Diagnosis and management of colorectal cancer: summary of NICE guidance

G J Poston,1 D Tait,2 S O’Connell,3 A Bennett,3 S Berendse,3 on behalf of the Guideline Development Group

Colorectal cancer is the third leading cause of death from cancer in the United Kingdom, with a lifetime risk of about 2% in England and Wales, and its incidence is rising.1 The outcome for people with colorectal cancer is improving, but the overall five year survival rates are still lower than 60%.1 There is a need for greater accuracy in diagnosis and staging, more appropriate use of neoadjuvant and adjuvant therapies when treating potentially curable disease, and more effective use of resources when managing patients with advanced disease. This article summarises the most recent recommendations from the National Institute for Health and Clinical Excellence (NICE) on the diagnosis and management of people with colorectal cancer in secondary care.2 Recommendations for referral from primary care for patients with suspected colorectal cancer are in the NICE clinical guideline 27.3

Recommendations

NICE recommendations are based on systematic reviews of best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the Guideline Development Group’s experience and opinion of what constitutes good practice. Evidence levels for the recommendations are in the full version of this article on bmj.com.

Investigations for diagnosis and staging

Confirming a diagnosis of colorectal cancer

The recommendations in this section refer to people whose condition is being managed in secondary care. For recommendations for urgent referral from primary care for patients with suspected colorectal cancer, see the NICE clinical guideline 27.3

• Advise the patient that more than one investigation may be necessary to confirm or exclude a diagnosis of colorectal cancer.
• Offer colonoscopy to patients without major comorbidity. If a lesion suspicious of cancer is detected, perform a biopsy unless contraindicated (for example, in patients with bleeding disorders).

Staging of colorectal cancer

Stage I—Primary tumour into but not through muscularis propria, and no metastases
Stage II—Primary tumour grown through to serosa and peritoneal surface but no metastases
Stage III—Any size of primary tumour with lymph node metastases
Stage IV—Presence of distant metastatic disease

• For patients with major comorbidity, offer flexible sigmoidoscopy followed by a barium enema. If a lesion suspicious of cancer is detected perform a biopsy unless contraindicated.
• Consider computed tomographic colonography as an alternative to colonoscopy or to flexible sigmoidoscopy with a barium enema, if the local radiology service can show competency in this technique. If a lesion suspicious of cancer is detected, offer colonoscopy with biopsy to confirm the diagnosis, unless it is contraindicated.
• Offer patients who have had an incomplete colonoscopy:
  – Repeat colonoscopy or
  – Computed tomographic colonography, if the local radiology service can show competency in this technique or
  – A barium enema.

Information about bowel function

• Offer all patients information on all treatment options available to them (including no treatment) and the potential benefits and risks of these treatments, including the effect on bowel function.
• Before surgery offer all patients information about the likelihood of having a stoma, why it might be necessary, and how long it might be needed for.
• Ensure that a trained stoma professional gives specific information on the care and management of stomas to all patients considering surgery that might result in a stoma.

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Management of local disease

Patients whose primary rectal tumour appears resectable at presentation

- Do not offer short course preoperative radiotherapy or chemoradiotherapy to patients with operable rectal cancer at low risk of local recurrence, unless as part of a clinical trial.
- For patients with operable rectal cancer at moderate risk of local recurrence consider short course preoperative radiotherapy then immediate surgery.
- For patients whose tumours fall between moderate and high risk of local recurrence, consider preoperative chemoradiotherapy then surgery, but with an interval before surgery to allow the tumour to respond and shrink.
- For patients with operable rectal cancer at high risk of local recurrence offer preoperative chemoradiotherapy then surgery, but with an interval before surgery to allow the tumour to respond and shrink (rather than short course preoperative radiotherapy).

Patients whose primary tumour appears unresectable or borderline resectable

- For patients with locally advanced rectal cancer at high risk of local recurrence, offer preoperative chemoradiotherapy then surgery, but with an interval before surgery to allow the tumour to respond and shrink.
- Do not offer preoperative chemoradiotherapy solely to facilitate sphincter sparing surgery.
- Do not routinely offer preoperative chemotherapy alone for patients with locally advanced colon or rectal cancer unless as part of a clinical trial.

Colonic stents in acute large bowel obstruction

- If stenting is being considered for patients presenting with acute large bowel obstruction, offer CT scanning of the chest, abdomen, and pelvis to confirm the diagnosis of mechanical obstruction and to determine whether the patient has metastatic disease or colonic perforation.
- Do not use contrast enema studies as the only imaging modality.
- The decision to insert a stent should be made by a consultant colorectal surgeon with an endoscopist or a radiologist, or both. Only healthcare professionals experienced in placing colonic stents and with access to fluoroscopic equipment and trained support staff should insert colonic stents.
- Consider placing a self expanding metallic stent to initially manage left sided complete or near complete colonic obstruction; do not dilate the tumour beforehand.
- Do not place self expanding metallic stents:
  - In low rectal lesions or
  - To relieve right sided colonic obstruction or
  - If there is clinical or radiological evidence of colonic perforation or peritonitis.
- If a self expanding metallic stent is suitable try insertion urgently and no longer than 24 hours after patients present with colonic obstruction.

Stage I colorectal cancer

- For patients with locally excised, pathologically confirmed stage I colon cancer:
  - The colorectal multidisciplinary team should consider offering further treatment, taking into account pathological characteristics of the lesion, imaging results, and previous treatments.
  - Offer further treatment to patients whose tumour had involved resection margins of less than 1 mm.
- For patients with stage I rectal cancer a multidisciplinary team specialising in early rectal cancer\(^{4}\) should decide which treatment to offer, taking into account previous treatments, such as radiotherapy.

Laparoscopic surgery

The recommendations on laparoscopic surgery for colorectal cancer are covered by NICE’s technology appraisal 105.\(^{5}\)

Adjuvant chemotherapy

After fully discussing the risks and benefits with the patient, consider adjuvant chemotherapy for patients with stage II rectal cancer with high risk of recurrence and all patients with stage III rectal cancer, and for patients with stage II colon cancer with high risk of recurrence and all patients with stage III colon cancer.

Management of metastatic disease

Stage IV colorectal cancer

- Prioritise treatment to control symptoms if at any point the patient has symptoms from the primary tumour.
- If both primary and metastatic tumours are considered resectable, site specific multidisciplinary teams (teams specialising in all relevant anatomical sites of the cancer) should consider initial systemic treatment followed by surgery, after full discussion with the patient.

Imaging metastases

- Offer contrast enhanced CT scanning of the chest, abdomen, and pelvis to patients being assessed for metastatic colorectal cancer.
- Discuss all imaging with the patient after review by the appropriate site specific multidisciplinary team.
- If the CT scan shows metastatic disease only in the liver and there are no contraindications to further treatment, a specialist hepatobiliary multidisciplinary team should decide if further imaging is needed to confirm whether surgery is suitable or potentially suitable after further treatment.
- If intracranial disease is suspected offer contrast enhanced MRI of the brain.
- If the CT scan shows possible extrahepatic metastases that could be amenable to further radical surgery, consider if positron emission tomography with computed tomography (PET-CT) of the whole body is appropriate.
- If contrast enhanced CT scanning suggests disease in the pelvis, offer an MRI of the pelvis.
and discuss management in the colorectal cancer multidisciplinary team.

- If the diagnosis of extrahepatic recurrence remains uncertain, keep the patient under clinical review and offer repeat imaging at intervals agreed with the patient.

Chemotherapy and biological therapies

Full details on the use of these therapies can be found in NICE guidance.9-10

In patients with advanced colorectal cancer:

- Consider one of the following sequences of chemotherapy:
  - 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.

- Consider raltitrexed only for patients with advanced colorectal cancer who are intolerant to fluorouracil and folinic acid or for whom these drugs are not suitable.

Note that at the time of publication (November 2011), irinotecan did not have UK marketing authorisation for use in second line combination therapy (FOLFIRI (folinic acid plus fluorouracil plus irinotecan)). Informed consent should be obtained and documented.

Ongoing care and support

Follow-up after apparently curative resection

- Offer follow-up to all patients—to start at a clinic visit four to six weeks after potentially curative treatment.

- Offer regular surveillance with:
  - At least two CT scans of the chest, abdomen, and pelvis in the first three years and
  - Regular serum carcinoembryonic antigen tests (at least every six months in the first three years).

- Offer a surveillance colonoscopy at one year after initial treatment. If this is normal consider further colonoscopy after five years, and thereafter as determined by cancer networks. Determine the timing of surveillance for patients with subsequent adenomas by the risk status of the adenoma.

- Start investigations again if there is any clinical, radiological, or biochemical suspicion of recurrent disease.

- Stop regular follow-up when:
  - The patient and the healthcare professional have discussed and agreed that the likely benefits no longer outweigh the risks of further tests or
  - The patient cannot tolerate further treatments.

- After any treatment, offer all patients specific information on managing the effects of the treatment on their bowel function. This could include information on incontinence, diarrhoea, difficulty emptying their bowels, bloating, excess flatus, diet, and where to go for help in the event of symptoms.

- Offer verbal and written information in a way that is clearly understood by patients and free of jargon. Include information about support organisations or internet resources recommended by the clinical team.

Overcoming barriers

The guideline deals with many major uncertainties in the diagnosis and treatment of colorectal cancer, including the uncertainty about which patients to refer for consideration of resection of colorectal cancer liver metastases (currently the best performing hospital refers 10 times as many patients as the worst performing hospital).11 The guidance on referral for all patients with liver limited disease who are fit for further surgery (that they should be referred to specialist liver surgery multidisciplinary teams for decisions on further definitive imaging) will substantially increase the chance of such patients being offered potentially curative surgery. Successful treatment of colorectal cancer depends highly on good multiprofessional and multidisciplinary working, requiring effective communication among the different healthcare teams.

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MEANING POINTS

In acute angio-oedema a detailed history may show that a food, drug, or sting triggers acute angio-oedema.

Stop angiotensin converting enzyme (ACE) inhibitors in any patient who develops angio-oedema.

In recurrent angio-oedema without urticaria, consider conditions including angio-oedema induced by ACE inhibitors and C1 inhibitor deficiency. Screen for C1 inhibitor deficiency in these patients (including those taking ACE inhibitors) by measuring C4 levels, and if levels are low refer for confirmation of diagnosis.

Chronic spontaneous urticaria associated with angio-oedema is unlikely to be IgE mediated, and investigation for the presence of specific IgE is rarely indicated.

LEARNING POINTS

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RATIONAL TESTING

Investigating recurrent angio-oedema

Penny Fitzharris, Anthony Jordan

Where do you start with investigating causes of angio-oedema? This article will guide you through key information and tests.

A 57 year old man visited his local emergency department with his fourth episode of non-itchy swelling affecting the tongue and mouth in the past four months. Previous episodes had resolved over one to two days without treatment. On this occasion the patient woke from sleep and had difficulty swallowing and speaking. He took an antihistamine, but it had no clear effect. Clinical examination confirmed non-erythematosus swelling, mainly affecting the tongue and lips (fig 1). The airway was adequate on first assessment, with an oxyhemoglobin saturation of 97% on room air, blood pressure 150/90 mm Hg, respiratory rate of 20 breaths/min, pulse 90 beats/min. No urticaria or other rash were present.

What is the next investigation?

This patient is most likely to have angio-oedema (box 1 describes this and the related conditions urticaria and anaphylaxis). Additional clinical information is essential to guide relevant investigation in angio-oedema. This patient had no history of urticaria. Swelling began hours after last eating, and he had taken no over the counter medications such as non-steroidal anti-inflammatory drugs, which may precipitate angio-oedema. He had been diagnosed with hypertension two years ago and been prescribed enalapril 10 mg daily, increased to 20 mg daily five months ago, with sitagliptin 100 mg daily also started five months ago. He had no family history of angio-oedema. Box 2 outlines key items in the history and examination to direct investigation and management.

In patients taking ACE inhibitors

Recurrent angio-oedema of the tongue and oropharynx, without urticaria, suggests that his angiotensin converting enzyme (ACE) inhibitor (enalapril) may be the underlying cause. Recurrent angio-oedema is experienced by 0.1-0.7% of those taking ACE inhibitors.2 No specific diagnostic tests can determine whether a patient’s angio-oedema results from use of an ACE inhibitor.

Typically angio-oedema affects the tongue and oropharynx, but intestinal involvement may result in recurrent abdominal pain and other gut symptoms. Angiotensin converting enzyme also functions as a kininase, which degrades bradykinin. Thus, angiotensin converting enzyme inhibition degrades bradykinin and so bradykinin accumulates in the presence of an ACE inhibitor, interacts with bradykinin B2 receptors, and results in vasodilation and increased vascular permeability (fig 2).4 Clinical trials are under way to examine the role of icatibant, a bradykinin B2 receptor antagonist, in acute management of this condition.

Fig 1 Angio-oedema affecting both lips (real case to illustrate scenario)

Although symptoms often develop within weeks of starting an ACE inhibitor, they may not develop for months or even years. A dose change (usually an increase) or addition of another medication may precede onset. Angio-oedema...
usually stops after drug withdrawal, but sometimes persists for months or even years. Clinical response to antihista-
mines, steroids, and adrenaline is relatively poor, and deaths have been reported. All ACE inhibitors are subsequently contraindicated as this is a class effect.\footnote{A meta-analysis identified that the risk of any subsequent angio-oedema with angiotensin receptor blockers was 2.5% (1.5% for confirmed cases).} No test is available to determine who is at risk of angio-oedema induced by ACE inhibitors.

**Exclusion of hereditary and acquired C1 inhibitor deficiency**

C1 inhibitor deficiency should be excluded in all patients with recurrent angio-oedema without associated urticaria, including those taking an ACE inhibitor, as this drug may precipitate angio-oedema in patients with C1 inhibitor deficiency. C1 inhibitor has several anti-inflammatory functions in the contact and complement systems (fig 2), and a deficiency in these may result in insufficient local anti-inflammatory control at times of physiological or psychological stress (with generation of excess bradykinin) and associated vascular permeability.

Hereditary C1 inhibitor deficiency or hereditary angio-
œdema, an autosomal dominant condition, typically present by young adulthood, though diagnosis is often delayed. Facial, limb, and abdominal angio-oedema are common; death from laryngeal attacks and unnecessary abdominal surgery are well recognised. Acquired C1 inhibitor deficiency is less common and is usually associated with lymphoproliferative or autoimmune diseases in older adults.

**Screening tests for hereditary and acquired C1 inhibitor deficiency**

Although uncontrolled activation of the classic comple-
ment pathway is the basis of the diagnostic tests, it is not responsible for the major symptoms.\footnote{Measurement of the level of complement component C4 is an excellent screening test, with a negative predictive value of 100% in some studies. It is widely available and cost effective as the initial investigation in these patients. A normal C4 level is only rarely seen in C1 inhibitor deficiency. The level of complement component C3 is expected to be normal and measurement is not indicated.}  

Investigating angio-oedema with urticaria

Consensus guidelines recommend that if episodes are acute (that is, occasional and lasting no more than six weeks) and the clinical history does not identify a likely cause, no investigation is needed.\footnote{When chronic “idiopathic” or “spontaneous” urticaria and/or angio-oedema are present for more than six weeks, they are rarely IgE mediated, and skin tests or specific IgE measurement are unhelpful. Full blood count and measurement of C reactive protein or erythrocyte sedimentation rate are recommended for evidence of an underlying inflammatory or parasitic disorder. Investigation for underlying chronic infection may be relevant. Measurement of thyroid stimulating hormone is usually recommended as thyroid autoantibodies are increased in frequency. IgG autoan-
tibodies that cross link the FceR1 receptor on mast cells have been identified in 30-50% of cases, but the value of measurement of these is controversial.}

**Suspected allergic angio-oedema**

Suspect an allergic cause if angio-oedema accompanies anaphylaxis or acute urticaria; symptoms almost always occur within two hours (often within minutes) of exposure to the trigger (food, drug, or insect sting). Refer for further...
Lymphogranuloma venereum is the most likely diagnosis. Differential diagnosis includes infection with non-LGV Chlamydia trachomatis, herpes simplex, and enteric pathogens in addition to gonorrhoea and inflammatory bowel disease. A first line treatment of lymphogranuloma venereum is a 21 day uninterrupted course of doxycycline 100 mg twice daily. A microbiological test of cure should be offered at five weeks, HIV testing at one month, and hepatitis C testing at six months.

Referral
For patients with recurrent angio-oedema, referral to clinical immunology, allergy, dermatology, or paediatric specialist services is appropriate. Caution is needed when what seems to be angio-oedema persists as this may indicate misdiagnosis of other conditions (such as obstruction of the superior vena cava, orofacial granulomatosis, retobulbar lymphoma, and acromegaly).

Outcome
This patient was treated with adrenaline (0.5 mg intramuscularly) because of concern about his airway, although it was recognised that his response to adrenaline may be poor in angio-oedema induced by an ACE inhibitor. His angio-oedema resolved slowly over 48 hours and he did not need intubation or tracheostomy. His ACE inhibitor was stopped immediately and replaced with an angiotensin receptor blocker, after discussion with him about the much lower risk of angio-oedema with this agent. Levels of C4 and C1 esterase inhibitors were normal limits. He had no further angio-oedema episodes during six months of follow-up.