Patient

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Colorectal cancer

Most colorectal cancers are adenocarcinomas that evolve from polyps, which may be present for ten years or more before malignancy develops. Colorectal cancer is locally invasive but metastatic spread may be evident before local growth produces symptoms. The most common site for metastatic spread is the liver. Other sites (eg, the lungs, brain and bone) are unusual in the absence of liver metastases.

Important information
Early diagnosis is essential for effective treatment to provide the greatest chance of survival. See the separate Screening for the Early Detection of Colorectal Cancer article.

Epidemiology[1]

In the UK:

- Bowel cancer is the fourth most common cancer in the UK (after breast, prostate and lung cancer), accounting for 11% of all new cancer cases.
- Incidence rates for bowel cancer in the UK are highest in people aged 85 to 89.
- Each year more than 4 in 10 (44%) of all new bowel cancer cases in the UK are diagnosed in people aged 75 and over.
- The most common site is the rectum (32% men, 23% female).
- Over half of bowel cancer cases are diagnosed at a late stage.
- Bowel cancer is more common in White people than in Asian or Black people.

Risk factors[2]

- Family history of colorectal neoplasia: carcinoma; adenoma under the age of 60 years.[3]
- Past history of colorectal neoplasm: carcinoma, adenoma.
- Inflammatory bowel disease: ulcerative colitis, Crohn's colitis.
- Polyposis syndromes: familial adenomatous polyposis (Gardner's syndrome), Turcot's syndrome, attenuated adenomatous polyposis coli, flat adenoma syndrome, hamartomatous polyposis syndromes (Peutz-Jeghers syndrome, juvenile polyposis syndrome, Cowden's syndrome).
- Hereditary non-polyposis colorectal cancer (HNPCC).
- Hormonal factors: nulliparity, late age at first pregnancy, early menopause.
- Diet: rich in meat and fat; poor in fibre, folate and calcium.
- Sedentary lifestyle, obesity, smoking, high alcohol intake.
- Diabetes mellitus.
- Previous irradiation, occupational hazards - eg, asbestos exposure.
- History of small bowel cancer, endometrial cancer, breast cancer or ovarian cancer.

Presentation

- The presentation depends on the site of the cancer:
    - Right colon cancers: weight loss, anaemia, occult bleeding, mass in right iliac fossa, disease more likely to be advanced at presentation.
    - Left colon cancers: often colicky pain, rectal bleeding, bowel obstruction, tenesmus, mass in left iliac fossa, early change in bowel habit, less advanced disease at presentation.
- The most common presenting symptoms and signs of cancer or large polyps are rectal bleeding, persisting change in bowel habit and anaemia.

- All patients with symptoms suspicious of colorectal cancer must have a thorough abdominal examination and rectal examination.
- In some patients, symptoms do not become apparent until the cancer is far advanced.
- Jaundice and hepatomegaly indicate advanced disease with extensive liver metastases. Peritoneal metastases with ascites are often also present. 20-25% of patients have clinically detectable liver metastases at the time of the initial diagnosis and a further 40-50% of patients develop liver metastases within three years of primary surgery.
- Rarer clinical signs include: pneumaturia, gastrocolic fistula, ischiorectal or perineal abscesses, deep vein thrombosis.

Differential diagnosis

- Diverticular disease.
- Irritable bowel syndrome.
- Inflammatory bowel disease - eg, Crohn's disease, ulcerative colitis.
- Local rectal pathology - eg, haemorrhoids.
- Anal cancer.
- Ischaemic colitis.
- Pneumatosis coli.

Investigations[4] [5]

Initial investigations include blood tests, particularly for full blood count and liver function.

Editor's note

Dr Krishna Vakharia, 12th September 2023

Suspected cancer: recognition and referral

The National Institute for Health and Care Excellence (NICE) has updated its guidance [6] to use faecal immunochemical testing (FIT) to guide referral for suspected colorectal cancer in all adults with:

An abdominal mass, or

A change in bowel habit, or

Iron-deficiency anaemia, or

Aged 40 and over with unexplained weight loss and abdominal pain, or

Aged under 50 with rectal bleeding and either unexplained abdominal pain or weight loss, or

Aged 50 and over with unexplained rectal bleeding, abdominal pain or weight loss, or

Aged 60 and over with anaemia even in the absence of iron deficiency.

Furthermore, FIT should be offered even if there has been a previous negative FIT result through the NHS bowel screening programme.

People with a rectal mass, an unexplained anal mass or unexplained anal ulceration **do not** need to be offered FIT before referral is considered.

If there is a FIT result of at least 10 micrograms of haemoglobin per gram of faeces- adults should be referred for a 2 week wait, suspected colorectal cancer appointment using the local suspected cancer referral pathways.

Importantly, for those people who have not returned a faecal sample or who have a FIT result below 10 micrograms of haemoglobin per gram of faeces: Safety netting processes should be put in place.

Referral should not be delayed if there is a strong clinical concern of cancer due to unexplained symptoms.

Colonoscopy should be offered to patients without major comorbidity to confirm the diagnosis of colorectal cancer. If a lesion suspicious of cancer is detected, a biopsy sample should be sent for histology. Flexible sigmoidoscopy, then barium enema, can be used as an alternative to colonoscopy but an audit suggests these are much less effective and should be reserved as second-line for patients with major comorbidity. [7]

Computerised tomographic (CT) colonography can also be used as an alternative if the local radiology service can demonstrate competency in this technique. If a lesion suspicious of cancer is detected on CT colonography, a colonoscopy with biopsy to confirm the diagnosis should be performed.

- Proctoscopy with or without sigmoidoscopy if available but don't delay referral.
- Flexible sigmoidoscope can reach deep enough into the bowel to detect about 60% of tumours.
- Colonoscopy is the gold standard for diagnosis of colorectal cancer.
- Barium enema may be used if colonoscopy fails to visualise the caecum and/or the patient is unable to tolerate the procedure.
- CT colonography is an effective, safe method for examining the colon and rectum to detect abnormalities such as polyps and cancer.[8]
- Liver ultrasound (occasionally intra-rectal ultrasound) and CT or magnetic resonance imaging (MRI) are useful in staging. MRI is more specific than CT in showing liver metastases.
- Positron emission tomography (PET) is valuable for detection of recurrent colorectal cancer but has little effect on staging of primary cancer.
- No consensus has been reached about the most sensitive method for detection of liver metastases of colorectal cancer. A meta-analysis showed that PET is the most sensitive modality and is also especially valuable for detection of extrahepatic disease. However, no randomised study has yet proved the value of PET in this setting and therefore CT and MRI remain the diagnostic standards.
- Elevated pre-treatment serum levels of carcinoembryonic antigen (CEA) have a negative prognostic significance (CEA is of no use in screening but can be helpful in predicting relapse in patients after surgery suitable for further resection).

Referral criteria [6]

Refer patients, using a suspected cancer pathway referral (to be seen within two weeks):

- Aged 40 years and over with unexplained weight loss and abdominal pain; **or**
- Aged 50 and over with unexplained rectal bleeding; **or**
- Aged 60 and over with:
    - Iron-deficiency anaemia; **or**
    - Changes in bowel habit; **or**
- Tests show occult blood in their faeces.
- Consider a suspected cancer pathway referral in adults with an abdominal or rectal mass.
- Consider a suspected cancer pathway in adults aged under 50 with rectal bleeding and any of the following unexplained symptoms or findings:
    - Abdominal pain.
    - Weight loss.
    - Change in bowel habit.
    - Iron-deficiency anaemia.

Editor's note
Dr Krishna Vakharia, 16th October 2023 **Suspected cancer: recognition and referral** [6] NICE has recommended that a person should receive a diagnosis or ruling out of cancer within 28 days of being referred urgently by their GP for suspected cancer.

Staging

Contrast-enhanced CT of the chest, abdomen and pelvis should be used to estimate the stage of disease for patients with colon cancer. MRI should be used to assess the risk of local recurrence (as determined by anticipated resection margin, tumour and lymph node staging) in all patients with rectal cancer. Endorectal ultrasound should be offered if MRI shows disease amenable to local excision or if MRI is contra-indicated.[4]

The Dukes' staging classification is as follows:

- Dukes' A - the cancer is only in the innermost lining of the bowel or slightly growing into the muscle layer.
- Dukes' B - the cancer has grown through the muscle layer of the bowel.
- Dukes' C - the cancer has spread to at least one lymph node close to the bowel.
- Dukes' D - the cancer has metastasised to other areas - eg, the liver, lungs or bones.

The Dukes system is now gradually being replaced by the tumour/node/metastases (TNM) classification:

- TX: primary cannot be assessed:
    - T0: no evidence of primary carcinoma in situ (Tis) - intraepithelial or lamina propria only.
    - T1: invades submucosa.
    - T2: invades muscularis propria.
    - T3: invades subserosa or non-peritonealised pericolic tissues.
    - T4: directly invades other tissues and/or penetrates visceral peritoneum.

- NX: regional nodes cannot be assessed:
    - N0: no regional nodes involved.
    - N1: 1-3 regional nodes involved.
    - N2: 4 or more regional nodes involved.
- MX: distant metastasis cannot be assessed:
    - M0: no distant metastasis.
    - M1: distant metastasis present (may be transcoelomic spread).

Colorectal cancer can then be staged as follows:[9]

- Stage 0: carcinoma in situ (CIS).
- Stage 1: cancer growth through the inner lining of the bowel, or into the muscle wall, but no further. There is no cancer in the lymph nodes (T1, N0, M0 or T2, N0, M0).
- Stage 2: further local spread of the cancer but no lymph nodes are affected (N0) and the cancer has not spread to another area of the body (M0):
    - Stage 2a: cancer growth into the outer covering of the bowel wall (T3, N0, M0).
    - Stage 2b: cancer growth through the outer covering of the bowel wall and into tissues or organs next to the bowel (T4).
- Stage 3: lymph node involvement:
    - Stage 3a: cancer growth into the muscle layer, and between 1 and 3 nearby lymph nodes contain cancer cells (T1, N1, M0 or T2, N1, M0).
    - Stage 3b: cancer growth into the outer lining of the bowel wall or into surrounding body tissues or organs, and between 1 and 3 nearby lymph nodes contain cancer cells (T3, N1, M0 or T4, N1, M0).
    - Stage 3c: cancer growth of any local size but has spread to 4 or more nearby lymph nodes (any T, N2, M0).

- Stage 4: cancer has spread to other parts of the body - eg, liver or lungs - (any T, any N, M1).

Grading [9]

Colorectal cancer can also be graded according to the cancer cell differentiation:

- Grade 1 (low grade): well differentiated.
- Grade 2 (moderate grade): moderately differentiated.
- Grade 3 (high grade): poorly differentiated.

Management

Editor's note

Dr Sarah Jarvis, 24th February 2022

NICE quality standard on colorectal cancer

NICE has updated its quality standard on colorectal cancer. The four quality statements are now as follows: [10]

Testing for Lynch syndrome is carried out on all adults with a new diagnosis of colorectal cancer.

Adults with early rectal cancer discuss the implications of all potential treatment options with their healthcare professional.

Adults with metastatic colorectal cancer suitable for systemic anti-cancer treatment undergo testing to identify tumours with RAS and BRAF V600E mutations.

Adults who have had potentially curative surgical treatment for non-metastatic colorectal cancer have follow-up for the first three years to detect local recurrence and distant metastases.

Surgery remains the definitive treatment for apparently localised colorectal cancer. Both radiotherapy and chemotherapy can improve survival rates after potentially curative surgery.

If colonic stents are considered for patients presenting with acute large bowel obstruction, CT of the chest, abdomen and pelvis should be offered to confirm the diagnosis of mechanical obstruction, and to determine whether the patient has metastatic disease or colonic perforation. [4]

Surgery

May be performed either to attempt cure (removing the draining lymphatic field) or to relieve symptoms:

- Right hemicolectomy: for tumours in the caecum, ascending and proximal transverse colon.
- Left hemicolectomy: if in the distal transverse colon or descending colon.
- Sigmoid colectomy: for tumours of the sigmoid colon.
- Anterior resection: if in the low sigmoid or high rectum. Anastomosis is achieved at the first operation.
- Abdomino-perineal (AP) resection: for tumours low in the rectum (less than approximately 8 cm from the anal canal). Permanent colostomy and removal of rectum and anus.
- Laparoscopic surgery has become the gold standard for surgical treatment. However, a recent meta-analysis has shown no difference in oncological outcomes of laparoscopy for treating rectal cancer. [11]
- One of the most important advances for surgery of rectal cancer has been the concept of total mesorectal excision, which reduces local recurrences and peri-operative morbidity. The transanal route seems to be comparable to the laparoscopic route although further research is needed. [12]
- Pre-operative high-dose rate brachytherapy can be used in patients with cancer in the middle or lower third of the rectum to shrink the tumour. There is evidence for short-term safety and efficacy in reducing tumour bulk. However, there is no evidence for any additional benefit when used as a boost to external beam radiotherapy. Evidence on the clinical efficacy if used without external beam radiotherapy is inadequate in quantity. [13]
- All patients with resectable liver metastases should be considered for surgical resection.

Editor's note

Dr Sarah Jarvis, 20th December 2021

Transanal total mesorectal excision for rectal cancer [14]

NICE has issued interventional procedures guidance on the above. It concludes that while evidence on the efficacy of transanal total mesorectal excision of the rectum is adequate, evidence on its safety is inconsistent. The procedure also shows the potential for major safety concerns, including damage to adjacent structures and seeding of malignancy. As such, NICE recommends this procedure should only be used in the context of research. NICE has also updated it guidance on colorectal cancer [4] to reflect this recommendation.

Radiotherapy

- Radiotherapy is an established treatment for locally advanced rectal cancer. However, it has significant adverse effects and there is a range of opinion on its risks and benefits in individual patients. [15]
- NICE recommends that radiofrequency ablation should be considered for colorectal liver metastases in patients unfit or otherwise unsuitable for hepatic resection, or in those who have previously had hepatic resection. [16]
- Selective internal radiation therapy (SIRT) for unresectable colorectal metastases in the liver can cause serious complications but these are well recognised and infrequent. NICE recommends that this procedure should only be used with special arrangements for clinical governance, consent, and audit or research for people who cannot tolerate chemotherapy or have liver metastases that are refractory to chemotherapy, and should only be used in the context of research for people who can have chemotherapy. [17]

Chemotherapy [4]

- NICE recommends that when offering multiple chemotherapy drugs to patients with advanced and metastatic colorectal cancer, one of the following sequences of chemotherapy should be considered unless contra-indicated:

    - FOLFOX (= folinic acid plus fluorouracil plus oxaliplatin) as first-line treatment, then single agent irinotecan as second-line treatment; **or**
    - FOLFOX as first-line treatment, then FOLFIRI (= folinic acid plus fluorouracil plus irinotecan) as second-line treatment; **or**
    - XELOX (= capecitabine plus oxaliplatin) as first-line treatment, then FOLFIRI as second-line treatment.
    - Raltitrexed should only be considered for patients with advanced colorectal cancer who are intolerant to 5-fluorouracil and folinic acid, or if these drugs are not suitable.

- NICE has recommended that oral therapy with capecitabine be used as an option for first-line treatment of metastatic colorectal cancer (although initially recommended, tegafur with uracil is no longer available).[18]

- Capecitabine and oxaliplatin are recommended as possible adjuvant treatments after surgery for stage III (Dukes' C) colon cancer:[19]

    - Capecitabine is given on its own.
    - Oxaliplatin is given together with 5-fluorouracil and folinic acid.

- Cetuximab in combination with FOLFOX or FOLFIRI is recommended for the first-line treatment of metastatic colorectal cancer only when all of the following criteria are met:
    - The primary colorectal tumour has been resected or is potentially operable.
    - The metastatic disease is confined to the liver and is unresectable.
    - The patient is fit enough to undergo surgery to resect the primary colorectal tumour and to undergo liver surgery if the metastases become resectable after treatment with cetuximab.
- Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine is not recommended for the treatment of metastatic colorectal cancer.[20]

Editor's note

Dr Krishna Vakharia, 16th October 2023

Pembrolizumab for previously treated endometrial, biliary, colorectal, gastric or small intestine cancer with high microsatellite instability or mismatch repair deficiency
[21]

NICE has recommended pembrolizumab as an option for treating tumours with high microsatellite instability (MSI) or mismatch repair (MMR) deficiency in adults with:
Advanced or recurrent endometrial cancer that has progressed during or after a platinum-based therapy, who cannot have curative surgery or radiotherapy.
Unresectable or metastatic gastric, small intestine or biliary cancer that has progressed during or after having one therapy.
Colorectal cancer after fluoropyrimidine combination therapy, only if they cannot have nivolumab with ipilimumab.
Pembrolizumab should be stopped at 2 years of uninterrupted treatment or earlier if the cancer progresses.
Results of indirect trials suggest that people having pembrolizumab live for longer and have longer before their cancer gets worse than people having chemotherapy - though these results are not certain. It is thought that the possibility of its effect on quality and length of life mean that this is an option.

Metastatic disease[22]

- Over 50% of patients with colorectal cancer will develop liver metastases but only a minority of patients present with technically resectable disease.
- Liver resection, with neoadjuvant and adjuvant chemotherapy, is the optimal treatment for colorectal metastases. Around 40% of those undergoing surgical resection are alive five years after their diagnosis.
- Recurrence rate is significant and may require further resection.
- The lungs are the second most common site of metastasis for colorectal cancer after the liver. Management is multidisciplinary and therapeutic options include systemic therapy, radical local treatment (eg, surgical resection, stereotactic radiation therapy, and ablation therapy), and local palliative treatment.[23]

Editor's note
Dr Krishna Vakharia, 22nd February 2023 **Regorafenib for previously treated metastatic colorectal cancer**[24] NICE has recommended the use of regorafenib as an option for metastatic colorectal cancer in adults who have had previous treatment - these include fluoropyrimidine-based chemotherapy, anti-VEGF therapy and anti-EGFR therapy. It can also be used if any of the mentioned previous treatments are unsuitable. Clinical trial evidence suggests that this medication could help people live longer compared to best supportive care.

Follow-up after apparently curative resection

NICE recommends:[4]

- A minimum of two CT scans of the chest, abdomen, and pelvis in the first three years; **and**
- Regular serum CEA tests (at least every six months in the first three years).

Future trends

Current research centres on the identification of specific biomarkers which could be used to tailor chemotherapy to the individual patient.[25]

Prognosis

Around half of people diagnosed with colorectal cancer survive for at least five years after diagnosis:[4]

- 60% are amenable to radical surgery and 70% of these will be alive at seven years (or will have died from non-tumour-related causes).
- Survival rates relative to age-matched groups without colorectal cancer, are now about 45% at five years after diagnosis. Beyond five years, relative survival rates decline only slightly (most of those who live this long are cured).
- Survival rates in the UK have been rising steadily over a period of three decades.

Prevention

Lower risk has been linked with:

- Lifestyle: infrequent consumption of meat, matching calorie consumption to need, low dietary fat, active lifestyle, not smoking, frequent consumption of vegetables and possibly fruit, high-fibre diet.[26]
- Nutritional supplements and medication: vitamin supplements containing folic acid, selenium, calcium, regular use of non-steroidal anti-inflammatory drugs (NSAIDs), hormone replacement therapy.[26] [27] [28]
- A UK general practice study found that patients starting low-dose aspirin therapy (75-300 mg daily) have a reduced risk of stages B-D colorectal cancer, suggesting a role for low-dose aspirin in the progression of established disease; a substantial reduction in the risk of Dukes' A colorectal cancer may occur after five years of therapy.[29]

Further reading

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