

Research Article

Establishing Absolute Iron Deficiency Anemia before Referring Patients to Colorectal Fast Track Clinics can Help to Increase the Diagnostic Yield of the Bowel Cancer Screening Programme

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Abstract

Background: Although there are strict and specific guidelines for referring patients with Iron Deficiency Anaemia (IDA) to Fast Track Colorectal Cancer (FT CRC) clinics for further assessment and investigation, patients with other types of anaemia are still referred by primary care physicians in the UK.

Aim: Our aim is to find out whether this practice is correct, or if it is causing an overburden on colorectal clinics and endoscopy services. We also want to find out whether true/absolute IDA has a higher predictive value for diagnosing Colorectal Cancer (CRC) compared to other types of anaemia and specific bowel symptoms.

Our hypothesis was that patients with IDA are more likely to have CRC compared to patients with no anaemia or non-IDA anaemia. By confirming this hypothesis, we can identify high risk patients from the population who can then be preferentially subjected to investigations mandated by guidelines. This strategy can help to increase the diagnostic yield of FT CRC clinics.

Materials and methods: A retrospective cohort study was conducted from 2016-18 in a single busy district general hospital providing services to a population of 700,000 people.

Results: In our study, patients with true IDA (low MCV and ferritin) were found to be more likely to have CRC compared to any other type of anaemia which confirmed the latest guidelines for management of IDA. Compared to symptoms, only the presence of a mass on abdominal examination and rectal examination was found to be more likely associated with cancer.

Conclusion: Physicians should be able to stratify patients based on blood indices when referring them to FT CRC clinics. Diagnostic yield of these clinics can be increased if clinicians strictly adhere to fast track guidelines and confirm true IDA before referring patients to clinic.

Keywords: Iron deficiency anaemia; Colorectal cancer; Fast track clinics; Functional iron deficiency anaemia; Microcytic anaemia; True iron deficiency anaemia; Department of health referral criterion

Introduction

The Department of Health in the UK implemented a two-week fast track referrals rule in July 2000 based on the recommendations from NICE, ACPGIB and BGS. A set of diagnostic referral criteria were devised to help general practitioners stratify patient risk based on age, symptoms and blood results. Guidelines were also made to assist primary care clinicians in deciding which patient should be referred urgently based on this criterion (ACPGIB 2002 guidelines). It was claimed that with the use of the diagnostic criteria almost 90% of cancer cases will be picked up in fast track clinics [1].

The diagnostic criteria consist of all high-risk factors related to bowel cancer such as age, bowel related signs and symptoms, evidence of rectal bleeding and presence of IDA. Efforts have been made in the past to increase the diagnostic yield of FT CRC clinics. At present overall diagnostic yield of these clinics has been reported anywhere between 9% to 13% [2].

An issue arises when patients are referred with anaemia without investigating them for IDA first. This is contrary to guidelines mapped out for FT CRC referrals and this practice overburdens the fast track clinics and endoscopy services which are designed for patients strictly fulfilling diagnostic criteria. There are NICE guidelines which are based on recommendations from BGS guidelines for the management of IDA. These suggest urgent referral to FT CRC clinics only if the patient is above 60 years of age with IDA or of any age with the symptom of rectal bleeding or a positive faecal occult blood test [3].

The aim of this study was to find out whether the practice of referring patients with anaemia indiscriminately to FT CRC clinics is correct and how can we further stratify high risk patients based on their symptoms and blood indices to increase the diagnostic yield of these clinics for patients with anaemia.

Citation: Majeed T, Chauhan MN, Allan J, Magee C. Establishing Absolute Iron Deficiency Anemia before Referring Patients to Colorectal Fast Track Clinics can Help to Increase the Diagnostic Yield of the Bowel Cancer Screening Programme. *Gen Surg.* 2019; 1(2): 1008.

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Publisher Name: Medtext Publications LLC

Manuscript compiled: June 25th, 2019

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Materials and Methods

This was a retrospective observational study from a busy district general hospital. A retrospective analysis of prospectively maintained data for FT CRC was performed. Data was selected from 2016-18. A cohort of 4177 patients presented to FT clinics. Among them 950 (22.74%) patients were referred with anaemia. The primary outcome was comparing diagnostic yield of FT CRC clinics for different types of anaemia. We also compared diagnostic yield based on presenting bowel symptoms. Secondary outcomes were the possibility of finding the feasibility of common anaemia pathway for asymptomatic anaemia and straight to imaging guidelines for patients who are more likely to have an extraluminal malignancy. A third secondary outcome was to assess the effectiveness of FT services for diagnosing cancers at an early Dukes stage.

Two types of data were analyzed for a relationship to the diagnosis of cancer. T-tests were used to compare those with and without a cancer diagnosis on Red Blood Cell (RBC) indices, including Mean Corpuscular Hemoglobin Concentration (MCHC), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), as well as serum ferritin levels. Levene's tests were used to assess differences in variance, and a t-test not assuming equal variances was used when the Levene's test was statistically significant. Pearson chi-square analyses were used to compare those with versus without a cancer diagnosis on the presence of various symptoms as well as on frequencies above and below the standard cut points for RBC indices and serum ferritin. Fisher's exact tests were used when expected cell frequencies were below five. A Mantel-Haenszel test was used to assess the trend in cancer prevalence across combined categories of serum ferritin and MCV. An alpha of 0.05 was used as the level of significance.

Results

4177 patients were referred to FT CRC clinics out of which 950 patients were referred for anaemia. 90 patients were diagnosed with cancer, 62 with colorectal cancer, 21 with extra luminal cancer and 7 with esophagogastric cancer. 40% of patients diagnosed with cancer had been offered imaging first because of frailty, symptoms and patient preference. 81% of patients (17/21) were radio logically diagnosed with extra luminal malignancies. 60% of patients were diagnosed on endoscopy and only 4 (19%) of these were confirmed with subsequent staging scans.

Red blood cell indices

The results of t-tests on the RBC indices and serum ferritin are presented in Table 1. As shown, mean levels of all indices were significantly lower in those diagnosed with cancer.

The presence of a cancer diagnosis was assessed for with RBC indices and serum ferritin below the standard cut-offs. Table 2 presents the results. Except for MCHC, the incidence of cancer was significantly higher in patients with values below the cut-offs. The Mantel Haenszel trend test indicated that the incidence of cancer was highest in patients with a combination of low serum ferritin and low MCV (9.7%), and decreased across categories, with only 1.8% of patients diagnosed with cancer when both MCV and serum ferritin were within normal ranges.

Symptomatology

The presence of a cancer diagnosis was assessed in patients with a variety of symptoms in addition to their diagnosis of IDA. Table 3 presents the results. Of the seven symptoms reviewed, only the

presence of an abdominal mass was significantly related to a diagnosis of cancer.

Discussion

CRC is the third most common cancer in UK with few cases being diagnosed at an early stage [1]. Most patients present with advanced cancer as acute surgical admissions with malignant obstruction, bleeding and perforation [2]. The diagnostic yield of routine CRC clinics is low, and this causes delays in the diagnosis of cancer [3]. Almost 90% of the health budget allocated for cancer diagnosis and screening is used on patients who do not have cancer. Since 2000, the Department of Health has introduced a two week wait referral pathway for patients with specific signs, symptoms and blood results for early screening, diagnosis and treatment.

The diagnostic criteria introduced in 2000 has been recently modified. It includes specific bowel related symptoms, signs such as abdominal or rectal masses and IDA with or without the presence of rectal bleeding. In the latest guidelines, the symptom duration and threshold for diagnosis for anaemia have been decreased. The signs and symptoms in the diagnostic criteria are specific to bowel except for asymptomatic IDA (Table 4).

Anaemia affects one third of the human population and half of these are iron deficient. IDA occurs in two forms; functional and absolute. Absolute or true IDA arises when total body iron stores are low, while functional IDA is defined when total body iron stores are normal or increased, but the iron supply to the bone marrow is inadequate.

Latest guidelines for IDA from BSG suggest that red blood indices (mean cell volume, mean cell hemoglobin) and ferritin levels below cut-off are most specific indicators to diagnose IDA. Hb levels are

Table 1: RBC indices and serum ferritin in patients with versus without a cancer diagnosis.

| | Cancer Diagnosis | | | | | | | | |
|----------------|------------------|-------|-------|-----|--------|--------|-------|-------|--------|
| | Yes | | | No | | | t | df | p |
| | N | Mean | SD | N | Mean | SD | | | |
| MCHC | 69 | 99.90 | 20.48 | 834 | 105.66 | 15.95 | 2.82 | 901 | 0.005 |
| MCV | 69 | 79.25 | 8.23 | 830 | 82.50 | 8.70 | 3.00 | 897 | 0.003 |
| MCH | 69 | 24.47 | 3.64 | 825 | 26.03 | 3.65 | 3.41 | 892 | 0.001 |
| Serum Ferritin | 54 | 27.15 | 49.34 | 657 | 59.55 | 149.64 | 3.64* | 156.2 | <0.001 |

*t-test not assuming equal variances

Table 2: Incidence of cancer by low versus normal RBC indices and serum ferritin.

| RBC/ Ferritin | Cutoffs | Cancer Diagnosis | Total | Percent | χ ² | P |
|----------------|----------------------------|------------------|-------|---------|-------------------|-------|
| MCHC | under 130 | 65 | 853 | 7.60% | a | 0.788 |
| | 30+ | 4 | 50 | 8.00% | | |
| MCV | ≤ 90 | 66 | 753 | 8.80% | 7.77 | 0.005 |
| | over 90 | 3 | 146 | 2.10% | | |
| MCH | ≤ 30 | 67 | 802 | 8.40% | 4.43 | 0.035 |
| | over 30 | 2 | 92 | 2.20% | | |
| Serum Ferritin | under 30 | 48 | 534 | 9.00% | 5.94 | 0.015 |
| | 30+ | 6 | 177 | 3.40% | | |
| MCV/ Ferritin | Microcytic/low ferritin | 47 | 485 | 9.70% | 8.50 ^b | 0.004 |
| | Microcytic/normal ferritin | 5 | 120 | 4.20% | | |
| | Normocytic/low ferritin | 1 | 45 | 2.20% | | |
| | Normocytic/normal ferritin | 1 | 57 | 1.80% | | |

^aFisher's exact test

^bMantel-Haenszel trend test

less specific and only a very low Hb indicates significant underlying pathology [4]. IDA with normal Hb is very common presentation and should be investigated regardless of Hb levels. Prior to 2017, the NHS National Institute for Health and Clinical Excellence referral guidelines for suspected lower GI cancer suggested that only patients with Hb concentration <11 g/dl in men or <10 g/dl in non-menstruating women should be referred. With new recommendations it was accepted that these cut-off values can miss patients with colorectal cancer, particularly males. It is therefore recommended that any level of anaemia should be investigated in the presence of IDA. For the same reason NICE recommendations changed from a Hb cut off value to a more liberal definition of IDA to accommodate more patients at risk of CRC [5]. Ferritin level is the second most sensitive indicator of IDA. However, its value is limited in certain patient groups because ferritin levels can be altered independent of iron levels in conditions such as chronic and inflammatory diseases. Ferritin levels below cut off values defined by local laboratory protocols along with low red cell indices are considered more sensitive in diagnosing IDA [4].

Reporting of IDA is also unreliable as the diagnostic criteria to establish IDA varies. The same problem is faced in situations where patients are referred to FT CRC clinics with low HB but no confirmation of IDA. Physicians referring patients with non-IDA types of anaemia results in low diagnostic yield of CRC clinics (Table 5).

Patients with anaemia of no apparent cause are typically referred to colorectal surgeons, gastroenterologists or haematologists. As there are no clear guidelines on when to refer to the latter two, primary care physicians preferentially refer to colorectal clinics regardless of the diagnostic criteria. This practice leads to overburdening of FT CRC services.

In a large retrospective cohort analysis, Thompson et al. [6] showed that a combination of symptoms, age, IDA and mass can be used to further stratify patients into high and low risk groups before referral. Our study is proving the same rationale for IDA but in more detail.

Panagiotopoulou et al. [7] have done a similar study in 2014 and

Table 3: Incidence of cancer by presence versus absence of symptoms.

| Symptom | | Cancer diagnosis | Total | Percent | χ^2 | P |
|------------------------|---------|------------------|-------|---------|----------|-------|
| Change in Appetite | Absent | 69 | 897 | 7.70% | a | 1.000 |
| | Present | 0 | 6 | 0.00% | | |
| Lethargy/Fatigue | Absent | 68 | 901 | 7.50% | a | 0.147 |
| | Present | 1 | 2 | 50.00% | | |
| Rectal Mass | Absent | 68 | 897 | 7.60% | a | 0.380 |
| | Present | 1 | 6 | 16.70% | | |
| Rectal Bleeding | Absent | 61 | 812 | 7.50% | 0.19 | 0.663 |
| | Present | 8 | 91 | 8.80% | | |
| Change in Bowel Habits | Absent | 56 | 776 | 7.20% | 1.41 | 0.235 |
| | Present | 13 | 127 | 10.20% | | |
| Abdominal Mass | Absent | 65 | 890 | 7.30% | a | 0.013 |
| | Present | 4 | 13 | 30.80% | | |
| Abdominal Pain | Absent | 67 | 890 | 7.50% | a | 0.261 |
| | Present | 2 | 13 | 15.40% | | |

^afisher's exact test

Table 4: Diagnostic yield of symptomatic vs. asymptomatic IDA.

| Mode of presentation | Number of patients with cancers | Diagnostic yield % |
|-------------------------|---------------------------------|--------------------|
| Asymptomatic IDA | 53 | 8.28 |
| IDA with bowel symptoms | 29 | 13.55 |
| IDA with rectal bleed | 8 | 8.33 |

though their focus was different, there results are relevant to our study. The conclusion of their study was that there is no difference in diagnostic yield of CRC between patients with microcytic and normocytic anaemia. They recommended that primary care clinicians should refer patients to FT CRC clinic without confirming IDA. These results were actually interesting and give further strength to our study. The overall diagnostic yield in the study was anywhere from 2.8% to 30% between sub-groups. They found that microcytosis alone has a diagnostic yield of 17.5% while combination of microcytosis and low iron was as high as 30% compared to overall diagnostic yield of 11%. A recent review of 1500 consecutive patients referred to FT CRC clinics has showed similar results (Table 6) [8].

All evidence, including our own data, suggests that patients who are fulfilling diagnostic criteria for IDA should be referred to FT CRC clinics based on red cell indices and ferritin. In contrast, patients who do not qualify for IDA criterion should either be considered for routine CRC referral or a straight to imaging approach, depending on factors such as age or symptoms. These findings can become a basis for future referral guidelines and can help to improve the diagnostic yield of FT CRC clinics by ensuring it is high risk patients that are attending these clinics.

Our study has found that a large proportion of patients are diagnosed on imaging as opposed to endoscopy and a significant number were diagnosed with renal, prostate, hematological and gynecological malignancies. This demonstrates that a straight to scans approach is more efficacious in IDA patients with no bowel symptoms. A recent systematic review and meta-analysis has proved the utility of CT colonography for detection of CRC [9]. Kim et al. [10] have showed similar results for imaging versus colonoscopy for diagnosing both early and advanced stage carcinoma.

A limitation of our study included patients being referred without ferritin levels; almost half of the referrals were made without iron studies, which made it impossible to include these patients in the final analysis. This highlights a major lapse in our services as ferritin levels are as important as red cell indices for diagnosing IDA [11,12].

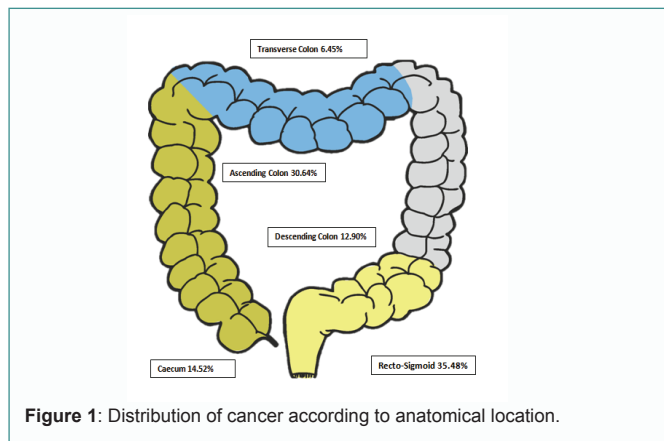
The next question we wanted to answer is whether the fast track referral system is allowing us to diagnose cancer at an early curable stage. This study has focused specifically on patients referred for IDA, but it is helpful to understand what stage of cancer patients are

Table 5: Summary of results.

| | |
|-----------------------------------|-----------------|
| Age (median=m) | 75.6 +/- 10.4 |
| Gender (%) | M/F 49.3%/50.7% |
| Colorectal cancers diagnosed | 62 |
| Esophagogastric cancers | 7 |
| Extraluminal cancers | 21 |
| Inappropriate referrals (%) | 245 (25.78%) |
| Time between referrals to FTC (m) | 10 DAYS |
| Referral to test (m) | 13 DAYS |
| Cancers diagnosed with scan (%) | 40% (36/90) |
| Cancers diagnosed with scopes % | 60% (56/90) |

Table 6: Distribution of cancers based on type of anaemia.

| Types of Cancer | Microcytic with low ferritin | Microcytic with normal ferritin | Normocytic with low ferritin | Normocytic with normal ferritin |
|--------------------------------|------------------------------|---------------------------------|------------------------------|---------------------------------|
| Colorectal Cancer (n=62) | 88.70% | 8.06% | 1.61% | 1.61% |
| Esophagogastric junction (n=7) | 100% | 0% | 0% | 0% |
| Extra-luminal cancers (n=21) | 23.80% | 28.57% | 33.33% | 14.30% |



presenting at. More than 60% of patients were diagnosed at Dukes stage C or D while only 9.67% were diagnosed at Dukes stage A and 29% at Dukes stage B (Table 7). Thornton et al. have also showed that there is no difference in likelihood of curative resection in patients presenting with either FT or non-FT route [13].

Table 7: Duke staging for diagnosed cancer patients' overall trend and based on blood results.

| Stage of cancer | Proportion of patients with cancer | Microcytic with low ferritin | Microcytic with normal ferritin | Normocytic with low ferritin | Normocytic with normal ferritin |
|-----------------|------------------------------------|------------------------------|---------------------------------|------------------------------|---------------------------------|
| Duke A | 9.67% | 57.14% | 42.85% | 0% | 0% |
| Duke B | 29% | 100% | 0% | 0% | 0% |
| Duke C | 22.58% | 93.33% | 6.66% | 0% | 0% |
| Duke D | 38.70% | 82.60% | 17.39% | 0% | 0% |

The last question is what to do with patients who have anaemia with no confirmation of IDA and with no symptoms. Our data suggest that first we need to establish that they are not iron deficient and then refer them to an MDT anaemia clinic run by Colo-rectal surgeons, gastroenterologist and haematologist. Although this is a hypothetical idea, but it is quite feasible in busy units. There is also a need to provide provisions to general practitioners to arrange straight to scan facility for patients with IDA with no symptoms and an unknown aetiology of their anaemia.

Conclusion

Establishing IDA and exploration of symptoms must be a pre-requisite before referring patients to FT CRC to increase the diagnostic yield of colorectal cancer diagnosis. Patients with IDA should be referred preferentially over patients with no anaemia or other types of anaemia.

What this Paper is Adding

The concepts of functional IDA and actual or true IDA were not very clear in previous literature and just recently BGS guidelines have published updated criteria to diagnose IDA. Patients are referred to CRC clinics without confirmed IDA and are still considered appropriate for referral if their Hemoglobin (Hb) and ferritin are below normal levels. Hb and ferritin levels can easily be affected by the presence of chronic diseases, concomitant iron therapy and inflammatory conditions making them unreliable indicators when used as sole criteria for diagnosing IDA.

Our recommendations are based on recent high-level evidence [4,12] and our own results suggest that patients with true IDA should get a priority for referral to FT CRC clinics while low risk patients with no anaemia or functional IDA should be investigated routinely

rather than immediate referral to FT CRC clinics. Simple full blood count with peripheral film and ferritin levels are all that are required to refer a patient based on true IDA.

As there is a high incidence of extraluminal cancers in this cohort and most of these are diagnosed with imaging, going straight to imaging without needing a FT CRC clinic visit can avoid overburdening FT and endoscopy services, especially in patients with no symptoms.

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