Colorectal cancer

Prevention, investigation and treatment

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The incidence of colorectal cancer has been falling overall but increasing among younger people, so prevention and detection of the disease remain important population health concerns. Early diagnosis and treatment confer a substantial survival advantage, and appropriate screening can aid with detecting the disease at an earlier, curable stage.

Each year, about 15,000 Australians will be diagnosed with colorectal cancer (CRC), and one in 25 Australians will receive this diagnosis before the age of 75 years.[1] Overall age-adjusted incidence of CRC has been declining modestly this century, whereas its incidence in people younger than 55 years has been increasing.[1] The reasons for this increase are unclear, although those aged under 55 years still represent only 7% of all cases.[1] CRC is thus an important disease from a population health point of view and it is not uncommon for patients to be managed in a primary healthcare setting.

The survival advantage arising from early diagnosis and treatment of CRC offers an opportunity for clinicians to significantly improve outcomes for their patients. The treatment options for CRC, particularly for metastatic disease, have evolved in recent years and may involve various specialists, including gastroenterologists, surgeons, medical and radiation oncologists and palliative care physicians.

KEY POINTS

- In Australia, colorectal cancer remains a major cause of morbidity for adults and is the sixth most common cause of death.
- Appropriate screening increases the likelihood that precancerous lesions can be removed and cancers can be detected at a curable stage.
- Prompt colonoscopic investigation of rectal bleeding and other gastrointestinal symptoms also enables diagnosis of colorectal cancer at an earlier stage.
- Treatment of advanced cancers is often multidisciplinary, involving GPs, gastroenterologists, surgeons, medical and radiation oncologists and palliative care physicians.
- There has been increasing success in curatively treating selected patients with distant metastatic disease.

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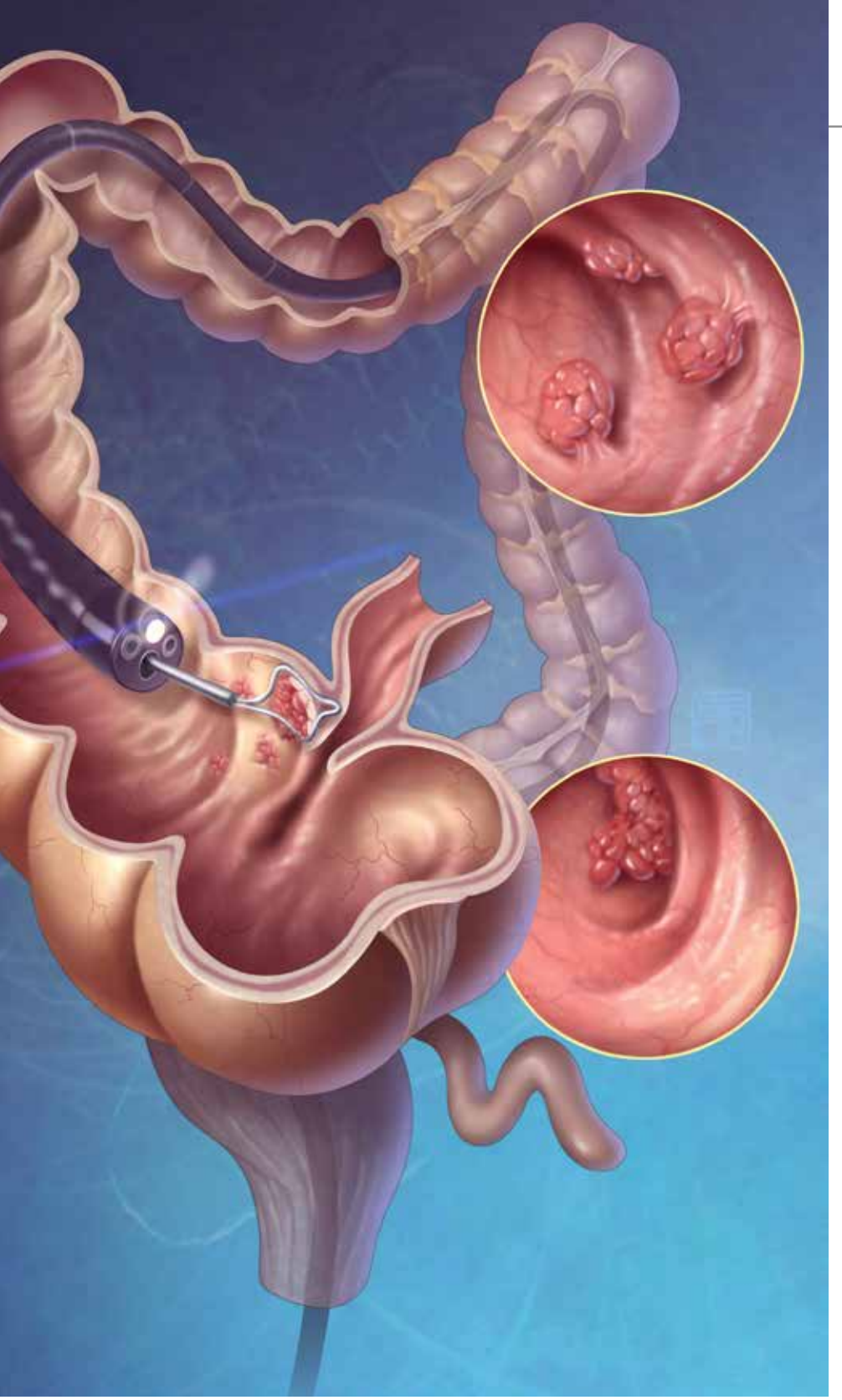
This article focuses on adenocarcinoma, which accounts for most cases of CRC. Other types of CRC, such as squamous cell carcinoma (around the anorectal junction), colonic lymphoma and colonic stromal tumours, have their own distinct clinical behaviour and treatment regimens. Adenocarcinoma develops from the epithelium of the bowel following an accumulation of mutations. The resulting neoplastic cells are thought to frequently



develop into an adenomatous polyp, which, if left to further mutate, may become invasive cancer. The clinical significance of this is that removal of an adenoma using polypectomy (or occasionally surgery) removes the early neoplastic cells and thus the potential for malignancy. This explains the established finding that appropriate colonoscopic screening with polypectomy reduces the incidence of CRC.[2]

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Risk factors and prevention

About 5% of CRC is attributable to high-risk syndromes, mostly familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer (HNPCC; also known as Lynch syndrome). Patients with high-risk syndromes require specialist referral and early colonoscopic screening, generally starting between the ages of 12 and 15 years for those with familial adenomatous polyposis and at age 25 years, or five years younger than the youngest affected relative, for those with HNPCC.[3] Ulcerative colitis and Crohn's disease with colitis are known to confer a long-term risk of CRC, and patients with these conditions should also undergo endoscopic screening. However, most patients with CRC will have neither a genetic syndrome nor inflammatory bowel disease.

In epidemiological studies, CRC has been positively associated with heavy alcohol use (the most significant modifiable risk factor), smoking, obesity and high intake of red meat, whereas physical activity has been found to be protective.[4] Medical practitioners can therefore give lifestyle advice in line with measures that are known to also reduce the risk of cardiovascular disease, although the magnitude of risk reduction for each of these individual factors is small in CRC.

Low-dose aspirin has been shown to reduce the risk of CRC in population and randomised studies, and the US Preventive Services Task Force has recommended the use of aspirin as a preventive agent against CRC in adults aged 50 to 70 years who are also at increased risk of cardiovascular disease.[5-7] Australian NHMRC guidelines recommend that aspirin (100 to 300 mg/day) be considered for CRC prevention in people aged between 50 and 70 years who are at average risk of CRC.[6] However, the decision must be personalised to the patient's situation and risk of adverse effects, with particular care taken for those with risk of bleeding, peptic ulcer disease or renal impairment.[6] The guidelines acknowledge that the magnitude of benefit is small and that any benefit is delayed by about 10 years after starting aspirin. Aspirin is more firmly recommended for patients with

USEFUL RESOURCES FOR DOCTORS AND PATIENTS

- Cancer Council Australia, Clinical Practice Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer: https://wiki.cancer.org.au/australia/Guidelines:Colorectal_cancer[6]
- Gastroenterological Society of Australia, Early Detection, Screening and Surveillance for Bowel Cancer, including recommendations on indications for and frequency of colonoscopy: http://www.gesa.org.au/resources/clinical-guidelines-and-updates/bowel-cancer[3]
- Bowel Cancer Australia website, including patient information resources: https://www.bowelcanceraustralia.org/media-and-resources

high-risk syndromes, such as HNPCC, for whom randomised controlled trial data have shown a reduction in risk.[8] Ongoing research, including an Australian-led study that is assessing the efficacy of aspirin in secondary prevention of CRC, will help delineate which patient population may benefit most from aspirin use.

Screening

CRC may be asymptomatic even in patients with advanced disease. For an adult at average risk of CRC, the Australian guidelines recommend second-yearly faecal occult blood tests (FOBTs) from the age of 50 to 74 years.[3,6] FOBTs have been shown to reduce CRC mortality, with early studies showing a relative risk reduction of about 15% with biyearly screening.[9] Patients whose CRC is diagnosed as part of the Australian National Bowel Cancer Screening Program (NBCSP) are diagnosed at an earlier stage and have a far lower mortality rate than those who are diagnosed only after they develop symptoms.[10] Various commercial FOBTs are available, but all modern tests should use immunochemical testing rather than the older guaiac-based testing. GPs can contact the manufacturer of the immunochemical FOBT used in the NBCSP (Sonic Healthcare) or their local laboratory to have their patients' results linked with practice software.

In the past few years, the NBCSP has been increasing the number of age groups targeted, and by 2019 it intends to target all adults with even-numbered ages from 50 to 74 years (50, 52, 54, etc), thus achieving the aim of second-yearly screening across this population.[11] Screening test kits are mailed out with instructions, and recipients are asked to take two samples and mail them back in an enclosed return envelope. Positive findings are communicated to the patient, who is asked to present to their GP. A positive test result is an indication for colonoscopy referral. The participation rate in the NBCSP is currently about 40% of the targeted population,[11] leaving considerable room for improvement and showing the need for greater promotion of the program.

Patients can be reassured that only one in 28 people with a positive FOBT result on screening will be found to have CRC, whereas less than 0.1% of people with a negative FOBT result will be diagnosed with CRC in the two years before their next test.[12] The FOBT is a screening test only and is generally not appropriate for investigating a symptomatic patient. It certainly should not be ordered for a patient who presents with rectal bleeding.

People with a personal history of adenomatous polyps, CRC or inflammatory bowel disease, or a strong family history of CRC, are at increased risk and should have screening colonoscopies. The Gastroenterological Society of Australia (GESA) has published guidelines that include indications for screening colonoscopy and recommended intervals between colonoscopies, according to baseline risk and number of polyps identified at the previous colonoscopy.[3] In the GESA guidelines, an individual with a parent diagnosed after the age of 55 years as their only relative with CRC does not warrant a colonoscopy but should have FOBT screening, as for the general population.

Cancer Council Australia has recently released NHMRC-approved clinical practice guidelines on CRC, including recommendations for screening and diagnosis, which contain useful information for both professionals and patients (Box).[6]

The symptomatic patient

Symptoms indicating CRC are often nonspecific, but rectal bleeding, abdominal pain, weight loss, change in bowel habit and anaemia have been shown to be associated with an increased likelihood of CRC.[13] Rectal bleeding is the most specific of these symptoms (particularly in the absence of perianal symptoms)[13] and should warrant referral for colonoscopy in almost all middle-aged or older adults. Iron deficiency anaemia in a middle-aged or older adult should raise a strong suspicion of gastrointestinal malignancy; it should also be viewed as a concerning finding in young adults, unless there is an obvious attributable cause for iron deficiency, such as heavy menstrual bleeding.

Young adults presenting with rectal bleeding pose a challenge, as the incidence of sporadic CRC in both symptomatic patients[14] and the general population younger than 40 years is low;[1] however, the potential benefit of an early diagnosis is significant. For a young patient with bright-red rectal bleeding, the endoscopist may choose to obtain consent for a sigmoidoscopy rather than a full colonoscopy, as it poses a lower risk of complication and requires only an enema rather than a full bowel preparation.

Patients without rectal bleeding but with unexplained nonspecific gastrointestinal symptoms are also often referred for colonoscopy. A multinational European study of more than 6000 GP presentations of patients with abdominal symptoms found that 3% of patients were eventually diagnosed with an abdominal cancer.[15] However, referring a patient for invasive investigation must be a clinical decision, individualised to the patient's symptoms, risk factors and overall health and weighed up in a risk versus benefit discussion between the clinician and

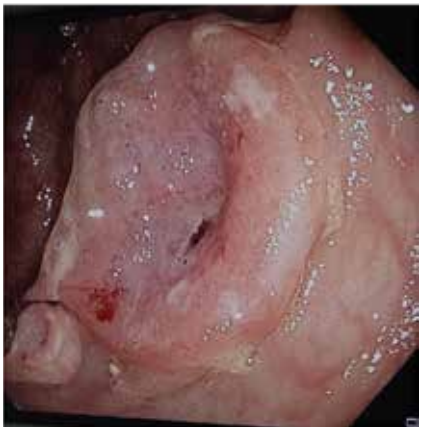


Figure. An early-stage colonic adenocarcinoma seen on colonoscopy.

patient. Ultimately, a colonoscopy may be a reasonable step in investigating nonspecific abdominal complaints and, in combination with an abdominal CT scan, may also help reassure patients who are anxious about their symptoms.

Investigations and staging

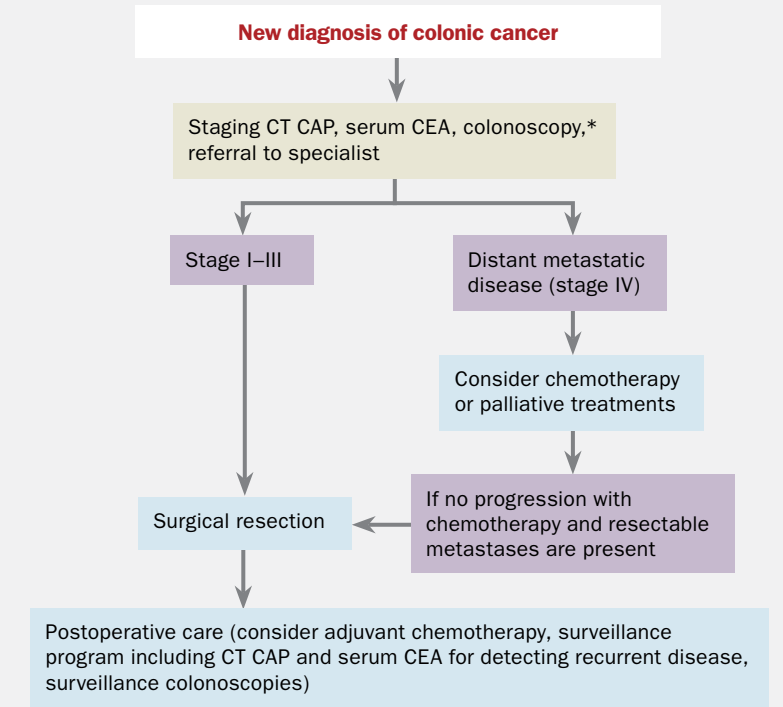
Colonoscopy with biopsy is the gold standard for the diagnosis of CRC (Figure). The risk of significant morbidity during a screening colonoscopy has been found to be about 0.3%.[16] Bowel preparation, which patients often find unpleasant, is required before the procedure and sedation or a light general anaesthetic is often used during the procedure.

CT colonography is a radiological technique developed as a less invasive alternative to colonoscopy. It has a sensitivity of about 96% for CRC,[17] but as it does not permit biopsy or polypectomy and still requires bowel preparation, its application is mostly limited to patients for whom colonoscopy is for some reason unsuitable (e.g. those with high anaesthesia risk).

In CRC staging, the TNM (tumour invasion depth, lymph node metastases, distant metastases) Classification of Malignant Tumours, as defined by the American Joint Committee on Cancer, remains the backbone of prognosis and treatment algorithms. Colonic tumour depth and lymph node status are usually confirmed by a pathologist after bowel resection. Distant metastases are detected with preoperative CT scans of the chest, abdomen and pelvis for staging of newly diagnosed CRC, as well as in surveillance during and after treatment. CT scans can often show the location of a cancer, and CT is a not infrequent method of initial disease detection. Pelvic MRI is also used in the staging of rectal cancers, as it can estimate the depth of invasion of the cancer and the presence of local lymphadenopathy, which in turn determines the initial treatment modality used.

Although the tumour marker carcinoembryonic antigen (CEA) is not used in CRC screening or initial diagnosis, it may be helpful in providing prognostic information after the diagnosis of CRC and in monitoring for cancer recurrence.[18]

1. SIMPLIFIED INVESTIGATION AND TREATMENT ALGORITHM FOR COLONIC ADENOCARCINOMA



Abbreviations: CEA = carcinoembryonic antigen; CT CAP = computed tomography of the chest, abdomen and pelvis.
* Colonoscopy should be performed if it has not already been done and the patient is considered a surgical candidate.

Treatment

As with many cancers, the treatment of CRC involves multiple specialties and should be managed by a multidisciplinary team.[6] Simplified investigation and treatment algorithms for colonic and rectal cancer are shown in Flowcharts 1 and 2, respectively.

Surgery

Surgical resection remains the primary treatment option for potentially curable colonic cancer. Resection also includes the colonic mesentery containing the lymph nodes and blood vessels that supply the relevant segment of colon. There is evidence that patients with CRC treated by surgeons who frequently perform bowel resections or who specialise in colorectal surgery may benefit from improved short- and long-term outcomes.[19]

Minimally invasive surgical techniques using laparoscopy are now widespread and have been shown to reduce length of hospital stay and perioperative complications while probably not affecting oncological or long-term outcomes.[20,21] In patients with rectal cancer, there is some concern that laparoscopic techniques may be associated with an inferior rate of adequate resection margins.[22] Minimally invasive surgical techniques have been combined with anaesthesia and perioperative principles to create the concept of enhanced recovery after surgery (commonly known as ERAS), which aims to hasten a patient's return to bowel function and mobility and thus reduce hospital length of stay (typically to five days or less) and risk of postoperative complications.[23]

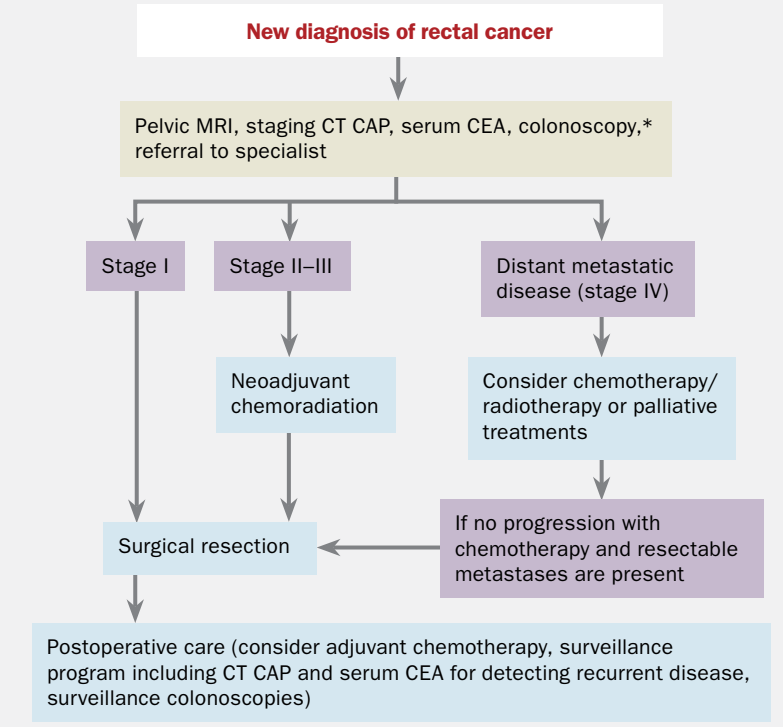
Patients with low rectal cancers may require a permanent colostomy. Patients at increased risk of an anastomotic leak may require a temporary diverting ileostomy, which the surgeon creates to protect the anastomosis while it heals. Diverting ileostomies can usually be closed at a second operation about three months later.

Transanal excision is an option for early-stage rectal cancers that has been found to have acceptable outcomes.[24] More recently, transanal total mesorectal excision, which combines transanal and transabdominal approaches to treat some low rectal cancers, has been developed. However, this operation's safety has not yet been confirmed in randomised controlled trials.[25]

Surgery for metastatic disease is an evolving field. The liver and lungs are the most common sites of distant CRC metastases, and resection of these metastases has been performed for decades. However, although surgical advances and developments in patient selection are seeing an increasing number of patients becoming candidates for curative resection, most patients with liver or lung metastases at diagnosis will not be candidates for resection.[26] Published five-year postoperative survival rates are generally below 50%, but these are still far better than rates for patients who do not have resections.[27]

Metastases to other organs are also potentially amenable to resection, but the chance of long-term cure in these patients is poor. Although these resections are performed in some centres, further work is required to clarify in which situations aggressive surgery is appropriate. In specialised centres, peritoneal metastases are resected in combination with intraperitoneal chemotherapy. Chemotherapy is often used before surgery for patients with metastatic disease. Those whose disease burden increases despite chemotherapy are generally considered poor candidates for further surgery. Radiofrequency ablation may also play a role in treating liver metastases.

2. SIMPLIFIED INVESTIGATION AND TREATMENT ALGORITHM FOR RECTAL ADENOCARCINOMA



Abbreviations: CEA = carcinoembryonic antigen; CT CAP = computed tomography of the chest, abdomen and pelvis.
* Colonoscopy should be performed if it has not already been done and the patient is considered a surgical candidate.

Chemotherapy

Chemotherapy is generally used for patients with locally advanced CRC or those with lymph node or distant organ metastases. It can be administered before curative surgery (neoadjuvant), after surgery to reduce the risk of recurrence (adjuvant) or in patients with unresectable disease to slow down or reduce metastatic disease. Typical regimens are capecitabine and oxaliplatin, and fluorouracil and oxaliplatin. After a bowel resection, chemotherapy should be started within eight weeks,[27] and the course typically continues for about six months.

Monoclonal antibody drugs such as bevacizumab, cetuximab and panitumumab may also be used in conjunction with chemotherapy in patients with metastatic disease to extend overall survival.

TABLE 1. OVERALL FIVE-YEAR SURVIVAL ESTIMATES FOR PATIENTS WITH COLORECTAL CANCER, BY STAGE

Stage	Five-year survival*
I (early disease)	93 to 97%
II (locally advanced)	72 to 85%
III (lymph node metastases)	44 to 83%
IV (distant metastases)	<8%

* Source: BMJ Best Practice. Colorectal cancer.[32]

A small proportion of initially unresectable metastatic disease may respond sufficiently to chemotherapy such that surgical resection can be reconsidered.[26]

Radiotherapy

Radiotherapy is used primarily for rectal cancers, where radiation and chemotherapy may be used before curative surgery, as it has been shown to reduce the rate of local recurrence in locally advanced rectal cancer.[28] Radiotherapy regimens can be a 'short course' (five-day course followed by surgery one week later) or 'long course' (about a five-week course followed by surgery four to eight weeks later); the latter is combined with chemotherapy.[29]

Palliative treatment

Many patients will present with advanced-stage CRC or with comorbidities that make their cancer unresectable. Local symptoms such as pain, obstruction or discharge (blood or mucus) may be treated with medical palliation, surgery, chemotherapy or radiotherapy, and palliative patients are therefore often discussed in a multidisciplinary setting. Large bowel obstruction can occur in unresected CRC and may be amenable to endoscopic stent insertion. As with most incurable cancers, early referral to palliative care services is recommended. This has been shown to improve quality of life and reduce rates of acute hospital admission and possibly even to increase length of survival compared with patients who have not been referred for palliative care.[30]

Postoperative care and prognosis

As postoperative hospital length of stay shortens, GPs may increasingly see patients earlier in the postoperative course. Patients are often discharged on a regimen of opioid analgesia as required, but dependence may develop if opioid use continues. Attempts should be made to wean use of opioids and replace them with nonopioid analgesics as soon as possible.

Wound issues, such as superficial wound breakdown or infection, can often be treated by allowing the wound to open and managing it with dressings. Surgical follow up or referral to an emergency department are options if there are further concerns.

Patients with new stomas are usually connected to a stoma therapy service, but they are encouraged to monitor the volume and consistency of their stomas' output. Stoma output and consistency are variable in the early postoperative period, but a high stoma output (more than 1.5 to 2 litres/day) may cause dehydration and electrolyte abnormalities.

Major complications such as anastomotic leak, intra-abdominal abscess or small bowel obstruction can occur, and patients should be referred back to their surgeon and an emergency department if these complications are suspected.

Surveillance after resection of CRC with curative intent will usually be led by the patient's surgeon or oncologist. A typical surveillance program would involve symptom review with physical examination and serum CEA measurement three- to six-monthly, and chest and abdomen CT scans annually. Surveillance aims to identify recurrent disease at a stage when it can be treated with further surgery. Positron emission tomography scans are not part of routine staging or surveillance, but they may be ordered by an oncologist or surgeon if surgery or other treatment is being considered after metastatic recurrence is detected.[31] GESA's colonoscopy surveillance guidelines generally recommend beginning with a colonoscopy 12 months after the initial diagnosis.[3]

The prognosis of CRC is related to its stage, with the presence of metastases to mesenteric lymph nodes conferring an increased risk of distant recurrence, and distant metastases (most commonly to the liver, lung or peritoneal cavity) conferring high mortality rates (Table 1).

Conclusion

CRC remains a major cause of morbidity and mortality in Australia. Appropriate screening and early recognition of suspicious symptoms are the keys to enabling diagnosis at a curable stage. With increased levels of screening and advances in all treatment modalities, there is hope of reducing the burden of this disease on our society. MT

COMPETING INTERESTS: None.

Colorectal cancer

Screening and treatment advances improve survival

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