Diagnosis of colorectal cancer in primary care: the evidence base for guidelines

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**Background.** Colorectal cancer is common, causing ~11% of cancer deaths in the UK. However, a GP would only expect to see one new presentation each year. Referral guidelines outlining clinical scenarios of high risk have been published. These aim to help GPs select patients for rapid investigation.

**Objectives.** The purpose of this study was to review the presenting features of colorectal cancer in primary care, using the basic structure of the UK Referral Guidelines for Suspected Cancer.

**Methods.** A structured literature review was carried out.

**Results.** Two symptoms have a high predictive value for cancer: rectal bleeding and change in bowel habit towards increased looseness or increased stool frequency. Other symptoms, such as abdominal pain, are so prevalent in the community that they have little predictive value. There is little published evidence on abdominal or rectal masses and iron deficiency anaemia as presenting features for colorectal cancer. However, these are so likely to have an important cause, investigation is mandated. Two areas in the Referral Guidelines are questioned: the need to defer investigation of change in bowel habit towards increased looseness or increased stool frequency for 6 weeks, and the low risk nature of constipation.

**Conclusion.** The Referral Guidelines have a reasonable evidence base.

**Keywords.** Colorectal cancer, diagnosis, primary care.

Introduction

Colorectal cancer (CRC) is common, with >30 000 new cases each year in the UK. It accounts for 14% of male and 12% of female cancers, and 11% of cancer deaths in both sexes. Incidence rates have risen slowly in the last 30 years, but mortality has steadily declined.

Although common nationally, a full-time GP would expect to encounter only one new patient each year with CRC. As each GP will diagnose relatively few cancers during their career, various guidelines have been written to assist in selection of patients for investigation. Other guidelines make recommendations about surveillance of particular populations at higher risk, such as patients with polyposis coli or inflammatory bowel disease. The UK Referral Guidelines for Suspected Cancer, devised by the Department of Health, were sent to all GPs in 2000. They are currently being revised. The Scottish Intercollegiate Guideline Network published a guideline on CRC in 1997, which was updated 2 years later. The National Institute for Clinical Effectiveness are currently updating guidance first issued in 1997 aimed at the whole NHS entitled, ‘Improving Outcomes in Colorectal Cancer’. These latter two documents give recommendations across the whole spectrum from prevention and surveillance to hospital organization. In both, the sections relating to primary care diagnosis are brief, and so this review uses as its base the UK Referral Guidelines for Suspected Cancer. These are called simply the UK guidelines from now on.

*The UK Referral Guidelines for Suspected Cancer* These outline criteria for urgent referral. They were published to coincide with the establishment of ‘2-week clinics’, which offer a specialist appointment within 2 weeks of a GP referral for suspected cancer.

Six criteria are documented: two symptoms, rectal bleeding and change in bowel habit; two secondary effects, iron deficiency anaemia and intestinal obstruction; and two physical findings, abdominal or rectal masses. In addition, three symptoms associated with a low risk of cancer are described: rectal bleeding with anal symptoms; change in bowel habit to decreased...
frequency of defecation and harder stools; and abdominal pain without clear evidence of intestinal obstruction. The purpose of this review is to examine the research evidence for these nine criteria: the six positive criteria and three negative ones.

Methods

We searched Medline and Embase from 1966 (Embase 1980) to 2002 for common symptoms of CRC: rectal bleeding, abdominal pain, change in bowel habit and weight loss. Inclusion criteria were: studies from the general population, primary care or hospital series of CRC patients. Exclusion criteria were: reports on children or non-Western societies. This list was then expanded by secondary searches of reference lists. Referral guidelines were found by Medline, Embase and Internet searches using the words colorectal cancer and guidelines.

The rationale for and derivation of guidelines

The diagnosis of cancer in general practice is not straightforward. Symptoms and physical signs that may signify an underlying cancer can be, and frequently are, of benign origin. Guidelines attempt to define clinical scenarios with a reasonably high chance of finding an underlying cancer. If they can help GPs to discriminate between malignant and benign conditions, two complementary outcomes occur: patients with cancer will be investigated rapidly; and those without cancer will not be subjected to inappropriate investigation. Over-investigation may have psychological or costs. Furthermore, if investigations are used indiscriminately in a system with finite capacity, waiting times will rise.

Guidelines do not tell if a patient has cancer. They are designed to assist the GP in identifying patients in whom the risk of cancer is high enough to warrant urgent investigation. This implies that there is a threshold level of risk mandating urgent investigation (and below which urgent investigation is not required). However, this threshold level is not made explicit in any of the guidelines. The most useful figure to use in setting a threshold level is the positive predictive value (PPV). It is the probability of having the condition when you have the symptom. PPVs are usually calculated for single symptoms, for pairs, or even for groups, of symptoms. Where possible, we have quoted PPVs in this review. One problem, however, is that the CRC research literature is dominated by hospital series, with few reports from primary care. This matters because the presenting features in primary care differ from those in secondary care. Furthermore, most hospital research reports are retrospective cohort studies, or case–control series, elucidating symptoms from patients after the diagnosis has been made. These methods may introduce several biases: selection bias, whereby hospital series are unrepresentative of primary care presentation; recall bias, whereby patients—perhaps prompted by interviewers—remember symptoms they would otherwise have forgotten; and bias induced by progression of the disease between primary care and secondary care presentation. The relative rarity of CRC in primary care makes it difficult to design a study large enough to yield meaningful results. This is particularly so for prospective studies.

Mode of presentation

Some CRCs present with surgical emergencies, principally obstruction or perforation; these account for 3–21% of hospital series, with UK figures among the highest. Although the majority of patients presenting with bowel obstruction have a very short duration of symptoms, some have persistent symptoms before the emergency presentation. Indeed, early diagnosis may benefit this group most of all by avoiding the mortality and morbidity that accompany a surgical emergency.

At the other end of the spectrum, asymptomatic cancers account for 5–20% of hospital series, with the highest figures from the USA. These cancers have usually been detected in a screening procedure in those who are recognized to be at additional risk: this is usually because of a family history of CRC, or because the patient has inflammatory bowel disease. Cancers diagnosed by screening have a better Duke’s staging and, as screening increases, fewer CRCs present as an emergency. Thus the pattern of presentation is changing, with a slow move towards more asymptomatic cancers being identified. Despite these changes, the large majority of patients with CRC in the UK present with symptoms to their GP, and this is likely to continue to be the case for the foreseeable future.

Symptomatic diagnosis

Rectal bleeding

This is a classical symptom of CRC and a frequent first symptom. However, it is also a symptom of haemorrhoids, inflammatory bowel disease and many other non-malignant conditions. The UK guidelines for rectal bleeding are given in Box 1.

The prevalence of rectal bleeding in different populations is illustrated in Figure 1. In questionnaire studies of the general population, 14–33% report that
they have experienced rectal bleeding at some time in their life. Rectal bleeding in the last year is reported by 14–19% in UK surveys, but new onset bleeding in the last year by only 2.2%. The symptom is reported less in older age groups. However, the majority of those with rectal bleeding do not report it to their GP. An estimated seven per 1000 people consult their GP each year with the symptom, with ~2 per 1000 per year deemed by the GP to have clinically important bleeding. The difference between the community incidence of rectal bleeding and the reporting of it to primary care is accounted for by patients considering themselves to have benign disease, principally haemorrhoids. Other patients may delay presentation of their bleeding from a wish not to create work for their doctor. One possible marker for a malignant diagnosis is the gap between primary care consultations: as the interval since the patient last attended increases, so does the chance of cancer. The duration of bleeding is, however, not related to the likelihood of reporting the symptom to primary care.

The prevalence of rectal bleeding in the population who have been referred to hospital is much higher than in primary care. Although this presumably reflects the selection process by the GP, some may be new onset bleeding in the interval between referral and assessment. One study of 2268 GP referrals for investigation of distal colonic symptoms has been published after the referral guidelines were disseminated. Seventy percent of referred patients described rectal bleeding in response to a questionnaire. This is the highest percentage in hospital series of cancers, with others finding rates of 20–58%. Once the symptom has been reported to primary care, the PPV rises to 2–3%. GPs are selective in making referrals in patients reporting rectal bleeding, this is reflected in a rise in the PPV for referred patients to 5–7%. When a history of rectal bleeding is confirmed by a positive test for fecal occult blood, implying continuous bleeding, the PPV increases to 36%. The nature of the bleeding itself may be helpful in deciding on the importance of the symptom. Blood mixed with the stool has a higher PPV than blood coating the stool. Dark blood is particularly unfavourable, with a PPV in referred patients of 10–13%.

Other factors used in combination with rectal bleeding

Age. The UK guidelines in Box 1 use additional factors in suggesting which patients to select for urgent referral. In studies of primary care patients with rectal bleeding, the only additional factors with predictive power are change in bowel habit, age and abdominal pain. The reported incidence of rectal bleeding in the general population decreases with age, while the risk of CRC increases. Rectal bleeding occurs in the same proportion of older CRC patients as it does in younger patients. Thus, the PPV of the symptom increases as the patient ages, with figures of 2% in the age group 50–59 rising to 21% at ages 70–79. Despite the lower PPV at younger ages, one analysis suggests that investigation of younger patients with rectal bleeding as a sole symptom is still cost-effective. This is acknowledged by the UK guidelines, which regard 60 years as a maximum, but allow local cancer networks to use a lower age threshold. For instance, the Scottish guidelines use 45 years as their cut-off.

Inflammatory bowel disease. Both ulcerative colitis and Crohn’s disease can cause rectal bleeding, and both conditions predispose to cancer, with 1–2% of all CRCs arising in patients with inflammatory bowel disease. The risk of developing a complicating cancer is similar in the two diseases, and increases with the duration and extent of the inflammatory bowel disease.

**Colorectal cancer in primary care**

<table>
<thead>
<tr>
<th>Box 1</th>
<th>Referral guidelines relating to rectal bleeding</th>
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</thead>
<tbody>
<tr>
<td>Urgent referral: rectal bleeding WITH a change in bowel habit to looser stools and/or increased frequency of defecation persistent for 6 weeks at all ages</td>
<td></td>
</tr>
<tr>
<td>Urgent referral: rectal bleeding persistently without anal symptoms (such as soreness, discomfort, itching, lumps or prolapse) in patients over 60 years</td>
<td></td>
</tr>
<tr>
<td>Low risk: rectal bleeding with anal symptoms</td>
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</table>

2,000 population

280–660 have rectal bleeding sometime in their life

280–380 have bleeding in the last year, 44 for the first time

14–30 report it to their GP

1 has cancer

Refs 38, 39

FIGURE 1 Incidence of rectal bleeding in the community and in primary care. The figures have been adjusted to an approximate GP list size of 2000 patients
symptoms may change when a CRC develops, and this is an area that is likely to remain one of clinical judgement rather than illumination by research. Partly for this reason, one guideline recommends surveillance by colonoscopy starting 10 years after onset of symptoms.7 These recommendations are not based on randomized controlled trials, however, and decision analysis suggests that they may be ineffective.68 Neither condition is mentioned in the UK guidelines.4

Local symptoms. The UK guidelines differentiate between rectal bleeding with and without local symptoms. The assumption is that local symptoms suggest a local cause such as haemorrhoids, or an anal fissure. Although intuitive, this is not supported by research evidence. Symptoms such as pain on defecation, tenesmus and pruritis have all been reported in cancer series.20,41,51 In the referred population, each of these symptoms predicts cancer after investigation.51 However, their frequencies in the general population are largely unknown, making calculation of the predictive value in primary care impossible.

Change in bowel habit
This symptom is probably as important as rectal bleeding.69 In most studies, it is described more specifically as constipation or diarrhoea. Diarrhoea, either increased loosening or increased frequency of the stools, is more predictive of cancer than constipation.51 These symptoms have been studied less than rectal bleeding, perhaps because of the categorical nature of bleeding (one either bleeds or one does not), but perhaps also because of the variability of bowel habit in the general population. Change in bowel habit is the symptom most associated with patient delay in presentation,33 and diarrhoea the symptom most associated with doctor delay.53

Recommendations for urgent referral in the UK guidelines are summarized in Box 2.

Constipation and diarrhoea are very common in the general population. Between 10 and 25% of the UK population describe that they have to strain to pass a stool,40,70,71 with 14% describing themselves as constipated.40 Some 23% describe urgency of defecation, and 10% have loose stools frequently.40 However, only 9% of the population describe a recent change in bowel habit,40 and 1.5% describe a change which they regard as significant enough to report to primary care.72 In patients referred for investigation, 13% describe constipation and 40% increased stool frequency.51 In hospital series of CRC patients, the percentage reporting any of diarrhoea, constipation or a change in bowel habit is 39–86%.22,24,41,51,73 Change in bowel habit is a more common symptom of cancer in the elderly.63 The presence of mucus in the stool may predict cancer, being described by 6–29% of cancer patients,20,41,51 but only 3–5% of the general population.71

Using the figure of 1.5% who describe a change in bowel habit that they deem significant enough to report to their doctor and using an approximate incidence of CRC as one person in 2000, a PPV of 3% can be estimated.72 In the referred population, the PPV of increased stool frequency is 7% and looseness of the stools 8%. In contrast, constipation has a PPV of 1.4%.51 The UK guidelines reflect this in stating that constipation alone is not a good predictor of cancer.

Duration of symptoms
No studies have reported on the relationship between duration of symptoms and the likelihood of CRC. There is a complex relationship between the duration of symptoms and Duke’s staging (and thus survival). Cancers with a longer duration of symptoms are more likely to be Duke’s A or B.74 This counter-intuitive finding may be explained by differences in tumour aggressiveness,75 whereby aggressive tumours have a shorter period of symptoms but have more advanced disease at diagnosis. Overall, there is no relationship between duration of symptoms and survival.75,76 Thus, there is no research evidence to support the recommendation in the UK guidelines that change in bowel habit should be persistent for 6 weeks before the patient qualifies for urgent referral.

Abdominal or rectal masses and iron deficiency anaemia
The guidelines recommend urgent referral of any of these findings (Box 3).

These recommendations are uncontroversial. The proportion of CRC patients with a palpable abdominal mass is reported as 4–6% in hospital series.53,77 Rectal masses are more common; reported as being present in 24–50% of CRCs in two hospital series.78 However, no figures are available from primary care.78 Whatever the true proportion of palpable masses in primary care

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**Box 2 Referral guidelines relating to change in bowel habit**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Urgent referral: rectal bleeding with a change in bowel habit to looser stools and/or increased frequency of defecation persistent for 6 weeks at all ages (as above)</td>
<td></td>
</tr>
<tr>
<td>Urgent referral: change of bowel habit to looser stools and/or increased frequency of defecation, without rectal bleeding and persistent for 6 weeks</td>
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<tr>
<td>Low risk: change in bowel habit to decreased frequency of defecation and harder stools</td>
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**Box 3 Referral guidelines relating to masses and anaemia**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urgent referral: a definite palpable right-sided abdominal mass</td>
<td></td>
</tr>
<tr>
<td>Urgent referral: a definite palpable rectal mass</td>
<td></td>
</tr>
<tr>
<td>Urgent referral: iron deficiency anaemia without an obvious cause</td>
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</tbody>
</table>
presentations of CRC, it is clear that, once detected, they merit urgent referral.

Iron deficiency anaemia is a classical pointer to CRC. It generally signifies an underlying illness, so would be investigated as a matter of course. CRC is the initial differential diagnosis, but may not initially be the most likely cause. Iron deficiency is present in 11–57% of cancers, and is particularly suggestive of caecal tumours. The PPV of anaemia for CRC in adults is 14%, so investigation is mandatory, and positive findings should lead to a rapid referral.

Abdominal pain
The guidelines only mention abdominal pain as a symptom of low risk (Box 4).

Abdominal pain is extremely prevalent in the general population. In population surveys, >20% of the US population reported abdominal pain in the previous month. A quarter of the UK population reported it in the previous year. Pain is reported less frequently by the elderly. As with rectal bleeding, the patient's decision to consult their doctor depends on whether they perceive the symptom as a health problem or part of normal experience. Roughly a quarter do consult, and most of these have a self-limited illness for which no definitive diagnosis can be found. In a large prospective study, only 0.4% of primary care patients who attended with abdominal pain had a diagnosis of CRC established within the next year. The number of CRCs in this study was too small for further analysis, so all neoplasms (including benign polyps) were put into a single group. The only features to significantly predict a neoplastic cause were: the pain having no specific character, the patient being male, increasing age, and a raised erythrocyte sedimentation rate. The proportion of patients describing abdominal pain in the population referred for investigation of suspected cancer is 54%, with a PPV of 2.7%. However, the PPV for patients with rectal bleeding and abdominal pain is no higher than for rectal bleeding alone. Colonoscopies for investigation of non-specific abdominal symptoms (without rectal bleeding, weight loss or change in bowel habit) have the same yield of significant pathology as in asymptomatic patients. This all suggests that abdominal pain on its own is a very poor predictor of cancer, in marked contrast to rectal bleeding and change in bowel habit.

The role of family history
The UK guidelines make no mention of family history of CRC. There are several inherited syndromes with CRC as a feature, such as polyposis coli, hereditary non-polyposis coli and Peutz–Jeghers syndrome. Guidelines for the management of individuals with these syndromes have been published. Management of these conditions is usually in secondary care. For those outside such families, the contribution of inheritable factors has been estimated from twin studies to be 35%. Recent guidelines recommend referral of patients with two first-degree relatives with CRC or one first-degree relative under 45 years, although the author acknowledged that the evidence for this recommendation was indirect, and benefit marginal. The value of using the family history in primary care is illustrated by a study from one UK general practice. A postal questionnaire was sent to all patients aged 30–69 enquiring about any family history of CRC and led to the diagnosis of two cancers in symptomatic patients who had not consulted their doctor.

Discussion
The major single predictors of cancer are rectal bleeding and change in bowel habit towards increased looseness or increased stool frequency. These are strongly supported by research evidence. One of these symptoms, plus being aged over 60, is as powerful a predictor as any of the other symptom complexes described in the guidelines. In contrast, other symptoms in isolation have very low predictive power, although when they accompany rectal bleeding or change in bowel habit the likelihood of cancer is increased. The evidence base is weak for the three rarer presentations of CRC, abdominal or rectal masses, or iron deficiency anaemia. This may not matter: all three presentations require investigation, and CRC is a likely diagnosis for them all. Although the UK guidelines were established to help GPs with referral decisions, local services will determine the exact patient pathway. In some instances, the GP may perform the initial investigations in primary care instead of selecting immediate referral to a rapid access clinic.

However, two points in the UK guidelines are questionable. First, there is no evidence for deferring investigation of increased stool frequency for 6 weeks. In the absence of a clear cause for diarrhoea, we suggest immediate referral. This applies particularly to the elderly. Even with an apparently clear cause, such as infective diarrhoea, it may be wise to set a time limit before referral lest the initial diagnosis be wrong. Change in bowel habit is the symptom most associated with both patient and doctor delay: deferring investigation risks perpetuating this. It is also illogical to require a 6 week delay before requesting a referral with a maximum 2 week wait. No doubt this was a practical decision. However, it ignores the issue that patients select which symptoms to report and, once they have

**Box 4  Referral guidelines relating to abdominal pain**

Low risk: abdominal pain without clear evidence of intestinal obstruction
chosen to report a change in bowel habit, the PPV is already high enough to warrant referral.

Secondly, it is debatable whether constipation can safely be regarded as low risk. A PPV of 1.4% (albeit in the referred population) is one chance in 70. We would caution against labelling all constipation as low risk.

The research literature largely bypasses one other important issue: the experience of the doctor and patient. The higher predictive value of symptoms in the population referred for investigation when compared with the predictive value on first presentation to primary care shows that doctors are able to identify (at least partly) those who are likely to harbour cancer.11,19,51,96 This is not to forget that there has been a higher relative rise from the predictive value in the general population to those presenting to primary care, so patients can also identify which symptoms matter.²⁵,²⁷,⁹⁷ It is a sobering thought that patients do this at least as well as doctors.

Acknowledgements

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