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The variation in post-endoscopy upper gastrointestinal cancer rates among endoscopy providers in England and associated factors: a population-based study

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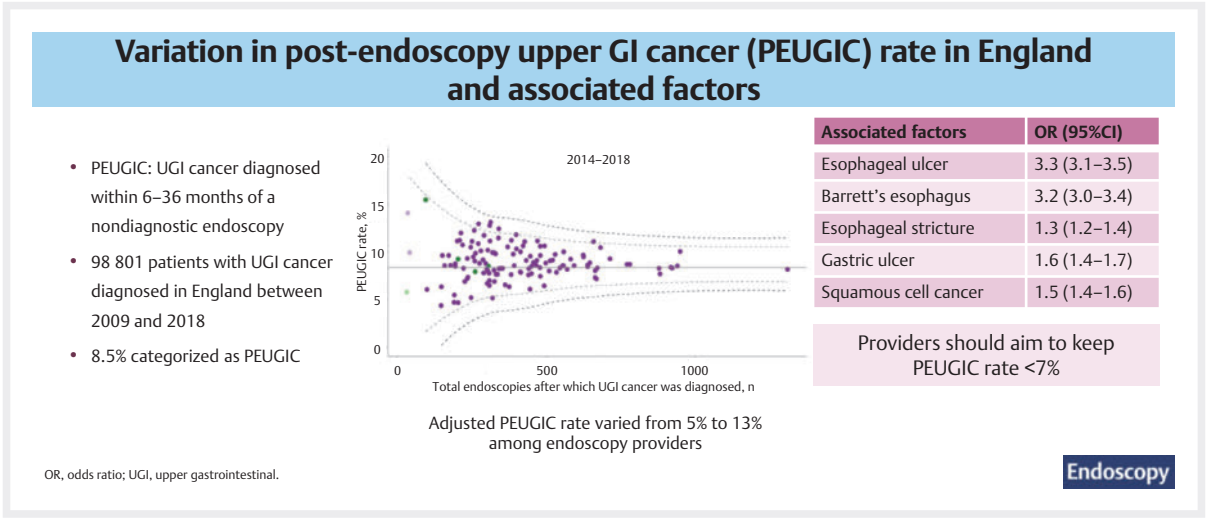
GRAPHICAL ABSTRACT



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ABSTRACT

Background Post-endoscopy upper gastrointestinal cancer (PEUGIC) is an important key performance indicator for endoscopy quality. We examined variation in PEUGIC rates among endoscopy providers in England and explored associated factors.

Methods The was a population-based, retrospective, case–control study, examining data from National Cancer Registration and Analysis Service and Hospital Episode Statistics databases for esophageal and gastric cancers diagnosed between 2009 and 2018 in England. PEUGIC were cancers diagnosed 6 to 36 months after an endoscopy that did not diagnose cancer. Associated factors were identified using multivariable logistic regression analyses.

Results The national PEUGIC rate was 8.5%, varying from 5% to 13% among endoscopy providers. Factors associated with PEUGIC included: female sex (odds ratio [OR] 1.29 [95%CI 1.23–1.36]); younger age (age >80 years, OR 0.52 [0.48–0.56], compared with ≤60 years); increasing comorbidity (Charlson score >4, OR 5.06 [4.45–5.76]); history of esophageal ulcer (OR 3.30 [3.11–3.50]), Barrett's esophagus (OR 3.21 [3.02–3.42]), esophageal stricture (OR 1.28 [1.20–1.37]), or gastric ulcer (OR 1.55 [1.44–1.66]); squamous cell carcinoma (OR 1.50 [1.39–1.61]); and UK national endoscopy accreditation status – providers requiring improvement (OR 1.10 [1.01–1.20]), providers never assessed (OR 1.24 [1.04–1.47]).

Conclusion PEUGIC rates varied threefold among endoscopy providers, suggesting unwarranted differences in endoscopy quality. PEUGIC was associated with endoscopy findings known to be associated with upper gastrointestinal cancer and a lack of national endoscopy provider accreditation. PEUGIC variations suggest an opportunity to raise performance standards to detect upper gastrointestinal cancers earlier and improve outcomes.

Introduction

In the UK, 16 800 people are diagnosed with upper gastrointestinal (UGI) cancer each year, including cancers in the esophagus and stomach [1, 2]. Unfortunately, the outlook for these cancers is often poor, with only 17% surviving esophageal and 21% surviving gastric cancer for 5 years [1, 2]. UGI cancer survival rates in the UK are worse than in other European countries [3], and delays in diagnosis are likely to contribute to these poor outcomes.

Endoscopy is the investigation of choice for diagnosing UGI cancer. However, studies have shown that 6%–11% of people with UGI cancer had a nondiagnostic endoscopy prior to their cancer diagnosis [4, 5, 6]. This is termed post-endoscopy upper gastrointestinal cancer (PEUGIC) and is recommended as a key performance indicator for endoscopy providers by the British Society of Gastroenterology and Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland [7]. Younger age, female sex, and increasing comorbidity have been reported to be associated with PEUGIC [6, 8, 9].

In the UK, around 1.2 million UGI endoscopies are performed each year [10]. Although efforts have been made to try to ensure high quality endoscopy in the National Health Service (NHS), for example through the voluntary provider accreditation scheme operated by the Joint Advisory Group on GI Endoscopy (JAG), there is a lack of direct evidence of the impact of such initiatives on clinical outcomes. Colorectal cancer (CRC) diagnosed 6 months to 3 years after a colonoscopy that did not diagnose a CRC is called post-colonoscopy colorectal cancer (PCCRC). A recent study showed up to fourfold variation in PCCRC rates among NHS providers, indicating unwarranted variation in the quality of colonoscopy among providers [11]. The variation in PEUGIC rates among providers has not been studied.

We aimed to examine the variation in PEUGIC rates within 3 years of endoscopy among endoscopy providers in England and to determine factors associated with PEUGIC.

Methods

Study design and data sources

This was a population-based, retrospective, case–control study. Study data were obtained from linked National Cancer Registration and Analysis Service (NCRAS) and Hospital Episode Statistics (HES) databases. NCRAS (hosted by NHS Digital) is responsible for registration of all patients diagnosed or treated in England with an invasive malignancy or specific premalignant conditions. The HES database gathers information on all NHS-funded elective and emergency care episodes in hospitals in England. Diagnostic data are coded using ICD-10 codes. Procedure data are coded using the Office of Population Censuses and Surveys Classification of Interventions and Procedures, 4th re-

vision (OPCS-4). Endoscopy data included procedures performed by NHS providers and by independent providers funded by the NHS.

JAG provided contemporaneous data on accreditation status of all endoscopy providers in England. JAG accreditation is a supportive process of service evaluation using a quality framework. Currently, over 400 endoscopy services in England participate in the JAG accreditation process [12].

The authors of a recently published national study on PCCRC variation in England were contacted to provide PCCRC rates for all endoscopy providers in England [11].

Study population

The study population included all adults diagnosed with a first esophageal (ICD 10 – C15) or gastric (ICD 10 – C16) cancer in England between January 2009 and December 2018 who had undergone an endoscopy within the 3 years prior to their cancer diagnosis. Patients were excluded if there was no record of an endoscopy within the 3 years prior to their cancer diagnosis. Small-bowel cancers including duodenal cancers were excluded as a standard endoscope may not be able to reach beyond the second part of the duodenum. Other exclusion criteria were previous esophageal or gastric cancers and cancers other than adenocarcinomas or squamous cell carcinomas. The cohort was split into two groups (2009–13 and 2014–18) based on year of cancer diagnosis.

PEUGIC calculation

We adapted the methods recommended by the World Endoscopy Organization for PCCRC [13]. Endoscopies were categorized into positive and negative tests depending on the interval between the procedure and UGI cancer diagnosis. True positive tests were those where cancer was diagnosed within 6 months after an endoscopy and false negative tests where cancer was diagnosed between 6 and 36 months after an endoscopy. Cancers were defined as detected cancers if preceded by a true positive endoscopy and as PEUGIC if they were preceded by a false negative endoscopy. If patients with PEUGIC underwent more than one endoscopy in the period 6–36 months prior to diagnosis, the endoscopy closest to the true positive endoscopy was classified as the false negative or index endoscopy and included in the analysis. For detected cancers, the endoscopy closest to the cancer diagnosis date was the index endoscopy.

The PEUGIC rate was calculated by dividing the number of false negative endoscopies by the sum of false negative and true positive endoscopies.

Cohort characteristics

Data on patient demographics were collected at the time of index endoscopy. Age was used as a categorical variable and grouped into five categories (≤60, 61–69, 70–75, 76–80, and >80 years). Ethnicity was grouped into White, South Asian, Black/Black British, Chinese, mixed ethnicity, other minority ethnicities, and ethnicity unknown. Deprivation was calculated using the Index of Multiple Deprivation, an aggregate score for English Lower Layer Super Output Areas, based on employment status, income, crime levels, and living environment [14]. Deprivation was categorized into quintiles, with 1 being the least deprived and 5 the most deprived. A modified Charlson Comorbidity Index score was calculated using ICD-10 codes for secondary diagnoses, excluding any form of cancer as all patients had UGI cancer, subdivided into 0, 1–4, and ≥5. The Charlson Comorbidity Index score has previously been validated in HES [15]. We also identified patients with a previous HES-coded diagnosis of Barrett's esophagus (K22.7), esophageal ulcer (K22.1), esophageal stricture (K22.2), gastric ulcer (K25x), and gastric atrophy (K29.4) within the 5 years prior to cancer diagnosis.

Data were collected for the following tumor characteristics: clinical stage – categorized as 1–4, or unknown when data were missing; tumor location – classified as upper, middle, or lower third of the esophagus, or unspecified site in the esophagus when the exact location was not available, and proximal or distal stomach, or unspecified site in the stomach when the exact location was not available; histological type – categorized as adenocarcinoma and squamous cell carcinoma. Data on the cancer diagnosis route were classified as urgent outpatient (2-week wait), routine outpatient, or emergency presentation.

Additionally, we identified patients who had undergone a previous endoscopy, which was any endoscopy performed before the endoscopy that diagnosed the cancer or the false negative test that did not diagnose the cancer.

Endoscopy provider characteristics

Healthcare providers were identified using a unique code recorded in HES indicating where the relevant endoscopy was performed. Organizations change over time, for example due to hospital mergers, and therefore historical organizations were mapped to current providers, as they existed on 30 June 2020. Information was collected on whether the provider was an NHS organization or an independent provider. Provider average annual volume of endoscopies was estimated by dividing the total number of endoscopies recorded in HES by the number of years of data that were available for each provider. Healthcare providers were grouped into tertiles and the range of the number of procedures in each tertile was the natural consequence of having an equal number of providers in each tertile.

The JAG accreditation status of each endoscopy provider was categorized as: accredited (if JAG accreditation was awarded and maintained during the study period); assessed, improvement required (providers were close to being accredited but further actions were required); assessed, accreditation not awarded (providers failed to meet required standards); and not assessed (providers have never had an assessment). If organizations were assessed more than once during the study period and their accreditation status changed, the most common status during the study period was used in the analysis. Esophagogastric cancer resection sites were identified from the National Oesophago-Gastric Cancer Audit [16]. Providers were also categorized based on their PCCRC rates: <5.55%, 5.55%–6.35%, 6.36%–6.95%, 6.96%–8.02%, >8.02%, and missing data when PCCRC rates were not available.

Statistical analysis

Categorical variables were summarized as numbers and percentages and the chi-squared test was used for comparison. A few endoscopy providers had very low endoscopy volumes and UGI cancer rates, making the comparison of PEUGIC rates with other providers potentially unreliable [17]. To avoid increased uncertainty due to small sample size, we performed a priori calculation to determine the minimum number of UGI cancers needed to detect an important difference among endoscopy providers. Using a PEUGIC rate of 8% based on previously published population-based studies [18, 19], a doubling of this rate to 16% was considered to be unacceptably high. Based on this number and 80% power at a 0.05 significance level, an endoscopy provider would need to detect at least 90 UGI cancers during the study period to have sufficient statistical power to be labeled as a significant outlier.

PEUGIC rates were calculated for each year and the chi-squared test was used as a significance test of change over time. We estimated what the number of people with PEUGIC would be if the unadjusted PEUGIC rate in each year of the study period was reduced to the 25th centile as a potential benchmark. This would indicate the potential number of cancers that could be diagnosed earlier if the overall PEUGIC rate was reduced to this level. We also explored the change in PEUGIC rate for each provider over time by grouping each provider in the earlier study period (2009–13) into quintiles based on their PEUGIC rate. Similar quintiles were then produced for the later study period (2014–18), and movements of providers between the quintiles for the two periods were examined.

Multivariable logistic regression models were used to explore the association of variables with PEUGIC. We explored multilevel models with endoscopies nested within patients, and with the providers included as a random intercept. Owing to the small number of patients with multiple endoscopies, the models without a random intercept at patient level performed better. Based on the previous studies [8, 9], clinical experience, availability and accuracy of the data, all variables included in the model were determined a priori. An evaluation of collinearity of variables was undertaken. Models with and without endoscopy provider characteristics (as described above) were compared to confirm whether these variables significantly improved the model fit. For ease of interpretation, all exploratory variables were included as categorical variables. Clinical staging was not included in regression models as data on staging were missing for one third of patients and multiple imputation was considered inappropriate for such a large proportion of missing data. Subgroup analyses were performed for people with esophageal and gastric cancers and people with Barrett's esophagus.

Funnel plots for unadjusted and adjusted PEUGIC rates were produced using logistic regression models and the Spiegelhalter method [20] to examine variation in PEUGIC rates for each provider during both time periods (2009–13 and 2014–18). Providers who fall outside the control limits have PEUGIC rates significantly different from the national mean, independently of the factors adjusted for, indicating potential unwarranted variation. We also created unadjusted and adjusted histograms to show PEUGIC rates for each provider in each time period.

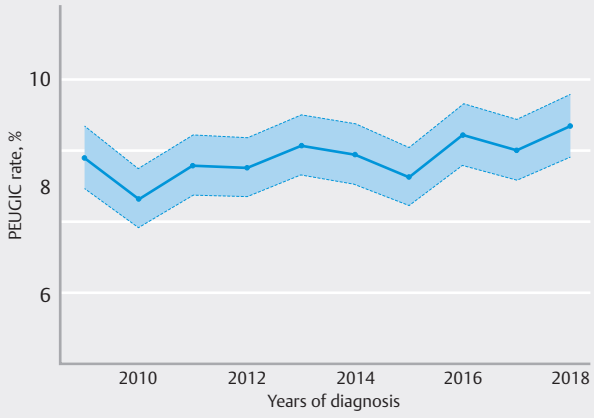
All analyses were performed using Stata version 15.1SE (StataCorp, College Station, Texas, USA) and graphs were generated using R (R Core Team [2022]. R Foundation for Statistical Computing, Vienna, Austria).

Patient and public involvement

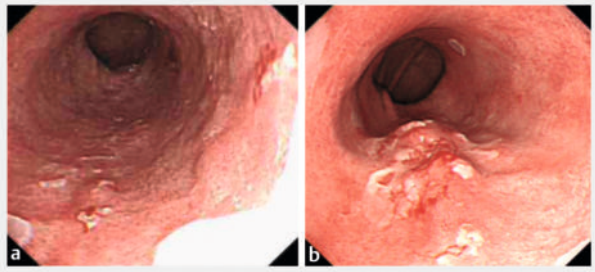
A patient and public group, including members from the charities Heartburn Cancer UK and Upper GI Blues, was involved in the study design. A patient and public representative (M.M.) was also part of the study steering group.

Ethics

The study protocol was approved by London – South East Research Ethics Committee (IRAS project ID # 289695).



▶ **Fig. 1** The unadjusted rates of post-endoscopy upper gastrointestinal cancer (PEUGIC) between 2009 and 2018. *P* value for the difference in rate between 2009 and 2018 = 0.03.



▶ **Fig. 2** Endoscopic images of a patient with post-endoscopy upper gastrointestinal cancer. **a** Segment of Barrett's esophagus with an irregular area. Biopsies from this area were indefinite for dysplasia. **b** Repeat endoscopy 2 years later showed an abnormal area with central depression. Biopsies confirmed invasive adenocarcinoma.

▶ **Table 1** Characteristics of the study population with upper gastrointestinal cancer, and associated post-endoscopy upper gastrointestinal cancer rates.

Characteristics	Patients, n	Endoscopies with UGI cancer diagnosed within 3 years			PEUGIC rate, %
		Total, n	True positive (controls), n (%)	False negative (cases), n (%)	
Total	98 801	106 557	97 479	9078	8.5
Year of diagnosis					
▪ 2009–2013	48 957	52 645	48 250 (49.5)	4395 (48.4)	8.4
▪ 2014–2018	49 844	53 912	49 229 (50.5)	4683 (51.6)	8.7
Age at endoscopy, years					
▪ ≤60	16 673	17 835	16 192 (16.6)	1643 (18.1)	9.2
▪ 61–69	22 483	24 012	21 856 (22.4)	2156 (23.7)	9.0
▪ 70–75	19 403	20 584	18 729 (19.2)	1855 (20.4)	9.0
▪ 76–80	16 390	17 277	15 784 (16.2)	1493 (16.4)	8.6
▪ >80	25 340	26 849	24 918 (25.6)	1931 (21.3)	7.2
Sex					
▪ Male	67 711	72 874	66 920 (68.7)	5954 (65.6)	8.2
▪ Female	31 090	33 683	30 559 (31.3)	3124 (34.4)	9.3
Ethnicity					
▪ White	92 169	99 523	90 948 (93.3)	8575 (94.5)	8.6
▪ Black/Black British	1408	1517	1381 (1.4)	136 (1.5)	9.0
▪ South Asian	1505	1628	1486 (1.5)	142 (1.6)	8.7
▪ Chinese	199	204	192 (0.2)	12 (0.1)	5.9
▪ Mixed	251	264	247 (0.3)	17 (0.2)	6.4
▪ Other minority ethnicity	790	841	775 (0.8)	66 (0.7)	7.9
▪ Unknown	2479	2580	2450 (2.5)	130 (1.4)	5.0
IMD quintiles					
▪ 1 – Least deprived	17 186	18 573	16 960 (17.4)	1613 (17.8)	8.7
▪ 2	20 546	22 111	20 281 (20.8)	1830 (20.2)	8.3
▪ 3	20 559	22 193	20 279 (20.8)	1914 (21.1)	8.6
▪ 4	20 265	21 869	20 001 (20.5)	1868 (20.6)	8.5
▪ 5 – Most deprived	20 245	21 811	19 958 (20.5)	1853 (20.4)	8.5
CCI score					
▪ 0	74 760	78 633	74 214 (76.1)	4419 (48.7)	5.6
▪ 1–4	22 788	26 356	22 101 (22.7)	4255 (46.9)	16.1
▪ ≥5	1253	1568	1164 (1.2)	404 (4.)	25.8

CCI, Charlson Comorbidity Index; IMD, Index of Multiple Deprivation; PEUGIC, post-endoscopy upper gastrointestinal cancer; UGI, upper gastrointestinal.

▶ **Table 2** Previous endoscopic findings and tumor characteristics in patients with upper gastrointestinal cancer, and associated post-endoscopy upper gastrointestinal cancer rates.

Characteristics	Patients	Endoscopies with UGI cancer diagnosed within 3 years			PEUGIC rate, %
		Total, n	True positive (controls), n (%)	False negative (cases), n (%)	
Total	98 801	106 557	97 479	9078	8.5
Previous endoscopic findings					
▪ Esophageal ulcer	9728	12 307	9467 (9.7)	2840 (31.3)	23.1
▪ Esophageal stricture	12 466	13 796	12 300 (12.6)	1496 (16.5)	10.8
▪ Barrett's esophagus	9785	12 231	9645 (9.9)	2586 (28.5)	21.1
▪ Gastric ulcer	8560	9769	8364 (8.6)	1405 (15.5)	14.4
▪ Gastric atrophy	694	845	672 (0.7)	173 (1.9)	20.5
Location of cancer					
▪ Upper third esophagus	2707	2960	2645 (2.7)	315 (3.5)	10.6
▪ Middle third esophagus	9311	10 121	9235 (9.5)	886 (9.8)	8.8
▪ Lower third esophagus	32 878	35 300	32 680 (33.5)	2620 (28.9)	7.4
▪ Unspecified site in esophagus	15 805	17 406	15 420 (15.8)	1986 (21.9)	11.4
▪ Proximal stomach	20 721	22 059	20 546 (21.1)	1513 (16.7)	6.9
▪ Distal stomach	5857	6269	5793 (5.9)	476 (5.2)	7.6
▪ Unspecified site in stomach	11 522	12 442	11 160 (11.4)	1282 (14.1)	10.3
Histology					
▪ Adenocarcinoma	74 620	80 370	74 051 (76.0)	6319 (69.6)	7.9
▪ Squamous cell carcinoma	18 703	20 189	18 501 (19.0)	1688 (18.6)	8.4
▪ Histology unknown	5478	5998	4927 (5.0)	1071 (11.8)	17.9
Clinical stage					
▪ 1	7157	8656	7088 (7.3)	1568 (17.3)	18.1
▪ 2	10 377	11 134	10 318 (10.6)	816 (9.0)	7.3
▪ 3	18 929	19 915	18 851 (19.3)	1064 (11.7)	5.3
▪ 4	25 786	26 959	25 474 (26.1)	1485 (16.4)	5.5
▪ Unknown	36 552	39 893	35 748 (36.7)	4145 (45.7)	10.4

PEUGIC, post-endoscopy upper gastrointestinal cancer; UGI, upper gastrointestinal.

Results

PEUGIC rates

The study included 106 557 endoscopies in 98 801 patients who were diagnosed as having UGI cancer within 3 years of their endoscopy. In this population, 9078 (8.5%) were classified as PEUGIC. There was a statistically significant increase in the PEUGIC rate from 8.4% in 2009 to 8.9% in 2018 (P =0.03) (▶ **Fig. 1**). The PEUGIC rate was 8.8% in patients with esophageal cancer and 8.0% in patients with gastric cancer (see **Fig. 1s** and **Fig. 2s** in the online-only Supplementary material). For cancers diagnosed in patients with Barrett's esophagus, the PEUGIC rate was 21%. ▶ **Fig. 2** shows a PEUGIC example in a patient with Barrett's esophagus.

PEUGIC characteristics

Tables 1–3 show the proportions of true positive and false negative endoscopies and the PEUGIC rates in relation to demographic factors (▶ **Table 1**), tumor characteristics and endoscopy findings (▶ **Table 2**), and the characteristics of the providers where the index endoscopy was performed (▶ **Table 3**). The PEUGIC rate was higher in younger people, women, people with more comorbidity, and those with a previous esophageal ulcer, esophageal stricture, Barrett's esophagus, gastric ulcer, or gastric atrophy. The PEUGIC rate was lower among those

▶ **Table 3** Diagnostic pathways and characteristics of endoscopy providers for patients with upper gastrointestinal cancer, and associated post-endoscopy upper gastrointestinal cancer rates.

Characteristics	Patients	Endoscopies with UGI cancer diagnosed within 3 years			PEUGIC rate, %
		Total, n	True positive (controls), n (%)	False negative (cases), n (%)	
Total	98 801	106 557	97 479	9078	8.5
Diagnosis route					
▪ Urgent outpatient	35 651	36 772	35 548 (36.5)	1224 (13.5)	3.3
▪ Routine outpatient	33 672	38 004	33 235 (34.1)	4769 (52.5)	12.6
▪ Emergency admission	19 544	21 101	18 998 (19.5)	2103 (23.2)	10.0
▪ Unknown	9934	10 680	9698 (9.9)	982 (10.8)	9.2
Provider type					
▪ NHS	96 991	104 498	95 627 (98.1)	8871 (97.7)	8.5
▪ Independent	2016	2059	1852 (1.9)	207 (2.3)	10.1
Annual endoscopy volume per provider					
▪ <3974.2	16 346	17 275	15 887 (16.3)	1388 (15.3)	8.0
▪ 3974.2–6374.1	32 399	34 621	31 687 (32.5)	2934 (32.3)	8.5
▪ >6374.1	50 929	54 661	49 905 (51.2)	4756 (52.4)	8.7
PCCRC rate					
▪ <5.55%	18 119	19 332	17 729 (18.2)	1603 (17.7)	8.3
▪ 5.55%–6.35%	21 581	22 959	21 080 (21.6)	1879 (20.7)	8.2
▪ 6.36%–6.95%	19 761	21 086	19 237 (19.7)	1849 (20.4)	8.8
▪ 6.96%–8.02%	20 179	21 534	19 693 (20.2)	1841 (20.3)	8.6
▪ >8.02%	18 864	20 166	18 413 (18.9)	1753 (19.3)	8.7
▪ Unknown	1437	1480	1327 (1.4)	153 (1.7)	10.3
Esophagogastric cancer resection center					
▪ No	71 432	76 267	69 931 (71.7)	6336 (69.8)	8.3
▪ Yes	28 166	30 290	27 548 (28.3)	2742 (30.2)	9.1
National accreditation status					
▪ Accredited	51 161	54 632	50 095 (51.4)	4537 (50.0)	8.3
▪ Assessed and improvements required	28 533	30 488	27 899 (28.6)	2589 (28.5)	8.5
▪ Assessed and not awarded	17 707	18 917	17 218 (17.7)	1699 (18.7)	9.0
▪ Not assessed	2391	2520	2267 (2.3)	253 (2.8)	10.0

NHS, National Health Service; PCCRC, post-colonoscopy colorectal cancer; PEUGIC, post-endoscopy upper gastrointestinal cancer; UGI, upper gastrointestinal.

from the most deprived regions and with an increasing number of additional endoscopies. The PEUGIC rate was higher among patients with squamous cell carcinoma and those whose cancer was located in the upper third of the esophagus. Additionally, the PEUGIC rate was higher in people with early-stage cancer (stage 1). A higher proportion of patients who had their UGI cancer diagnosed on a routine outpatient pathway (12.6%) and after an emergency presentation (10.0%) had PEUGIC compared with those diagnosed on an urgent outpatient pathway (3.3%). In comparison with endoscopy providers who achieved and maintained JAG accreditation, PEUGIC rates were higher among endoscopy providers that required improvement and those that were not assessed during the study period.

In multivariable logistic regression analysis, these associations were sustained and remained statistically significant. The results of multivariable regression analysis for the whole cohort are shown in ▶ **Table 4**, ▶ **Table 5**, and ▶ **Table 6**, and those for subgroups of people with esophageal cancers, gastric cancers,

▶ **Table 4** Patient factors associated with post-endoscopy upper gastrointestinal cancer on multivariable logistic regression analysis.

Characteristics	OR (95%CI)	*P* value
Age group (vs. ≤60 years)		
▪ 61–69	0.85 (0.79–0.91)	<0.01
▪ 70–75	0.79 (0.73–0.85)	<0.01
▪ 76–80	0.68 (0.63–0.73)	<0.01
▪ Over 80	0.52 (0.48–0.56)	<0.01
▪ Female sex (vs. male)	1.29 (1.23–1.36)	<0.01
Ethnicity (vs. White)		
▪ Black	1.10 (0.91–1.34)	0.31
▪ South Asian	0.93 (0.77–1.12)	0.42
▪ Chinese	0.69 (0.38–1.27)	0.23
▪ Mixed	0.77 (0.46–1.29)	0.32
▪ Other minority ethnicity	1.01 (0.77–1.31)	0.97
▪ Unknown	0.72 (0.59–0.87)	<0.01
IMD quintiles (vs. 1 – Least deprived)		
▪ 2	0.93 (0.87–1.01)	0.08
▪ 3	0.96 (0.89–1.03)	0.28
▪ 4	0.92 (0.85–0.99)	0.02
▪ 5 – Most deprived	0.86 (0.80–0.93)	<0.01
CCI score (vs. 0)		
▪ 1–4	2.90 (2.76–3.05)	<0.01
▪ ≥5	5.06 (4.45–5.76)	<0.01

CCI, Charlson Comorbidity Index; IMD, Index of Multiple Deprivation; OR, odds ratio.

▶ **Table 5** Tumor factors and previous endoscopy findings associated with post-endoscopy upper gastrointestinal cancer on multivariable logistic regression analysis.

Characteristics	OR (95%CI)	*P* value
Tumor site (vs. upper third esophagus)		
▪ Middle third esophagus	0.77 (0.66–0.89)	<0.01
▪ Lower third esophagus	0.63 (0.55–0.72)	<0.01
▪ Unspecified site in esophagus	0.91 (0.80–1.05)	0.20
▪ Proximal stomach	0.85 (0.74–0.99)	0.03
▪ Distal stomach	0.93 (0.79–1.11)	0.43
▪ Unspecified site in stomach	1.27 (1.09–1.48)	<0.01
Histology (vs. adenocarcinoma)		
▪ Squamous cell carcinoma	1.50 (1.39–1.61)	<0.01
▪ Histology unknown	2.39 (2.20–2.59)	<0.01
Esophageal ulcer	3.30 (3.11–3.50)	<0.01
Esophageal stricture	1.28 (1.20–1.37)	<0.01
Barrett's esophagus	3.21 (3.02–3.42)	<0.01
Gastric ulcer	1.55 (1.44–1.66)	<0.01
Gastric atrophy	2.39 (1.99–2.88)	<0.01

OR, odds ratio.

and Barrett's esophagus are shown in **Table 1s**, **Table 2s**, and **Table 3s**, respectively. Among patients with gastric adenocarcinoma, PEUGIC was more common with diffuse type (9%), compared with intestinal type (6.7%; $P < 0.001$).

Institutional variation

In total, 130 and 129 endoscopy providers were operational in the English NHS during the time periods 2009–2013 and 2014–2018, respectively. The majority (68%) of providers remained within the same quintile for PEUGIC rate for the two study periods or moved by only one quintile (**Table 4s**). Across each time period, significant variation was found in unadjusted and adjusted PEUGIC rates. In 2014–2018, unadjusted rates ranged from 3.4% to 18.8%, and adjusted rates ranged from 3.8% to 14.7% (▶ **Table 7**). **Table 5s** shows the centiles for unadjusted PEUGIC rates; in 2014–2018, the best performing 5% of providers had an unadjusted PEUGIC rate of under 5.7% and the worst performing 5% had a PEUGIC rate of over 12.7%.

In the unadjusted funnel plot for the years 2014–2018, four providers were outside the upper 99.8% control limit and nine providers were outside the upper 95% control limit, indicating higher PEUGIC rates than expected. After adjusting for associated factors described above, one provider was outside the upper 99.8% control limit and seven providers were above the 95% control limit. ▶ **Table 7**, ▶ **Fig. 3**, and ▶ **Fig. 4** show provider comparisons for each of the time periods.

We estimated the potential benefit if the PEUGIC rate was reduced to the 25th centile rate. If the PEUGIC rate was reduced to 7% for the entire study period, there would have potentially been 162 fewer patients with PEUGIC each year. **Fig. 3s** shows the results of these estimates.

Discussion

This is the first study to examine PEUGIC rates across all endoscopy providers in England using national cancer data. We observed an increase in the national PEUGIC rate over the study period and significant unwarranted variations in PEUGIC rates among endoscopy providers following adjustment for associated factors. The threefold variation in PEUGIC rates among endoscopy providers represents an opportunity to improve UGI endoscopy performance up to the level of the best performing providers, increase early cancer detection rates, and improve outcomes for UGI cancer.

This study reported a slight increase in the PEUGIC rate in England. Despite technological advancements in endoscopy over the past decade, PEUGIC rates have not improved and were similar to those reported in 2014/2015 [18, 19]. This is in

▶ **Table 6** Diagnostic pathways and endoscopy provider factors associated with post-endoscopy upper gastrointestinal cancer on multivariable logistic regression analysis.

Characteristics	OR (95%CI)	*P* value
Diagnosis route (vs. urgent outpatient)		
▪ Routine outpatient	2.80 (2.62–3.00)	<0.01
▪ Emergency admission	2.37 (2.19–2.56)	<0.01
▪ Missing	2.30 (2.10–2.52)	<0.01
Previous endoscopy prior to false negative or true positive endoscopy	0.74 (0.70–0.78)	<0.01
NHS provider(vs. independent)	0.91 (0.73–1.14)	0.43
Annual endoscopy volume per provider (vs. <3974)		
▪ 3974–6374	0.98 (0.89–1.08)	0.69
▪ >6374	1.01 (0.92–1.11)	0.82
Esophagogastric cancer resection center	1.04 (0.96–1.12)	0.31
National accreditation status (vs. accredited)		
▪ Assessed and improvements required	1.10 (1.01–1.20)	0.02
▪ Assessed and accreditation not awarded	1.03 (0.96–1.11)	0.40
▪ Not assessed	1.24 (1.04–1.47)	0.01
Adjusted PCCRC rate (vs. <5.55%)		
▪ 5.55%–6.35%	0.98 (0.88–1.08)	0.63
▪ 6.36%–6.95%	1.00 (0.90–1.11)	0.95
▪ 6.96%–8.02%	1.04 (0.94–1.16)	0.44
▪ >8.02%	1.02 (0.92–1.14)	0.66
▪ No data	1.21 (0.93–1.57)	0.16

NHS, National Health Service; OR, odds ratio; PCCRC, post-colonoscopy colorectal cancer.

▶ **Table 7** Provider variation in adjusted and unadjusted rates of post-endoscopy upper gastrointestinal cancer for each study time period.

	2009–2013	2014–2018	Whole cohort
Adjusted			
▪ Highest PEUGIC rate*	15.6	14.7	13.0
▪ Lowest PEUGIC rate*	2.4	3.8	5.1
▪ Number of providers	130	129	131
▪ Above 99.8% control limit	3	1	3
▪ Above 95% control limit	3	7	5
▪ Within 95% control limits	121	112	118
▪ Below 95% control limit	3	9	5
▪ Below 99.8% control limit	0	0	0
Unadjusted			
▪ Highest PEUGIC rate*	19.2	18.8	16.6
▪ Lowest PEUGIC rate*	2.3	3.4	4.4
▪ Number of providers	130	129	131
– Above 99.8% control limit	3	4	7
– Above 95% control limit	11	9	8
– Within 95% control limits	106	108	103
– Below 95% control limit	10	7	9
– Below 99.8% control limit	0	1	4

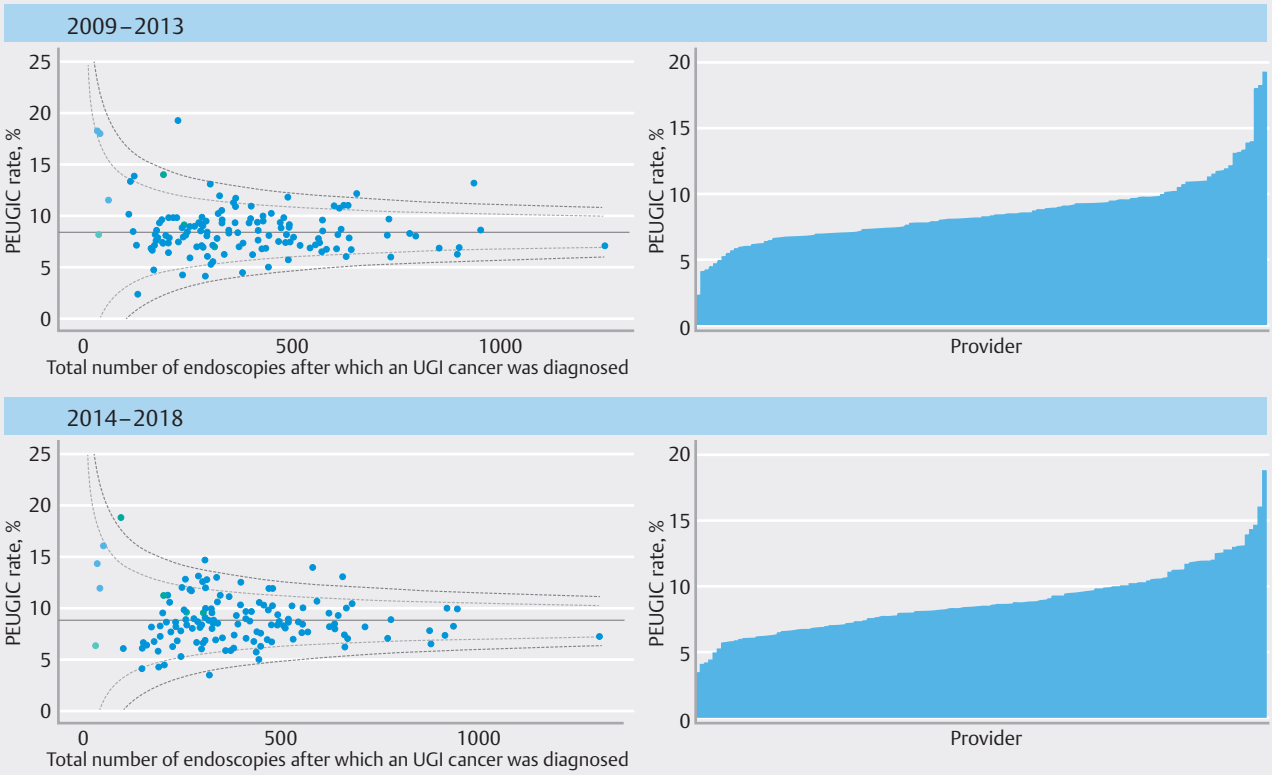
PEUGIC, post-endoscopy upper gastrointestinal cancer.
*Providers that detected at least 90 upper gastrointestinal cancers.

contrast to PCCRC rates, which significantly improved in the UK between 2005 and 2013 [11]. PCCRC rates were significantly lower for colonoscopies performed as part of the national bowel cancer screening program, which involves selection and accreditation of experienced colonoscopists with continuous performance monitoring and feedback [21]. Such efforts to ensure high quality endoscopy in England are lacking for UGI endoscopy and cancer.

A recent study reported that up to 6% of UGI cancers are potentially missed at endoscopy and adenocarcinomas are more commonly missed in the esophagus than squamous cell cancers [6]. Potentially missed cancers were more commonly diagnosed at an advanced stage. These observations are different from the findings of the present study. Esophageal adenocarcinoma is more common in Northern and Western Europe than in Central European countries [22], and surveillance of Barrett's esophagus is established in the UK, which may lead to earlier detection of dysplastic changes and adenocarcinoma [23]. These differences in the baseline risk of different cancers and surveillance practices may explain the difference in results between the present study and the Polish study [6].

JAG accreditation is a quality assurance program in the UK that promotes quality improvement through highlighting areas of best practice and areas for change. Endoscopy providers are assessed against a set of standards, which cover four domains: clinical quality, patient experience, clinical workforce, and training [24]. Endoscopies performed at endoscopy providers who did not engage with the JAG accreditation process and at providers who were assessed but required improvement were more likely to be associated with PEUGIC. These important findings suggest that engagement with JAG accreditation and compliance with quality standards improve the quality of endoscopy and other aspects of care around endoscopy to reduce PEUGIC, as well as reinforcing the importance of all endoscopy providers engaging with external accreditation of their service.

The present study confirms a number of factors with an established association with PEUGIC including younger age, female sex, increasing comorbidity, and Barrett's esophagus [6, 8, 9, 25, 26]. Previous diagnoses of esophageal and gastric ulcers, esophageal stricture or gastric atrophy were also found to be associated with PEUGIC. Careful endoscopic examination,

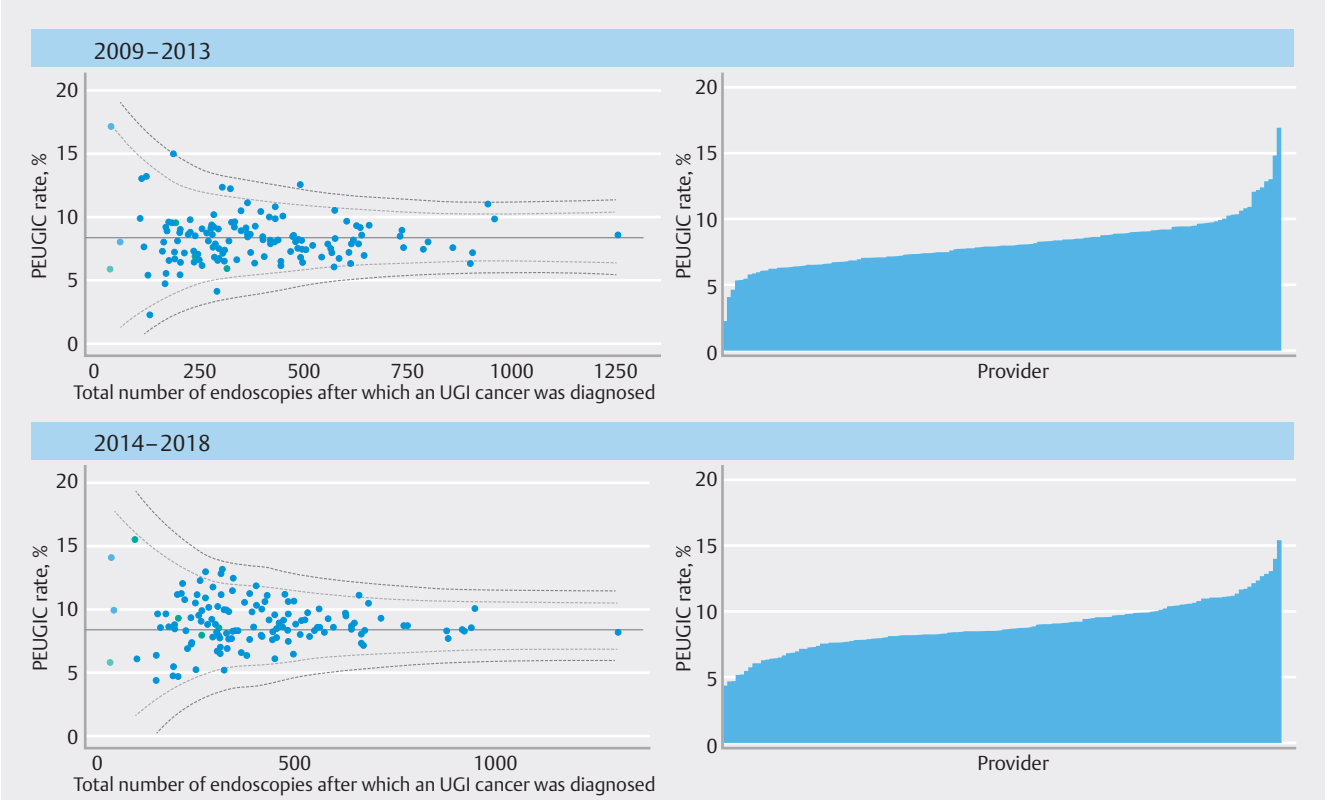


▶ **Fig. 3** The variation in unadjusted rates of post-endoscopy upper gastrointestinal cancer (PEUGIC) by endoscopy provider for 2009–13 and 2014–18. In the funnel plots, each dot represents an individual provider. Dashed lines represent 95% and 99.8% control limits outside the national PEUGIC rate (solid line). Purple dots represent National Health Service providers and green dots represent independent providers. The faded colors represent those providers with <90 procedures. In the bar charts, each line represents an individual provider. UGI, upper gastrointestinal.

follow-up, and surveillance of these high risk conditions is recommended [7,27]. In a multicenter root cause analysis of PEUGIC cases, inadequate surveillance or follow-up plans and administrative delays were important contributing factors to PEUGIC [26]. Endoscopy providers in the UK audit their gastric ulcer follow-up rates as part of the JAG accreditation process. We suggest that endoscopy services should also audit their follow-up rates for other cancer-associated lesions (e.g. esophageal ulcer, esophageal stricture) and surveillance of premalignant conditions (e.g. Barrett's esophagus, gastric atrophy, and gastric intestinal metaplasia). Cancer in the upper esophagus and squamous cell carcinoma were both associated with PEUGIC. Smoking, excess alcohol intake, and a history of head and neck cancer are all known to be associated with an increased risk of esophageal squamous cell carcinoma. Training UK endoscopists in the recognition of early squamous cell carcinoma is clearly needed, with a particular focus on people known to be at increased risk.

In the UK, patients with alarm symptoms are investigated on an urgent suspected cancer 2-week wait outpatient pathway. PEUGIC rates were significantly lower for UGI cancer diagnosed on this pathway. This is likely to be due to the high index of suspicion in these patients and advanced stage of cancers causing alarm symptoms, which are potentially easier to detect. These findings are consistent with the results of a recent systematic review [8]. In addition, a negative association with the most deprived quintile was found. People from socioeconomically deprived areas have overall more advanced cancer at presentation, which would be expected to have a higher symptom burden and be easier to detect [28,29].

This study has several limitations. Data are based on clinical codes and as such are subject to ascertainment bias. This risk is considered low as previous validation studies have reported over 99% accuracy for the NCRAS database [30], and an annual report on HES records in 2012/13 described an accuracy of 99.3% for primary diagnostic codes and 99.9% for primary procedure codes [31]. Not all data on endoscopy reports are included in administrative databases and it was not possible to examine some important potential factors contributing to PEUGIC in our analyses. For example, data were not available for use of sedation for endoscopy, tolerance of endoscopy, quality of views during endoscopy, procedure time, whether an abnormality was seen and assessed appropriately, and experience and training of endoscopists. We suggest that these factors should be investigated in future studies where information on the endoscopy reports is available and future efforts should be focused on identifying quality indicators for UGI endoscopy relevant to PEUGIC. This study excluded neuroendocrine tumors



▶ **Fig. 4** The variation in adjusted rates of post-endoscopy upper gastrointestinal cancer (PEUGIC) by endoscopy provider for 2009–13 and 2014–18. In the funnel plots, each dot represents an individual provider. Dashed lines represent 95% and 99.8% control limits outside the national PEUGIC rate (solid line). Purple dots represent National Health Service providers and green dots represent independent providers. The faded colors represent those providers with <90 procedures. In the bar charts, each line represents an individual provider. GI, gastrointestinal.

and gastrointestinal stromal tumors as the natural history of these cancers is not well understood. We suggest future studies should consider including these cancers in their analyses. Duodenal cancers were also excluded as it was not possible to reliably differentiate cancers located in the first and second part of duodenum from cancers located in the third and fourth part of duodenum and not within the reach of a standard endoscope in the cancer registry database. Gastric intestinal metaplasia is an important precancerous condition, but it is not coded in the HES database and therefore it was not possible to include it in the analysis. Data on clinical staging were missing for a third of people and therefore could not be included in multivariable regression analyses.

Conclusions

There was a threefold difference in rates of PEUGIC among endoscopy providers in England, suggesting unwarranted variation in endoscopy quality. PEUGIC was associated with Barrett's esophagus, gastric atrophy, and other endoscopy findings known to be associated with UGI cancer and in particular squamous cell carcinoma. National endoscopy provider accreditation was associated with lower PEUGIC rates, emphasizing the key role of engagement with external quality assurance and accreditation in maintaining endoscopy standards. We would recommend initiatives to address variation in endoscopy standards among providers, with a benchmark provider PEUGIC rate of 7% as a quality standard.

Conflict of Interest

The authors declare that they have no conflict of interest.

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