Margaret P Astin, Tanimola Martins, Nicky Welton, Richard D Neal, Peter W Rose and William Hamilton

Diagnostic value of symptoms of oesophagogastric cancers in primary care:

a systematic review and meta-analysis

Abstract

Background
Selection of primary care patients for investigation of potential oesophagogastric cancer is difficult, as the symptoms may represent benign conditions, which are also more common.

Aim
To review systematically the presenting features of oesophagogastric cancers in primary care, including open-access endoscopy clinics.

Design and setting
Systematic review and meta-analysis.

Method
MEDLINE®, Embase, the Cochrane Library, and CINAHL were searched for studies of adults who were symptomatic and presented in primary care or open-access endoscopy clinics. Exclusions were being asymptomatic, screening, or recurrent cancers. Data were extracted to estimate the diagnostic performance of features of oesophagogastric cancers and summarised in a meta-analysis.

Results
Fourteen studies were identified. The strongest summary sensitivity and specificity estimates were for: dyspepsia 0.42 (95% confidence interval [CI] 0.29 to 0.56) and 0.48 (95% CI = 0.31 to 0.65); pain 0.41 (95% CI = 0.24 to 0.62) and 0.75 (95% CI = 0.51 to 0.89); and dysphagia 0.32 (95% CI = 0.17 to 0.52) and 0.92 (95% CI = 0.81 to 0.97). Summary positive likelihood ratios (LR+) and diagnostic odds ratios were: dyspepsia 0.79 (95% CI = 0.55 to 1.15) and 0.65 (95% CI = 0.32 to 1.33); pain 1.64 (95% CI = 1.20 to 2.24) and 2.09 (95% CI = 1.57 to 2.77); and dysphagia 4.32 (95% CI = 2.46 to 7.58) and 5.91 (95% CI = 3.56 to 9.82). Corresponding LR+ were: anaemia 4.32 (95% CI = 2.64 to 7.08); nausea/vomiting/bloating 1.07 (95% CI = 0.52 to 2.19); reflux 0.78 (95% CI = 0.47 to 1.78) and; weight loss 5.46 (95% CI = 3.47 to 8.60).

Conclusion
Dysphagia, weight loss, and anaemia show the strongest association but with relatively low sensitivity and high specificity. The findings support the value of investigation of these symptoms, but also suggest that, in a population of patients who are low risk but not no-risk, investigation is not currently recommended.

Keywords
diagnosis; primary health care; oesophageal neoplasms; stomach neoplasms; symptom; systematic review.

INTRODUCTION

More than 15 000 new diagnoses of oesophageal or gastric cancers are made annually in the UK. From a diagnostic viewpoint, the two cancers are generally considered together, as the main diagnostic test, upper gastrointestinal endoscopy, is the same for both. For both cancers, 5-year survival is relatively poor, as many are diagnosed at an advanced stage. Diagnostic delays are common, with 29% and 36% of patients with oesophageal and gastric cancer respectively having three or more primary care consultations before diagnosis;[1–3] furthermore, 22% and 33% of patients are diagnosed with oesophageal and gastric cancer respectively following emergency presentation.[4]

An estimated 600 deaths in the UK from oesophagogastric cancer annually are deemed 'avoidable' by comparison with mean European figures.[5] Expedited diagnosis may be beneficial either by identifying the tumour at a less-advanced stage, or by avoiding the emergency presentation, with its extra mortality.[6] Two main prospects for expediting the diagnosis (in the absence of screening) are:

- improved selection of patients for endoscopy (investigate 'smarter'); or
- liberalisation of endoscopy recommendations (investigate 'more').

The latter may help: UK general practices with a high gastroscopy rate have lower emergency admission rates and mortality for oesophagogastric cancer.[7]

The main recommendations for endoscopy are those of the National Institute of Health and Care Excellence (NICE), which cover two topics: dyspepsia[8] and cancer diagnosis.[9] Much of the evidence behind these recommendations came from secondary care. In contrast, here the authors sought to use primary care evidence in a systematic review of the diagnostic performance of oesophagogastric symptoms and likelihood of cancer, as it is in primary care that the clinical problem exists.

METHOD

Data sources and search methods

With the OVID platform, comprehensive searches of electronic databases were conducted using:

- MEDLINE® (1950 to May 2014);
- Embase (1974 to May 2014);
- CAB Abstracts (1973 to May 2014); and
- MEDLINE In-Process (May 2014).

The Wiley interface was used to search the Cochrane Library (Database of Reviews of Effectiveness, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, May 2014); and

MP Astin, MSc, research associate; **N Welton**, PhD, reader in Evidence Synthesis, NIHR Centre for Academic Primary Care, University of Bristol. Bristol. **T Martins**, PhD, research associate; **W Hamilton**, MD, professor of primary care diagnostics, University of Exeter Medical School, Exeter. **RD Neal**, PhD, FRCGP, professor of primary care medicine, North Wales Centre for Primary Care Research, Bangor University, Wrexham. **PW Rose**, FRCGP, lecturer in primary care, Department of Primary Care and Public Health, University of Oxford, Oxford.

Address for correspondence
William Hamilton, University of Exeter Medical School, College House St Luke's Campus, Magdalen Road, Exeter EX1 2LU, UK.
E-mail: w.hamilton@exeter.ac.uk

Submitted: 5 March 2015; **Editor's response:** 30 March 2015; **final acceptance:** 9 April 2015.

How this fits in

Oesophagogastric cancer is relatively common in the UK, but most patients are diagnosed late, with a poor prognosis. National guidance for upper gastrointestinal endoscopy is largely based on secondary care data, which will not pertain to the primary care decision on whether or not to refer. Dysphagia, weight loss, and anaemia show a relatively strong association with oesophagogastric cancer even in primary care populations. Each is of relatively low sensitivity, but high specificity. Other features, such as dyspepsia and other types of abdominal pain, were less likely to be associated with cancer. Despite supporting current referral recommendations, these findings also demonstrate that such recommendations miss a group of patients with symptomatic cancer. Any expansion to identify such patients would need rigorous health-economic evaluation.

CINAHL (1998 to May 2014). The terms were used to:

- identify upper gastrointestinal neoplasia;
- identify common symptoms, for example, dyspepsia, dysphagia, reflux, weight loss, pain, vomiting, anaemia, haematemesis, and 'alarm'; and
- for primary care settings, including spelling variations.

All sets included Medical Subject Heading (MeSH) and free-text terms, without language restrictions; the search terms are available from the authors on request).

Further searches were made of databases from relevant cancer websites. These were:

- European Organisation for Research and Treatment of Cancer: http://www.eortc.be;
- National Cancer Institute of Canada Clinical Trials Group: http://www.ctg.queensu.ca;
- Cancer Research UK Directory of Funded Research: http://www.cancerhelp.org.uk/trials/trials/; and
- UK Clinical Research Network Study Portfolio: http://public.ukcrn.org.uk/search/.

Reference lists of included studies were screened for relevance; personal literature collections and contacts with authors were also used.

Inclusion and exclusion criteria

Diagnostic studies of any design in Westernised countries with well-developed primary and secondary healthcare systems were eligible; as cancer incidence differs in Asian and African countries, where environmental factors may also differ, these were excluded. Eligible studies were those of patients who were:

- adult;
- symptomatic; and
- within primary care or referred by GPs for investigation to secondary care open-access endoscopy clinics.

Patients' symptom(s) had to be documented. The target condition was upper gastrointestinal (GI) cancers of the oesophagus, stomach, or duodenum of any stage (including carcinoma in situ). Lymphomas were excluded, as were studies of:

- individuals who were asymptomatic;
- screening;
- recurrent cancers;
- secondary causes of upper GI symptoms (from drug therapy and cancer treatment); and
- patients referred from secondary or tertiary care for endoscopy.

Study selection

One researcher ran the electronic searches and screened all titles and abstracts against inclusion and exclusion criteria. All potentially relevant abstracts were then reviewed independently by two researchers. Any disagreements including the healthcare setting were resolved by consensus; if uncertainty remained, the full article was obtained to assess its eligibility. Full articles of included studies were obtained and reference lists of all studies were checked for eligibility.

Data extraction and quality assessment

Definitions of dyspepsia (Appendix 1) and 'alarm' symptoms varied across studies, increasing clinical heterogeneity. Similar symptoms reported with different synonyms were grouped where possible (Box 1). In some studies, several discrete symptoms were reported;[10–16] these were collated separately.

Diagnostic accuracy methods with symptoms representing 'tests' were used to predict oesophagogastric cancer. Symptoms could be recorded by the clinician, self-reported by questionnaire, or coded. Valid reference standards were endoscopy, histology, double contrast

Box 1. Symptoms grouping

Classification for analysis	Symptom(s) reported
Dysphagia	• Dysphagia
Dyspepsia	• Dyspepsia
Reflux	• Regurgitation, heartburn, reflux-like symptom
Pain	• Upper abdominal pain, epigastric or retrosternal pain, cardiac-like symptom, ulcer-like symptom
Weight loss	• Weight loss, appetite loss, anorexia
Anaemia	• Anaemia, low haemoglobin, gastrointestinal bleeding
Haematemesis	• Haematemesis, if reported separately from anaemia
Nausea/vomiting/bloating	• Nausea, vomiting, bloating, dysmotility-like symptom
Bloating	• Abdominal distension, bloating, dysmotility-like symptom

barium meal, cancer registration, or clinical follow-up of 1 year.

Data extraction was conducted by one researcher and checked independently by a second researcher. The authors were contacted for further information when necessary. Methodological quality of full text included articles was ascertained using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool at the study level.[17] One question, relating to the adequacy of the description of symptoms, was added to the QUADAS and one question on the presence of clinical information was removed; as symptoms were used as a 'test', it was assumed that clinical information was available.

Data synthesis and analysis

The authors completed 2×2 contingency tables using the counts of true–positives, false–positives, true–negatives, and false–negatives for each symptom. Review Manager (version 5.2) was used for data collation and Stata (version 12) to analyse diagnostic performance with bivariate mixed-effects binary regression modelling, in line with the findings of Reitsma *et al*.[18] Sensitivity, specificity, positive and negative likelihood ratios (LR+, LR–), and diagnostic odds ratios (DORs) were calculated as outcome measures. Univariate random effects meta-analysis of DORs were used to explore heterogeneity between studies. Summary receiver operating characteristic (SROC) curves were generated for each symptom when four or more studies were available.

Heterogeneity was examined from Forest plots of DORs of individual studies, sub-grouped by study design (primary care referrals to endoscopy clinics and national database studies); if heterogeneity was observed, subgroups were compared. For symptoms without heterogeneity by study design, outliers were examined using bivariate box plots of sensitivity–specificity pairs, and sensitivity analyses were performed excluding outliers.

Analysis of possible factors influencing heterogeneity between studies (such as prospective versus retrospective designs, clinic settings, and sample sizes) was planned by univariable meta-regression, when ≥10 studies of each symptom were available. The effects of QUADAS items scoring <50% were assessed by univariable meta-regression, comparing the ratio of DORs across all studies meeting a criterion versus not met or unclear.

RESULTS

The electronic searches identified 7892 records after de-duplication; one additional study was identified from reference lists. In total, 77 studies were obtained for appraisal and 14 met inclusion criteria for evidence syntheses (Figure 1).

More than 22 600 participants were recruited in primary care cohort studies; another 3 142 582 participants were identified from three large retrospective studies using primary care databases. Study characteristics are shown in Appendix 2. Most originated in the UK ($n = 6$) or Europe ($n = 7$), and one was from Canada. Eight studies were prospective, two involved consecutive samples, and four were retrospective, including three national database studies. Sample sizes ranged from 100 to 10 061 in prospective and consecutive studies; and from 1000 in a locally-based retrospective study to between 40 348 and 2 140 194 in three database studies.

All studies except those of the national databases were of primary care referrals to endoscopy clinics; henceforth termed endoscopy clinic studies. The point prevalence of oesophageal and gastric cancers ranged from 0.08% to 7.14%, with a median 0.68% (Appendix 2). Studies were conducted between 1985 and 2010; data collection varied between 6 months and 129 months.

Heterogeneity

Methodological heterogeneity due to the presence of the database studies[10,11,16] was found for dysphagia, dyspepsia, reflux, and nausea/vomiting/bloating; conversely, no heterogeneity for anaemia, weight loss, or pain was identified. As the databases reported stronger diagnostic performance than small studies when heterogeneity between study designs was present, meta-analyses of the smaller studies, representing endoscopy clinics separately,

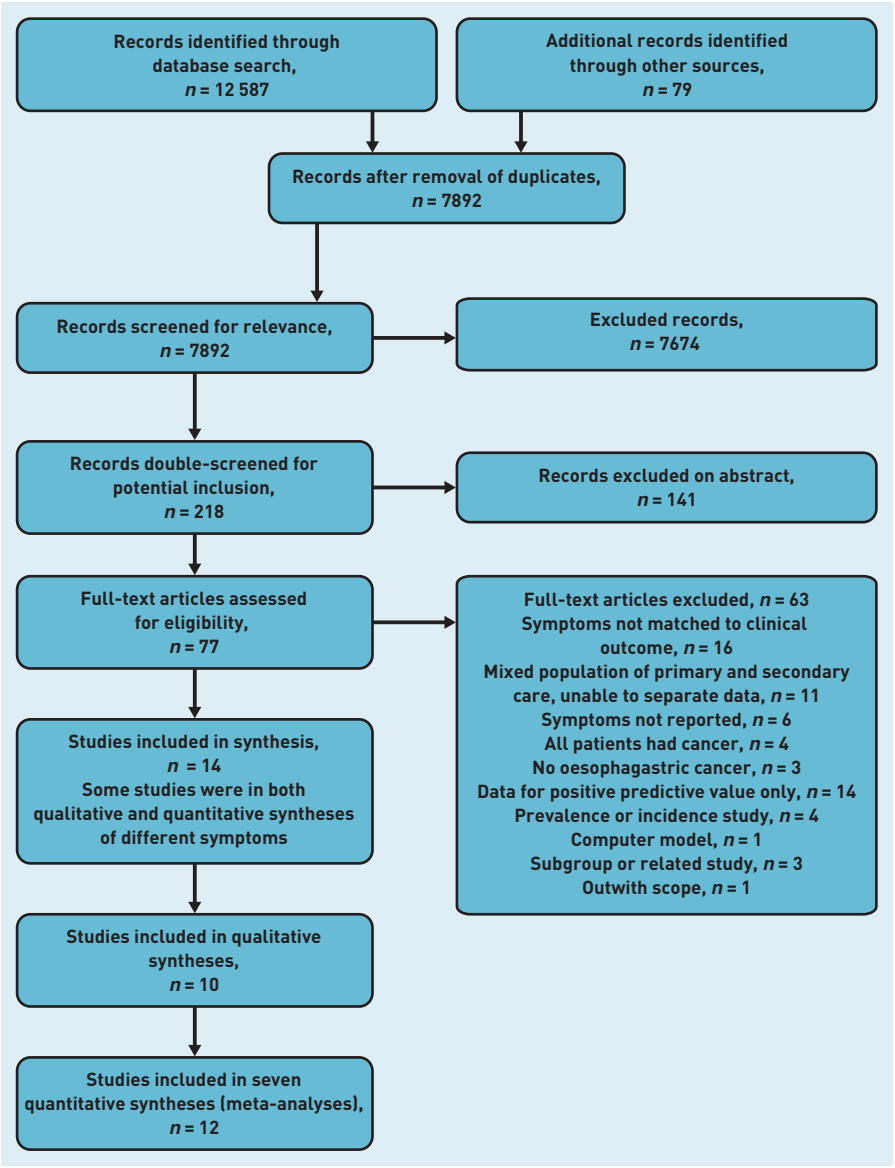


Figure 1. Flowchart of study inclusion.

was performed. There were insufficient studies to examine publication bias or to conduct meta-regression analyses.

Anaemia

Anaemia was reported in seven studies evaluating over 3 million patients.[10,11,13,15,16,19,20] It was defined as a recorded haemoglobin of <11 g/dl over the previous year in two studies[10–11] and grouped with gastrointestinal bleeding in another.[15] Sensitivity of anaemia for oesophagogastric cancer was low, with high specificity; LR+ ranged between 1.32 and 8.33, excluding one study[20] where few patients presented with anaemia, cancer was rare, and most patients were aged <50 years (Table 1).

LR– estimates were close to 1.00. The area under the curve (AUC) of 0.50 (95% confidence interval [CI] = 0.45 to 0.54) indicates poor discrimination of anaemia for oesophagogastric cancers. However, summary estimates for specificity (0.97), LR+ (4.32), and DOR (4.79) suggest that cancer cannot be ruled out (Table 1).

Meta-analysis of the studies in endoscopy clinics found a statistically significantly lower DOR (Table 1). No outliers were present from a bivariate box plot. Removing two endoscopy clinic studies[13,20] with no cancers identified moderately increased the summary sensitivity to 0.16 (95% confidence interval [CI] = 0.10 to 0.26, data not shown).

Pain

Pain was grouped to include upper abdominal, epigastric, retrosternal, cardiac-like, and ulcer-like pain; seven studies involving over 3 million patients evaluated these symptoms.[10–12,14,16,20,21] Studies reporting epigastric or retrosternal pain are reported separately (Table 2). Sensitivity was low with the exception of two endoscopy clinic studies;[12,14] specificity varied widely from 0.26 to 0.96. LR+ values were ≤3.04.

Meta-analyses of all studies, and for a subgroup of endoscopy clinic studies, showed poor discrimination of pain for oesophagogastric cancer (Table 1). When three outliers[12,14,16] were excluded, the summary sensitivity for pain reduced to 0.28 (95% CI = 0.18 to 0.41, data not shown); other metrics changed little.

Weight loss

Weight loss was evaluated in nine studies of 3 159 817 patients.[10–16,19,20] Sensitivity ranged between 0.00 and 0.78, and was <0.50 in two-thirds of studies; specificity was more precise ranging between 0.72 and 0.99 (Table 1). The LR+ ranged between 1.87 and 9.81, with the exception of one study (Table 1).[20]

The SROC curve shows some discriminatory value of weight loss to detect oesophagogastric cancer (Figure 2). A meta-analysis of endoscopy clinic studies increased the summary estimate for sensitivity (Table 1).

One outlier was identified;[19] exclusion of this study increased summary estimates of LR+ and DOR (sensitivity 0.24 [95% CI = 0.16 to 0.35], specificity 0.97 [95% CI = 0.94 to 0.98], LR+ 7.13 [95% CI = 5.67 to 8.95], LR– 0.78 [95% CI = 0.70 to 0.87], DOR 9.52 [95% CI = 7.19 to 11.54], data not shown).

Dysphagia

Nine studies reported dysphagia, evaluating over 3 million patients.[10,11,13–16,19,20] The sensitivity of dysphagia to detect

Table 1. Sensitivity, specificity, LR+, and LR– of symptoms associated with oesophagogastric cancer

Symptom	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR–(95% CI)	Summary DOR (95% CI)
Anaemia					
National databases					
Collins & Altman[10]	0.07 (0.05 to 0.08)	0.99 (0.99 to 0.99)	7.70 (6.46 to 9.19)	0.94 (0.93 to 0.95)	
Hippisley-Cox & Coupland[11]	0.09 (0.07 to 0.11)	0.99 (0.99 to 0.99)	8.33 (7.01 to 9.90)	0.92 (0.91 to 0.94)	
Stapley *et al*[16]	0.27 (0.26 to 0.28)	0.90 (0.89 to 0.90)	2.68 (2.56 to 2.82)	0.81 (0.80 to 0.82)	6.23 (2.96 to 13.1)[a]
Endoscopy clinic studies					
Kapoor *et al*[19]	0.13 (0.06 to 0.23)	0.90 (0.89 to 0.92)	1.32 (0.71 to 2.48)	0.97 (0.88 to 1.06)	
Meineche-Schmidt & Jørgensen[13]	0.00 (0.00 to 0.37)	0.98 (0.97 to 0.98)	2.26 (0.15 to 34.04)	0.97 (0.83 to 1.13)	
Salo *et al*[15]	0.13 (0.06 to 0.24)	0.93 (0.92 to 0.93)	1.87 (1.01 to 3.44)	0.93 (0.85 to 1.02)	
Thomson *et al*[20]	0.00 (0.00 to 0.98)	0.99 (0.98 to 1.00)	24.8 (2.08 to 294.1)	0.76 (0.34 to 1.69)	
Endoscopy clinic summary estimate	0.06 (0.01 to 0.31)	0.96 (0.91 to 0.99)	1.68 (0.34 to 8.25)	0.97 (0.88 to 1.01)	1.72 (0.73 to 4.04)
Summary estimates (all studies)	0.12 (0.08 to 0.19)	0.97 (0.94 to 0.99)	4.32 (2.64 to 7.08)	0.90 (0.86 to 0.94)	4.79 (2.92 to 7.85)
Pain					
National databases					
Collins & Altman[10]	0.25 (0.23 to 0.27)	0.88 (0.88 to 0.89)	2.15 (1.98 to 2.33)	0.85 (0.83 to 0.87)	
Hippisley-Cox & Coupland[11]	0.23 (0.21 to 0.25)	0.91 (0.90 to 0.91)	2.42 (2.20 to 2.67)	0.85 (0.83 to 0.88)	
Stapley *et al*[16]	0.12 (0.11 to 0.13)	0.96 (0.96 to 0.96)	3.04 (2.80 to 3.30)	0.92 (0.91 to 0.92)	2.89 (2.43 to 3.42)[a]
Endoscopy clinic studies					
Hansen *et al*[21]	0.25 (0.01 to 0.81)	0.74 (0.70 to 0.77)	0.95 (0.17 to 5.21)	1.02 (0.58 to 1.80)	
Johannessen *et al*[12]	0.78 (0.40 to 0.97)	0.26 (0.23 to 0.29)	1.05 (0.74 to 1.49)	0.85 (0.25 to 2.91)	
Numans *et al*[14]	0.68 (0.43 to 0.87)	0.47 (0.43 to 0.50)	1.29 (0.94 to 1.76)	0.67 (0.35 to 1.31)	
Thomson *et al*[20]	0.00 (0.00 to 0.98)	0.55 (0.52 to 0.58)	0.56 (0.05 to 6.19)	1.35 (0.61 to 3.02)	
Endoscopy clinic summary estimate	0.58 (0.30 to 0.81)	0.50 (0.33 to 0.68)	1.17 (0.84 to 1.63)	0.83 (0.52 to 1.34)	1.41 (0.64 to 3.14)
Summary estimates (all studies)	0.41 (0.24 to 0.62)	0.75 (0.51 to 0.89)	1.64 (1.20 to 2.24)	0.78 (0.71 to 0.87)	2.09 (1.57 to 2.77)
Weight loss					
National databases					
Collins & Altman[10]	0.12 (0.11 to 0.13)	0.99 (0.99 to 0.99)	9.37 (8.27 to 10.6)	0.89 (0.87 to 0.90)	
Hippisley-Cox & Coupland[11]	0.08 (0.07 to 0.10)	0.99 (0.99 to 0.99)	8.45 (7.04 to 10.2)	0.93 (0.91 to 0.94)	
Stapley *et al*[16]	0.08 (0.08 to 0.09)	0.99 (0.99 to 0.99)	9.81 (8.53 to 11.3)	0.93 (0.92 to 0.93)	10.3 (9.36 to 11.2)[a]
Endoscopy clinic studies					
Johannessen *et al*[12]	0.78 (0.40 to 0.97)	0.74 (0.71 to 0.76)	2.94 (2.04 to 4.23)	0.30 (0.09 to 1.03)	
Kapoor *et al*[19]	0.53 (0.41 to 0.65)	0.72 (0.70 to 0.74)	1.87 (1.48 to 2.36)	0.66 (0.51 to 0.84)	
Meineche-Schmidt & Jørgensen[13]	0.38 (0.09 to 0.76)	0.87 (0.85 to 0.88)	2.81 (1.14 to 6.94)	0.72 (0.42 to 1.23)	
Numans *et al*[14]	0.67 (0.43 to 0.85)	0.77 (0.74 to 0.80)	2.87 (2.07 to 3.98)	0.43 (0.24 to 0.80)	
Salo *et al*[15]	0.22 (0.13 to 0.34)	0.97 (0.97 to 0.98)	8.48 (5.34 to 13.5)	0.80 (0.71 to 0.91)	
Thomson *et al*[20]	0.00 (0.00 to 0.98)	0.99 (0.99 to 1.00)	40.0 (3.22 to 497.0)	0.75 (0.34 to 1.68)	
Endoscopy clinic summary estimate	0.39 (0.22 to 0.59)	0.91 (0.74 to 0.97)	4.16 (2.05 to 8.43)	0.68 (0.55 to 0.84)	6.15 (3.35 to 11.3)
Summary estimates (all studies)	0.25 (0.12 to 0.43)	0.96 (0.88 to 0.98)	5.46 (3.47 to 8.60)	0.79 (0.68 to 0.92)	6.91 (4.95 to 9.65)

... continued

oesophagogastric cancers ranged from 0.12 to 0.62 excluding one study of few patients presenting with dysphagia (Table 1), and detection of only one oesophageal cancer. Specificity was stronger, ranging between 0.67 and 0.99. LR+ ranged between 1.77 and 7.81 in endoscopy clinic studies, excluding Thomson *et al*'s study,[20] and was much larger from the database studies (Table 1).[10,11,16]

LR– estimates ranged from 0.48 to 0.9 (Table 1). Findings between the databases were consistent. A Forest plot (data not shown) of DORs showed marked heterogeneity between the endoscopy clinic studies and the database studies. An SROC curve for the subgroup of endoscopy clinic studies showed moderate discrimination of dysphagia to detect oesophagogastric cancers with an AUC of 0.68 (95% CI = 0.64

Table 1 continued. Sensitivity, specificity, LR+, and LR– of symptoms associated with oesophagogastric cancer

Symptom	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR–(95% CI)	Summary DOR (95% CI)
Dysphagia					
National databases					
Collins & Altman[10]	0.46 (0.44 to 0.48)	0.99 (0.99 to 0.99)	53.2 (50.5 to 56.1)	0.55 (0.52 to 0.57)	
Hippisley-Cox & Coupland[11]	0.32 (0.30 to 0.35)	0.99 (0.99 to 0.99)	60.3 (55.5 to 65.4)	0.68 (0.66 to 0.71)	
Stapley *et al*[16]	0.32 (0.31 to 0.33)	0.99 (0.99 to 1.00)	57.6 (49.7 to 66.7)	0.68 (0.67 to 0.69)	91.4 (84.199)[a]
Endoscopy clinic studies					
Boulton-Jones *et al*[22]	0.47 (0.21 to 0.73)	0.94 (0.92 to 0.95)	7.81 (4.31 to 14.18)	0.57 (0.35 to 0.91)	
Kapoor *et al*[19]	0.59 (0.46 to 0.70)	0.67 (0.65 to 0.69)	1.77 (1.44 to 2.18)	0.62 (0.47 to 0.82)	
Meineche-Schmidt & Jørgensen[13]	0.38 (0.09 to 0.76)	0.87 (0.85 to 0.88)	2.82 (1.14 to 6.97)	0.72 (0.42 to 1.23)	
Numans *et al*[14]	0.62 (0.38 to 0.82)	0.79 (0.76 to 0.82)	2.96 (2.07 to 4.25)	0.48 (0.28 to 0.83)	
Salo *et al*[15]	0.12 (0.05 to 0.22)	0.98 (0.98 to 0.99)	6.92 (3.55 to 13.5)	0.90 (0.82 to 0.98)	
Thomson *et al*[20]	0.00 (0.00 to 0.98)	0.99 (0.98 to 0.99)	19.3 (1.65 to 225.0)	0.76 (0.34 to 1.69)	
Endoscopy clinic summary estimate	0.32 (0.17 to 0.52)	0.92 (0.81 to 0.97)	4.32 (2.46 to 7.58)	0.73 (0.60 to 0.89)	5.91 (3.56 to 9.82)
Dyspepsia					
National databases					
Stapley *et al*[16]	0.17 (0.16 to 0.18)	0.98 (0.98 to 0.98)	7.45 (6.84 to 8.12)	0.85 (0.84 to 0.86)	8.81 (8.02 to 9.67)
Endoscopy clinic studies					
Boulton-Jones *et al*[22]	0.53 (0.27 to 0.79)	0.20 (0.18 to 0.23)	0.67 (0.41 to 1.07)	2.34 (1.34 to 4.07)	
Meineche-Schmidt & Jørgensen[13]	0.50 (0.16 to 0.84)	0.80 (0.79 to 0.82)	2.55 (1.27 to 5.11)	0.62 (0.31 to 1.24)	
Numans *et al*[14]	0.35 (0.15 to 0.59)	0.36 (0.32 to 0.39)	0.55 (0.30 to 0.99)	1.81 (1.30 to 2.53)	
Salo *et al*[15]	0.35 (0.24 to 0.48)	0.49 (0.48 to 0.50)	0.69 (0.50 to 0.96)	1.32 (1.11 to 1.58)	
van Kerkhoven *et al*[23]	0.70 (0.47 to 0.87)	0.39 (0.37 to 0.42)	1.15 (0.87 to 1.51)	0.77 (0.42 to 1.44)	
Voutilainen *et al*[24]	0.18 (0.04 to 0.43)	0.61 (0.59 to 0.63)	0.45 (0.16 to 1.27)	1.35 (1.08 to 1.68)	
Endoscopy clinic summary estimate	0.42 (0.29 to 0.56)	0.48 (0.31 to 0.65)	0.79 (0.55 to 1.15)	1.23 (0.86 to 1.74)	0.65 (0.32 to 1.33)
Nausea/vomiting/bloating					
National databases					
Stapley *et al*[16]	0.13 (0.12 to 0.14)	0.98 (0.98 to 0.98)	6.76 (6.14 to 7.45)	0.89 (0.88 to 0.89)	7.63 (6.88 to 8.46)
Endoscopy clinic studies					
Hansen *et al*[21]	0.00 (0.00 to 0.60)	0.73 (0.69 to 0.77)	0.37 (0.03 to 5.18)	1.23 (0.91 to 1.65)	
Johannessen *et al*[12]	0.33 (0.07 to 0.70)	0.56 (0.53 to 0.59)	0.76 (0.30 to 1.91)	1.19 (0.75 to 1.90)	
Numans *et al*[14]	0.38 (0.18 to 0.62)	0.76 (0.72 to 0.78)	1.56 (0.89 to 2.72)	0.82 (0.58 to 1.15)	
Salo *et al*[15]	0.01 (0.00 to 0.08)	0.99 (0.98 to 0.99)	1.05 (0.15 to 7.40)	1.00 (0.97 to 1.03)	
Thomson *et al*[20]	0.00 (0.00 to 0.98)	0.82 (0.80 to 0.85)	1.41 (0.13 to 15.6)	0.91 (0.41 to 2.03)	
Endoscopy clinic summary estimate	0.17 (0.05 to 0.46)	0.84 (0.60 to 0.94)	1.07 (0.52 to 2.19)	0.99 (0.85 to 1.15)	1.08 (0.46 to 2.57)
Reflux: National databases					
Stapley *et al*[16]	0.11 (0.11 to 0.12)	0.98 (0.98 to 0.99)	7.22 (6.49 to 8.04)	0.90 (0.89 to 0.91)	
Endoscopy clinic studies					
Boulton-Jones *et al*[22]	0.00 (0.00 to 0.22)	0.86 (0.84 to 0.88)	0.22 (0.01 to 3.42)	1.13 (1.03 to 1.24)	
Hansen *et al*[21]	0.50 (0.07 to 0.93)	0.72 (0.68 to 0.75)	1.78 (0.66 to 4.78)	0.70 (0.26 to 1.86)	
Johannessen *et al*[12]	0.33 (0.07 to 0.70)	0.49 (0.46 to 0.52)	0.65 (0.26 to 1.65)	1.36 (0.86 to 2.18)	
Numans *et al*[14]	0.57 (0.34 to 0.78)	0.59 (0.55 to 0.62)	1.39 (0.95 to 2.03)	0.73 (0.44 to 1.20)	
Salo *et al*[15]	0.15 (0.07 to 0.25)	0.76 (0.75 to 0.77)	0.62 (0.35 to 1.09)	1.12 (1.01 to 1.24)	
Thomson *et al*[20]	1.00 (0.03 to 1.00)	0.62 (0.59 to 0.65)	1.99 (0.89 to 4.44)	0.40 (0.04 to 4.43)	
van Kerkhoven *et al*[23]	0.52 (0.31 to 0.73)	0.52 (0.50 to 0.55)	1.09 (0.74 to 1.62)	0.91 (0.59 to 1.41)	
Voutilainen *et al*[24]	0.00 (0.00 to 0.20)	0.89 (0.88 to 0.90)	0.25 (0.02 to 3.89)	1.09 (1.01 to 1.18)	
Endoscopy clinic summary estimate	0.23 (0.10 to 0.46)	0.70 (0.59 to 0.80)	0.78 (0.47 to 1.28)	1.09 (0.97 to 1.24)	0.71 (0.38 to 1.32)

[a] *Univariate random effects meta-analysis. DOR = diagnostic odds ratio. LR+ = positive likelihood ratio. LR– = negative likelihood ratio.*

Table 2. Sensitivity, specificity, LR+, and LR– of other symptoms associated with oesophagogastric cancer

Symptom	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR– (95% CI)
Appetite loss				
Collins & Altman[10]	0.02 (0.01 to 0.03)	1.00 (1.00 to 1.00)	7.72 (5.61 to 10.63)	0.98 (0.98 to 0.99)
Hippisley-Cox & Coupland[11]	0.03 (0.02 to 0.04)	1.00 (1.00 to 1.00)	7.70 (5.54 to 10.69)	0.98 (0.97 to 0.99)
Johannessen *et al*[12]	0.67 (0.30 to 0.93)	0.78 (0.76 to 8.81)	3.09 (1.91 to 4.98)	0.43 (0.17 to 1.07)
Bloating				
Numans *et al*[14]	0.74 (0.49 to 0.91)	0.30 (0.27 to 0.34)	1.06 (0.81 to 1.39)	0.87 (0.41 to 1.85)
Salo *et al*[15]	0.00 (0.00 to 0.05)	0.99 (0.99 to 0.99)	0.00 (0.00 to 0.00)	1.01 (1.01 to 1.01)
Constipation				
Stapley *et al*[16]	0.08 (0.08 to 0.09)	0.97 (0.97 to 0.97)	2.49 (2.26 to 2.75)	0.95 (0.94 to 0.96)
Diarrhoea				
Salo *et al*[15]	0.00 (0.00 to 0.05)	0.99 (0.99 to 0.99)	0.00 (0.00 to 0.00)	1.01 (1.01 to 1.01)
Epigastric pain				
Johannessen *et al*[12]	0.33 (0.07 to 0.70)	0.74 (0.71 to 0.77)	1.28 (0.51 to 3.26)	0.90 (0.57 to 1.43)
Numans *et al*[14]	0.67 (0.41 to 0.87)	0.17 (0.15 to 0.20)	0.80 (0.58 to 1.12)	1.95 (1.00 to 3.81)
Stapley *et al*[16]	0.08 (0.08 to 0.09)	0.99 (0.99 to 0.99)	10.21 (8.86 to 11.76)	0.92 (0.92 to 0.93)
Haematemesis				
Collins & Altman[10]	0.06 (0.05 to 0.07)	0.99 (0.99 to 1.00)	12.47 (10.39 to 14.96)	0.94 (0.93 to 0.95)
Hippisley-Cox & Coupland[11]	0.08 (0.06 to 0.09)	1.00 (1.00 to 1.00)	16.53 (13.67 to 19.98)	0.93 (0.91 to 0.94)
Numans *et al*[14]	0.05 (0.00 to 0.25)	0.95 (0.93 to 0.96)	0.93 (0.13 to 6.38)	1.00 (0.91 to 1.11)
Melaena				
Meineche-Schmidt & Jørgensen[13]	0.13 (0.00 to 0.53)	0.93 (0.92 to 0.94)	1.82 (0.29 to 11.48)	0.94 (0.72 to 1.22)
Numans *et al*[14]	0.16 (0.03 to 0.40)	0.92 (0.90 to 0.94)	2.03 (0.70 to 5.88)	0.91 (0.75 to 1.11)
Retrosternal pain				
Johannessen *et al*[12]	0.33 (0.07 to 0.70)	0.71 (0.68 to 0.74)	1.15 (0.45 to 2.91)	0.94 (0.59 to 1.49)
Numans *et al*[14]	0.68 (0.43 to 0.87)	0.47 (0.43 to 0.50)	1.29 (0.94 to 1.76)	0.67 (0.35 to 1.31)
Stapley *et al*[16]	0.10 (0.09 to 0.10)	0.95 (0.95 to 0.95)	2.01 (1.85 to 2.19)	0.95 (0.94 to 0.96)
Treatment failure				
Boulton-Jones *et al*[22]	0.07 (0.00 to 0.32)	0.73 (0.70 to 0.76)	0.25 (0.04 to 1.64)	1.28 (1.11 to 1.47)
van Kerkhoven *et al*[23]	0.30 (0.13 to 0.53)	0.42 (0.40 to 0.45)	0.53 (0.28 to 0.98)	1.65 (1.25 to 2.17)
Voutilainen *et al*[24]	0.06 (0.00 to 0.29)	0.94 (0.93 to 0.95)	1.03 (0.15 to 6.93)	1.00 (0.89 to 1.12)

to 0.72) (Figure 3).

Dyspepsia

Dyspepsia was reported in seven studies evaluating over 58 000 patients.[13–16,22–24] The sensitivity of dyspepsia to detect oesophagogastric cancers ranged from 0.17 to 0.70; however specificity varied across endoscopy clinics, possibly reflecting different dyspepsia definitions and study settings.

LR+ were generally low ranging from 0.45 to 2.55 in endoscopy clinic studies (Table 1), and was strong in one large national database study.[16] LR– estimates were low, ranging from 0.62 to 2.34. An AUC of 0.42 (95% CI = 0.38 to 0.46) and summary estimates from meta-analysis of the subgroup of endoscopy clinics suggested low discrimination of dyspepsia for oesophagogastric cancers.

Both low sensitivity and specificity values suggest a weak association of dyspepsia as a sole symptom with oesophagogastric cancers.

Nausea, vomiting, or bloating

This group encompassed the symptoms classified as dysmotility-like; bloating was also collated separately when data was available. Six studies of over 53 000 patients reported any of these symptoms.[12,14–16,20–21] The sensitivity was low, ranging from 0.00 to 0.38; specificity varied between 0.56 and 0.99 (Table 1). The LR+ ranged between 0.37 and 1.56 for endoscopy clinics, although it was 6.76 in one database study. An AUC of 0.50 (95% CI = 0.45 to 0.54) and meta-analysis of endoscopy clinics, suggests low discrimination of these symptoms for oesophagogastric cancer.

Reflux

Reflux symptoms were reported as regurgitation, heartburn, and 'reflux-like' symptoms in nine studies of over 59 000 patients.[12,14–16,20–24] Sensitivity overall was low, ranging between 0.0 and 0.57, excluding the study by Thomson *et al* because only one patient in the whole series had upper GI cancer (and had reflux); specificity was higher ranging from 0.49 to 0.98. The LR+ were, in the main, <2.00; an exception being one database study (Table 1).[16] An AUC of 0.55 (95% CI = 0.50 to 0.59) and summary estimates from meta-analysis of endoscopy clinics suggests low discrimination of these symptoms for oesophagogastric cancers.

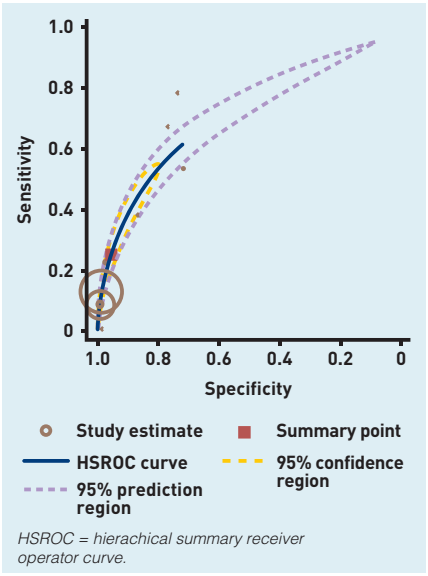
Other symptoms

One study from a dyspepsia clinic reported 'alarm' symptoms as a single entity;[25] these included weight loss, dysphagia, anaemia, and vomiting. Sensitivity was relatively high, although specificity, LR+, and LR– were low in comparison.

Although appetite loss and haematemesis were of low sensitivity, both specificity and LR+ were strong in two national database studies;[10,11] the LR+ values of all other remaining symptoms were relatively low, with the exception of one database study reporting an LR+ of 10.2 for epigastric pain (Table 2).[16] Diagnostic performance for failure of antacid medication from three studies[22–24] showed a low association with oesophagogastric cancer (Table 2).

Quality of studies

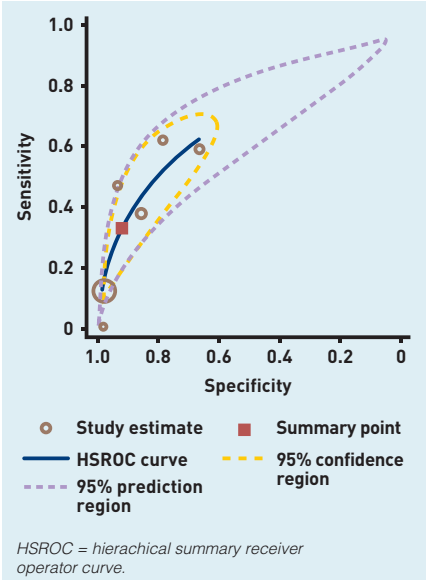
The reporting of QUADAS items is shown



HSROC = hierachical summary receiver operator curve.

Figure 2. SROC curve for sensitivity and specificity of weight loss.

Figure 3. SROC curve for sensitivity and specificity of dysphagia.



HSROC = hierachical summary receiver operator curve.

in Figure 4, with more detail in Appendix 3. QUADAS items met by <50% of studies were:

- acceptable delay between index and reference tests; and
- blinded interpretation of the index test without knowledge of the reference standard.

Forty-three per cent of studies were considered not to be representative samples (patients at high risk with alarm symptoms, or a majority of patients aged ≤50 years). Appendix 4 shows the meta-regression of the ratio of DORs, suggesting little evidence of an effect of these factors on the summary estimates; however, heterogeneity between studies was substantial.

DISCUSSION

Summary

This systematic review examined studies undertaken in primary care (including open-access endoscopy clinics) of the features of oesophagogastric cancer. A low sensitivity for detection of these cancers was found in all studies, with the highest sensitivity symptoms being dysphagia, weight loss, dyspepsia, and any pain symptom. From the DORs, all clinical features showed an association with cancer, with dyspepsia and reflux having the weakest associations. However, the LR+s suggest the symptoms of dysphagia, weight loss, and anaemia would be the most useful in the selection of patients for investigation. Pain, nausea/vomiting/bloating, reflux, and dyspepsia were less likely to be associated with cancer.

Each of the clinical features assessed in this review was associated with cancer, with the notable exceptions of dyspepsia and reflux. The strength of the associations varied, with summary DORs highest in weight loss, moderate in dysphagia and anaemia, and lowest for pain and nausea/vomiting/bloating.

Strengths and limitations

Systematic review findings are only as good as the data reported from the candidate studies. The assessment of study quality using the QUADAS tool was adequate across seven of 11 items (63.6%); ratio of DORs showed no effects of study quality on the meta-analyses.

Differences in diagnostic performance between the large database studies (all from the UK) and smaller endoscopy clinic studies were found. The diagnostic performance was consistent across the three database studies; however, LR+s were larger for most symptoms than in endoscopy clinic studies; there are several possible reasons for this. The database studies used coded symptoms in the medical records of confirmed cases of oesophagogastric cancer, and from other patients without cancer. These data are likely to differ from those collected in smaller prospective studies using questionnaires or patients' self-reported symptoms; these differences may underpin the methodological heterogeneity identified for some symptoms between the databases and endoscopy clinic studies.

The symptoms of anaemia, weight loss, and pain are easier to define uniformly and were unaffected by study design, while more complex symptoms like reflux, dyspepsia, nausea/vomiting/bloating, and dysphagia produced stronger diagnostic outcomes in the databases than endoscopy clinic studies.

Another factor almost certainly influencing investigation decisions, and contributing to clinical heterogeneity, is symptom severity. No studies reported this factor. Similarly it was not possible for the authors of this review to analyse the findings by age or sex, as the data were limited.

Another possible limitation is that some studies of patients who were symptomatic were identified but excluded from the review as none developed oesophagogastric cancer. These studies may represent a different population. Similarly, the prevalence of cancer was as high as 7.14%; again, this is likely to reflect different populations, especially for selection by age criteria.

One methodological improvement may be individual patient data meta-analysis: this would require considerably more resources than the authors had available and the need for authors of included studies to be able and willing to release their patient data.

The decision to report measures of relative association, such as DORs and LRs, followed current best practice. Absolute measures of risk, such as positive predictive values (PPVs), are also useful metrics. However, absolute measures of risk depend not only on the strength of the association between the symptom and cancer, but also on the prevalence of cancer in the study population. This latter parameter varied considerably, despite restriction to primary care, so summary PPV estimates could obscure, rather than enlighten, the strength of association between a symptom and cancer.

Open-access endoscopy clinics were included where the clinical responsibility was retained by primary care. This may have increased the strength of association

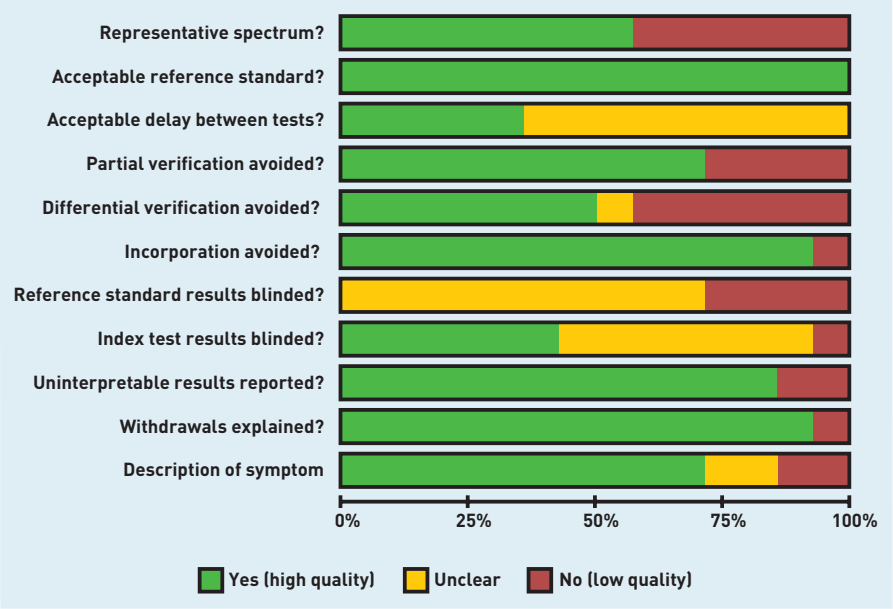


Figure 4. Methodological quality graph of proportions of studies for each QUADAS item.

Funding

This review was funded by Cancer Research UK (grant number A12218). Richard D Neal receives funding from Betsi Cadwaladr University Health Board and Public Health Wales.

Provenance

Freely submitted; externally peer reviewed.

Competing interests

William Hamilton is the clinical lead for the current revision of guidance from the National Institute for Health and Care Excellence (NICE) on the topic of selecting patients for cancer investigation. His contribution to this article is in a personal capacity and is not to be interpreted as representing the view of NICE's Guideline Development Group, or of NICE itself. He has received travel support to give lectures and attend conferences, plus occasional speaker's fees from conference organisers in the charitable and educational sector, although none have come from commercial sources. William Hamilton, Peter W Rose, and Richard D Neal were co-authors of one of the articles included in the review. An abstract of an oral presentation of this article is cited in: *Eur J Cancer Care* 2014; **23(S1):** 24–33.

Acknowledgements

We would like to thank Professor Julian Higgins for statistical support.

Discuss this article

Contribute and read comments about this article: **bjgp.org/letters**

with oesophagogastric cancer, especially for dyspepsia, as it is unlikely that all patients presenting to primary care were investigated; as a result, those in the endoscopy clinic had undergone a selection process, thereby increasing the population risk.

Gastric and oesophageal cancers were not separated as a pre-hoc decision; furthermore, only two studies did separate these. Some symptoms may be more relevant to oesophageal cancers, especially dysphagia; this is of minor clinical relevance, as the same main diagnostic test is used for both cancers.

Comparison with existing literature

This review overlaps with another systematic review by Vakil *et al*.[26] The review reported here included some of the same studies, but excluded those with mixed cohorts of patients from primary and secondary care for which the data could not be separated. Unlike Vakil *et al*, study selection was restricted to primary care settings.

The summary sensitivity and specificity values in this review were similar to those of Vakil *et al* for dysphagia, weight loss, and anaemia, presumably because most patients with these symptoms would be referred. An earlier meta-analysis of eight studies (four included in the current analysis) by Fransen *et al*[27] reported summary sensitivity and specificity values for weight loss, nausea/vomiting, anaemia, and dysphagia that are comparable to the meta-analyses in this review.

Implications for research and practice

Many of the symptoms reported in this review are found in a range of clinical conditions. It was unlikely that any would exhibit strong specificity; similarly, symptoms are usually not as precise as laboratory measures, because of their subjective nature. However, quantification adds some value, by highlighting the symptoms with the strongest associations with cancer, and comparing relative diagnostic values. It also allows consideration of which symptoms warrant specialist investigation.

Current UK guidance suggests investigation for possible cancer in patients with dyspepsia and additional chronic gastrointestinal bleeding, unintentional weight loss, persistent vomiting, iron deficiency anaemia, or an epigastric mass.[8,9] At any age, dysphagia and, in patients aged >55 years, persistent unexplained dyspepsia, are recommended for investigation. The findings of this review clearly support investigation for patients with dysphagia, weight loss, or anaemia.

No studies reported epigastric masses, but investigation appears uncontroversial. For dyspepsia and reflux, the summary diagnostic ORs in this review were close to 1.0 (with upper CIs as high as 2.0); even accepting that some selection bias was introduced by the decision to include open-access endoscopy clinics, it remains clear that these symptoms have a lower association with oesophagogastric cancer.

Nausea/vomiting and abdominal pain represent small risks; the so-called 'low-risk-but-not-no-risk' symptoms.[28] If recommendations for endoscopy were liberalised to include these, then some cancers would be detected earlier; this would, however, come with a clinical and economic cost, which may be considerable.[8]

Currently, there is a 2.7-fold difference in the rate of gastroscopy between the highest and lowest clinical commissioning groups, which is hard to justify clinically.[29] Even so, a policy decision to expand criteria for investigation would need rigorous health economic evaluation. Nonetheless, if the UK is to narrow the mortality gap with Europe, this is worthy of consideration, alongside improvements in awareness, waiting times, and possible biomarkers and reduced costs of endoscopy. Expecting GPs to exercise 'better' selection of patients with existing resources is unrealistic, however, as current guidance already identifies those patients who are most at risk.

REFERENCES

1. Grotenhuis BA, van Hagen P, Wijnhoven BPL, *et al*. Delay in diagnostic workup and treatment of esophageal cancer. *J Gastrointest Surg* 2010; **14:** 476–483.
2. Lyratzopoulos G, Neal RD, Barbiere JM, *et al*. Variation in number of general practitioner consultations before hospital referral for cancer: findings from the 2010 National Cancer Patient Experience Survey in England. *Lancet Oncology* 2012; **13(4):** 353–365.
3. Lyratzopoulos G, Abel GA, McPhail S, *et al*. Measures of promptness of cancer diagnosis in primary care: secondary analysis of national audit data on patients with 18 common and rarer cancers. *Br J Cancer* 2013; **108(3):** 686–690.
4. Elliss-Brookes L, McPhail S, Ives A, *et al*. Routes to diagnosis for cancer — determining the patient journey using multiple routine data sets. *Br J Cancer* 2012; **107:** 1220–1226.
5. Abdel-Rahman M, Stockton D, Rachet B, *et al*. What if cancer survival in Britain were the same as in Europe: how many deaths are avoidable? *Br J Cancer* 2009; **101(S2):** S115–S124.
6. McPhail S, Elliss-Brookes L, Shelton J, *et al*. Emergency presentation of cancer and short-term mortality. *Br J Cancer* 2013; **109(8):** 2027–2034.
7. Shawihdi M, Thompson E, Kapoor N, *et al*. Variation in gastroscopy rate in English general practice and outcome for oesophagogastric cancer: retrospective analysis of Hospital Episode Statistics. *Gut* 2014; **63(2):** 250–261.
8. National Institute for Health and Care Excellence. *Dyspepsia: management of dyspepsia in adults in primary care*. NICE. https://www.nice.org.uk/guidance/cg17 (accessed 5 Aug 2015).
9. National Institute for Health and Care Excellence. *Referral guidelines for suspected cancer*. NICE. https://www.nice.org.uk/guidance/cg27 (accessed 5 Aug 2015).
10. Collins GS, Altman DG. Identifying patients with undetected gastro-oesophageal cancer in primary care: external validation of QCancer® (Gastro-Oesophageal). *Eur J Cancer* 2013; **49(5):** 1040–1048.
11. Hippisley-Cox J, Coupland C. Identifying patients with suspected gastro-oesophageal cancer in primary care: derivation and validation of an algorithm. *Br J Gen Pract* 2011; DOI: 10.3399/bjgp11X606609.
12. Johannessen T, Petersen H, Kleveland PM, *et al*. The predictive value of history in dyspepsia. *Scand J Gastroenterol* 1990; **25(7):** 689–697.
13. Meineche-Schmidt V, Jørgensen T. 'Alarm symptoms' in patients with dyspepsia: a three-year prospective study from general practice. *Scand J Gastroenterol* 2002; **37(9):** 999–1007.
14. Numans ME, van der Graaf Y, de Wit NJ, de Melker RA. How useful is selection based on alarm symptoms in requesting gastroscopy? An evaluation of diagnostic determinants for gastro-oesophageal malignancy. *Scand J Gastroenterol* 2001; **36(4):** 437–443.
15. Salo M, Collin P, Kyrönpalo S, *et al*. Age, symptoms and upper gastrointestinal malignancy in primary care endoscopy. *Scand J Gastroenterol* 2008; **43(1):** 122–127.
16. Stapley S, Peters TJ, Neal RD, *et al*. The risk of oesophago-gastric cancer in symptomatic patients in primary care: a large case-control study using electronic records. *Br J Cancer* 2013; **108(1):** 25–31.
17. Whiting P, Rutjes AWS, Reitsma JB, *et al*. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Med Res Methodol* 2003; **3:** 25.
18. Reitsma JB, Glas AS, Rutjes AWS, *et al*. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol* 2005; **58(10):** 982–990.
19. Kapoor N, Bassi A, Sturgess R, Bodger K. Predictive value of alarm features in a rapid access upper gastrointestinal cancer service. *Gut* 2005; **54(1):** 40–45.
20. Thomson ABR, Barkun AN, Armstrong D, *et al*. The prevalence of clinically significant endoscopic findings in primary care patients with uninvestigated dyspepsia: the Canadian Adult Dyspepsia Empiric Treatment – Prompt Endoscopy (CADET–PE) study. *Aliment Pharmacol Ther* 2003; **17(12):** 1481–1491.
21. Hansen JM, Bytzer P, Schaffalitzky De Muckadell OB. Management of dyspeptic patients in primary care: value of the unaided clinical diagnosis and of dyspepsia subgrouping. *Scand J Gastroenterol* 1998; **33(8):** 799–805.
22. Boulton-Jones JR, Follows MC, Mahmoud AA. Open-access endoscopy: are age-based guidelines justified? An audit of experience of 1000 open-access endoscopies at a district general hospital. *Endoscopy* 2003; **35(1):** 68–73.
23. van Kerkhoven LAS, van Rijswijck SJ, van Rossum LGM, *et al*. Is there any association between referral indications for open-access upper gastrointestinal endoscopy and endoscopic findings? *Endoscopy* 2007; **39(6):** 502–506.
24. Voutilainen M, Mäntynen T, Kunnamo I, *et al*. Impact of clinical symptoms and referral volume on endoscopy for detecting peptic ulcer and gastric neoplasms. *Scand J Gastroenterol* 2003; **38(1):** 109–113.
25. Melleney EM-A, Willoughby CP. Audit of a nurse endoscopist based one stop dyspepsia clinic. *Postgrad Med J* 2002; **78(917):** 161–164.
26. Vakil N, Moayyedi P, Fennerty MB, Talley NJ. Limited value of alarm features in the diagnosis of upper gastrointestinal malignancy: systematic review and meta-analysis. *Gastroenterology* 2006; **131(2):** 390–401.
27. Fransen GAJ, Janssen MJR, Muris JWM, *et al*. Meta-analysis: the diagnostic value of alarm symptoms for upper gastrointestinal malignancy. *Aliment Pharmacol Ther* 2004; **20(10):** 1045–1052.
28. Hamilton W. Cancer diagnosis in primary care. *Br J Gen Pract* 2010; DOI: 10.3399/bjgp10X483175.
29. Public Health England. *The NHS Atlas of Variation in Diagnostic Services*. http://www.rightcare.nhs.uk/index.php/atlas/diagnostics-the-nhs-atlas-of-variation-in-diagnostics-services/ (accessed 5 Aug 2015).

Appendix 1. Definitions of dyspepsia used in included studies

Study	Definition
Boulton-Jones *et al*[22]	Based on British Society of Gastroenterology guidelines
Collins & Altman[10]	Dyspepsia not reported
Hansen *et al*[21]	Epigastric or retrosternal pain or discomfort, with or without heartburn, nausea, vomiting, and any other symptom related to the proximal alimentary tract
Hippisley-Cox & Coupland[11]	Dyspepsia not reported
Johannessen *et al*[12]	No definition
Kapoor *et al*[19]	No definition
Melleney & Willoughby[25]	No definition
Meineche-Schmidt & Jørgensen[13]	Pain or discomfort in the abdomen judged by the GP to be related to the gastrointestinal tract
Numans *et al*[14]	Disease history
Salo *et al*[15]	Chronic and recurrent pain, discomfort in upper abdomen, abdominal distension or postprandial upper gastrointestinal complaints
Stapley *et al*[16]	General Practice Research Database coding for dyspepsia or indigestion
Thomson *et al*[20]	Upper gastrointestinal symptom complex characterised by epigastric pain or discomfort, and may include heartburn, acid regurgitation, excessive burping/belching, abdominal bloating, feeling of abnormal or slow digestion, early satiety, or nausea
van Kerkhoven *et al*[23]	Upper abdominal complaints, nausea, vomiting, pain, belching, or fullness
Voutilainen *et al*[24]	Epigastric pain and/or other chronic or recurrent symptoms centred in the upper abdomen (bloating or distension, belching, nausea, or early satiety)

Appendix 2. Study characteristics

Study authors	Country	Design	Setting	Age, years	Categories of presenting symptoms	Participants, *n* Alarm symptoms, %	Prevalence of oesophogeal cancer	Data collection tool	Reference standard
Boulton-Jones *et al*[22]	UK	Retrospective cohort (audit), 1997–1999 (29 months)	GP referrals to open access endoscopy, according to BSG guidance, at a district general hospital	Not reported	1. Dyspepsia 2. Dyspepsia with anorexia, weight loss or anaemia (any alarm) 3. Dysphagia 4. Reflux 5. Recurrent dyspepsia 6. Any alarm	Total cohort, *n* = 1000 Single symptom, *n* = 471 Multiple symptoms, Alarm symptoms 15%	Gastric cancers, *n* = 8 Oesophageal cancers, *n* = 9 Prevalence, *n* = 529 1.70% (95% CI = 0.99 to 2.71)	GP used standard tick-box form listing commonly accepted indications for referral from BSG guidance	Endoscopy and histology
Collins & Altman[10]	UK	Retrospective cohort, 2000–2008 (90 months)	Primary care validation study of QResearch data using THIN database. Exclusions: history of gastrooesophageal cancer, registration <12 months with practice, invalid dates, aged <30years or ≥85years	Range 30–84	Alarm symptoms 1. Dysphagia 2. Haematemesis 3. Appetite loss 4. Weight loss 5. Abdominal pain 6. Anaemia	Validation set *n* = 2 140 194 Cases, *n* = 1256 Controls, *n* = 2 138 938 Alarm symptoms 100%	Gastric and oesophageal cancers, *n* = 1256 Prevalence 0.08% (95% CI =0.08 to 0.09)	THIN database	Read Clinical Classification (version 2)
Hansen *et al*[21]	Denmark	Prospective cohort, 1991–1992 (13 months)	66 GPs in a Danish city referred all patients with dyspepsia, of any severity to open-access endoscopy. Exclusions: upper GI bleeding jaundice, abdominal surgery, previous upper GI surgery	47 (SD 17) 62% >40	1. Dyspepsia 2. Reflux-like 3. Ulcer-like 4. Dysmotility-like	*n* = 612 Alarm symptoms: unknown	Upper GI cancers, *n* = 3 Unclassified, *n* = 1 Prevalence 0.65% (95% CI= 0.18 to 1.67)	Structured interview by endoscopist	Endoscopy and histology when indicated
Hippisley-Cox & Coupland[11]	UK	Retrospective, cohort 2000–2010 (129 months)	Primary care population of all practices in England and Wales, recorded in QResearch database. Exclusions: history of gastro-oesophageal cancer, registration <12 months with a practice, invalid dates, aged <30years or ≥85years	50 (SD 15) Range 30–84	Alarm symptoms 1. Dysphagia 2. Haematemesis 3. Appetite loss 4. Weight loss 5. Abdominal pain 6. Anaemia	Validation set *n* = 963 040 Alarm symptoms 100%	Gastric and oesophageal cancers, *n* = 986 Prevalence 0.14% (95% CI = 0.13 to 0.15)	QResearch database. Incident diagnosis of gastric or oesophageal cancer >2 years after study entry, recorded in GP record or linked ONS record	ICD-9 or 10 recording of disease classification
Johannessen *et al*[12]	Norway	Prospective cohort, 1985–1987 (18 months)	Mainly GP referrals to open-access endoscopy at a regional hospital. Exclusions: jaundice, upper GI haemorrhage, acute abdominal pain, previous gastric surgery or endoscopy	50 (SD 15) 67% >40	1. Abdominal pain 2. Nausea 3. Reflux 4. Appetite loss 5. Weight loss 6. Retrosternal pain 7. Epigastric pain	*n* = 930 Alarm symptoms: not calculable, >1 symptom/patient	Gastric cancers, *n* = 9 Prevalence 0.97% (95% CI = 0.44 to 1.83)	Self-administered questionnaire of 112 items including demographic, medical history and present symptoms	Endoscopy and histology if suspicion of malignancy

... continued

Appendix 2 continued. Study characteristics

Kapoor *et al*[19]	UK	Prospective consecutive cohort, 2000–2002 (20 months)	GP referrals of patients at high risk with pre-determined alarm features to rapid access endoscopy according to NHS 2-week rule criteria	Mean 59, range 17–96 63% >55	1. Dysphagia 2. Weight loss 3. Anaemia 4. Others — data not available	Evaluation cohort *n* = 1852 Alarm symptoms: not calculable, >1 symptom/ patient	Gastric cancers, *n* = 25 Oesophageal cancers, *n* = 45 Prevalence 3.78% (95% CI = 2.96 to 4.75)	Standardised referral proforma completed by GPs noting the presence/absence of each designated alarm feature	Gastroscopy and histology
Meineche-Schmidt & Jørgensen[13]	Denmark	Prospective cohort, 1991–1993 (36 months)	General practice referrals of patients with dyspepsia from 63 centres in Denmark	Range 18–≥65 74% >38 50% >51	1. Dysphagia 2. Weight loss 3. Anaemia 4. Melaena 5. Dyspepsia	Uncomplicated and complicated cohorts *n* = 1491 Alarm symptoms 41%	Gastric and oesophageal cancers, *n* = 8 Prevalence 0.54% (95% CI = 0.23 to 1.05)	Diagnostic chart based on structured interview by GPs; included 18 dyspepsia symptoms and six alarm symptoms. Follow-up by postal questionnaire to GPs	Endoscopy, radiograph, ultrasound
Melleney and Willoughby[25]	UK	Prospective audit, 1999–2000 (6 months)	'One-stop' unrestricted dyspepsia clinic for GP referrals at single hospital. Proton pump inhibitors and H_2-receptor agonists were stopped ≥2 weeks before clinic appointment	Median 59 Range 15–84	1. Any alarm	*n* = 100 (84 analysed) Alarm symptoms 42%	Upper GI cancers, *n* = 6 Prevalence 7.14% (95% CI = 2.68 to 14.91)	Special referral form designed in consultation with local GP practices	Endoscopy, blood tests and abdominal ultrasound if needed. Histology if endoscopy uncertain
Numans *et al*[14]	Netherlands	Prospective, consecutive cohort, 1986–1988 (25 months)	GP referrals of patients with dyspepsia for first-time gastroscopy at nine hospitals in one city	Not reported	1. Dysphagia 2. Weight loss 3. Anaemia 4. Melaena 5. Reflux 6. Retrosternal pain 7. Epigastric pain 8. Haematemesis 9. Vomiting 10. Bloating 11. Dyspepsia	Study population *n* = 861 Alarm symptoms: not calculable, >1 symptom/patient	Gastric and oesophageal cancers, *n* = 21 Prevalence 2.44% (95% CI = 1.52 to 3.70)	GPs referred patients on basis of disease history and symptoms for endoscopy. Gastroscopy views were reported uniformly	Gastroscopy and histology if suspicion of malignancy
Salo *et al*[15]	Finland	Consecutive cohort, 1998–2000 (24 months maximum)	Primary care referrals to open-access endoscopy in one city	Range 11–93 52% >55	1. Dysphagia 2. Weight loss 3. Anaemia/ GI bleeding 4. Vomiting 5. Bloating 6. Reflux 7. Diarrhoea 8. Dyspepsia 9. Any alarm	*n* = 10 061 Alarm symptoms 13%	Gastric cancers, *n* = 52 Oesophageal cancers, *n* = 15 Duodenal cancers, *n* = 1 Prevalence 0.68% (95% CI = 0.53 to 0.86)	Experienced physicians who performed endoscopies interviewed patients. Alarm symptoms considered most. significant when present. gastrointestinal complaints also reported	Endoscopy, Finnish registry, histology

... continued

Appendix 2 continued. Study characteristics

Stapley *et al*[16]	UK	Retrospective matched case–control, 2000–2009 (120 months)	GPRD contains copies of anonymised medical records of participating UK general practices. Exclusions: metastatic, cancers controls who had ever had gastro-oesophageal cancer	Range 40–≥85	1. Dysphagia 2. Weight loss 3. Low haemoglobin 4. Nausea or vomiting 5. Abdominal pain 6. Chest pain 7. Epigastric pain 8. Reflux 9. Constipation 10. Dyspepsia 11. Any alarm	*n* = 40 348 Cases, *n* = 7471 Controls, *n* = 32 877	Gastric cancers, *n* = 28 Oesophageal cancers, *n* = 18 Prevalence not available	GPRD database searched using codes for 18 oesophageal and 28 gastric cancers. Five controls matched on year of birth, sex, and practice; also identified using computer-generated random sequence	GPRD coding for gastro-oesophageal cancers
Thomson *et al*[20]	Canada	Prospective cohort, 1999–2001 (16 months) One of the CADET series of studies	49 family physician practices across Canada linked to gastroenterology unit referred patients with uninvestigated dyspepsia. Exclusions: patients with heartburn or acid regurgitation as sole symptom, recent *Helicobacter pylori* eradication, previous endoscopy or radiology	Mean 46, range 18–84 64% of endoscopy patients <50	1. Dyspepsia 2. Reflux-like 3. Ulcer-like 4. Dysmotility-like 5. Dysphagia 6. Weight loss 7. Anaemia 8. Any alarm	*n* = 1040 Alarm symptoms 3%	Oesophageal cancers, *n* = 1 One patient with dyspepsia had a gastric MALToma, this was not a target condition for the review. Prevalence 0.10% (95% CI = 0.02 to 0.54)	Patients completed 14-item symptom checklist ranking the three most bothersome symptoms	Endoscopy (urea breath test if refuse) and histology
van Kerkhoven *et al*[23]	Netherlands	Prospective, consecutive cohort, 2002–2004 (36 months)	GP referrals for open-access upper GI endoscopy at a single general hospital. Exclusions: age <18 years, failed/previous endoscopy	Mean 54 (SD 15)	1. Dyspepsia-like 2. Reflux-like 3. Failure of empirical treatment 4. Any alarm	*n* = 1298 Alarm symptoms: not calculable, >1 symptom/ patient	Gastric and oesophageal cancers, *n* = 23 Prevalence 1.77% (95% CI = 1.13 to 2.65)	GPs completed referral indications on standardised form. Endoscopic findings recorded in database	Endoscopy
Voutilainen *et al*[24]	Finland	Consecutive cohort, 1996 (12 months)	GP referrals of patients with dyspepsia for upper GI endoscopy at two hospitals and eight healthcare centres. Exclusions: previous *Helicobacter pylori* eradication or gastrooesophageal surgery	Mean 58 (IQR 25)	1. Dyspepsia 2. Reflux 3. Failure of empirical treatment 4. Any alarm	*n* = 3378 Alarm symptoms 33%	Gastric cancers, *n* = 17 on symptoms, 0.50% Prevalence (95% CI = 0.29 to 0.80)	GPs completed structured questionnaire duration, and medication. Endoscopic data recorded on pre-structured questionnaire	Endoscopy, biopsy and histology. Cancer registries

BSG = British Society of Gastroenterology. CADET = Canadian Adult Dyspepsia Empiric Treatment. GI = gastrointestinal. GPRD = General Practice Research Database. ICD = International Classification of Diseases. IQR – interquartile range. ONS = Office of National Statistics. SD = standard deviation. THIN = The Health Improvement Network.

Appendix 3. QUADAS item scoring of individual studies.

Appendix 4. Ratio of DOR of low-scoring QUADAS items

QUADAS item	Studies meeting the criterion, *n*	Ratio DOR (95% CI)	*P*-value	Heterogeneity, T^2
Representative sample	8	0.40 (0.05 to 3.26)	0.36	2.76
Acceptable delay	5	0.73 (0.08 to 6.96)	0.76	2.67
Blinding of index test	6	0.58 (0.081 to 4.08)	0.55	2.38

DOR = diagnostic odds ratio. QUADAS = Quality Assessment of Diagnostic Accuracy Studies