Colonoscopy first for iron-deficiency anaemia: a Numbers Needed to Investigate approach

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Summary

Background: British Society of Gastroenterology guidelines recommend that gastrointestinal investigations should be considered in males and postmenopausal women presenting with iron-deficiency anaemia (IDA).

Aim: To compare the diagnostic yields and clinical effectiveness of upper and lower gastrointestinal (GI) investigation in detecting malignancy among patients presenting with IDA.

Design: Retrospective review of case notes, endoscopy records and radiology reports.

Methods: We reviewed the results of 3798 investigations in 2600 patients presenting to our hospital with IDA from October 1995 to December 2003. The findings of the 2318 gastroscopies were compared with those of the 896 colonoscopies and the 584 barium enemas. Patients diagnosed with GI malignancy were identified and their outcomes determined.

Results: Gastroscopy identified 44 patients with newly-diagnosed upper GI cancer (18 oesophageal, 26 gastric). Thus for patients being gastroscoped for IDA, the Numbers Needed to Investigate (NNI) to detect each cancer was 53. Five-year survival for these 44 patients was 10%, so the NNI to identify each curable upper GI malignancy was 527. Colonoscopy or barium enema identified 111 (7.5%) patients with newly diagnosed colorectal cancer, giving a NNI of 13. Their 5-year survival was 35%, giving a NNI to identify each curable colorectal cancer patient of 38.

Discussion: Potentially curable gastrointestinal malignancy was diagnosed over 13 times more commonly using colonoscopy or barium enema vs. gastroscopy. For patients presenting with IDA, our findings favour investigating the lower GI tract first, or performing both gastroscopy and colonoscopy during the same endoscopy list.

Introduction

Iron-deficiency anaemia (IDA) has a prevalence of between 2% and 5% in men and postmenopausal women in the Western world1,2 and is responsible for up to 13% of referrals to the gastroenterology out-patient clinic.3 Occult blood loss or malabsorption are the commonest causes of IDA in this group of patients. The prime concern is to exclude colorectal or gastric malignancy. The investigation and management of IDA is often suboptimal,4 and the presence of associated gastrointestinal symptoms is an unreliable guide to its cause.3 The British Society of Gastroenterology (BSG) guidelines therefore advise that patients with unexplained IDA should be considered for both upper gastrointestinal (GI) endoscopy (including small-bowel biopsy) and colonoscopy or barium enema, but are ambivalent...
as to the order of the investigations. Although studies suggest an upper GI abnormality will be detected in between 30% and 50% of patients with unexplained IDA, up to 15% of patients will have dual (both upper and lower GI) lesions. BSG guidelines therefore stipulate that lower GI examination is mandatory unless prior gastroscopy confirms a malignancy or coeliac disease, and Hopper’s recent study has suggested that even patients with proven coeliac disease should have lower GI investigation.

The choice of investigation to assess the colon is a further area of debate. Colonoscopy has the advantage of allowing biopsy and identifying angiodysplasia, but the endoscopist may fail to reach the caecum in 17–45% of cases. Given that most colonic lesions presenting with IDA are right-sided, a barium enema is a suitable alternative.

The aims of this study were: (i) to compare the diagnostic yield of upper and lower gastrointestinal tract investigation in diagnosing malignancy among patients with IDA; and (ii) to compare the outcomes of patients with upper and lower gastrointestinal malignancy so diagnosed. This was done by determining the numbers of patients requiring investigation by each method in order to identify each patient with cancer (i.e. the numbers needed to investigate, or NNI).

Methods

Upper and/or lower gastrointestinal investigations were performed for 2600 patients with IDA in a single district general hospital between 1 October 1995 and 31 December 2003. The results were analysed retrospectively using the hospital endoscopy database, clinical workstation, and the individual case-notes. All patients had haematologically proven IDA as the indication for the investigation, and none had evidence of overt bleeding (melaena, haematemesis or rectorrhagia) or localizing symptoms to suggest the location of the underlying pathology. Patients diagnosed with a new gastrointestinal malignancy were identified and their outcomes determined. To ensure all cancer cases were captured, the patient database was cross-referenced with lists of all cases of colorectal and upper gastrointestinal cancer, provided by the respective multidisciplinary teams. For each investigation (upper GI endoscopy, colonoscopy, and barium enema) the diagnostic yield of new malignancy was calculated to provide a NNI. The NNI to identify each patient who would go on to long-term survival following surgery for their malignancy was also calculated, using the following formula:

\[
\text{Total number of patients with IDA having this investigation} \\
\text{Cancers identified} \times \text{Proportion of patients surviving 5 years}
\]

Tumour node metastasis (TNM) staging was used to facilitate comparison between upper and lower gastrointestinal cancers. Survival times were calculated to the end of December 2004.

Statistical analysis

Statistical analysis appropriate for non-parametric data was used. Grouped data were expressed as medians (range). Cumulative survival was calculated by the Kaplan-Meier life-table method. Differences in survival times between groups of patients were analysed by the log rank method. Data analysis used SPSS, version 12.0.

Results

Details of the patients and investigations

The median age of the 2600 patients investigated for IDA was 71 years (range 10–98) and 1047 (40.3%) were male. The patients underwent a total of 3798 individual investigations: 2318 upper GI endoscopies (OGDs), 896 colonoscopies, and 584 barium enemas. Of the 1054 (41%) who had both upper and lower GI investigations, 144 (6%) had all three investigations. This was either because of the need to colonoscope patients with equivocal findings on barium enema, or due to the requirement for barium enema following incomplete colonoscopy. Of the 1546 patients who underwent investigation of only one end of the GI tract, none was subsequently diagnosed with a cancer of the other end.

Endoscopy department workload

Over the study period, a total of 26 112 OGDs and 14 280 lower GI endoscopies were performed in the hospital’s endoscopy department. The 2318 OGDs and 896 colonoscopies performed to investigate IDA therefore accounted for 8% of the total OGD and colonoscopy caseload.

Relationship between age and choice of investigation

Patients undergoing barium enema were significantly older than those undergoing OGD (median 73 years vs. 71 years, \(p=0.003\)) or colonoscopy.
(73 years vs. 70 years, \(p<0.001\)). Patients undergoing colonoscopy were also significantly younger than those undergoing OGD (70 years vs. 71 years, \(p<0.001\)). There was no significant difference in the proportions of patients aged <45 years undergoing OGD, colonoscopy, and barium enema (7.9%, 11.4%, 3.8%, respectively, \(p=0.468\)).

### Relationship between gender and choice of investigation

There was a male preponderance among patients undergoing colonoscopy, compared to those undergoing barium enema (42.7% vs. 36.3%, \(p=0.013\)). There was a trend towards differences in gender ratio between patients undergoing colonoscopy and those undergoing OGD, but this did not reach statistical significance (42.7% vs. 39.3%, \(p=0.071\)).

### Details of the OGD findings

The details of the findings of the 2318 OGDs are shown in Table 1. Taking a hiatus hernia as a normal finding, 1415 (61%) patients had no abnormality detected on OGD. The investigation identified 26 (1.1%) patients with a new gastric cancer, and 18 (0.8%) patients with a new oesophageal cancer.

### Details of the colonoscopy findings

The details of the findings of the 896 colonoscopies are shown in Table 2. No abnormality was detected in 421 patients (47%). Colorectal cancer was identified in 83 patients (9.3%).

### Details of the barium enema findings

The details of the findings of the 584 barium enemas are shown in Table 3. No significant abnormality was revealed in 504 (86%). Colorectal cancer was identified in 34 patients (5.8%).

### Details of the patients identified as having a gastrointestinal malignancy

The 3798 investigations on the 2600 patients identified a total of 155 new gastrointestinal malignancies, giving a diagnostic yield of 6% among the patients investigated for IDA. Forty-four patients were diagnosed with an upper GI malignancy (26 gastric carcinoma, 18 oesophageal carcinoma) and 111 were diagnosed with a lower GI malignancy. The demographic details of the cancer patients, in relation to the site of cancer, are shown in Table 4.

### Degree of anaemia in relation to site of malignancy

The median haemoglobin value at the time of referral for investigation was 9.0 g/dl (range 4.5–11.4) for patients with an upper GI malignancy compared with a median of 10.1 g/dl (5.4–12.2) for patients with a colorectal malignancy (\(p<0.001\)).

### Stage of cancer in relation to site of cancer

Details of the stage of cancer in relation to the site of the tumour are shown in Table 4. Patients diagnosed...
with an upper GI malignancy had a significantly more advanced stage of cancer at the time of diagnosis, compared with those diagnosed with colorectal cancer ($p = 0.003$).

### Survival for patients with gastrointestinal malignancy in relation to site of cancer

The 5-year survival for patients with an upper gastrointestinal malignancy presenting with IDA was 10%, compared with a 35% for those with a colorectal malignancy presenting with IDA (log rank $6.81$, df 1, $p = 0.009$). Figure 1 shows the survival plot for patients in relation to the site of cancer.

### Survival for patients with gastrointestinal malignancy in relation to mode of detection

The 5-year survival for patients with malignancy diagnosed using an OGD was 10%, compared with 26% for patients diagnosed using a barium enema and 40% for patients diagnosed using colonoscopy (log rank $9.01$, df 2, $p = 0.011$). Figure 2 shows the survival plot for patients with gastrointestinal malignancy in relation to mode of detection.

### Multivariate analysis

Table 5 shows the factors significantly associated with durations of survival for patients diagnosed

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**Table 4** Demographic details of patients with gastrointestinal malignancy presenting with iron-deficiency anaemia, in relation to the site of cancer

<table>
<thead>
<tr>
<th></th>
<th>Upper gastrointestinal</th>
<th>Lower gastrointestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>44</td>
<td>111</td>
</tr>
<tr>
<td>Median age (range) (years)</td>
<td>76 (57–89)</td>
<td>73 (31–94)</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>25:19</td>
<td>59:52</td>
</tr>
<tr>
<td>Site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oesophagus</td>
<td>18 (41%)</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>26 (59%)</td>
<td></td>
</tr>
<tr>
<td>Caecum</td>
<td></td>
<td>30 (27%)</td>
</tr>
<tr>
<td>Ascending colon</td>
<td>40 (36%)</td>
<td></td>
</tr>
<tr>
<td>Hepatic flexure</td>
<td>4 (4%)</td>
<td></td>
</tr>
<tr>
<td>Transverse colon</td>
<td>8 (7%)</td>
<td></td>
</tr>
<tr>
<td>Splenic flexure</td>
<td>6 (5%)</td>
<td></td>
</tr>
<tr>
<td>Descending colon</td>
<td>8 (7%)</td>
<td></td>
</tr>
<tr>
<td>Sigmoid colon</td>
<td>8 (7%)</td>
<td></td>
</tr>
<tr>
<td>Recto-sigmoid junction</td>
<td>2 (2%)</td>
<td></td>
</tr>
<tr>
<td>Rectum</td>
<td>5 (5%)</td>
<td></td>
</tr>
<tr>
<td>Stage of cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1 (2.3%)</td>
<td>3 (2.7%)</td>
</tr>
<tr>
<td>II</td>
<td>3 (6.8%)</td>
<td>30 (27%)</td>
</tr>
<tr>
<td>III</td>
<td>13 (29.5%)</td>
<td>36 (32.4%)</td>
</tr>
<tr>
<td>IV</td>
<td>27 (61.4%)</td>
<td>42 (37.8%)</td>
</tr>
</tbody>
</table>

The upper GI malignancies presented at a more advanced stage ($p < 0.003$).

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**Figure 1.** Cumulative survival for patients diagnosed with gastrointestinal cancer presenting with iron-deficiency anaemia, in relation to site of cancer. Solid line, colorectal cancer. Dotted line, upper gastrointestinal cancer. Log rank 6.81, df 1, $p = 0.0091$. 
with gastrointestinal malignancy presenting with unexplained iron deficiency anaemia. These factors were entered into a multivariate analysis using Cox’s proportional hazards model. The stage of disease at diagnosis emerged as the only factor significantly and independently associated with duration of survival (hazard ratio 5.309, 95%CI 3.536–7.970, \(p < 0.001\)).

The NNI to detect a gastrointestinal malignancy

The 2318 upper GI investigations revealed a total of 44 cancers, giving a NNI of 53. The 896 colonoscopies identified 83 colorectal cancers, giving a NNI of 11. The 584 barium enemas identified 34 colorectal cancers, giving a NNI of 17. Combining all 1480 lower GI investigations, a total of 111 cancers were identified, giving a NNI of 13. Had all 2600 referred with IDA undergone both upper and lower GI investigation, the NNI for upper GI malignancy would increase to 59, and the NNI for lower GI malignancy to 23.

The NNI to detect a potentially curable malignancy

The 5-year survival for patients with an upper gastrointestinal malignancy presenting with IDA was 10%, hence the NNI to diagnose a potentially curable cancer was 527. By contrast, the 5-year survival for patients with colorectal cancer presenting with IDA was 35%, giving a NNI to diagnose each potentially curable cancer of 38. If the choice of investigation at the time is disregarded, by using the entire cohort of 2600 as the denominator, the NNI to detect a potentially curable upper GI malignancy was 590, compared with the NNI to detect a potentially curable lower GI malignancy of 67.
Details of the patients who underwent both upper and lower GI imaging

Eighty-three malignancies were diagnosed amongst the 1054 patients who underwent both upper and lower GI investigation (diagnostic yield 8%, 76 colorectal cancer, 7 upper gastrointestinal malignancy). The NNI for upper GI cancer was therefore 150 and the NNI for lower GI cancer was 14. The 5-year survival for the 76 patients with lower GI cancer was 42% and the NNI to find a potentially curable colorectal cancer was therefore 33. None of the 7 patients with upper GI cancer survived for 5 years.

Discussion

The principal finding of this study is that potentially curable gastrointestinal malignancy was almost 14 times more likely to be identified by investigation of the lower gastrointestinal tract than by gastroscopy. The importance of thoroughly investigating patients with unexplained IDA is highlighted by the fact that 6% of the patients investigated were diagnosed with gastrointestinal malignancy, of whom 30% went on to be successfully treated and survive at least 5 years. The difference in diagnostic yields is partly explained by the unexpectedly poor prognosis for patients with upper gastrointestinal cancer presenting with IDA which is a reflection of their advanced stage of disease at diagnosis.

In this study, 4% of patients referred for investigation of unexplained IDA were diagnosed with a colorectal malignancy, a figure comparable with previous studies. There is little information in the literature on the prevalence of upper gastrointestinal malignancy amongst patients presenting with IDA (1.7% in the present study), but the 39% overall diagnostic yield of upper GI pathology identified here is comparable with previously published data.

Over the 8-year study period, no less than 8% of the OGD and colonoscopy caseload at our hospital was accounted for by the investigation of IDA. Other authors also have found that it accounts for at least this proportion of gastroenterology out-patient workload. There is therefore potential for freeing of resources, if this area of the gastroenterology service could be streamlined. These results suggest that performing either a colonoscopy or barium enema as the first investigation could reduce the numbers of OGDs performed to investigate IDA.

Most previously published research into the investigation of IDA was conducted over 10 years ago and, as far as we are aware, there have been no previous studies relating anaemia as a presenting feature to outcomes for patients with gastrointestinal cancer. The lengthy study period and the robust follow-up data (none of the patients were lost to follow-up) add weight to the findings.

Clearly, this is not a prospective study, and retrospective case-note review depends on adequate documentation of appropriate data at the time of presentation. Statistical comparisons between various treatment groups may be invalidated by older patients with significant co-morbidity being treated by non-surgical means. Analysis of subgroups within a study may lead to bias, while comparisons of groups may prove to be ‘not statistically significant’ simply because the study has insufficient power to demonstrate real differences. There is undoubtedly a degree of selection bias in the choice of first investigation, as illustrated by the differences in age and gender distribution between the three investigation groups. In an effort to correct for this, we performed a separate NNI analysis for the 1054 patients who underwent both upper and lower GI investigation. The results were almost identical to those obtained from calculating NNI for each individual investigation. We also reanalysed the NNI data using the entire cohort of 2600 patients as the denominator; the NNI to detect a potentially curable malignancy by means of gastroscopy remained nearly ten times greater than that from lower GI investigation.

Perhaps understandably, given its lower morbidity, patients undergoing a barium enema tended to be older than those undergoing colonoscopy. The patients with colorectal cancer diagnosed on barium enema subsequently had a poorer survival than those diagnosed by means of colonoscopy. This may be a reflection of greater age and co-morbidity among those referred for barium enema. It is not clear why there was a female preponderance amongst the barium enema group.

The higher 5-year survival experienced by the colorectal cancer patients, compared with the upper GI cancer patients, cannot be explained by patients having been selected for colonoscopy on the basis of more pronounced anaemia; in fact, the opposite was true. Degree of anaemia was significantly associated with survival duration on the basis of univariate analysis, although this was not independent prognostic factor on multivariate analysis. More research with greater patient numbers into the relationship between the degree of anaemia and outcomes from GI cancer would certainly be of interest. While there is likely to have been some selection bias in this study, it is highly unlikely to account for the large differences in NNI between the upper and lower GI cancer groups.
In conclusion, the investigation of unexplained IDA continues to account for a significant proportion of endoscopy workload and, despite clear guidelines, is inadequate in at least half of all patients. In the absence of pointers towards an upper gastrointestinal cause (such as the presence of dysphagia), choosing colonoscopy first or performing bidirectional endoscopy during the same session is more clinically effective than choosing gastroscopy first. This policy would not only reduce the need for two separate procedure bookings, but would also enable earlier diagnosis of colorectal cancer in patients presenting with IDA.

Acknowledgements

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References