BRIEF ARTICLE

Predictive value of symptoms and demographics in diagnosing malignancy or peptic stricture

Iain A Murray, Joanne Palmer, Carolyn Waters, Harry R Dalton

Iain A Murray, Carolyn Waters, Harry R Dalton, Department of Gastroenterology, Royal Cornwall Hospital, Truro, Cornwall TR1 3LJ, United Kingdom
Joanne Palmer, Research and Development, Knowledge Spa, Royal Cornwall Hospital, Truro, Cornwall TR1 3LJ, United Kingdom
Author contributions: Murray IA and Dalton HR designed the research; Waters C obtained the data and maintained the database; Palmer J analyzed the data; Murray IA wrote the paper; and all authors contributed to the editing for the final version.
Correspondence to: Dr. Iain A Murray, Consultant Gastro-enterologist, Department of Gastroenterology, Royal Cornwall Hospital, Truro, Cornwall TR1 3LJ,
United Kingdom. iain.murray@rcht.cornwall.nhs.uk
Telephone: +44-23-80424536 Fax: +44-23-80424830
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Abstract

AIM: To determine which features of history and demographics predict a diagnosis of malignancy or peptic stricture in patients presenting with dysphagia.

METHODS: A prospective case-control study of 2000 consecutive referrals (1031 female, age range: 17-103 years) to a rapid access service for dysphagia, based in a teaching hospital within the United Kingdom, over 7 years. The service consists of a nurse-led telephone triage followed by investigation (barium swallow or gastroscopy), if appropriate, within 2 wk. Logistic regression analysis of demographic and clinical variables was performed. This includes age, sex, duration of dysphagia, whether to liquids or solids, and whether there are associated features (reflux, odynophagia, weight loss, regurgitation). We determined odds ratio (OR) for these variables for the diagnoses of malignancy and peptic stricture. We determined the value of the Edinburgh Dysphagia Score (EDS) in predicting cancer in our cohort. Multivariate logistic regression was performed and $P < 0.05$ considered significant. The local ethics committee confirmed ethics approval was not required (audit).

RESULTS: The commonest diagnosis is gastro-esophageal reflux disease (41.3%). Malignancy (11.0%) and peptic stricture (10.0%) were also relatively common. Malignancies were diagnosed by histology (97%) or on radiological criteria, either sequential barium swallows showing progression of disease or unequivocal evidence of malignancy on computed tomography. The majority of malignancies were esophago-gastric in origin but ear, nose and throat tumors, pancreatic cancer and extrinsic compression from lung or mediastinal metastatic cancer were also found. Malignancy was statistically more frequent in older patients (aged >73 years, OR 1.1-3.3, age < 60 years 6.5%, 60-73 years 11.2%, > 73 years 11.8%, $P < 0.05$), males (OR 2.2-4.8, males 14.5%, females 5.6%, $P < 0.0005$), short duration of dysphagia ($\leqslant$ 8 wk, OR 4.5-20.7, 16.6%, 8-26 wk 14.5%, > 26 wk 2.5%, $P < 0.0005$), progressive symptoms (OR 1.3-2.6: progressive 14.8%, intermittent 9.3%, $P < 0.001$), with weight loss of $\geqslant$ 2 kg (OR 2.5-5.1, weight loss 22.1%, without weight loss 6.4%, $P < 0.0005$) and without reflux (OR 1.2-2.5, reflux 7.2%, no reflux 15.5%, $P < 0.0005$). The likelihood of malignancy was greater in those who described true dysphagia (food or drink sticking within 5 s of swallowing than those who did not (15.1% *vs* 5.2% respectively, $P < 0.001$). The sensitivity, specificity, positive predictive value and negative predictive value of the EDS were 98.4%, 9.3%, 11.8% and 98.0% respectively. Three patients with an EDS of 3 (high risk EDS $\geqslant$ 3.5) had malignancy. Unlike the original validation cohort, there was no difference in likelihood of malignancy based on level of dysphagia (pharyngeal level dysphagia 11.9% *vs* mid sternal or lower sternal dysphagia 12.4%). Peptic stricture was statistically more frequent in those with longer duration of symptoms (> 6 mo, OR 1.2-2.9, $\leqslant$ 8 wk 9.8%, 8-26 wk 10.6%, > 26 wk 15.7%, $P < 0.05$) and over

60 s (OR 1.2-3.0, age < 60 years 6.2%, 60-73 years 10.2%, > 73 years 10.6%, *P* < 0.05).

CONCLUSION: Malignancy and peptic stricture are frequent findings in those referred with dysphagia. The predictive value for associated features could help determine need for fast track investigation whilst reducing service pressures.

INTRODUCTION

Esophageal cancer accounts for 3% of all cancer diagnoses in the United Kingdom (an annual incidence of nearly 8000) and has poor prognosis[1-4]. The Department of Health in the United Kingdom has produced guidelines to identify patients with dyspepsia at higher risk of upper gastro-intestinal malignancy and requiring rapid referral and investigation[5]. Dysphagia is an alarm symptom with a high predictive value for finding significant pathology [odds ratio (OR) 2.0-3.1 for malignancy in 3600 referrals to a rapid access upper gastro-intestinal cancer service][6].

However, dysphagia is common, occurring in 5%-8% of those over 50[7]. It can be due to many different underlying conditions, including malignancy.

Many patients referred to secondary care with "dysphagia" do not actually have any swallowing difficulties[8]. Despite it being a relatively good predictive symptom for cancer diagnosis, even in those with true dysphagia, less than 10% have cancer[8]. Patients presenting with dysphagia require rapid assessment, diagnosis and treatment. An accurate diagnosis is dependent upon history and appropriate investigations, which may include barium swallow, gastroscopy or esophageal manometry[9-13].

If it were possible to predict which patient demographics and symptoms were most highly predictive of serious pathology, especially malignancy or peptic stricture and which predicted a non-serious problem, it would allow health resources to be targeted towards rapid investigation in the high risk group. A scoring system, the Edinburgh Dysphagia Score (EDS) has been devised to predict which patients require fast track investigations[14].

The aim of our study is to identify which factors are strongest predictors of malignancy or peptic stricture in patients referred to a rapid access service with dysphagia. We use our data to validate the EDS on a larger patient cohort.

MATERIALS AND METHODS

The Royal Cornwall Hospital serves a largely rural population of 450 000, more than 99% of whom are white. The county is one of the poorest in the United Kingdom.

The dysphagia hotline (DHL) service consists of an initial telephone triage by our nurse endoscopist with barium swallow or endoscopy within one week. The radiology department hot report DHL barium swallow examinations and if the examination is abnormal, the patient is given diet Cola and metoclopramide and undergoes gastroscopy after 2 h[15].

We prospectively collect data on patient demographics and final diagnosis following gastroscopy or barium swallow based on test results and clinical opinion. Duration of dysphagia, whether for both liquids and solids, and whether there are associated features (reflux, odynophagia, weight loss, regurgitation) are all prospectively recorded. Review of demographics, patient presentation and final diagnosis showed highly predictive variables for each major diagnosis, so these were formally analysed.

The EDS was determined for each patient (determined by scores for age, weight loss (> 3 kg), duration of symptoms, sex, location of dysphagia and presence of acid reflux)[14].

Statistical analysis

Statistical analysis of the data was performed using IBM SPSS 19 software. The relationship between the variables and the diagnosis was explored using Pearson's χ^2 Independence test. The predictive value of each variable in diagnosing malignancy and in diagnosing peptic stricture was explored using logistic regression. In both analysis, a *P* value less than 0.05 was considered statistically significant.

The South West Regional Ethics committee determined that formal ethics approval was not required as the study fell within the category of audit.

RESULTS

From April 2004 to January 2011, 2000 patients were referred, 48.5% male, age range 17-103 years, mean 68.1 years (SD 14.1 years). Of these, 225 (11.2%) did not undergo investigation through the dysphagia hotline, mainly because they refused any investigations but also because we were unable to contact them by telephone, or they were admitted prior to test. Two patients' data could not be interpreted for clerical reasons. Three hundred and thirty-five patients (20% of those investigated) denied true dysphagia, defined as the feeling of food or
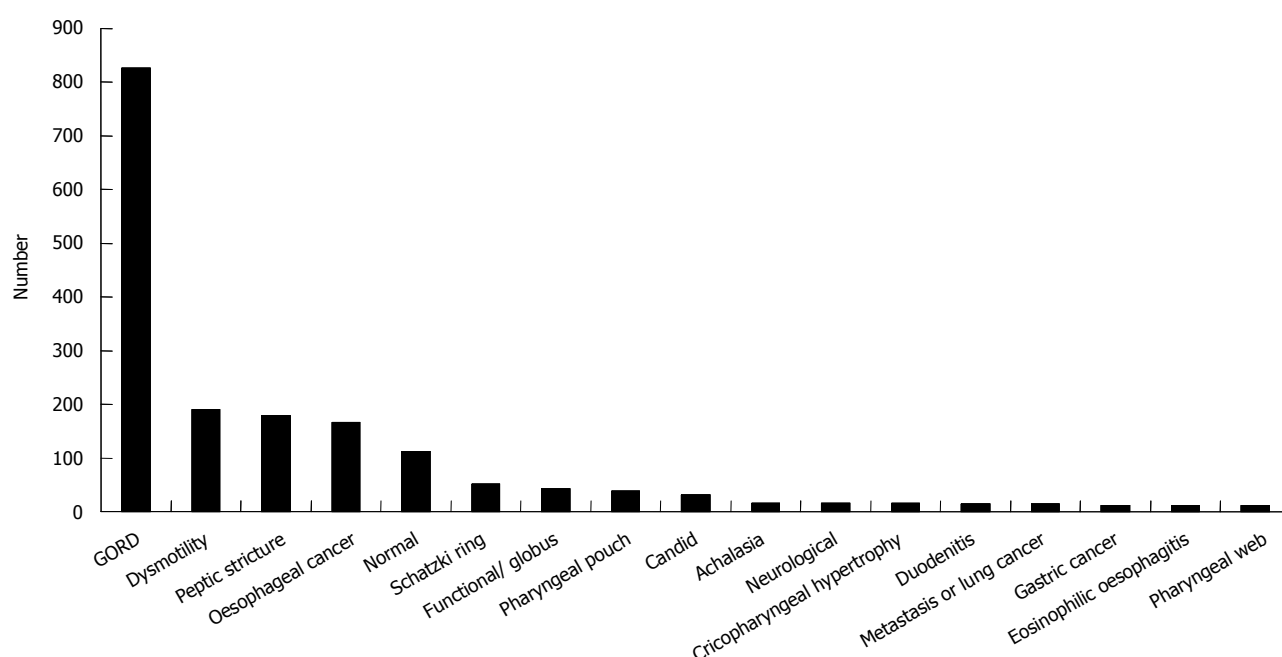
Figure 1 The outcome following investigation of 2000 consecutive patients referred with dysphagia. Some patients had more than one diagnosis and some had a diagnosis endoscopically which was unlikely to be the cause of the dysphagia. Only outcomes with an occurrence of 10 or more are shown. Other diagnoses with lower frequency were gastric (7), esophageal (5) and duodenal ulcers (4), compression from vascular structures including left atrium (4), pancreatic cancer (3), ear, nose and throat cancers (2), esophageal gastrointestinal stromal tumors (2), drug reaction (2), esophageal spasm (2) or diverticulum (2) and 1 each of respiratory infection, celiac disease, small intestinal stricture, goitre, post-operative stricture, pseudomembranous esophagitis, varices, pyloric ulcer, scleroderma, thyroglossal cyst and pharyngitis. Oesophageal cancer includes adenocarcinoma (98), squamous cancer (46), unspecified oesophageal cancers (4) and junctional cancers (18). GORD: Gastro-oesophageal reflux disease.

drink sticking within 5 s of swallowing, the majority describing globus although some presented with dyspepsia or weight loss.

Of those having investigations, 259 (14.6%) had barium swallow only, 1341 (75.5%) gastroscopy only and 175 (9.9%) had both procedures. Twenty patients failed to attend an appointment for procedures (7 barium swallows, 9 gastroscopies, the remainder unspecified) giving a DNA (did not attend) rate of 1.1% for patients referred for procedures.

The most common diagnosis was gastro-esophageal reflux disease 826 (41.3%) with the more serious diagnoses of malignancy [199 (11.0%), 183 of gastrointestinal origin], peptic stricture 179 (10.0%), pharyngeal pouch 38 (2.1%) and achalasia 16 (0.9%). All outcomes are shown in Figure 1.

We investigated the likelihood of various significant pathologies based on patient demographics and presenting symptoms, including age (divided empirically into three similar sized groups of under 60 years, 60-73 years and over 73 years), sex, the type of dysphagia (to liquids, solids or both), whether the symptoms were progressive, whether "true dysphagia" or globus, and associated features including weight loss (defined as > 2 kg loss of weight in preceding 3 mo, the Department of Health criterion for a 2 wk wait referral), duration of dysphagia and presence or absence of reflux (percentages of each are shown on Table 1).

A diagnosis of malignancy or of peptic stricture was significantly associated with a history of true dysphagia

(feeling of food or drink sticking within 5 s of swallowing) than in those who did not ($P < 0.001$).

Logistic regression was performed using the Enter method to assess the impact of a number of factors on the likelihood of someone presenting with dysphagia having malignancy. The model contained seven independent variables (sex, age, duration of symptoms, nutrition, progressive symptoms, reflux and weight loss) however, the type of dysphagia was found to be highly non-significant ($P = 0.727$) and so the model was run again with removal of this variable.

The strongest predictor of a cancer diagnosis was the duration of symptoms (Table 2). If a patient reported symptom duration of less than eight weeks, the OR of having cancer was 9.6 higher than for symptoms more than twenty six weeks (95% CI: 4.5-20.7). The OR was 6 (95% CI: 2.8-12.8) for symptom duration between eight and twenty six weeks. The next strongest predictor was the presence of weight loss greater than 2 kg where the OR of 3.6 (95% CI: 2.5-5.1). Being male increased the likelihood of malignancy 3.3 fold (95% CI: 2.2-4.8) compared to females. Being less than sixty years old reduced the likelihood of a cancer diagnosis by 47.1% compared to being over 73 (OR 0.53, 95% CI: 0.3-0.9). If the patient had reflux, the OR of 0.54 (95% CI: 0.4-0.8) showed the likelihood of malignancy was significantly reduced and if symptoms were progressive then the OR of a cancer diagnosis was 1.8 (95% CI: 1.3-2.6). The sensitivity and specificity values are 97.6% and 31.1% respectively.

Table 1 Demographics and clinical features of the first 2000 patients referred to the dysphagia hotline (%)			
Demographics			
Age	< 60 yr	60-73 yr	> 73 yr
	26.4	34.9	38.7
Sex	Male	Female	
	48.5	51.5	
Clinical features			
Nature of dysphagia	Solids	Liquids	Both
	79.6	0.7	19.7
Symptoms progressive	Yes	No	
	40	60	
"True" dysphagia	Dysphagia	Globus	
	81.3	18.7	
Weight loss ⩾ 2 kg in past 3 mo	Yes	No	
	28.5	71.5	
Presence of reflux	Yes	No	
	60.6	39.4	
Duration of dysphagia	< 8 wk	8-26 wk	> 26 wk
	34.5	42	23.5

Table 2 Demographics and clinical features suggestive of malignancy in a dysphagic population				
	Odds ratio	95% CI		Significance
		Lower	Upper	
Sex (male)	3.358	2.273	4.961	0.000
Progressive	1.807	1.259	2.593	0.001
Weight loss				
⩾ 2 kg	3.572	2.501	5.104	0.000
Reflux	0.528	0.369	0.754	0.000
Age				
< 60 yr	0.529	0.320	0.872	0.013
60-73 yr	1.170	0.788	1.737	0.437
Duration				
< 8 wk	11.019	4.897	24.794	0.000
8-26 wk	6.936	3.124	15.398	0.000

Logistic regression analysis by the Enter method of 1400 patients investigated for dysphagia showing odds ratio with 95% CI and significance level compared to female patients, without progressive symptoms, without 2 kg or more weight loss, without reflux symptoms, aged over 73 years and with symptom duration of greater than 26 wk. The level of dysphagia (pharyngeal, mid chest or lower retrosternal) and the type of dysphagia (to liquids, solids or both) were removed as these were not statistically significant.

Using an EDS > 3.5 (10) to predict likelihood of cancer gave sensitivity, specificity, positive and negative predictive values of 98.4%, 9.3%, 11.8% and 98.0%. The three cancer cases that did not fall into the high risk group as defined in the original paper, had an EDS of 3.

Of patients with pharyngeal level dysphagia, 11.9% had malignancy, compared to 12.4% of patients with dysphagia affecting mid or lower chest (P = NS), i.e., in our cohort, the level of dysphagia was not significant for a diagnosis of malignancy.

Logistic regression was also used to assess the impact of a number of factors on the likelihood of someone presenting with dysphagia of having peptic stricture. The model originally contained seven independent variables. However five of these variables were not statistically significant and therefore were removed from the model [reflux (P = 0.703), sex (P = 0.247), progressive symptoms (P = 0.196), type of dysphagia (P = 0.156) and weight loss (P = 0.069). The only significant factors were age (P = 0.012) and duration of symptoms (P = 0.008)].

The OR of having a peptic stricture diagnosis is reduced by 48.9% for patients under 60 years old (OR 0.51, 95% CI: 0.33-0.80), and by 24.5% for patients between 60-73 years old (OR 0.76, 95% CI: 0.52-1.1) compared to those older than 73 years. The OR of having a peptic stricture diagnosis is reduced by 47.9% in patients presenting with symptoms of duration less than 8 wk (0.52, 95% CI: 0.34-0.81) and 37% in patients with symptoms of duration of between 8-26 wk (0.63, 95% CI: 0.43-0.92) compared to patients with symptom duration greater than 26 wk. The sensitivity and specificity values were 95.2% and 8.1% respectively.

In summary, in patients presenting with dysphagia, the likelihood of a diagnosis of cancer is increased by being male, over the age of 60 years, experiencing weight loss of > 2 kg with progressive symptoms but without reflux and a symptom duration of less than eight weeks. Patients who have had their symptoms for greater than twenty six weeks and are over the age of 73

years are more likely to have a peptic stricture diagnosis than those presenting with the same symptoms that are younger and have symptoms for less than 26 wk.

DISCUSSION

For the past 7 years we have offered a telephone triage and one stop procedure service for dysphagia and have been referred 2000 patients. The commonest underlying cause for dysphagia is reflux disease but we have found malignancy in 10% of those referred and peptic stricture in 9%. We have prospectively collected data on patient demographics and symptoms at time of referral. Logistic regression analysis has enabled us to determine which symptoms and features make the diagnosis of malignancy or peptic stricture more likely.

Previous studies have found an incidence of cancer in 4%-15% of those referred with dysphagia[6,16-19] making this an alarm symptom with a relatively high positive predictive value. We have confirmed this and also shown that in those referred to the DHL without dysphagia, the likelihood of malignancy is considerably lower.

Malignancy is more common in older men with a shorter duration of symptoms (less than 8 wk), with weight loss and without associated reflux. The negative association with reflux and positive association with weight loss has been noted previously[8,14] as has the negative association with long duration of symptoms (greater than either 6 mo[14] or 1 year[8]). Because of the size of our cohort we have been able to demonstrate that those with particularly short duration of symptoms (less than 8 wk) have a markedly increased likelihood of malignancy (increased 11 fold) compared to those with symptoms from 8 wk to 6 mo (nearly 7 fold increase from those with symptoms of more than 6 mo).

Our findings are similar to those of Rhatigan *et al*[14]

who have produced the "Edinburgh dysphagia score" to triage patients referred with dysphagia into low or high risk for malignancy. They have also found an increased likelihood of malignancy in patients who were male, older, with shorter duration of symptoms and have noted a negative association with symptoms of reflux. They found a significant relationship between type of dysphagia and the likelihood of cancer in univariate but not in multivariate analysis and hence they do not include it in their final calculation. In our study, the relationship was not statistically significant. Conventionally it is thought that dysphagia to solids is most likely due to organic obstruction whilst that to liquids is due to neuromuscular incoordination so it is interesting that both studies failed to demonstrate a significant relationship. It is possible in our own study that this was due to few patients having dysphagia to liquids alone.

There are several differences between their study and this one however. We failed to confirm a positive association of a malignant diagnosis with localisation of disease (in study of Rhatigan *et al*[14], dysphagia below the pharyngeal level was more likely to be associated with malignancy) or with progressive nature of symptoms (found to be an independent risk for malignancy but not included in their final scoring system). The reasons for this are not clear, although we did have 10 fold more patients with pharyngeal level dysphagia making it possible that the difference found previously had been a type 1 error due to a relatively small sample size. Alternatively there may be some unrecognised difference in referral patterns between the 2 hospitals.

We chose to group patients into three age ranges rather than investigating age as a continual variable but confirmed a strong association with older patients more likely to have malignancy and we chose 2 kg weight loss cut-off for weight loss as this is the weight chosen by the Department of Health in their guidelines for referral under the suspected cancer pathway. Only 8.4% of our patients fell into the low-risk group compared to 30.0% in study of Rhatigan *et al*[14]. This may have been because of the older age of our patients (mean age 68.1 years against 61.4 years in the original development cohort).

The high specificity and positive predictive value of the EDS was confirmed although again concerningly there were 3 patients who had malignancy but an EDS of less than 3.5. This figure is comparable to the study of Rhatigan *et al*[14] where the EDS failed to detect one malignancy in a cohort of 574 patients investigated, compared to 3 patients with malignancy in 1775 investigated. Clearly, whilst high risk patients with scores of 3.5 and above require urgent investigation, those with scores below this also require still to be investigated, albeit with a lower incidence of malignancy.

Further studies are required to determine whether the ORs are generalizable in other populations and in particular in non-whites. It would also be useful to record the effect of smoking and alcohol consumption on likelihood of both diagnoses.

As with malignancy, the likelihood of peptic stricture is greater in older patients but in contrast to a diagnosis of malignancy which is associated with a shorter duration of symptoms, a longer duration of symptoms (greater than 26 wk) is considered a feature of a peptic stricture diagnosis. No other clinical features were significantly associated with a diagnosis of peptic stricture. The associated with long duration of symptoms in older patients was recognized nearly 20 years ago but is worth re-iterating[20-22].

Interestingly type of dysphagia (to solids rather than liquids), was not significant for neither malignancy nor peptic stricture. It is recognized that a history of dysphagia to solids progressing to both solids and liquids is indicative of mechanical obstruction whereas dysphagia to both at the onset is likely to be functional in origin[23]. Relatively few of our patients had dysphagia to liquids only or both and we did not ask about the nature of the dysphagia at the onset which might explain this.

Likewise a history of reflux did not predict peptic stricture and appeared protective against a diagnosis of malignancy. Reflux is a known risk factor for esophageal adenocarcinoma and cardial tumors (OR 7.7 and 2.0 respectively)[24]. In this and study of Rhatigan *et al*[14] it may simply have been more strongly associated with a final alternative diagnosis, namely reflux esophagitis[21].

Future studies could focus on other factors which are recognized as risk factors for esophageal malignancy such as alcohol intake and smoking[25-29] and this could improve the model of malignancy prediction.

We have prospectively obtained history from patients undergoing investigation for dysphagia and have demonstrated which factors are most likely to be indicative of malignancy or peptic stricture disease and hence which necessitate urgent investigation. We have confirmed the value of the EDS in recognising a smaller group of patients with dysphagia who require less urgent investigation.

COMMENTS

Background
Dysphagia can be the presenting symptom of a serious pathology, namely malignancy or peptic stricture. Determining which patients are more likely to have malignancy or stricture could help determine which patients need urgent investigation.

Research frontiers
A previous study from Scotland has shown malignancy to be more common in older males, with short duration of progressive symptoms, no reflux, weight loss and dysphagia not at the pharyngeal level and produced the Edinburgh Dysphagia Score (EDS).

Innovations and breakthroughs
The authors investigated 1775 patients with dysphagia and confirmed earlier findings malignancy to be more common in older men with progressive symptoms of less than 8 wk duration and weight loss of at least 2 kg. Malignancy was more common in those without reflux but level of dysphagia did not predict malignancy. An EDS of less than three predicted no malignancy. Peptic stricture was more common in older patients with longer duration of symptoms.

Applications
The authors confirmed the value of the EDS but caution that a score of 3 may still predict malignancy (contrary to the original article). Authors also defined

predictors of peptic stricture. Where resources are limited these predictors could be used to expedite investigations in high risk patients.

Peer review

It is larger scale cohort of validation study for the EDS than ever before. EDS is useful for primarily diagnosing esophageal malignancy associated with dysphagia.

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