Colorectal cancer: features and investigation

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Abstract

Colorectal cancer (CRC) is common, affecting >40,000 people a year in the UK. Most cancers are sporadic but a few, such as those occurring at a younger age, have a clear genetic basis. Most are situated in the rectum or rectosigmoid and cause rectal bleeding, often with a looser or more frequent stool. Right-sided cancers typically result in anaemia, because the blood in the stool is occult and unnoticed by the patient. Almost all symptoms of malignancy can also be caused by benign disease. Diagnosis relies on luminal imaging, with colonoscopy being the gold standard. Prognosis is based on the stage of disease at presentation, so screening programmes have been introduced to reduce incidence and identify earlier stage disease. Preoperative staging includes imaging of the chest, abdomen and pelvis with computed tomography (CT). For rectal cancers, magnetic resonance imaging (MRI) of the pelvis provides accurate information about the local tumour and nodal status, and is used to inform decisions regarding preoperative chemo-radiotherapy. When standard staging cannot confidently exclude metastatic disease, further investigations such as MRI of the liver or CT positron emission tomography are used. To optimise treatment, all patients with CRC should be discussed at multidisciplinary meetings.

Keywords Colonoscopy; colorectal neoplasms; colorectal surgery; mass screening; MRCP; neoplasm staging; virtual colonoscopy

Introduction

Colorectal cancer, often known simply as bowel cancer, is a common solid organ malignancy. In 2015, there were 41,804 new cases of bowel cancer in the UK, and colorectal cancer is associated with an overall mortality of approximately 43%. At all ages, colorectal (especially rectal) cancer is more common in male patients, but because of the greater longevity of women the overall sex distribution is equal. It is generally a disease of advancing years, with a peak age at diagnosis of 70 years, and a lifetime risk of 5–7%.

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Key points

- Colorectal cancer is common; most lesions are distal and may be within the reach of the examining finger or rigid sigmoidoscope
- Typical symptoms include rectal bleeding and looser or more frequent bowel movements
- Right-sided cancers are a common cause of iron deficiency anaemia
- The use of screening programmes means that more early stage cancers and polyp cancers are being diagnosed
- Faecal occult blood tests are being replaced by a more sensitive and specific quantitative faecal immunochemical test to further improve screening outcomes
- Staging of most bowel cancers is best provided by CT scans of the chest, abdomen and pelvis
- Pelvic MR scanning is essential for locally staging rectal cancers and to direct preoperative therapy

Epidemiology

Colorectal cancer is common in 'Westernized' populations, particularly with increasing age. It arises from the combined effects of hereditary predisposition, exposure to environmental agents, lifestyle and chance.

Known risk factors include red/processed meat, obesity, alcohol and smoking, a personal history of adenomatous polyps or previous colorectal cancer, and long-standing colonic inflammatory bowel disease (IBD). Increased dietary fibre, increased physical activity and aspirin are thought to protect against polyps and cancer.

Dominantly inherited strongly penetrant syndromes, such as familial adenomatous polyposis (FAP) and Lynch syndrome (formally known as hereditary non-polyposis colon cancer), are responsible for approximately 5% of colorectal cancers, often developing before the age of 40 years. Further study of patients with a phenotype suggestive of FAP but lacking a mutation in the causative *APC* gene led to the discovery of *MYH* polyposis, which is inherited in an autosomal recessive fashion.

Outside these and other known inherited conditions, there is a much greater proportion of the population who could be at increased risk of colorectal cancer as the result of weakly penetrant, but more common, susceptibility genes that are yet to be identified.

Pathology and pathogenesis

Adenoma–carcinoma sequence

Almost all colorectal cancers are adenocarcinomas arising from the mucosa. Analysis of the histological and molecular changes of colorectal polyps and malignancies has led to the adenoma

—carcinoma hypothesis. It has been shown that cancer risk increases with increased size of an adenoma, villous adenomas and increased dysplasia within the adenoma. There are three distinct molecular pathways resulting in CRC: the 'classical' or chromosomal instability pathway which most sporadic CRC follows, where large segments or whole chromosomes can be lost or duplicated; the microsatellite instability pathway, which about 15% of CRC follow whereby small changes in DNA, often at repeated nucleotide sequences (microsatellites), occurs resulting in deficient mismatch repair genes; and the serrated polyp pathway which may account for up to a third of CRCs. This most recent pathway has been identified with serrated adenocarcinomas being identified as separate entities. The precursor lesion is a serrated polyp rather than an adenoma. In this pathway hyperplastic polyps acquire genetic mutations and progress to other serrated polyps such as sessile serrated adenomas and then on to cancers via mutations in genes such as *BRAF, KRAS* and *CIMP*. They can also have associated microsatellite instability (MSI) due to tumour methylation and inactivation of *MLH1*.

These pathways have their counterparts in hereditary syndromes — FAP cancer follows the classical pathway, Lynch syndrome cancers follow the microsatellite instability pathway and serrated polyposis syndrome follows the serrated polyposis pathway. Detailed genetic analysis of individual tumours is now being used more routinely and helps to predict tumour behaviour and response to therapy, and guide adjuvant therapy.

Distribution

About two-thirds of sporadic cancers arise distal to the splenic flexure, with about 40% of all CRCs arising in the rectum. In patients with Lynch syndrome, this proportion is reversed, with the caecum being the most common site.

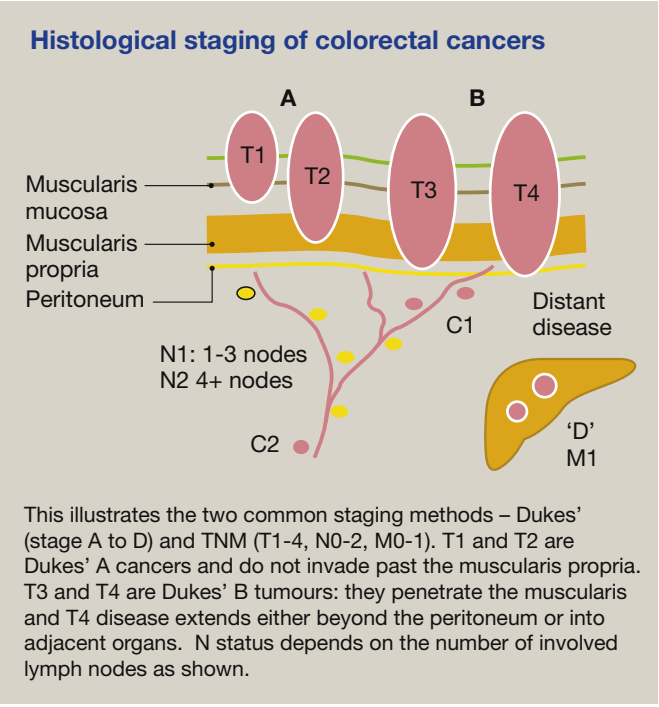
Spread

Like many cancers, colorectal carcinoma spreads locally, via lymphatics and through the bloodstream. The liver is the most common site for metastases, via the portal venous system, followed by pulmonary spread. Less common sites for metastases include the skin, brain and bone. Transcoelomic spread leads to the development of multiple peritoneal nodules, although ascites is usually minimal.

Pathological staging

Histological staging of colorectal cancers is performed postoperatively. TNM (tumour, node, metastasis) staging is the preferred international standard and has largely superseded the Dukes' classification for communicating the pathological extent of disease (Figure 1).

TNM staging: in 2018, the updated 8th edition of the American Joint Committee on Cancer colorectal cancer staging guidelines were brought into clinical practice.[1] These give precise information regarding individual tumour stage, allowing decisions to be made with regard to preoperative or adjuvant therapy and groups to be compared within clinical trials. This update includes changes in each of the stages of TNM. T4 has now been divided into T4a (if the peritoneum is breached) and T4b (if another organ, including the retroperitoneum, is invaded), N1 and N2 are subclassified based on the number of lymph node metastases.



This illustrates the two common staging methods – Dukes' (stage A to D) and TNM (T1-4, N0-2, M0-1). T1 and T2 are Dukes' A cancers and do not invade past the muscularis propria. T3 and T4 are Dukes' B tumours: they penetrate the muscularis and T4 disease extends either beyond the peritoneum or into adjacent organs. N status depends on the number of involved lymph nodes as shown.

Figure 1

Metastatic disease M1 is subclassified based on the number of sites involved and/or spread to the peritoneum.

Dukes' staging: node-negative tumours are staged A if they have not penetrated the muscularis propria, and B if they have. If there is lymph node spread, the tumour is automatically classified as Dukes' C. A C2 tumour is one in which there is lymphatic invasion at the node furthest away from the tumour — at the 'high tie'. Although not described by Dukes, it is now conventional to label any metastatic spread as stage D.

Circumferential margin: for surgery to be potentially curative, especially for rectal cancers, it is important to remove a margin of normal tissue around a cancer. Measurement of whether the circumferential resection margin is involved with cancer can be a very useful predictor of local and even distant recurrence.

Clinical features

Presentation

Gastrointestinal symptoms are common, even in the absence of pathology, and those produced by malignant and benign causes overlap widely. Given the frequency with which gastrointestinal symptoms are encountered, the National Institute for Health and Care Excellence (NICE) has developed guidelines to aid clinicians in deciding which patients require urgent referral for investigations to diagnose or exclude colorectal cancer (Table 1)[2]; however, only about 3% of patients meeting such criteria harbour a malignancy.

Obstructive symptoms — as tumours enlarge, they tend to narrow the bowel lumen. This commonly leads to a looser and more frequent stool rather than constipation, although any persistent change in bowel habit should be investigated. Distal tumours are more likely than proximal ones to lead to an

NICE guidelines for referral of suspected lower gastrointestinal cancer

- Aged ≥40 years with unexplained weight loss and abdominal pain
- Aged ≥50 with unexplained rectal bleeding
- Aged ≥60 with iron deficiency anaemia/changes in bowel habit or tests showing occult blood in the faeces

Consider referral for:

- Any adult with a palpable rectal or abdominal mass
- Any adult aged <50 years with rectal bleeding and any of the following:
  - Abdominal pain
  - Change in bowel habit
  - Weight loss
  - Iron deficiency anaemia

It is recommended that quantitative faecal immunochemical tests should be performed for patients without rectal bleeding but with unexplained symptoms that do not otherwise meet the criteria for a suspected cancer pathway referral

Table 1

alteration in bowel habit, as the stool consistency is more solid. Proximal tumours may produce no symptoms at all until they produce complete obstruction. In the rectum, the mass effect of a cancer leads to tenesmus (a feeling of incomplete evacuation).

Bleeding – rectal bleeding, especially if associated with a change in bowel habit, is a worrying symptom. Low rectal tumours can bleed bright blood just like haemorrhoids; bleeding from left-sided tumours can be darker red and mixed in with the stool. Although right-sided tumours bleed, this is generally not visible in the stools, so these cancers classically present with iron deficiency anaemia.

Acute presentation – about 20% of patients with colorectal cancer present as emergencies, usually with gastrointestinal obstruction but occasionally with perforation and/or abscess formation. Most require emergency surgery.

Palpable mass – many colorectal cancers are palpable. Typically, a right colon cancer gives rise to a firm mass in the right iliac fossa. Rectal cancers can often be felt on digital examination, and a rolled edge or circumferential nature can easily be appreciated. If a tumour is found, the surgeon will be greatly helped by information about the height of tumour from the anal verge, whether it is mobile, tethered or fixed, and which quadrants are involved.

Differential diagnosis

There is a wide differential diagnosis for CRC. Alteration in bowel habit can be caused by (among others) irritable bowel syndrome, diverticular disease, infections, thyroid dysfunction, coeliac disease or IBD. Rectal bleeding can be caused by haemorrhoids, anal fissure, IBD or polyps. Iron deficiency anaemia can arise from gastric or small bowel pathology, poor diet, coeliac disease or bleeding from other organ systems (e.g. renal or genital tract).

Detection by population screening

A number of randomized control trials have shown a reduction in colorectal cancer mortality with screening. Asymptomatic patients in the UK are currently offered screening from age 60 years with biannual guaiac faecal occult blood testing (gFOBT), followed by colonoscopy if occult blood is detected. gFOBT lacks specificity and can be affected by dietary factors. As a result, faecal immunochemical testing (FIT) specific to the globin moiety of human haemoglobin has been developed. This is cost-effective and has higher patient acceptability.[3]

FIT is shortly to be incorporated into screening across the UK. Flexible sigmoidoscopy screening is also currently performed as a one-off screening test for patients aged 55 years; this is, however, to be phased out and replaced by FIT and colonoscopic screening commencing at an earlier age. With the adoption of screening, a greater number of early-stage and polyp cancers are being diagnosed. Many of these are cured by polypectomy alone. Use of other staging methods that take into account the depth of invasion, such as the Haggitt and Kikuchi classifications, along with tumour grade and presence of lymphovascular invasion, is helpful in judging the risk of lymph node metastasis and whether formal resection is indicated.

Investigations

Diagnosis

Biochemical tests: no blood test will confirm or refute the diagnosis of colorectal cancer. A full blood count is useful to detect anaemia, and a low ferritin concentration confirms whether this is the result of chronic blood loss. Although carcinoembryonic antigen is commonly assayed, it is more valuable in follow-up than in diagnosis.

Sigmoidoscopy: a rigid sigmoidoscope can examine most of the rectum and sometimes the distal sigmoid, so it can easily be used in the outpatient clinic to identify rectal tumours. It can also reveal bleeding and inflamed mucosa from IBD as an alternative explanation of the patient's symptoms. Streaks of blood in the lumen of the rectum are strongly indicative of pathology in the sigmoid above the reach of the rigid scope – usually a large polyp or cancer.

Colonoscopy: this is the gold standard investigation for colorectal cancer and polyps. Completion rates should be >90%, with a perforation rate <0.1%. Colonoscopy can identify cancers and allow biopsies to be taken. It also has therapeutic potential for removing polyps distant from the cancer to prevent metachronous malignancy developing during follow-up. Endoscopically placed tattoos allow the site of a tumour to be recognized at subsequent laparoscopic resection (Figure 2). Even if a rectal cancer is diagnosed in the clinic, luminal imaging is still required to rule out synchronous disease, which is present in around 2% of patients.

Computed tomography (CT): particularly for elderly patients, CT of the abdomen and pelvis is a useful diagnostic tool and is non-invasive. Spasm on the right side of the colon occasionally mimics the appearances of cancer on CT. In this instance, a colonoscopy is required to visualize the right colon and corroborate the CT findings.

CT colonography: because of multislice volume acquisition techniques, CT is being more widely used. Excellent luminal

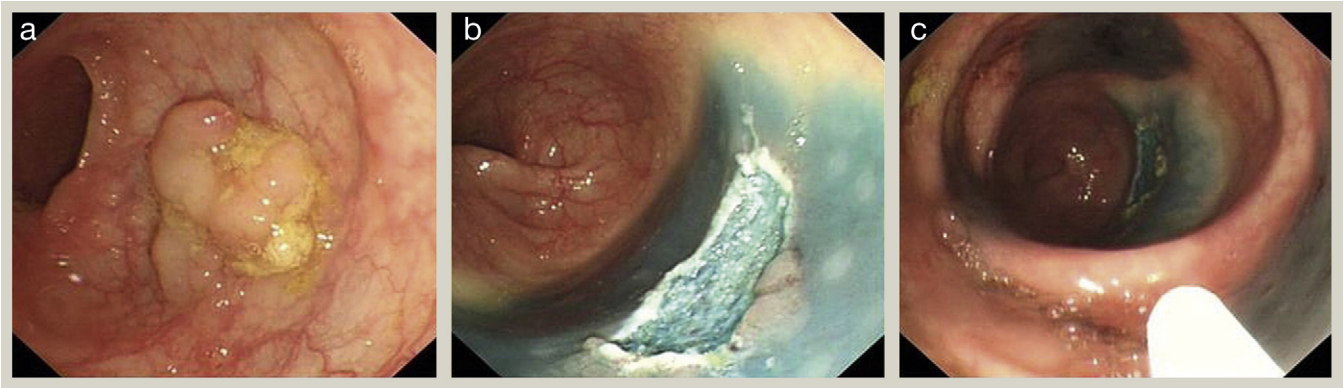


Figure 2 (**a**, **b**) This polyp in the descending colon was removed by endoscopic mucosal excision after raising it off the muscularis propria by injecting gelofusine and methylene blue in the submucosal plane. (**c**) The site of the polyp was marked with black tattoo ink either side of the polyp. Histological analysis revealed it to be a malignant polyp, and the patient subsequently underwent a laparoscopic colectomy; the tattoo was essential for the surgeon to know exactly which part of the colon to remove.

views can be obtained by insufflating air into a prepared colon. CT colonography is almost as accurate as colonoscopy and can visualize bowel proximal to an obstructing tumour. A recent randomized control trial has shown similar sensitivity between colonoscopy and CT colonography in detecting cancers and polyps >10 mm in diameter. Although any pathology found needs direct luminal imaging, the great majority of tests will be negative, and a more invasive test will be avoided.

Biopsy: all rectal cancers require biopsy proof of malignancy before treatment is decided. This is also important for colonic cancers, but if biopsies show an adenomatous lesion which has the endoscopic appearances of an invasive cancer or is not amenable to endoscopic resection, then it is reasonable to proceed to surgical resection without subjecting the patient to repeated colonoscopy.

Preoperative clinical staging

Once a colorectal cancer has been diagnosed, clinical staging investigations should be performed to detect synchronous polyps and cancer, local spread and metastatic disease. CT of the chest, abdomen and pelvis is used for all patients to detect distant spread. Rectal cancers should be discussed at a multidisciplinary meeting before surgery; all tumours are discussed postoperatively.

Magnetic resonance imaging (MRI) of the liver: Benign incidental lesions in the liver are a common finding throughout the general population. These lesions are, however, often incompletely characterized by single-phase portal venous CT performed for staging. To fully characterize these lesions and distinguish them from liver metastases, MRI of the liver is frequently required and is very sensitive and specific investigation for this purpose.

CT positron emission tomography (CT-PET) is a nuclear medicine functional imaging technique. When assessing for colorectal metastases, it uses radio-labelled fluorodeoxyglucose, a

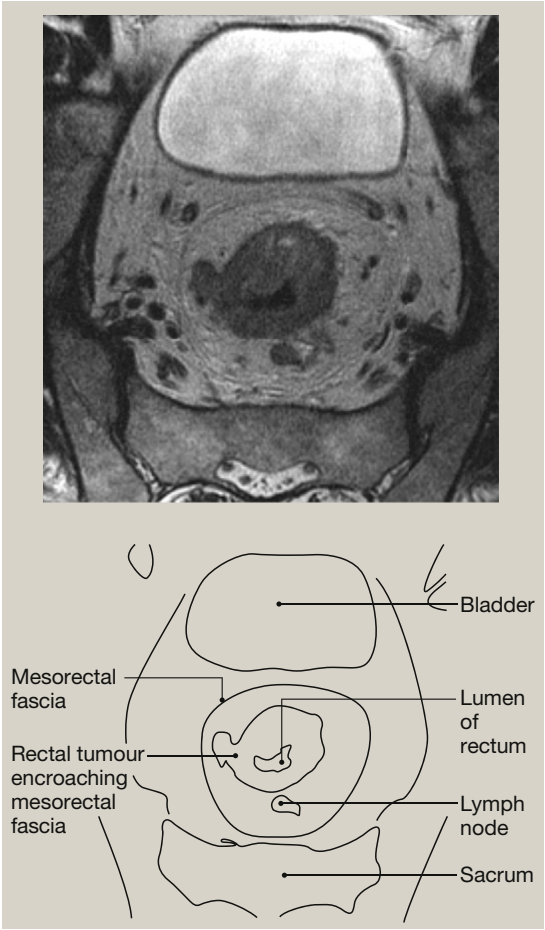


Figure 3 MRI scan of a locally advanced rectal cancer. This transverse section clearly demonstrates the mesorectal fascial envelope, which is the boundary of surgical excision. The tumour is extending through the full thickness of the bowel wall and is very close to the edge of the mesorectum. One of many enlarged lymph nodes is shown on this image. This patient was given preoperative chemo-radiotherapy to down-stage the tumour and then underwent a potentially curative resection of his rectal carcinoma.

glucose analogue. Tissues with higher metabolic activity (e.g. most types of colorectal cancer) use more fluorodeoxyglucose and this therefore concentrates in these tissues, creating 'hot-spots' on the scan. CT-PET is not a routine staging investigation for colorectal cancer but can change surgical and oncology decision-making in up to 30% of cases where standard imaging produces equivocal findings. CT-PET also has a role in the assessment of patients with locally advanced colorectal cancer who are being considered for extended or exenterative resections that are generally precluded by the presence of distant disease.

Rectal cancer: the extent of local spread determines preoperative therapy so pelvic imaging is very important. Transrectal ultrasound can accurately stage bowel wall invasion but is less accurate at detecting lymph node involvement. MRI is probably the most useful method for determining tumour invasion and nodal status (Figure 3). More importantly, it is the best way of assessing whether the tumour is close to the edge of the mesorectal envelope[4]; this has implications for the surgeon and informs decisions regarding preoperative chemo-radiotherapy[5] (see Colorectal cancer: management on pages 405–409 of this issue). ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 54-year-old man presented with a 3-month history of intermittent bright red rectal bleeding. He had no tenesmus, change in bowel habit, weight loss or abdominal pain.
Abdominal examination and digital rectal examination were unremarkable.

What is the next most appropriate course of action?

A. Treat empirically for haemorrhoids and review in 4 weeks
B. Perform a faecal immunochemical test
C. Refer for urgent assessment to exclude colorectal cancer
D. Perform rigid sigmoidoscopy and reassure him if haemorrhoids are identified
E. Check carcinoembryonic antigen concentrations

Question 2

A 65-year-old man presented with tiredness and breathlessness on exertion. He had no other complaints. There was no significant past medical or family history, and he was taking no prescribed or over-the-counter medication.
On clinical examination, he looked pale but there were no other abnormalities.

Investigations

- Haemoglobin 84 g/litre (130–180)
- Mean cell volume 72 femtolitres (80–96)

What is the most important investigation to carry out next?

A Serum iron and total iron-binding capacity
B Faecal immunochemical test
C Colonoscopy
D Flexible sigmoidoscopy
E CT scan of the abdomen

Question 3

A 76-year-old woman presented with a 2-month history of intermittent blood in her stools. She had no other symptoms. She had a past history of episodes of collapse associated with a ventricular tachycardia and had had a defibrillator implanted. Colonoscopy showed a carcinoma in the rectum.

What investigation is most appropriate to determine if the tumour is amenable to local rather than radical resection?

A. CT positron emission tomography (PET) scan
B. Transrectal ultrasound
C. CT scan of the chest, abdomen and pelvis
D. MR scan of the pelvis
E. Full blood count