Bowel cancer

A guide for the GP

Paul McMurrick
FRACS, is a colorectal surgeon, Malvern, and Senior Lecturer in Surgery, Cabrini Monash University Academic Surgical Department, Victoria. pjm@colorectal.com.au

Simone Dorien
MBBS(Hons), FRACGP, DRANZCOG, is a general practitioner, Prahran, Victoria.

Jeremy Shapiro
MBBS, FRACP, is a medical oncologist, Cabrini and Alfred Hospitals, Melbourne, and Senior Lecturer, Monash University, Department of Medicine, Victoria.

BACKGROUND
Many patients will remain asymptomatic until the advanced stages of colorectal cancer and hence, will only be identified by means of a coordinated screening program.

OBJECTIVE
This article outlines the risk assessment, early detection primary prevention and management of colorectal cancer.

DISCUSSION
It is vital that general practitioners recognise the enormous variation in the patterns of clinical presentation of colorectal neoplasia such as rectal bleeding, iron deficiency anaemia, change in bowel habit, and unexplained weight loss. Any patient over 40 years of age presenting with rectal bleeding should be considered for colonoscopy. In patients in whom a colorectal neoplasm has been diagnosed, preoperative workup and counselling is of paramount importance. Primary treatment of colorectal cancer is surgical resection and often adjuvant chemotherapy. Patients with rectal tumours have a greater risk of complications of surgery and local recurrence than those with colonic tumours. Patients with node positive cancer remain at significant risk for recurrence, despite optimal surgery and removal of the primary tumour. Adding oxaliplatin to standard (5FU based) chemotherapy has improved disease free survival for high risk patients.

Understanding the mechanisms of screening, preoperative work up and definitive treatment of colorectal neoplasia is fundamental to any family medical practice. This article aims to highlight appropriate guidelines and then apply these guidelines in selected case reports.

Risk assessment in the asymptomatic patient

All adult patients should be considered for screening for colorectal cancer (CRC) in the same way that women are routinely considered for breast or cervical cancer. At what age and which test needs to be tailored to individual patients.

Family history

A family history of significant benign colorectal neoplasia (those that are large and have villous architecture and/or high grades of dysplasia) may confer as much subsequent risk on the patient as a history of confirmed CRC. Tumours such as ovarian, ureteric, and endometrial cancer may be linked with hereditary nonpolyposis colon cancer (HNPCC).

NHMRC guidelines

The National Health and Medical Research Council (NHMRC) have produced guidelines for screening in asymptomatic patients (*Table 1*). After assessment of patient risk factors, it is recommended that people aged 50 years and over have faecal occult blood tests (FOBT) at least every 2 years. The one significant weakness with these guidelines relates to the arbitrary cut-off age of 55 years for the age at diagnosis of CRC in first degree relatives. It is obviously difficult to suggest to patients with a first degree relative who developed CRC after this age, that they themselves should not be screened with colonoscopy.

The general guidelines for primary prevention provided by the NHMRC should be offered to all patients (*Table 2*).

Faecal occult blood testing

We recommend the newer, low cost and readily available enzymatic faecal occult blood testing kits. In addition to the high level of sensitivity of these kits, they are easy to use with clear instructions provided, and patients are automatically placed on an annual recall list, thus reducing

Table 1. NHMRC guidelines for colorectal cancer screening in asymptomatic patients

Category 1 – those at or slightly above average risk (covers about 98% of the population)

Asymptomatic people fit into this category if there is:

i. No personal history of CRC or ulcerative colitis and no confirmed family history of colorectal cancer, or

ii. One first degree (parent, sibling, child) or second degree (aunt, uncle, niece, nephew, grandparent, grandchild) relative with CRC diagnosed at age 55 or over

Screening guidelines

- Faecal occult blood testing (FOBT) at least every 2 years from the age of 50
- Consider sigmoidoscopy (preferably flexible) every 5 years from the age of 50
- It is important to advise individuals to see their doctor if they develop symptoms of CRC

Category 2 – those at moderately increased risk (covers 1–2% of the population)

Asymptomatic people fit into this category if there is:

i. One first degree relative with CRC diagnosed before the age of 55, or

ii. Two first or second degree relatives on the same side of the family with CRC diagnosed at any age

Screening guidelines

- Offer colonoscopy every 5 years starting at 50, or at an age 10 years younger than the age of CRC in the family, whichever comes first
- Sigmoidoscopy plus double contrast barium enema is an acceptable alternative to colonoscopy if colonoscopy is unavailable
- Consider FOBT in intervening years. Colonoscopic follow up (or sigmoidoscopy plus double contrast barium enema) is necessary for those with a positive FOBT

Category 3 – those at potentially high risk (covers <1% of the population)

Asymptomatic people fit into this category if there are:

i. Three or more first or second degree relatives on the same side of the family diagnosed with CRC (suspected hereditary nonpolyposis colon cancer (HNPCC)], or

ii. Two or more first or second degree relatives on the same side of the family diagnosed with CRC, including any of the high risk features:
   – multiple CRC in one person
   – CRC before the age of 50 years
   – at least one relative with endometrial or ovarian cancer (suspected HNPCC), or

iii. At least one first degree or second degree relative with CRC, with a large number of adenomas throughout the large bowel (suspected familial adenomatous polyposis [FAP]), or

iv. Someone in the family in whom the presence of a high risk mutation in the adenomatous polyposis coli (APC) or one of the mismatch repair (MMR) genes has been identified

Screening guidelines

- These high risk families should be managed with the support of clinical genetics and cancer genetic services underpinned by family registries
- Screening of at risk members of proven HNPCC families should be by annual or 2 yearly colonoscopy, commencing around the age of 25 years. Annual screening should be offered to individuals carrying a germline mutation

Source: NHMRC

the burden on the administration of family practices. It is the authors' opinion that all NHMRC Category 1 patients who do not require colonoscopy should be offered FOBT.

Recognition of patterns of clinical presentation

It is vital that GPs recognise the enormous variation in the patterns of clinical presentation of colorectal neoplasia. Many patients will remain asymptomatic until the advanced stages of their disease and hence, will only be identified by means of a coordinated screening program.

Any patient with rectal bleeding over the age of 40 years should be considered for colonoscopy regardless of how trivial the bleeding. Below the age of 40, the decision may lean toward further investigation if a family history of CRC is found or if 'high risk' symptoms are present such as:

- bleeding which is not bright in nature
- change in bowel habit
- unexplained weight loss
- abdominal pain, or
- mucous discharge.

Patients with persistent change in bowel habit, unexplained

weight loss associated with abdominal discomfort or bleeding should be referred for further assessment.

Any patient with iron deficiency anaemia should at a minimum, undergo FOBT and preferably gastroscopy and colonoscopy, even if menorrhagia or dietary inadequacy is reported. The response or otherwise to oral iron supplements does not differentiate between patients with significant gut pathology.

When can I attribute bleeding to haemorrhoids?

In the opinion of the authors, any patient with haemorrhoids and rectal bleeding over the age of 40 years should be encouraged to undergo colonoscopy. Patients aged 30–40 years should be offered colonoscopy, particularly if there is a family history of CRC.

All too often younger patients with significant colorectal neoplasia have a delayed diagnosis because symptoms were attributed to haemorrhoids. If haemorrhoids are presumed without colonoscopy, interval FOBT should follow, after resolution of the bleeding, particularly if there is a family history of CRC.

The patient with a diagnosed neoplasm

In patients in whom a colorectal neoplasm has been diagnosed, preoperative workup and counselling is of paramount importance. As well as being prepared psychologically for major surgery, patients need to be provided with background information about the likely course of treatment and in selected patients, a general medical assessment should commence early.

What to tell patients

Generally, guidelines can be provided to the patient at the initial consultation with the GP. The NHMRC handbook, *Guidelines for the prevention, early detection and management of CRC: a guide for patients, their family and friends* is recommended (see *Resources*).

Timing

Surgery generally takes between 1–4 hours, depending on the patient's tumour. Most patients will remain in hospital for between 5–10 days; sometimes up to 2 weeks. After surgery most patients will be 'off work' for 6 weeks and it may be 8 weeks before vigorous physical labour can be undertaken.

Risks

Risks vary between individual patients and specific calculation of risk of adverse outcome is complex. In general however, for an average risk patient, under the age of 80 years, without major medical comorbidities and undergoing elective surgery, perioperative mortality is between 1–2%. In right sided lesions, the risk of anastomotic leakage and stoma formation should be in the order of 2%. With more distal lesions, particularly rectal lesions, the risk is elevated, with most patients with distal rectal cancer having a loop ileostomy formed electively at the time of surgery. This is best discussed by the treating specialist.

Prognosis

Patients should be allocated to the TNM staging system, which forms the basis of almost all guidelines for adjuvant treatment and assessment of prognosis (*Table 3, 4*). Given the frequency of this diagnosis within the general community, it is worth all GPs keeping a copy of this staging system within their practice.

Patient work up

Of primary importance is the staging computerised tomography (CT) scan of the chest, abdomen and pelvis, the result of which may alter the entire management process. Other routine tests include:

- full blood examination (FBE)
- urea, electrolytes and creatinine (UEC)
- liver function tests (LFT)
- carcino-embryonic antigen (CEA), and
- baseline electrocardiogram (ECG)

Table 2. General guidelines to reduce the risk of colorectal cancer

Diet

People's risk of CRC can be reduced if they:

- restrict energy intake (fewer than 2500 kcal per day for men; fewer than 2000 kcal per day for women)
- reduce dietary fat (<25% of total energy as fat)
- eat five or more portions per day of a variety of vegetables and fruit all year round
- consume poorly soluble cereal fibres (eg. wheat bran), especially if at high risk of CRC
- ensure a dietary calcium intake of 1000–1200 mg per day

Healthy lifestyle

The following healthy lifestyle recommendations may be protective against CRC and should be followed by all people:

- participate in regular physical activity
- restrict alcohol intake
- do not smoke

Chemoprevention

Agents such as selenium supplements, aspirin, nonsteroidal anti-inflammatory drugs (NSAIDS), and selective COX-2 inhibitors may be important in the prevention of CRC but are not recommended until further research is conducted

Source: NHMRC

Recognition of the patient at high operative risk

Patients over 80 years of age, or in whom other significant risk factors are identified (eg. known ischaemic heart disease or obstructive airways disease, known other significant medical comorbidities, a significant history of smoking) should be identified early. As the time frame for surgery for CRC is usually not urgent, patients with significant underlying cardiorespiratory disease may benefit from a period of stabilisation or definitive therapy before undergoing resection. It is not uncommon for patients with, for example, significant angina, to undergo either cardiac stenting or bypass surgery before semi-elective resection of a colorectal neoplasm (see *Case history 1*). In this case, consultation with a peri-operative physician or medical specialist is indicated. Many patients will undergo elective stress testing or exercise thallium assessment before surgery if considered 'high risk'.

Surgery – what is involved?

Surgical techniques and the projected risks will vary between tumour site, preference and experience of the surgical team, and the age and risk profile of the patient. 'Colonic' cancer has different risks and outcomes compared to 'rectal' cancers.

Colonic cancers

These include cancers from the right colon through to and including the mid to distal sigmoid colon as reported on colonoscopy. It is not uncommon for 'sigmoid' cancers to be finally differentiated into either colonic lesions or more distal rectal lesions with imaging after colonoscopy. The risk of stoma formation in colonic lesions is low and permanent stoma formation would usually only occur if extensive disease is present or complications occur. Adjuvant treatment for colonic cancer (see below) usually comprises chemotherapy. Radiation therapy is rarely required. The risk of significant bowel dysfunction or sexual dysfunction after resection of a colonic neoplasm is lower than for rectal neoplasms.

Rectal cancers

For technical reasons, 'rectal' cancers often include distal sigmoid neoplasms, where resection needs to be taken well into the pelvis if the lesion is large or significant diverticular disease or other pathology is found. Rectal cancers have a significant risk of local recurrence, which is very uncommon after resection of colonic cancer. Thereafter, patients with lower rectal cancers are often treated with preoperative neo-adjuvant treatment (see below) and occasionally postoperative chemo-radiation. In addition, a significant change in rectal function is common. Depending upon whether or not radiation is required and the height of the anastomosis, as well giving consideration to pre-existing rectal function, patients may suffer significant dysfunction including frequency, urgency and faecal leakage after rectal surgery; although in the majority of patients the altered function remains socially satisfactory. In addition, the proximity of the pelvic autonomic nerves to the rectum means that significant sexual dysfunction, particularly in men, is more common after rectal than colonic surgery.

Table 3. TNM classification for colorectal cancer

T Primary tumour	TX: primary tumour cannot be assessed
	TO: no evidence of primary tumour
	Tis: carcinoma in situ
	T1: tumour invades submucosa
	T2: tumour invades muscularis propria
	T3: tumour invades through muscularis propria into the subserosa or nonperitonealised pericolic or perirectal tissues
	T4: tumour directly invades other organs or structures and/or perforates visceral peritoneum
N Regional lymph nodes	NX: regional nodes cannot be assessed
	N0: no regional node metastasis
	N1: metastasis in 1–3 regional lymph nodes
	N2: metastasis in 4 or more regional lymph nodes
M Distant metastases	MX: distant metastasis cannot be assessed
	M0: no distant metastasis
	M1: distant metastasis

Case history 1

A man, 74 years of age and a long term smoker, presented with rectal bleeding and increasing angina. His haemoglobin was 8.0 g\dL. Colonoscopy revealed a large carcinoma in the lower third of the rectum. A CT scan of the chest, abdomen and pelvis showed no evidence of metastatic disease. An endorectal ultrasound demonstrated full thickness muscularis propria (T3) penetration with probable surrounding rectal lymphadenopathy. There were no obstructive symptoms. After transfusion, the patient underwent coronary angiography which demonstrated a tight lesion in the circumflex artery, thought to be responsible for the patient's chest pain.

After consultation between the patient's cardiologist, oncologist and colorectal surgeon, the decision was made to place a drug eluding stent in the circumflex lesion, place the patient on Plavix for a period of 6 weeks and commence neo-adjuvant preoperative chemo-radiation. The patient underwent long course chemo-radiation lasting 6 weeks followed by a hiatus period of 5 weeks after completion of the radiation. The patient then underwent successful ultra low anterior resection.

Adjuvant treatment of resected colon cancer

The 5 year survival rates for colon cancer are stage dependent (*Table 4*).[1] Patients with node positive (stage III) cancer remain at significant risk for recurrence, despite optimal surgery and removal of the primary tumour. This prompted the evaluation of adjuvant chemotherapy in the 1980s. Initial clinical trials[2] demonstrated a 10–15% survival benefit for patients receiving 1 year of 5FU/levamisole following surgery, and this was incorporated into patient management after the results were published in the early 1990s. For the next 15 years, little further advances were made, although 6 months of 5FU with leucovorin were found to be equivalent and replaced the 12 month program.

Table 4. Pathological TNM staging and 5 year survival[1]

Stage	T	N	M	%
0	Tis	NO	MO	
I	T1	NO	MO	93
	T2	NO	MO	
II	T3	NO	MO	85
	T4	NO	MO	72
III	Any T	N1	MO	64–83
	Any T	N2	MO	44
IV	Any T	Any N	M1	

Source: NHMRC Guidelines for the prevention, early detection and management of colorectal cancer

Case history 2

A woman, 54 years of age, presented with increasing shortness of breath and was found by her GP to be anaemic. At colonoscopy, a carcinoma of the caecum was present. At preoperative CT scanning there was evidence of a 3 cm metastatic lesion in the right lobe of the liver, but no other metastatic disease.

The patient underwent a laparoscopic assisted right hemicolectomy and recovered successfully. Six weeks later the patient underwent a partial right hemi hepatectomy. Subsequent PET scanning showed no evidence of further metastatic disease and the patient underwent adjuvant chemotherapy. At 18 months the patient remains well and disease free.

Case history 3

A woman, 75 years of age, presented with rectal bleeding, weight loss and lethargy. A colonoscopy demonstrated a stenosing, near obstructing carcinoma in the upper third of the rectum. Preoperative CT scanning demonstrated widespread pulmonary and hepatic metastases occupying more than 50% of the volume of the liver. The patient rapidly developed obstructive symptoms from the rectal carcinoma. At colonoscopy, a palliative stent was placed, allowing relief of symptoms while the patient underwent palliative chemotherapy potentially avoiding the need for surgery. The patient passed away 14 weeks later, without requiring surgery, and free from obstructive symptoms.

Over the past 2 years, the results of recent large phase III studies have made a significant impact on clinical practice. Adding oxaliplatin to standard (5FU based) chemotherapy has improved disease free survival for high risk stage II and stage III patients by around 5%, with greater improvement in patients at highest risk.[3,4] At the same time, oral chemotherapy (capecitabine) was shown to be at least equivalent, but with fewer side effects than 5FU, thereby providing an oral 'chemo-lite' choice for patients unwilling, or unsuitable for more intensive treatment.[5]

In addition to chemotherapy, radiotherapy is also considered for patients with locally advanced rectal cancer in view of the increased risk of local recurrence. Utilising better preoperative staging (magnetic resonance imaging (MRI) and transrectal ultrasound), patients with transmural (T3) and/or node positive spread are usually offered neo-adjuvant chemo-radiation (treatment before surgery), resulting in reduced side effects (compared with postoperative), and additional clinical benefits.

Current research is focusing on evaluating oxaliplatin and capecitabine combinations along with the new biological agents, as well as trying to better predict which patients require and will benefit from therapy (prognostic and predictive factors).

Stage IV and recurrent colon cancer

Approximately 30–40% of patients with CRC have metastatic disease at the time of diagnosis and cannot be cured with surgery, although a subset with liver isolated disease are still potentially curable (see *Case history 2*). For patients with metastatic CRC, treatment is palliative and generally consists of systemic chemotherapy (see *Case history 3*).

Surgical resection of metastatic disease

The only potentially curative option for patients with liver isolated CRC is surgical resection. For patients with four or less isolated hepatic lesions, 5 year relapse free survival rates after resection range from 24–58%.[6,7] However, no more than 10% of patients with isolated hepatic metastases are amenable to potentially curative resection. The majority are not surgical candidates because of tumour size, location, multifocality, or inadequate hepatic reserve. Patients with limited pulmonary metastases, and patients with both pulmonary and hepatic metastases, may also be considered for surgical resection with 5 year survival

possible in highly selected patients.

Other loco-regional approaches (eg. radiofrequency ablation, cryosurgery, embolisation) have been used in some patients, however, none have been evaluated in randomised studies. Another modality of uncertain, but promising utility is selective internal radiation therapy (SIR-Spheres®). These 20–40 µm micro-spheres, labelled with the radioisotope, Yttrium [90Y], are delivered selectively to the tumour via a hepatic catheter. Preliminary data has been encouraging, leading to USA Federal Drug Administration approval, however 10% of patients develop significant side effects and results of phase III studies are awaited.

Palliative chemotherapy

For decades, 5FU was the only active agent for metastatic CRC. Median survival was 5–6 months and many questioned the value of treatment. In 2006, the average survival is close to 2 years, and it is not uncommon for patients to be alive 3–4 years following diagnosis. While some of this improvement is due to earlier detection and better supportive care, much of the benefit resides with the introduction of five new drugs: irinotecan, oxaliplatin, capecitabine, and more recently two humanised monoclonal antibodies that target vascular endothelial growth factor (bevacizumab) and the epidermal growth factor receptor (cetuximab). Current studies are attempting to clarify the sequencing, and duration of these new agents.

Like other biological therapies (rituximab for lymphoma, trastuzumab for breast cancer, infliximab for rheumatoid arthritis and Crohn disease), drug costs are substantial, and strategies to identify those patients most likely to benefit are urgently required.

Conclusion

Many patients with CRC remain asymptomatic until the advanced stages of their disease and therefore a coordinated screening program is vital. Any patient over 40 years of age with rectal bleeding should be considered for colonoscopy, and in patients younger than this age, colonoscopy should be selectively offered after assessment of the nature and history of rectal bleeding. Primary treatment of CRC is surgical resection. Patients with rectal tumours are more likely to have rectal dysfunction and sexual dysfunction after surgery and have greater risk of local recurrence than patients with colonic tumours. Adjuvant treatment for colonic cancer usually comprises chemotherapy whereas patients with lower rectal cancers are often treated with preoperative neo-adjuvant treatment and occasionally postoperative chemo-radiation. Patients with node positive cancer remain at significant risk for recurrence. Adding oxaliplatin to standard (5FU based) chemotherapy has improved disease free survival for high risk patients. A subset of patients with isolated liver metastases are still potentially curable, but for other patients with metastatic CRC, treatment is palliative, and generally consists of systemic chemotherapy.

Resources

- NHMRC Guidelines for the prevention, early detection and management of colorectal cancer: a guide for patients, their family and friends available at www.nhmrc.gov.au/publications/_files/cp63.pdf
- NHMRC Guidelines for the prevention, early detection and management of colorectal cancer available at www.nhmrc.gov.au/publications/_files/cp62.pdf
- NHMRC Guidelines for the prevention, early detection and management of colorectal cancer: a guide for general practitioners available at www.nhmrc.gov.au/publications/_files/cp64.pdf

Conflict of interest: none declared.

References

1. O'Connell JB, Maggard MA, Ko CY J. Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging. NCI 2004;96:1420–5.
2. Moertel CG, Fleming TR, Macdonald JS, et al. Fluorouracil plus levamisole as effective adjuvant therapy after resection of stage III colon carcinoma: a final report. Ann Int Med 1995;122:321–6.
3. Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343–51.
4. Wolmark N, Wieand S, Kuebler JP, et al. A phase III trial comparing FULV to FULV and oxaliplatin in stage II or III carcinoma of the colon: results of NSABP protocol C-07 (abstract). J Clin Oncol 2005;23:1092s.
5. Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med 2005;352:2696–704.
6. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 1999;230:309–18.
7. Steele G Jr, Bleday R, Mayer RJ, et al. Gastrointestinal Tumour Study Group Protocol 6584. A prospective evaluation of hepatic resection for colorectal carcinoma metastases to the liver. J Clin Oncol 1991;9:1105–12.

afp CORRESPONDENCE email: afp@racgp.org.au