RESEARCH

Upper gastrointestinal cancer in its early stages is predominantly asymptomatic

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Abstract

Background Current guidelines for urgent endoscopic investigation of dyspepsia are based on alarm features and age criteria. However, there is concern that this type of guideline may delay the diagnosis of upper gastrointestinal (GI) cancer.

Objective To evaluate the timescale of symptoms in upper GI cancer, determining whether patients experience dyspepsia before developing alarm features, and hence whether the current guidelines may delay diagnosis.

Method A prospective study of patients diagnosed with upper GI cancer between May 2004 and January 2007. A structured interview was performed directly after endoscopic diagnosis regarding the nature and duration of symptoms.

Results Alarm features were present in 56 of the 60 patients interviewed. Only eight patients reported dyspepsia before developing their alarm feature; three of these had complained of dyspepsia for >10 years, one reported dyspepsia preceding the alarm feature by 18 months and in four patients dyspepsia preceded the alarm feature by ≤8 weeks. Preceding dyspepsia did not cause significant delay in referral for endoscopy ($p=0.670$), or affect tumour stage at diagnosis ($p=0.436$) or length of survival ($p=0.325$).

Conclusion It is rare for patients with upper GI cancer to experience significant dyspepsia before the onset of their alarm symptoms, therefore limiting the prospect of an earlier diagnosis. Early upper GI cancer is largely asymptomatic, and guidelines should limit the availability of open-access gastroscopy in simple dyspepsia. Increased awareness of the need to urgently investigate patients with concurrent anaemia or weight loss is required.

Introduction

Dyspepsia is a common symptom in the UK, with up to 40% of people experiencing

it annually.^{1,2} In the vast majority there will be no significant underlying disease and the symptoms will settle with simple lifestyle changes or medical treatment. Given that widespread use of endoscopy in this large proportion of the population would be both impracticable and inappropriate, guidelines have been constructed to assist clinicians in selecting those patients who require urgent endoscopic investigation.^{3,4}

The All Wales Dyspepsia Management Guideline, closely modelled on the NICE and SIGN guidelines,^{3,4} advises urgent endoscopy for those patients who have alarm features (dysphagia, weight loss, iron-deficiency anaemia, gastrointestinal (GI) bleeding, persistent vomiting, abdominal mass, suspicious barium meal results), and routine investigation in patients aged >55 years with unexplained and persistent dyspepsia of recent onset. However, there is concern that strict adherence to this type of guideline, based on alarm features and age criteria, may delay the diagnosis of upper GI cancers.^{5,6} Alarm features are generally associated with advanced disease, whereas those oesophageal and gastric cancers diagnosed in patients without alarm features are at an earlier stage and have an improved survival rate.⁵⁻⁷ In view of this it has been suggested that early-stage upper GI cancer can present with non-specific symptoms such as dyspepsia, and that patients need to be investigated at this stage to improve their prognosis.⁸

The aim of this study is to evaluate the timescale of symptoms in upper GI cancer; to determine if patients with this diagnosis experience dyspepsia before developing their alarm features, and hence whether the current guidelines may lead to a delay in diagnosis, with curative opportunities being missed.

Method

Patients who had findings suspicious of malignancy on gastroscopy, between May 2004 and January 2007, were invited to take part in this prospective study. After the procedure they underwent a structured interview which took place before their discharge from hospital. Information about the nature and duration of their presenting symptoms, and the number and timing of any primary care reviews before endoscopy referral was recorded. Those patients whose pathology results did not confirm malignancy were subsequently excluded. Stage of tumour at diagnosis was documented. Patient outcome data were collected until September 2010 (more than 3 years after the initial diagnosis of the last case studied). This study was approved by the medical clinical governance department of Cardiff and Vale NHS Trust.

Statistical analysis was performed with SPSS (version 18.0). The Kolmogorov–Smirnov and Shapiro–Wilk test at $p < 0.05$ were used to test data for normal distribution if necessary. The independent samples t test, the χ^2 test, Mann–Whitney U test and Fisher's exact test were used as appropriate.

Results

A total of 68 patients with suspected upper GI malignancy on gastroscopy were interviewed. In eight of these patients the histology was benign and so their results were excluded from the data analysis.

The 60 patients with confirmed malignancy included 43 men and 17 women, with a median age of 77 years (range 44–92). Thirty-six patients had oesophageal cancer and 24 gastric cancer; the histology results are shown in table 1. Median survival was 291 days (range

8–2022), with eight patients still alive at the end of follow-up.

Alarm features were present in 56 (93%) patients at the time of their index gastroscopy, the most common being weight loss and dysphagia (table 2). The median duration of alarm features before diagnosis was 8 weeks (range 1–72). The four cases in whom no alarm features were present included two patients with no upper GI symptoms who had incidental findings on abdominal imaging, a patient with chest pain and one patient with a 6-week history of dyspepsia alone.

Only 17 of the 56 patients with an alarm feature experienced dyspepsia at any stage, and in only eight of these did the dyspepsia actually occur before the onset of the alarm feature. (In the other nine patients dyspepsia had occurred at the same time or after the alarm feature.) In the eight patients whose dyspepsia preceded the alarm feature: three had complained of dyspepsia for over 10 years; one patient reported that dyspepsia had preceded the alarm feature by 18 months; and in the other four patients dyspepsia had only preceded the alarm feature by ≤ 8 weeks. There was no statistically significant difference in the number of primary care consultations, use of acid suppression medication, delay in referral (defined as the period of time from first primary care consultation to referral for endoscopy), tumour stage at diagnosis, or length of survival when comparing those patients who had preceding dyspepsia with those who did not (table 3).

Twenty (33%) patients were seen in primary care on more than one occasion for their GI symptoms or anaemia before referral for endoscopy. Sixteen of these patients had reported alarm symptoms at their first consultation—12 with weight loss and four with dysphagia. In the eight patients who experienced dyspepsia before developing an alarm feature, four were seen in primary care on multiple occasions. Multiple primary care consultations were associated with a significantly higher use of proton pump inhibitor medication and a significant delay in referral, but it did not significantly affect tumour stage at diagnosis or mean length of survival (table 4).

Upper GI cancer was diagnosed in five patients aged under <55 years (8% of all cases). All presented with an alarm feature, and none of them complained of dyspepsia. Four were referred at their initial primary care visit, and four had a tumour stage $\leq T_3N_xM_0$ at diagnosis. Their median survival was 442 days, with one patient alive at the end of follow-up.

Discussion

This prospective study illustrates the timescale of symptoms in upper GI cancer. In our cohort 93% of patients had an alarm feature at diagnosis, and the median length of these features was relatively short at 8 weeks. Only a small proportion of these patients experienced dyspepsia before the onset of their alarm feature, and in most of these instances the dyspepsia

Table 1 Location and histology of tumours

Tumour	Patients N (%)
Oesophageal	
Adenocarcinoma	26 (43)
Squamous cell carcinoma	9 (15)
Small cell carcinoma	1 (2)
Gastric	
Adenocarcinoma	20 (33)
Lymphoma	2 (3)
Gastrointestinal stromal tumour	2 (3)

Table 2 Frequency of alarm features

Alarm feature	Patients N (%)
Weight loss	37 (62)
Dysphagia	33 (55)
Anaemia	9 (15)
Vomiting	9 (15)
Gastrointestinal bleeding	7 (12)

Table 3 Comparison of those patients who had dyspepsia preceding their alarm symptom with those who did not

	Preceding dyspepsia (n=8)	No dyspepsia (n=48)	
Median age (range)	73 (62–90)	77 (44–92)	p=0.519 (Mann–Whitney test)
Sex			
Female	4	11	p=0.190 (Fisher's exact test)
Male	4	37	
Cancer			
Oesophageal	4	30	p=0.698 (Fisher's exact test)
Gastric	4	18	
GP visits			
Single	4	31	p=0.431 (Fisher's exact test)
Multiple	4	15	
ASM use			
Yes	5	17	p=0.260 (Fisher's exact test)
No	3	27	
Mean delay to referral, days (SD)	8 (10.8)	16 (26.0)	p=0.670 (Mann–Whitney test)
Tumour stage			
≤T3NxM0	4	28	p=0.436 (Fisher's exact test)
>T3NxM0	4	14	
Median length of survival, days (range)	709 (46–1834)	264 (8–2022)	p=0.325 (Mann–Whitney test)

ASM, acid suppression medication (proton pump inhibitors or H₂ receptor antagonists).

Table 4 Comparison of patients with upper gastrointestinal symptoms who were referred after initial primary care consultation with those who had multiple consultations before referral

	Single (n=35)	Multiple (n=20)	
Median age (range)	77 (44–91)	74 (49–92)	p=0.497 (independent samples t test)
Sex			
Female	8	7	p=0.331 (χ^2 test)
Male	27	13	
Cancer			
Oesophageal	23	9	p=0.134 (χ^2 test)
Gastric	12	11	
ASM use			
Yes	8	14	p<0.001 (χ^2 test)
No	25	4	
Mean delay to referral, days (SD)	5 (12.7)	35 (30.0)	p<0.001 (Mann–Whitney test)
Tumour stage			
≤T3NxM0	21	12	p=0.740 (χ^2 test)
>T3NxM0	10	7	
Median length of survival, days (range)	198 (8–2022)	639 (51–1834)	p=0.133 (Mann–Whitney test)

ASM, acid suppression medication (proton pump inhibitors or H₂ receptor antagonists).

was either a chronic complaint unrelated to the cancer, or the duration of preceding dyspepsia was so short that earlier intervention would not have produced any improvement in outcome. These results suggest that early upper GI cancer is largely asymptomatic until alarm features develop, and that current guidelines do not delay its diagnosis.

Discovering upper GI cancer at an early stage creates an opportunity for curative treatment, with 5-year survival rates for oesophageal and gastric cancers at 90%.^{9 10} Unfortunately, in the UK, and for much of the Western world, a significant proportion of cases are still diagnosed when the disease is more advanced, and the prognosis for these patients is bleak. The great

difficulty facing clinicians is to develop an efficient and reliable method by which to identify these cancers in their early stages.

Only four patients (6.7%) in our study did not have alarm features at the time of diagnosis. This is similar to other reports in which the proportion of upper GI cancer that presents without alarm features is relatively small at 5–7%.^{11–12} In the 56 patients with alarm features, only eight (14%) had a period of preceding dyspepsia. In the three cases for whom dyspepsia had been a chronic problem, and had been present for many years, the symptoms appeared to pre-date the cancer. Given the high prevalence of chronic dyspepsia in Western populations, cancer will inevitably develop in a proportion of these patients. If diagnosis is reliant on symptoms of dyspepsia alone, then detection at an early stage in this group is very difficult unless screening endoscopies are performed at regular intervals. In four of the patients the dyspepsia preceded the alarm feature by only a very short time period, with a maximum of 8 weeks' duration. In view of the fact that progression of early gastric cancer to an advanced stage is considered a relatively slow process, with estimates of a median period of 37 months,¹³ then this short time period of up to 8 weeks is unlikely to significantly influence the staging of the tumour. Finally, one patient had an 18-month history of dyspepsia preceding an alarm feature. Interestingly this woman had had a barium meal to investigate her dyspepsia at its onset but this was reported as normal. It was not until 18 months after her initial presentation that a blood test was checked and she was found to be severely anaemic. A malignant pre-pyloric ulcer was subsequently diagnosed.

Only one of the patients diagnosed with cancer in this study was referred for endoscopy with dyspepsia alone. His dyspeptic symptoms had been present for no more than 6 weeks, and were improving with acid suppression. Gastroscopy disclosed a 2 cm gastric ulcer in the cardia, and it was staged as a T₂N₀M₀ adenocarcinoma. In view of the endoscopic findings it seems likely that his dyspepsia was caused by the gastric cancer; however, given the short timescale of events it is uncertain as to whether he would have developed an alarm feature soon afterwards. The actual frequency of malignancy in this type of uncomplicated dyspepsia in European and North American populations is very low at 0.1–0.3%.^{14–17} It has been suggested that this low prevalence may be similar to that found in the asymptomatic population, and that although a very small number of patients with uncomplicated dyspepsia will be found to have upper GI cancer, in the majority of cases this is not the cause of their symptoms.¹⁸

European studies suggest that dyspepsia is often reported in early gastric cancer, with a frequency of 60–85%.^{19–22} However, referral for gastroscopy in Europe is predominantly to investigate upper GI symptoms, of which dyspepsia is by far the most common,

and only a minority will be asymptomatic patients undergoing surveillance procedures for conditions such as Barrett's oesophagus or oesophageal varices. With this in mind it is not surprising that dyspepsia is often present when early gastric cancer is diagnosed. It is also interesting to note that no association has been found between the duration of dyspepsia and the stage of gastric cancer at diagnosis,⁷ unlike in oesophageal cancer, in which the duration of reflux symptoms appears to increase the risk of developing malignancy.²³

The timescale of symptoms in gastric cancer has been examined previously in patients aged <55 years.²⁴ This retrospective study of case notes and GP records found that only one out of 25 cases presented with simple dyspepsia, and so concluded that the age limit for open-access gastroscopy (OAG) for simple dyspepsia could be raised safely to 55 years. However, our own results would question the benefit of performing OAG for simple dyspepsia at any age, if the intention is purely to diagnose cancer. Clearly, the incidence of cancer is higher in an older population, but the use of dyspepsia as an indicator for effectively screening this age group does not appear to be useful. Clinical symptoms are not a useful method for diagnosing upper GI cancer at an early stage, and further research is needed into non-symptom-based biomarkers. There are also important implications for service delivery given the demand that currently exists on limited resources; a proposed referral criterion that did not perform OAG in patients with simple dyspepsia reduced urgent service workload by one-third while maintaining a sensitivity of 92% for malignancy.¹⁵

Our results suggest that identifying anaemia and recognising its significance is an area that may need improvement. Nine of our patients were anaemic at the time of referral for endoscopy. On reviewing the results of previous blood tests, it was noted that two of these patients had been anaemic for a significant period of time (up to 3 years) before developing any GI symptoms but had not been investigated. Another patient had consulted primary care on several occasions about dyspepsia before a blood test was performed and anaemia was diagnosed. Iron-deficiency anaemia is the only alarm feature that cannot be elicited from the history so it is essential a full blood count is checked in all dyspeptic patients. Further investigation should be considered if anaemia is present.²⁵

Of the 16 patients with alarm features who were not referred at their initial primary care consultation, the majority had weight loss. This symptom has many causes and so it is possible that other more common diseases were excluded initially, thus leading to a delay in the referral for gastroscopy.

It is interesting to note that use of proton pump inhibitors or H₂ receptor antagonists was significantly higher in those patients who had multiple primary care consultations than in those who were referred immediately. While obtaining accurate data about when this

drug had been started was not possible, we speculate that a trial of this drug in primary care might have contributed to the significant delay in referral for this group. Data on the investigation and treatment of *Helicobacter pylori* were also unavailable but might have been another factor in delaying referral.

Generalisation of the results of this study may be limited by several factors. The sample size is small and is based on the patients referred to a single centre. A total of 87 patients were diagnosed with upper GI cancer during the investigation period but only 60 consented to interview. The study involves both oesophageal and gastric cancers, and in future research it may be useful to examine these conditions separately owing to their potentially differing modes of presentation. The lack of statistical difference between some of the results, such as length of survival and delay in referral, in which a trend seems to be apparent, may be due to a type 2 statistical error owing to the small number of cases included. Lastly, the term dyspepsia can have a varied interpretation, and this combined with the fact that several different members of the research team conducted the interviews, might potentially influence the results of the study.

In conclusion, it is recognised that most cases of upper GI cancer present with alarm features and advanced disease. These patients rarely report a significant period of dyspepsia before the onset of their alarm feature that could have enabled earlier investigation and diagnosis. Indeed, malignant pathology is very unusual in patients who are over 55 years with simple dyspepsia, and we would question whether they should be eligible for OAG as advised in the current guidelines. To ensure a timely referral for endoscopy it is essential that upper GI cancer is included in the differential diagnosis for weight loss, and that a full blood count is checked as part of the primary care management of dyspepsia.

Competing interests None.

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