, further raise the possibility of Lynch syndrome.[18]

Immunohistochemical testing for the four MMR proteins (MLH1, MSH2, MSH6 and PMS2) is now widely available, and universal testing of colorectal cancers (or at least in patients under the age of 70) has been recommended for the detection of Lynch syndrome. See Lynch syndrome. The identification of a MMR deficient colorectal cancer also may have implications for selection of patients for adjuvant 5-FU based chemotherapy, and long term post-operative follow up..

11.7.2.2 BRAF mutation

Immunohistochemistry for the V600E mutated BRAF is now available, and is useful in distinguishing between sporadic and familial (Lynch syndrome) cases of MMR deficient colorectal cancer. Sporadic loss of MLH1 is commonly seen in elderly patients due to methylation of its promoter site, and BRAF mutation is commonly associated with hypermethylation.[19] In the context of MLH1 loss, the presence of mutated BRAF almost certainly indicates that the loss is due to MLH1 promoter methylation, and can be used to virtually exclude the possibility of Lynch syndrome.[20]

11.7.2.3 RAS mutation and anti-EGFR therapy

KRAS mutation status has been reported to be associated with response to anti-epidermal growth factor receptor (EGFR) therapy.[21] These agents have been shown to have a beneficial effect in some colorectal cancer patients with metastatic disease, and tumours harbouring mutations in KRAS and subsequently other genes in the RAS family have been found to be resistant to such treatment. Testing of tumour tissue for extended RAS (KRAS/NRAS) mutation status is recommended for patients with advanced colorectal cancer for whom anti-EGFR treatment is being considered.

Practice point

DNA mismatch repair status studies should be performed on all cases of colorectal cancer for the detection of Lynch syndrome.

Practice point

BRAF mutation studies should be performed in conjunction with DNA mismatch repair status studies to differentiate between sporadic and familial (Lynch syndrome) cases of DNA mismatch repair status-deficient colorectal cancer.

Practice point

Extended RAS mutation testing should be carried out on all patients at the time of diagnosis of metastatic colorectal cancer. Note: RAS testing is not currently pathologist-determinable and therefore can only be performed for metastatic colorectal cancer following a request from a specialist (surgeon or oncologist).

11.7.3 Structured reporting of colorectal cancer

The use of structured reporting in synoptic format has been recommended to ensure the consistent quality and completeness of data. Each variable should be recorded individually and explicitly in pathology reports. 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 13.6.[7]

11.7.3.1 Table 8.6. Reporting on colorectal cancer specimens

Pre-analytical data	
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	Measurement in mm
Site of the tumour	Caecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon, rectosigmoid junction, rectum

Maximal tumour diameter	Measurement in mm
Distance of tumour to nearer proximal or distal resection margin	Measurement in mm
Distance of the tumour to the circumferential margin	Measurement in mm
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 fascial envelope enclosing the perirectal fat (mesorectum)	Incomplete (grade 1), nearly complete (grade 2), complete (grade 3)
ˆAny involvement of the peritoneum	By direct spread, tumour nodule(s) discrete from the tumour mass
ˆNumber of lymph nodes placed in each cassette	
ˆNumber, diameter and gross configuration of polyps	
ˆAny 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, 2010[22])
Histological grade	Low grade (well and moderately differentiated) High 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	Involved or not involved

distal resection margins	Specify involved margin(s), microscopic clearance (specify in mm if less than 10mm)
Status of nonperitonealised circumferential margin in rectal tumours	Involved or not involved, microscopic clearance in mm
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 and Dukes
Venous and small vessel invasion	Intramural vein invasion, extramural vein invasion, small vessel invasion (not identified, present or extensive)
^Perineural invasion	Not identified, present or extensive
Histologically confirmed distant metastases	Present or absent Specify sites
Relevant coexistent pathological abnormalities	Polyps, ulcerative colitis, Crohn's disease, dysplasia, other
Microscopic residual tumour status (completeness of resection)	Text
Response to neoadjuvant therapy	Grade 0 (complete response): No viable cancer cells Grade 1 (moderate response): Single cells or small groups of (viable-appearing) 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)
^RAS gene mutation	KRAS and NRAS (exons 2, 3, 4)
Synthesis and summary	
	pTNM and Stage grouping

Tumour stage	ACPS stage (substage)
Year and/or edition of staging system	AJCC 2010, 7th edition ACPS
Residual tumour status	R classification
^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	Free text

^Guidelines

Source: RCPA 2016[7]

Practice point

Synoptic reporting is strongly recommended to capture the key variables to enable translation between major internationally recognised staging systems and facilitate multidisciplinary patient management.

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11.8 Optimal molecular profiling of CRC

Contents

11.8.1 Background

In recent years there has been an increasing focus on gene expression profiling to provide additional criteria for tumour sub-classification and improve prognostication, with the ultimate goal of individualising patient therapy. Numerous abnormalities in gene expression have been reported, the significance of which needs to be evaluated in well-designed studies of large clinical populations.

See Molecular pathology and biomarkers – implications for systemic chemotherapy.

11.8.2 Sampling and specimen handling considerations

The procurement of adequate tissue to determine the status of predictive and or prognostic biomarkers has become necessary to guide important treatment decisions.

The primary pathologist plays a central role in reviewing all available tissue samples and selecting the most appropriate tissue suitable for biomarker analysis. If there is inadequate quantity of neoplastic cells for analysis, false-negative results may occur due to dilution of mutant alleles. This is particularly relevant to RAS mutation analysis.[1][2] Most molecular testing can now be performed on archival paraffin embedded tissue, and this may be required several years after resection of the primary tumour. It is recommended that a suitable tissue block be designated for this purpose, which contains a high proportion of cancer (preferably >70%).[3]

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.

11.8.3 Systematic review evidence

In patients diagnosed with colorectal cancer who have undergone surgical resection or biopsy of the primary colorectal tumour, which molecular marker (BRAF/KRAS/NRAS/DNA mismatch repair /microsatellite instability) best predicts response to surgery, or adjuvant therapy or radiotherapy (disease-free survival, overall survival, disease-specific mortality, overall mortality, or relapse incidence)? (PTH1)

A total of 39 level II studies[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] and 66 level III-3 studies[43][44][45][46][47][48][49][50][51][52][53][54][55][56][57][58][59][60][61][62][63][64][65][66][67][68][69][70][71][72][73][74][75][76][77][78][79][80][81][82][83][84][85][86][87][88][89][90][91][92][93][94][95][96][97][98][99][100][101][102][103][104][105][106][107][108] were identified that evaluated the prognostic value of microsatellite stability status, DNA mismatch repair function, KRAS or BRAF mutation status for various outcomes related to patient response to treatment. All studies were at high risk of bias except 6 which were at medium risk of bias.[17][24][48][72][77][107]

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

11.8.4 Overall survival

11.8.4.1 KRAS mutation status

A total of 35 studies[6][12][15][19][23][24][28][29][30][39][42][45][46][49][55][56][58][62][64][65][74][77][79][80][81][85][86][91][95][97][98][99][102][106][108] reported the outcome of overall survival with respect to KRAS mutation status (any mutation versus wild type). All stages of colorectal cancer were included, as well as patients with metastatic disease.

Most studies reported a trend towards increased survival in those without KRAS mutations (wild-type KRAS), with half of the studies reporting at statistically significant difference.

No trends in overall survival and KRAS mutation status were reported against the clinical stage of colorectal cancer.

Thirteen studies[6][10][12][15][42][45][52][56][79][80][97][99][106] reported overall survival with respect to KRAS mutation status (any mutation versus wild type) in those who had anti-epidermal growth factor receptor (EGFR) treatment (cetuximab or panitumumab). Most studies reported a trend towards increased survival in those without KRAS mutations (wild-type KRAS), with nine of the studies reporting at statistically significant difference.

Nine studies[6][15][28][36][70][77][100][106][108] reported overall survival in respect to KRAS mutation status (any mutation versus wild-type) in those treated with the combination of leucovorin calcium (folinic acid), 5-fluorouracil (5FU) and oxaliplatin (FOLFOX). All but one study reported no statistically significant difference.

11.8.4.2 BRAF mutation status

A total of 25 studies[4][14][15][18][19][24][29][30][42][43][52][53][55][58][60][62][77][79][90][95][96][97][99][102][103] reported overall survival as an outcome with respect to BRAF mutation status. The majority of studies report better survival in those with wild-type BRAF tumour gene, and this was statistically significantly different in all but six studies.[4][14][55][58][62][103]

Six studies[18][42][52][60][79][97] reported overall survival as an outcome with respect to BRAF mutation status in those who had anti-EGFR treatment (cetuximab or panitumumab). All studies report better survival in those with wild-type BRAF tumour gene, and this was statistically significantly different in all six studies.

Five studies[4][15][18][43][77] reported overall survival as outcome with respect to BRAF mutation status (any mutation versus wild type) in those who had FOLFOX. All studies report a trend towards increased survival in those without BRAF mutations (wild-type BRAF), with all but one study[4] reporting a statistically significant difference.

11.8.4.3 Microsatellite stability status

A total of 20 studies[13][19][20][24][30][34][35][41][48][61][62][63][71][75][86][89][90][92][96][104] reported overall survival as an outcome with respect to microsatellite stability status. There was a slight trend towards better overall survival in those with microsatellite instability, with only nine studies[20][30][34][35][41][61][75][86][104] reporting a statistical significant difference.

Eighteen studies[4][5][14][15][17][21][31][32][34][35][53][61][67][68][69][76][93][107] reported overall survival as an outcome with respect to DNA mismatch repair function (proficient verse deficient, and vice versa). There was no reported consistent trends of significant between studies.

11.8.4.4 DNA mismatch repair status

Five studies[4][15][67][69][107] reported overall survival as an outcome with respect to DNA mismatch repair function (proficient verse deficient, and vice versa) in those who had FOLFOX treatment. There were no consistently reported trends across the studies.

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11.8.5 Progression-free survival

11.8.5.1 KRAS mutation status

A total of 21 studies[7][10][12][18][28][29][36][39][42][45][52][56][57][60][70][78][97][100][102][106][108] reported progression-free survival as an outcome with respect to KRAS mutation status. All studies reported a trend towards longer progression-free survival in those without primary tumour KRAS mutation, but fewer than 50% of studies reported a statically significant difference.

A total of 10 studies[7][10][39][45][52][56][57][60][97][106] reported progression-free survival as outcome with respect to KRAS mutation status (any mutation versus wild type) in those who had anti-EGFR treatment (cetuximab or panitumumab). Most studies reported a trend towards longer progression-free survival in those without KRAS mutations (wild-type KRAS), with six of the studies[7][39][52][56][57][97] reporting at statistically significant difference.

Six studies[7][18][36][70][100][108] reported progression-free survival as outcome in respect to KRAS mutation status (any mutation versus wild type) in those who had FOLFOX treatment. There were no consistently reported trends across the studies.

11.8.5.2 BRAF mutation status

Ten studies[18][26][29][42][52][57][60][96][97][102] reported progression-free survival as an outcome with respect to BRAF mutation status. All studies consistently reported longer progression free survival in those without BRAF mutation, and all but one study reported a statistically significant difference. All clinical grades of colorectal cancer were reported across these nine studies.[18][26][42][52][57][60][96][97][102]

A total of seven studies[18][26][42][52][57][60][97] reported progression free survival as an outcome with respect to BRAF mutation status in those who had anti-EGFR treatment (cetuximab or panitumumab). All studies reported longer progression-free survival in those with wild-type BRAF tumour gene, and this was statistically significantly different in six studies.[18][26][42][52][57][97]

11.8.5.3 Microsatellite stability status and DNA mismatch repair status

Five studies[21][66][68][69][96] reported progression-free survival as an outcome with respect to either microsatellite stability status or mismatch repair function status. No significant trends or differences were reported.

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11.8.6 Disease-free survival

11.8.6.1 KRAS mutation status

Twelve studies[19][23][24][25][40][46][49][51][55][62][73][77] reported disease-free survival as an outcome with respect to KRAS mutation status. Most studies consistently reported a trend towards longer disease free survival in those without KRAS mutations (wild-type KRAS). This difference was statistically significantly in only 5 of these studies.[19][25][49][51][73]

Four studies[25][51][73][77] reported disease-free survival as an outcome with respect to KRAS mutation status in those who had FOLFOX treatment. All studies consistently reported a trend towards longer disease-free survival in those without KRAS mutations (wild-type KRAS), but only two studies reported a statistically significantly difference.[25][73]

11.8.6.2 BRAF mutation status

Ten studies[14][19][24][53][55][62][74][77][82][90] reported disease free survival as an outcome with respect to BRAF mutation status. All studies consistently reported a trend towards longer disease free survival in those without BRAF mutations (wild-type BRAF). This difference was statistically significantly in five studies.[53][55][77][82][90]

11.8.6.3 Microsatellite stability status

Seventeen studies[13][19][22][24][34][35][40][41][54][59][62][71][75][82][89][90][105] reported disease-free survival as an outcome with respect to microsatellite stability status. Reported results were inconsistent across studies.

11.8.6.4 DNA mismatch repair status

Twelve studies[5][14][17][31][32][34][35][53][59][67][76][107] reported disease free survival as an outcome with respect to mismatch repair function. Most studies consistently reported a trend towards longer disease free survival in those with deficient mismatch repair function. This difference was statistically significant in eight studies.[5][14][17][31][32][35][53][107]

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11.8.7 Objective response rate

11.8.7.1 RAS mutation status

Five studies[10][12][27][70][79] reported objective response rate as an outcome with respect to KRAS or RAS (KRAS or NRAS) mutation status.

All studies consistently reported a trend towards greater response rate in those with wild-type KRAS tumours. This was statistically significant in three[12][27][79] of the five studies.

11.8.7.2 BRAF mutation status

One study[79] reported objective response rate as an outcome with respect to tumour BRAF mutation status. This single study reported a significantly greater objective response rate in those with tumour BRAF mutations.

11.8.7.3 DNA mismatch repair status

Three studies[21][68][69] reported objective response rate as an outcome with respect to mismatch repair function. No significant trends or differences were reported.

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11.8.8 Other outcomes

A number of other outcomes relating to treatment response were reported. These outcomes included pathological complete response, overall mortality, disease control rate, disease-specific survival, time to progression, disease recurrence, recurrence free survival, recurrence-free interval, distant metastases, clinical response, risk of recurrence, and time to recurrence. All these outcomes were reported in a single or very few studies, with few or no reported significant trends.

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11.8.9 Evidence summary and recommendations

Evidence summary	Level	References
Current evidence remains controversial as to the use of presently available molecular markers to predict prognosis and identify those patients who may benefit most from conventional adjuvant postoperative chemotherapy. There is emerging evidence to support the use of markers to inform specific targeted therapy.	II, III-2	[4], [5], [6], [7], [10], [12], [13], [14], [15], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28], [29], [30], [31], [32], [34], [35], [36], [39], [40], [41], [42], [43], [45], [46], [48], [49], [51], [52], [53], [54], [55], [56], [57], [58], [59], [60], [61], [62], [63], [64], [65], [66], [67], [68], [69], [70], [71], [73], [74], [75], [76], [77], [78], [79], [80], [81], [82], [85], [86], [89], [90], [91], [92], [93], [95], [96], [97], [98], [99], [100], [102], [103], [104], [105], [106], [107], [108]
RAS There is consistent evidence that KRAS mutations are predictive of decreased overall survival (all stages of diseases including metastatic disease), decreased progression free survival (all stages of diseases including metastatic disease), and poorer objective response rate. There is moderate consistent evidence that KRAS mutation predicts decreased disease free survival (stages I–IV) and decreased recurrence free survival (stages I–IV). There is moderate evidence that, among patients who received anti-EGFR treatment, those with RAS (KRAS or NRAS) mutated tumours had decreased overall survival and progression-free survival compared to anti-EGFR treated patients with wild-type RAS tumours.	II, III-2	[6], [12], [15], [19], [23], [24], [28], [30], [29], [39], [42], [45], [46], [49], [55], [56], [58], [62], [65], [64], [74], [77], [79], [80], [81], [85], [86], [91], [95], [97], [98], [99], [102], [106], [108], [7], [10], [18], [25], [27], [36], [40], [51], [52], [57], [60], [70], [73], [78], [100]
BRAF	II, III-2	[4], [14], [15], [18], [19], [24], [26], [29], [30], [42], [43], [52], [53], [55], [57], [58], [60], [62], [74], [77], [79], [82], [90], [95], [96], [97], [99], [102], [103]

Evidence summary	Level	References
There is consistent evidence that BRAF gene mutation is predictive for both decreased overall survival (all stages of diseases including metastatic disease) and progression free survival (all stages of diseases including metastatic disease). There is moderate consistent evidence that BRAF mutation is predictive for decreased disease free survival (stages I-IV) and recurrence free survival (stages I-IV). There is moderate evidence that, among patients who received anti-EGFR treatment, those with BRAF mutated tumours had decreased overall survival and progression-free survival than those with wild-type BRAF tumours. There is moderate evidence that, among patients who received FOLFOX treatment, those with BRAF mutated tumours had decreased overall survival than those with wild-type BRAF tumours.		
Microsatellite Instability There is consistent evidence that tumour microsatellite instability predicts longer time to disease recurrence (stages I–IV), increased recurrence free survival (stages II–III), and a longer recurrence free interval (stages II–III). There is inconsistent evidence that tumour microsatellite instability predicts increase overall survival (stages I-IV). Microsatellite stability status was not shown to predict progression-free survival or disease-free survival.	II, III-2	[4], [5], [13], [14], [15], [17], [19], [20], [21], [22], [24], [30], [31], [32], [34], [35], [40], [41], [48], [53], [54], [59], [61], [62], [63], [66], [67], [68], [69], [71], [75], [76], [82], [86], [89], [90], [92], [93], [96], [104], [105], [107]
Mismatch repair	II, III-2	[4], [5], [14], [15], [17], [21], [31], [32], [34], [35], [53], [59]

Evidence summary	Level	References
There is consistent evidence that tumour mismatch repair deficiency predicts increased disease free survival (stage II–III) and decreased risk of recurrence (stages I–IV). There is no consistent evidence that mismatch repair status predicts patient overall survival, progression free survival, or objective response rate.		[66], [67], [68], [69], [76], [96], [107]

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**

11.8.10 Health system implications of these recommendations

11.8.10.1 Clinical practice

Implementation of the recommendation would not change the way that care is currently organised.

11.8.10.2 Resourcing

No additional resourcing will be necessary to implement the recommendation.

11.8.10.3 Barriers to implementation

No barriers to the implementation of this recommendation are envisaged.

11.8.11 Discussion

11.8.11.1 Unresolved issues

The prognostic value of molecular markers is yet to be defined to a degree that can be used in routine pathological analysis.

11.8.11.2 Studies currently underway

Clinical trials are currently underway to test targeted therapies in BRAF-mutated metastatic colorectal cancer, akin to the development of therapies for BRAF-mutated metastatic melanoma. Early results are promising but have generally been less favourable than the melanoma trials.[109][110][111][112]

It is not known if there are other studies underway in this field.

11.8.11.3 Future research priorities

It is suggested that further studies are done to more precisely define the prognostic value of these molecular markers.

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11.8.12 References

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11.8.13 Appendices

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12 Preparation for surgery and perioperative optimisation

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 Chapter subsections

Please see sections:

- 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)

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12.1 Introduction: preparation for surgery and perioperative optimisation

12.1.1 Background

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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.

No randomised controlled trials (RCTs) were identified 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]

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.

Next section: perioperative anaemia management
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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]

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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]

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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]

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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] There 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]

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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.

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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.

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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]

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.

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12.4.3 References

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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.

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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 Screening for malnutrition and assessment of nutritional status

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 screening for malnutrition and also for formally assessing nutritional status which have been well validated in cancer patients. The nutritional risk index (NRI) and the Malnutrition Screening Tool (MUST) can be used to screen for malnutrition in cancer patients.[3] MUST can also be used for formal assessment of nutritional status, however the Patient Generated-Subjective Global Assessment Tool (PG-SSA) is the most accurate and comprehensive tool for assessing nutrition in cancer patients. For practical purposes, the MUST tool appears to be the cheapest and easiest tool to use in screening and assessment of colorectal cancer patients for malnutrition.

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12.5.2.2 Nutritional support and intervention

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.

Next section: Stomal therapy

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12.5.3 References

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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.

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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.

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12.6.3 References

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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]

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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]

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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.

Next section: enhanced recovery after surgery

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12.7.3 References

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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.

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12.8.3 References

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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.

Recent WHO Guidelines on surgical site infection prevention[22] suggested that oral antibiotics should be used routinely in combination with mechanical bowel preparation in patients undergoing elective colorectal surgery. This was a conditional recommendation on the basis of firstly examining studies comparing MBP with oral antibiotics compared to MBP without oral antibiotics, and secondly another comparison of patients receiving MBP compared to no MBP.[22] No RCT has yet been completed directly comparing patients receiving MBP, with oral and IV antibiotics with no MBP. Two studies are currently recruiting, one in Finland[23] and one in the USA[24], examining this question.

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.[25] 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.[25]

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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.[26][27][28][29][30][31][32][33][34][35][36][37][38][39][40][41]

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.[26][27][28][29][30][31][32][33][34][35][36][37][38][39][40][41] One study performed in Western Australia was directly applicable to Australian colorectal cancer patients.[35]

Outcomes of interest analysed included anastomotic leakage/dehiscence, surgical site/wound infection (including abscess), postoperative ileus and length of hospital stay.

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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.[26][27][28][29][31][32][33][35][36][38][41] No trial showed a statistically significant difference in anastomotic leak rate.

One trial[26] marginally favoured no mechanical bowel preparation, while two further trials}}[27][38] 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.[39]

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.[27][28][29][35]

One trial from Western Australia, compared patients receiving MBP (with PEG) to patients receiving a phosphate enema and found a trend favouring mechanical MBP with patients experiencing lower rates of anastomotic leaks in the MBP group (2% versus 4.8%).[35] In this study, the clinical anastomotic leak rate in the MBP group was lower than in 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). This did not reach statistical significance, however there was a significant difference between the groups in the number of patients requiring reoperations for anastomotic leaks (0% versus 4.1%: odds ratio (OR) 2.1; 95% confidence interval (CI) 1.83 to 2.30, p=0.01) The authors of this study were concerned regarding this finding and used this information on reoperation to terminate their study prematurely.

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.[28] 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).[39]

Three RCTs[27][28][29] and one subgroup analysis[39] 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[35][36][37][28][41][29][37][33] and one subgroup analysis[39] 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[34], and in another study in patients who had a diverting loop ileostomy.[39] In contrast, another study showed a non-significant trend to lower overall surgical site infection rate in patients with no MBP compared with MBP (29.2% versus 17.2%, p-value NS).[33]

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12.9.2.2.2 Deeper abdominal, intra-abdominal or wound abscess

Six RCTs[26][27][28][31][35][41] and one subgroup analysis[39] 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).[27][28][31][35][41] One trial[26]{{ 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 (with antibiotic prophylaxis) than the no-MBP group (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).[28]

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12.9.2.2.3 Organ/space surgical site infection

Two RCTs[40][33] reported organ/space surgical site infection rates and one RCT[36] reported intra-abdominal infection rates. There was no significant difference between groups taking MBP and not taking MBP.

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12.9.2.2.4 Mild or superficial surgical site/wound infection

Seven RCTs[33][40][26][38][31][30][28] and one subgroup analysis[39] 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[26][33][40] 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.

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12.9.2.2.5 Severe wound infection/subcutaneous wound disruption

One RCT[28] and one subgroup analysis of low anterior resection and diverting ileostomy[39] 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.[31]

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12.9.2.2.6 Wound dehiscence

One RCT[36] that reported wound dehiscence within 6 weeks post operation and one subgroup analysis[39] 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).[39]

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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).[29][31][36][38][40] There was no statistically significant difference in the incidence or duration of ileus between the groups.

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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).[27][28][29][30][31][32][35][36][38][40]

Five trials reported less than a day difference between arms with no statistically significant differences (p-values ranging from 0.4 to 0.73).[28][31][35][36][41] Four trials reported one day difference between arms but were not statistically significant.[27][29][30][32] One further trial[38] reported a 4.4 median day difference between arms, which favoured no MBP (with antibiotic prophylaxis) and similarly another trial[40] 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.[40][38]

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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	[26], [27], [28], [29], [31], [33], [35], [36], [38], [41]
	II	[27], [28], [31], [35],

Evidence summary	Level	References
Overall surgical site infection rates are not significantly altered by the use of MBP, regardless of antibiotics taken. One study (Contant 2007) did show a significant reduction in the intra-abdominal abscess rate in patients who received MBP.		[36], [37], [39], [41]
Incidence and duration of postoperative ileus is not impacted by usage of MBP.	II	[32], [34], [39], [40]
There is no statistically significant difference in hospital stay associated with usage of MBP.	II	[28], [31], [35], [36], [41], [27], [29], [30], [32], [38], [40]

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**

12.9.3.1 Considerations in making this recommendation

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.

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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.[42]

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.

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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.[23]

12.9.5.3 Future research priorities

There are two studies currently recruiting, one from Finland[23] and one from the USA[24], which are randomizing patients undergoing elective colorectal surgery to receive either mechanical bowel preparation and oral antibiotics or no mechanical bowel preparation with oral antibiotics. These studies should help determine the role of mechanical bowel preparation and oral antibiotics in elective colorectal surgery.

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12.9.6 References

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12.9.7 Appendices

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13 Elective and emergency surgery for colon and rectal cancer

Chapter subsections

Please see subsections:

- 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)

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? (COL1-2a)

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.

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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.

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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).

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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.

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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).

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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

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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]

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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]

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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.

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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

There is some evidence emerging of improved oncological results for colon cancer surgery with complete mesocolic excision and central vascular ligation.[49] Long-term data are awaited.

Next section: optimal approach to elective resection for rectal cancers

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13.1.4 References

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13.1.5 Appendices

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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? (COL1-2b)

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.

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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.

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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]

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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.

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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.

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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 are 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]

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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	**C**

Evidence-based recommendation	Grade
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.

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.

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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 two of the recent large randomised control trials which have not demonstrated pathological equivalence between open and laparoscopic rectal resection are awaited.[25][27] Long-term local recurrence and survival data are available for two other multicentre randomised controlled trials comparing open and laparoscopic rectal cancer resection which do demonstrate equivalence.[7][15] 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.

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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.

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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.

Next section: local versus radical resection for T1-T2 rectal tumours

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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? (REC3)

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.

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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.

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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.

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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]

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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]

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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	II, III-1	[3], [4], [5], [7], [8], [10], [11]

Evidence summary	Level	References
resection patients.		, [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]
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]

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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.

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.

Accurate pathological assessment of the specimen requires that the specimen is removed as a single specimen, regardless of the technique used. Piecemeal resection, whether performed as a surgical resection via local excision, TEMS or TAMIS, or endoscopically through endoscopic submucosal dissection (ESD) or endoscopic mucosal resection (EMR), will result in a compromised specimen with respect to the ability to assess it pathologically.

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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.

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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.

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13.3 Emergency management of malignant large bowel obstruction (COLMNG5)

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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.

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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? (COLMNG5)

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.

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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]

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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]

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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 ($p = 0.843$).

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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]
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]

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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.

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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.

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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.

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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.

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13.3.7 References

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13.3.8 Appendices

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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.

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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? (COLMNG3)

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.

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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]

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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.

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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
For patients with colorectal peritoneal metastases (either synchronous or metachronous to the primary), consider cytoreduction with perioperative intraperitoneal chemotherapy. Where this procedure is suitable, offer 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.

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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.

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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.

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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.

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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.

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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.

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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.

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13.4.5 References

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13.4.6 Appendices

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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] Patients 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 are seen in those with high risk clinicopathological features, which include a presentation with perforation or obstruction and pathology findings of T4 stage, less than 12 lymph nodes sampled, poor differentiation, neural or vascular invasion, and proficient mismatch repair.[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.

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14.1.1 Chapter subsections

Subsections:

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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.
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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] Patients 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 are seen in those with high risk clinicopathological features, which include a presentation with perforation or obstruction and pathology findings of T4 stage, less than 12 lymph nodes sampled, poor differentiation, neural or vascular invasion, and proficient mismatch repair.[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.

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14.1.1.1 Chapter subsections

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

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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.
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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]

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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] No benefit for overall survival was found.

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14.2.2.2 Addition of oxaliplatin to capecitabine (XELOX)

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 a control arm of 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).[6] 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 alternative to FOLFOX for adjuvant treatment for patients with stage III colon cancer.

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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.
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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]

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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] No benefit for overall survival was found.

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14.2.1.2.2 Addition of oxaliplatin to capecitabine (XELOX)

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 a control arm of 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).[6] 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 alternative to FOLFOX for adjuvant treatment for patients with stage III colon cancer.

Next section: adjuvant therapy elderly stage III CRC
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14.2.1.3 References

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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 are 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.

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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.

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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.

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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.

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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.

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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.

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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.

Next section: adjuvant therapy for stage II colon cancer

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14.2.2.4 References

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14.2.2.5 Appendices

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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.

Next section: Irinotecan and targeted agents (stage II-III colon)
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14.3.3 References

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14.3.1 Adjuvant therapy for stage II colon

14.3.1.1 Background

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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.

Next section: Irinotecan and targeted agents (stage II-III colon)
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14.3.1.3 References

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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 have 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 nor a biological agent (either bevacizumab or cetuximab) should be used as adjuvant therapy for patients with stage II or III colon cancer.

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14.4.2 References

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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 have 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.

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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.

Contents

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 Chapter subsections

Sections:

- 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

15.3 References

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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.

Contents

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 Chapter subsections

Sections:

- 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

15.1.3 References

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.
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15.2 Neoadjuvant therapy for rectal cancer

Contents

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 in determining T stage, 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 but may not impact on management.[10]

See Imaging for rectal cancer chapter

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.

15.2.2.1 Chapter subsections

Please see sections:

- Short course radiation treatment
- Neoadjuvant long-course chemoradiation (NEO1b)

15.2.3 References

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15.2.1 Neoadjuvant therapy for rectal cancer

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See Imaging for rectal cancer chapter

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15.2.1.2.1 Chapter subsections

Please see sections:

- Short course radiation treatment
- Neoadjuvant long-course chemoradiation (NEO1b)

15.2.1.3 References

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15.2.2 Short course radiation treatment

Contents

15.2.2.1 Background

Short-course radiation treatment (usually as 25 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.

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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.

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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 (50.4 Gy in 28 fractions) plus bolus fluoropyrimidine chemotherapy in 312 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.

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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.

Next section: neoadjuvant long-course chemoradiation
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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]

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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.

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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).

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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.

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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 undergoing 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 preoperative treatment 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
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.

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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.

Next section: 'watch and wait' approach after clinical complete response to neoadjuvant chemoradiation

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15.2.3.7 Appendices

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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.

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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][16] 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. Six[8][10][11][12][13][14] of the 12 studies compared patients who had a clinical complete response to neoadjuvant therapy who were then placed into a ‘watch and wait’ follow-up protocol to those that had incomplete clinical response to neoadjuvant treatment and then proceeded to surgery. One study[6] compared patients with a radiologic complete response across three treatment groups: radical surgery, local excision, or wait-and see and another study[15] compared patients who had a complete clinical response and underwent either radical resection or watch’-and-wait’ treatment. For the remainder of the studies, the comparison arm consisted of patients who had a pathological complete response to neoadjuvant treatment and proceeded to surgery[5][6][7][9]. There was variability between studies as to the timing of, and method/s by which cCR was determined, including several combinations of examination, endoscopic, CEA, MRI, CT and PET studies. 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 four studies had a low risk of bias.[12][13][14][15]

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.

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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]

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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.

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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]

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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]

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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	[4], [5], [6], [7], [8], [9], [11], [12], [14], [15], [16], [18]
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
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.	**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.

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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.

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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.

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15.3.5 Appendices

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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.

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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.

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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.

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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.

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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.

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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.

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15.6 Adjuvant therapy for rectal cancer

Chapter subsections

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15.6.1 Adjuvant therapy for rectal cancer

Chapter subsections

See sections:

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- 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.

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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 an 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 were no differences 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.

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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.

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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 are 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.

Next section: postoperative radiation treatment
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15.6.3 Postoperative radiation treatment

15.6.3.1 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.

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.

Next section: discussion

15.6.3.2 References

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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.

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16 Management resectable locally recurrent and metastatic disease

Following curative treatment of colorectal cancer, 15–20% of stage II and 30–40% of stage III colorectal cancers will recur.[1][2][3] The purpose of follow-up after curative resection is to allow early detection of these recurrences so that further curative resection may be undertaken if appropriate (see Follow-up after curative resection for colorectal cancer).

Previous studies documenting the patterns of recurrence after curative resection of colorectal cancer have found systemic recurrence to be most common followed by locoregional recurrence and both systemic and locoregional recurrence.[4][5] The management of these recurrences is complex and needs to be tailored to individual needs, based on the extent of disease, the severity of symptoms, physical fitness for further treatment, and the patient's values and preferences.

Multidisciplinary care is important as most of these patients will have complex needs that will require input from surgical teams, medical oncology teams, radiation oncology teams and palliative care. Although clinicians are at the forefront of these patients' management, input from nurses (palliative care nurses) and other allied health members (stomal therapists, dietitians, physiotherapists, psychologists and social workers) is also indispensable in ensuring holistic care, a seamless transition from hospital to community care and, if appropriate, end-of-life care.

Surgical treatment of resectable metastatic disease and resectable local recurrences has come a long way in the past decade. Improved staging modalities, understanding of what drives long-term survival in patients and improved chemotherapy options have all allowed increasingly aggressive management of systemic and local recurrences. Depending on the pattern of recurrence (e.g. systemic versus locoregional), patients will require slightly different investigations, although the key objectives remain the same:

- to confirm the presence of recurrence
- to stage the disease accurately so as to determine disease resectability
- to rule out more widespread disease that may preclude curative resection.

See also:

Imaging a patient with diagnosis of colon/rectal adenocarcinoma

Follow-up after curative resection for colorectal cancer

Chapter subsections

Sections:

- Investigation of recurrent colorectal cancer
- Management of locally recurrent resectable colorectal cancer (MNG13)
- Management of resectable metastatic colorectal cancer (MNG14)

1. ↑ 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.
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16.1 Introduction: management resectable locally recurrent and metastatic disease

Following curative treatment of colorectal cancer, 15–20% of stage II and 30–40% of stage III colorectal cancers will recur.[1][2][3] The purpose of follow-up after curative resection is to allow early detection of these recurrences so that further curative resection may be undertaken if appropriate (see Follow-up after curative resection for colorectal cancer).

Previous studies documenting the patterns of recurrence after curative resection of colorectal cancer have found systemic recurrence to be most common followed by locoregional recurrence and both systemic and locoregional recurrence.[4][5] The management of these recurrences is complex and needs to be tailored to individual needs, based on the extent of disease, the severity of symptoms, physical fitness for further treatment, and the patient's values and preferences.

Multidisciplinary care is important as most of these patients will have complex needs that will require input from surgical teams, medical oncology teams, radiation oncology teams and palliative care. Although clinicians are at the forefront of these patients' management, input from nurses (palliative care nurses) and other allied health members (stomal therapists, dietitians, physiotherapists, psychologists and social workers) is also indispensable in ensuring holistic care, a seamless transition from hospital to community care and, if appropriate, end-of-life care.

Surgical treatment of resectable metastatic disease and resectable local recurrences has come a long way in the past decade. Improved staging modalities, understanding of what drives long-term survival in patients and improved chemotherapy options have all allowed increasingly aggressive management of systemic and local recurrences. Depending on the pattern of recurrence (e.g. systemic versus locoregional), patients will require slightly different investigations, although the key objectives remain the same:

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- to stage the disease accurately so as to determine disease resectability
- to rule out more widespread disease that may preclude curative resection.

See also:

Imaging a patient with diagnosis of colon/rectal adenocarcinoma

Follow-up after curative resection for colorectal cancer

Chapter subsections

Sections:

- Investigation of recurrent colorectal cancer
- Management of locally recurrent resectable colorectal cancer (MNG13)
- Management of resectable metastatic colorectal cancer (MNG14)

1. ↑ 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.
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16.2 Investigation of recurrent colorectal cancer

Contents

16.2.1 Background

16.2.1.1 Presentation of local recurrence

Patients with local recurrence may be symptomatic or asymptomatic.

Symptoms of local recurrence depends on the site of recurrence and therefore can vary between patients:

- In patients with anastomotic or luminal recurrences, symptoms are usually similar to those of patients with primary colorectal cancer in that patients usually present with rectal bleeding, anaemia or altered bowel habits. Depending on the extent of the local recurrence, patients may also present with varying degrees of bowel obstruction. Where there has been a previous low rectal anastomosis, the luminal recurrence may be readily palpable on digital rectal examination during routine follow up. In patients who have previously undergone an abdominoperineal excision, clinical findings may be limited.
- Patients with nodal or surgical bed recurrences may present with pain from mass effect on neighbouring structures (such as obstruction of ureters or neuropathic pain from the sciatic nerve compression) or may present as a palpable mass.
- Patients with pelvic recurrences are typically symptomatic, with pain as the most common presentation.

Asymptomatic patients may present with a rising serum carcinoembryonic antigen (CEA) level or have a new abnormality detected on surveillance imaging or surveillance colonoscopy.

16.2.1.2 Presentation of systemic recurrence

The most common sites of systemic recurrence following curative treatment of colorectal cancer are hepatic followed by pulmonary metastases. Other visceral metastases such as adrenal metastases, metastases to distant nodal basins such as the para-aortic nodes, bony metastases and brain metastases can also occur but do so much less frequently. As with patients with local recurrence, patients with systemic recurrences may be symptomatic or asymptomatic. Symptoms varies depending on the site of recurrence, and may include abdominal pain from hepatomegaly, jaundice, pleuritic chest pain or shortness of breath. Patients with extensive disease may also have anorexia, cachexia and weight loss. Most recurrences present within the first 3 years after curative resection. Asymptomatic disease is usually detected during routine surveillance as a result of an elevated CEA or a new abnormality detected on surveillance CT scan.

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16.2.2 Overview of evidence (non-systematic literature review)

No systematic reviews were undertaken for this topic. Practice points were based on selected evidence. Please see Guidelines Development for more information.

16.2.3 Investigation of suspected local recurrence

Initial assessment of patients with suspected local recurrence should include:

- serum CEA
- (unless contraindicated) contrast computed tomography (CT) scan of the chest, abdomen and pelvis
- positron emission tomography (PET) scan
- pelvic MRI (for pelvic recurrences).

Depending on individual circumstances, additional investigations may also be necessary, including colonoscopy (if appropriate) prior to further surgery, CT or magnetic resonance angiography (MRA) for suspected mesenteric or iliac vessel involvement, or cystoscopy for potential bladder involvement. Particularly with isolated pelvic recurrences, an examination under anaesthesia can be very helpful as pain often limits the utility of clinical examination. Furthermore, an examination under anaesthesia may also permit other investigations or procedures to be undertaken at the same time such as biopsies, cystoscopy with ureteric stent insertion in the event of ureteric obstruction..

As re-operative surgery is usually complex and may be associated with significant surgical morbidity, histological confirmation of recurrent disease should ideally be obtained prior to embarking on surgery. This is also preferable if neoadjuvant chemoradiation is to be considered prior to surgery. Where the recurrence is extra-luminal, options for biopsies include transvaginal biopsies (where the recurrence is adjacent to the vagina) at the time of an examination under anaesthesia or CT-guided percutaneous biopsies. In situations where the recurrence site is difficult to access for histological confirmation and patient history, serum CEA, MRI as well as PET-CT corroborates the diagnosis of recurrence, biopsies may not be necessary following discussion on a multi-disciplinary team meeting. Further, although CT guided biopsies may carry the potential risk of biopsy tract seeding, reports on this are scant and the risk is likely to be negligible. On balance, histological confirmation is preferred because of the potential morbidity of re-operative procedures.

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16.2.4 Investigation of suspected systemic recurrence

Initial assessment of patients with suspected metastasis should include all of the following:

- serum CEA
- (unless contraindicated) contrast CT scan of the chest, abdomen and pelvis
- PET.

Depending on the site of the metastasis, further investigations are usually necessary to determine the local extent of the disease so as to facilitate decision making about appropriateness of further surgical intervention.

In an era where CT and MRI are readily available, the role of liver ultrasound is somewhat limited although it remains a useful investigation in patients with extensive liver metastases where curative resection is impossible. The reported sensitivity of liver ultrasound varies between 50% and 76%, but it is noteworthy that

not only is ultrasound user-dependent but also size-dependent. Sensitivity of liver ultrasound can be as low as 20% for lesions under 10mm.[1] For most patients with hepatic metastases, magnetic resonance imaging (MRI) of the liver is currently considered the most accurate staging modality for liver metastases. The addition of diffusion weighted imaging may improve the yield of MRI in detecting smaller liver metastases. MRI using a liver-specific contrast agent, disodium gadoxetate (Gd-EOB-DTPA; Primovist)) is currently the most sensitive and specific test for liver metastases. A recent systematic review has confirmed its superiority over CT.[2]

The purpose of a PET scan in patients with systemic recurrences is to confirm the presence of metastatic disease, but it is also useful for further systemic staging to rule out the presence of extra-hepatic disease. A recent study from Adelaide found PET to be superior CT in staging extra-hepatic disease and that this was useful in guiding patient selection for consideration of liver resection.[3]

Intra-operative ultrasound of the liver is a useful adjunct in patients to rule out the presence of small hepatic metastases that may otherwise be otherwise missed on other imaging modalities. It also allows the surgeon to assess the anatomical relations between the metastasis and hepatic vascular and biliary anatomy so as to determine the best surgical approach. Liver biopsies are generally not needed to confirm the diagnosis of liver metastases as imaging alone is usually sufficient for diagnosis. Nor is this recommended, because of concerns of biopsy tract seeding.[4] Biopsying colorectal liver metastases has been shown to cause tumour dissemination and adversely affect survival.[4]

As most colorectal cancer related lung metastases are usually located within the lung parenchyma in the periphery of the lung, the most important diagnostic investigations are CT scan of the chest and a PET scan. Comparison with previous imaging is important as interval changes are usually significant. While most patients do not require additional investigations, depending on the anatomic location of the metastasis, diagnostic certainty or whether or not there may be co-existing abnormalities such as questionable uptake within mediastinal nodes, additional investigations such as endobronchial ultrasound, bronchoscopy, or even mediastinoscopy, may be required.

Patients with metastatic disease should be fully assessed with imaging (MRI, PET scan) or additional tests prior to commencement of any chemotherapy. Chemotherapy may render small metastatic tumour deposits invisible on subsequent imaging, although 80–90% of these will reappear after surgery or cessation of chemotherapy.[5]

Practice point

Initial assessment of patients with suspected local or systematic recurrence should include serum CEA, contrast CT scan of the chest, abdomen and pelvis (unless contraindicated) and PET.

Practice point

Depending on the type of recurrence, additional investigations are likely to be necessary. A high-quality pelvic MRI is recommended for patients with locally recurrent rectal cancer. Additional local investigations may also need to be considered depending on patient and disease factors such as CT or MRA if mesenteric or iliac vessel involvement is suspected, or cystoscopy if bladder involvement is suspected.

Practice point

If possible, local recurrence should be histologically confirmed before surgery. If this is not possible because of the extraluminal location of the disease, a transvaginal biopsy may be feasible where the recurrence abuts the vagina. Alternatively, CT-guided percutaneous biopsies can be considered after assessing the need for biopsy at a multidisciplinary team meeting.

Practice point

In patients with liver metastases, an MRI of the liver is usually also necessary if surgery is being considered. The use of disodium gadoxetate (*Primovist*) contrast can increase the sensitivity and specificity of MRI for detecting liver metastases. Colonoscopy may be needed if further resection is planned.

Practice point

In patients with suspected lung metastases, CT chest and PET are usually sufficient to confirm diagnosis. In patients where there is diagnostic uncertainty or concerns for mediastinal nodal involvement, an endobronchial ultrasound or bronchoscopy may be needed.

Practice point

All patients with locally recurrent disease or metastatic disease should be discussed in a multidisciplinary team meeting taking into consideration patient's previous surgical history, current imaging, fitness and desire for further treatment.

Next section: management of recurrent, resectable colorectal cancer

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16.3 Management of recurrent, resectable CRC (MNG13)

Contents

16.3.1 Background

‘Locoregional recurrences’ refers to anastomotic recurrences, recurrences in the surgical bed or regional nodal recurrences.

Local failure after colonic resection is relatively uncommon and is reported to occur in less than 5% of patients.[1][2] Rates of local recurrences following rectal cancer surgery were previously as high as 33%, but this has diminished dramatically over the past three decades to 5–10%.[3][4] This reduction in local recurrence has been achieved mainly through improved surgical techniques and pre-operative imaging which has improved patient selection for neoadjuvant treatment. These include:

- total mesorectal excision (see Elective and emergency surgery for colon and rectal cancer REC3 and COL1-2b)
- improved preoperative staging with pelvic magnetic resonance imaging (MRI) (see Imaging rectal cancer)

- the judicious use of preoperative radiotherapy with or without chemotherapy (see Neoadjuvant and adjuvant therapy for rectal cancer).

Notwithstanding the improvements in surgical techniques, there remain disease factors that predispose to local recurrence. These factors include nodal involvement, vascular invasion, grade of tumour, as well as surgical complications such as anastomotic leaks.

16.3.1.1 The role of surgical treatment

Re-resection for locally recurrent colorectal cancer should be undertaken where possible with a clear resection margin and with curative intent.

While multi-visceral en bloc resection of locally recurrent colon cancer has long been accepted by the wider surgical community as the standard of care,[5] the uptake of pelvic exenteration for locally recurrent rectal cancers has been much slower because of the lack of evidence from randomised controlled trials (RCTs), the high rates of surgical morbidity and the potential quality of life implications following such radical resections. The past two-to-three decades, however, have seen increasing acceptance of pelvic exenteration for patients with isolated locally recurrent rectal cancer because of the number of studies demonstrating reduced operative mortality and improved overall survival in large case series, as well as quality-of-life outcomes particularly in selected Australian centres.[6][7][8][9] In an early cross sectional quality of life study in patients with locally recurrent rectal cancers, long-term survivors after pelvic exenteration for local recurrence were found to have comparable quality of life to patients who had primary rectal cancer.[6] Subsequently, a much larger prospective and longitudinal comparative quality of life study in these patients found that quality of life in pelvic exenteration patients was preserved compared to patients who underwent palliative treatment.[8] As part of the quality of life study, a cost-effectiveness analysis was also undertaken which found pelvic exenteration to be cost-effective when compared to palliative treatment.[9]

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16.3.1.2 The role of radiation treatment

The role of neoadjuvant chemoradiation is well established for locally advanced rectal cancer (see Neoadjuvant therapy for rectal cancer).

Radiotherapy-naïve patients with locally recurrent rectal cancer should receive neoadjuvant chemoradiation prior to curative surgery. In patients who have previously undergone radiation for their primary rectal cancer, the role of re-irradiation is less clear. The concerns of re-irradiation are tissue tolerance and the risk of cumulative toxicity to all pelvic viscera – in particular, to adherent pelvic small bowel loops after previous surgery and the bony pelvis.

Re-irradiation using external beam radiotherapy through hyperfractionated doses has been described by several large centres with an interest in locally recurrent rectal cancer:

- A team from the US MD Anderson Cancer Center[10] recently described their treatment algorithm for patients with locally recurrent rectal cancer, which entailed pre-operative long-course chemoradiation for patients who are radiotherapy naïve, and re-irradiation of patients who have previously received radiotherapy using a

hyperfractionated dose of 39 Gy over 26 fractions (1.5 Gy twice daily).[10] The authors reported improved survival among patients with locally recurrent rectal cancer over their 24-year experience, and attributed this to increased use of pre-operative treatment including rate of re-irradiation (increased from 63% to 89%).[10] Radiotherapy-related toxicities were not reported, although the authors also published a separate study using a smaller subset of the original cohort,[11] which reported the rate of grade 3–4 toxicity as 34% over 3 years.

- A US retrospective case series study from Duke Cancer Center[12] reported on the outcomes of re-irradiation from 33 patients with locally recurrent rectal cancer. Early and late grade 3 toxicities were reported in 6% and 21% of their cohort, respectively.[12] However, neither re-irradiation nor other pre-operative regimes were found to be associated with improved survival or local progression-free survival.[12]
- An Italian multicentre phase II study[13] described a re-irradiation protocol using a twice daily hyperfractionated regime of 1.2 Gy each session for a total of 30 Gy.[13] Radiotherapy was administered with concurrent chemotherapy using 5-flourouracil. Of the 59 enrolled patients, 10% had temporary treatment interruption because of toxicity or compliance issues. Only 3.4% of patients had treatment terminated prematurely because of toxicity. Grade 3 lower gastrointestinal toxicity developed in 5.1% of patients and there were no grade 4 toxicities. Late toxicity was reported in 7 patients, of which the most significant events were urinary outflow tract obstruction needing nephrostomy (2 patients) and small bowel fistula (1 patient). Of 24 patients who had pain pre-treatment, 20 (83%) reported reduced pain. Response rate (partial and complete responders) was 44.1% on repeat imaging. Overall median survival was 42 months. The authors concluded that re-irradiation was safe, well tolerated and associated with symptomatic improvement.[13]
- A Chinese cohort study[14] included 72 patients with LRRC who received re-irradiation using a 1.2 Gy twice daily hyperfractionated regimen for a total of 36 Gy over 30 fractions. Non-responders after 36 Gy continued with re-irradiation to a total of 51 to 56 Gy. Seventy patients completed the intended treatment and two patients interrupted treatment because of grade 4 toxicity. The overall response rate was 59.7%.[14] The authors described clinical benefit in 93% of patients from improved symptom control. Early grade 3–4 toxicity with diarrhoea or neutropaenia was reported in 9.7% and 8.3% of patients, respectively. Late toxicity with small bowel obstruction was seen in 1.4% of patients. The authors also concluded that re-irradiation was safe and effective in reducing symptoms.[14]

When interpreting the safety and efficacy findings reported in these re-irradiation studies , it should be acknowledged that most were single-institution small case series with highly selected patients and no comparative arms.[15]

Despite the limited experience with re-irradiation, this is offered in some centres and forms part of their treatment algorithms for patients with locally recurrent rectal cancer. This highlights the importance of institutional experience and also the importance of discussion within an expert multidisciplinary team. Before recommending re-irradiation, it is vital that the team takes into consideration what can be achieved surgically by the surgical team (likelihood of R0 resection).

Concerns about the possibility of collateral injury to other pelvic viscera have led to the development of intra-operative radiotherapy (IORT) specifically to target the recurrence while shielding other radiosensitive tissues. While the biological rationale of this practice makes sense, the evidence behind this is somewhat limited. A

Dutch group[16] recently published the largest multi-centre series on IORT in patients with locally recurrent rectal cancer. The authors concluded that radicality of resection (R0 resection margins) remained the key factor that determined long term outcome. Although pre-operative treatment improved the likelihood of R0 resection, what IORT offered was reduced risk of further local recurrence when used in combination with re-irradiation.[16] Similar findings were reported in a study by the German Cancer Research Center[17], in which 97 patients with locally recurrent rectal cancer underwent radical resection and IORT. Although the combination of external beam radiotherapy and IORT (≥ 15 Gy) seemed to improve local control, once margin status was corrected for on multivariate analysis, no other factors remained significant.[17] Therefore, overall, it would seem that a complete resection (R0 resection margin) remains the linchpin in achieving long-term local control and survival.

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16.3.2 Systematic review evidence

In patients with locally recurrent colon or rectal cancer, what are the outcomes of curative surgery (+/- chemotherapy, +/- radiotherapy) when compared with surgical palliation +/- palliative chemotherapy +/- palliative radiotherapy or other palliative interventions (overall survival, disease free survival, quality of life and complications)? (MNG13)

A systematic review was undertaken to determine the outcomes of curative resection (with or without radiation or chemotherapy) in the management of locally recurrent colorectal cancer, compared with palliative treatment options including palliative surgery (with or without palliative chemoradiation) or other palliative interventions for locally recurrent colorectal cancer.

One prospective observational cohort study[18] and three retrospective observational cohort studies[19][20][21] were identified that reported outcomes for patients with locally recurrent rectal cancer who underwent different management strategies:

- A US prospective cohort study[18] reported the outcomes of 105 patients with locally recurrent rectal cancer, of whom 62 (59%) underwent curative surgery and 43 (41%) underwent non-curative treatment. Of the 43 patients in the non-curative treatment group, 13 (12%) underwent non-curative surgery where an exploratory laparotomy was undertaken in conjunction with biopsies, intestinal bypass or diversion, and 30 (29%) underwent non-surgical treatment with chemoradiation, brachytherapy or supportive care. Duration of follow-up was not reported.[18]
- A UK retrospective cohort study[19] included 127 patients with locally recurrent rectal cancers, of whom 22 (16%) had both synchronous local and systemic recurrence. The type of primary resection varied and included prior anterior resection (69%), abdominoperineal excision (15%), Hartmann's procedure (5%), pelvic exenteration (5%), proctocolectomy (4%), and local excision (2%). Seventy (55%) patients were offered curative surgery. Patients who were radiotherapy-naïve were also offered preoperative long-course chemoradiation. Patients with node-positive disease on imaging and patients with a threatened margin were

also offered neoadjuvant chemotherapy prior to surgery. Of 70 patients who underwent curative surgery, 45 (64%) had a clear resection margin (R0), 14 (20%) had a microscopically involved margin (R1) and 11 (16%) had macroscopic residual disease (R2). Of the 57 (45%) patients who did not undergo surgery, 26 had non-resectable disease, 15 had extensive metastatic disease that precluded curative resection, 6 were unfit for surgery, 3 declined further surgery and a further 7 patients were awaiting further assessments. Mean follow-up was 3 years.[19]

- A Korean retrospective cohort study[20] included 67 patients with locally recurrent rectal cancer of whom 45 underwent curative resection and 22 underwent chemoradiation alone. Three of the 45 patients who underwent curative surgery also received pre-operative chemoradiation, while the remaining 42 received postoperative chemoradiation. For the 45 patients who underwent curative surgery, resection margins were R0 in 19 (42%) patients, R1 in 24 (53%) and R2 in 2 (4%). Regardless of the treatment intent, following completion of treatment, 59 of 67 patients also received maintenance chemotherapy with flouropyrimidine, irinotecan or oxaliplatin. Median follow up was 41 months (range 16–108 months).[20]
- Another Korean retrospective cohort study[21] reported on the outcomes of 62 patients who had locally recurrent rectal cancer following some form of total mesorectal excision, whether sphincter sparing or not. Of these patients, 23 (37%) underwent curative resection with or without preoperative chemoradiation, while 39 (63%) underwent palliative treatment: 15 (38%) had palliative resection, 20, (51%) had palliative chemoradiation, and 4 (10%) had supportive care. Preoperative chemoradiation for the curative resection group was administered for patients who were radiotherapy naïve. In patients who previously received radiation for their primary rectal cancer, radiotherapy was restricted to the recurrence alone using 3-dimensional conformal techniques. Median follow-up was 49 months, with a range of 8–120 months.[21]

All studies were at high risk of bias. No studies comparing management strategies for locally recurrent colon cancer were identified.

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

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16.3.2.1 Perioperative mortality, morbidity and adverse events

Treatment-associated mortality, morbidity and adverse events outcomes were reported only by the two Korean studies.[20][21]

The study comparing curative resection with chemoradiation alone[20] reported no severe grade I to grade III complications associated with chemoradiation. Surgical adverse events were not reported.

The other study[21] reported no perioperative mortality. Of the 38 patients who underwent either curative or palliative surgery, 12 (31.6%) experienced postoperative complications: wound complications (6), intestinal obstruction (2), anastomotic leakage (1), enterocutaneous fistula (1), and pelvic abscess (1).[21]

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16.3.2.2 Survival outcomes

Three studies[19][20][21] reported overall survival, while two studies[18][19] reported median survival and two [19] [20] reported locoregional relapse-free survival.

16.3.2.2.1 Overall survival

The UK retrospective cohort study[19] reported 3-year overall survival rates of 69%, 56% and 20% for patients who had R0, R1 and R2 resections respectively. This difference between the three groups was statistically significant (p=0.011).[19]

Both Korean studies[20][21] reported 5-year overall survival rates. One study reported no survival difference between surgically treated patients and patients who received chemoradiation alone (53% versus 41%; p = 0.181).[20] The other study reported a significantly higher 5-year survival among surgically treated patients than among those who did not undergo curative resection (35% versus 0%; p = 0.0002).[21]

16.3.2.2.2 Median survival

In the UK retrospective cohort study, median survival has not been reached by the end of 3-year follow-up but was 24 months amongst patients who underwent a R2 resection.[19]

Median survival in the US prospective cohort study [18] was 7.1 years (85.2 months) in patients within the curative surgery group, compared with 1.4 years (16.8 months) among patients treated non-curatively and 1.9 years (22.8 months) among patients treated non-surgically.[18]

16.3.2.2.3 Locoregional relapse-free survival

The UK retrospective cohort study[19] reported a non-significant increase 3-year locoregional relapse-free survival in the curative surgery group compared with the non-curative group (80% versus 60%; p = 0.824).[19]

The Korean study comparing curative resection with chemoradiation alone[20] reported no significant difference in 5-year locoregional relapse-free survival rates between the curative surgery group and the non-curative group (16% versus 5%; p = 0.113).[20]

16.3.2.3 Quality-of-life outcomes

The US prospective cohort study[18] was the only study that reported quality-of-life outcomes, measured using the Brief Pain Inventory (BPI) and FACT-C, a colorectal cancer specific quality of life measure.[18] The only domain that demonstrated statistically significant differences between treatment groups was ‘physical well-being’, which was largely preserved among curative surgery patients but declined rapidly in patients who received non-curative or non-surgical treatments (p = 0.049).[18]

Pain scores did not differ between treatment groups and did not adversely affect the use of restricted narcotic medications.[18]

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16.3.3 Evidence summary and recommendations

Evidence summary	Level	References
In observational studies in patients with recurrent rectal cancer, curative surgery resulted in significantly better overall survival, relapse-free survival and distant metastasis-free survival than other management strategies.	III-2	[18], [19], [21]
In an observational study of patients with recurrent rectal cancer, overall quality-of-life score was not different between patients undergoing curative surgery and non-curative treatments, with the exception that better physical well-being was seen amongst patients who underwent curative surgery.	III-2	[18]
In an observational study, pain intensity and interference in daily life were not significantly different between patients undergoing curative surgery and non-curative treatments for recurrent rectal cancer.	III-2	[18]
In an observational study of patients with recurrent rectal cancer, curative surgery was associated with significant treatment morbidity.	III-2	[21]

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.

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16.3.3.1 Considerations in making these recommendations

The UK study by Bhangu et al[19] was included as the study population had patients with systemic recurrence as well as synchronous local recurrence; this study did not alter survival outcomes.

16.3.3.1.1 Limitations of the body of evidence

The systematic review did not identify any randomised controlled trials (RCTs) that compared curative surgery with palliative treatments in either colon or rectal cancer. This lack reflects the difficulties of conducting RCTs in these patients because of the relative rarity of the condition and institutional differences in the management of these patients.

Considering the available evidence for re-operative surgery for locally recurrent colorectal cancers, it is unlikely that large randomised controlled trials will ever be performed in these patients.

Anecdotally, locally recurrent rectal cancers are associated with a 0% 5-year survival and a median survival of 6–9 months. Chemotherapy with or without radiation can result in a modest improvement in survival, with a median survival of 12–18 months, but this is rarely curative when used in isolation. Radical re-resection is the only curative option, provided that R0 resection margins can be achieved.30 Contemporary large case series have reported 5-year survival rates of over 40% (median survival of over 40 months).[18][22][23] Even in the absence of randomised trials, this represents a large and significant survival benefit over non-curative treatment options. In view of this, RCTs to establish the role of radical resection in the future are neither ethical nor necessary.

16.3.3.1.2 Additional evidence from case series in rectal cancer

In addition to the included observational cohort studies, several large uncontrolled, non-comparative case series have recently been published by internationally renowned centres at the forefront of locally recurrent rectal cancer treatment and research.[18][22][24]

Experienced centres with an interest in locally recurrent rectal cancer in Australia have also published on pelvic side wall resection and en bloc sacrectomy, with R0 rates in excess of 66%.[25] This is an excellent R0 result, considering the technical challenges with these dissections and the published R0 rates for more centrally based recurrences (and therefore simpler resections) from other centres.

These radical surgical approaches have previously been controversial in the surgical literature, but are no longer controversial in view of the strong and overwhelming evidence that suggests that R0 resection margin is the main predictor of long-term survival.

16.3.3.1.3 Post-operative complications and quality of life

Although surgical mortality with radical re-resection has improved, post-operative complication rates following such procedures remain high. Depending on the reporting methodology and classification, complication rates can range from 27% and 82%.

Quality-of-life outcomes have been assessed by a handful of studies including two larger Australian studies.[4][5] The first of these studies was a cross-sectional quality of life study comparing quality of life between patients with locally recurrent rectal cancers and that of patients with primary rectal cancer. Long-term survivors of locally recurrent rectal cancer were found to have quality of life comparable to that of patients who had primary rectal cancer.[6]

A subsequent and much larger prospective and longitudinal comparative quality-of-life study in these patients found that quality of life was preserved in patients who underwent pelvic exenteration , compared with patients who underwent palliative treatment.[8]

16.3.3.1.4 Cost effectiveness

A cost-effectiveness analysis was also undertaken as part of the large Australian quality-of-life study. It found pelvic exenteration to be cost-effective when compared with palliative treatment.[9]

16.3.3.1.5 Application of the evidence to colon cancer

Although the systematic review did not identify any suitable studies that compared curative surgery (with or without radiation and with or without chemotherapy) with non-curative treatments for locally recurrent colon cancer, the same treatment principles that apply to patients with recurrent rectal cancer are likely to be applicable to patients with locally recurrent colon cancer.

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16.3.3.2 Health system implications

16.3.3.2.1 Clinical practice

The management of patients with locally recurrent colorectal cancer requires a multidisciplinary approach. The expertise needed is not restricted to surgeons alone. Expert radiologists to review the relevant pre-operative imaging so as to allow clinicians to arrive at the appropriate recommendation is important. The peri-operative management requires an experienced multi-disciplinary team comprised not just of clinicians but also allied health members and senior nurses to manage the complex peri-operative complications that may arise. Demonstration of improved survival outcomes without any compromise to long-term patient quality of life may result in an increased interest in these complex resections. This in turn may lead to increased referrals to centres with the necessary expertise and an increase in workload. This may also require establishment of more expert centres to ensure equity of care and services to patients in regional areas.

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16.3.3.2.2 Resourcing

The recommendation to refer patients with locally recurrent colorectal cancer to a centre with the necessary expertise to perform curative surgery may necessitate the establishment of more expert centres. These expert centres will require more experienced surgeons and other members of the multidisciplinary team. These expert centres are also likely to be located in metropolitan cities where the large tertiary referral centres are located, which necessarily means that patients are still having to travel long distances for treatment.

16.3.3.2.3 Barriers to implementation

No barriers to the implementation of these recommendations are envisaged.

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16.3.4 Discussion

16.3.4.1 Unresolved issues

One of the unresolved issues in locally recurrent colorectal cancer remains patient selection for surgery. Because a clear resection margin is the key determinant of long term survival, it is currently the most important criteria that most surgeons rely on when determining disease resectability and patient suitability for surgery. Whether or not there are other disease factors that play an important role in patient selection remains unclear. Furthermore, the role of palliative resections in selected patients with intractable symptoms remains unclear.

The role of adjuvant therapy following curative surgery is also unclear. Because of the long recovery times associated with most re-operative procedures, it is not uncommon that many patients remain unwell for consideration of adjuvant therapy after surgery within conventional time frames for chemotherapy. Whether or not these patients benefit from adjuvant therapy is not clear and warrant further evaluation.

Quality-of-life outcomes and other functional outcomes have not been well studied in patients with locally recurrent colorectal cancers. These outcomes need to be evaluated as part of a prospective study.

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16.3.4.2 Studies currently underway

We are not aware of any large randomised trials currently underway comparing curative surgery to non-curative treatment options. There are, however, studies currently underway to examine the role of adjuvant therapy in patients with recurrent colorectal cancer and also vaccine trials in these patients to determine its utility.

Prospective quality-of-life studies are continuing drawing on patients with locally advanced and locally recurrent malignancies of the pelvis.

Studies evaluating prognostic factors (such as CEA, time to recurrence and other disease factors) are also underway and should facilitate future decision making about patient selection.

16.3.4.3 Future research priorities

Future research should look to facilitate patient selection and refine patient treatment (e.g. adjuvant therapy), rather than defining the role of curative surgery which, within the confines of existing literature, has demonstrated improved survival relative to non-curative treatment options.

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16.3.5 References

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16.3.6 Appendices

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16.4 Management of metastatic resectable CRC (MNG14)

Contents

16.4.1 Background

Systemic recurrence may occur in up to 40% of patients after curative treatment of their primary colorectal cancer.[1] Although less common, some patients may also present with stage IV disease at the time of initial presentation.

Liver and lungs are the most common sites of metastases. Liver and lung metastases may be amendable to curative resection, thereby improving survival. With improved imaging, surgical technique, understanding of what drives long-term survival, as well as improved chemotherapy options, clinicians are now increasingly aggressive with the oncological management of these metastases.

Bony metastases, brain metastases, other soft tissue metastases and metastases to distant, non-draining nodal basins such as the para-aortic nodes, are less common. Although palliative interventions may be required to prevent complications, metastases at these sites are generally not amendable to curative surgical interventions.

While liver resection has been accepted as the standard of care for patients with resectable liver metastases, the role of curative resection at other sites remains unclear.

The purpose of this review was to determine the role of curative surgery in patients with synchronous or metachronous metastatic disease in patients with colorectal cancer.

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16.4.2 Systematic review evidence

In patients with resectable synchronous or metachronous metastatic colorectal cancer, what are the outcomes of surgical resection, with or without chemotherapy, when compared with non-surgical /palliative interventions (overall survival, disease-free survival, progression-free survival, quality of life and complications)? (MNG14)

A systematic review was performed to compare outcomes of surgical resection (with or without chemotherapy) with non-surgical or palliative interventions in the management of metastatic colorectal cancer. The outcomes of interest included survival, disease free survival, quality of life, and complications.

Five cohort studies were identified, all of which involved patients with liver metastases:

- An European Organization for Research Treatment of Cancer (EORTC) multicentre cohort study [2] reported outcomes in 356 patients, of whom 263 underwent hepatectomy and 93 received palliative treatments. The most commonly performed liver resections were segmentectomies (46%) and hemihepatectomies (34.6%), followed by wedge resections of the liver (8.7%). Palliative treatment included chemotherapy (91%) and radiofrequency ablation (6%). Patients in the palliative group were twice as likely to have symptomatic hepatic disease (19% versus 8.4%) and were less likely to have disease detected as part of surveillance (31% versus 58.6%), compared with the hepatectomy group, which suggests that these patients had more extensive disease at diagnosis. The primary objective of this study was to test the validity and reliability of the EORTC Cancer Quality of Life questionnaire liver module (QLQ-LMC21), an EORTC quality-of-life instrument for patients with liver metastases. Follow-up was limited to 3 months only, as the QLQ-LMC21 was re-administered after treatment.[2]
- A Japanese single-centre cohort study [3] reported outcomes in 41 patients with synchronous liver metastatic disease (defined as liver metastases that occurred within 12 months of resection of the primary colorectal cancer), of whom 15 (37%) underwent liver resection and 26 (63%) received palliative treatment. The main aim of the study was to evaluate the benefit of alternating hepatic artery infusion and systemic chemotherapy in patients who did and did not undergo hepatectomy. Of the hepatectomy group, seven patients underwent synchronous resection of the metastatic disease and the primary colorectal cancer. Although the authors did not define what constituted disease that was amendable to simultaneous liver and colorectal resection, they referred to Japanese guidelines for managing colorectal cancer. Duration of follow-up was 3 years.[3]
- An Australian study [4] using data from the South Australian Metastatic Colorectal Cancer Database reported outcomes for 455 patients with liver-only metastases who underwent either the combination of chemotherapy and surgery with curative intent (121), surgery alone with curative intent (87), or chemotherapy alone (247). The cohort included 317 patients (69.7%) with synchronous liver metastases and 139 (30.5%) with metachronous liver metastases. The large proportion of patients with synchronous liver metastases in this study suggests that it is much more likely for patients with metachronous liver metastases to receive no intervention or to have metastatic disease not confined to the liver alone. Clear resection margins at hepatectomy were achieved in 86.2% of patients who underwent surgery alone and 95.9% of those who received combinational therapy ($p = 0.038$). In patients treated with chemotherapy and surgery, chemotherapy regimens varied considerably and were most commonly oxaliplatin-based. Timing of chemotherapy was preoperative (33.9%), perioperative (26.4%), or postoperative (37.2%). Median follow-up was 16.7 months.[4]
- A US single-centre cohort study based on Memorial Sloan-Kettering Cancer Center's prospectively maintained surgical and interventional radiology databases [5] reported outcomes in 52 patients with solid liver metastases of colorectal cancer, of whom 30 underwent non-anatomic wedge resection of the liver, with or without adjuvant systemic chemotherapy, and 22 underwent radiofrequency ablation, which routinely included tract ablation. The main aim of the study was to compare outcomes between non-anatomic wedge resections of the liver with radiofrequency ablation of solitary liver metastases. The surgical database

identified 1144 patients with liver metastatic disease from colorectal cancer, of whom 580 patients had solitary liver metastases and only 30 (2.6%) underwent a non-anatomic wedge resection of the liver. Patients undergoing radiofrequency ablation were much more likely to have previously undergone liver resection(s) than those undergoing non-anatomic wedge resection (55% versus 23%; $p < 0.01$). Follow-up was carried out at 3- to 6-monthly intervals, with routine imaging for 2–3 years after treatment.[5]

- A Polish single-centre cohort study study [6] reported outcomes for 130 patients with synchronous (50; 38%) or metachronous (80; 62%) liver metastases who underwent either liver resection with or without adjuvant systemic chemotherapy (96 patients), or palliative radiofrequency ablation with or without palliative liver resection (34 patients). Of the resection group, 48 underwent hemihepatectomies, 28 underwent segmentectomies and 20 underwent metastasectomies. R0 resection (defined R0 as a microscopically clear resection margin including cases where the margins were clear by < 1 mm) was achieved in 78 (81%) of patients and 18 (19%) of patients had a R1 resection margin. Postoperatively, 25 (26%) patients in the resection group received adjuvant chemotherapy. Overall, the mean follow-up period was 39.3 months (range 2–156 months). Group-specific follow-up, however, was considerably longer for patients in the liver resection group (mean 44 months, range 6–156 months) than for the thermoablation group (mean 26 months, range 2–67 months).

All five cohort studies were at high risk of bias.[2][3][4][5][6] No eligible studies were found that compared strategies for managing metastatic disease involving other organs.

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

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16.4.2.1 Survival outcomes

Survival outcomes for curative surgical resection versus chemotherapy were reported by four studies: the Japanese cohort study,[3] the South Australian Metastatic Colorectal Cancer Database study,[4] the Memorial Sloan-Kettering Cancer Center database study,[5] and the Polish cohort study.[6] Overall, survival outcomes favoured the curative treatment group.

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16.4.2.1.1 Overall survival

All four studies reported overall survival. All studies reported improved overall survival in the curative group relative to the non-curative group:

- In the Japanese cohort study, overall survival rates were higher in the hepatectomy group than the palliative group at 1 year (90% versus 63%), 2 years (72% versus 55%) and 3 years (52% versus 0%), but statistical analysis was not reported.[3]

- In the South Australian Metastatic Colorectal Cancer Database study, 1-year overall survival rates were 95.1% in the surgery alone group, 98.3% in the surgery plus adjuvant chemotherapy group, and 63.8% in the palliative group.13 At 3 years, overall survival was 73.8% in the surgery alone group, 73.7% in the surgery plus adjuvant chemotherapy group, and 19.5% in the palliative group. Statistical analysis was not reported.[4]
- In the Memorial Sloan-Kettering Cancer Center database study, overall survival at 1 year was 100% in both groups, but this rapidly declined in the non-curative group to 69% at 2 and 27% at 3 years, compared with 88% and 82% in the curative group at 2 and 3 years, respectively. Statistical analysis was not reported.[5]
- The Polish cohort study reported significantly higher overall survival rates in the liver resection group than the palliative radiofrequency ablation group at 3 years (64.5% versus 33%) and at 5 years (46.6% versus 9.5%) ($p = 0.002$ for both comparisons).[6]

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16.4.2.1.2 Disease-free survival

Disease-free survival was reported by the Polish cohort study only for the curative group: 32% at 3 years and 30.5% at 5 years.[6]

16.4.2.1.3 Progression-free survival

Progression-free survival was reported only by the Memorial Sloan-Kettering Cancer Center database study. At 1-year follow-up, progression free survival rates were 88% in the curative group and 29% in the non-curative group. At 2-year follow-up progression-free survival rates were 55% in the curative group and 18% in the non-curative group.[5] Statistical analyses were not reported.

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16.4.2.1.4 Mean survival

Mean survival was reported only by the Japanese cohort study, which reported a significantly longer survival in the curative group compared with the non-curative group (1441 days versus 748 days; $p = 0.038$).[3]

16.4.2.2 Perioperative mortality, morbidity and adverse events

Complications were reported by only two studies: the Memorial Sloan-Kettering Cancer Center database study[5] and the Polish cohort study.[6]

In both studies, complication rates were significantly higher in the curative group, compared with the non-curative group.

The Memorial Sloan-Kettering Cancer Center database study[5] reported a significantly higher rate of major complications of in the curative group than the non-curative group (14% versus 4%; ($p < 0.01$).[5]

The Polish cohort study[6] reported a post-operative complication rate of 24.9% in the curative group, compared with a post-operative complication rate of 8.7% in the non-curative group.15 Rates for all complications were higher in the curative group. The most common were sepsis pneumonia, wound infection and urinary tract infection (13.5%), followed by intestinal complications and prolonged biliary drainage (5.2% each) and postoperative bleeding (1%). No statistical comparisons between groups were made.[6]

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16.4.2.3 Quality-of-life outcomes

Only the EORTC study[2] reported quality-of-life outcomes, measured using the EORTC QLQ-C30 questionnaire, for which reduction in functional or global health status score equates to worse function or quality of life while greater symptom status scores equates to higher level of symptomatology.

For patients in the hepatectomy group, there was a reduction in the global quality of life score as well as a reduction in scores in three of five domains (physical function, role function and social function, but not emotional function). These decreases in scores were all statistically significant for this group (p values ranged from < 0.001 to 0.033). This contrasts with patients in the palliative treatment group, where the only domain which was affected was the physical function domain which declined ($p < 0.001$).[2]

At baseline, patients in the palliative group had worse symptoms (pain, fatigue, and nausea and vomiting) measured using symptom scores, compared with patients in the hepatectomy group. Although symptoms worsened for all patients at 3 months compared with pre-treatment levels, patients in the hepatectomy group had a greater increase in symptom severity compared with patients in the palliative group. This difference was statistically significant for all three symptoms in the hepatectomy group only (p-values ranging from < 0.001-0.002).[2]

Quality of life and symptoms were also measured using the EORTC QLQ-LMC21 questionnaire.[2] At baseline, patients in the palliative group also generally had worse symptoms in most aspects (nutritional problems, fatigue, pain, emotional problems, weight loss, taste problems, dry mouth, jaundice, social problems and sexual problems) compared with patients in the hepatectomy group, consistent with more advanced disease at baseline. At 3 months, patients in both groups had worsening of symptoms, except for emotional problems in the palliative group and talking problems in both treatment groups, where there was either no change or slight improvement.

The deterioration in symptoms were slightly greater in the hepatectomy group compared to the palliative group (p-value range from <0.001 to 0.459), with the exception of taste problems, dry mouth, sore mouth, peripheral neuropathy, talking problems and sexual problems, where the deterioration was greater for the palliative group (p-value range from <0.001 to 0.658).[2]

It is however also noteworthy that this study was designed to validate the EORTC QLQ-LMC21. The follow up time period of only 3 months was probably insufficient to allow full recovery of quality of life after surgery in the liver resection group which in turn accounts for the worse quality of life in the short term. The short follow up period in this study is a limitation of the study. Furthermore, despite the statistical differences between groups, the minimal important difference was not clear. Therefore, whether or not the differences were also clinically significant is somewhat unclear.[7]

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16.4.3 Evidence summary and recommendations

Evidence summary	Level	References
In observational studies of patients with hepatic metastases, liver resection with or without adjuvant therapy improved survival, compared with non-curative treatment options.	III-2	[3], [4], [5], [6]
In an observational study with a limited follow up of 3 months of patients with hepatic metastases, liver resection, with or without adjuvant therapy, was associated with a faster decline in quality of life compared with palliative treatment. However whether or not these changes were also clinically relevant is unclear.	III-2	[2]
In observational studies of patients with hepatic metastases, liver resection was associated with higher rates of complications compared with non-curative treatment options.	III-2	[5], [6]

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.

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16.4.3.1 Considerations in making these recommendations

In patients with liver metastases, a clear resection margin is the most important factor that predicts for survival benefit and reduces the likelihood of further local recurrences within the liver.

Although the systematic review did not identify any suitable studies that compared curative surgery (with or without chemoradiation) for pulmonary metastases, the same principles that applies to patients with liver metastases are likely to be applicable to patients with pulmonary metastases. At present, patients should be considered for pulmonary resection provided the pulmonary metastases can be resected with clear margins.

An important consideration when offering liver or lung resection is ensuring that the remnant liver or lung retains adequate functional capacity while ensuring adequate resection with a clear resection margin. Multiple techniques (e.g. portal vein embolization or ligation) have been described to encourage hemi hypertrophy of the liver so as to increase remnant liver size and functional capacity. Some of these techniques remain experimental and more studies are needed to evaluate the safety of these techniques.

Patients with liver metastases should be discussed in an experienced multidisciplinary team because of the ongoing progress and evolution in the surgical options available to these patients.[8] Broadly speaking, patients with liver metastases may be sub-classified into one of three categories based on the extent of their disease: those with definitely resectable disease, those with borderline resectable disease and those with nonresectable disease. The current systematic review supports liver resection in patients who belong to the definitely resectable category. However, the definition of what constitutes resectable disease may vary between centres, depending on the experience and expertise of the multidisciplinary team.

Decision making in the case of an individual patient is often complex and requires thorough consideration of performance status and accurate staging, as well as patient preferences and circumstances. For patients in the borderline resectable category, neoadjuvant chemotherapy should be considered, as the disease may become resectable following chemotherapy.

The experience of the multidisciplinary team is crucial to ensure optimal outcomes are achieved and it is now accepted as standard practice for patients with metastatic disease. The composition of the multidisciplinary team in patients with liver metastases should also include an experienced liver surgeon. In a recent review of the multidisciplinary team in an English centre without liver expertise, 60% of patients with liver metastases were denied potentially curative resection as compared to when the patients' imaging were reviewed by experienced liver surgeons.[8]

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16.4.3.2 Health system implications

16.4.3.2.1 Clinical practice

The management of patients with metastatic disease requires a multidisciplinary approach. The expertise needed is not restricted to surgeons alone and includes experienced radiologists, medical and radiation oncologists. The input from each member will allow clinicians to arrive at the appropriate recommendation which should be individually tailored to the patient's disease. These guidelines and recommendations may result in more referrals to tertiary referral centres and may therefore increase the workload of these centres.

16.4.3.2.2 Resourcing

The peri-operative management of these patients can be complex and typically requires the input of intensive care physicians, rehabilitation physicians, pain physicians as well as senior nursing and allied health members. With increased awareness and demand, there may be the need for more experienced centres to be established.

16.4.3.2.3 Barriers to implementation

No barriers to the implementation of these recommendations are envisaged.

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16.4.4 Discussion

16.4.4.1 Unresolved issues

16.4.4.1.1 Liver metastases

In patients with multiple liver metastases, the extent of liver resection needs to be balanced against the functioning capacity of the liver remnant so as to avoid liver failure. Techniques such as portal vein embolisation or ligation to trigger hemi-hypertrophy of the non-ligated half of the liver from the ischaemic insult have been increasingly utilised (see Management of non-resectable locally recurrent disease and metastatic disease). Although feasibility and safety of such techniques have been demonstrated, these techniques have not been fully evaluated in comparative studies.

The same principles of treatment may be applied to patients who present with stage IV disease at the time of presentation where there is isolated liver metastases alone. However, unlike primary non-metastatic colorectal cancer, the appropriate sequence of interventions remain unclear. These patients often require chemotherapy, resection of their colorectal primary and liver resection at some stage. Whether a liver first approach is superior or whether a more conventional surgical approach is more appropriate is unclear. Currently, clinicians usually tailor treatment sequence to the individual patient's disease, but the evidence behind this approach is also somewhat limited.

The role of adjuvant therapy in reducing further systemic or local recurrences needs to be defined and warrants further evaluation in prospective randomised trials.

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16.4.4.1.2 Other sites of metastasis

There is inadequate evidence at present to inform recommendations about the role of lung resection in patients with resectable pulmonary colorectal metastases. A large multicentre randomised trial evaluating the role of pneumonectomy for colorectal metastases has recently been completed and the results of this are awaited.[9]

Similarly contentious are resection of other colorectal metastases such as para-aortic node resection, and bony resection for seemingly isolated metastases. As isolated metastases involving these sites are rare, multicentre collaborations are likely necessary to gain insight into the role of these resections.

16.4.4.2 Studies currently underway

A large multicentre randomised trial evaluating the role of pneumonectomy in patients with resectable pulmonary metastases have recently been completed.[9] Outcomes are awaited and will be highly informative about the role of pneumonectomy in these patients.

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16.4.4.3 Future research priorities

Metasectomy of metastases involving sites other than liver needs to be evaluated to determine the utility of surgical resection at these sites.

In patients with stage IV disease with liver metastases at presentation, the optimal treatment sequence needs further evaluation. Techniques such as portal vein ligation, embolisation or other techniques to stimulate liver hypertrophy, so as to boost potential functional capacity of the liver, warrant further evaluation.

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16.4.6 Appendices

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16.5 Introduction: management of non resectable recurrent metastatic CRC

16.5.1 Background

Management of patients with newly diagnosed with metastatic colorectal cancer (mCRC) may be complex, and treatment decisions benefit from multidisciplinary input. The optimal treatment strategy for patients with non-resectable metastatic colorectal cancer is rapidly evolving. Management must be individualised based on the overall medical condition of the patient, the extent and distribution of metastatic disease and the patient's wishes. Among patients with mCRC, curative treatment can only be proposed for those in whom both the

primary and distant metastases are resectable either initially or following “conversion” therapy. It is important to identify this group of patients as they have the greatest likelihood of cure. Unfortunately, only a minority of patients are suitable for curative resection; approximately 20% of mCRC patients.[1] The majority of patients 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.

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. For select patients with liver limited non-resectable disease, loco-regional liver-directed therapies may be considered. In this situation with goal of therapy is not necessarily cure but may allow discontinuation of standard systemic therapy, with the possibility of a (meaningful) relapse/disease free-interval. There are a number of evolving liver directed therapies to consider including (but not limited to) invasive local ablation (RFA), embolization techniques (particle, bead, Selective internal radiation therapy (SIRT)) and precision radiotherapy (Stereotactic body radiotherapy (SBRT)).

Another important group of mCRC (up to 25% of mCRC patients) are those who at the time of diagnosis of their primary colorectal cancer have synchronous metastases.[2] Initial management of the primary site in patients who present with metastatic disease is controversial and not fully addressed by currently available literature. In general, 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. Such decisions are usually made by a multidisciplinary team (MDT) with expertise in the management of mCRC.

16.5.1.1 Chapter subsections

Subsections:

- Liver-directed therapies for patients with incurable metastatic colorectal cancer (MNG16)
- How should a synchronous primary be managed in patients with metastatic disease?
- Discussion

16.5.2 References

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16.6 Liver directed therapies, unresectable metastatic CRC (MNG16)

Contents

16.6.1 Background

The liver is the most common site for metastases of colorectal cancer.[1] Nearly 50% of mCRC 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] However, 80-90% of patients with liver metastases are not amenable to surgery at diagnosis[3][4][5][6], and liver metastases remain the dominant cause of death for patients with mCRC.[7][8][9][10]

Multiple liver-directed therapies 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 may include:

- Embolisation techniques:
  - selective internal radiation treatment (SIRT) known as radioembolisation (SIR-Spheres®, Sirtex Medical Limited, Sydney, Australia[11]), –which delivers a single, measured targeted radiation dose to liver tumours via injection into the hepatic artery. Yttrium-90 (90Y)–labeled resin microspheres have a median diameter of 32.5 µm, considerably smaller than the particles of other liver-directed therapies such as transarterial chemoembolization, which enables the microspheres to lodge distally within the microvascular plexus of tumors.[12]
  - trans-arterial chemoembolization (TACE) (e.g. the use of drug-eluting beads to deliver chemotherapy to the site)that rely on the unique differential blood supply of the liver[13], in which hepatic metastases are preferentially supplied by the hepatic artery. These techniques are used for more diffuse liver metastases.
- Invasive thermal ablation with distinct size limitations (e.g. radiofrequency ablation, RFA) RFA can be performed with open, laparoscopic, or percutaneous approaches. Some studies have reported that the approach by which RFA is performed has an impact on tumor recurrence rates, with the fewest local recurrences after open RFA, followed by laparoscopy, and finally percutaneous RFA.[14][15][16] The best results with RFA are in patients with three or fewer lesions that are each 3 cm or less in diameter and are not located near major vascular structures.[17]
- Hepatic arterial infusion (HAI) of chemotherapy agents. This technique relies on the differential blood supply of the liver. Liver macrometastases (>0.5 cm) derive more than 80 percent of their blood supply from the hepatic arterial circulation, while normal hepatocytes are supplied primarily by the portal circulation.[13] As a result, the administration of chemotherapy into the hepatic artery allows the selective delivery of drug to the tumor with relative sparing of normal hepatocytes.[18] Depending upon a drug's clearance and toxicity profile, a marked increase in the local concentration of drug may be achieved by injection into the hepatic artery. Regional administration of drugs that are rapidly metabolized in the liver by a first-pass effect leads to higher levels of drug exposure and minimizes systemic side effects.
- Conformal radiation treatment techniques (e.g. stereotactic body radiotherapy (SBRT) and high-dose rate brachytherapy). SBRT is a technique that utilizes precisely targeted radiation to a tumor while minimizing radiation to adjacent normal tissue. This targeting allows treatment of small- or moderate-sized tumors in either a single or limited number of dose fractions.

The roles of liver-directed therapies in patients with non-resectable MCRC have not been completely defined. Liver-directed therapies 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. 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.

European Society for Medical Oncology (ESMO) consensus guidelines for the management of patients with colorectal cancer (2016)[19], that patients whose disease is not amenable to surgical resection, but who have a limited number of metastases and involved sites (oligometastatic disease (OMD)), may be considered for local liver ablative treatments as part of a 'situation-adapted' treatment strategy following systemic therapy.

The selection of the most appropriate liver-directed therapy for a patient is dependent on a number of factors including[19]:

- the size and localisation of the metastases
- the invasiveness of the procedure
- local expertise regarding the use of a particular ablative technique
- patient preference
- patient co-morbidity, performance status and life expectancy.

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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.

Seven randomised controlled trials (RCTs) evaluated liver ablative therapies with or without systemic therapy, compared with to systemic therapy alone.

Selective Internal Radiation Therapy (SIRT)

- SIRFLOX[20] was a multicentre Australian phase III RCT of systemic chemotherapy with modified FOLFOX (mFOLFOX6) plus or minus selective internal radiation therapy (SIRT) as first-line treatment of patients with non-resectable liver-only or liver-dominant mCRC. Liver-dominant mCRC was defined as the presence of liver metastases and limited lung (fewer than five nodules of ≤ 1 cm diameter or a single nodule of ≤ 1.7 cm diameter), and/or lymph node involvement (a single anatomic area of < 2 cm diameter). Bevacizumab was allowed, combined with mFOLFOX[20], at the investigator's discretionPatients included were WHO performance status 0-1.
- A German open-label phase III RCT[21] compared the combination of SIRT plus intravenous fluorouracil (FU) to FU alone in 44 patients with chemotherapy refractory (5FU, irinotecan and oxaliplatin) liver limited mCRC. Presence of extrahepatic disease was an exclusion factor. Patients enrolled were ECOG 0-2.[21]
- A small Australian phase 2 RCT[22] compared the combination of SIRT (*SIR-Spheres*) plus systemic fluorouracil /leucovorin chemotherapy (FULV) with FULV alone in 21 patients receiving first line therapy for mCRC with liver metastases +/- extrahepatic disease. Patients were WHO performance status <3.[22]

Radiofrequency Ablation (RFA)

- An RCT by the European Organisation for Research and Treatment of Cancer (EORTC), the Chemotherapy + Local Ablation Versus Chemotherapy (CLOCC) study[23], compared the combination of radiofrequency ablation (RFA) plus FOLFOX4 with FOLFOX4 alone, and with modified FOLFOX4 with bevacizumab (mFOLFOX4) in 119 patients with non-resectable liver-limited mCRC. Patients with extra hepatic disease were excluded. There had to be <10 liver metastases, with maximum diameter of 4 cm lesions to be treated by RFA. Metastatic involvement of the liver need to be ≤50% and complete treatment of all liver lesions was judged possible, either by RFA alone or by combination with resection of resectable lesions and RFA of the remaining non-resectable liver deposits. A minority of patients (16%) had prior chemotherapy for liver-only metastatic disease. The CLOCC study was initially designed as a phase III study, but transitioned to a phase II study because of slow accrual.[23]

Trans arterial Chemoembolisation (TACE)

- A US phase II multicentre RCT[24] compared the combination of trans arterial chemoembolization (TACE) using irinotecan drug-eluting beads (DEBIRI) plus mFOLFOX plus bevacizumab, with the combination of mFOLFOX plus bevacizumab in 70 patients who were chemotherapy naïve for metastatic disease and had liver-dominant disease (defined as ≥80% of the tumor body burden being confined to the liver) but less than 60% liver replacement by the tumor, and have an Eastern Cooperative Oncology Group performance status score ≤2.[24]
- An Italian multicentre RCT[25] compared DEBIRI with systemic irinotecan, fluorouracil and leucovorin (FOLFIRI) in 74 patients, all were pre-treated, including patients who had received a minimum of 2-3 lines of prior chemotherapy which may have included irinotecan. Patients had liver limited disease occupying up to 50% of the liver with no extrahepatic disease.[25]

Hepatic Arterial Infusion (HAI)

- An RCT by the US Cancer and Leukemia Group B (CALGB 9481) evaluated hepatic arterial infusion (HAI): this US study[26] compared hepatic arterial infusion with systemic bolus FULV in 135 treatment naïve patients. Eligible patients had non-resectable liver-limited (occupying <70% of the liver parenchyma) mCRC with no radiologic evidence of extra-hepatic metastatic disease. Patient included were of performance status 0-2.

There were no RCTs of conformal radiation techniques identified by the systematic review process and thus this form of liver directed therapy is not included in the discussion.

Of these studies, one study had low risk of bias[20] two studies had a moderate risk of bias[22][26], and four studies had a high risk of bias overall.[21][23][24][25]

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.

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16.6.2.1 Liver-directed therapies - Outcomes

16.6.2.1.1 Tumour response

Tumour response outcomes were reported by six of the RCTs.[20][21][22][24][25][26]

SIRT

The small Australian SIRT study reported a significantly improved response (both the first integrated and best confirmed tumour responses at 36 months follow-up) with the addition of SIRT to FULV.[22] Compared with the FULV only group, the SIRT treatment group showed greater complete and partial responses and fewer patients with stable disease ($p < 0.001$).8 No disease progression was reported in the treatment group.[22]

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%; $p = 0.113$).[20] 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%; $p = 0.02$).[20]

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.[21] 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 were not reported.[21]

TACE

The US DEBIRI study[24] 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.[24] 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.[24] 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.[24]

The Italian DEBIRI study did not report significant differences in outcomes between patients who received DEBIRI alone and those who received to systemic chemotherapy.[25] 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.[25]

HAI

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).[26] 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 were not reported.[26]

RFA

Tumour response rates associated with RFA were not reported in the CLOCC study.[23]

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16.6.2.1.2 Progression-free survival

Progression-free survival was reported by all the included RCTs.

SIRT

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).[20] In a planned subgroup analysis of patients with liver only metastases there was also no improvement in progression free survival with the addition of SIRT (n=318, HR 0.9 (0.7-1.15)). 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).[20] Whether this improvement in control of liver metastases will result in improved overall survival is unknown.

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.[21] 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).[21]

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).[22] 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.[22]

RFA

The CLOCC study[23] reported increased median time to progression in the RFA 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).[23]

TACE

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).[24] 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 for overall extra-hepatic disease and(p = 0.35). median progression-free survival overall (p = 0.18) .[24]

The Italian DEBIRI study[25] 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). DEBIRI was also associated with a nonsignificant increase in median time to extra-hepatic progression (p=0.64).[25]

HAI

The CALGB 9481 study[26] 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).[26] This effect was also seen at 2 years' follow-up (51% versus 25%), although the statistical significance of this finding was not reported.[26] 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).[26] 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).[26]

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16.6.2.1.3 Overall survival

Overall survival was reported by four of the RCTs.[21][22][23][25]

SIRT

The Australian SIRT study[22] (n=21) reported significantly greater overall survival in patients who received both SIRT and FULV, compared with those who received FULV only in first line therapy: 29.4 months vs. 12.8 months for patients treated with chemotherapy alone; HR 0.33 (95% CI 0.12 to 0.91; p=0.025). The improvement in survival was not statistically significant and less pronounced for censored data: (HR 0.39 (95% CI 0.14 to 1.13; p = 0.07).[22] 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[21] did not find any significant increase in median overall survival among patients who received SIRT plus 5FU, compared with those who received 5FU only for chemo refractory disease(10 months versus 7.3 months, p = 0.8): HR 0.92 (95% CI 0.47 to 1.78).[21]

RFA

The CLOCC study reported a small nonsignificant increase in median overall survival at 4.4 years' median follow-up among patients who received RFA 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).[23]

TACE

The Italian DEBIRI study[25] 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). 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.[25]

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16.6.2.1.4 Resection rate

Resection rates were reported by two RCTs.[20][24]

SIRT

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).[20]

TACE

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).[24]

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16.6.2.1.5 Adverse events

Adverse event rates were reported by all the RCTs.

SIRT

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).[20] 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).[20] There were no significant differences in the rates of other adverse events.[20]

This finding was also seen in the German trial.[21] After 24.8 months' median follow up, there were more reports of gastrointestinal events, neurological and other toxicities in the SIRT group than the non-SIRT group. In contrast to the SIRFLOX findings, fewer Grade ≥ 3 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).[21]

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).[22] 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.[22]

RFA

In the CLOCC study the addition of RFA to systemic chemotherapy was associated with numerically higher incidences of Grade 3–4 toxicity compared to systemic treatment alone, although the impact of this finding cannot be determined as statistical analysis was not reported.[23]

TACE

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).[24] 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.[24]

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).[25]

HAI

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 ($p = 0.075$).[26] However, bilirubin elevation ≥ 3 mg/dL was reported in a higher proportion of the hepatic arterial infusion group than the systemic chemotherapy ($p = 0.006$).[26]

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16.6.2.1.6 'Quality of life

Quality-of-life outcomes were reported by four of the RCTs.[22][23][25][26]

TACE

The Italian DEBIRI study[25] 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, $p = 0.0002$).[25]

SIRT

The Australian SIRT study[22] 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.[22]

RFA

The CLOCC study[23] reported no significant differences in quality of life between patients receiving radiofrequency ablation in addition to systemic chemotherapy and those receiving chemotherapy alone.

HAI

The CALGB 9481 study assessed quality-of-life (physical functioning domain) using the Rand 26-item Health Status Profile.[26] 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.[26]

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16.6.3 Evidence summary and recommendations

Evidence summary	Level	References
Overall, the evidence suggests some benefit to tumour response rate with the use of	II	[20], [21], [22]

Evidence summary	Level	References
DEBIRI (TACE), HAI, or the addition of SIRT for colorectal cancer patients with non-resectable liver limited disease, but the clinical relevance of these endpoints remain unclear.		[24], [25], [26]
There is limited evidence that liver directed therapies prolong progression free survival. Some phase II studies suggest benefit for RFA and DEBIRI, and for SIRT in chemotherapy refractory disease, but there are no phase III studies showing improved PFS for liver directed therapies.	II	[23], [22]
Liver directed therapies with RFA and DEBIRI have been shown to improve overall survival in single phase II studies, however there are no phase III studies demonstrating improved overall survival with liver directed therapies.	II	[23], [25]
Overall, liver-directed therapies provide little or no benefit in improving quality of life in metastatic colorectal cancer patients with non-resectable liver limited disease.	II	[22], [23], [25], [26]
There is inconclusive evidence to suggest a definitive benefit given by liver directed 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.	II	[20], [21], [22], [23], [24]

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.

16.6.3.1 Considerations in making these recommendations

There is only limited evidence to suggest that liver-directed therapies (selective internal radiation treatment, radiofrequency ablation, hepatic arterial infusion of chemotherapy agents or transarterial chemoembolisation) improve response rates, survival times, resection rates or quality of life in patients with non-resectable liver metastatic colorectal cancer.

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16.6.4 Health system implications

16.6.4.1 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 loco-regional 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.

16.6.4.2 Resourcing

The present recommendations would have little effect on current resourcing because they would only affect referral centres with the necessary expertise and infrastructure required to perform liver ablative therapies. Only highly selected group of mCRC would be suitable for such therapies based on current evidence.

16.6.4.3 Barriers to implementation

No barriers to the implementation of these recommendations are envisaged

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16.6.6 Appendices

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16.7 Synchronous primary in metastatic CRC

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16.7.1 Background

At the time of diagnosis, up to 25% of patients with colorectal cancer present with synchronous metastases.2 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.[1][2]

Initial management of the primary site in patients who present with metastatic disease is controversial and there does not appear to be a consensus amongst international guidelines. The choice and sequence of treatment is guided by the presence and absence of symptoms from the primary tumour, whether or not the metastases are potentially resectable, patient co-morbidity, performance status and life expectancy.

With the exception of obstructing 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. Please see Guidelines Development for more information.

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.[3][4][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21] Published studies were predominantly non-randomised, mostly retrospective and reported by single institutions. The major draw backs in these studies were that surgery was offered to the patients with the best performance status and the preferred treatment for the other patients was systemic therapy alone.[22] In addition, those patients with a heavy burden of metastatic disease were more likely to be offered systemic therapy rather than surgery.[22] Another limitation is that the majority of published studies have included colon and rectal cancers together; the issues can be very different for these two localisations. Surgery is often more complex for rectal cancer patients and symptoms relating to local progression of rectal tumours can be associated with significant morbidity (e.g. rectal pain) which can be difficult to manage.[22]

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.[23] The authors acknowledged significant cross-study heterogeneity and selection biases in the majority of studies, with healthier patients and those felt to have better prognosis more likely to undergo resection.[23]

Importantly, none of the above series reporting a survival benefit for resection of the primary site has assessed the contribution of systemic chemotherapy to outcomes, or controlled for all possible variables that could have favourably affected outcomes in the resected patients.

Results of meta-analyses that have taken the effect of chemotherapy into account have been conflicting. A meta-analysis of 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).[24]

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).[25] Despite conflicting evidence, retrospective data show that approximately 50% of all patients with mCRC undergo resection of the primary tumour.[26][27] This is in keeping with Australian data indicating 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.[28] Of those patients, 70% were considered palliative at multidisciplinary team meeting.[28] And of those 45% had their colorectal primary tumours resected.[28] 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.[28] 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.[28]

Two RCTs of primary site resection in patients who present with non-resectable metastatic disease are yet to be reported and may influence recommendations for this group of patients:

- the Dutch Colorectal Cancer Group's CAIRO4 study[29] 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[30] 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.[30][31][32][33]

16.7.2.2 Morbidity of primary tumour resection in the setting of non-resectable mCRC

For patients operated for their primary tumour as part of their initial management, the question of the potential extra-risk of postoperative morbidity associated with the resection of the tumor in metastatic setting should be considered. Several studies have suggested that resection of the primary tumor in the presence of metastatic disease is associated with high postoperative morbidity and mortality rates.[19][34] One study by Stelzner et al. reported that 15 out of 128 patients (11.7%) patients died within 30 days of surgery.[19] The results however, are likely biased as many of these patients were symptomatic and underwent emergency surgery. The same series found a 27.8% mortality rate in patients who underwent emergency surgery compared to a 7.3% mortality rate for elective procedures ($p = 0.002$). These mortality rates were higher than those found in a recently-published meta-analysis in which collectively, perioperative mortality was 1.7% (95% CI 0.7%-3.9%).[35]

Most patients within this meta-analysis were asymptomatic and were managed electively likely explaining the lower reported mortality. In this meta-analysis, postoperative morbidity occurred in 68 of 299 patients for a pool proportion of 23% (95% CI 18.5-21.8). The most frequent complication was wound infection which could be managed conservatively; however, in some instances, a major complication arose requiring additional surgery. Anastomotic leakage, occurring in 1.7% of patients (5/299 patients) can lead to sepsis, significantly prolongs hospital stays and delays or even precludes the administration of chemotherapy.[35]

The type of surgery performed may be important as suggested by another systematic review and meta-analysis that identified five studies comparing open palliative colectomies with laparoscopic palliative colectomies in this setting and found laparoscopic procedures were associated with reduced post-operative complications, blood loss and length of hospital stays.[36]

16.7.2.3 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.[18]

Leaving the primary tumour intact may not lead to unacceptable local complications (or significantly compromise survival).[37][38][39] 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.[25][38][40]

Moreover, this group of patients appear to have higher rates of postoperative morbidity (20–30%) and perioperative mortality (1–6% percent)[10][17][18] which may lead to delays in the initiation of systemic therapy and detrimental effects on survival.

The prospective multicentre phase II NSABP C-10 trial[37] showed that patients with an asymptomatic primary colon tumour and non-resectable metastatic disease who received modFOLFOX 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 two 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.[41] 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 colonoscopy 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.[42] The current National Comprehensive Cancer Network Guidelines[43] recommend leaving the primary tumour intact and starting systemic therapy first in patients with non-resectable metastatic colorectal cancer and asymptomatic intact primaries.

16.7.2.4 Symptomatic primary tumour

A small number of patients (approximately 6%) with mCRC present with acute complications related to their primary tumours such as obstruction, significant haemorrhage, and perforation, where an urgent intervention is usually indicated prior to starting systemic therapy.[25][44][45][46]

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 rectal resections.[47]

Nonsurgical methods of palliation can be considered for patients not suitable for surgical procedures. Successful local palliation of an obstructing or nearly obstructing tumour may be achieved through endoscopic or radiographic placement of self-expanding metal stent (SEMS). Among the advantages of SEMS over palliative surgery are a faster recovery time (permitting earlier administration of chemotherapy) and a shorter hospital stay If the tumour is not completely obstructing, electrofulguration or laser ablation (using an Nd:YAG or argon ion [argon plasma coagulation or APC] laser) can be attempted to maintain the patency of the lumen.[48] Radiation therapy directed at the primary tumour is another alternative to control bleeding.

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16.7.2.5 Practice points

Practice point
Routine palliative resection of asymptomatic synchronous primary lesion in patients with unresectable metastatic colorectal cancer remains controversial and there are no prospective randomised studies to guide treatment. Recruitment into such trials has been difficult.

Practice point
All patients with an asymptomatic primary and unresectable metastatic colorectal cancer should be discussed in a multi-disciplinary team meeting and the risks and benefits of a palliative resection for an individual patient be carefully discussed bearing in mind the volume of metastatic disease, degree of stenosis/risk of impending obstruction, comorbidities and patient preferences.

Practice point

Patients with an asymptomatic primary and good medium to long term disease control after initial systemic therapy could be re-evaluated for potential resection of both the primary tumour and metastases in the absence of widespread disease progression.

Practice point

For patients with a symptomatic primary tumour (obstruction, bleeding or perforation) and synchronous metastatic disease, resection of the primary tumour should be considered before initiation of systemic therapy. For candidates not suitable for primary tumour resection other palliative options to control symptoms including surgical bypass, radiotherapy, stents, laser ablation in addition to systemic treatment should be considered.

Practice point

For patients with unresectable metastatic rectal cancer with symptomatic primary tumour, irradiation (+/- chemotherapy) of the primary tumour should be considered after multidisciplinary discussion in order to obtain optimal symptom control and reduce patient morbidity.

Next section: discussion
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16.7.3 References

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16.8 Discussion

16.8.1 Discussion

16.8.1.1 Studies currently underway

The combined overall survival analysis of the three first-line studies, SIRFLOX, FOXFIRE and FOXFIRE Global are planned for 2017 will hopefully give clinicians guidance as to the role of SIRT in chemo-naive patients and the current guidelines will be updated when this information is available::

- SIRFLOX (NCT00724503): a randomised multicentre trial comparing SIRFLOX - FOLFOX plus SIR-SPHERES MICROSPHERES vs. FOLFOX alone in patients with liver metastases from primary colorectal cancer.
- FOXFIRE (ISRCTN83867919): an open-label randomised phase III trial of 5-Fluorouracil, Oxaliplatin and Folinic acid +/- Interventional Radio-Embolisation as first line treatment for patients with unresectable liver-only or liver-predominant metastatic colorectal cancer.
- FOXFIRE Global (NCT01721954): a randomised multicentre trial comparing FOLFOX6m Plus SIR-Spheres Microspheres vs FOLFOX6m Alone in patients with liver metastases from primary colorectal cancer.

It has been hypothesized that pulmonary metastases may behave in a more indolent fashion and control of hepatic metastases will therefore improve survival, however, this question will not be answered until the overall survival results are presented (in combination with FOXFIRE and FOXFIRE Global studies).

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17 Role systemic therapies in non-resectable metastatic CRC

The last 10 to 15 years have seen major advances in the treatment of metastatic colorectal cancer. The average median survival duration is now approaching 3 years, and 5-year survival rates as high as 20% are reported in some trials of patients treated with chemotherapy alone.[1] These improvements have been mainly driven by the availability of new active agents, which include conventional cytotoxic agents other than 5-fluorouracil (5FU), and biologic agents targeting angiogenesis and the epidermal growth factor receptor (EGFR).

There are now eight different classes of drugs with antitumour activity in metastatic colorectal cancer:

- fluoropyrimidines:
  - 5FU – usually given intravenously (IV) with leucovorin (LV)
  - capecitabine (oral pyrimidine analogue)
  - S-1 (orally active combination of tegafur, 5-chloro-2, 4-dihydroxypyridine and potassium oxonate). S-1 is not registered in Australia by the Therapeutic Goods Administration (TGA)[i]
  - tegafur plus uracil (oral). This combination is not registered in Australia by the TGA[i]
  - raltitrexed - a folate analogue and thymidylate synthase inhibitor
- irinotecan

- oxaliplatin
- monoclonal antibodies targeting EGFR:
  - cetuximab
  - panitumumab
- monoclonal antibodies targeting vascular endothelial growth factor (VEGF):
  - bevacizumab – recombinant humanised anti-VEGF monoclonal antibody
  - ramucirumab – recombinant monoclonal antibody that binds to and blocks activation of VEGF receptor 2 (VEGFR-2)
- aflibercept – an intravenous recombinant fusion protein that functions as a decoy receptor that prevents intravascular and extravascular VEGF-A, VEGF-B, and placenta growth factor (PlGF) from binding to their receptors.
- regorafenib – an orally active inhibitor of angiogenic tyrosine kinases (including the VEGF receptors 1 to 3), as well as other membrane and intracellular kinases.
- trifluridine-tipiracil (Lonsurf ®) – an oral cytotoxic agent that consists of the nucleoside analogue trifluridine (a cytotoxic antimetabolite that inhibits thymidylate synthase and, after modification within tumour cells, is incorporated into DNA, causing strand breaks) and tipiracil (a potent thymidine phosphorylase inhibitor, which inhibits trifluridine metabolism and also has antiangiogenic properties). Trifluridine-tipiracil is not registered in Australia by the TGA.[i]

Despite the pace of clinical research, the best way to combine and sequence all of these drugs to optimise treatment is not yet established. In general, exposure to all active drugs, as appropriate, is more important than the specific sequence of administration.

[i] As of May 2017

17.1 Chapter subsections

Please see sections:

- Molecular pathology and biomarkers – implications for systemic therapy
- Systemic chemotherapy treatment options for first-line treatment
- Role of biological agents in first-line treatment of metastatic colorectal cancer
- Subsequent treatment and the continuum-of-care model
- Systemic options for second-line treatment
- Systemic options for third-line treatment
- Supportive care options

17.2 References

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17.1 Introduction: role systemic therapies in non-resectable metastatic CRC

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There are now eight different classes of drugs with antitumour activity in metastatic colorectal cancer:

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  - tegafur plus uracil (oral). This combination is not registered in Australia by the TGA[i]
  - raltitrexed - a folate analogue and thymidylate synthase inhibitor
- irinotecan
- oxaliplatin
- monoclonal antibodies targeting EGFR:
  - cetuximab
  - panitumumab
- monoclonal antibodies targeting vascular endothelial growth factor (VEGF):
  - bevacizumab – recombinant humanised anti-VEGF monoclonal antibody
  - ramucirumab – recombinant monoclonal antibody that binds to and blocks activation of VEGF receptor 2 (VEGFR-2)

- aflibercept – an intravenous recombinant fusion protein that functions as a decoy receptor that prevents intravascular and extravascular VEGF-A, VEGF-B, and placenta growth factor (PlGF) from binding to their receptors.
- regorafenib – an orally active inhibitor of angiogenic tyrosine kinases (including the VEGF receptors 1 to 3), as well as other membrane and intracellular kinases.
- trifluridine-tipiracil (Lonsurf ®) – an oral cytotoxic agent that consists of the nucleoside analogue trifluridine (a cytotoxic antimetabolite that inhibits thymidylate synthase and, after modification within tumour cells, is incorporated into DNA, causing strand breaks) and tipiracil (a potent thymidine phosphorylase inhibitor, which inhibits trifluridine metabolism and also has antiangiogenic properties). Trifluridine-tipiracil is not registered in Australia by the TGA.[i]

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- Subsequent treatment and the continuum-of-care model
- Systemic options for second-line treatment
- Systemic options for third-line treatment
- Supportive care options

17.1.2 References

1. ↑ Heinemann V, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, et al. *FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial.* Lancet Oncol 2014 Sep;15(10):1065-75 Available from: http://www.ncbi.nlm.nih.gov/pubmed/25088940.

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17.2 Molecular pathology and biomarkers for systemic therapy

Contents

17.2.1 Background

Increasingly, biomarker expression is driving therapeutic decision-making in medicine. Obtaining tissue to confirm the diagnosis of suspected colorectal cancer is fundamental prior to commencement of systemic therapy.

See also:

- Additional information on pathology reporting
- Optimal molecular profiling.

17.2.2 Overview of evidence (non-systematic literature review)

No systematic reviews were undertaken for this topic. Practice points were based on selected reviews, primary studies, and other clinical practice guidelines (see Guideline development process).

17.2.2.1 RAS mutation testing

Among patients with metastatic colorectal cancer, RAS mutation status permits clinicians to identify individuals who might benefit from strategies targeting the epidermal growth factor receptor (EGFR). Anti-EGFR monoclonal antibodies (cetuximab and panitumumab) should only be prescribed for patients whose tumours are RAS wild-type. As yet, there are no accepted biologic or molecular markers of responsiveness to bevacizumab or to conventional cytotoxic chemotherapy agents, although these are active areas of research.

Tumour overexpression of several genes involved in the EGFR signalling pathway and downstream events might identify patients who are most likely to respond to anti-EGFR agents. It is now well established that activating mutations in KRAS, which result in constitutive activation of the RAS-RAF-ERK pathway, result in resistance to anti-EGFR therapy.[1][2][3][4][5][6][7][8][9][10][11][12] Activating mutations in KRAS are detected in approximately 40% of metastatic colorectal cancers.

In metastatic colorectal cancer, KRAS mutations are mainly found in exon 2 (codons 12, 13).[13] Retrospective analyses of pivotal clinical trials for the anti-EGFR monoclonal antibodies, cetuximab and panitumumab, have shown that patients with metastatic colorectal cancer whose tumours contain activating mutations in KRAS exon

2 (codons 12, 13) do not derive a benefit from EGFR monoclonal antibody therapy.[2][6][12][14][15][16] Furthermore, evidence from the PRIME study with panitumumab,[17] from the CRYSTAL study with cetuximab,[18] and from other studies of EGFR monoclonal antibody therapies, has shown that mutations other than those in KRAS exon 2 – i.e. exons 3 and 4 of KRAS and exons 2, 3 and 4 of NRAS (extended RAS analysis) – also predict a lack of response to EGFR-targeting monoclonal antibodies and that these therapies may, in fact, have a detrimental effect in patients with RAS-mutant disease, specifically when combined with an oxaliplatin-based cytotoxic backbone.[17][18][19][20][21][22][23]

These findings were supported by results from the phase II PEAK study, in which patients with KRAS and NRAS exon 2, 3 and 4 wild-type metastatic colorectal cancer treated with the combination of leucovorin calcium (folinic acid), 5-fluorouracil (5FU) and oxaliplatin (FOLFOX) regimen ‘6’ (FOLFOX6) plus panitumumab showed longer progression-free survival than those treated with FOLFOX6 plus bevacizumab, and a trend towards improved overall survival.[22]

Next-generation sequencing techniques to identify additional RAS-activating mutations were used to analyses tumour samples previously tested for KRAS exon 2 mutations from patients previously enrolled in the phase III trial of panitumumab in chemorefractory metastatic colorectal cancer.[21] When treated with panitumumab, patients with RAS wild-type tumours achieved response rates with of 15%, compared with 1% among those with RAS-mutant tumours.

Similar findings have been reported with cetuximab in patients with RAS wild-type tumours (according to extended RAS analysis). The addition of cetuximab to FOLFOX regimen ‘4’ (FOLFOX4) or to the combination of folinic acid, 5FU and irinotecan hydrochloride (FOLFIRI) was associated with improved treatment outcomes across all efficacy end points.[18][19]

The importance of extended RAS testing was accentuated in the phase III FIRE-3 trial, in which patients with previously untreated metastatic colorectal cancer with RAS wild-type tumours receiving FOLFIRI and cetuximab showed an improvement in overall survival, compared with patients with RAS mutation receiving the same regimen (median 33.1 versus 28.7 months).[24]

The weight of evidence indicates that anti-EGFR monoclonal antibody therapy should be restricted to those patients whose tumours lack mutations after extended RAS testing.

Harbouring a RAS mutation is therefore a negative predictive marker of treatment outcome in patients with metastatic colorectal cancer who receive anti-EGFR therapies. Extended RAS testing is therefore required for all patients who are candidates for anti-EGFR therapy. To allow for the development of a strategic management plan, patients with metastatic colorectal cancer should have their tumour tested for RAS mutations at the time of diagnosis of their metastatic disease.

See Optimal molecular profiling.

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Practice point

RAS testing should be carried out on all patients at the time of diagnosis of metastatic colorectal cancer.

Practice point

RAS mutational status is a negative predictive biomarker for therapeutic choices involving EGFR antibody therapies in metastatic colorectal cancer.

Practice point

Cetuximab and panitumumab should only be considered for the treatment of patients with RAS wild-type metastatic colorectal cancer.

17.2.2.2 BRAF mutation testing

BRAF is a component of the RAS-RAF-MAPK signalling pathway. Activating mutations, which are mutually exclusive with KRAS mutations, are found in approximately 5–10% of metastatic colorectal cancers.

BRAF mutations (most of which are V600E mutations) have consistently been associated with poor prognosis overall and as such their presence is considered to be a negative prognostic marker in metastatic colorectal cancer patients.[16][25][26][27][28][29] An Australian retrospective analysis of patients with metastatic colorectal cancer demonstrated that two-thirds of BRAF-mutant patients' primary lesions were located on the right side of the colon and associated with an increased incidence of peritoneal and distant lymph node metastases, but fewer pulmonary metastases.[27] This study also reported a median survival of 10.4 months among patients with BRAF-mutant tumours, compared with 34.7 months for patients with BRAF wild-type tumours.

Moreover, BRAF mutations also appear to have predictive value, according to accumulating data. Evidence increasingly suggests that response to EGFR-targeted agents is less likely in patients whose tumours harbor BRAF mutations (particularly the BRAF V600E mutation).

At least two meta-analyses have addressed the efficacy of EGFR antibody therapies in patients with RAS wild-type/BRAF mutated tumours. Although neither analysis found a survival advantage for the addition of EGFR antibody therapy, they reached somewhat different conclusions:[30][31]

- The first meta-analysis[30] included 10 randomised controlled trials (RCTs) comparing cetuximab or panitumumab alone or plus chemotherapy with standard therapy or best supportive care (one phase II and nine phase III trials). Six trials were conducted in the first-line treatment setting, two for second-line therapy and two in patients with chemorefractory disease.[30] Among patients with RAS wild-type/BRAF-mutant tumours, compared with control regimens, the addition of an anti-EGFR monoclonal antibody did not significantly improve progression-free survival (hazard ratio [HR] 0.88, 95% confidence interval [CI] 0.67 to 1.14), overall survival (HR 0.91, 95% CI 0.62 to 1.34), or objective response rate (relative risk [RR] 1.31, 95% CI 0.83 to 2.08).
- The second meta-analysis included eight RTCs; four conducted in the first-line setting, three in the second-line setting, and one in patients with chemorefractory disease.[31] Among patients with RAS wild-type/BRAF mutant metastatic colorectal cancer, there was no significant overall survival benefit for the addition of anti-EGFR therapies (HR 0.97, 95% CI 0.67 to 1.41). In contrast, overall survival was significantly greater in patients with RAS wild-type BRAF wild-type tumours (HR 0.81; 95% CI 0.7 to 0.95). When comparing the overall survival benefit between BRAF mutant and BRAF wild-type tumours, the test for interaction was not statistically significant. The authors concluded that the observed differences in the effect of anti-EGFR therapies on overall survival according to BRAF mutation status could have been due to chance, and that the evidence was insufficient to state that BRAF-mutant tumours attain a different treatment benefit from anti-EGFR agents compared to individuals with BRAF wild-type tumours.

Results from TRIBE study[9] has shown promising outcomes for patients with BRAF-mutated tumours treated with aggressive systemic therapy consisting of leucovorin calcium (folinic acid), 5FU, oxaliplatin and irinotecan hydrochloride (FOLFOXIRI) plus bevacizumab. In this trial, patients with metastatic colorectal cancer who received FOLFOXIRI plus bevacizumab showed 2.5 months longer progression-free survival than those who were treated with FOLFIRI. However, the overall survival results remained disappointing for patients with BRAF-mutated tumours, compared with those with BRAF wild-type tumours (19.0 months versus 41.7 months).

Clinical trials are currently underway to test targeted therapies in BRAF-mutated metastatic colorectal cancer, akin to the development of therapies for BRAF-mutated metastatic melanoma. Early results are promising but have generally been less favourable than the melanoma trials.[32][33][34][35] Early studies evaluating single-agent BRAF inhibitor therapy or combination BRAF/mitogen-activated protein kinase (MEK) inhibition has yielded disappointing results.

EGFR activation has been implicated in the pathogenesis of BRAF mutant colorectal cancer. Therefore, the combination of BRAF/MEK inhibition and anti-EGFR therapy has recently been evaluated in a trial comparing (i) dabrafenib plus panitumumab, (ii) trametinib plus panitumumab, and (iii) the combination of dabrafenib, trametinib and panitumumab.[36] In the dabrafenib/panitumumab treatment arm, the objective response rate was 10%, and 80% of patients achieved stable disease. With trametinib/panitumumab no patients attained objective response but 53% showed stable disease. However, combined BRAF/MEK inhibition with panitumumab yielded an 18% objective response rate and 67% of patients showed stable disease.[36]

Somatic BRAF V600E mutations have been associated with sporadic cases of DNA mismatch repair deficiency showing microsatellite instability stability (MSI) phenotype.[37] On the contrary, BRAF V600E mutation is not associated with the MSI phenotype due to a germline mutation in mismatch repair (Lynch Syndrome).[38][39] BRAF V600E mutations have been proposed as a means of excluding Lynch syndrome. Subsets of patients with BRAF mutations in codons 594 and 596 have been shown to have microsatellite stability and significantly longer survival times, compared with those who have BRAF V600E disease.[40]

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Practice point

The BRAF mutation status should ideally be performed at the time of diagnosis of metastatic colorectal cancer, as this represents a distinct biologic subtype.

Practice point

The presence of a BRAF mutation in metastatic colorectal cancer is considered a poor prognostic marker.

Practice point

BRAF mutation status in combination with testing for DNA mismatch repair deficiency can assist in the identification of a germline versus somatic cause of DNA mismatch repair deficiency.

Practice point

The preponderance of the available evidence is that response to EGFR-targeted agents is less likely in patients whose tumours harbour a BRAF mutation.

Practice point

Metastatic colorectal cancer patients with a BRAF mutation should be considered for a clinical trial where available or triplet chemotherapy if suitable.

17.2.2.3 Microsatellite instability (MSI) testing

Approximately 10% of colorectal carcinomas demonstrate MSI. Distinct from the majority of colorectal cancers with chromosomal instability, tumours with MSI retain intact chromosomal numbers but contain microsatellite repeats due to deficiency in DNA mismatch repair which are thought to contribute to the early steps of tumorigenesis in colorectal cancer.[41] While emerging clinical data have highlighted improved prognosis of tumours with MSI in early colorectal cancer, potentially circumventing the need for adjuvant chemotherapy, the implications of MSI in metastatic colorectal cancer remain uncertain.

A retrospective analysis in patients with metastatic colorectal cancer[42] observed that MSI phenotype was associated with younger age (median 67 years), higher risk of poor differentiation (58%), and a higher risk of stage IV disease at presentation 45%. BRAF V600E mutations were present in 30% of patients with MSI.[42]

Most studies have shown MSI not to be relevant as a predictive marker for various chemotherapeutic agents. However in a pooled analysis of four phase III studies (CAIRO, CAIRO2, COIN and FOCUS), BRAF mutations have been shown to be more frequent in patients with tumours exhibiting MSI than in those with microsatellite-stable tumours.[28] Furthermore, in this analysis, progression-free survival and overall survival were significantly worse for patients with tumours with MSI, compared with those with microsatellite-stable tumours (HR, 1.33; 95% CI 1.12 to 1.57 and HR 1.35; 95% CI 1.13 to 1.61, respectively), and for patients with BRAF-mutant tumours when compared with those with BRAF wild-type tumours (HR 1.34; 95% CI 1.17 to 1.54 and HR 1.91; 95% CI 1.66–2.19, respectively).[28]

Emerging data have shown DNA mismatch repair status to predict the clinical benefit of immune checkpoint blockade with pembrolizumab in patients with metastatic colorectal cancer. A phase II study evaluating pembrolizumab in patients with colorectal cancer[43] reported immune-related objective response rates and immune-related 6-month progression-free survival rates of 40% (4 out of 10 patients) and 78% (7 out of 9 patients), respectively, for patients with DNA mismatch repair deficiency tumours, and 0% and 11% for those with DNA mismatch repair-proficient tumours. The study reported excellent rates of median progress-free survival and overall survival (maturity not reached) in the cohort with DNA mismatch repair deficiency tumours versus 2.2 and 5.0 months, respectively, in the cohort with DNA mismatch repair-proficient tumours.[43]

CheckMate-142[44] is a phase II study evaluating the role of nivolumab, alone or in combination with ipilimumab, in heavily pre-treated MSI-high colorectal cancer. This study also had a cohort of non-MSI patients. In preliminary results, the objective response rate in the nivolumab-alone arm was 27%, compared with 15% in the combination treatment arm. Stable disease was reported in 24% in the nivolumab arm and 65% in the combination treatment arm. Median overall survival was more than 16 months in the nivolumab arm and has not been reached in the combination arm.[44]

While these data provide proof of principle as to the potential for benefit from immunotherapy in metastatic colorectal cancer, it is premature to conclude, based upon these small studies, that immune checkpoint inhibitors represent a standard treatment for metastatic DNA mismatch repair-deficient colorectal cancer. Confirmation in larger data sets is needed, as is further exploration of the data from these trials, to understand why there was a complete lack of response in microsatellite-stable tumours, which represents the vast majority of patients with metastatic colorectal cancer.

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Practice point

MSI testing in the metastatic setting can be useful to help identify patients who require referral for further genetic testing and counselling.

Practice point

BRAF V600 mutational analysis should be done in conjunction with MSI testing for prognostic stratification.

Practice point

MSI testing may be a predictive marker for the use of immune checkpoint inhibitors in the treatment of patients with metastatic colorectal cancer.

17.2.2.4 Emerging biomarkers

There is a growing list of additional biomarkers that may impact on responses to agents we have available for the treatment of metastatic colorectal cancer. At the present time, emerging biomarkers are not recommended for routine patient management outside of clinical trial settings.

In particular, there is a growing list of biomarkers beyond RAS mutations that may influence responses to EGFR targeted therapies. These include HER2, MET and KRAS gene amplification, ligands such as transforming growth factor-α (TGF-α), amphiregulin and epiregulin, EGFR mutations and alterations/mutations in HER3, PI3KCAand PTEN.[45]

It seems likely in the future that a comprehensive biomarker analysis will be required to identify the subgroup of patients with metastatic colorectal cancer who will truly benefit from treatment with an anti-EGFR agent.

Although metastatic colorectal cancer is primarily considered to be a genetic disease characterised by the sequential accumulation of genetic of genetic mutations, evidence now suggests that epigenetic alterations[46] add further complexity to pathogenesis, aetiology and prognosis of subgroups of the disease.

Practice point

Emerging biomarkers are not recommended for routine patient management outside of the clinical trial setting.

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17.2.2.5 Left-sided versus right-sided tumours

Evidence is emerging to support the premise that left-sided and right-sided colon tumours have clinically significant differences. They differ with respect to biology, pathology and epidemiology, and previous data suggest a mortality difference between left- and right-sided colon tumours.[47][48] Patients with right-sided colon tumour tend to have more poorly differentiated, higher incidence of mutant KRAS, mutated PIK3CA and mutant BRAF tumours, fewer liver and lung metastases, and shorter interval between diagnosis and study entry.[49]

Two recent meta-analyses have provided data on the prognostic and predictive value of primary tumour location in patients with RAS wild-type metastatic colorectal cancer:

- The first meta-analysis[50] included five first line randomised controlled studies and performed two separate analyses. One evaluated the predictive relevance of primary tumour location for anti-EGFR therapy combined with standard chemotherapy compared with chemotherapy alone (CRYSTAL and PRIME studies), and the other evaluated the impact of primary tumour location on therapy with either anti-EGFR plus chemotherapy or anti-VEGFR combined with chemotherapy (CALGB/SWOG 80405, FIRE-3 and PEAK studies). In addition, 14 first line studies were evaluated assessing prognostic impact of primary tumour location.[50]
- The second meta-analysis[51] included the same 5 first line randomised controlled studies (CRYSTAL, PRIME, PEAK, FIRE-3 and CALGB 80405) and one second line study (20050181) and performed a pooled analysis of all 6 trials.

The primary tumour was located in the right colon in 27% of patients in the first meta-analysis[50] and 23.9% in the second.[51] Both meta-analyses showed that right sided colon cancer was associated with a poorer prognosis. Overall survival for right sided colon cancer remained below 20 months in many studies[50], and in both the first and second line setting patients with right sided colon cancer had a worse prognosis regardless of treatment type received. However, this was numerically less pronounced and not statistically significant in those patients receiving chemotherapy and bevacizumab in the CALGB trial.[51]

In terms of predictive role of primary tumour location, both meta-analyses showed a significant benefit from the addition of anti-EGFR therapy in patients with left sided colon cancer.[50][51] In the meta-analysis by Holch et al [50] a significant benefit was seen with the addition of anti-EGFR therapy to chemotherapy compared with chemo-therapy alone for both overall survival (HR 0.69; 95% CI 0.58-0.83, p<0.0001), progression free survival (HR 0.65; 95% CI 0.44-0.88, p=0.008) and response rate. When comparing chemotherapy plus anti-EGFR to chemotherapy plus anti-VEGF therapy, left sided colon cancer was associated with improved outcomes in those who received anti-EGFR therapy. This benefit was significant for overall survival (HR 0.71; 95% CI 0.58-0.85, p=0.0003), and response rate (HR 1.49; 95% CI 1.16-1.9, p=0.002) but not for progression free survival (HR 0.86; 95% CI0.73-1.02, p=0.084).[50]

These findings were confirmed in the meta-analysis by Arnold et al[51] which performed a pooled analysis of all six included studies comparing chemotherapy plus anti-EGFR to chemotherapy +/- bevacizumab and observed a significant benefit of chemotherapy plus anti-EGFR in left sided colon cancers for both overall survival (HR 0.75; 95% CI 0.67-0.84, p<0.001) and progression free survival (HR 0.78; 95% CI 0.70-0.87, p<0.001).[51]

In contrast, the Holch et al meta-analysis did not show any significant benefit to the addition of an anti-EGFR to chemotherapy in right sided colon cancer, however the sample size was small (right sided n=172).[50] When comparing chemotherapy plus anti-EGFR to chemotherapy plus anti-VEGF there was a significant improvement in progression free survival for those who received anti-VEGF (HR 1.53; 95% CI 1.16-2.01, p=0.003), and a trend to improved overall survival which was not statistically significant (HR 1.3; 95% CI 0.97-1.74, p=0.081). There was no significant difference between the two treatment in terms of response rate but numerically favoured anti-EGFR (HR1.2; 95% CI 0.77-1.87, p=0.432).[50]

These findings were confirmed in the Arnold meta-analysis.[51] In a pooled analysis of all 6 trials comparing chemotherapy plus anti-EGFR with chemotherapy +/- anti-VEGF there was no benefit seen from anti-EGFR in right sided colon cancer for overall survival (HR 1.12; 95% CI 0.87-1.45, p=0.381), or progression free survival (1.12; 95% CI 0.87-1.44, p=0.365). There was a non-significant trend to improved response rate with anti-EGFR (HR 1.47; 95% CI 0.94-2.29, p=0.089). In analysis of the individual studies by side, there was limited if any benefit seen with the addition of anti-EGFR therapy in right sided colon cancer in any study. Only the CRYSTAL (n=84) and second-line 20050181 (n=70) numerically favoured the addition of anti-EGFR therapy but this was not statistically significant and included only small numbers of patients. As in the first meta-analysis there was a significant improvement in outcome for patients with right sided tumours receiving chemotherapy and anti-VEGF compared with anti-EGFR plus chemotherapy in the CALGB 80405 study (progression free survival 10.2 months vs 7.5 months, p=0.007, n=149) and a non-significant trend to improved outcome in FIRE-3 (n=88) and PEAK (n=36).[51]

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Practice point

The location of the primary tumour is a strong prognostic factor. Patients with left sided primary tumours have a favourable outcome compared with those with right sided tumours regardless of treatment type received.

Practice point

Left sided colorectal cancer should be considered for initial doublet chemotherapy and anti-EGFR therapy where appropriate. Alternate options remain appropriate based on patient preference and comorbidity.

Practice point

Right sided colorectal cancer should be considered for initial doublet chemotherapy plus or minus anti-VEGF. There may be a role for initial chemotherapy with anti-EGFR in right sided colon cancer where the aim of treatment is down staging for resection given the improved response with anti-EGFR. However, this should be done with caution given the lack of benefit on overall survival or progression free survival.

Practice point

Sequential use of all available therapies should continue to be utilised in patients with colorectal cancer regardless of the side of the primary tumour, provided it is appropriate for the individual patient.

Practice point

Future trials for colon cancer should stratify patients by 'sidedness,' to better understand this issue.

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17.3 Systemic chemotherapy first-line treatment

Contents

17.3.1 Background

Chemotherapy combinations commonly used in the treatment of metastatic colorectal cancer include:

- fluorouracil (5FU) and leucovorin (FU/LV)
- leucovorin calcium (folinic acid), 5FU and oxaliplatin (FOLFOX)
- leucovorin calcium (folinic acid), 5FU and irinotecan hydrochloride (FOLFIRI)
- leucovorin calcium (folinic acid), 5FU, oxaliplatin and irinotecan hydrochloride (FOLFOXIRI)
- capecitabine plus oxaliplatin (XELOX) – also called CAPOX

- capecitabine plus irinotecan hydrochloride (XELIRI) (see eviQ protocols: Colorectal Metastatic CAPIRI (XELIRI) (Capecitabine Irinotecan) and Colorectal Metastatic CAPIRI (XELIRI) (Capecitabine Irinotecan) with Bevacizumab).

First line chemotherapy for metastatic colorectal cancer typically contains a fluoropyrimidine (intravenous 5FU or oral capecitabine) in combination with either oxaliplatin or irinotecan in various schedules.

For information on protocols, see eviQ cancer treatments.

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17.3.2 Overview of evidence (non-systematic literature review)

No systematic reviews were undertaken for this topic. Practice points were based on selected reviews, primary studies, and other clinical practice guidelines (see Guideline development process).

17.3.2.1 The cytotoxic chemotherapy backbone

Systemic chemotherapy produces clinically meaningful improvements in median survival and progression-free survival. These benefits are most pronounced with regimens containing irinotecan or oxaliplatin in combination with 5FU.

Therapy should be individualised, based upon biomarker studies (see Molecular pathology and biomarkers), previous treatment, disease extent, organ function, and medical comorbidities. For most patients, treatment will be palliative, not curative. The treatment goals may be to prolong overall survival and maintain quality of life for as long as possible. Although specific regimens may be designated as initial therapy, second line therapy after progression, maintenance and beyond, it is important to clarify that these designations represent a continuum of care and that these lines of therapy are blurred rather than distinct.

Combination chemotherapy with a fluoropyrimidine plus either oxaliplatin or irinotecan (FOLFOX or FOLFIRI) achieves higher response rates and improved progression free survival times than a fluoropyrimidine or 5FU/LV alone.[1][2] FOLFOX and FOLFIRI are both acceptable choices for first-line therapy. This recommendation is consistent with consensus-based guidelines by the US National Comprehensive Cancer Network (NCCN)[3] and the European Society for Medical Oncology (ESMO).[4]

5FU chemotherapy can be delivered in a number of different ways. Continuous infusion 5FU is generally less toxic than some bolus and oral regimens. See eviQ protocol Colorectal Metastatic De Gramont (Modified) (Fluorouracil and Leucovorin). Capecitabine, the oral formulation, can be used as an alternative to 5FU/LV alone [5] (XELOX and XELIRI) or as monotherapy in patients with poor performance status or medical comorbidities precluding the use of combination therapy approaches. The combination of capecitabine and irinotecan (XELIRI) has been shown to be inferior and more toxic (higher rates of severe vomiting, diarrhoea and dehydration) than infusional fluorouracil and irinotecan (FOLFIRI).[6][7] The preferred regimen of the eviQ reference committee is FOLFIRI or irinotecan monotherapy.

When determining the choice, duration and specific combination of systemic therapies a patient's performance status, comorbidities and treatment related toxicities need to be taken into consideration. The major dose-limiting side effect of oxaliplatin is a cumulative, late-onset predominantly sensory neuropathy, which may require drug discontinuation despite ongoing tumour response. It occurs with increasing frequency above cumulative doses of 680 mg/m2.[8] Guidelines for dosing modifications for all common toxicities of agents described in this section are available at eviQ Cancer Treatments online.

The following monoclonal antibodies have been shown to improve the clinical outcome of patients with metastatic colorectal cancer when combined with combination chemotherapy in the first-line setting:[9][10][11][12][13][14][15][16][17][18]

- bevacizumab
- cetuximab
- panitumumab. See Role of biological agents in first-line treatment of metastatic colorectal cancer.

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17.3.2.2 Patients who are candidates for intensive chemotherapy

For patients who are able to tolerate it, we suggest combination chemotherapy with a doublet (FOLFOX, XELOX, or FOLFIRI) rather than a single-agent sequential therapy for initial treatment of metastatic colorectal cancer, particularly for those who have limited liver metastases that might become potentially resectable. This recommendation is consistent with consensus-based guidelines from NCCN)[3] and ESMO.[4]

The three active conventional chemotherapy agents for metastatic colorectal cancer are fluoropyrimidines, irinotecan, and oxaliplatin. The proportion of patients exposed to all three drug classes at some point in the continuum of care correlates with an increased median survival as evidenced from a combined analysis of data from seven phase III clinical studies.[19]Results from a randomised study to evaluate the efficacy of FOLFIRI and FOLFOX regimens as initial therapy and to evaluate the effect of using sequential therapy with the alternate regimen on progression showed no sequence to be superior with respect to progression free survival or overall survival.[20]

The triplet combination chemotherapy regimen FOLFOXIRI with or without bevacizumab can be considered for first-line therapy in selected patients who are able to tolerate intensive therapy and for whom a more aggressive initial approach is chosen due to patient factors such as excellent performance status, younger age, higher tumour load, conversion therapy for initially non-resectable liver metastases, contraindication to cetuximab/panitumumab (e.g. RAS/BRAF mutation). In an Italian study FOLFOXIRI was shown to be superior to FOLFIRI in terms of response rate (the primary end point, 66% versus 41%) the number of patients able to undergo complete secondary surgical cytoreduction of liver metastases, median progression-free survival, and median overall survival (23 versus 17 months).[21][22]

Similar high response rates and improved median overall survival were noted with FOLFOXIRI plus bevacizumab as compared to FOLFIRI plus bevacizumab in the TRIBE trial, but it did not confirm higher rates of secondary surgical resection of liver metastases with an initial three-drug chemotherapy backbone.[23] Furthermore, grade 3 to 4 toxic effects that were more common with FOLFOXIRI included diarrhoea, stomatitis, neutropenia, and peripheral neuropathy. Not all studies have concluded a benefit from triplet cytotoxic therapy versus a standard doublet[24] and the contribution bevacizumab makes to the triplet regimen remains uncertain.

For patients in whom either oxaliplatin or irinotecan need to be withheld because of toxicity, it is reasonable to continue the fluoropyrimidine plus bevacizumab. See Discontinuation of treatment and maintenance therapy.

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17.3.2.3 Patients who are not candidates for intensive chemotherapy

For patients who are not candidates for an intensive first-line oxaliplatin or irinotecan-based combination regimen, we suggest fluoropyrimidine therapy alone.[25] This recommendation is consistent with consensus-based guidelines from the NCCN[3] and ESMO.[4]

Capecitabine monotherapy is an effective first-line regimen when fluoropyrimidines alone are indicated. If intravenous 5FU is used, short-term infusional FU/LV rather than bolus 5FU administration is preferable because of its favourable toxicity profile.

The use of FU/LV or capecitabine plus bevacizumab is also appropriate in patients who are not good candidates for oxaliplatin or irinotecan and who do not have contraindications to antiangiogenesis therapy. In two phase II randomised controlled trials (RCTs) in which previously untreated patients were assigned to bolus FU/LV with or without bevacizumab (5 or 10 mg/kg every two weeks), response rates were approximately two fold higher with bevacizumab, and median survival was extended by 7.7 and 3.7 months for the two doses, respectively.[26][27]

Furthermore, in the multi-centre AVEX trial, 280 patients age 70 or older with previously untreated metastatic colorectal cancer were randomly assigned to capecitabine with or without bevacizumab at standard doses.[28] Combined therapy was associated with significantly longer median progression-free survival (the primary endpoint, 9.1 versus 5.1 months) and a non-significant trend toward longer overall survival (median 21 versus 17 months). However, there were significantly more events leading to treatment discontinuation in the bevacizumab arm (25 versus 15 percent), and higher rates of all-grade haemorrhage (25 versus 7 percent), hypertension (19 versus 5 percent), and venous thromboembolic events (12 versus 5 percent, grade 3 or higher, 8 versus 4 percent). There were six arterial thromboembolic events in the combined therapy group, compared with three with capecitabine monotherapy (4 versus 2 percent). Although rates of grade 5 (fatal) toxicities were not higher with bevacizumab (8.2 versus 11.8 percent with capecitabine alone), they were higher than expected in both groups.[28]

Combination of capecitabine and bevacizumab is therefore an option for elderly patients or those not suitable for more intensive regimens. Caution is warranted when prescribing bevacizumab in combination with chemotherapy for elderly patients with a history of atherosclerotic cardiovascular disease. The risks probably outweigh the benefits in patients with a history of stroke or myocardial infarction within the preceding 6 to 12 months, or a history of thromboembolic disease, and the drug is contraindicated in patients with severe uncontrolled hypertension. See eviQ protocol Colorectal Metastatic Capecitabine with Bevacizumab

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17.3.2.4 Practice points

For patients who are candidates for intensive chemotherapy

Practice point
For patients who are able to tolerate it, combination chemotherapy with a doublet (FOLFOX, XELOX [CAPOX], or FOLFIRI) rather than a single agent sequential therapy for initial treatment of metastatic colorectal cancer, is preferred.

When the aim is cytoreduction prior to surgical resection

Practice point
Patients with potentially resectable metastatic disease should be discussed at a multidisciplinary meeting, and treatment plans should consider patient comorbidity and suitability for an aggressive treatment strategy

Practice point
Monotherapy is not appropriate and combination chemotherapy with a doublet (FOLFOX, XELOX [CAPOX], or FOLRIR) should be used where the aim of therapy is significant cytoreduction. For those with RAS wild-type tumours, an anti-EGFR antibody in conjunction with combination chemotherapy can be considered especially in those with left sided primaries.

Practice point

For those with good performance status and without significant comorbidities intensive triplet chemotherapy with FOLFIRINOX can be considered.

For patients who are not candidates for intensive chemotherapy

Practice point

Patient comorbidities, ECOG performance status, and location and burden of metastatic disease should be considered in treatment decisions.

Practice point

For patients who are medically unfit with poor performance status, a supportive care approach may be appropriate.

Practice point

In patients with poor performance status or significant comorbidities palliative treatment with single agent fluoropyrimidine (with or without bevacizumab) may be preferred to doublet chemotherapy. Fluoropyrimidine-based therapy alone (or in combination with bevacizumab) can be considered in patients with low-volume unresectable disease.

Next section: biological agents first-line treatment of metastatic CRC
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17.4 Biological agents in first-line tx of metastatic CRC

Contents

17.4.1 Background

Biological agents are generally indicated for the first-line treatment of patients with metastatic colorectal cancer unless contraindicated due to, for example, reduced organ function, poor performance status or cardiovascular insufficiency.

Biological agents reimbursed for use in the treatment of patients with metastatic colorectal cancer in Australia include:

- Anti-VEGF therapy: bevacizumab – a humanised monoclonal antibody that targets vascular endothelial growth factor-A (VEGF-A), a member of a family of VEGF receptor-activating ligands.
- Anti EGFR therapy: cetuximab and panitumumab – monoclonal antibodies that target epidermal growth factor receptor (EGFR).

17.4.2 Overview of evidence (non-systematic literature review)

No systematic reviews were undertaken for this topic. Practice points were based on selected reviews, primary studies, and other clinical practice guidelines (see Guideline development process).

17.4.2.1 Anti-VEGF therapy – bevacizumab

In a pivotal early randomised controlled trial (RCT), the addition of bevacizumab to the bolus irinotecan, leucovorin (folinic acid), and fluorouracil (IFL) regimen significantly improved response rates (45% versus 35%), increased time to tumour progression (11 versus 6 months), and prolonged overall survival (20 versus 16 months).[1]

Since then, benefit for adding bevacizumab to a variety of fluoropyrimidine, irinotecan, and oxaliplatin-containing regimens used for first-line therapy has been confirmed, although the magnitude of both the overall and progression-free survival benefits are relatively modest.[2] To date, there are still only limited data on the benefit of adding bevacizumab to an oxaliplatin-based regimen[3] although this has been a standard first-line treatment in many patients, and no RCT comparing FOLFIRI versus FOLFIRI plus bevacizumab has been published.

XELOX [CAPOX] can also be combined with bevacizumab. The evidence supporting this and FOLFOX4 combined with bevacizumab in the first line comes from the randomised phase III, NO16966 trial by Saltz et al[3]. Patients were randomly assigned in a 2 X 2 factorial design to FOLFOX 4 or XELOX followed by bevacizumab or placebo. After a median follow-up of 27.6 months, PFS was significantly increased with bevacizumab compared with placebo when combined with oxaliplatin-based chemotherapy (HR=0.83; p=0.0023), the median PFS duration being 9.4 months with bevacizumab plus chemotherapy versus 8.0 months with placebo plus chemotherapy.[3]

However, the overall survival differences did not reach statistical significance, and response rate was not improved by the addition of bevacizumab. The lack of continuation of either bevacizumab or flluoropyrimidine until disease progression may have blunted the contribution of bevacizumab, thereby diminishing its impact on OS and PFS.[3]

An open-label, phase 3 trial (the TRIBE study) reported that the combination of leucovorin calcium (folinic acid), 5FU, oxaliplatin and irinotecan hydrochloride (FOLFOXIRI) in combination with bevacizumab enhanced response rate and progression-free survival, compared with FOLFIRI plus bevacizumab[4] and reported a median overall survival of 29.8 months. The use of FOLFOXIRI–bevacizumab treatment is limited to select patients with excellent performance status and minimal comorbidities. The contribution bevacizumab makes to the triplet regimen is uncertain.

Bevacizumab can be associated with a number of potentially serious side effects, including proteinuria, hypertension, bleeding, bowel perforation, impaired wound healing, arterial (but not venous) thromboembolic events (such as transient ischemic attack, stroke, angina, myocardial infarction), and reversible posterior multifocal leukoencephalopathy.[5]

For patients with RAS and BRAF wild-type tumours, an important question is whether a bevacizumab-containing regimen provides superior outcomes as compared with an initial regimen that contains an anti-EGFR agent. Emerging data suggest that first-line cetuximab-containing regimens may provide superior outcomes for patients with RAS/BRAF wild-type metastatic colorectal cancer with a primary tumour site in the left colon (see Left-sided versus right-sided tumours).[6]

Currently there is no validated predictive biomarker for bevacizumab.

See eviQ protocols:

- FOLFIRI and Bevacizumab
- FOLFOX and Bevacizumab
- XELOX and Bevacizumab
- FOLFOXIRI and Bevacizumab

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17.4.2.2 Anti-EGFR therapy

The EGFR antibodies cetuximab and panitumumab are active in various combinations, either alone or with cytotoxic chemotherapy agents.

The activity of EGFR antibodies is limited to patients with RAS wild-type tumours. Thus, knowledge of the RAS mutational status of the patient is a prerequisite to treatment with EGFR antibodies.

Unlike cetuximab (a chimeric monoclonal antibody produced in a murine culture), panitumumab is a fully human monoclonal antibody, and has a lower incidence of infusion reactions. The available evidence suggests that antitumor efficacy is similar to that of cetuximab, and that the two drugs might be interchangeable.[7][8]

The addition of cetuximab to FOLFIRI has been shown to improve response rate, median progression-free survival rate and overall survival rate in first-line use, compared with FOLFIRI alone in metastatic colorectal cancer patients with RAS wild-type tumours.[9][10][11] Both cetuximab and panitumumab also increase the activity of the cytotoxic doublet FOLFOX in metastatic colorectal cancer patients with RAS wild-type tumours.[12][13][14][15][16][17] In contrast, benefits have not been shown for the addition of EGFR antibodies to oxaliplatin-based regimens where non-infusional fluoropyrimidines were used, such as bolus administration, the combination of 5-flourouracil (5FU), calcium leucovorin (folinic acid) and oxaliplatin (FLOX), capecitabine, or capecitabine plus oxaliplatin (CAPOX).[16][18] Capecitabine-based therapy should not be used in combination with EGFR antibody therapies.[16]

Combinations of cetuximab or panitumumab plus an irinotecan or oxaliplatin-based cytotoxic regimen that contains infusional 5FU (i.e, FOLFIRI and FOLFOX) are safe and effective. These are a reasonable first-line option for patients with RAS and BRAF wild-type tumours, especially for patients with a primary tumour on the left side.

See eviQ protocols for cetuximab:

- FOLFIRI and Cetuximab
- FOLFIRI and Cetuximab (two weekly)

See eviQ protocols for panitumumab:

- FOLFOX and Panitumumab
- FOLFIRI and Panitumumab

Practice point

Biological agents targeting EGFR or VEGF in combination with chemotherapy are recommended in the first-line treatment of most patients unless contraindicated.

Practice point

EGFR antibodies should:

- be used in patients with RAS wild-type tumours
- be used in combination with FOLFIRI or FOLFOX
- not be combined with capecitabine-based and bolus 5FU-based regimen.

Practice point

Patients with left sided colorectal cancer should be considered for initial doublet chemotherapy and anti-EGFR therapy where appropriate. Alternate options remain appropriate based on patient preference and comorbidity.See left vs. right section

Practice point

EGFR antibodies may be less efficacious in patients with BRAF mutations.

Practice point

VEGF antibody (bevacizumab):

- should be used in combination with cytotoxic doublets including FOLFOX, XELOX and FOLFIRI
- can be used in combination with the triplet cytotoxic regimen FOLFOXIRI in select fit patients where tumour shrinkage is the goal, and potentially in fit patients with a BRAF mutation
- can be used in combination with fluoropyrimidine monotherapy in less fit patients unlikely to be suitable for a doublet cytotoxic regimen.

Practice point

Patients with right sided colorectal cancer should be considered for initial doublet chemotherapy plus or minus anti-VEGF. See left vs. right section

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17.5 Subsequent treatment & continuum-of-care model

Contents

17.5.1 Background

After initial systemic therapy for colorectal cancer, the approach to subsequent therapy is variable. It might include maintenance chemotherapy (particularly for patients treated initially with an oxaliplatin-containing regimen to minimise cumulative neurotoxicity) or a switch to a different regimen altogether because of disease progression or intolerance to the initial regimen.

17.5.2 Overview of evidence (non-systematic literature review)

No systematic reviews were undertaken for this topic. Practice points were based on selected reviews, primary studies, and other clinical practice guidelines (see Guideline development process).

17.5.2.1 Continuum-of-care model

For patients with metastatic colorectal cancer, a 'continuum-of-care' approach is now favoured over the model of distinct 'lines' of chemotherapy (in which regimens containing non-cross-resistant drugs are each used in succession until disease progression).[1]

This approach emphasises an individualised treatment strategy that might include periods of maintenance chemotherapy interspersed with more aggressive treatment protocols, rechallenging patients who responded to first-line treatment with the same agents used first-line[2][3] as well as reutilisation of previously administered chemotherapy agents in combination with other active drugs.

For medically unfit patients with a poor performance status or extensive comorbidity, supportive care without chemotherapy should be considered.

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17.5.2.2 Discontinuation of treatment and maintenance therapy

The optimal duration of initial chemotherapy for non-resectable disease in the absence of disease progression is debated. In general, the decision to permit treatment breaks during initial therapy (i.e. intermittent rather than continuous therapy) must be individualised and based upon several factors, including tolerance of and response to chemotherapy, disease bulk and location, quality of life, patient preferences and symptomatology.

In many cases, particularly with oxaliplatin-based regimens, toxicity occurs before progressive disease and thus cumulative toxicity can be problematic. As a result, discontinuation/de-escalation/intermittent combination therapy or maintenance strategies provide an attractive treatment options for patients who have responded or reached stable disease.

For patients who are responding to an oxaliplatin based initial regimen, it is reasonable to discontinue oxaliplatin before the onset of severe neurotoxicity (usually after three to four months of therapy). Continuation of oxaliplatin is an alternative for responding patients who have no clinically significant neuropathy. The administration of intermittent combination chemotherapy has been investigated in a number of studies. The OPTIMOX1 trial randomised patients to receive FOLFOX4 until progression or unacceptable toxicity or FOLFOX7 (using a higher dose of oxlaplatin) for six cycles only, followed by reintroduction of oxaliplatinat the time of progression after 12 cycles of a non-oxaliplatin-containing 5FU/LV maintenance regimen.[4] No difference in progression free survival or overall survival was noted. This was interpreted as an indication that oxaliplatin-free intervals did not shorten survival times. The subsequent randomised OPTIMOX-2 trial[5] and the MRC COIN[6] trials took this concept a step further by addressing whether complete chemotherapy-free intervals (CFIs) instead of maintenance might provide the same overall treatment benefit. In both studies, a detrimental effect of CFIs could not be excluded based on the data. These data mandate caution and both careful patient selection and vigilant patient monitoring so that therapy can be reinstated promptly at progression when considering chemotherapy-free intervals.

The concept of treatment discontinuation after active induction therapy has been further refined by studies assessing the concept of “maintenance” therapy with biologicals with or without chemotherapy and a CFI. The optimal maintenance treatment following induction with oxaliplatin containing regimen in combination with bevacizumab is a combination of a fluoropyrimidine (cacepcitabine) plus bevacizumab has been demonstrated by the CAIRO-3[7] and AIO 0207 trials[8].

The Dutch CAIRO3 trial[7] randomly assigned patients with stable disease or better after six cycles of XELOX plus bevacizumab to continued capecitabine plus bevacizumab or observation alone. Maintenance therapy was associated with a significantly longer progression free survival (calculated from the time of randomisation) and there was a trend toward improved overall survival. Similarly, a benefit for continued fluoropyrimidine plus bevacizumab as compared with observation alone was also shown in the German AIO KRK 0207 trial[8].

For patients who have no disease progression after an initial course of bevacizumab plus oxaliplatin-containing chemotherapy, bevacizumab alone for maintenance therapy is not recommended in consensus-based guidelines for the treatment of metastatic colorectal cancer from NCCN[9] and ESMO[10] The Spanish MACRO trial investigated this concept.[11] Patients received six cycles of first-line XELOX plus bevacizumab followed by a randomization to continued therapy or bevacizumab maintenance therapy alone until progression or treatment intolerance.[11] The trial failed to achieve its primary endpoint of non-inferiority for progression free survival. Similarly, Swiss SAKK 41-06 trial randomly assigned patients to bevacizumab continuation versus no maintenance after four to six months of first-line bevacizumab-containing chemotherapy.[12] Like the MACRO trial, the trial failed to achieve its primary endpoint of non-inferiority for time to progression.

Although data from the OPTIMOX-2, MRC COIN, NO16966, and CAIRO3 trials suggested that a complete stop of chemotherapy (with or without biologics) might be associated with an inferior outcome, these results have been called into question by a more recent meta-analysis[13] that did not find adverse survival with an intermittent as compared with continuous treatment strategy.

This recent meta-analysis of randomised controlled trials (RCTs) of continuous versus intermittent strategies of delivering systemic chemotherapy to previously untreated patients with metastatic colorectal cancer.[13] It included eight trials, four of which did not employ maintenance therapy, one of which used maintenance therapy with a fluoropyrimidine alone, two trials which used biologic therapy alone, and one trial, a fluoropyrimidine plus a biologic agent.[13] Intermittent delivery of chemotherapy did not result in a significantly reduced overall survival compared with continuous delivery, whether or not maintenance treatment was included. Quality of life was the same or better with intermittent therapy.[13]

The advantage of intermittent treatment with irinotecan-based regimens is unclear, given the relative lack of cumulative toxicity. Furthermore, the available data suggest similar overall outcomes (progression-free survival and overall survival) whether or not the regimen is administered continuously until progression or toxicity, or in 2 months on/2 months off intervals. The benefits/risks of intermittent chemotherapy with an irinotecancontaining regimen were addressed in an Italian trial, which demonstrated that patients started on FOLFIRI as first-line therapy had similar overall outcome (progression free survival and overall survival) whether or not the regimen was administered continuously until progression or toxicity or in "two months on/two months off" intervals.[14] There were no demonstrable differences in treatment-related toxicity between the continuous versus intermittent treatment groups.

Benefit from anti-epidermal growth factor receptor (EGFR) therapies is limited to patients whose tumours lack mutations in one of the RAS oncogenes (i.e., wild-type [WT] RAS). Data on maintenance strategies involving EGFR- antibody therapies are inconclusive at this time.

The future challenge is to determine which patients should be deescalated to a maintenance strategy and which can be safely stopped completely.

Practice point

Individualisation and discussion with the patient is essential when planning treatment breaks and or de-escalation/maintenance schedules.

Practice point

When the combination of leucovorin calcium (folinic acid), 5-fluorouracil (5FU) and oxaliplatin (FOLFOX), with or without bevacizumab, is used for first-line therapy, the available data suggest that it is reasonable to discontinue oxaliplatin temporarily while maintaining a fluoropyrimidine with or without bevacizumab.

Practice point

When the combination of folinic acid, 5FU and irinotecan hydrochloride (FOLFIRI), with or without bevacizumab, is used for first- line therapy, patients can continue on induction therapy for as long as tumour shrinkage continues and the treatment is tolerable.

Practice point

For patients receiving initial therapy with folinic acid, 5FU, oxaliplatin and irinotecan hydrochloride (FOLFOXIRI), with or without bevacizumab, a fluoropyrimidine plus bevacizumab may be considered as maintenance therapy (as was done in the pivotal trials examining FOLFOXIRI).

Practice point

For patients receiving initial therapy with a single-agent fluoropyrimidine (plus bevacizumab), induction therapy should be maintained.

Practice point

Initial induction therapy or a second-line therapy should be reintroduced at radiological or first signs of symptomatic progression.

Practice point

If a second-line therapy is chosen, re introduction of the initial induction treatment should be a part of the entire treatment strategy as long as no relevant residual toxicity is present.

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17.6 Systemic second-line treatment

Contents

17.6.1 Background

'Second-line therapy' currently refers to therapy administered from the time the first-line chemotherapy backbone has to be changed. The aim is to offer second-line therapy to as many patients with metastatic colorectal cancer as possible. It is usually proposed for patients with good performance status and adequate organ function and is dependent on the treatment used in the first line setting. Treatment strategies will also depend on predictive biomarkers (e.g. tumour RAS mutation status for EGFR antibody therapy).

Chemotherapy combinations commonly used in the second-line treatment of non-resectable metastatic colorectal cancer include:

- leucovorin calcium (folinic acid), 5-fluorouracil (5FU) and oxaliplatin (FOLFOX)
- leucovorin calcium (folinic acid), 5FU and irinotecan hydrochloride (FOLFIRI)
- capecitabine plus oxaliplatin (XELOX) – also called CAPOX.

Biologic agents used in the second line setting include:

- Anti-VEGF therapy: bevacizumab
- Anti EGFR therapy: cetuximab and panitumumab

For information on protocols, see eviQ cancer treatments.

17.6.2 Overview of evidence (non-systematic literature review)

No systematic reviews were undertaken for this topic. Practice points were based on selected reviews, primary studies, and other clinical practice guidelines (see Guideline development process).

17.6.2.1 Second-line choice following FOLFOX or FOLFIRI

Most patients initially treated with FOLFOX (or XELOX) are offered FOLFIRI, while those initially treated with FOLFIRI are generally offered FOLFOX (or XELOX). The treatment model of FOLFOX followed by FOLFIRI, or FOLFIRI followed by FOLFOX was the evaluated in the GERCOR study[1] which still represents one of the longest median survivals (21 months) for patients with metastatic colorectal cancer reported in the prebiologics era.

17.6.2.2 Second-line choice following 5FU monotherapy

Patients initially progressing on 5FU monotherapy should be offered an irinotecan or oxaliplatin-containing regimen if they have adequate performance status.[2][3][4] As shown in the GERCOR study, treatment with all three cytotoxic agents during the treatment of metastatic colorectal cancer is associated with longer survival times.[5]

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17.6.2.3 Anti-EGFR therapy

Both of the therapeutic monoclonal antibodies that target the epidermal growth factor receptor (EGFR), cetuximab and panitumumab, have well-documented and comparable single-agent activity in patients with previously treated metastatic colorectal cancer that lacks mutations in RAS (and, possibly, BRAF).[6][7] Regimens that combine an anti-EGFR agent with irinotecan alone or a chemotherapy doublet have been shown to increase response rates, progression free survival but not overall survival in the second line setting[8][7][9] and can be considered if not previously used in RAS wild type patients. Alternatively, they can be used as monotherapy in the third line setting with similar relative benefit.[10]

The combination of cetuximab or panitumumab with second-line FOLFIRI after failure of initial FOLFOX is associated with improved response rates and prolonged progression-free survival. The Erbitux Plus Irinotecan in Colorectal cancer (EPIC) trial[10] reported on 1300 patients with EGFR-expressing, but not RAS-selected, metastatic colorectal cancer who had failed initial FOLFOX therapy and were randomly assigned to single-agent irinotecan with or without cetuximab. The addition of cetuximab quadrupled the response rate (16% versus 4%), significantly prolonged progression-free survival (4 versus 2.6 months) and, despite the higher frequency of side effects, was associated with better quality of life.[10] Similar results were reported in a phase III randomised controlled trial (RCT) of panitumumab plus FOLFIRI versus FOLFIRI alone after failure of initial 5FU-containing chemotherapy.[8] In the KRAS wild-type group (n = 597), the addition of panitumumab was associated with a significant improvement in response rate (35% versus 10%) and median progression-free survival (5.9 versus 3.9 months).[8]

Emerging data support the view that anti-EGFR antibodies do not appear to be useful for right-sided tumours in the setting of first-line therapy[11] (see Role of biological agents in with the treatment of metastatic colorectal cancer.)

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17.6.2.4 Anti-VEGF therapy

Therapy targeting vascular endothelial growth factor (VEGF) also has a role in second-line systemic therapy for metastatic colorectal cancer.

If bevacizumab (anti-VEGF monoclonal antibody) was not used as the first-line biological agent, it should be considered in second line. FOLFOX plus bevacizumab was shown to improve overall survival, compared with FOLFOX alone, in a phase III trial[12] and this finding was confirmed by subsequent studies.

For patients treated with a first-line bevacizumab-containing chemotherapy regimen, the use of bevacizumab beyond progression in conjunction with a second-line fluoropyrimidine-based chemotherapy regimen can be considered, based on the available data. However, this approach is not subsidised by the Australian Pharmaceutical Benefits Scheme (PBS) as of May 2017. Data from two RCTs, the phase III TML study[13] and the BEBYP study,[14] showed that continuation of bevacizumab treatment with second-line chemotherapy benefited patients previously treated with bevacizumab. The benefit of continuing bevacizumab beyond progression in the European phase III TML trial was a modest improvement in overall survival (median 11.2 versus 9.8 months) without an increase in bevacizumab-related adverse events.[12] In the BEBYP study there was an improvement in progression free survival by 1.5 months utilising this strategy. This degree of benefit was more modest than prior retrospective analyses of registry data had suggested.

There are only limited data as to whether bevacizumab should be continued into 2nd line therapy in RAS WT patients or whether it is a better strategy to initiate anti-EGFR therapy. Phase II PRODIGE 18 trial[11] preliminary report presented at the ASCO 2016 suggested continuation with bevacizumab was associated with a numerically higher but not statistically significant PFS rate at four months (79 versus 67 percent, p = 0.09) and overall survival (15.9 versus 10.6 months, p = 0.08) compared to cetuximab plus chemotherapy. Data from this small phase 2 study (n=135) should be interpreted with caution and further data are needed to guide practice in this sub-set of patients.[11]

Aflibercept, an anti-angiogenic fusion protein, has shown benefit in combination with FOLFIRI for the treatment of patients with metastatic colorectal cancer that is resistant to, or has progressed following, an oxaliplatin-containing regimen. The placebo-controlled VELOUR trial, in which 1226 patients with oxaliplatin-refractory metastatic colorectal cancer were randomly assigned to aflibercept (4 mg/kg IV) or placebo, plus FOLFIRI, every 2 weeks until progression, reported improved median overall survival in patients treated with aflibercept (13.5 versus 12.1 months).[15] Benefit and safety were similar regardless of prior bevacizumab exposure, but side effect profile and discontinuation rates for toxicity were higher than what would be expected with bevacizumab in this trial. This cost of this agent is not reimbursed in Australia by PBS[i].

Ramucirumab, a recombinant monoclonal antibody of the IgG1 class that binds to the VEGFR-2, blocking receptor activation, has also shown second line efficacy in metastatic colorectal cancer. In the double-blind phase III RAISE trial[16], 1072 patients with progression after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine were randomly assigned to FOLFIRI with ramucirumab (8 mg/kg IV every two weeks) or placebo until disease progression, unacceptable toxicity, or death. Median survival was modestly but significantly greater with ramucirumab (13.3 versus 11.7 months), as was median progression-free survival.[16] Given the modest benefit and expense the role of this agent remains uncertain. Ramucirumab treatment is not subsidised by PBS.

Emerging data suggest that anti-EGFR antibodies are not useful in first-line therapy for right-sided tumours[11] (see Role of biological agents in with the treatment of metastatic colorectal cancer.) However, whether these results can be extrapolated to later lines of therapy is not clear. Nevertheless, some clinicians would favour the use of continued bevacizumab over an anti-EGFR antibody for right-sided tumours.

[i] As of May 2017.

Practice point

Patients who did not receive bevacizumab as part of first-line therapy should be considered for bevacizumab in second-line therapy, in combination with a second-line cytotoxic regimen.

Practice point

Patients who received bevacizumab as part of the first-line regimen and have RAS wild-type (BRAF wild-type) metastatic colorectal cancer should be considered for combination EGFR monoclonal antibodies with FOLFIRI/irinotecan.

Practice point

Patients who received a first-line oxaliplatin-containing regimen should be switched to an irinotecan-containing regimen, and vice versa.

Practice point

Patients who experience disease progression during first-line 5FU monotherapy should be offered an irinotecan or oxaliplatin-containing regimen if they have adequate performance status.

Next section: systemic options third-line treatment
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17.7 Systemic third-line treatment

Contents

17.7.1 Background

In the situation of disease progression in mCRC after patients have received two lines of therapy, the survival is poor at approximately 4-6 months with best supportive care alone.[1] Patients in the third-line setting have limited therapeutic options and typically have reduced quality of life; therefore physicians must carefully balance any efficacy benefit associated with therapy with its toxicity profile.

However, many patients retain adequate performance status to be considered for further systemic therapy and a number of systemic agents have been shown to modestly improve survival in this situation. This remains an area where further clinical trials are needed to determine the best therapeutic approach. Decisions regarding the choice of therapy depend on previously utilised therapies, tumour biology, patient comorbidities, performance status and patient preference.

After failure of all conventional agents/combinations, if performance status is adequate and a tumour-directed therapeutic approach is still warranted, enrolment into a clinical trial testing novel agents/combinations should be considered.

The benefits of palliative care involvement on quality of life for cancer patients and their families have been widely demonstrated.[2] Both Australian and international data show patients with metastatic CRC experience significant symptoms throughout the course of their disease.[3] Integration of palliative care in the management of patients with advanced malignancy improves symptom control and quality of life for patients and their families[2] and as such represents an important component of the continuum of care for patients with mCRC.

17.7.2 Overview of evidence (non-systematic literature review)

No systematic reviews were undertaken for this topic. Practice points were based on selected reviews, primary studies, and other clinical practice guidelines (see Guideline development process).

Patients who maintain adequate performance status should be considered for third-line therapy.

17.7.2.1 Cetuximab and panitumumab

In patients with RAS wild-type metastatic colorectal cancer, both cetuximab and panitumumab have shown efficacy in the third-line/salvage-therapy setting,[4][5] and are equally active as single agents.[6] Combination therapy with cetuximab and irinotecan appears more active than cetuximab alone in patients with irinotecan-refractory tumours.

See eviQ protocols:

- Panitumumab
- Cetuximab
- Cetuximab (2 weekly)
- Colorectal Metastatic Cetuximab (Weekly) and Irinotecan (Two Weekly)
- Colorectal Metastatic Cetuximab and Irinotecan (Two Weekly)

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17.7.2.2 Regorafenib

Regorafenib is an orally active inhibitor of angiogenic tyrosine kinases (including the VEGF receptors 1 to 3), as well as other receptor and intracellular kinases. It has reported activity versus placebo plus best supportive care in two phase III trials.[7][8]

Based on these data, regorafenib may be considered for patients with refractory metastatic colorectal cancer after treatment with all available cytotoxic agents, bevacizumab and EGFR antibodies (in RAS wild-type tumours) . The CORRECT trial[9] compared best supportive care plus regorafenib (160 mg orally once daily for three of every four weeks) or placebo in 760 patients with chemotherapy refractory disease. It demonstrated a significant survival benefit for regorafenib (median 6.4 versus 5 months, Hazard Ratio 0.77), albeit with little objective antitumor response, but with maintained quality of life over time.[9]

The dosing regimen has been questioned by many clinicians; many start with a lower dose and then increase the dose to the approved dose if no toxicity is observed. Frequent and close monitoring for regorafenib toxicity is recommended. See eviQ protocol: Colorectal Metastatic Regorafenib

Regorafenib is approved in Australia by the Therapeutic Goods Administration (TGA).

17.7.2.3 Trifluridine-tipiracil

Recently, trifluridine-tipiracil (Lonsurf ®), an oral cytotoxic agent that consists of the nucleoside analogue trifluridine and tipiracil, a potent thymidine phosphorylase inhibitor, which inhibits trifluridine metabolism and has antiangiogenic properties as well has been shown to be effective in patients with refractory metastatic colorectal cancer.[10]

In the phase III trial (RECOURSE) 800 patients who were refractory to or intolerant of fluoropyrimidines, irinotecan, oxaliplatin, bevacizumab, and anti-EGFR agents (if wild-type KRAS) were randomly assigned to trifluridine-tipiracil (35 mg/m2 orally twice daily on days 1 through 5, and 8 to 12 of each 28-day cycle) or placebo.[9]

The final survival results of the RECOURSE phase III trial were presented at 2016 ASCO meeting. The updated survival analysis confirmed that OS benefit with trifluridine-tipiracil was maintained and increased to a full 2 months - improvement in 1-year survival surpassed 10% in these heavily pre-treated patients. OS benefit appears to be maintained for all patients in the trial regardless of prognostic status at trial entry.[11]

The benefit of this agent is similar to that of regorafenib, but with a better toxicity profile.

Trifluridine-tipiracil is not registered in Australia by the TGA as of May 2017.

Practice point

Patients with mCRC considering treatment in the third-line setting have limited therapeutic options and typically have reduced quality of life; therefore physicians must carefully balance any efficacy benefit associated with therapy with its toxicity profile.

Practice point

Cetuximab or panitumumab treatment should be considered in patients with RAS wild-type and BRAF wild-type metastatic colorectal cancer not previously treated with these agents, taking into account the following:

- Cetuximab and Panitumumab are equally effective as single agents.
- Cetuximab in combination with irinotecan is more active than cetuximab alone in patients refractory to irinotecan with adequate performance status to receive combination therapy.

Practice point

If available, regorafenib or trifluridine/tipiracil can be considered for patients with metastatic colorectal cancer refractory to all standard available therapies.

Practice point

Patients receiving third-line therapy should be offered participation in clinical trials, wherever available.

Practice point

Symptom burden is often high in patients with mCRC especially as the disease progresses. Early palliative care intervention should be considered for all patients with mCRC as they can improve the quality of life of patients with cancer.

Next: Supportive care options for patients with non resectable metastatic CRC

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17.8 Supportive care options

This includes management of physical and psychological symptoms and side effects across the continuum of the cancer experience from diagnosis through anticancer treatment to post-treatment care. Patients with advanced colorectal cancer should have access to multidisciplinary care including but not limited to:

- Palliative care specialists
- Dietitians and nutritional counsellors
- Spiritual care practitioners
- Rehabilitation therapists, including occupational therapy, physical therapy and speech therapy
- Wound or stoma care specialists
- Intimacy and sexuality counsellors
- Fertility therapists
- Geneticists

Patients with advanced colorectal cancer should be regularly screened for psychosocial distress, including depression, financial distress and employment issues in addition to the common physical problems that arise from late toxicities of chemotherapy and radiation therapy and the cancer. Guidelines regarding the management of common problems faced by patients with advanced colorectal cancer including bowel dysfunction, fatigue, urinary incontinence and sexual dysfunction, peripheral neuropath are available from National Comprehensive Cancer Network (NCCN).[1] Links to comprehensive palliative care resources are available at eviQ Cancer treatments on line. Management of common chemotherapy toxicities in patients with advanced colorectal cancer are available at eviQ Cancer Treatments online.

Evidence also suggests that early referral to palliative care in advanced cancer is associated with better outcomes in terms of quality of life and aggressiveness of care at the end of life.[2][3] Patients should be encouraged to develop an advance care plan.[4] Ensure carers and families receive information, support and guidance about their role according to their needs and wishes.[5]

See Additional resources for further supportive care resources.

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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 Chapter subsections

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.

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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 Chapter subsections

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 with improved quality of life 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.

Next section: optimal surveillance protocol

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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 Clinical Practice Guidelines for Surveillance Colonoscopy.)

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.

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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 between 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%, $p = 0.33$).

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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 of 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.

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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.

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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]

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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.

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18.3.2 Evidence summary and recommendations

Evidence summary	Level	References
Survival and mortality	II	[1], [2], [3], [4]

Evidence summary	Level	References
No difference between intensive and less intensive follow-up groups was observed for both overall survival and mortality.		[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/CT) 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 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.

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18.3.2.1 Considerations in making these recommendations

A Cochrane review of follow-up strategies for patients who had curative surgery for non-metastatic colorectal cancer was published after the literature cut-off date of this systematic review.[6] The findings of the systematic review and Cochrane review were consistent. The Cochrane review concluded that there was no survival benefit for intensive follow up but did show a higher rate of resectable recurrent disease if patients were followed up in the intensive group. However, despite having surgery this did not improve their survival. The limitations of the Cochrane review included the heterogeneity of the follow up strategies and of the definitions for 'intensive follow-up'.

The benefits from intensive 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[7][8] support no survival advantage for patients who are followed up intensively after curative resection of colorectal cancer.

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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.

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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.[7] 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).[9] 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.).[9]

Next section: health professionals performing follow-up and suggested follow-up schedule

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18.3.5 Appendices

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

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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.

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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, T4 disease and/or lymph node involvement, 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 organisations 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. Less intensive follow-up may be considered for patients with early cancers (T1-2, N0) after discussion with the patient.

Clinical assessment includes history and physical examination. Regular carcinoembryonic antigen (CEA) measurement (at each consultation) and annual 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]

Colonoscopy should be performed 12 months after surgery to exclude missed lesions. If the patient did not have complete colonoscopy prior to surgery, then this should be performed at the latest 6 months after surgery. If the post-operative colonoscopy is normal then future surveillance should be according to the Clinical Practice Guidelines for Surveillance Colonoscopy.

Future studies should focus on the cost-effectiveness and efficiency of investigations employed.[7]

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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.

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19.2 Overview of evidence (non-systematic literature review)

No systematic reviews were undertaken for this topic. Practice points were based on selected evidence. Please see guideline development process for more information.

19.2.1 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.

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19.2.2 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]

19.2.3 Psychological challenges

19.2.3.1 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]

19.2.3.2 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]

19.2.3.3 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.

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19.2.3.4 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.

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19.2.4 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.

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19.3 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.

19.3.1 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]

19.3.2 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]

19.3.3 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.

Practice point

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

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19.3.4 Information needs and decision aids

19.3.4.1 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.

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19.3.5 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.

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20 Appendices

See:

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

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 guideline 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.

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20.1.2 Guidelines development group

Cancer Council Australia approached key stakeholders from the Working Party 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 prevantion, diagnosis and management of CRC were represented. Two consumer representatives were invited to be part of the Working Party.

The guideline questions were allocated to specific guideline 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.

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20.1.3 Steps in preparing clinical practice guidelines to NHMRC criteria

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.

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

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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.

20.1.3.2 Search for existing relevant guidelines and systematic reviews

For each PICO question, the National Guideline Clearinghouse, the 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.

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20.1.3.3 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.

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20.1.3.4 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).

20.1.3.5 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.

20.1.3.6 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 were extracted and summarised in study characteristics and evidence tables. Extracted data were checked by a second assessor. These tables are included in the technical report for each question (see Technical report).

20.1.3.7 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 in 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.

20.1.3.7.1 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)

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20.1.3.8 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.

20.1.3.8.1 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.

20.1.3.8.2 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.

20.1.3.8.3 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

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20.1.3.9 Writing the content

For each clinical 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.

For sections not based on systematic review, the lead author was asked to draw on high-level evidence, particularly international guidelines, consensus statements and key literature considered to be relevant to Australian practice, to develop information and practice points.

The content draft was then reviewed by subcommittee members who were available. The draft documents often underwent several iterations.

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20.1.3.10 Review of the draft chapters

The draft guideline 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 version of the draft guideline was 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) reached consensus. See the administrative report for information on conflict of interest declarations and action required.

20.1.3.11 Areas of major debate

There was major debate and robust discussion within the Working Party and/or subcommittee members on the following chapters:

- **Primary prevention (Chemopreventive candidate agents [PPR1 – aspirin systematic review]) –** There was robust discussion within the chapter subcommittee regarding the clinical background of the participants in the reported randomised controlled trials; the gender imbalance across these trials; and the potential harms and benefits of taking aspirin, both in the context of colorectal cancer prevention, prevention of other cancers, and the role of aspirin in preventing cardiovascular events. However the group was able to come to a decision about the guidance in this chapter, based on the interpretation of the systematic review evidence.
- **The symptomatic patient: Optimal maximum time from referral to diagnosis and treatment (SPT1-2b systematic review) –** The Working Party and subcommittee members had robust discussion regarding the maximum optimal time from first healthcare presentation to diagnostic colonoscopy and treatment. Although the group was in agreement about the interpretation of the systematic review evidence, there was concern about de-emphasising the need for prompt evaluation. The Working Party acknowledges that the guideline may be read with the expectation that it will assist in triage of colonoscopy patients. The authors resolved it was appropriate to maintain the evidence-based recommendations, acknowledging the grade and limitations of the available evidence, but also add the practice point about the ideal interval for symptomatic patients.
- **Risk and screening based on family history: Colorectal cancer risk according to family history (FHS2) –** There was robust discussion by the Working Party about the categories of risk outlined in this chapter. For Category 3, there was discussion regarding the decision to exclude people known to have, or with a high probability of having, a high-risk familial syndrome due to a genetic predisposition to colorectal cancer. Ultimately the Working Party was in agreement about the three-level risk categorisation and feel this is adequately outlined in the chapter.

In each instance, the guideline development working group was able to reach a decision about the content and recommendations.

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20.1.4 Public consultation

A complete draft of the guideline was sent out for public consultation from 10 March 2017 to 8 April 2017. 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 was 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 assessed by the methodologist team against the systematic review protocol to determine if it could be included.

Another face-to-face Working Party meeting was held in April 2017 to review all public consultation comments and the amended guideline content. Subsequent changes to the draft were 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 were documented and will be made accessible once the guideline is published.

A final independent review was conducted before the final draft was submitted to NHMRC Council. Further suggestions by the independent expert reviewers were considered and integrated in the final draft and then submitted to NHMRC Council for approval.

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20.1.5 Organisations formally endorsing the guidelines

The following medical colleges and professional bodies may 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).

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20.1.6 Dissemination and implementation

Cancer Council Australia have created a plan regarding the dissemination of the guideline in Australia.

The guideline will 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 home screen 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 guideline 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.

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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 partial). It is recommended that the guideline be updated after 5 years.

20.1.8 References

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20.2 Clinical question list

This page lists the questions answered by systematic review and modelling. For full details about the reviews, including the inclusion and exclusion criteria, please see the Technical report.

Contents

20.2.1 Primary prevention (section lead: Finlay Macrae)

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.

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20.2.2 Population screening for colorectal cancer (section leads: James St. John and Hooi Ee)

Clinical Question PSC1:
Is population screening based on testing with (a) immunochemical FOBT (iFOBT), (b) flexible sigmoidoscopy, (c) colonoscopy, (d) CT colonography, (e) faecal biomarkers such as DNA (f) plasma biomarkers such as DNA (g) 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? a) Is population screening starting at an earlier age more effective, feasible, acceptable and cost-effective, compared with starting at age 50 years? b) In population screening, do the harms outweigh the benefits if routine screening by any method is continued beyond the age of 75 years?

PICO Question PSC1a (Screening benefit):
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, reduces colorectal cancer mortality, or the incidence of metastases at diagnosis?

Population	Intervention	Comparator	Outcomes
Persons without a colorectal cancer diagnosis or	■ Immunochemical FOBT, or ■ Flexible sigmoidoscopy, or ■ Colonoscopy, or	No screening	■ Colorectal cancer specific mortality

Population	Intervention	Comparator	Outcomes
symptoms that might indicate colorectal cancer	■ Faecal biomarkers, or ■ Blood biomarkers, or ■ Any combinations.	test	■ Metastatic colorectal cancer diagnosis

PICO Question PSC1b (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 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

PICO Question PSC1c (Screening cost effectiveness - modelling):

In persons without a colorectal cancer diagnosis or symptoms that might indicate colorectal cancer, what is the most cost-effective, feasible and acceptable screening modality (iFOBT, flexible sigmoidoscopy, colonoscopy, CT colonography, faecal or blood biomarkers test, or any combinations) compared with no screening?

PICO Question PSC1d (Screening age - modelling):

Is population screening starting at an earlier age more effective and as feasible, acceptable and cost-effective as screening starting at age 50 years? In population screening, do the harms outweigh the benefits if routine screening is continued beyond the age of 75 years?

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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 CRC and what is the optimal maximum time from referral to diagnosis and treatment (diagnostic interval)?

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

Clinical Question SPT1-2:
What signs/symptoms alone or in combination are most predictive of CRC and 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 than or equivalent outcomes in terms of survival, mortality, and diagnosis of metastatic disease?

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

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:
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?

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

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20.2.5 Pathology and staging (section leads: Charles Chan and Pierre Chapuis)

Clinical Question PTH1:
What is the optimal molecular profiling of colorectal cancer?

PICO Question PTH1:
In patients diagnosed with colorectal cancer who have undergone surgical resection or biopsy of the primary colorectal tumour, which molecular marker (BRAF/KRAS/NRAS/DNA mismatch repair /microsatellite instability) 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) PCR markers: BRAF Microsatellite instability (which loci?) KRAS NRAS	Response to surgery, or adjuvant therapy or radiotherapy, including: ■ disease-free survival ■ overall survival ■ disease-specific mortality ■ overall mortality ■ relapse incidence

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20.2.6 Preparation for surgery and peri-operative optimisation (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

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20.2.7 Elective and emergency surgery for colon and rectal cancer

Clinical Question COL1-2a and b:
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
			■ Colorectal cancer mortality ■ Perioperative morbidity

Population	Intervention	Comparator	Outcomes
Patients diagnosed with colon cancer and undergoing tumour resection	Laparoscopic colon resection	Open colon resection (colectomy)	■ Perioperative mortality ■ Length of hospital stay ■ Post-op time to return of bowel function ■ Length of operation ■ Quality of life ■ Adverse events

PICO Question COL1-2b (section lead: Alexander (Sandy) Heriot):

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
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	■ Colorectal cancer mortality ■ 30-day mortality rate ■ Perioperative mortality ■ 2-year survival ■ 5-year survival ■ Local recurrence rate ■ Perioperative morbidity ■ Permanent stoma rate ■ Quality of life ■ Adverse events

Clinical Question REC3:

What is the most effective treatment for early rectal cancer?

PICO Question REC3 (section lead: Alexander (Sandy) Heriot):

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 ■ Adverse events ■ Stoma rates

Clinical Question COLMNG5:
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 COLMNG5 (section leads: Alexander (Sandy) Heriot and Andrew Luck):
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
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 mortality ■ Perioperative morbidity ■ 5 year survival ■ Cancer specific survival ■ Length of hospital stay ■ Stoma rate (temporary or permanent) ■ Quality of life ■ Adverse events

Clinical Question COLMNG3: (Section leads: Cherry Koh and Andrew Luck)
What is the role for peritonectomy with or without PIC in the treatment recurrent as well as primary colorectal cancer with peritoneal involvement (not including appendiceal neoplasia)?

PICO Question COLMNG3 (Section leads: Cherry Koh and Andrew Luck):
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

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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 based) 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	Surgery in combination with one of the following: ■ Chemotherapy (either 5-Fluoruracil, Capecitabine, or Oxaliplatin)	Surgery with a single chemotherapeutic agent	■ Colorectal cancer mortality ■ Colorectal recurrence

Population	Intervention	Comparator	Outcomes
years)	AND an additional adjuvant chemotherapy drug (either 5-fluoruracil, capecitabine, or oxaliplatin)	(Fluoropyrimidine based).	■ Quality of life ■ Adverse events

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20.2.9 Neo-adjuvant and adjuvant therapy for rectal cancer (section leads: Desmond Yip and Kathryn Field)

Clinical Question NEO1a-b:

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 NEO1b:

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
Patients diagnosed with stage I-III rectal cancer	Surgery without neoadjuvant therapy	Short/long course 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

PICO Question NEO1a:
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 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

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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
	Curative surgery with or without		■ Overall survival

Population	Intervention	Comparator	Outcomes
Patients diagnosed with locally recurrent colon or rectal cancer	chemotherapy, with or without radiotherapy	Surgical palliation with or without palliative chemotherapy or radiotherapy and/or palliative care	■ Disease-free survival ■ Quality of life ■ Complications

Clinical Question MNG14:
Which patients with resectable synchronous or metachronous metastatic colon or rectal cancer are suitable for curative surgery?

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, progression 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

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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 with incurable metastatic colorectal cancer, what are the effects of liver-directed therapies on survival and quality-of-life outcomes, compared with standard care?

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

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20.2.12 Follow up after curative resection for colorectal cancer (section lead: Peter Lee)

Clinical Question FUR1-2:
What is the optimal intensity of follow up post curative resection of colorectal cancer? And where?

PICO Question FUR1-2a:
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?

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

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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.

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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 associated technical documentation appears at the bottom of the relevant content pages.

The questions were given alphanumeric codes when they were developed, please refer to the codes below and see the clinical question list for more detail.

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, CT colonography, faecal or blood biomarkers, or any combinations) compared with no screening, reduces colorectal cancer mortality, or the incidence of metastases at diagnosis?*
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, 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?*
Modelling report PSC1c

PSC1d: *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?*
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 than or equivalent outcomes in terms of survival, mortality, and diagnosis of metastatic disease?
Evidence statement form SPT1-2b
Systematic review report SPT1-2b

FHS2: *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?*
Evidence statement form FHS2
Systematic review report FSH2

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)?*
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 based) 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: *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?*
Evidence statement form NEO1b
Systematic review report NEO1b

NEO1a: *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 neoadjuvant chemoradiotherapy alone?*
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, progression free survival, quality of life and complications?)
Evidence statement form MNG14
Systematic review report MNG14

MNG16: *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?*
Evidence statement form MNG16
Systematic review report MNG16

FUR1-2a: *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?*
Evidence statement form FUR1-2a
Systematic review report FUR1-2a

20.4.3.1 Cohort studies (risk factors) risk of bias assessment tool

- Cohort studies risk of bias assessment form
- Cohort studies risk of bias assessment help sheet

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20.5 Additional resources

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20.5.1 Additional resources

There are many evidence-based resources on colorectal cancer available. This list of resources is provided to help direct stakeholders to other resources on colorectal cancer. It is not intended to be a comprehensive list.

Please note that some of these resources have not been produced in Australia and the guidance may not be applicable in the Australian context.

People diagnosed and treated for colorectal cancer have unique supportive care needs based on their individual circumstances. They should discuss this with their health practitioners and ask to be directed to specific consumer-focused resources, including information about dealing with side effects and the emotional impact of cancer.

20.5.1.1 Prevention, diagnosis, treatment, follow-up guidance

Organisation	Resource/guideline
Cancer Care Ontario (CCO)	Gastrointestinal Cancer Evidence-based Series (EBS) and Practice Guidelines (PG)
Clinical Oncology Society of Australia (COSA)	The use of complementary and alternative medicine by cancer patients - position statement
European Society for Medical Oncology (ESMO)	■ Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up ■ Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up ■ ESMO Consensus Guidelines for the Management of Patients with Metastatic Colorectal Cancer ■ Familial risk-colorectal cancer: ESMO Clinical Practice Guidelines ■ ESMO Consensus Guidelines: Management of Patients with Colon and Rectal Cancer. A personalized approach to clinical decision making
National Comprehensive Cancer Network (NCCN)	■ Clinical practice guidelines in oncology - colon cancer ■ Clinical practice guidelines in oncology - rectal cancer
National Institute for Health and Care Excellence (NICE)	Colorectal cancer: diagnosis and management
New Zealand Guidelines Group (NZGG)	Management of Early Colorectal Cancer
Scottish Intercollegiate Guidelines Network (SIGN)	Diagnosis and management of colorectal cancer
Victorian Department of Health	Optimal care pathway for people with colorectal cancer

20.5.1.2 Survivorship guidance (including health and lifestyle wellness, physical activity, diet)

Organisation	Resources/guideline
American Cancer Society (ACS)	■ American Cancer Society Colorectal Cancer Survivorship Care Guidelines ■ Nutrition and Physical Activity Guidelines for Cancer Survivors
Australian Government Department of Health	Improving Bowel Function after Bowel Surgery
Cancer Care Ontario (CCO)	Follow-up Care, Surveillance Protocol, and Secondary Prevention Measures for Survivors of Colorectal Cancer
National Comprehensive Cancer Network (NCCN)	Clinical practice guidelines in oncology - survivorship care

20.5.1.3 Websites for consumers and carers

Organisation	Resources/guideline
Cancer Council Australia	Cancer Council Australia
Australian Cancer Survivorship Centre	Australian Cancer Survivorship Centre
American Cancer Society (ACS)	National Cancer Survivorship Resource Center (USA based)
American Society of Clinical Oncology (ASCO)	Cancer.Net (USA based)
National Cancer Institute (NCI)	Coping with cancer - survivorship (USA based)

20.5.1.4 Other relevant resources

Organisation	Resources/guideline
Australian Cancer Trials	australiancancertrials.gov.au
Australian Clinical Trials	australianclinicaltrials.gov.au
Cancer Institute NSW eviQ	eviq.org.au

20.6 Glossary and abbreviations

Term	Definition
5-fluorouracil	A chemotherapy drug commonly used to treat patients with cancer.
Abdomen	The part of the body between the chest and hips, which contains the stomach, spleen, pancreas, liver, gall bladder, bowel, bladder and kidneys.
Abdominoperineal resection	An operation for rectal cancer. This involves removing part of the colon, and the rectum and anus, and creating a permanent colostomy.
Absolute risk	The risk a subject has for developing the tested disease over a stated time period.
Adenocarcinoma	A type of cancerous tumour that forms from glandular structures in epithelial tissue.
Adjuvant therapy	A treatment given with or shortly after another treatment to make it more effective. This usually refers to surgery followed by chemotherapy or radiotherapy.
Analgesic	A type of drug used to achieve pain relief.
Anaemia	A reduction in the oxygen-carrying component of the blood (haemoglobin or red blood cells).
Anterior resection	A surgical procedure to remove cancer in the rectum with the bowel being re-joined to leave a functioning anus.
Antibiotic	A medicine that destroys or kills microorganisms.
Anus	The opening between the buttocks at the end of the bowel, through which solid waste (poo, stool) leaves the body.
Aspirin	A common medication used to treat pain, fever, and inflammation. Also known as acetylsalicylic acid (ASA).
Biopsy	The removal of a small sample of tissue from the body for examination under a microscope to help diagnose a disease.
Bisphosphonates	Medication used to slow down or prevent bone loss.
Bowel cancer	Cancer of the large bowel; also known as colorectal cancer, colon cancer or rectal cancer.
Bowel obstruction	Partial or complete blocking of the bowel, which prevents waste matter passing (bowel movements).
Bowel preparation	The process of cleaning out the bowel before a test, scan or operation to allow the doctor to see the bowel more clearly.
Carcinoembryonic antigen (CEA)	A protein that may be found in the blood of a person with colorectal cancer.
Close margin	When cancer cells are close to the edge of the removed tissue.
Chemoprevention	The use of drugs or natural substances to prevent or delay the development of cancer.
	The surgical removal of all or part of the colon. The affected areas of the colon are cut out

Term	Definition
Colectomy	and the two ends are joined back together. Colectomies are named for the part removed. They include: right and left hemicolectomies, and transverse, sigmoid, subtotal and total colectomies.
Colon	The main part of the large bowel, which absorbs water and electrolytes from undigested food (solid waste). Its four parts are the ascending colon, transverse colon, descending colon and sigmoid colon.
Colonoscopy	An examination of the large bowel using a camera on a flexible tube, which is passed through the anus.
Colorectal	Referring to the large bowel, comprising the colon and rectum.
Confidence interval	A measure that quantifies the uncertainty in measurement. When reported as 95% CI, it is the range of values within which we can be 95% sure that the true value for the whole population lies.
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.
Cost-effectiveness analysis	A form of economic analysis comparing the relative costs and outcomes (effects) of different courses of action.
CT colonography	Also known as virtual colonoscopy, a medical imaging procedure that uses low dose radiation CT scanning to obtain an interior view of the colon (the large bowel) that is otherwise only seen with a more invasive procedure where an endoscope is inserted into the rectum and passed through the entire colon.
CT scan	A computerised tomography (CT) scan, which x-ray equipment to create detailed digital images, or scans, of areas inside the body.
Cytoreductive surgery	A surgery to remove as much cancerous growth as possible from multiple sites in the abdomen.
Dehiscence	A surgical complication where a wound ruptures along a surgical incision.
Distant metastasis	Cancer that has spread from the original (primary) tumour to distant organs or distant lymph nodes.
Distant recurrence	When the cancer has spread (metastasised) to organs or tissues far from the place of the original cancer.
Dyspepsia	Indigestion.
Endorectal ultrasound (ERUS)	An imaging procedure where a probe is inserted into the rectum and high frequency sound waves (ultrasound waves) are generated to look for abnormalities in the rectum and nearby structures.
Evidence-based recommendation	A recommendation formulated after a systematic review of the evidence, indicating supporting references.
Faecal	

Term	Definition
immunochemical test (FiT)	See FOBT.
Faecal occult blood test (FOBT)	A test that can detect microscopic amounts of blood in stools. Types of FOBT include immunochemical FOBTs (iFOBTs), which directly detect haemoglobin using antibodies specific for the globin moiety of human haemoglobin, and guaiac FOBTs (gFOBTs), which detect peroxidase activity, an indirect method for identification of haemoglobin.
Familial syndromes	Genetic disorders in which inherited genetic mutations in one or more genes predispose a person to developing cancer, particularly at an early age.
First presentation	In this guideline, first presentation is defined as a positive screening iFOBT.
Flexible sigmoidoscopy	A procedure used by physicians to examine the inner lining of the rectum, particularly the lower portion of the colon (unlike the colonoscopy that examines the entirety of the colon). It consists of a flexible tube that is approximately 60 cm long, a small light and a camera attached at the tip of the tube.
FOLFOX	Systemic chemotherapy using a combination of the drugs Leucovorin (folinic acid), Fluorouracil, and Oxaliplatin.
General practitoner (GP)	A medical professional who treats acute and chronic illnesses and provides preventive care and health education to a wide range of patients.
Hazard ratio	A measure of how often a particular event happens in one group compared to how often it happens in another group, over time. In cancer research, hazard ratios are often used in clinical trials to measure survival at any particular moment in a group of patients who have been given a specific treatment or a placebo. A hazard ratio of one means that there is no difference in survival between the two groups. A hazard ratio of greater than one or less than one means that survival was better in one of the groups.
Helicobacter pylori	A type of bacteria that grows in the digestive tract.
High anterior resection	A type of surgical procedure sometimes referred to as sigmoid colectomy or sigmoidectomy, where the sigmoid colon is removed, along with the upper rectum and a portion of the left colon.
Hyperthermic intraperitoneal chemotherapy	A highly concentrated, heated chemotherapy treatment that is delivered directly to the abdomen during surgery.
Imaging	Using scans, including nuclear medicine, to create images of the interior of a body for clinical analysis and medical intervention.
Incidence	An epidemiological term reporting number of new cases in a population within a specified period of time.
Incisional hernia	A type of hernia caused by an incompletely healed surgical wound.
Intention-to-treat	This analysis includes all subjects originally enrolled and allocated to treatment irrespective of whether treatment was adhered to, treatment changed or even if they were

Term	Definition
analysis	lost to follow-up.
Laparoscopic surgery	A procedure where small multiple incisions are made to perform an operation, rather than making a large open incision.
Laparotomy	A surgical procedure involving a large incision through the abdominal wall to gain access into the abdominal cavity.
Local recurrence	The reappearance of cancer at a site that was previously treated and responded to therapy.
Local transanal resection	The local resection of tumour through the anus.
Lymphorrhea	The leakage of the lymph node which can be through cutting, tearing or the bursting of blood vessels.
Medical Benefits Schedule (MBS)	A listing of Medicare services subsidised by the Australian Government.
Metastasis	The spread of cancer cells to new areas of the body (often by way of the lymph system or bloodstream).
Metastatic	Cancer that has spread from the primary site of origin (where it started) into different area (s) of the body.
Metformin	A medication used to control blood sugar levels.
MRI scan	Magnetic resonance imaging scan. A procedure in which radio waves and a magnet linked to a computer are used to create detailed digital images of areas inside the body.
Narcotic	Drugs used to treat severe pain.
National Bowel Cancer Screening Program (NBCSP)	An Australian screening program that aims to reduce illness and death from bowel cancer through early detection or prevention of the disease.
Negative margin	When cancer cells are not at the edge of the tissue.
Neoadjuvant therapy	A type of treatment given as a first step to shrink a tumour before main treatment (usually surgery) is given.
Non-steroidal anti-inflammatory drugs (NSAIDs)	Medications commonly used to manage the pain and inflammation.
Normothermia	Normal body temperature.
Odds ratio	A comparison of the odds (probability) of something happening in 1 group with the odds of it happening in another.
Pathology	A medical specialty that determines the cause and nature of diseases by examining and testing body tissues, for instance from laboratory examination of samples of body tissue.
Peri-operative	Measures and interventions used at or around the time of surgery to improve patient

Term	Definition
optimisation	outcomes.
Peritoneal involvement	A tumour that occurs in the peritoneal cavity.
Peritonectomy	A surgical procedure to remove the cancerous part of the lining of the abdominal cavity.
Polyp	A small growth protruding from a mucous membrane, such as the lining of the bowel.
Polypectomy	The removal of polyps from the bowel.
Positive margin	When cancer cells are located all the way to the edge of the removed tissue.
Positive predictive value	A measure for the likelihood (probability) that the subject with a positive screening result has the disease being tested for.
Positron emission tomography (PET)	A scan in which a person is injected with a small amount of radioactive glucose solution to find cancerous areas.
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.
Primary care	The first point of contact people have with the health system, generally through a general practitioner.
Primary prevention	Measures to prevent the onset of disease. This may include prevention strategies to modify cancer risk factors, such as dietary and lifestyle interventions, and medical interventions to enhance resistance to the effects of exposure to a disease agent, such as chemoprevention and vaccines.
Prophylaxis	Treatment given or action taken to prevent disease.
Quality-adjusted life year	A generic measure of disease burden, including both the quality and the quantity of life lived. It is used in economic evaluation to assess the value for money of medical interventions.
Randomised controlled trial (RCT)	A study in which people are allocated at random (by chance alone) to receive one of several clinical interventions. One of these interventions is the standard of comparison or control.
Rectum	The final section of the large bowel, ending at the anus.
Regional recurrence	Tumour growth in the lymph nodes or tissues near the place of the original cancer.
Robotic-assisted laparoscopic surgery	A method to perform laparoscopic surgery using small tools attached to a robotic arm. The surgeon controls the robotic arm with a computer.
Screening	Performing tests to identify disease in people before any symptoms appear.
Secondary prevention	Strategies such as screening and early detection programs to identify a disease or condition early in its development, to reduce the morbidity and mortality by improving the outcome of disease that has already developed.

Term	Definition
Sigmoid colon	The last section of the colon before it connects to the rectum.
Staging	The last section of the colon before it connects to the rectum.
Statins	Drugs used to reduce levels of cholesterol in the blood.
Systemic chemotherapy	Anti-cancer drugs that are injected into a vein or given by mouth. These drugs travel through the bloodstream to all parts of the body.
Thromboembolism	The obstruction of a blood vessel by a blood clot that has become dislodged from another site.
Total mesorectal excision	A procedure used in the treatment of colorectal cancer in which a significant length of the bowel around the tumour is removed.
Transanal excision	A local excision of rectal cancer performed through the anus.
Transanal minimally invasive surgery	A surgical approach to remove benign polyps and some cancerous tumours within the rectum and lower sigmoid colon without making an excision.
Transverse colectomy	Surgical removal of the middle part of the colon.
TNM staging system	A system that describes the amount and spread of cancer in a patient's body. T describes the size of the tumour and its spread into nearby tissue; N describes the spread to nearby lymph nodes and M describes metastasis (spread of cancer to other parts of the body).
Venous thromboembolism	The formation of blood clots in the vein.

20.7 Working party members & contributors

Contents

20.7.1 Colorectal Cancer Guidelines Working Party members and contributors

Please see the Administrative Report for information on the process and criteria for selecting members.

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Dr Hooi Ee	Gastroenterology	Population screening for colorectal cancer (co-lead)
Professor Mark Jenkins	Genetic epidemiology, cancer epidemiology (colorectal cancer, Lynch syndrome, genetic epidemiology)	Risk and screening based on family history
Professor Jon Emery	General practice	The symptomatic patient
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
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Name	Specialty	Section
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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)
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20.7.1.3 Additional working party members

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Jillian Arnott	Consumer representative
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20.7.2.2 Primary prevention

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20.7.2.4 The symptomatic patient

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

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20.7.2.8 Pathology and staging

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20.7.2.9 Preparation for surgery and peri-operative optimisation

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20.7.2.10 Elective and emergency surgery for colon and rectal cancer

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Dr Cherry Koh*	Colorectal surgeon, Royal Prince Alfred Hospital, Sydney
Dr Carina Chow	Colorectal Surgeon , Royal Brisbane Hospital, QLD
Dr Chip Farmer	Colorectal Surgeon, The Alfred Hospital, Melbourne, VIC
Dr Henry Hicks	General Surgeon, Wagga Wagga Specialist Medical Centre, NSW
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20.7.2.11 Adjuvant therapy for colon cancer

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20.7.2.12 Neoadjuvant and adjuvant therapy for rectal cancer

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20.7.2.13 Management of resectable locally recurrent disease and metastatic disease

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

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20.7.2.15 The role of systemic therapies in non-resectable metastatic disease

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20.7.2.16 Follow up after curative resection for colorectal cancer

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20.7.2.17 Psychosocial care

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20.8 Project team contributions

Cancer Council Australia project team contributions

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20.9 Conflict of interest register

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