Colorectal cancer and the blood loss paradox

Orouba Almilaji MSc [1 2], Sally D Parry MD FRCP [1], Sharon Docherty PhD [2], Jonathon Snook MA DPhil FRCP [1]

[1] Gastroenterology Unit, Poole Hospital, University Hospitals Dorset, Poole, UK

[2] Department of Medical Science and Public Health, Bournemouth University, Bournemouth, UK

Correspondence: Dr Jonathon Snook

Consultant Gastroenterologist

Poole Hospital, UHD

Longfleet Road, Poole

Dorset BH15 2JB

Tel : 0044 300 0198678

E-mail : Jonathon.Snook@gmail.com

Abstract

Background

Faecal occult blood (FOB) positivity and iron deficiency anaemia (IDA) are common manifestations of colorectal cancer (CRC) and both potentially facilitate diagnosis at an earlier, more treatable stage. It has been assumed that both are the consequence of low-grade blood loss from the tumour bed.

Method

A retrospective analysis of 1121 cases of CRC diagnosed at a single centre between 2010 and 2016, comparing cases presenting via FOB-based bowel cancer screening programme (BCSP) and IDA pathways for a series of variables including age, sex, tumour location and prevalence of anaemia.

Results

The BCSP and IDA pathways each accounted for about 15% of the total case load. There were significant differences between the BCSP and IDA sub-groups in median age (68 v 78 years : $P<0.001$), median Hb (138 v 89 g/l : $P<0.001$) and proportion of lesions in right colon (31.1% v 82.5% : $P<0.001$). The major disparity in the prevalence of anaemia (overall 20.0% v 98.2% : $P<0.001$) persisted when controlled for tumour location.

Conclusion

Paradoxically, CRC screening through the detection of FOB positivity and IDA identifies distinctly different sub-populations of cases. The theoretical implication is that an additional mechanism may be required to explain the development of IDA in CRC. The practical implication is that screening for IDA may have a complementary role to the BCSP in population screening for CRC.

Summary box

What is already known about this subject?	Faecal occult blood (FOB) positivity and iron deficiency anaemia (IDA) are common early manifestations of colorectal cancer (CRC), presumed due to low-grade blood loss from the tumour bed.
What are the new findings?	Patients with CRC diagnosed via FOB and IDA pathways show significant differences in the proportion with right-sided cancer (31% v 82%, P<0.001) and anaemia (20% v 98%, P<0.001). This might imply that they identify distinct CRC sub-populations.
How might it impact on clinical practice in the foreseeable future?	The findings have theoretical implications for the mechanism of IDA in CRC. The major practical impact is support for the concept that systematic monitoring of at-risk populations for IDA may complement the current bowel cancer screening programme.

Keywords

Colorectal cancer

Bowel cancer screening programme

Iron deficiency anaemia

Abbreviations

CRC	Colorectal cancer
IDA	Iron deficiency anaemia
Hb	Blood haemoglobin concentration
BCSP	Bowel Cancer Screening Programme
FOB	Faecal occult blood
gFOBt	Guaiac-based faecal occult blood testing
FIT	Faecal immunochemical testing

Introduction

Colorectal cancer (CRC) is the fourth commonest cancer in the United Kingdom, accounting for 12% of all new cases; and the second commonest cause of cancer-related death, responsible for about 10% of events [1 2]. Although the mortality from CRC is slowly falling, the 5-year survival rate for CRC is still relatively poor at 58% [3 4].

Because CRC may not cause symptoms until the disease is already advanced, the focus over recent years has been on early diagnosis by screening of the pre-symptomatic at-risk population [1 5]. The English Bowel Cancer Screening Programme (BCSP) was developed with the aim of reducing the mortality rate [5]. Guaiac-based faecal occult blood testing (gFOBt) was introduced in 2006 (and switched to the faecal immunochemical test (FIT) in 2019), the aim being to detect in stool samples the presence of small quantities of blood derived from the tumour bed. Bowel cancer screening by gFOBt has been shown to reduce the mortality rate of CRC by about 15%, primarily because cases are detected at an earlier stage [6-8].

The second major pathway for pre-symptomatic diagnosis of CRC is through the detection of iron deficiency anaemia (IDA) [9-14], believed to be due to chronic low-grade loss of (iron-rich) blood from the tumour bed, resulting in the slowly progressive depletion of iron stores. As IDA often occurs before any other clinical manifestations of CRC [13 14], and may precede the diagnosis of CRC by up to 2 years [15], detection of it can also provide an opportunity to diagnose CRC earlier in the disease course. This is the major rationale for the investigation of unexplained IDA in the at-risk population on an urgent basis [16 17].

It could be argued that FOB positivity and IDA are two sides of the same coin, both being manifestations of chronic blood loss from the CRC tumour bed. It

might therefore be predicted that these two approaches to the early diagnosis of CRC might identify broadly similar CRC sub-populations. The aim of this study was to assess whether this is in fact the case, by comparing the clinical characteristics of patients with CRC diagnosed via BCSP and IDA pathways, based on the analysis of a large single centre database.

Method

We undertook statistical analysis of anonymised clinical data for all 1258 cases on the Poole Hospital CRC MDT database for the years 2010 to 2016 inclusive. The data was assessed in 2018 for the purposes of a service audit and included:

- age at diagnosis
- sex
- haemoglobin concentration (Hb) at presentation – anaemia was defined as an Hb below the lower limit of normal for the local laboratory (130 g/l for males, 115 g/l for females)
- tumour number, histology and location(s)
- presentation pathway - (1) symptomatic, (2) BCSP or (3) IDA

For the purposes of this study, CRCs located at or distal to the splenic flexure were considered left-sided, whilst those proximal to splenic flexure were labelled right-sided. Cases with synchronous tumours were considered right-sided if any tumour was proximal to the splenic flexure.

All subjects in the IDA group had the diagnosis confirmed by haematinics according to standard criteria [14 16]. Most in this group were channelled through an IDA Clinic with a protocol for ensuring this [13].

The “symptomatic” presentation group comprised cases with symptoms relating directly to the underlying CRC (other than symptomatic anaemia) that resulted in GP referral or emergency admission to secondary care. Patients with both bowel symptoms and IDA were allocated to a presentation pathway based on which was felt to be the dominant feature – in a few cases this was rather arbitrary, but the allocation was made without knowledge of tumour site or stage.

About 11% of cases were removed from the database after applying exclusion criteria (listed in Table 1). The commonest reason for exclusion due to incomplete data was the absence of a blood count result in the patient record. Of the cases remaining, 90% had histologically confirmed colorectal adenocarcinoma, and most of the others had high-grade dysplasia on biopsy, undifferentiated carcinoma, or signet cell carcinoma. In the small minority without histological confirmation, cases were included only if the radiological features were regarded as characteristic of CRC, and they were managed as such clinically.

Pearson’s Chi-squared test was used to compare sex ratio, side proportions, and anaemia proportions in the IDA and BCSP groups. The Mann-Whitney test was used to compare age and Hb in IDA and BCSP groups. The significance level was set to 0.05. R (version 3.6.1) and RStudio (version 1.2.5001) were used to run the statistical tests and to produce the descriptive statistics.

Table 1 Exclusion criteria and numbers

Incomplete dataset	34
Second entry due to metachronous CRC	7
Other neoplasm eg neuroendocrine tumour, anal carcinoma	35
Non-incident presentation, CRC diagnosed elsewhere	27
CRC diagnosed on cancer follow-up or incidental finding on scan	34

Results

After applying the exclusion criteria, 1121 cases were available for detailed analysis, and eight of these had synchronous CRCs. Just under 70% of cases presented via the symptomatic pathway, with about 15% each through the BCSP and IDA routes (Table 2).

There was a major difference between the BCSP and IDA groups in the proportion of cases with anaemia at diagnosis (Table 2). The prevalence of anaemia in the IDA group was of course high by definition – the figure was 98.2% rather than 100% because a small number of cases with confirmed iron deficiency were not anaemic by laboratory criteria. In contrast, only a small minority of the BCSP group were anaemic, despite being FOB positive by definition - the figure was 20%, compared to 46.6% for the symptomatic group and 98.2% for the IDA group (Figure 1).

The other major difference between the BCSP and IDA groups was in the location of the CRCs identified. Whilst 39% presented with right-sided tumours overall, the proportion was markedly higher in the IDA group. Right sided tumours accounted for 31.6% in the symptomatic group and 31.1% in the BCSP group, compared to 82.5% of the IDA group (Table 2).

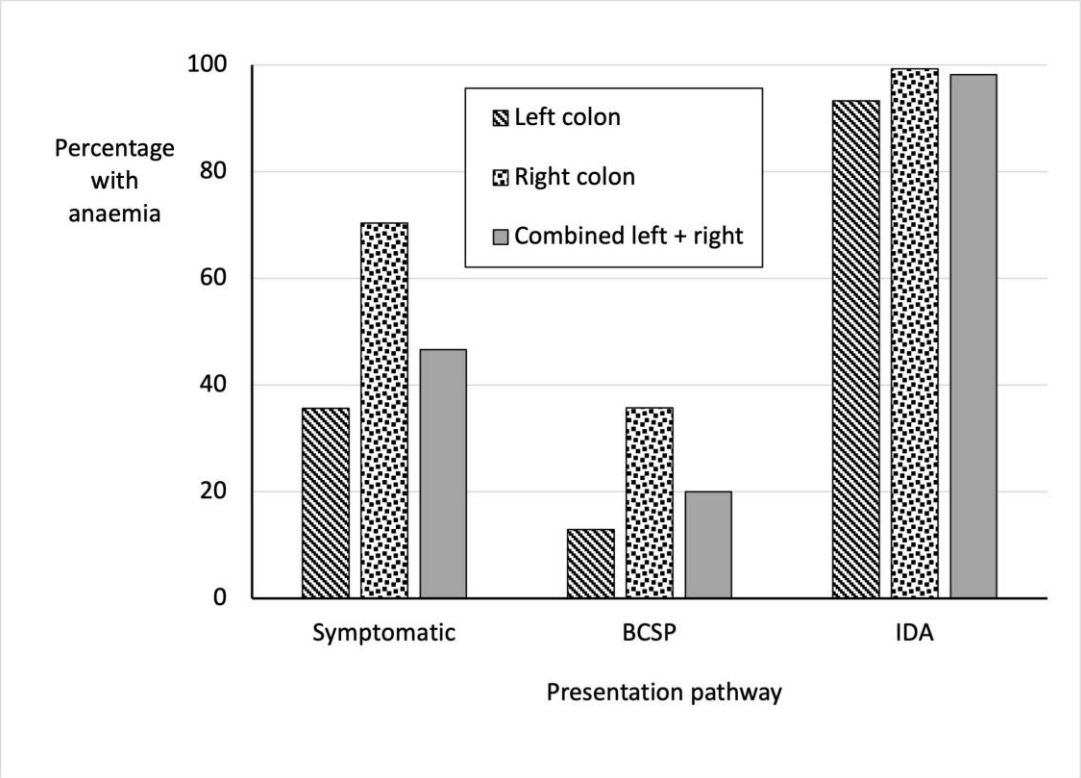
To explore the possibility that tumour location might account for the observed difference in the prevalence of anaemia in the two groups, the percentage of cases meeting laboratory criteria for anaemia were broken down by presentation pathway and tumour location. Figure 1 shows that regardless of location, only a small minority of BCSP subjects were anaemic.

Table 2 also reveals differences between the BCSP and IDA groups in terms of the other variables assessed. Predictably, subjects with CRC presenting through the BCSP pathway were younger at diagnosis. There was a trend towards BCSP cancers being commoner in males than females, though this did not reach statistical significance.

Table 2 Descriptive statistics of the CRC dataset according to presentation pathway (BCSP : Bowel Cancer Screening Programme; IDA : iron deficiency anaemia; Q1 – Q3 : interquartile range; Hb : haemoglobin concentration at diagnosis)

		Symptomatic	**BCSP**	**IDA**	**P value [BCSP v IDA]**
Number	n (% of cohort)	770 (68.7%)	180 (16.1%)	171 (15.3%)	-
Sex ratio	M / F	1.3	1.4	1.1	0.34
Age (years)	Median (Q1-Q3)	75 (64 - 82)	68 (64-71)	78 (71-86)	<0.001
Hb (g/l)	Median (Q1-Q3)	124 (106-140)	138 (126-147)	89 (80-100)	<0.001
Anaemic	n (% of group)	359 (46.6%)	180 (20.0%)	168 (98.2%)	<0.001
Right-sided	n (% of group)	243 (31.6%)	56 (31.1%)	141 (82.5%)	<0.001

Figure 1 The percentage of cases with anaemia at the time of diagnosis, subdivided by presentation pathway and tumour location. See text for definitions



Discussion

The first key observation reported here is that whilst anaemia is commonly associated with CRC, most cases presenting via the BCSP pathway are not anaemic – despite being FOB positive by definition. The literature suggests that conversely, the sensitivity of occult blood positivity for IDA-related CRC is limited. Several large case-series of FIT in the assessment of bowel-related indications have revealed that 10 – 15% of CRCs identified on investigation had a quantitative FIT < 10ug/g, and the dominant indication in this sub-group was IDA [18-20]. In keeping with this, a limited meta-analysis suggests that gFOBt and FIT both have a sensitivity of 0.83 for CRC in IDA populations – possibly over-estimated through reporting bias [21].

The second key observation is that CRC diagnosed through the IDA pathway appears to be quite distinct from that identified via the BCSP pathway – with a striking predominance of right-sided tumours, confirming previous observations [9-14]. BCSP cancers were more commonly diagnosed in males, and although this didn't reach statistical significance, it may be a relevant observation as men are less likely to take up the screening [8]. Subjects with CRC presenting through the BCSP were also younger, probably reflecting selection by the age-groups to which screening is offered [5 8].

In summary, the prevalence of anaemia in BCSP-detected tumours is paradoxically low, the prevalence of occult blood positivity in IDA-related tumours is limited, and there are major phenotypic differences between CRCs and subjects identified by the two pathways. This disconnect challenges the assumption that occult blood positivity and iron deficiency are simply parallel manifestations of chronic blood loss from the tumour bed in CRC, and has both theoretical and practical implications.

The observations require a pathophysiological explanation. Tumour location may be relevant, as the yield of occult blood testing [22] and faecal haemoglobin concentrations on quantitative FIT [18] both appear to be lower for right-sided CRCs. It is unclear whether this reflects differences in tumour biology, or the partial degeneration of haemoglobin to non-immunoreactive forms during passage through the colon from right-sided lesions. The persistence of differences in the prevalence of anaemia when controlling for the side of the lesion shown in the current study implies that laterality is not the whole explanation – although it may be a contributory factor.

As the development of IDA is gradual prior to the diagnosis of CRC [15], an alternative explanation might be that BCSP tumours are picked up at an earlier stage than IDA cancers, so that although they are bleeding there has not been time to deplete body iron stores. However, whilst IDA-related CRC was historically notorious for presenting late, this may no longer be true [23].

Finally, differences in tumour biology between the right and left colon [24-30] might be relevant. One area of interest is hepcidin, a key inhibitor of dietary iron absorption [31 32]. Functionally significant tumour release of hepcidin has been described [33], and limited studies to date have revealed increased hepcidin expression in 34-66% of colorectal cancers [34 35]. It is not known whether this correlates with tumour location in the colon, or influences iron balance.

The strength of this study is the population size and homogeneity, whilst limitations include the uncertain applicability of a single centre experience. Anaemia was used as a surrogate marker of iron deficiency because the results of iron studies were not universally available, but we feel that this was reasonable as iron deficiency is the dominant mechanism of anaemia in CRC [1 9 14]. Finally, the BCSP group was screened using gFOBt, as the timeframe was prior to the change-over to FIT – although the sensitivity of gFOBt and FIT for IDA-related CRC appears to be similar [21].

The practical implication of our findings is that as BCSP and IDA pathways appear to identify different CRC sub-populations, there is a case for introducing systematic blood count monitoring to complement the BCSP [23]. The premise is that IDA screening would predominantly detect right-sided CRC, whilst the BCSP primarily targets left-sided CRC, and may be less effective for right-sided lesions [7 8].

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