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Improving detection of colorectal cancer

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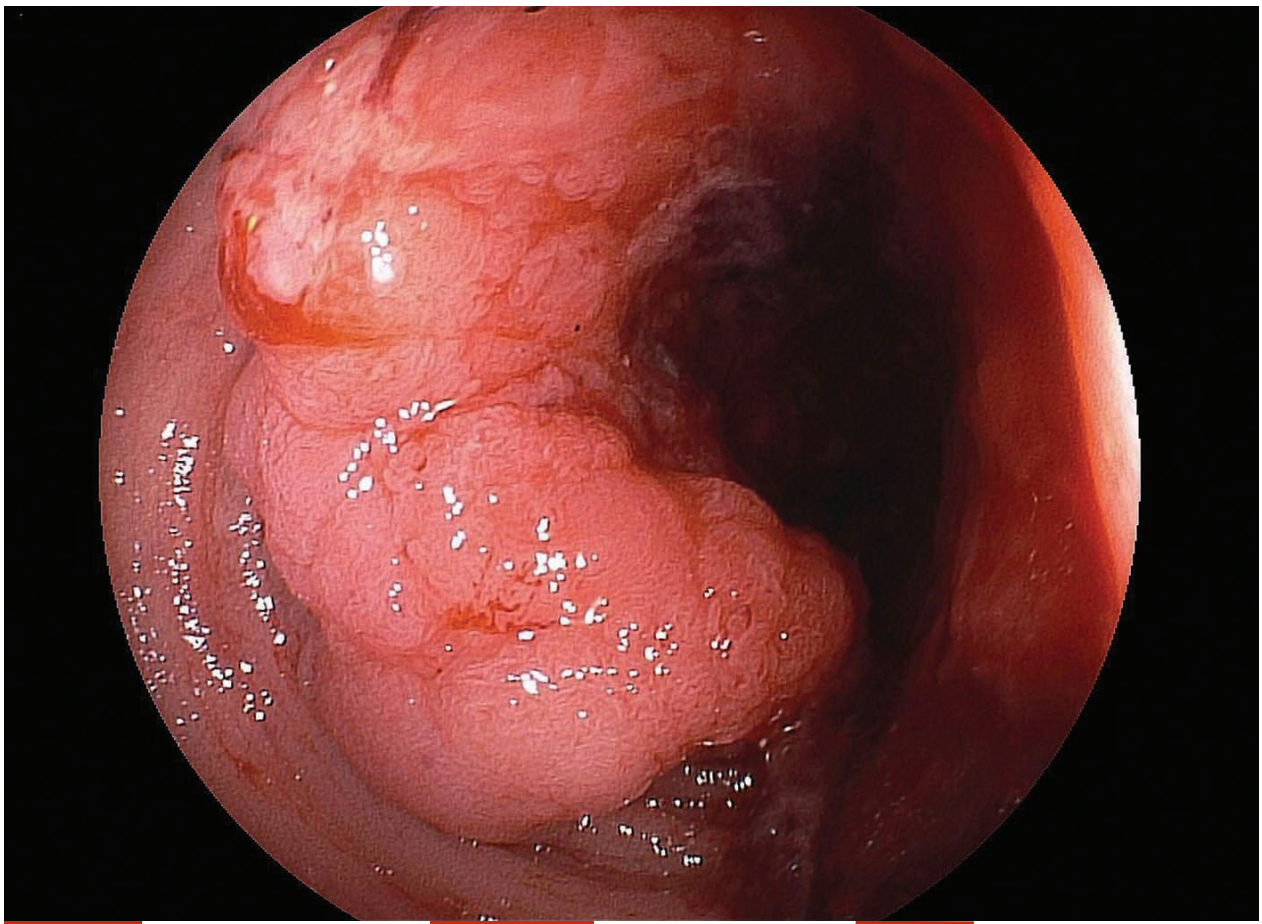

What are the risk factors for colorectal cancer?

COLORECTAL CANCER IS THE THIRD MOST COMMON CANCER IN THE UK, WITH AN ANNUAL incidence of 36,100 in England and Wales. It is also the second leading cause of death from cancer in the UK.[1] However, there has been a significant increase in five-year survival over the past decade, from 22% to 50% despite more than 55% of patients presenting with lymph node or distant metastases.[1]

Guidelines published by the Department of Health[2] and subsequently by NICE[3] have set down criteria for the urgent referral of patients with clinical features suggestive of colorectal cancer. Analysis of this referral system, however, shows that it lacks sensitivity for detecting cancers (only 10.3% of referrals are ultimately found to have cancer) and that it fails to identify those with earlier, more treatable disease.[4] Nevertheless, it is important to remember that the clinical features included within the guidelines have been selected because of their strong association with the disease.

Which patients should be referred?

How should patients be investigated?

RISK FACTORS

Around 80% of colorectal cancer is sporadic i.e. caused by the interaction of genetic and environmental factors via the adenoma-carcinoma sequence and cancer may take up to ten years to develop in this way.[5] Adenomas are more common with age and one in four of the population aged over 50 will develop one or more polyps, with 10% of these polyps progressing to cancer over time.[6,7] »

Table 1

General recommendations for referral[3]

Patients presenting with symptoms suggestive of colorectal or anal cancer should be referred to a team specialising in the management of lower GI cancer
In patients with equivocal symptoms who are not unduly anxious, it is reasonable to 'treat, watch and wait'
In patients with unexplained lower GI symptoms, a digital rectal examination should be performed
Only patients with new and persistent symptoms, listed in table 2, right, should be referred via the fast track (two-week rule) system

Table 2

Specific recommendations for referral[3]

Urgent referral should be made in the following cases:

- Age ≥40 years, with rectal bleeding, and a change in bowel habit to looser stools and/or increased stool frequency persisting for ≥6 weeks
- Age ≥60 years, with rectal bleeding persisting for ≥6 weeks without a change in bowel habit and no anal symptoms
- Age ≥60 years, with a change in bowel habit to looser stools and/or more frequent stools persisting for ≥6 weeks without rectal bleeding
- Right lower abdominal mass consistent with involvement of the large bowel, irrespective of age
- Palpable rectal mass (intraluminal and not pelvic), irrespective of age. (A pelvic mass outside the bowel should be urgently referred to a urologist or gynaecologist.)
- Men of any age with *unexplained iron deficiency anaemia and haemoglobin of ≤11 g/100 ml
- Non-menstruating women with *unexplained iron deficiency anaemia and haemoglobin of ≤10 g/100 ml

* Unexplained means a patient whose anaemia is considered on the basis of a history and examination in primary care not to be related to other sources of blood loss (e.g. NSAID treatment or blood dyscrasia)

Risk factors implicated in the development of sporadic colorectal cancer include:

- age over 60
- K-ras and p53 mutations[8]
- diet high in saturated animal fat[9] and low in fibre[10] and vegetables[11]
- lack of exercise
- obesity[12]
- excessive alcohol intake[13]

With adjustments to lifestyle the majority of colorectal cancer may therefore be avoided.

Inflammatory bowel disease, both Crohn's disease and ulcerative colitis, is a risk factor for development of colorectal cancer through the association of chronic inflammation with development of malignancy. The risk rises with the duration of disease from the time of diagnosis (2% after 10 years and 18% after 30 years,[14] and the intervals for surveillance colonoscopy decrease accordingly.

Around 20% of colorectal cancer cases are familial (two or more first-degree relatives affected) and people with this family history have a two- to three-fold risk of developing the disease.[15] True hereditary syndromes include:

- the Lynch syndrome (hereditary non-polyposis colorectal cancer)
- familial adenomatous polyposis (FAP)
- MYH-associated polyposis.

Familial cases of syndrome-type cancer account for approximately 6% of cases.[15] In a primary care setting taking a family history may determine those with a higher than average risk who may need onward referral.

CLINICAL PRESENTATION

A large proportion of patients with rectal or sigmoid cancers present with a combination of rectal bleeding and a change in bowel habit (usually an increased frequency of defecation and/or looser stools). Fewer patients will present with only one of these symptoms.[16, 17] Rectal bleeding in the absence of anal symptoms occurs in over 60% of those with cancer,[18] and a palpable rectal mass, with or without tenesmus, is present in 40-80% of those with rectal cancer.[17, 19]

Patients with more proximal tumours are more likely to present as emergencies with bowel obstruction, symptomatic iron deficiency anaemia or an abdominal mass.[16, 17]

REFERRAL

NICE has produced guidance for primary care referral including general recommendations (see table 1, above left) and specific recommendations for high-risk patients (see table 2, above).[3]

Screened patients without symptoms are found with cancer and therefore the risk of bowel cancer in asymptomatic patients is not zero. Some patients will have cancer found incidentally on testing for symptomatic benign conditions and it can develop in those with functional problems or piles.

The Association of Coloproctologists of Great Britain and Ireland (ACGBI) recommends routine referral to a specialist for those with persistent low-risk symptoms or for those with

FIGURE 2
The distribution of colorectal cancer

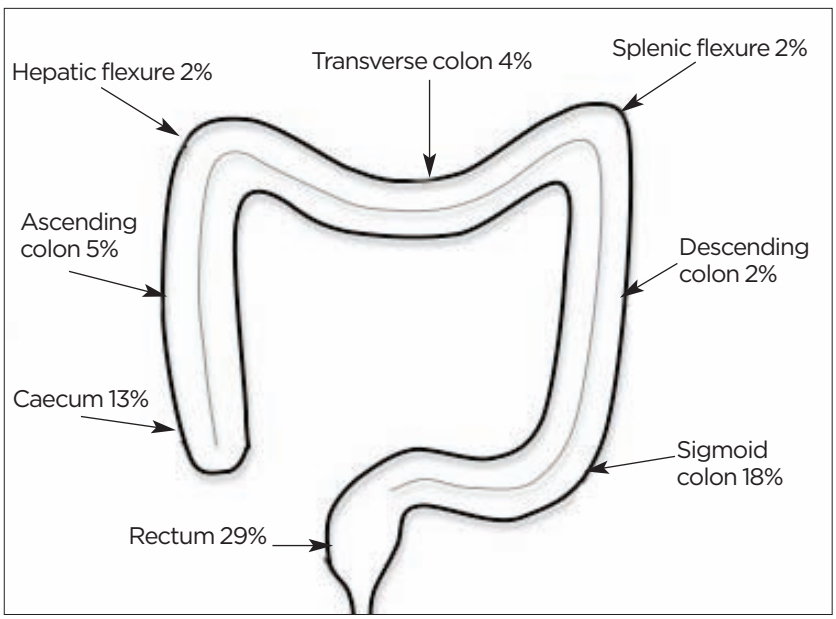

Table 3

Low-risk symptoms
Rectal bleeding with anal symptoms or with an obvious external visible cause such as prolapsed piles, rectal prolapse and anal fissures
Transient change in bowel habit < 6 weeks, particularly if decreased frequency of defecation and harder stools
Abdominal pain without iron deficiency anaemia or an easily palpable abdominal mass, and not associated with loss of appetite causing weight loss or other higher-risk symptoms

Table 4

Dukes staging for colorectal cancer

Dukes stage	Histology	Prognosis (5 year survival)
A	Muscularis propria not breached	90%
B	Breached muscularis propria	70%
C1	Positive mesenteric lymph node(s) (apical node negative)	60%
C2	Positive mesenteric lymph node(s) (apical node positive)	35%
D	Distant metastases	5%

symptoms resistant to treatment.[20] The criteria indicating a low risk of colorectal cancer are listed in table 3, above. However, these features in combination with a positive family history or positive faecal occult blood test (FOBT) warrant an urgent referral.

Isolated normocytic anaemia without abdominal or bowel symptoms is not normally a criterion for referral to a colorectal clinic. However, if no other cause for the anaemia is obvious, a serum ferritin and/or FOBT may be useful and if results are abnormal, a specialist referral would be appropriate.

Carcinoembryonic antigen (CEA) is a serum tumour marker used to monitor patients already treated for colorectal cancer for signs of recurrence or for response to treatment in those patients undergoing chemotherapy. It is not useful as a diagnostic investigation and the practice of requesting CEA in this context should be discouraged.

Table 5

TNM staging for colorectal cancer

T categories for colorectal cancer

T categories describe the depth of invasion through the layers of the bowel wall

Tx No description of the tumour's extent is possible because of incomplete information
Tis The cancer is in the earliest stage (in situ). It involves only the mucosa. It has not grown beyond the muscularis mucosa (inner muscle layer)
T1 The cancer has grown through the muscularis mucosa and extends into the submucosa
T2 The cancer has grown through the submucosa and extends into the muscularis propria (thick outer muscle layer)
T3 The cancer has grown through the muscularis propria and into the outermost layers of the colon or rectum but not through them. It has not reached any nearby organs or tissues
T4a The cancer has grown through the serosa (also known as the visceral peritoneum), the outermost lining of the intestines
T4b The cancer has grown through the wall of the colon or rectum and is attached to or invades nearby tissues or organs

N categories for colorectal cancer

N categories indicate whether or not the cancer has spread to nearby lymph nodes and, if so, how many lymph nodes are involved. To get an accurate idea about lymph node involvement, most specialists recommend that at least 12 lymph nodes be removed during surgery and looked at under a microscope

Nx No description of lymph node involvement is possible because of incomplete information
N0 No cancer in nearby lymph nodes
N1a Cancer cells are found in 1 nearby lymph node
N1b Cancer cells are found in 2 to 3 nearby lymph nodes
N1c Small deposits of cancer cells are found in areas of fat near lymph nodes, but not in the lymph nodes themselves
N2a Cancer cells are found in 4 to 6 nearby lymph nodes
N2b Cancer cells are found in 7 or more nearby lymph nodes

M categories for colorectal cancer

M categories indicate whether or not the cancer has metastasised to distant organs, such as the liver, lungs, or distant lymph nodes

M0 No distant spread is seen
M1a The cancer has spread to 1 distant organ or set of distant lymph nodes
M1b The cancer has spread to more than 1 distant organ or set of distant lymph nodes, or it has spread to distant parts of the peritoneum

INVESTIGATIONS

Specialist investigations following referral will depend on symptoms. A full history and examination with per rectal examination and usually sigmoidoscopy and proctoscopy will be performed in clinic.

The majority of cancers presenting with rectal bleeding and/or a change in bowel habit, without other diagnostic features will be found within 60 cm of the anal verge and these may be diagnosed at flexible sigmoidoscopy. Figure 2, opposite, shows the distribution of colorectal cancer.

The majority of those patients with a suspicion of colorectal cancer will, however, undergo full colorectal visualisation, most commonly with colonoscopy. Barium enema (in conjunction with sigmoidoscopy) or CT colonography may be used in place of colonoscopy.

If a tumour is diagnosed on flexible sigmoidoscopy complete full large bowel investigation will be undertaken to eliminate the presence of synchronous tumours (or within 6 months postoperatively for an endoscopically impassable tumour or one resected as an emergency). The quoted risks for colonoscopy include significant bleeding (1:500) and perforation (1:1,000).

STAGING

Preoperative staging is essential to determine both the local and distant status of the disease. Subsequent treatment (neo-adjuvant, adjuvant, surgical and palliative) can be planned following this. Staging investigations consist of CT chest, abdomen and pelvis with MRI for rectal cancers. Endorectal ultrasound may be performed for early rectal tumours, when local excision is planned. The most common staging systems for colorectal cancer are the Dukes and TNM systems (see table 4, above and table 5, left). »

key points

SELECTED BY
Dr Peter Saul
GP, Wrexham and associate GP Dean for North Wales

Colorectal cancer is the third most common cancer in the UK with an annual incidence of 36,100 in England and Wales. It is also the second leading cause of death from cancer in the UK. Guidelines published by NICE have set down criteria for the urgent referral of patients with clinical features suggestive of colorectal cancer. Around 80% of colorectal cancer is sporadic caused by the interaction of genetic and environmental factors via the adenoma-carcinoma sequence. Adenomas are more common with age and one in four of the population aged over 50 will develop one or more polyps.

Risk factors for colorectal cancer include: age over 60; K-ras and p53 mutations; a diet high in saturated animal fat, low in fibre and vegetables; lack of exercise; obesity and excessive alcohol intake. Inflammatory bowel disease is a risk factor for development of colorectal cancer through the association of chronic inflammation and development of malignancy. Around 20% of colorectal cancer cases are familial and in a primary care setting taking a family history may determine those with a higher than average risk who may need onward referral.

A large proportion of patients with rectal or sigmoid cancers present with a combination of rectal bleeding and a change in bowel habit (usually an increased frequency of defecation and/or looser stools). Rectal bleeding in the absence of anal symptoms occurs in over 60% of those with cancer, and a palpable rectal mass with or without tenesmus is present in 40-80% of those with rectal cancer. The majority of those patients with a suspicion of colorectal cancer will undergo full colorectal visualisation, most commonly with colonoscopy. If a tumour is diagnosed on flexible sigmoidoscopy complete full large bowel investigation will be undertaken.

Preoperative staging is essential to determine both the local and distant status of the disease. All patients with colorectal cancer should be managed by a specialist multidisciplinary team. Resection, either laparoscopic or open, should be performed by specialist surgeons. Certain patients with rectal cancer may be selected for neo-adjuvant (preoperative) radiotherapy. This form of treatment has been shown to reduce local recurrence rates, although no survival benefit has been demonstrated. Advances in chemotherapy have resulted in improved survival for colorectal cancer over the past few years. Postoperative radiotherapy is used but not commonly and also reduces local recurrence but to a lesser degree and also with no survival benefit. Patients with liver or lung metastases may be considered for resection irrespective of age.

TREATMENT

All patients with colorectal cancer should be managed by a specialist multidisciplinary team and have access to a colorectal nurse specialist.

Surgery

Resection, either laparoscopic or open, should be performed by specialist surgeons as it has been shown that outcomes are better under the care of surgeons who have been through a specialised training programme[21] or who have a high degree of specialisation.[22]

Laparoscopic surgery is becoming more widespread and the patient has the right to be offered a laparoscopic resection either locally or elsewhere.

Neo-adjuvant therapy for rectal cancer

Following discussion with the multidisciplinary team, certain patients with rectal cancer may be selected for neo-adjuvant (preoperative) radiotherapy. This will be decided on fixity within the pelvis (on per rectal examination); distance of tumour to the outer mesorectal fascia and presence of nodes within the mesorectum or the pelvis as demonstrated on staging MRI scanning.

This form of treatment has been shown to reduce local recurrence rates, although no survival benefit has been demonstrated.[23]

Neoadjuvant chemoradiation may be offered to those with non-metastatic but irresectable disease with a view to downstaging the tumour prior to curative resection or to palliate patients with incurable disease.

Adjuvant treatment

Advances in chemotherapy have resulted in improved survival for colorectal cancer over the past few years. Overall five-year survival for patients with node positive disease (Dukes C) has increased from 51% to 64% for patients undergoing surgery with adjuvant (postoperative) chemotherapy (5-fluorouracil modulated by folinic acid) compared with surgery alone.[24]

The addition of oxaliplatin to this regimen further increases survival,[25, 26] with three-year disease-free survival improving from 72.9% to 78.2%.[25]

Chemotherapy carries a risk of morbidity, however, and its use needs to be carefully discussed with the patient and oncologist. Its benefit in Dukes B disease is less clear but it may be offered to those with features of high-risk disease (such as serosal involvement, perforated or obstructed tumours, poor differentiation and perineural or extramural vascular invasion).

Postoperative radiotherapy is used but not commonly and also reduces local recurrence but to a lesser degree and also with no survival benefit.[27] Because of its limited benefit and side-effects it is only recommended in cases of incomplete surgical resection.[20]

RESECTABLE METASTATIC DISEASE

Patients with liver or lung metastases may be considered for resection irrespective of age. These patients will be staged with CT scan for chest disease and MRI for liver metastases and discussed at dedicated hepatobiliary or thoracic multidisciplinary team meetings. The five-year survival following resection of liver metastases is approximately 33%.[28, 29]

FOLLOW-UP

The ACGBI recommends CT chest, abdomen and pelvis for fit, asymptomatic patients within two years following resection, to screen for resectable metastases. Colonoscopy should be performed at five-yearly intervals.[20] Local protocols for colorectal cancer follow-up may vary slightly.

SCREENING

Eight out of ten people affected by colorectal cancer are over 60. The lifetime risk for developing colorectal cancer is 5%.[30] Screening is designed to identify and remove early cancers or polyps before malignant change and in doing so reduce the incidence of colorectal cancer and improve the survival of those with asymptomatic cancer. Screening with FOBT has been shown to reduce colorectal cancer mortality rates by 15-18%.[31]

The NHS Bowel Cancer Screening Programme (NHS BCSP) in England started in April 2006 and currently invites men and women aged 60–69 (planned to be extended to 74) to participate via submission of an FOBT every two years. Those with a positive result will be offered colonoscopy as the next investigation of choice.

In Northern Ireland, as for England, men and women aged between 60 and 69 years old are screened with FOBT every two years. In Scotland, the population aged between 50 and 74

years is screened and in Wales the screening programme sends FOBT kits to people aged between 60 and 69, but this is planned to be extended to people between the ages of 50 and 74.

The NHS BCSP is arranged around five programme hubs across England, with up to 20 local screening centres assigned to a hub. The hub sends out the FOBT to the subject in the post. It is then completed and posted back.

Those subjects with a positive test will be offered a colonoscopy, performed by an accredited colonoscopist. Twenty out of every 1,000 patients will have a positive FOBT and be offered colonoscopy. Sixteen will attend colonoscopy, with eight (50%) being normal, six (38%) being diagnosed with polyps and entering a surveillance programme and two (12.5%) will have a cancer. Incomplete colonoscopy will require completion barium enema or CT colonography.[30] A more detailed account of the background and structure of the NHS BCSP has been recently published.[30]

CONCLUSION

The challenges over the next few years, as bowel cancer rates continue to increase and the NHS rationalises funding, will be to focus first on prevention of the disease via changes to lifestyle, in which primary care physicians will be directly involved and second, to increase the proportion of the population screened. Screening will continue to target the removal of potentially malignant polyps and to detect tumours at an earlier stage, which will yield benefits both in terms of patient survival and quality of life and consequently reduce the requirements for costly adjuvant and palliative treatments.

In light of recent work assessing the benefits of bowel cancer screening via flexible sigmoidoscopy and the interest shown in this by the Department of Health, the method by which screening occurs may change in the future.[32]

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