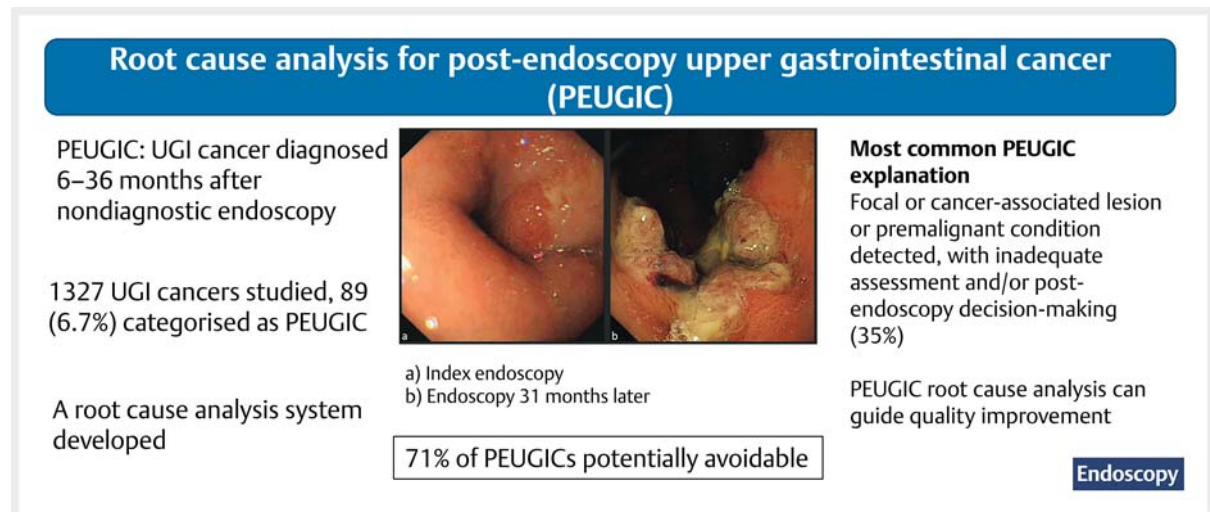


A root cause analysis system to establish the most plausible explanation for post-endoscopy upper gastrointestinal cancer

GRAPHICAL ABSTRACT



Authors

Umair Kamran¹ , Dominic King¹ , Abdullah Abbasi², Ben Coupland³, Nosheen Umar¹, Warren C. Chapman¹, Srishya Hebbar², Nigel J. Trudgill¹

Institutions

- 1 Department of Gastroenterology, Sandwell and West Birmingham NHS Trust, West Bromwich, UK
- 2 Department of Gastroenterology, University Hospitals of North Midlands NHS Trust, Stoke-on-Trent, UK
- 3 Health Informatics, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

submitted 15.12.2021

accepted after revision 7.7.2022

published online 31.8.2022

Bibliography

Endoscopy 2023; 55: 109–118

DOI 10.1055/a-1917-0192

ISSN 0013-726X

© 2022. Thieme. All rights reserved.

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

 Table 1 s, Fig. 1 s

Supplementary material is available under

<https://doi.org/10.1055/a-1917-0192>

Corresponding author

N. J. Trudgill, MD, Consultant Gastroenterologist, Sandwell and West Birmingham NHS Trust, Lyndon, West Bromwich, B17 4HJ, UK
nigel.trudgill@nhs.net

ABSTRACT

Background Missing upper gastrointestinal cancer (UGIC) at endoscopy may prevent curative treatment. We have developed a root cause analysis system for potentially missed UGICs at endoscopy (post-endoscopy UGIC [PEUGIC]) to establish the most plausible explanations.

Methods The electronic records of patients with UGIC at two National Health Service providers were examined. PEUGICs were defined as UGICs diagnosed 6–36 months after an endoscopy that did not diagnose cancer. An algorithm based on the World Endoscopy Organization post-colonoscopy colorectal cancer algorithm was developed to categorize and identify potentially avoidable PEUGICs.

Results Of 1327 UGICs studied, 89 (6.7%) were PEUGICs (patient median [IQR] age at endoscopy 73.5 (63.5–81.0); 60.7% men). Of the PEUGICs, 40% were diagnosed in patients with Barrett's esophagus. PEUGICs were categorized as: A – lesion detected, adequate assessment and decision-making, but PEUGIC occurred (16.9%); B – lesion detected, inadequate assessment or decision-making (34.8%); C – possible missed lesion, endoscopy and decision-making

adequate (8.9%); D – possible missed lesion, endoscopy or decision-making inadequate (33.7%); E – deviated from management pathway but appropriate (5.6%); F – deviated inappropriately from management pathway (3.4%). The majority of PEUGICs (71%) were potentially avoidable and in 45% the cancer outcome could have been different if it had been diagnosed on the initial endoscopy. There was a

negative correlation between endoscopists' mean annual number of endoscopies and the technically attributable PEUGIC rate (correlation coefficient -0.57 ; $P=0.004$).

Conclusion Missed opportunities to avoid PEUGIC were identified in 71% of cases. Root cause analysis can standardize future investigation of PEUGIC and guide quality improvement efforts.

Introduction

Upper gastrointestinal cancers (UGICs) are usually diagnosed by endoscopy; however, UGIC can be diagnosed after an endoscopy that did not identify the cancer. These are termed post-endoscopy UGICs (PEUGICs). The British Society of Gastroenterology (BSG) recommends that PEUGIC should be a quality standard and regularly audited [1]. In a meta-analysis, 11.3% of UGICs were not diagnosed at an endoscopy performed up to 3 years before the diagnosis [2], and more recent studies report PEUGIC rates of 6.7%–9.4% [3–6]. PEUGICs are less likely to present with alarm symptoms and are more commonly associated with less advanced clinical stage [7]. Other associated factors include younger age, female sex, increasing deprivation, and an inadequate number of biopsies [5, 6, 8], but not endoscopist experience [9]; however, the studies published to date have lacked a systematic analysis approach to the causes of PEUGIC.

Colorectal cancer (CRC) diagnosed following a colonoscopy that did not diagnose the CRC is termed post-colonoscopy CRC (PCCRC) [10]. The World Endoscopy Organization (WEO) has proposed that PCCRC should be categorized into interval and non-interval cancers and has provided a system to determine the most plausible etiologies [11]. This was subsequently validated, with suggestions made to improve the categorization system [12].

We have undertaken a detailed analysis of PEUGICs to establish how many were interval and non-interval cancers, and have developed a root cause analysis system based on the WEO PCCRC system to identify the most plausible explanations.

Methods

Patient identification and data collection

Using International Classification of Diseases 10th revision codes, adults (>18 years) diagnosed with esophageal (C15), gastric (C16), and duodenal (C17) cancers were identified at two UK endoscopy providers: Sandwell and West Birmingham NHS trust (January 2010 to December 2019) and University Hospitals of North Midlands NHS Trust (January 2017 to March 2020). Patients were excluded if they did not have an endoscopy prior to their diagnosis or were referred from other hospitals. Other exclusion criteria included: non-UGI cancers, neuroendocrine tumours, sarcomas, and gastrointestinal stromal tumours.

PEUGICs were defined as cancers in patients who had an endoscopy that did not diagnose their cancer 6–36 months prior to the UGIC diagnosis. Patients who had an endoscopy

within 6 months of the UGIC diagnosis were deemed UGIC controls. If PEUGIC patients had more than one endoscopy 6–36 months prior to diagnosis, the endoscopy that did not diagnose cancer that was closest to the date of the cancer diagnosis was classified as the index endoscopy. For controls, the endoscopy closest to the date of the cancer diagnosis was the index endoscopy. All patients with UGIC or dysplasia at the two providers are reported by an expert GI pathologist and confirmed by a second pathologist.

Endoscopies were performed with the patient under conscious sedation (using midazolam) or with xylocaine throat spray alone, depending on the patient's preference and the clinical judgment of the endoscopist. Data collected included: patient variables (age at endoscopy, sex); endoscopy variables (indication, photodocumentation of J maneuver [gastric retroflexion] and view quality in gastric body and second part of duodenum [D2], tolerance [well or poorly tolerated based on the endoscopy report], and endoscopy findings); endoscopist variables (total endoscopies performed over the study period); cancer information (diagnosis date, site, staging, differentiation, tumor size, treatment received [endoscopic resection, surgical resection, chemotherapy, or best supportive care only] and histological diagnosis); and other management information (surveillance or follow-up plan, reasons for deviation from plan [patient related or administrative]).

The total number of UGI endoscopies performed by each endoscopist was extracted from the endoscopy reporting systems. Endoscopies performed on training lists were considered to have been undertaken by the trainer in terms of endoscopy volume and PEUGIC analysis.

Interval and non-interval cancers and root cause analysis of the most plausible explanation for PEUGIC

Interval and non-interval cancers

Interval PEUGICs were identified before the next planned surveillance endoscopy [11]. Non-interval PEUGICs were identified at (type I) or after (type II) the next planned surveillance endoscopy, or when no further surveillance or follow-up was planned (type III). Examples of the PEUGIC subcategories are provided in **Table 1 s** (see online-only Supplementary material).

Root cause analysis of the most plausible explanation for PEUGIC

PEUGICs were categorized into six types (A to F), involving a four-step process:

Step 1 Focal or cancer-associated lesion or premalignant condition detected in the same segment as the subsequent PEUGIC?

If Yes, proceed to Step 2; if No, proceed to Step 3.

Step 2 Lesion adequately described and photographed, adequate biopsy samples taken, and the surveillance/follow-up plan was appropriate?

If Yes, PEUGIC categorized as “A”: lesion detected, adequate assessment and decision-making, but PEUGIC still occurred.

If No, PEUGIC categorized as “B”: lesion detected, inadequate assessment or decision-making.

Step 3 Index endoscopy adequate or, if inadequate, recognized by the endoscopist as inadequate and planned follow-up was appropriate?

If Yes, PEUGIC categorized as “C”: possible missed lesion, endoscopy and decision-making adequate.

If No, PEUGIC categorized as “D”: possible missed lesion, endoscopy or decision-making inadequate.

Step 4 If the management pathway deviated from the recommendations following the index endoscopy, the following categories were identified:

Where due to patient choice or the decision of the responsible clinician that the patient was not fit for further investigations, “E”: deviated from management pathway but appropriate.

Where due to administrative delays (i.e. surveillance or follow-up procedures not booked within the recommended timeframe), “F”: deviated inappropriately from management pathway.

More than one PEUGIC explanation was allowed for individual patients. Detected lesions in the PEUGIC segment included premalignant (Barrett’s esophagus, gastric atrophy, or gastric intestinal metaplasia), and focal or cancer-associated lesions (esophageal ulcer or stricture, Los Angeles grade C or D reflux esophagitis, or gastric ulcer).

Endoscopies performed 6 weeks beyond the planned follow-up date (for focal lesions) and 12 weeks beyond the planned surveillance dates (for premalignant conditions) were categorized as inappropriate and related to administrative factors, in the absence of patient choice or an intercurrent illness that delayed the endoscopy.

An endoscopy was considered adequate if the following criteria were met:

1. high definition video-endoscopy with image capture and biopsies
2. J maneuver performed and photographed
3. D2 intubated and photographed
4. view quality in the stomach photographed and classified as excellent, good, or satisfactory, with no foam, mucus, blood, or food limiting the view
5. tolerance excellent, good, or satisfactory and not limiting the view.

Photodocumentation of the J maneuver, D2, and gastric body were the minimum criteria for adequate photodocumentation.

Avoidability

The previously described approach used to define avoidable PCCRC [12] was used to determine whether a PEUGIC was potentially avoidable based on cancer size at diagnosis and the factors identified on root cause analysis. Small PEUGICs were categorized as unavoidable if they were growing by <5 mm/year, as they would have been unlikely to be detectable during the index endoscopy. PEUGICs were also considered unavoidable if the recommended pathway was not followed because the patient declined investigations or was deemed by the responsible clinician to be too frail to proceed with further investigation. All other PEUGICs were considered potentially avoidable.

Potential impact of delay in diagnosis on PEUGIC clinical outcomes

The outcome for a PEUGIC was unlikely to be different if patients were diagnosed at an early stage despite a negative index endoscopy and later underwent successful endoscopic resection. The outcome was also unlikely to be different for patients who were frail at index endoscopy and were unlikely to be eligible for curative treatment at any stage. Patients diagnosed with their cancer at an advanced stage that precluded curative treatment or endoscopic resection were considered to have potentially had a different outcome had they been diagnosed at index endoscopy.

Attribution

PEUGICs were attributable to individual endoscopists if technical endoscopic or decision-making factors were identified on the root cause analysis [12]:

1. premalignant, focal, or cancer-associated lesion identified but not described according to the recommended criteria (e.g. Prague classification [13, 14]) or lesion site or morphology not recorded in the endoscopy report or photographed
2. premalignant, focal, or cancer-associated lesion identified but not biopsied appropriately or according to recommended guidelines where relevant (e.g. Seattle protocol for Barrett’s esophagus [13, 15] and Sydney protocol for gastric atrophy and intestinal metaplasia [16])
3. endoscopist did not recommend an appropriate surveillance or follow-up plan
4. if the index endoscopy was inadequate, the endoscopist did not recognize it as inadequate or did not recommend a repeat procedure.

PEUGICs were not deemed attributable in the following situations:

1. small PEUGIC (growing at <5 mm/year)
2. the patient declined further investigations or was deemed by the responsible clinician to be too unwell for further investigation.

For each endoscopist, the total and mean annual number of UGI endoscopies performed over the study period were extracted. The “technically attributable” rate per 1000 endoscopies was

calculated for each endoscopist by dividing the technically attributable PEUGIC number by the total number of UGI endoscopies.

Statistical analysis

The Mann–Whitney *U* test and chi-squared test were used for continuous and categorical variables respectively, and two-sided *P* values <0.05 were considered significant. Spearman's rank correlation was used to assess correlations between the technically attributable PEUGIC rate per 1000 endoscopies and the mean annual number of endoscopies by endoscopists.

A funnel plot examined variation in technically attributable PEUGIC rates between endoscopists. It was constructed as a scatter plot with superimposed control limits, representing one and two SDs from the mean. Endoscopists outside the control limits had a significantly higher technically attributable PEUGIC rate than the mean. Scatter plots were used to correlate the delay in diagnosis (interval from index endoscopy to PEUGIC diagnosis) and cancer stage (I, II, III, or IV) and histological differentiation (categorized as well, moderately, and poorly differentiated) for all PEUGICs and also separately for PEUGICs with and without Barrett's esophagus.

Stata statistical software, release 16, was used for the statistical analysis.

Ethics

This work was undertaken as a service improvement project and ethics approval was not sought. It was registered with Trust Audit and Quality Improvement Departments of Sandwell and West Birmingham NHS Trust and University Hospitals of North Midlands NHS Trust.

Patient and public involvement

There was no patient or public involvement in this study.

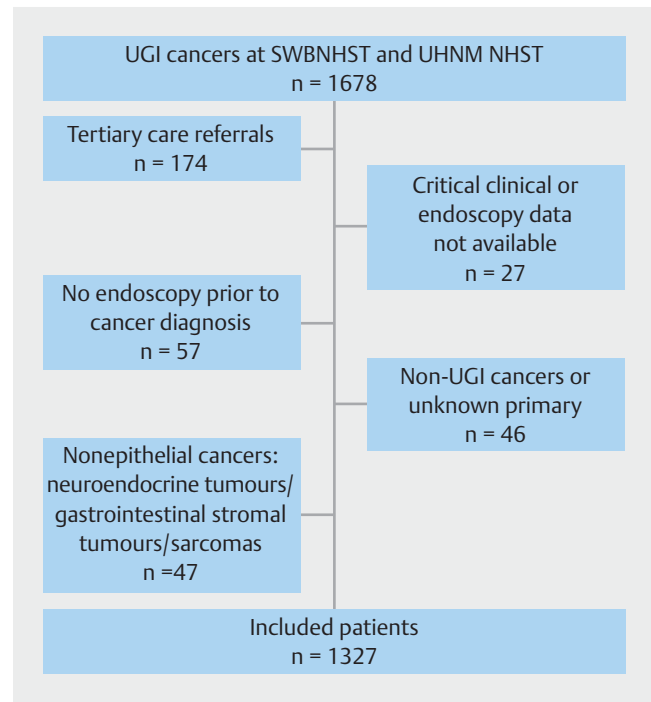
Results

Study subjects

A total of 1327 UGICs met the inclusion criteria (► **Fig. 1**); 89 (6.7%) were PEUGICs. Of these, 48% were diagnosed 6–18 months after the index endoscopy and 52% were diagnosed 18–36 months after the index endoscopy. The patient demographic details and characteristics of the index endoscopy for patients with PEUGIC and the UGIC controls are shown in ► **Table 1**.

Cancer details

The majority of PEUGICs were esophageal (83%), with 17% being gastric. Data on the clinical staging, treatment received, and stratification based on an index endoscopy finding of Barrett's esophagus are presented in ► **Table 2**. Among the PEUGICs, 57% were early stage (i.e. stage I or II), compared with 22% of the UGIC controls. No correlation was found between the interval from the index endoscopy to PEUGIC diagnosis and tumor size, staging at diagnosis, or histological differentiation (**Fig. 1 s**). More than half of PEUGIC patients received treatment with curative intent (53%), compared with 29% of the UGIC controls ($P=0.002$). Patients with PEUGICs were more



► **Fig. 1** Flowchart describing reasons for exclusion and selection of study patients.

UGI, upper gastrointestinal; SWBNHST, Sandwell and West Birmingham NHS trust; UHNM NHST, University Hospitals of North Midlands NHS Trust.

likely to undergo endoscopic resection than the UGIC controls (31.3% vs. 5.1%; $P=0.002$).

Index endoscopy details for PEUGIC patients

In 27% of the PEUGIC patients, the index endoscopy was for Barrett's surveillance compared with 1.1% in the UGIC control group. In PEUGIC patients, views were excellent or good in 47.2% and satisfactory in 25.8%; four patients (4%) had poor views due to gastric food residue and in 22.5% the view quality was not recorded. Procedure tolerance was not recorded in 30% of patients, but the procedure was reported as well tolerated in 64% of the PEUGIC endoscopies.

Photodocumentation of gastric retroflexion was found in 38% of the index endoscopies. Duodenal intubation was reported in 89% of the PEUGIC patients, but D2 photodocumentation was found in only 32.6%. No images were recorded in 34.8% of endoscopies, with only one recording that the endoscopy reporting system failed to capture images. The indications for the index endoscopy and endoscopic diagnoses differed between the PEUGIC and UGIC control groups (► **Table 1**).

Correlation between the attributable PEUGIC rate and endoscopist data

Technical endoscopic factors were identified in 52 PEUGIC patients (58.4%). It was not possible to calculate the mean annual endoscopy volume for one endoscopist, who was consequently excluded from further analyses. The technically attributable PEUGIC rate was calculated for 23 endoscopists. A negative cor-

► **Table 1** Patient demographic details and index endoscopy characteristics of the post-endoscopy upper gastrointestinal cancer (PEUGIC) and upper gastrointestinal cancer (UGIC) control groups.

Total	UGIC control (n = 1238)	PEUGIC (n = 89)	P value
Location, n (%)			<0.001
▪ Esophagus	750 (60.6)	74 (83.1)	
▪ Stomach	467 (37.7)	15 (16.9)	
▪ Duodenum	1 (0.1)	0	
▪ Unknown	20 (1.6)	0	
Sex, male, n (%)	839 (67.8)	54 (60.7)	0.16
Age at endoscopy, median (IQR), years	73 (65–80)	73.5 (63.5–81)	0.87
Indication for endoscopy, n (%)			<0.001
▪ Alarm symptoms	1017 (82.1)	40 (44.9)	
▪ Non alarm symptoms	117 (9.5)	22 (24.7)	
▪ Barrett's esophagus surveillance	14 (1.1)	24 (27.0)	
▪ Follow-up focal or cancer-associated lesion	34 (2.7)	2 (2.2)	
▪ Abnormal imaging	56 (4.5)	1 (1.1)	
Role of endoscopist, n (%)			0.39
▪ Gastroenterology consultant	659 (53.2)	46 (51.7)	
▪ Trainee gastroenterologist	174 (14.1)	12 (13.5)	
▪ Nurse endoscopist	265 (21.4)	16 (18.0)	
▪ Upper gastrointestinal surgeon	94 (7.6)	12 (13.5)	
▪ Others ¹	46 (3.7)	3 (3.4)	
Endoscopic diagnosis, n (%)			<0.001
▪ Normal	0 (0.0)	12 (13.5)	
▪ Suspected cancer	1057 (85.4)	2 (2.2) ^{†2}	
▪ Barrett's esophagus	19 (1.5)	36 (40.5)	
▪ Esophageal ulcer	24 (1.9)	5 (5.6)	
▪ Esophageal stricture	9 (0.7)	3 (3.4)	
▪ Reflux esophagitis	11 (0.9)	6 (6.7)	
▪ Gastric ulcer	68 (5.5)	0 (0.0)	
▪ Other benign findings	48 (3.9)	31 (34.8)	

¹ Others comprised consultant physicians other than gastroenterologists.

² Declined curative therapy.

relation was found between the mean annual number of UGI endoscopies performed by endoscopists and the technically attributable PEUGIC rate, with a correlation coefficient of -0.57 ($P=0.004$). Three endoscopists were identified as outliers, one with a technically attributable PEUGIC rate higher than 2SDs from the mean and two above 1SD from the mean (► **Fig. 2**). The mean annual number of UGI endoscopies performed by these three endoscopists was 206 (SD 20.6).

Root cause analysis of the most plausible explanation for PEUGIC

PEUGICs were classified as non-interval in 98% of patients: 48% ($n=42$) type I; 5% ($n=4$) type II; and 47% ($n=41$) type III. Only two PEUGICs were interval cancers, both of which occurred in patients with Barrett's esophagus.

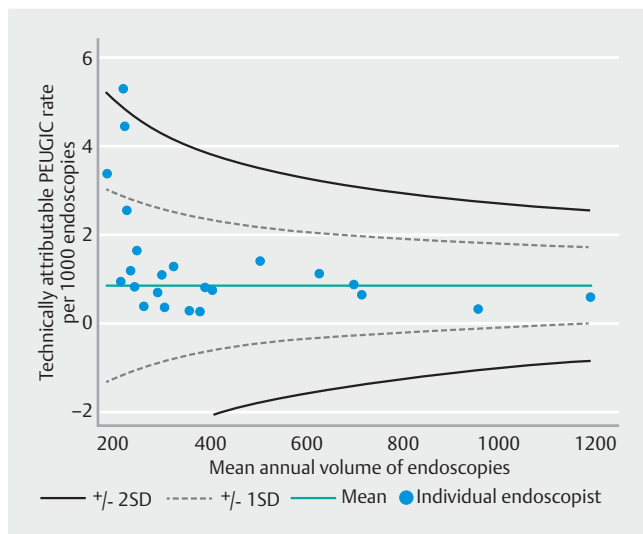
Premalignant lesions were identified in 39 patients (43.8%): 36 Barrett's esophagus, two gastric adenoma, and one gastric atrophy. Focal or cancer-associated lesions were identified in 12 patients (13.5%): four esophageal stricture, three abnormal

► **Table 2** Comparison of clinical staging and treatment received by all patients, with further stratification of the post-endoscopy upper gastrointestinal cancer (PEUGIC) patients by index endoscopy findings of Barrett's esophagus.

		All cancers				PEUGICs		
		Total, n (%)	UGIC control, n (%)	PEUGIC, n (%)	P value	Barrett's esophagus, n (%)	No Barrett's esophagus, n (%)	P value
Total		1327 (100)	1238 (100)	89 (100)		36 (100)	53 (100)	
Clinical stage at diagnosis								
Early	I	148 (11.2)	112 (9.0)	36 (40.5)	<0.001	29 (80.6)	7 (13.2)	<0.001
	II	179 (13.5)	164 (13.2)	15 (16.9)		3 (8.3)	12 (22.6)	
Advanced	III	401 (30.2)	390 (31.5)	11 (12.4)	0.260	1 (2.8)	10 (18.9)	0.141
	IV	450 (33.9)	429 (34.7)	21 (23.6)		3 (8.3)	18 (34.0)	
Not available		149 (11.2)	143 (11.6)	6 (6.7)		0 (0.0)	6 (11.3)	
Treatment								
Curative	Endoscopic resection	86 (6.5)	60 (4.8)	26 (29.2)	<0.001	20 (55.6)	6 (11.3)	<0.001
	Surgical resection	225 (17.0)	209 (16.9)	16 (18.0)		9 (25.0)	7 (13.2)	
	Chemo-radiotherapy	73 (5.5)	71 (5.7)	2 (2.2)		0 (0.0)	2 (3.8)	
Palliative therapy*		943 (71.1)	898 (72.5)	45 (50.6)		7 (19.4)	38 (71.7)	

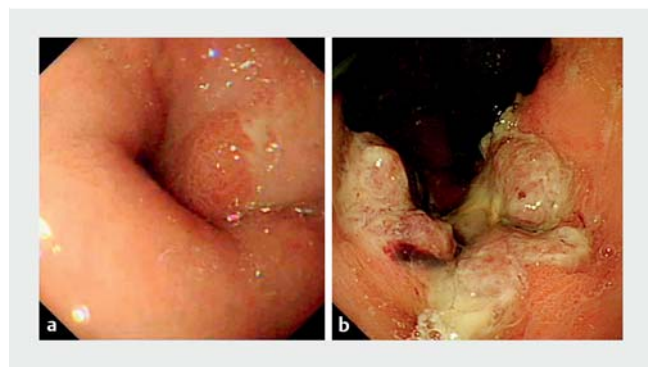
UGIC, upper gastrointestinal cancer.

* 657 patients had best supportive care only.



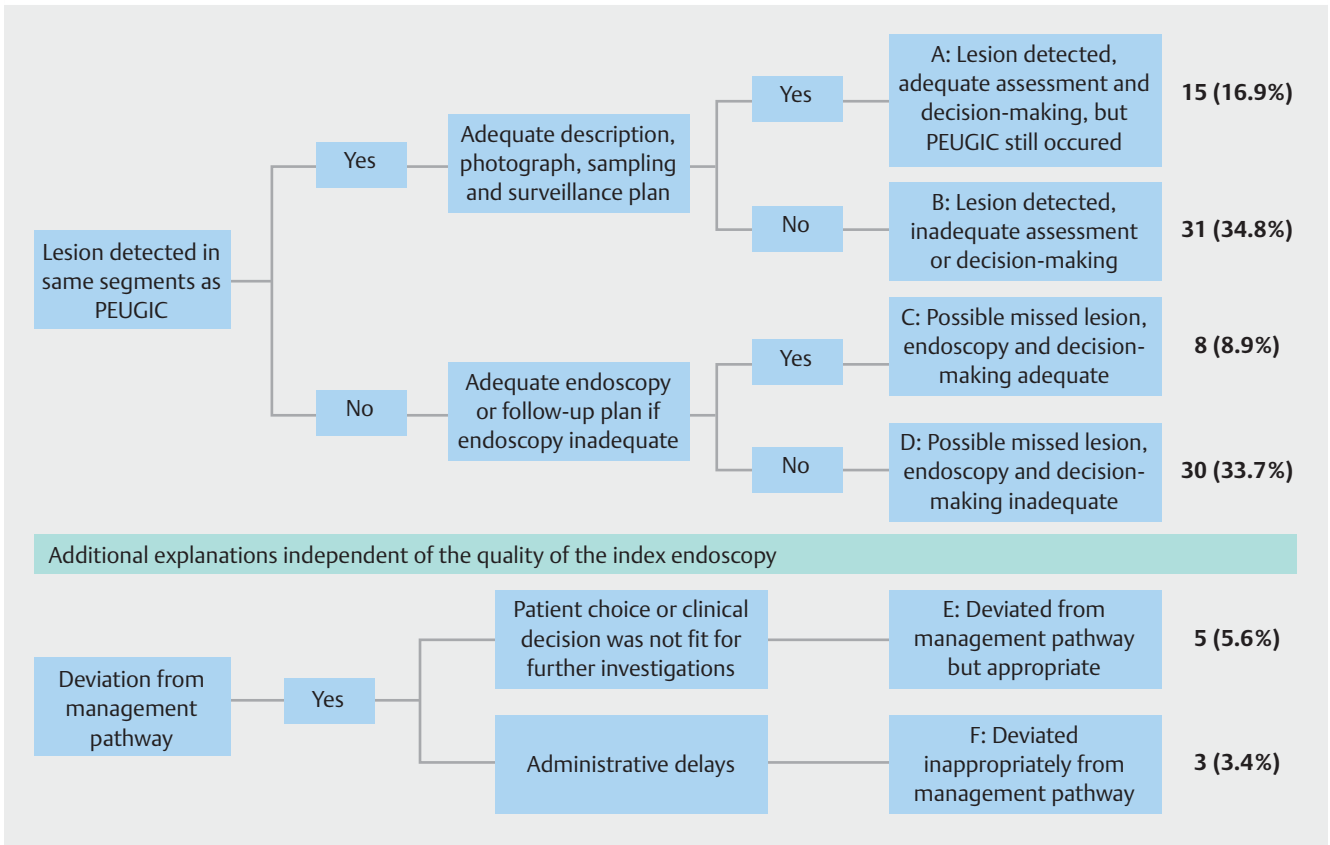
► **Fig. 2** Funnel plot showing the correlation between the annual number of endoscopies performed by individual endoscopists over the study period and the technically attributable post-endoscopy upper gastrointestinal cancer (PEUGIC) rate.

esophageal area, two esophageal ulcer, one severe esophagitis, one cardia inflammation, and one gastroesophageal junction nodule. No lesion was found in 38 patients (42.7%) (► **Fig. 3** shows PEUGIC examples).



► **Fig. 3** Endoscopic images of a patient with post-endoscopy upper gastrointestinal cancer showing: **a** in the lower esophagus of a patient with a history of chronic reflux, a small ulcer at the gastroesophageal junction that was not biopsied (no follow-up endoscopy was arranged); **b** after the patient had developed worsening dysphagia 31 months later, a large fungating adenocarcinoma (Siewert type II) at the gastroesophageal junction, which was found to be a stage 4 cancer with liver metastases, so the patient was referred for best supportive care.

The results of root cause analysis of the PEUGIC patients are shown in ► **Fig. 4** and ► **Table 3**. More than one plausible explanation was found in seven patients (7.9%): six had inadequate biopsies and an inadequate surveillance plan, and one had an inadequate surveillance plan and an administrative delay.



► **Fig. 4** Categorization of post-endoscopy upper gastrointestinal cancers (PEUGICs) based on the most plausible explanation. Lesions included premalignant (e.g. Barrett's esophagus, gastric atrophy, gastric intestinal metaplasia, or gastric adenoma) and focal or cancer-associated lesions (e.g. esophageal ulcer or stricture, Los Angeles grade C or D reflux esophagitis, or gastric ulcer).

Barrett's esophagus

Around 40% of PEUGICs were diagnosed in patients with Barrett's esophagus. The Prague criteria were used in 94% of patients and the Seattle biopsy protocol was followed in 42%. Planned surveillance intervals were incorrect in 25%. Among the PEUGICs in patients with Barrett's esophagus, 89% were diagnosed at an early stage (stage I or II) and 81% received treatment with curative intent (56% endoscopic resection and 25% surgery).

Of 38 non-Barrett's esophageal PEUGICs, 18 were squamous cell cancers and 20 were adenocarcinomas, including 17 that involved the gastroesophageal junction. Categories D (22/38) and B (12/38) were identified as the commonest most plausible explanations.

Avoidability

Of PEUGICs, 71% were categorized as potentially avoidable. The unavoidable PEUGICs included 21 small PEUGICs; there were also three related to patient's choice not to undergo further investigations and two where decisions were taken not to investigate further owing to multiple co-morbidities and patient frailty.

Impact on clinical outcome

The clinical outcome could potentially have been different for 45% of PEUGICs. This included 23 patients with advanced stage (stage III or IV) at diagnosis, 14 patients who underwent esophagectomy, and three patients who were too frail at the time of cancer diagnosis but could potentially have been offered endoscopic resection if their cancer had been detected at index endoscopy.

Discussion

This is the first study to report a detailed root cause analysis of unselected PEUGICs, develop a system of analysis to categorize the causes of PEUGIC, and identify contributing factors and missed opportunities to potentially avoid PEUGIC in 71% of patients. Inadequate assessment of premalignant or focal lesions, inadequate endoscopy quality, and poor decision-making around surveillance or follow-up plans were identified as the commonest explanations for PEUGIC. A negative correlation between the annual number of endoscopies performed by individual endoscopists and the technically attributable PEUGIC rate was noted.

► Table 3 Summary of the results of the root cause analysis of the most plausible explanation for the 89 post-endoscopy upper gastrointestinal cancers (PEUGICs).

Type 1	Premalignant lesion noted (e. g. Barrett's esophagus, gastric intestinal metaplasia or atrophy) in the same segment as the PEUGIC	39 (43.8%)
a	Biopsies adequate and, if Barrett's esophagus found, segment was adequately measured, and surveillance plan adequate and within correct timeframe, but PEUGIC still occurred	15 (16.9%)
b	Biopsies inadequate and/or Barrett's segment not measured	17 (19.1%)
c	Surveillance plan inadequate	11 (12.4%)
d	Surveillance not undertaken or not undertaken within the correct timeframe but appropriate owing to patient choice or co-morbidity	2 (2.2%)
e	Surveillance not undertaken or not within the correct timeframe and inappropriate	3 (3.4%)
Type 2	Focal or cancer-associated lesion noted in the same segment as the PEUGIC (e. g. esophageal ulcer or stricture, grade C or D reflux esophagitis, gastric ulcer)	12 (13.5%)
a	Site and morphology described and photographed, adequate biopsy sampling and follow-up undertaken in the correct timeframe but PEUGIC still occurred	0
b	Site or morphology not described or not photographed or biopsy sampling inadequate	7 (7.9%)
c	Follow-up plan inadequate	7 (7.9%)
d	Follow-up not undertaken or not undertaken within the correct timeframe but appropriate owing to patient choice or co-morbidity	3 (3.4%)
e	Follow-up not undertaken or not within correct timeframe and inappropriate	0
Type 3	No premalignant lesion/focal or cancer-associated lesion noted in the same segment as the PEUGIC	38 (42.7%)
a	Possible missed lesion but prior endoscopy adequate	8 (8.9%)
b	Possible missed lesion, with prior endoscopy not recognized by endoscopist as inadequate	28 (31.5%)
c	Possible missed lesion, with prior endoscopy recognized as inadequate but follow-up plan inadequate	3 (3.4%)
d	Possible missed lesion, with prior endoscopy recognized as inadequate and follow-up plan adequate, including no follow-up owing to patient choice or co-morbidity	0
More than one possible explanation was found in seven cases.		

The unadjusted PEUGIC rate was 6.7%, which was within the target of <10% proposed in a position statement on UK endoscopy quality standards [1]. However, both endoscopy providers are part of large conurbations and some patients may have been diagnosed with PEUGIC at different providers and would not have been captured in an analysis limited to local hospital records, meaning this is therefore likely to be an underestimate. Studying national datasets can circumvent this problem, as seen in the national UK PCCRC analysis [17], when 13% of PCCRCs were diagnosed in a different provider from the one that performed the index colonoscopy (personal communication from Drs. Roland Valori and Nicholas Burr).

Around 40% of PEUGICs occurred in patients with Barrett's esophagus. A systematic review has also described an esophageal cancer miss rate of 24% in Barrett's esophagus [18]; however, 89% of the PEUGICs in patients with Barrett's esophagus were diagnosed at an early stage and 81% were amenable to curative endoscopic or surgical resection. These results are supported by previous studies that have shown a positive impact of Barrett's surveillance on tumor staging and the survival of patients [19, 20]. Of the Barrett's PEUGICs, 56% were treated by endoscopic resection and can therefore be regarded as sur-

veillance successes; nine underwent surgical resection when earlier detection and endoscopic intervention might have avoided this outcome. The main reasons for PEUGIC included inadequate numbers of biopsies and inadequate surveillance plans. We would recommend that surveillance of Barrett's esophagus, and gastric intestinal metaplasia and atrophy should only be performed by endoscopists with adequate training, on dedicated lists with adequate time, and using optimal mucosal enhancement techniques [21–25].

Mucosal views were excellent or good in 47% of index endoscopies; however, there was no recommendation to repeat the endoscopy in the endoscopy reports where mucosal views were inadequate. We suggest endoscopies should be repeated if adequate views cannot be attained at index endoscopy despite mucosal cleansing with mucolytics and antifoaming agents [26, 27].

Photographs of D2 were recorded in 33% of index endoscopies among the PEUGIC patients and of retroflexion in 38%. National and international guidelines recommend photodocumentation of anatomical landmarks [1, 28–30] and the widespread availability of electronic image capture means there should be no excuse for not obtaining adequate endoscopic

images. Photodocumentation of cecal intubation and rectal retroflexion are established for colonoscopy to ensure examination completeness and the examination of high risk areas [31]. Similar efforts are needed for UGI endoscopy to ensure that high risk areas are adequately examined. Finally, an accurate description according to the established classification systems [32] is of critical importance to the ongoing management and follow-up of lesions, including correlation with histology.

We found a negative correlation between endoscopists' annual endoscopy number and the technically attributable PEUGIC rate. The BSG recommends that endoscopists should perform a minimum of 100 procedures each year to maintain proficiency [1]; however, in the current study, all of the endoscopists who had performed a PEUGIC endoscopy where an endoscopy-related contributing factor was identified had performed more than 100 annual endoscopies. This suggests that the annual endoscopy volume currently recommended may not be adequate, but it is important to emphasize that this assessment was based on the analysis of only a small number of endoscopists. These findings also highlight that further quality indicators are needed for endoscopy.

Although Barrett's esophagus was identified as the predominant premalignant condition in the current study, other premalignant conditions (e.g. gastric atrophy and intestinal metaplasia) may be more common in other regions. The root cause analysis system developed is however generalizable and will provide a framework to investigate PEUGIC in other settings.

The present study has a number of limitations. It was a retrospective study and although the most plausible explanations were identified, causality cannot be established. Clinical staging was not available for 11% of patients owing to the patient's choice not to have further investigations or because they had moved out of the catchment area.

Advanced imaging techniques and longer inspection times improve the diagnostic yield of endoscopy [22,25,33–35]; however, the recording of these parameters was not mandatory in the endoscopy reporting systems at the study providers. Owing to uncertainty around whether these techniques were used, they were not included in the proposed criteria for an adequate endoscopy examination. We would suggest that these important measures should be included in future PEUGIC studies. The impact of patient tolerance and sedation could not be assessed, but this clearly merits further study as a contributing factor to PEUGIC.

It is possible that some of the endoscopists had performed endoscopies outside of their national health service (NHS) provider and it was not possible to capture data on these endoscopies. This could potentially bias the results of the correlation between annual endoscopy number and technically attributable PEUGIC rate.

Evaluation of only the index endoscopy, as recommended by the WEO for PCCRC, has the potential limitation of missing important information on a small number of patients in whom a premalignant, focal, or cancer-associated lesion in the same segment as the PEUGIC was detected at a prior endoscopy (before the index endoscopy), with the lesion not being seen or recognized at the index endoscopy. Future studies should consid-

er examining all endoscopies prior to a cancer diagnosis, to identify if there is any additional benefit to reviewing all endoscopies within the 3 years prior to diagnosis. Finally, this study included two NHS providers in the UK, and the study findings and root cause analysis system should be validated in future studies in other parts of the world.

In conclusion, in a retrospective analysis of PEUGIC, the most common plausible explanations were inadequate assessment or decision-making concerning premalignant, focal, or cancer-associated lesions, and possible missed lesions in the context of an inadequate endoscopy or decision-making following endoscopy. A systematic approach using the root cause analysis framework developed can differentiate the technical endoscopic, decision-making, and administrative factors that can lead to missing UGICs at both endoscopist and institutional level, and guide quality improvement efforts to reduce the PEUGIC rate.

Acknowledgments

We gratefully acknowledge the advice of Dr. Roland Valori and Professor Pradeep Bhandari in the development of the PEUGIC root cause analysis system. We are also grateful for the help in data collection provided by Drs. Malik Magrabi, Sarah Faloon, Mohammed Dhanji, Rahman Hameed, Mohammed Abdul, and Mohit Inani.

Competing interests

The authors declare that they have no conflict of interest.

References

- [1] Beg S, Ragunath K, Wyman A et al. Quality standards in upper gastrointestinal endoscopy: a position statement of the British Society of Gastroenterology (BSG) and Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS). *Gut* 2017; 66: 1886–1899
- [2] Menon S, Trudgill N. How commonly is upper gastrointestinal cancer missed at endoscopy? A meta-analysis *Endosc Int Open* 2014; 2: E46–E50
- [3] Chadwick G, Groene O, Hoare J et al. A population-based, retrospective, cohort study of esophageal cancer missed at endoscopy. *Endoscopy* 2014; 46: 553–560
- [4] Chadwick G, Groene O, Riley S et al. Gastric cancers missed during endoscopy in England. *Clin Gastroenterol Hepatol* 2015; 13: 1264–1270
- [5] Pimenta-Melo AR, Monteiro-Soares M, Libânio D et al. Missing rate for gastric cancer during upper gastrointestinal endoscopy: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol* 2016; 28: 1041–1049
- [6] Cheung D, Menon S, Hoare J et al. Factors associated with upper gastrointestinal cancer occurrence after endoscopy that did not diagnose cancer. *Dig Dis Sci* 2016; 61: 2674–2684
- [7] Alexandre L, Tsilegeridis-Legeris T, Lam S. Clinical and endoscopic characteristics associated with post-endoscopy upper gastrointestinal cancers: a systematic review and meta-analysis. *Gastroenterology* 2022; 162: 1123–1135

- [8] Vradelis S, Maynard N, Warren BF et al. Quality control in upper gastrointestinal endoscopy: detection rates of gastric cancer in Oxford 2005–2008. *Postgrad Med J* 2011; 87: 335–339
- [9] Raftopoulos SC, Segarajasingam DS, Burke V et al. A cohort study of missed and new cancers after esophagogastroduodenoscopy. *Am J Gastroenterol* 2010; 105: 1292–1297
- [10] Rabeneck L, Paszat LF. Circumstances in which colonoscopy misses cancer. *Frontline Gastroenterol* 2010; 1: 52–58
- [11] Rutter MD, Beintaris I, Valori R et al. World Endoscopy Organization consensus statements on post-colonoscopy and post-imaging colorectal cancer. *Gastroenterology* 2018; 155: 909–925
- [12] Anderson R, Burr NE, Valori R. Causes of post-colonoscopy colorectal cancers based on World Endoscopy Organization system of analysis. *Gastroenterology* 2020; 158: 1287–1299
- [13] Fitzgerald RC, di Pietro M, Ragunath K et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's esophagus. *Gut* 2014; 63: 7–42
- [14] Sharma P, Dent J, Armstrong D et al. The development and validation of an endoscopic grading system for Barrett's esophagus: the Prague C & M Criteria. *Gastroenterology* 2006; 131: 1392–1399
- [15] Levine DS, Haggitt RC, Blount PL et al. An endoscopic biopsy protocol can differentiate high-grade dysplasia from early adenocarcinoma in Barrett's esophagus. *Gastroenterology* 1993; 105: 40–50
- [16] Banks M, Graham D, Jansen M et al. British Society of Gastroenterology guidelines on the diagnosis and management of patients at risk of gastric adenocarcinoma. *Gut* 2019; 68: 1545–1575
- [17] Burr NE, Derbyshire E, Taylor J et al. Variation in post-colonoscopy colorectal cancer across colonoscopy providers in English National Health Service: population based cohort study. *BMJ* 2019; 367: l6090
- [18] Visrodia K, Singh S, Krishnamoorthi R et al. Magnitude of missed esophageal adenocarcinoma after Barrett's esophagus diagnosis: a systematic review and meta-analysis. *Gastroenterology* 2016; 150: 599–607
- [19] Kastelein F, van Olphen SH, Steyerberg EW et al. Impact of surveillance for Barrett's oesophagus on tumour stage and survival of patients with neoplastic progression. *Gut* 2016; 65: 548–554
- [20] Quera R, O'Sullivan K, Quigley EM. Surveillance in Barrett's oesophagus: will a strategy focused on a high-risk group reduce mortality from oesophageal adenocarcinoma? *Endoscopy* 2006; 38: 162–169
- [21] Ooi J, Wilson P, Walker G et al. Dedicated Barrett's surveillance sessions managed by trained endoscopists improve dysplasia detection rate. *Endoscopy* 2017; 49: 524–528
- [22] Gupta N, Gaddam S, Wani SB et al. Longer inspection time is associated with increased detection of high-grade dysplasia and esophageal adenocarcinoma in Barrett's esophagus. *Gastrointest Endosc* 2012; 76: 531–538
- [23] Park JM, Huo SM, Lee HH et al. Longer observation time increases proportion of neoplasms detected by esophagogastroduodenoscopy. *Gastroenterology* 2017; 153: 460–469
- [24] Qumseya BJ, Wang H, Badie N et al. Advanced imaging technologies increase detection of dysplasia and neoplasia in patients with Barrett's esophagus: a meta-analysis and systematic review. *Clin Gastroenterol Hepatol* 2013; 11: 1562–1570
- [25] Coletta M, Sami SS, Nachiappan A et al. Acetic acid chromoendoscopy for the diagnosis of early neoplasia and specialized intestinal metaplasia in Barrett's esophagus: a meta-analysis. *Gastrointest Endosc* 2016; 83: 57–67
- [26] Neale JR, James S, Callaghan J et al. Premedication with N-acetylcysteine and simethicone improves mucosal visualization during gastroscopy: a randomized, controlled, endoscopist-blinded study. *Eur J Gastroenterol Hepatol* 2013; 25: 778–783
- [27] Li Y, Du F, Fu D. The effect of using simethicone with or without N-acetylcysteine before gastroscopy: A meta-analysis and systemic review. *Saudi J Gastroenterol* 2019; 25: 218
- [28] Rey JF, Lambert R. ESGE Quality Assurance Committee. ESGE recommendations for quality control in gastrointestinal endoscopy: guidelines for image documentation in upper and lower GI endoscopy. *Endoscopy* 2001; 33: 901–903
- [29] Bisschops R, Areia M, Coron E et al. Performance measures for upper gastrointestinal endoscopy: a European Society of Gastrointestinal Endoscopy (ESGE) Quality Improvement Initiative. *Endoscopy* 2016; 48: 843–864
- [30] Chiu PWY, Uedo N, Singh R et al. An Asian consensus on standards of diagnostic upper endoscopy for neoplasia. *Gut* 2019; 68: 186–197
- [31] Rees CJ, Thomas Gibson S, Rutter MD et al. UK key performance indicators and quality assurance standards for colonoscopy. *Gut* 2016; 65: 1923–1929
- [32] Participants in the Paris Workshop. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc* 2003; 58: S3–S43
- [33] Hajelssedig OE, Pu LZC, Thompson JY et al. Diagnostic accuracy of narrow-band imaging endoscopy with targeted biopsies compared with standard endoscopy with random biopsies in patients with Barrett's esophagus: A systematic review and meta-analysis. *J Gastroenterol Hepatol* 2021; 36: 2659–2671
- [34] Rodríguez-Carrasco M, Esposito G, Libânio D et al. Image-enhanced endoscopy for gastric preneoplastic conditions and neoplastic lesions: a systematic review and meta-analysis. *Endoscopy* 2020; 52: 1048–1065
- [35] Teh JL, Tan JR, Lau LJF et al. Longer examination time improves detection of gastric cancer during diagnostic upper gastrointestinal endoscopy. *Clin Gastroenterol Hepatol* 2015; 13: 480–487