The yield of colorectal cancer among fast track patients with normocytic and microcytic anaemia

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ABSTRACT

INTRODUCTION We receive fast track referrals on the basis of iron deficiency anaemia (IDA) for patients with normocytic anaemia or for patients with no iron studies. This study examined the yield of colorectal cancer (CRC) among fast track patients to ascertain whether awaiting confirmation of IDA is necessary prior to performing bowel investigations.

METHODS A review was undertaken of 321 and 930 consecutive fast track referrals from Centre A and Centre B respectively. Contingency tables were analysed using Fisher's exact test. Logistic regression analyses were performed to investigate significant predictors of CRC.

RESULTS Overall, 229 patients were included from Centre A and 689 from Centre B. The odds ratio for microcytic anaemia versus normocytic anaemia in the outcome of CRC was 1.3 (95% confidence interval [CI]: 0.5–3.9) for Centre A and 1.6 (95% CI: 0.8–3.3) for Centre B. In a logistic regression analysis (Centre B only), no significant difference in CRC rates was seen between microcytic and normocytic anaemia (adjusted odds ratio: 1.9, 95% CI: 0.9–3.9). There was no statistically significant difference in the yield of CRC between microcytic and normocytic anaemia ($p=0.515$, Fisher's exact test) in patients with anaemia only and no colorectal symptoms. Finally, CRC cases were seen in both microcytic and normocytic groups with or without low ferritin.

CONCLUSIONS There is no significant difference in the yield of CRC between fast track patients with microcytic and normocytic anaemia. This study provides insufficient evidence to support awaiting confirmation of IDA in fast track patients with normocytic anaemia prior to requesting bowel investigations.

KEYWORDS

Colorectal cancer – Normocytic anaemia – Microcytic anaemia – Colonoscopy

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Unexplained iron deficiency anaemia (IDA) is one of the higher risk criteria for suspected colorectal cancer (CRC) referral.^{1–4} The guidelines recommend referral when there is unexplained IDA with a haemoglobin level of <11g/dl in men and <10g/dl in postmenopausal women.^{1–5} The British Society of Gastroenterology (BSG) recommends investigation of any level of anaemia in the presence of iron deficiency.⁴ However, there is no consensus with regard to the investigation of iron deficiency without anaemia and that of anaemia without iron deficiency.

The aim of this study was to compare the yield of CRC between patients with different stages of anaemia (normocytic/microcytic/IDA) and no anaemia, who were referred under the two-week wait rule, in order to establish whether endoscopic evaluation should await confirmation of IDA. The views of local general practitioners (GPs) in

referring cases of normocytic and microcytic anaemia with or without iron studies were also explored.

Methods

A retrospective review was undertaken of all consecutive referrals for suspected CRC that were received at Centre A between November 2008 and June 2009 and at Centre B between April 2010 and March 2011 using the cancer services prospectively maintained database. A total of 321 and 930 fast track referrals were identified in the two centres, and 229 and 689 referrals were included in the analysis from Centre A and Centre B respectively. Cases were excluded for reasons such as no blood tests/notes available, previous history of CRC/panproctocolectomy and diagnosis of CRC in another hospital.

Table 1 The yield of colorectal cancer from the two patient cohorts (Centre A and Centre B) and within subgroups				
Patient group	Number of patients (male-to-female ratio)		CRC yield	
	Centre A	Centre B	Centre A	Centre B
All	229 (89M,140F)	689 (335M, 354F)	30 (13.1%)	76 (11.0%)
No anaemia	124 (53M, 71F)	432 (196M, 236F)	14 (11.3%)	41 (9.5%)
No anaemia and microcytosis	0	7 (2M, 5F)	0	0
Anaemia	105 (36M, 69F)	257 (139M, 118F)	16 (15.2%)	35 (13.6%)
Normocytic anaemia	65 (25M, 40F)	158 (95M, 63F)	9 (13.8%)	18 (11.4%)
Microcytic anaemia	40 (11M, 29F)	99 (44M, 55F)	7 (17.5%)	17 (17.2%)
Anaemia with low Fe	35 (12M, 23F)	81 (40M, 41F)	9 (25.7%)	10 (12.4%)
Anaemia with normal Fe	3 (2M, 1F)	92 (48M, 44F)	0	11 (12.0%)
No anaemia with low Fe	6 (2M, 4F)	14 (4M, 10F)	0	2 (14.3%)
No anaemia with normal Fe	9 (5M, 4F)	72 (29M, 43F)	0	2 (2.8%)
Microcytic anaemia with low Fe	20 (4M, 16F)	58 (24M, 34F)	6 (30.0%)	8 (13.8%)
Microcytic anaemia with normal Fe	1 (M)	22 (10M, 12F)	0	6 (27.3%)
Normocytic anaemia with low Fe	15 (8M, 7F)	23 (16M, 7F)	3 (20.0%)	2 (8.7%)
Normocytic anaemia with normal Fe	2 (1M, 1F)	70 (38M, 32F)	0	5 (7.1%)
CRC = colorectal cancer; Fe = serum iron for Centre A, ferritin for Centre B				

Data collection

Data were retrieved from hospital computer systems and individual patient notes. Blood test results around the time of the referral or up to a maximum of three months prior to the referral date were used to identify which patients had anaemia. The lower limit of the haemoglobin normal range for each laboratory was used to define anaemia as recommended by BSG guidelines.⁴ Patients with microcytosis were identified when the mean corpuscular volume value was <80fl. Serum ferritin (normal range: 20–300µg/l) was measured routinely in Centre B for the patients in whom iron deficiency was investigated. There were no patients with a diagnosis of colitis among the patients with a ferritin measurement. In the cohort from Centre A, serum iron (Fe) (normal range: 10–28µmol/l) was measured when iron studies were performed.

Statistical analysis

The statistical analysis was performed separately for each centre using Excel® (Microsoft, Redmond, WA, US), Prism® 5 (GraphPad Software, La Jolla, CA, US) and SPSS® version 19 (IBM, New York, US). A *p*-value of <0.05 was defined as statistically significant. Contingency tables were analysed using Fisher’s exact test.

A logistic regression analysis using a forward selection model was performed on the CRC outcome. The variables included were: anaemia, sex, age, change in bowel habit, weight loss, bleeding per rectum, mucus per rectum, abdominal mass, abdominal fullness, lesion on digital rectal examination, anal lesion, abdominal distension, abdominal pain, family history, previous polyps and faecal occult blood

test. A second logistic regression analysis was performed while replacing anaemia with microcytosis (microcytosis and anaemia were strongly correlated). For a third logistic regression, the interest was in comparing patients with normocytic anaemia with those with microcytic anaemia. Interactions between variables were tested for but none were found to be significant at the 1% significance level.

Results

CRC yield among fast track patients with/without anaemia and with/without GI symptoms

A total of 229 and 689 fast track referrals were included from Centres A and B respectively (Table 1). For patients in Centre A, the median age at referral was 73 years (inter-quartile range [IQR]: 62.6–80.9 years) whereas 51% of the patients in Centre B were female and the median age at referral was 71.7 years (IQR: 61.9–79.8 years). The yield of CRC between patients with and without anaemia was not significantly different in either centre (Centre A: *p*=0.434, Centre B: *p*=0.103) (Table 2).

When the yield of CRC for the microcytic anaemia group from each cohort was compared with the rest of the patients in each respective cohort, a statistically significant difference in the yield of CRC was seen in the larger group from Centre B but not in Centre A (Centre A: *p*=0.285, Centre B: *p*=0.019). When the yield of CRC between patients with microcytic anaemia and normocytic anaemia was examined, no statistically significant difference was seen in either cohort (Centre A: *p*=0.781, Centre B: *p*=0.196). The derived odds ratio (OR) for microcytic versus

Table 2 The yield of colorectal cancer among subgroups of Centre A and Centre B cohorts with unadjusted odds ratios				
CRC yield	OR (95% CI)		p-value	
	Centre A	Centre B	Centre A	Centre B
Anaemia vs no anaemia	1.4 (0.7–3.1)	1.5 (0.9–2.4)	0.434	0.103
Microcytic anaemia vs no anaemia	1.7 (0.6–4.5)	2 (1.1–3.7)	0.413	0.033
Microcytic anaemia vs rest of patients	1.7 (0.7–4.4)	2.1 (1.2–3.7)	0.285	0.019
Normocytic anaemia vs no anaemia	1.3 (0.5–3.1)	1.2 (0.7–2.2)	0.643	0.536
Microcytic anaemia vs normocytic anaemia	1.3 (0.5–3.9)	1.6 (0.8–3.3)	0.781	0.196
Anaemia with low Fe vs no anaemia with low Fe	4.7 (0.2–90.9)	0.9 (0.2–4.3)	0.309	1.000
Anaemia with low Fe vs anaemia with normal Fe	2.5 (0.1–53.3)	1.04 (0.4–2.6)	1.000	1.000
CRC = colorectal cancer; OR = odds ratio; CI = confidence interval; Fe = serum iron for Centre A, ferritin for Centre B				

normocytic anaemia was 1.3 (95% confidence interval [CI]: 0.5–3.9) for Centre A and 1.6 (95% CI: 0.8–3.3) for Centre B (Table 2).

A logistic regression analysis from Centre B showed that microcytosis, male sex, increasing age, bleeding per rectum, abdominal mass, lesion palpated on digital rectal examination and positive family history were significant in predicting CRC outcome. Patients with microcytosis were significantly more likely to have CRC detected than other patients (adjusted OR: 2.2, 95% CI: 1.2–4.1). Patients with anaemia were not significantly more likely to have CRC detected (adjusted OR: 1.5, 95% CI: 0.9–2.5) and this was the case even when considering the unadjusted effect. When comparing patients with normocytic anaemia and patients with microcytic anaemia, there was insufficient evidence of a difference in CRC detection rates (unadjusted OR: 1.6, 95% CI: 0.8–3.3; adjusted OR: 1.9, 95% CI: 0.9–3.9).

The yield was then investigated of CRC from patients who had either Fe or ferritin level measurements at Centre A and Centre B respectively (Tables 1 and 2). The yield of CRC from anaemic patients with low Fe or ferritin was not significantly different to that of non-anaemic patients with low Fe or ferritin (Centre A: $p=0.309$, Centre B: $p=1.000$) but this analysis was inhibited by low patient numbers. Although no CRC cases were seen in the three anaemic patients who had normal iron levels from Centre A, CRC cases were seen in patients with either microcytic (6/22 patients, 27.3%) or normocytic (5/70 patients, 7.1%) anaemia with normal ferritin measurement from the larger cohort in Centre B. Consequently, CRC cases can be seen in patients with microcytic or normocytic anaemia with or without low ferritin (Table 1).

CRC yield among fast track patients with anaemia only

Although the above analysis refers to fast track patients with/without anaemia and with/without gastrointestinal (GI) symptoms, a subgroup analysis was performed of 83 patients (34 normocytic and 49 microcytic) from Centre B who had anaemia as the only reason for referral. Even in this cohort, there was no significant difference in the yield of CRC between patients with microcytic and

normocytic anaemia ($p=0.515$). In addition, in fast track patients referred with anaemia only and no GI symptoms, CRC can occur even in the presence of normocytic anaemia with or without low ferritin (Table 1).

The timing of anaemia referral for specialist investigation

A survey was carried out among GPs in the Centre B catchment area to identify their views on anaemia referrals. Ninety questionnaires were sent to twenty-one GP surgeries. The response rate was 29%. Over four-fifths (81%) of GPs would organise a haematinic screen for microcytic anaemia patients with GI symptoms (84% if no GI symptoms) whereas just under two-thirds (64%) would organise a haematinic screen for normocytic anaemia patients with GI symptoms (46% if no GI symptoms). The distribution of referral choices for unexplained microcytic anaemia is shown in Figure 1 with the majority of GPs referring to gastroenterology clinics. Eighty-four per cent would not refer a patient with microcytic anaemia prior to confirming iron deficiency status and ninety-two per cent would not refer cases with unexplained normocytic anaemia prior to confirming iron deficiency status. Hence, the majority of GPs await confirmation of IDA prior to specialist referral.

Figure 1 The distribution of general practitioners' answers for referral of a patient with confirmed iron deficiency anaemia

Further analysis identified 257 patients from Centre B who were referred with anaemia with/without colorectal symptoms, of whom 136 had low haemoglobin levels even beyond 3 months prior to the time of the referral. The median time from the anaemia being first noted to the time of referral was 777.5 days (interquartile range [IQR]: 390.75–1,066 days). Of these 136 patients, 13 were diagnosed with CRC. The median patient age of this subgroup was 81.7 years (IQR: 80.9–84.4 years). Two out of these thirteen patients had no other colorectal symptoms. They both had Dukes' A ascending colon adenocarcinoma.

Discussion

Delays in the diagnosis, referral and investigation of IDA have been reported previously.^{5–8} In a large UK study of 20,000 patients with IDA, 44.8% had no recorded referral or had a referral unrelated to anaemia or the GI tract.⁵ Acher *et al* reported that 12% of CRC patients who had IDA at diagnosis were known to have IDA for more than six months before their CRC diagnosis.⁶ Another study found that suspected or even confirmed IDA was the most common cause associated with missed opportunities of diagnosing CRC and that these cases had the longest time to endoscopic referral (median: 393 days).⁷ In our study, 52.9% (136/257) of anaemic patients at Centre B who were referred under the 2-week wait rule had known low haemoglobin levels, for a median time of 777.5 days.

In view of the above timings, the views of GPs were explored with regard to the referral and investigation of anaemia. The majority (38%) of GPs would refer confirmed IDA to gastroenterology, 23% would refer to colorectal surgeons and 8% would refer to haematology (Fig 1). Damery *et al* showed that the median time to CRC diagnosis ranged from 2.5 months with referral to a surgical specialty (including gastroenterology) to 31.9 months with referral to haematology.⁵ Raje *et al* also found that patients with IDA were more likely to be referred as non-urgent cases to gastroenterologists, resulting in investigation delays.⁹

Our survey showed that 84% of GPs would not refer a patient with microcytic anaemia prior to confirming iron deficiency status and this would be in accordance with the suspected CRC referral guidelines.^{1–3} In addition, 92% of GPs would not refer unexplained normocytic anaemia prior to confirming iron deficiency status. Although the survey's response rate was low (29%), its results may explain the delays in the referral and investigation of anaemia. Such delays are due to the lack of consensus in the guidelines for the management of normocytic anaemia where iron deficiency is not confirmed (ie within the spectrum of the disease progression from iron depletion to normocytic and microcytic anaemia).¹⁰

In order to investigate the need for endoscopic evaluation in fast track patients at different anaemia states, their CRC yield was examined. A logistic regression analysis of results from Centre B showed that microcytosis (which is a sensitive indicator of iron deficiency)^{4,11} was significant in predicting CRC but overall anaemia did not reach

statistical significance. This finding would be in agreement with BSG guidelines recommending investigation of iron deficiency despite anaemia level.⁴

However, the results from both fast track patient cohorts showed that there was no statistically significant difference in the yield of CRC between patients with microcytic anaemia and normocytic anaemia (Centre A: $p=0.781$, Centre B: $p=0.196$). No statistically significant difference was seen even when a subgroup analysis was performed for patients with anaemia only and no GI symptoms. Our results provide insufficient evidence to support awaiting confirmation of IDA in fast track patients with normocytic anaemia and with/without colorectal symptoms prior to requesting bowel investigations.

Finally, we examined the yield of CRC in the anaemic and not anaemic state with the presence of low or normal/above normal Fe/ferritin. The yield of CRC in fast track patients with low Fe (for Centre A) or ferritin (for Centre B) was not significantly different between anaemic and non-anaemic patients (Table 2) although this analysis was based on low numbers.

Following a prospective study of 151 elderly patients with iron deficiency, Joosten *et al* reported that lower GI lesions were found in 32% of anaemic and in 16% of non-anaemic patients ($p=0.05$).¹² Park *et al* looked at 1,518 cases of patients with iron deficiency and found that clinically important lesions were identified to a similar extent in iron deficiency patients irrespective of whether they had anaemia and that the patients without anaemia were more likely to have early stage neoplasia.¹³ A large prospective population-based study of patients aged 65 years or older, where no selected groups of patients were included as in the previous studies described, showed that the prevalence of (both upper and lower) GI malignancy was 9% in IDA patients and 2.3% in iron deficient non-anaemic patients.¹⁴

The BSG guidelines are based on the latter large study and recommend investigation of iron deficiency at any level of anaemia.⁴ However, for iron deficiency without anaemia, they only tentatively recommend investigation following discussion of risks and benefits of GI evaluation in high risk patients.

The strengths of this study are that it involves two large fast track cohorts from different geographical regions. The demographic characteristics of the two patient groups were similar. However, potential limitations also exist. This study was based on a selected group of patients who were referred for suspected CRC. Consequently, the results may not be generalisable to the overall population of patients with microcytic or normocytic anaemia. Several cases were excluded when no blood tests or notes were available, thereby potentially introducing selection bias. Ferritin or Fe measurements were not performed in all patients from the microcytic and the normocytic anaemia groups, and so patients with no such measurements had to be excluded when the analysis concentrated on ferritin or Fe levels. In addition, some of the subgroups had low patient numbers and the subgroup analyses may therefore have been underpowered to detect clinically relevant differences.

Conclusions

The main finding of this study is that the yield of CRC in normocytic anaemia is not significantly different to that of microcytic anaemia in fast track patients. This study was performed in a selected group of patients but provides insufficient evidence to support awaiting confirmation of IDA in fast track patients with normocytic anaemia prior to requesting bowel investigations. Further studies are needed in order to examine the yield of CRC in normocytic anaemia and establish whether we should await confirmation of IDA prior to endoscopic investigations.

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References

1. Department of Health. *Referral Guidelines for Suspected Cancer*. London: DH; 2000.
2. National Institute for Health and Clinical Excellence. *Referral Guidelines for Suspected Cancer*. London: NICE; 2005.
3. ACPGBI Referral guidelines for colorectal cancer. *Colorectal Dis* 2002; **4**: 287–297.
4. Goddard AF, James MW, McIntyre AS, Scott BB. Guidelines for the management of iron deficiency anaemia. *Gut* 2011; **60**: 1,309–1,316.
5. Damery S, Ryan R, Wilson S *et al*. Iron deficiency anaemia and delayed diagnosis of colorectal cancer: a retrospective cohort study. *Colorectal Dis* 2011; **13**: e53–e60.
6. Acher PL, Al-Mishlab T, Rahman M, Bates T. Iron-deficiency anaemia and delay in the diagnosis of colorectal cancer. *Colorectal Dis* 2003; **5**: 145–148.
7. Singh H, Daci K, Petersen LA *et al*. Missed opportunities to initiate endoscopic evaluation for colorectal cancer diagnosis. *Am J Gastroenterol* 2009; **104**: 2,543–2,554.
8. Logan EC, Yates JM, Stewart RM *et al*. Investigation and management of iron deficiency anaemia in general practice: a cluster randomised controlled trial of a simple management prompt. *Postgrad Med J* 2002; **78**: 533–537.
9. Raje D, Mukhtar H, Oshowo A, Ingham Clark C. What proportion of patients referred to secondary care with iron deficiency anemia have colon cancer? *DisColon Rectum* 2007; **50**: 1,211–1,214.
10. Sadahiro S, Suzuki T, Tokunaga N *et al*. Anemia in patients with colorectal cancer. *J Gastroenterol* 1998; **33**: 488–494.
11. Kishida T, Sato J, Fujimori S *et al*. Clinical significance of serum iron and ferritin in patients with colorectal cancer. *J Gastroenterol* 1994; **29**: 19–23.
12. Joosten E, Ghesquiere B, Linthoudt H *et al*. Upper and lower gastrointestinal evaluation of elderly inpatients who are iron deficient. *Am J Med* 1999; **107**: 24–29.
13. Park JS, Park DI, Park SK *et al*. Endoscopic evaluation of significant gastrointestinal lesions in patients with iron deficiency with and without anaemia: a Korean Association for the Study of Intestinal Disease Study. *Intern Med J* 2009; **39**: 441–446.
14. Ioannou GN, Rockey DC, Bryson CL, Weiss NS. Iron deficiency and gastrointestinal malignancy: a population-based cohort study. *Am J Med* 2002; **113**: 276–280.