

Colorectal cancer: an overview

The Government plans to launch a bowel cancer screening programme in England next month. In this article, **Caroline Waters** presents an overview of colorectal cancer, from prevention through to treatment

Each year, approximately 35,000 new cases of colorectal cancer (CRC) are diagnosed in the UK, with a prevalence rate of 57.1 for men and 37.5 for women per 100,000. Incidence increases with age, from 25 per 100,000 in the 45–55 year age group to over 300 per 100,000 in those aged 75 years and over. The most common age range at diagnosis is 60–65 years. In the UK, about 16,000 people die of CRC each year and it is the second most common cause of cancer death. Five-year relative survival rates have, however, increased steadily over the past 30 years and now stand at about 50 per cent.

There is evidence that both environmental and genetic factors play a role in the development of CRC. Four clinical or hereditary conditions that predispose people to CRC are described in Panel 1. Outside these four conditions, 15–20 per cent of patients with CRC report a family history. The association of diets low in fibre and high in red meat and saturated fat with an increased incidence of CRC have long been recognised. Epidemiological evidence suggests that obesity and smoking also increase the risk of developing the disease.

Symptoms and screening

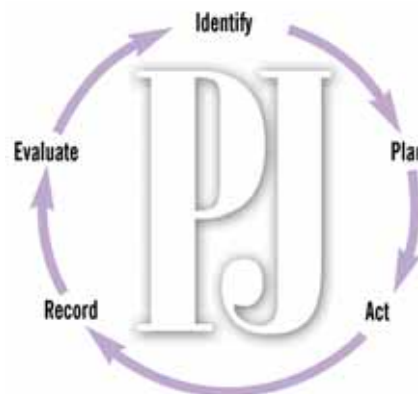
Patients may describe a number of different symptoms, including a change in bowel habit that may be accompanied by abdominal pain, rectal bleeding or blood in the stool, weight loss or symptoms of anaemia. Symptoms can be non-specific and this can delay diagnosis. In addition, many of the symptoms have a number of possible causes.

There is evidence that early detection leads to better outcomes. Screening can lead to early detection and removal of CRCs and precancerous adenomatous polyps. A national



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Polyps may be caused by a genetic disease called familial adenomatous polyposis. Genetic screening for FAP can be carried out



Identify knowledge gaps

1. What are the symptoms of colorectal cancer?
2. What chemotherapy agents are used to treat colorectal cancer?
3. How can pharmacists help prevent colorectal cancer?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in "Plan and record", (available at: www.rpsgb.org/education). This article relates to "common disease states" and "health education and promotion".

bowel cancer screening programme for England is planned to begin in April. Men and women aged 60–69 years will be invited to take part in screening every two years. They will be sent a test kit to use at home. A sample is then sent to a laboratory, which will look for faecal occult blood. In conjunction with this, large scale pilots of flexible sigmoidoscopy will be undertaken, involving people in their 50s.

The screening programme is expected to cost £37.5m in the first two years and is one of the first of its kind in Europe.

Prevention and health promotion

Pharmacists have several roles to play in preventing CRC. Primary prevention can include:

- Promoting a diet low in red meat, low in saturated fat, low in alcohol and high in fruit and vegetables
- Encouraging patients to undertake physical activity
- Providing smoking cessation support
- Encouraging obese patients to lose weight

Pharmacists can also advise and refer patients complaining of altered bowel habits and raise awareness of the national screening programme.

Cyclo-oxygenase-2 inhibitors and statins have been shown in population-based studies

Panel 1: Conditions linked to colorectal cancer

Adenomatous polyps Adenomatous polyps are benign neoplasms that have the potential to become malignant. Not all polyps will develop into cancer. The exact risk and time course is not known but larger polyps have a greater risk of developing into an invasive malignancy.

Familial adenomatous polyposis Familial adenomatous polyposis (FAP) is an autosomal dominant inherited disorder. In FAP, the colorectum is covered with thousands of adenomatous polyps. These typically occur at about 16 years of age and, unless a colectomy is performed, 90 per cent of affected patients have invasive cancer by 45 years.

Ulcerative colitis A history of early onset, long-standing and extensive ulcerative colitis may give rise to tumours that are multi-focal and poorly differentiated.

Hereditary nonpolyposis colorectal cancer syndrome Hereditary nonpolyposis colorectal cancer (HNPCC) syndrome is responsible for 10–15 per cent of all cases of colorectal cancer. People with HNPCC syndrome have mutations in DNA repair genes on chromosomes 2p and 3p. The overall lifetime risk of CRC developing in these people is 80 per cent.

Panel 2: DOH guidance for urgent referral

All patients:

- Who experience rectal bleeding with a change in bowel habit for six weeks
- With a right-sided abdominal mass
- With a rectal mass
- With iron deficiency anaemia and no obvious cause

Patients over 60 years:

- With rectal bleeding but no other anal symptoms
- With a change in bowel habit to looser stools or increased frequency of defaecation persistent for six weeks in the absence of rectal bleeding

to provide some protection against CRC, but these are not standard therapy.

Diagnosis and staging

Due to the non-specificity of CRC symptoms, there is often a delay between onset and diagnosis. The Department of Health has issued guidance for urgent referral and the patients listed in Panel 2 should be seen within two weeks. If CRC is suspected, patients will undergo total colonic imaging, which may consist of colonoscopy or a barium enema, or both, as well as a biopsy of any suspicious lesion being taken (most commonly during colonoscopy).

After a diagnosis of CRC, patients undergo further investigations to ascertain the stage of the disease. The prognosis depends on the stage at diagnosis. Historically, the Dukes staging system was used, but this is now being superseded by the "tumour, node, metastases" (TNM) classification system (see Table). The TNM system assesses the extent of tumour penetration through the layers of the bowel wall, whether or not there is any lymph node involvement (eg, N0 means no lymph nodes are affected, N1 means one to three nodes are involved and N2 means four or more nodes are involved) and if there are metastases. Staging is essential in planning treatment, which can be curative or, for patients with more advanced disease, palliative.

Treatment

Treatment options depend on the site and stage of the tumour and the patient's general condition. Surgery, chemotherapy and radiotherapy may all be used. Rectal tumours are not as easy to remove as colonic tumours. They spread more easily and local recurrence rates are higher so treatment may differ.

Surgery For patients with colon cancer, surgery to remove the primary tumour is usually the main therapy. This is normally a planned procedure but patients presenting with symptoms and signs of obstruction or perforation may require emergency surgery.

In rectal cancer, total mesorectal excision can be carried out by specialist surgeons. This involves meticulous dissection in the plane outside the mesorectum so that the rectum and tumour can be removed together, with minimal damage to the pelvic nerves. This and other advances in surgical techniques have reduced rates of relapse in rectal cancers.

Treatment options depend on the site and stage of the tumour and the patient's general condition

Surgery also has a role to play in the management of patients with metastases confined to the liver. Resection (removal) of liver metastases is potentially curative in about a third of patients. Surgery may also be indicated in the palliative management of obstructing tumours in advanced disease.

Radio- and chemotherapy

Rectal cancers are usually treated with a combination of chemotherapy and radiotherapy in both the neo-adjuvant (before surgery) and adjuvant (after surgery) setting. The aim is to reduce the size of the tumour to render it operable or to reduce the risk of local recurrence. Chemotherapy sensitises cancer cells to the radiotherapy.

In the US and Europe, neo-adjuvant treatment is given in preference to adjuvant treatment to enhance sphincter-preserving surgery and prevent local recurrence of the disease. Because pre-operative clinical staging (rectal examination) does not give a completely accurate picture, imaging techniques, such as computerised tomography and magnetic resonance imaging, are used to identify patients with stage II and III disease who would be eligible for neo-adjuvant treatment. If patients do not receive pre-operative radiotherapy, they may receive radiotherapy after surgery to remove any remaining cancer cells.

Radiotherapy may also be given to patients with locally advanced rectal cancer with the aim of reducing pain, discharge and haemorrhage.

Adjuvant chemotherapy for colon cancer

Patients at higher risk of residual disease or developing metastases are those with stage II (Dukes B) colonic tumours (with full thickness penetration of the bowel wall), or patients with lymph node involvement (stage III or Dukes C). Adjuvant chemotherapy is given to eradicate micrometastatic disease. The role of adjuvant chemotherapy for stage III colonic tumours is well established. However, evidence is now emerging from various overviews and large randomised trials that patients with stage II colon cancer may also benefit from adjuvant chemotherapy. Patients with stage II disease and at least one risk fac-

Table: Staging of colorectal cancer

Stages	TNM classification			Dukes classification*	5 yr survival	Extent of disease
	T	N	M			
I	T1	N0	M0	A	90%	Confined to bowel wall
	T2	N0	M0	B1		
II	T3	N0	M0	B2	70–80%	Involving full thickness of the bowel
	T4	N0	M0	B2		
III	T1, T2	N1, N2	M0	C1	50–60%	Involvement of mesenteric lymph nodes
	T3, T4	N1, N2	M0	C2		
IV	Any T	Any N	M1	D	<5%	Distant metastatic spread

*Astler-Coller modification

Panel 3: Summary of NICE guidance relating to drug treatment of advanced or metastatic CRC*

Technology appraisal

Guidance on the use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced CRC (no. 93) August 2005

Guidance on the use of capecitabine and tegafur with uracil for metastatic CRC (no. 61) May 2003

Guidance

Irinotecan and oxaliplatin, within their licensed indications, are recommended as treatment options for people with advanced CRC as follows:

- Irinotecan in combination with 5-fluorouracil and folinic acid as first-line therapy, or irinotecan alone in subsequent therapy
- Oxaliplatin in combination with 5-FU and folinic acid as first-line or subsequent therapy. Raltitrexed is not recommended for the treatment of advanced CRC. Its use for this patient group should be confined to appropriately designed clinical studies

Oral therapy with either capecitabine or tegafur with uracil (in combination with calcium folinate [folinic acid]) is recommended as an option for the first-line treatment of metastatic CRC. The choice of regimen (5-FU/LV or oral treatment) should be made jointly by the individual and the clinician(s) responsible for treatment. The use of capecitabine or tegafur with uracil should be supervised by oncologists who specialise in CRC

*Guidance on the use of cetuximab and bevacizumab in advanced CRC is due to be released in November

tor (such as those with intestinal obstruction, perforation or a poorly differentiated tumour) are predicted to have a poorer outcome, and these factors may help in the selection of patients for adjuvant chemotherapy.

The treatment of choice in the adjuvant setting since the 1990s has been six months of fluorouracil (5-FU) and calcium folinate (LV) but recent trials have shown that oral fluoropyrimidines (capecitabine or tegafur with uracil) offer equivalent efficacy to intravenous 5-FU.^{1,2}

Irinotecan and oxaliplatin have both been investigated in the adjuvant setting. The addition of oxaliplatin to 5-FU/LV increases the likelihood of patients remaining recurrence free after four years³ but clinical trials have as yet failed to show a benefit for irinotecan.

Capecitabine and oxaliplatin have recently been licensed for use in the adjuvant treatment of stage III colon cancer. National Institute for health and Clinical Excellence appraisals are due next month. The Scottish Medicines Consortium has agreed that capecitabine, for the adjuvant treatment of patients following surgery for stage III colon cancer, should be accepted for use within NHS Scotland. It has also advised that oxaliplatin is accepted for use for the adjuvant treatment of stage III colon cancer after surgery.

Tegafur with uracil is not licensed to treat colon cancer in the adjuvant setting.

Advanced disease If, at the time of presentation or recurrence, the tumour is so locally invasive that resection is impossible, or if the tumour has metastasised to distant organs, the patient is deemed to have advanced disease. Irinotecan is now well established as second-line treatment following a fluoropyrimidine. In addition, irinotecan in combination with 5FU/LV as first-line treatment produces a survival advantage when compared with 5FU/LV alone^{4,5} and its use in this setting is endorsed by NICE (see Panel 3). While oxaliplatin has not demonstrated an improvement in overall survival in the first-line setting, it has been shown to increase progression free survival and response rate.^{6,7} Oxaliplatin has also

demonstrated improvements in progression-free survival in the second-line setting and as such, NICE now recommends oxaliplatin in first-line or subsequent treatment. The optimal order in which to give these drugs is still unclear but therapy sequences using a fluoropyrimidine, irinotecan and oxaliplatin appear to give the longest median overall survival.

A summary of NICE guidance relating to drug treatment of advanced or metastatic CRC is given in Panel 3.

New drugs The most recent drugs to be introduced to treat CRC are the monoclonal antibodies, cetuximab and bevacizumab. Cetuximab binds to and inhibits the epidermal growth factor receptor (EGFR), which is over expressed in 25–80 per cent of CRCs. The actions of EGFR (cell proliferation, inhibition of apoptosis and angiogenesis) are, therefore, inhibited. Cetuximab has demonstrated activity in CRC and is currently licensed for use in patients with EGFR-expressing metastatic CRC after failure of irinotecan based chemotherapy.

News feature
See p316 for a news feature on vaccines against cancer

Panel 4: Side effects of drugs used to treat CRC

Drug	Side effects
Fluoropyrimidines	Mucositis, diarrhoea, nausea and vomiting, hand-foot syndrome, myelosuppression, cerebellar syndrome (rare), chest pain (rare)
Irinotecan	Late onset diarrhoea, myelosuppression, nausea and vomiting, alopecia, acute cholinergic syndrome
Oxaliplatin	Myelosuppression, nausea and vomiting, diarrhoea, neurotoxicity, injection site reactions
Raltitrexed	Myelosuppression, nausea and vomiting, diarrhoea, increase in liver function test results
Cetuximab	Asthenia, acne-like rash, hypersensitivity reactions
Bevacizumab	Hypertension, gastrointestinal perforation, thromboembolism, wound healing complications, haemorrhage

Bevacizumab is a recombinant humanised monoclonal antibody to vascular endothelial cell growth factor (VEGF). VEGF stimulates angiogenesis (new blood vessel formation), which is essential for tumour development. Bevacizumab is licensed for first-line use in combination with intravenous 5FU/LV or 5FU/LV/irinotecan. There are numerous clinical trials in progress assessing the impact of these and other new agents in the adjuvant and advanced settings.

Chemotherapy-related toxic effects Patients receiving chemotherapy can experience toxic effects. Panel 4 (p325) provides a summary of the side effect profile for drugs used in the treatment of CRC. There are specific side effects related to individual drugs, but some are common to most drugs.

Acute nausea and vomiting can be successfully managed by the use of 5-hydroxytryptamine 3 receptor antagonists and dexamethasone before highly emetogenic chemotherapy, or metoclopramide or domperidone with less emetogenic chemotherapy. Dexamethasone with metoclopramide is used to prevent delayed emesis.

Mucositis is common with fluoropyrimidines. This is inflammation of the membrane of the digestive tract, which can be accompanied by ulceration and pain. Good oral hygiene with regular brushing of the teeth and, where necessary, the use of an antiseptic mouthwash can help prevent mucositis. Once it occurs, treatment is of limited benefit but sucralfate suspension, saline mouthwashes and local analgesics are used to minimise discomfort and promote the healing process.

Diarrhoea is a common side effect of many chemotherapy drugs and is managed with loperamide, codeine phosphate and, occasionally, budesonide and octreotide. Patients should be advised to drink plenty of clear fluids and avoid spicy foods, high fibre foods, caffeine and alcohol. When diarrhoea occurs in patients on irinotecan, it is likely to be related to acute cholinergic syndrome if it occurs within 24 hours of the infusion and is treated with subcutaneous atropine sulphate. Diarrhoea occurring more than 24 hours after administration ("delayed diarrhoea") is treated with high dose loperamide for up to 48 hours and broad spectrum antibiotics (usually ciprofloxacin) if it occurs in conjunction with neutropenia.

Reversible alopecia is unusual with many of the drugs used in CRC, however it does occur with irinotecan. Scalp cooling is offered to reduce blood flow to hair follicles to prevent hair loss.

When toxic effects become severe or prolonged, dose reductions can be made to the chemotherapy.

Nutritional support

Nutritional support is an important part of care for patients with CRC. Some patients lose weight before diagnosis, while others lose weight peri-operatively. Malnutrition may result in a poorer prognosis and response to

Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. Promote healthy lifestyle and eating habits.
2. Encourage patients to report changes in bowel habit to their GPs. Work to break down the barriers of this taboo subject and raise awareness of the national screening programme.
3. Chemotherapy-related mucositis usually begins four or five days after the start of treatment. In the absence of complications, it lasts for about 10 days. Visit www.nhsdirect and find out about the advice given to patients. Answer the following:
 - Should patients with mucositis be advised to use mouth washes?
 - What kinds of foods might make the symptoms worse?
 - What drugs can be used to help with pain?
 - Which patients should be referred?
 - What evidence-based method can be tried to prevent mucositis?

Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following questions: What have you learnt? How has it added value to your practice? (Have you applied this learning or had any feedback?) What will you do now and how will this be achieved?

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treatment, which makes early intervention essential. All patients should undergo a nutritional assessment and, where appropriate, nutritional support should be instigated.

Stoma care

Despite the vast number of stoma care appliances and products, many patients will experience problems occasionally. These may be the pouch leaking, odours, shrinkage of the stoma or allergies to the adhesive. These can cause the patient embarrassment as well as pain and discomfort. Patients should have a stoma care nurse whom they can contact if they experience such problems. In addition, organisations such as CancerBACUP and the British Colostomy Association provide advice on issues such as travelling with a stoma.

Future issues

The new targeted therapies, cetuximab and bevacizumab are in the limelight and no doubt we will see these drugs introduced into the treatment of both advanced and early stage disease. There will be much change this year, with the screening programme plus NICE guidance due on the targeted therapies, adjuvant oxaliplatin and adjuvant capecitabine. The funding of these drugs will pose a significant economic challenge to the NHS. Although the national bowel cancer screening programme should improve outcomes for patients through early detection, it is unclear what impact the screening programme will have on the number of patients eligible to receive adjuvant treatment.

Resources

- Stoma care was discussed in a previous PJ article (2 December 2000, pp823-6)

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