

A population-based, retrospective, cohort study of esophageal cancer missed at endoscopy

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Background and study aims: Several studies have suggested that a significant minority of esophageal cancers are missed at endoscopy. The aim of this study was to estimate the proportion of esophageal cancers missed at endoscopy on a national level, and to investigate the relationship between miss rates and patient and tumor characteristics.

Patients and methods: This retrospective, population-based, cohort study identified patients diagnosed with esophageal cancer between April 2011 and March 2012 in England, using two linked databases (National Oesophago-Gastric Cancer Audit and Hospital Episode Statistics). The main outcome was the rate of previous endoscopy within 3–36 months of cancer diagnosis. This was calculated for the overall cohort and by patient characteristics, including tumor site and disease stage.

Results: A total of 6943 new cases of esophageal cancer were identified, of which 7.8% (95% confi-

dence interval 7.1–8.4) had undergone endoscopy in the 3–36 months preceding diagnosis. Of patients with stage 0/1 cancers, 34.0% had undergone endoscopy in the 3–36 months before diagnosis compared with 10.0% of stage 2 cancers and 4.5% of stage 3/4 cancers. Of patients with stage 0/1 cancers, 22.1% were diagnosed after ≥3 endoscopies in the previous 3 years. Patients diagnosed with an upper esophageal lesion were more likely to have had an endoscopy in the previous 3–12 months ($P=0.040$). The most common diagnosis at previous endoscopy was an esophageal ulcer (48.2% of investigations).

Conclusion: Esophageal cancer may be missed at endoscopy in up to 7.8% of patients who are subsequently diagnosed with cancer. Endoscopists should make a detailed examination of the whole esophageal mucosa to avoid missing subtle early cancers and lesions in the proximal esophagus. Patients with an esophageal cancer may be misdiagnosed as having a benign esophageal ulcer.

Introduction

In the United Kingdom (UK), the incidence of esophageal cancer has risen from 8.8 per 100 000 in 1975–1977 to 14.5 per 100 000 in 2006–2008 [1] and, in recent years, approximately 8500 cases are diagnosed annually. The prognosis for esophageal cancer is poor. Approximately 30–40% of patients are considered suitable for curative treatment [2], and only 1 in 7 patients survive for more than 5 years [1]. As survival is closely linked to stage at the time of diagnosis, the UK Department of Health has adopted various initiatives to improve the process of diagnosis, with the specific aim of promoting early diagnosis [3]. Endoscopy with biopsy is regarded as the investigation of choice for diagnosis of upper gastrointestinal cancer [4,5]. Many clinicians consider that once a patient has had a normal endoscopy, esophageal cancer has been excluded; however,

several studies have suggested a significant minority of cancers are missed at endoscopy [6–12]. These studies have investigated the proportion of patients diagnosed with upper gastrointestinal cancers who underwent an endoscopic examination within the previous 2–3 years, which did not find evidence of malignancy. For example, US investigators found that 10/110 patients (9.1%) with esophageal cancer had undergone an endoscopy within the 2 years preceding their diagnosis [7].

To date, studies investigating endoscopy miss rates for esophageal cancer have been limited by their small size, which has prevented them from investigating the indications for previous endoscopy. In particular, these studies provided little information on stage at diagnosis, and this makes it difficult to be certain that malignant lesions were missed at previous endoscopy. Previous endoscopy for some patients may be part of a

planned surveillance program, allowing the early detection of cancer, and therefore represents good practice rather than being evidence of a missed lesion. Consequently, making an inference about the rate of missed diagnosis on the basis of all previous endoscopies could overestimate the true value. But, if early esophageal cancers have a long natural history [13,14], then any cancers detected within 3 years of endoscopy were potentially missed (as previous studies have suggested).

The aim of this study was to estimate the proportion of patients diagnosed with esophageal cancer in England who had undergone a previous endoscopy within the previous 3 years, and to examine whether specific patient factors were associated with higher rates of past endoscopy. In addition, the clinical findings at endoscopy prior to the cancer diagnosis were investigated. Finally, the study assessed whether there was a relationship between previous endoscopy, planned treatment intent, and 1-year survival. The study used linked data from two national databases.

Methods



Data sources

This retrospective, population-based, cohort study was based on a linked dataset that combined data from two sources: the second National Oesophago-Gastric Cancer Audit (NOGCA) and the Hospital Episode Statistics (HES) database. The NOGCA covers adult patients (≥ 18 years) diagnosed with invasive epithelial cancer of the esophagus or stomach in England and Wales, and uses a prospectively collected national clinical dataset. Data are submitted by hospital staff, and NOGCA achieved 83% case ascertainment for English patients diagnosed between April 2011 and March 2012, the period covered by this study [15]. The HES [16] is a national administrative health database, which stores information on all day cases and admissions to English National Health Service hospitals. Each record describes the period during which a patient is under the care of a hospital consultant (an episode), and includes administrative data (e.g. dates of admission and discharge), a primary diagnosis, up to 19 secondary diagnoses (coded using the International Classification of Diseases, 10th edition [ICD-10] system [17]), and up to 24 procedures (coded using the classification of surgical operations from the UK Office of Population Censuses and Surveys system version 4 [OPCS-4] [18]). It is possible for more than one episode to occur during an admission. The extract of HES data used in the study covered admissions between January 2008 and March 2012.

Records of esophageal cancer patients from the NOGCA dataset were linked to their HES records using their NHS number (a unique identifier for each UK resident). This resulted in 93% of patients in the NOGCA dataset being linked to the HES records.

Study population

The initial cohort for the study was patients diagnosed with cancer of the esophagus or gastroesophageal junction (GEJ) between 1 April 2011 and 31 March 2012, whose NOGCA record had been linked to HES. The consistency of key information was assessed in the two data sources in two steps. First, all HES records in which a patient had a diagnosis of esophageal or GEJ cancer was identified by searching for ICD-10 codes C15 (malignant neoplasm of the esophagus), C160 (malignant neoplasm of stomach cardia including GEJ), and D001 (carcinoma in situ of the esophagus) [18]. HES records dating back to 1 January 2008 were reviewed.

In the second step, the first date on which a diagnosis of esophageal or GEJ cancer was recorded in HES (as HES does not include a date of diagnosis of cancer) was identified and compared with the date of diagnosis in the NOGCA dataset. Patients were excluded from the analysis if they did not have a diagnosis of esophageal or GEJ cancer recorded in HES, or if their date of cancer diagnosis in the audit was more than 1 month after a diagnosis of esophageal or GEJ cancer was first identified in HES. This was to ensure the accuracy of the date of diagnosis because this was used as a reference date to work out timings of previous endoscopies.

Data collection

The NOGCA dataset provided information on patient demographics and disease, including age at diagnosis, sex, tumor site, stage at diagnosis, delay between referral and diagnosis, and history of Barrett's esophagus. It also provided information about the date of diagnosis, and the route to diagnosis (see the NOGCA data manual for definitions [19]). Stage of cancer was defined using the Union for International Cancer Control (UICC) TNM 6 Classification [20]. Route to diagnosis differentiated between three referral pathways to the specialist cancer team: referral from a general practitioner (GP; nonemergency to outpatient clinics), referral after an emergency admission (via Accident and Emergency, Medical Admissions Unit, etc.), and "other hospital referral" (patients referred by a hospital consultant from a non-emergency setting). GP referrals were further divided into urgent referrals for suspected cancer and routine referrals.

A diagnostic endoscopy examination (esophagogastroduodenoscopy [EGD]) was identified from HES by searching for OPCS codes G16 (diagnostic fiberoptic examination of the esophagus) and G45 (diagnostic fiberoptic examination of the upper gastrointestinal tract) [18]. The ICD-10 codes relating to these episodes were then analyzed for the following common endoscopic findings: esophagitis (K20), gastroesophageal reflux disease (K21), esophageal ulcer (K221), esophageal obstruction (K222), gastrointestinal bleed (K226, K228, K920, K921, K922), alarm symptoms associated with upper gastrointestinal cancer (D500, D508, D509, D649, R11, R13, R190, R630, R634), and other upper gastrointestinal symptoms (K30, R07, R10, R12) (see [Appendix e1](#), available online, for further details).

The principal outcome measures used to describe patterns of past endoscopy were: 1) patients who had undergone endoscopy within 3–12 months of cancer diagnosis, and 2) patients who had undergone endoscopy within 1 and 3 years before diagnosis but not in the year preceding diagnosis. Endoscopies occurring within 3 months of diagnosis were excluded because these procedures could have formed part of the diagnostic work-up. This reduced the risk of including planned repeat endoscopies, for example, as follow-up for an esophageal ulcer or to obtain repeat histology due to a potentially concerning finding. Endoscopies performed more than 3 years before the diagnosis of cancer were ignored due to the unclear natural history of the disease.

Data analysis

The proportion of patients who had an endoscopy within 3–12 months of diagnosis, or within 1–3 years, was calculated from the complete cohort. To assess whether rates of past endoscopy were associated with patient characteristics, the cohort was then stratified by various patient characteristics including age at diagnosis, sex, site and type of cancer, history of Barrett's esophagus, stage at diagnosis, and route to diagnosis. The chi-squared test was used to compare differences across patient groups, and

P values of <0.05 were considered to be statistically significant. The total number of diagnostic endoscopies performed in the 3 years prior to diagnosis was also determined, as well as the frequency with which particular conditions were reported at previous endoscopies.

Finally, the relationship between a previous endoscopy and the proportion of patients having a curative treatment plan and 1-year survival was examined using multiple logistic regression models. The relative risk of having planned curative treatment and 1-year survival were estimated respectively for patients undergoing endoscopy within 3–12 months and 1–3 years and were compared with patients having no previous endoscopy. This was adjusted for TNM stage at diagnosis, age, sex, type of cancer, tumor site, and performance status. For variables with missing data, missing values were imputed using multiple imputation by chained equations [21]. The imputation model included age at diagnosis, sex, type of cancer, tumor site, performance status, and referral source. Ten imputation datasets were created. All statistical calculations were performed in STATA 11.2 (Statacorp, College Station, Texas, USA).

Results

The initial cohort of linked HES–NOGCA data contained 7497 patients diagnosed with esophageal or GEJ cancer between 1 April 2011 and 31 March 2012. Among these, 331 patients (4.4%) did not have a diagnosis of esophageal or GEJ cancer coded for in HES; these patients frequently had an ICD-10 code for gastric cancer recorded instead. A further 223 patients (3.0%) had a date of diagnosis recorded in the audit data that was more than 1 month after the date when cancer was first recorded in HES. These records were also excluded, leaving 6943 patients for analysis, 92.6% of the initial cohort (● Fig. 1).

The characteristics of the entire cohort are summarized in ● Table 1. The mean ($\pm$ SD) age of these patients at diagnosis was 70.6 ± 11.5 years, and 7 out of 10 patients were men. Three-quarters of the cancers (74.6%) were located in the lower esophagus or GEJ. Most cases of esophageal or GEJ cancer were diagnosed after referral from a GP, and 75.9% of these referrals were urgent for suspected cancer. A further 10.4% of cases were diagnosed after an emergency admission, and 17.2% followed referral from another hospital consultant. At diagnosis, 2.9% of the cohort were coded as having Barrett's esophagus. Among patients with known TNM stage at diagnosis, 72.2% had stage 3 or 4 cancers, whereas only 4.7% were diagnosed with stage 0 (carcinoma in situ) or stage 1 cancer.

Previous endoscopic examinations

Among the 6943 patients considered for analysis, 537 (7.8%; 95% confidence interval [CI] 7.1–8.4) had undergone at least one endoscopy in the 3 years before their cancer was diagnosed. Of these, 214 (3.1%; 95%CI 2.7–3.5) underwent endoscopy between 3 and 12 months prior to diagnosis, and a further 323 (4.7%; 95% CI 4.2–5.2) had an endoscopy between 1 and 3 years before diagnosis.

The rates of previous endoscopy were not associated with patient sex, different age groups, or cancer histology (● Table 1). However, the rate was significantly associated with overall pretreatment stage ($P<0.001$). Among patients in the cohort with TNM cancer stage 0 or 1 at diagnosis, 15.9% had undergone an EGD within 3–12 months and a further 18.1% had undergone EGD in

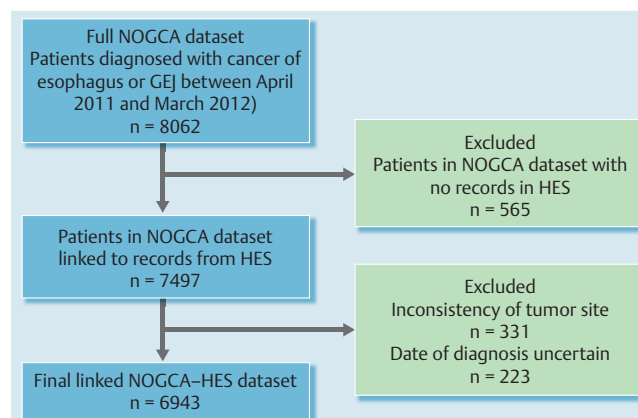


Fig. 1 Flow diagram describing the inclusion of patients from the National O-G Cancer Audit (NOGCA) dataset after linkage with data from Hospital Episode Statistics (HES) dataset. GEJ, gastroesophageal junction.

the 1–3 years preceding diagnosis. In contrast, EGD occurred in 4.0% and 6.1%, respectively, for patients with stage 2 cancers, and 1.5% and 3.0%, respectively, for those with stage 3 or 4 cancers. This pattern was determined predominantly by the size of the tumor (T stage). The proportion of patients who had undergone previous endoscopy was also associated with the site of tumor ($P<0.001$): 5.4% of patients diagnosed with upper esophageal cancers had undergone endoscopy within 3–12 months compared with 3.0% of patients with lower esophageal and GEJ cancers ($P=0.040$).

A previous endoscopy was also more common among patients with a history of Barrett's esophagus than among those without the disease ($P<0.001$). Where stage at diagnosis was known for these patients, 72.7% patients diagnosed within a year of a past endoscopy had stage 0/1 disease at diagnosis. Patients diagnosed within 1–3 years of endoscopy also tended to have early-stage cancer, with 33.3% diagnosed having stage 0/1 disease.

The rate of previous endoscopy was approximately twice as high among patients referred by another hospital consultant compared with those referred by a GP for both outcome measures. Stage at diagnosis varied significantly between the different routes to diagnosis for patients who underwent endoscopy in the previous 1–3 years ($P<0.001$): 34.7% of cases referred by another consultant were stage 0/1 at diagnosis, compared with 12.2% referred by GPs, and none referred as a result of an emergency admission. This pattern would be consistent with a proportion of referrals from other consultants coming from surveillance endoscopies. Among patients diagnosed after referral by a GP, those who underwent previous endoscopy waited significantly longer between referral and diagnosis than those without previous endoscopy, irrespective of the urgency of referral. For instance, 25.0% of urgent GP referrals for patients who had undergone an endoscopy in the preceding year waited more than 12 weeks from referral to diagnosis, whereas only 0.4% of those with no previous endoscopy waited this long ($P<0.001$).

Association between previous endoscopy, treatment intent, and 1-year survival

The variation in the rates of previous endoscopy across the specific patient characteristics resulted in distinct differences between the groups of patients with and without previous endoscopy (● Table 1). The prevalence of Barrett's esophagus was greater, and a larger number of patients were diagnosed after re-

Table 1 Characteristics of patients in the study cohort, and the proportion of patients who had undergone a previous endoscopy in the 3 years prior to diagnosis of esophageal cancer.

	Entire Cohort	Patients with no previous endoscopy	Patients endoscoped within 3–12 months of diagnosis		Patients endoscoped within 1–3 years of diagnosis	
			n (%)	Overall P value	n (%)	Overall P value
Patients, n	6943	6406	214 (3.1)		323 (4.7)	
Age group, years, n (%)						
<55	623 (9.0)	574 (9.0)	16 (2.6)	0.791	33 (5.3)	0.598
55–64	1457 (21.0)	1347 (21.0)	43 (3.0)		67 (4.6)	
65–74	2110 (30.4)	1936 (30.2)	73 (3.5)		101 (4.8)	
75–84	1971 (28.4)	1820 (28.4)	57 (2.9)		94 (4.8)	
≥85	782 (11.3)	729 (11.4)	25 (3.2)		28 (3.6)	
Sex, n (%)						
Male	4915 (70.8)	4538 (70.8)	149 (3.0)	0.671	228 (4.6)	0.935
Female	2028 (29.2)	1868 (29.2)	65 (3.2)		95 (4.7)	
Type of cancer, n (%)						
Adenocarcinoma	4827 (69.5)	4458 (69.6)	152 (3.2)	0.814	217 (4.5)	0.514
Squamous cell	1651 (23.8)	1524 (23.8)	47 (2.9)		80 (4.9)	
Other	465 (6.7)	424 (6.6)	15 (3.2)		26 (5.6)	
Site of cancer, n (%)						
Upper esophagus	351 (5.1)	315 (4.9)	19 (5.4)	0.040	17 (4.8)	0.099
Mid-esophagus	1411 (20.3)	1303 (20.3)	37 (2.6)		71 (5.0)	
Lower esophagus	2891 (41.6)	2648 (41.3)	94 (3.3)		149 (5.2)	
GEJ	2290 (33.0)	2140 (33.4)	64 (2.8)		86 (3.8)	
History of Barrett's esophagus, n (%)						
No	6742 (97.1)	6262 (97.8)	199 (3.0)	<0.001	281 (4.2)	<0.001
Yes	201 (2.9)	144 (2.3)	15 (7.5)		42 (20.9)	
T stage at diagnosis, n (%)						
0/1	302 (5.9)	203 (4.3)	47 (15.6)		52 (17.2)	
2	848 (16.6)	753 (16.0)	36 (4.3)	<0.001	59 (7.0)	<0.001
3	3268 (63.9)	3106 (65.9)	57 (1.7)		105 (3.2)	
4	694 (13.6)	654 (13.9)	16 (2.3)		24 (3.5)	
Missing values	1831	1690	58 (3.2)		83 (4.5)	
TNM stage at diagnosis, n (%)						
Stage 0/1	227 (4.7)	150 (3.4)	36 (15.9)		41 (18.1)	
Stage 2	1106 (23.1)	995 (22.4)	44 (4.0)	<0.001	67 (6.1)	<0.001
Stage 3	1600 (33.4)	1524 (34.3)	26 (1.6)		50 (3.1)	
Stage 4	1854 (38.7)	1775 (39.9)	26 (1.4)		53 (2.9)	
Missing values	2156	1962	82 (3.8)		112 (5.2)	
Route to diagnosis, n (%)						
GP routine	1085 (17.5)	978 (17.0)	43 (4.0)	<0.001	64 (5.9)	<0.001
GP urgent	3418 (55.0)	3307 (57.4)	32 (0.9)		79 (2.3)	
Emergency admission	645 (10.4)	594 (10.3)	22 (3.4)		29 (4.5)	
Other hospital referral	1069 (17.2)	886 (15.4)	80 (7.5)		103 (9.6)	
Missing values	726	641	37 (5.1)		48 (6.6)	

GEJ, gastroesophageal junction; GP, general practitioner.

ferral from a hospital consultant in both groups of previous endoscopy. In addition, patients who had a previous endoscopy had, on average, less-advanced tumors, and this meant these groups both had higher unadjusted rates of planned curative treatment (● **Table 2**). However, after adjusting for patient age at diagnosis, sex, cancer stage, type of cancer, tumor site, and performance status, there was no statistical evidence that treatment intent was associated with these groups. Similarly, the higher unadjusted 1-year survival rates among patients with a previous endoscopy were reduced after adjusting for confounding patient characteristics, and there was only a weak association between the groups of previous endoscopy and the adjusted 1-year survival rates (● **Table 2**).

Findings reported at previous endoscopy

● **Table 3** shows the frequency with which specific diagnostic codes were recorded in the HES for findings from the previous endoscopies. The most common condition reported at previous endoscopy was an esophageal ulcer (48.2%). Among the 537 patients who had undergone an endoscopy in the 3 years preceding diagnosis, 386 (71.9%) had only undergone one EGD in that period. The proportion of patients with a single previous EGD was lower among patients in whom this occurred 3–12 months before diagnosis (58.4%) compared with those in whom it had occurred 1–3 years before (80.8%). Among patients who had undergone an endoscopy 3–12 months before diagnosis, 32 (15.0%) had had three or more endoscopies in the previous 3 years. TNM Stage at diagnosis was significantly associated with the number of previous endoscopies patients had undergone in

Table 2 Relationship between endoscopic examination, treatment plan, and 1-year survival among patients diagnosed with esophagogastric cancer in English National Health Service trusts.

Patient group	Total patients, n	Patients with outcome, n (%)	Unadjusted OR [95%CI]	Adjusted OR ¹ [95%CI]
Patients with curative treatment intent	5939 ²	2200 (37.0)		
Patients without previous endoscopy	5493	1973 (35.9)	1	1
Patients endoscoped within 3–12 months of diagnosis	174	98 (56.3)	2.30 [1.68–3.14]	1.08 [0.66–1.75]
Patients endoscoped within 1–3 years of diagnosis	272	129 (47.4)	1.61 [1.24–2.08]	1.02 [0.68–1.54]
Patients who survived 1 year	6943	3246 (46.8)		
Patients without previous endoscopy	6406	2936 (45.8)	1	1
Patients endoscoped within 3–12 months of diagnosis	214	136 (63.6)	2.06 [1.56–2.72]	1.42 [1.02–1.99]
Patients endoscoped within 1–3 years of diagnosis	323	174 (53.9)	1.38 [1.10–1.72]	1.03 [0.80–1.33]

OR, odds ratio; CI, confidence interval.

¹ ORs adjusted for the effect of overall pre-treatment TNM stage, age, sex, type of cancer, site of cancer and performance status. Due to the high proportion of missing values on pre-treatment TNM stage a multiple imputation model was used for the adjusted analysis (with n = 10 number of imputations). The imputation model used all variables presented in Table 1.² Information on the outcome “treatment plan” was missing for 1004 patients (14.5%).

Diagnostic group	Patients endoscoped within 3–12 months of diagnosis (n = 214), n (%)	Patients endoscoped within 1–3 years of diagnosis (n = 323), n (%)
Esophageal ulcer	109 (50.9)	150 (46.4)
Alarm symptoms	39 (18.2)	81 (25.1)
Esophagitis	24 (11.2)	33 (10.2)
Gastrointestinal bleed	24 (11.2)	30 (9.3)
Esophageal obstruction	16 (7.5)	6 (1.9)
Other gastrointestinal symptoms	18 (8.4)	28 (8.7)

Table 3 Common gastrointestinal diagnoses recorded as the primary diagnosis at endoscopy examinations that occurred prior to the cancer diagnosis.

Total number of endoscopies in 3–36 months before diagnosis	TNM stage at diagnosis			
	0/1 (n = 77) n (%)	2 (n = 111) n (%)	3 (n = 76) n (%)	4 (n = 79) n (%)
1	39 (50.6)	85 (76.6)	58 (76.3)	64 (81.0)
2	21 (27.3)	19 (17.1)	9 (11.8)	11 (13.9)
3	6 (7.8)	3 (2.7)	6 (7.9)	3 (3.8)
4 or more	11 (14.3)	4 (3.6)	3 (3.9)	1 (1.3)

Table 4 Number of endoscopies performed prior to diagnosis, stratified by pretreatment stage at diagnosis.

the 3 years prior to diagnosis ($P=0.014$) (► **Table 4**): 81.0% of patients with stage 4 cancers had only had one endoscopy in the preceding 3 years compared with 50.6% of those with stage 0/1 cancers, and 22.1% of stage 0/1 cancers were diagnosed after 3 or more endoscopies in the previous 3 years.

Discussion

In this population-based study, 3.1% (95%CI 2.7–3.5) of patients diagnosed with esophageal cancer had undergone endoscopy between 3 and 12 months prior to diagnosis, and a further 4.7% (95%CI 4.2–5.2) of patients had undergone endoscopy between 1 and 3 years before diagnosis. This gives an overall estimated rate of missed diagnosis of 7.8% (95%CI 7.1–8.4) among patients with esophageal cancer. This figure is toward the lower range of estimates from previous studies, which have reported rates of 5.0%–14.3% [6–9], and is also more precise due to the population-based data in the current study. In addition, an association was found between patients having a previous endoscopy and stage at diagnosis, with endoscopy occurring more often in patients with stage 0/1 disease. Patients with upper-third esophageal cancers were also more likely to have previously undergone an endoscopy compared with patients with lower-third or GEJ lesions.

These results suggest that either some esophageal cancers are being missed at endoscopy or that the natural history of a significant number of cancers is sufficiently rapid that it may progress from an early endoscopically invisible lesion to an advanced cancer within a relatively short time. If the latter scenario is considered, an alternative interpretation would be that only stage 2–4 cancers diagnosed within 3–36 months of endoscopy are potentially missed. This would correspond to a more conservative estimated miss rate of 5.6% (with 2.0% missed within 3–12 months of endoscopy). However, the overall figure may be more accurate. Although studies on the natural history of untreated early esophageal cancer are few, two previous small cohort studies suggest that some patients with early cancer survive more than 5 years [13, 14], and there is increasing evidence of slow progression of endoscopically visible dysplasia in patients with Barrett's esophagus [22].

A limitation of this study was the inability to identify patients undergoing regular surveillance, and this might be another reason to focus on patients with stage 2–4 cancers and the more conservative miss rate. Previous endoscopies were more common among patients with early cancers, and some of these patients may have been under regular surveillance. This is supported by the finding that Barrett's esophagus was more common among these patients, as was cancer diagnosis after referral from another hospital consultant. Unfortunately, there is currently no na-

tional registry for Barrett's esophagus, which would enable the identification of patients on surveillance in England.

Various reasons have been proposed for failure to diagnose a cancer at initial endoscopy [6–8]. These include failure of the endoscopist either to identify a potential lesion, or, where the lesion is seen, failing to recognize its significance and choosing not to biopsy it or taking an insufficient number of biopsies. The endoscopic appearances of early cancer may be very subtle, and minor mucosal changes in color or contour may be the only sign [23,24]. This makes such lesions difficult to detect, and reinforces the need for high-resolution white-light endoscopy. Enhanced imaging techniques, such as narrow-band imaging, may be considered as an alternative but currently their use in preference to conventional white-light endoscopy is not recommended in guidelines, even in high-risk populations.

The use of proton-pump inhibitors prior to endoscopy may also increase the chance of a lesion being missed [25], by promoting mucosal healing. Ideally, endoscopies should be done prior to the prescription of acid suppressive medication. Finally, it has been suggested that the mid- and upper esophagus may be less-well inspected, as the endoscope may be rapidly withdrawn during the final stages of the procedure, thereby reducing the chance of visualizing subtle lesions [7]. In line with smaller studies [6,7,9], in the current study a greater proportion of patients were observed with upper-third esophageal lesions having an endoscopy in the year before diagnosis than among patients with lower-third or GEJ lesions. This highlights the need for a careful inspection in this area.

Diagnostic information from the HES database was used to analyze endoscopic findings within 3 years of cancer diagnosis. Less than a quarter of the endoscopies were performed for alarm symptoms such as dysphagia. This is consistent with alarm symptoms typically being associated with advanced disease [26], and the lower rate of previous endoscopy among patients with T stage 3 and 4. The most common endoscopic finding was esophageal ulcer, which was diagnosed in half of these examinations. Furthermore, of the 259 patients with an esophageal ulcer in the 3 years before diagnosis, 20 (7.7%) had three or more endoscopies before the diagnosis of cancer. One interpretation of this is that endoscopists had a clinical suspicion of malignancy and that patients were placed under regular surveillance. If so, this suggests that the estimate of missed cancer diagnosis may be slightly overestimated. Alternatively, the initial biopsies may have been inadequate for a diagnosis of cancer to be made. Although malignant disease is not a common cause of esophageal ulceration [27], these findings highlight the need to review current practices for biopsy and follow-up of an esophageal ulcer. There are currently no national guidelines regarding the timing and requirement for further surveillance endoscopies once an esophageal ulcer has been diagnosed. Such guidelines exist for gastric ulcers [5], and the malignant potential of esophageal ulcers in Barrett's esophagus is well recognized [28].

The consequences of a missed diagnosis are difficult to evaluate. In examining the relationship between previous endoscopy and clinical outcome, no evidence was found that missed diagnoses at endoscopy changed the pattern of treatment or survival compared with patients with similar characteristics at the time of diagnosis. But, these findings need to be interpreted with caution, and do not imply that missed diagnoses have no adverse consequence. An evaluation of the effect of the delay requires information about the stage of the disease at the time of a previous endoscopy before diagnosis. This information was not available

for this study and is difficult to obtain. Future studies might be able to re-examine biopsies from previous endoscopies, but this would still give incomplete information. False-negative results due to errors from the pathological examination could be corrected but no additional data would be obtained from inadequate biopsies. An alternative approach would be to use data on the length of the delay in diagnosis with information about the doubling time of an esophageal tumor. This method has been used to model the consequences of missed diagnoses in breast cancer and cervical screening [29]. However, the lack of information on the speed of progression for esophageal cancer would make this approach highly speculative, and illustrates the need for further research on the natural history of this cancer.

Strengths and weaknesses of the study

This study uses a population-based cohort of patients with esophageal cancer, which was created by linking two national databases. This design has the advantage of creating a large cohort, enabling the calculation of precise estimates. Being population-based, the results are more representative than single-center studies. In addition, the study is unique in exploring patient and tumor characteristics, such as stage at diagnosis, and their relationship to the occurrence of previous endoscopy.

The NOGCA database captured 83% of patients diagnosed with esophagogastric cancer in England during the study period [15], and 93% of the audit patients were linked to their HES records. As HES is an administrative dataset, its data are prone to coding errors, although the quality of coding has improved over time [30]. To reduce the impact of data entry errors, patients with data that did not agree between the two sources were excluded. Any selection bias resulting from this seems to be small. The analyzed cohort and overall NOGCA cohort had similar patient demographics (e.g. the average ages were 70.6 and 71.2 years, respectively, and the proportions of male patients were 70.8% and 70.0%, respectively).

The study has some limitations that might bias the estimates. First, the medical records of patients who had undergone previous endoscopy could not be accessed. This prevented a detailed description of endoscopic findings to be made or the administration or timing of proton-pump inhibitor therapy to be considered. Previous endoscopies within 3 months of cancer diagnosis were excluded to reduce the risk of including patients who were being followed up after a concerning initial finding. It was also not possible to identify patients undergoing regular surveillance for Barrett's esophagus, which may have led to the overall miss rate being slightly overestimated.

Second, the outcome variable relied on the complete coding of endoscopies in HES. A small proportion of patients will have had their initial endoscopy done within the private healthcare system, or (if living close to the border) in Scotland or Wales, and these endoscopies are not recorded in HES. This could mean that the calculated rates of previous endoscopy are slightly underestimated.

Third, there may be residual confounding in the analysis of the association between previous endoscopy, treatment intent, and 1-year outcomes. However, the logistic regression models included important prognostic factors such as age, stage of disease, type and site of cancer, and performance status. The analysis used multiple imputation models for two variables with missing data, which relied on the assumption that the data were "missing at random." This assumption seems plausible given the range of variables in the imputation model.

Conclusion

The study suggests that up to 7.8% of patients diagnosed with esophageal cancer who had a previous endoscopy in the 3 years before diagnosis could have had their cancer missed. Among patients with stage 2–4 disease at diagnosis, the proportion was 5.6% of cases. The results suggest that there is the potential to improve endoscopy practice. In particular, health services should review their use of endoscopic imaging techniques and pay attention to the proximal esophagus on intubation and extubation. Furthermore, clinicians should consider the option of repeat endoscopy when symptoms are ongoing or when alarm symptoms develop. However, prospective studies are required to establish the benefit of repeat endoscopy for patients with esophageal ulcers.

Competing interests: None

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Appendix e1

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