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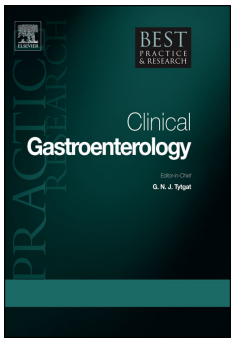

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Post-Endoscopy Upper Gastrointestinal Cancer: Emerging Data and Opportunities to improve Early Detection

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Practice points

- Post-endoscopy upper gastrointestinal cancer (PEUGIC) accounts for ~ 11% of upper GI malignancies nationally
- PEUGIC represent missed opportunities for prevention and early detection
- Avoidable delays in diagnosis are common
- Sub-optimal assessment and management of premalignant upper GI disease and cancer-related lesions, and administrative delays are contributory
- A focus on endoscopy quality improvement and decision-making is key to prevention of PEUGIC
- Endoscopy units should audit PEUGIC rates routinely and undertake root cause analysis

Research agenda

- Influence of endoscopy quality metrics on PEUGIC occurrence need to be evaluated
- Interventions to prevent PEUGIC need to be developed and evaluated
- Further research is needed to establish mechanisms underpinning differences in PEUGIC rates (by sex, morbidity and deprivation)

Abstract

The overall prognosis of upper gastrointestinal cancers remains very poor. Early diagnosis is key to avoid morbidity and improve long-term survival. While gastroscopy is the gold standard diagnostic test, premalignant or malignant abnormalities may be overlooked or subject to sub-optimal management, leading to delayed diagnosis and patient harm. Patients with persistent symptoms after a “cancer-negative” gastroscopy may be given false reassurance. Upper gastrointestinal malignancies diagnosed within three years of a “cancer-negative”, index gastroscopy are defined as post-endoscopy upper gastrointestinal cancers (PEUGIC). They are surprisingly common, accounting for 11% of upper gastrointestinal malignancies internationally. Abnormalities in the endoscopy preceding diagnosis are very common, and include premalignant findings and cancer-related lesions. Root cause analysis suggests deficiencies in endoscopy quality, decision-making and administration. This suggests avoidable PEUGIC cases, and crucially, an opportunity to improve endoscopy quality and outcomes. This narrative review summarises the epidemiology, presentation, contexts and root causes of PEUGIC and makes recommendations for clinical practice and research.

Keywords

PEUGIC; quality; premalignant lesions; decision-making

Introduction

In the UK per annum there are 15700 incident cases of oesophago-gastric (OG) cancer with 12300 related-deaths(1, 2). OG cancer collectively is the third highest cause of cancer-related mortality annually (behind lung and colorectal cancer) in the UK, accounting for 7.4% of all cancer-related deaths(1, 2). Unfortunately, most patients are diagnosed with advanced disease and as a result overall survival is poor: <17% survive to 10 years(3). Early diagnosis, before local and regional spread, permits treatments which are often better tolerated and less invasive with better long-term survival, however only 5.5% are currently diagnosed with T0/1 disease(4). Patients diagnosed at the earliest stage may undergo endoscopic resection, low-risk organ-preserving procedures with excellent long-term outcomes(5). Patients with localised invasive disease may be offered surgery with curative intent, with or without perioperative chemo/radiotherapy(6). However, surgery is associated with substantial morbidity and impaired long-term quality of life, and patients remain at high risk of recurrent cancer and death(6-8). Unfortunately, the majority(63%) diagnosed with OG cancer are managed on a non-curative pathway with palliative oncological therapy or best supportive care, focussing on symptom management and end-of-life care(6).

Gastroscopy is the gold standard diagnostic test for premalignant and malignant upper gastrointestinal disease, permitting direct visualisation, photo (and video) documentation, tissue acquisition and therapeutic intervention(9). Gastroscopy also has the potential to prevent malignancy by diagnosing and treating premalignant lesions. However, while it is the current gold standard for OG cancer, gastroscopy does not have perfect diagnostic accuracy and not all OG cancers are initially detected. Malignancy diagnosed within three years after an index “cancer-negative” gastroscopy are broadly defined as post-endoscopy upper gastrointestinal cancers (PEUGIC)(9, 10). On average, one cancer is diagnosed for every 56 gastroscopies performed(11). However, for every 400 “cancer-negative” tests performed, one will fail to detect an upper gastrointestinal cancer(12, 13). Assuming detectable disease at index endoscopy, the mean delay in diagnosis is 17 months (SD 8.5)(14-16). For avoidable PEUGIC, this is very likely to be clinically

significant: a modelling study has estimated even a three-month delay in definitive treatment for OG cancer leads to an absolute reduction in 10-year survival in those aged 30-60 years by 16%(17). The implications of failing to detect upper GI cancer are potentially serious: delayed diagnosis of aggressive epithelial malignancy limits treatment options and prognosis; and there are likely associated healthcare cost implications(17).

An understanding of the epidemiology and root causes of PEUGIC represents an opportunity to prevent PEUGIC and facilitate early detection to improve patient outcomes. This narrative review summarises the definition(s), epidemiology, presentation, contexts and root causes of PEUGIC and makes preliminary recommendations for clinical practice.

Definitions

Published definitions of PEUGIC vary in the literature, but broadly refer to any epithelial upper GI malignancy (adenocarcinoma or squamous cell carcinoma) within the reach of a gastroscope (oesophageal, gastric and duodenal [to D2]) diagnosed within three years of an index (non-diagnostic, “cancer-negative”) gastroscopy(9, 10). The definition is time-based and usually refers to malignancy diagnosed between 6 and 36 months after the index procedure(18, 19). As such, PEUGIC is an operational term and does not ascribe blame - not all PEUGICs are the result of undetected lesions or shortcomings in clinical decision making or administrative delays, and therefore, describing all PEUGIC as “missed” cancers is inaccurate.

A detailed rationale for a 36-month upper time limit to define PEUGIC is lacking in the published literature, however is consistent with the World Endoscopy Organisation (WEO) definition of Post-Colonoscopy Colorectal cancer (PCCRC) used for benchmarking services(20), (a definition which accounts for sample size considerations, a need to reflect contemporaneous practice and colorectal cancer biology) and the post-endoscopy esophageal neoplasia expert consensus (reflecting clinical

pragmatism as 3 years rather than 5 years is the most commonly selected surveillance interval for non-dysplastic Barrett's oesophagus)(10). While upper GI epithelial malignancies overall have a poor prognosis, they are a heterogenous group with differing tumour biology. One tacit assumption underlying the 36-month upper limit for PEUGIC is that it encompasses the mean sojourn time (in this context, the time period from asymptomatic endoscopically detectable malignancy to symptomatic diagnosis), for which evidence is lacking for oesophageal cancer, and limited in gastric cancer (~ 2 years)(21, 22). The threshold for somatic genome alterations which herald malignancy may occur at different rates: including slow accumulation in those who do not progress, and at the other extreme end of the spectrum, catastrophic somatic genome alterations, such as chromothripsis (chromosome shattering), which is well described in Barrett's carcinogenesis(23), leading to rapid malignant progression, potentially accounting for PEUGIC in some cases (we speculate the minority).

Similarly to WEO PCCRC definition, a 6-month grace period following the index gastroscopy is often applied, such that cancer diagnosed within 0 to 6 months are classified as detected rather than PEUGIC. In the context of UGI malignancy this distinction may enable more complex cases to be classified in the detected group, for example, Barrett's high-grade dysplasia at index procedure upstaged to adenocarcinoma following endoscopic resection, or gastric ulcer with initially benign histology at index procedure with adenocarcinoma demonstrated on further evaluation 6 weeks later. The UK national PEUGIC root cause analysis (RCA) project team revised the grace period to 3 months(24) given early experience indicating important lessons from avoidable PEUGIC cases diagnosed between 3-6 months. Similarly, to the WEO PCCRC definition, the PEUGIC definition is arbitrary and likely imperfect, however it has the major benefit of enabling a standardised approach to classification benefitting service evaluation and research efforts(20).

Once defined, PEUGIC can be further categorised into interval and non-interval cancers(19, 20). Interval cancers include cases identified before the next planned surveillance endoscopy. Non-interval cancers are subcategorised into those identified at (type 1) or after (type 2) planned surveillance endoscopy, or when no further follow-up was arranged (type 3).

Related terms to PEUGIC in the literature include site specific terms – PEEC ("post endoscopy esophageal cancer") or oesophageal PEUGIC, PEGC ("post endoscopy gastric cancer") or gastric PEUGIC, and specific to the context of Barrett's oesophagus – PEEN ("post endoscopy esophageal neoplasia") or PEBN ("post endoscopy Barrett's neoplasia"), both defined as Barrett's high-grade dysplasia / adenocarcinoma within 6 to 36 months of the negative index procedure(14, 25, 26).

Epidemiology

PEUGIC are surprisingly common internationally, accounting for 10.7% (95% confidence interval [CI] 8.0 to 13.7%; 23 studies) of all upper GI cancers(14, 27-51). There is marked variation in these proportions globally (I^2 = 99%), with heterogeneity explained by differences in PEUGIC definition (lowest rates observed with shortest time frame), PEUGIC site (7% for oesophageal and 11.9% for gastric PEUGIC), and gastroscopy indication (highest rates observed in surveillance or screening populations rather than unselected diagnostic procedures)(14). In the international literature, there are no significant differences in age at diagnosis (mean difference -0.16, 95% CI -1.50 to 1.19 years; 8 studies) between PEUGIC and initially detected upper GI cancers. In Western populations women were more likely to be diagnosed with PEUGIC than detected UGI cancers compared to men (OR 1.30, 95% CI 1.16 to 1.45; 13 studies). There are no significant differences between ethnicity and PEUGIC.

From an English perspective, while the PCCRC rate has improved over time (from 9% in 2005 to 6.5% in 2013, p <0.01)(52), PEUGIC rates have not and appear to have risen slightly (from 8.4% in

2009 to 8.9% in 2018, p = 0.03)(18). A population-based study demonstrated marked variation in the adjusted PEUGIC rate (between 3.8% to 14.7%) in 129 English endoscopy providers between 2014 to 2018(18). Such unwarranted variation strongly suggests avoidable PEUGIC and an opportunity to improve endoscopy quality and patient outcomes. Among the English population diagnosed with OG cancer (98801 cancers of which 9078 were PEUGIC), the main demographic risk factors for PEUGIC were younger age (age < 60 vs over 80, OR 1.92; 95% CI 1.79 to 2.08), female sex (OR 1.29; 95% CI 1.23 to 1.46), lower deprivation (index of multiple deprivation quintile 1 [least deprived] vs 5 [most deprived] OR 1.16; 95% CI 1.08 to 1.25) and higher co-morbidity burden (Charlson comorbidity index ≥ 5 vs 0, OR 5.06; 95% 4.45 to 5.76)(18). The mechanisms underpinning these associations are unclear, but may reflect differences in symptomatic presentation and the endoscopist's assumed pretest probability of GI malignancy, differential use of sedation, differential procedure tolerance, and shared risk factor profiles between comorbidities and malignant disease (e.g. alcohol and smoking with oesophageal squamous cell carcinoma).

Presentation

Symptom profiles of patients with PEUGIC and initially detected upper GI cancers differ. Compared to initially detected cancers, patients with PEUGIC less commonly present with alarm symptoms (OR 0.46, 95% CI 0.28 to 0.78), in particular dysphagia (OR 0.37, 95% CI 0.19 to 0.73) and weight loss (OR 0.58, 95% CI 0.35 to 0.97) and are more likely to present with reflux (OR 2.64, 95% CI 2.25 to 3.10)(14). Gastric PEUGIC are less commonly associated with anaemia (OR 0.29, 95% CI 0.18 to 0.49). On average, PEUGICs when diagnosed are significantly smaller when measured endoscopically compared with initially detected cancers, and were diagnosed at an earlier cancer stage(32, 37, 43, 46). These observations are all consistent – smaller, more subtle lesions (if present at the index procedure), may be more easily overlooked or subject to sampling error, and less likely to present with alarm symptoms and advanced disease. Assumed low expectation for malignancy in patients presenting with lower risk symptoms, in a wider UK context of low yield diagnostic gastroscopy(53), may impair cancer detection. The prevalence of individual endoscopic findings at

the initial “cancer-negative” endoscopy preceding diagnosis of PEUGIC are common. Abnormalities were reported in 76% and 83% with gastric and oesophageal PEUGIC, respectively(14). The most common premalignant findings in the index procedure preceding diagnosis of PEUGIC are Barrett’s oesophagus (28.5%) and gastric atrophy (1.9%); and the most common cancer-related lesions were oesophageal ulcer (31.3%), oesophageal stricture (16.5%) and gastric ulcer (15.5%)(18). PEUGIC which arise in the same segment as these listed abnormalities, implies avoidable cases and learning opportunities to improve practice.

PEUGIC in the context of Barrett’s oesophagus is important. Forty percent of PEUGIC arise in patients with Barrett’s oesophagus(19). A recent systematic review demonstrated 90.7% of Barrett’s high-grade dysplasia / adenocarcinoma is detected at or within 6 months of diagnosis of Barrett’s oesophagus, 2.5% is diagnosed within 6 to 36 months (PEEN/PEBN) and 6.8% is incident neoplasia, diagnosed after 36 months(26). Compared to non-dysplastic Barrett’s oesophagus at index procedure, confirmed low grade dysplasia is a risk factor for PEEN/PEBN (OR 13.2, 95% CI 2.6 to 66.7)(14, 34). Preliminary results of PROSPERO, a prospective multicentre study of protocolised diagnostic gastroscopy with mandated 10-picture standard photodocumentation and standardised biopsy protocol of the oesophagus and stomach demonstrated only a quarter of cases with gastric atrophy / intestinal metaplasia are suspected endoscopically, suggesting an unrecognised burden of the premalignant stomach(54).

Root cause analysis

The British Society of Gastroenterology (BSG) and Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS) recommends that endoscopy units audit their PEUGIC rates and undertake a root cause analysis of contributing factors(9). Exploring the plausible explanations for the occurrence of PCCRC informed the quality improvement initiatives to reduce their incidence(52, 55) Based on the WEO PCRCC classification(20), Kamran *et al.* developed a PEUGIC root cause analysis system to categorizes PEUGICs into 6 groups based on the most

plausible explanation (see table 1)(19). Categories B, D and F are considered definitely avoidable, and categories A and C are considered possibly avoidable and category E, unavoidable. This system has been applied to determine the aetiology of PEUGIC in two NHS trusts in 89 PEUGIC cases(19). Seventy percent of PEUGICs were considered potentially avoidable. In 45% the delay in diagnosis was felt to have adversely impacted the patient's outcome. Fifty two percent arose in patients with a detected abnormality (focal or cancer-associated lesion or premalignant condition) either with (17%) or without (35%) adequate assessment and decision-making. In those without detected abnormalities (43%), PEUGIC arose as a possible missed lesion either with (9%) or without (34%) adequate assessment or decision-making. Following this work, the UK national PEUGIC RCA audit, a landmark project to improve understanding of the causes of PEUGIC at a national level to inform preventive strategy, led by Professor Nigel Trudgill, has been launched in 144 NHS hospitals, with data collection now completed(56). While the final report is eagerly awaited, important lessons for endoscopists and endoscopy units are emerging(57).

Implications for clinical practice

In the UK, most NHS endoscopy services achieve accreditation from the Joint Advisory Group on Gastrointestinal Endoscopy (JAG)(58). This involves annual evaluation of clinical services against standards and engagement in continuous quality improvement. JAG also oversees the governance and quality assurance of all gastrointestinal endoscopy training and accreditation of endoscopists for independent practice(59). The impact of the BSG and JAG initiatives in improving endoscopy quality is well documented and likely accounts for the lower observed rates of post-colonoscopy colorectal cancer (PCCRC) in England over time and compared to other countries(52, 59, 60). Such initiatives are underpinned by high impact observational research(52, 61-64) and root cause analysis(55, 65). Given high national PEUGIC rates, quality improvement in diagnostic gastroscopy is now a major priority of the BSG and JAG, and key lessons from the national PEUGIC RCA project will almost certainly influence quality improvement recommendations(9).

Emerging evidence from the epidemiology of PEUGIC and RCA suggest key lessons for practicing endoscopists and endoscopy service providers (see Table 2). A wider psychological shift among endoscopists may be needed – moving away from an expectation of normality to one of heightened vigilance and professional curiosity – concern for and awareness of PEUGIC generally and improved anticipation for detecting subtle mucosal abnormalities (even if the pretest probability would ordinarily be perceived to be low – younger/female patients/presenting with reflux remain at risk). Other specific recommendations include the importance of ensuring excellent mucosal visualisation (including assessment of vascular pattern) and taking sufficient time to achieve this (thorough mucosal cleaning to clear residue, mucus, and bubbles using suction, washing with water, Simethicone or N-Acetyl Cysteine, and near views of the mucosa to sufficiently assess mucosal detail); meticulous photo-documentation; routine use of image enhancement (e.g. narrow band imaging in the oesophagus and stomach); upskilling in lesion recognition (particularly squamous dysplasia, early squamous cell carcinoma, Barrett's neoplasia, the premalignant stomach and early gastric adenocarcinoma), classification and delineation; optimising patient tolerance through sufficient sedation; generous biopsies from cancer-related lesions (oesophageal strictures or oesophageal or gastric ulcers); strict endoscopic follow-up of oesophageal / gastric ulcers and grade C or D oesophagitis (initiated by endoscopist and supported with robust administrative provision); a very low threshold for repeat a procedure if inadequate views were obtained (e.g. due to poor tolerance or significant residue that cannot be cleaned) or if clinical concerns persist despite negative biopsies (e.g. oesophageal stricture or abnormal gastric mucosa potentially heralding linitis plastica). Confirmed Barrett's low-grade dysplasia can herald more advanced oesophageal neoplasia(34), which would support early repeat gastroscopy (e.g. within 8 weeks) in this group with a Barrett's specialist.

At a service level, improved triage for UK endoscopy services is required to optimally allocate limited endoscopic resource to patients with the highest pretest probability of important pathology (such as premalignant and malignant disease), replacing the current widespread practice of low

yield (and defensive) gastroscopy(53, 66). Gastroscopy lists more enriched with pathology could, in turn, support more vigilant practice amongst endoscopists (diminishing an expectation of normality) and reducing the number of procedures per list would permit longer examination times(9, 67), and allow endoscopists to focus on quality rather than throughput. Dedicated surveillance lists have been shown to improve dysplasia detection in the context of Barrett's oesophagus(68, 69) and given that oesophageal PEUGIC arise in the context of Barrett's surveillance, more widespread adoption will likely be needed. However, given the burden of oesophageal neoplasia following diagnosis of Barrett's oesophagus sits outside of Barrett's surveillance (90% of high-grade dysplasia / adenocarcinoma are diagnosed within 6 months(26), wider upskilling of the endoscopic workforce is a priority. The occurrence of PEUGIC is arguably the most important performance indicator of gastroscopy quality. As part of the JAG accreditation scheme, endoscopy units are now expected to detect PEUGIC, undertake RCA and provide feedback to endoscopists where PEUGIC has occurred.

Conclusion

Delays in diagnosis of upper gastrointestinal malignancy lead to stage migration and missed opportunities for less morbid and/or curative treatment, and may lead to premature death. PEUGIC are common, most are avoidable and often result in delays in treatment and worse outcomes. Lessons from the epidemiology and root causes of PEUGIC represent an ongoing opportunity to improve practice at the individual and service level, to improve gastroscopy quality and prevent PEUGIC.

Table captions

Table 1: Categorisation of post-endoscopy upper gastrointestinal cancers (PEUGIC) based on the most plausible explanation (Adapted from Kamran et al(19). Lesions referred to include focal or cancer-associated lesions (e.g. oesophageal ulcer or stricture, reflux oesophagitis [Grade C or D], gastric ulcer) or premalignant lesions (e.g. Barrett's oesophagus, gastric atrophy or intestinal metaplasia)

Table 2: Endoscopist and service-level practice recommendations to prevent PEUGIC.

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Reference list

1. Stomach cancer statistics [Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/stomach-cancer.
2. Oesophageal cancer statistics [Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oesophageal-cancer.
3. Cromwell D, Wahedally H, Chadwick G, Park M, Maynard N, Crosby T, et al. National Oesophago-Gastric Cancer Audit. 2019.
4. Pucher PH, Park MH, Cromwell DA, Crosby TC, Thomas B, Trudgill N, et al. Diagnosis and treatment for gastro-oesophageal cancer in England and Wales: analysis of the National Oesophago-Gastric Cancer Audit (NOGCA) database 2012-2020. Br J Surg. 2023.
5. van Munster S, Nieuwenhuis E, Weusten B, Alvarez Herrero L, Bogte A, Alkhalaf A, et al. Long-term outcomes after endoscopic treatment for Barrett's neoplasia with radiofrequency ablation +/- endoscopic resection: results from the national Dutch database in a 10-year period. Gut. 2022;71(2):265-76.
6. Park M, Wahedally M, Maynard N, Crosby T, Thomas B, Trudgill N, et al. National Oesophago-Gastric Cancer Audit. 2022 Annual Report.: The Royal College of Surgeons of England; 2022 12 January 2023.
7. Muller-Stich BP, Probst P, Nienhuser H, Fazeli S, Senft J, Kalkum E, et al. Meta-analysis of randomized controlled trials and individual patient data comparing minimally invasive with open oesophagectomy for cancer. The British journal of surgery. 2021;108(9):1026-33.
8. Sunde B, Klevebro F, Johar A, Johnsen G, Jacobsen AB, Glenjen NI, et al. Health-related quality of life in a randomized trial of neoadjuvant chemotherapy or chemoradiotherapy plus surgery in patients with oesophageal cancer (NeoRes trial). The British journal of surgery. 2019;106(11):1452-63.
9. Beg S, Ragunath K, Wyman A, Banks M, Trudgill N, Pritchard DM, 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(11):1886-99.
10. Wani S, Yadlapati R, Singh S, Sawas T, Katzka DA, Post-Endoscopy Esophageal Neoplasia Expert Consensus P. Post-endoscopy Esophageal Neoplasia in Barrett's Esophagus: Consensus Statements From an International Expert Panel. Gastroenterology. 2022;162(2):366-72.
11. Rutter MD, Brookes M, Lee TJ, Rogers P, Sharp L. Impact of the COVID-19 pandemic on UK endoscopic activity and cancer detection: a National Endoscopy Database Analysis. Gut. 2021;70(3):537-43.
12. Ho KMA, Banerjee A, Lawler M, Rutter MD, Lovat LB. Predicting endoscopic activity recovery in England after COVID-19: a national analysis. Lancet Gastroenterol Hepatol. 2021;6(5):381-90.
13. Menon S, Trudgill N. How commonly is upper gastrointestinal cancer missed at endoscopy? A meta-analysis. Endosc Int Open. 2014;2(2):E46-50.
14. 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(4):1123-35.
15. Beck M, Bringeland EA, Qvigstad G, Fossmark R. Gastric Cancers Missed at Upper Endoscopy in Central Norway 2007 to 2016-A Population-Based Study. Cancers (Basel). 2021;13(22).
16. Januszewicz W, Witczak K, Wieszczy P, Socha M, Turkot MH, Wojciechowska U, et al. Prevalence and risk factors of upper gastrointestinal cancers missed during endoscopy: a nationwide registry-based study. Endoscopy. 2022;54(7):653-60.

17. Sud A, Torr B, Jones ME, Broggio J, Scott S, Loveday C, et al. Effect of delays in the 2-week-wait cancer referral pathway during the COVID-19 pandemic on cancer survival in the UK: a modelling study. Lancet Oncol. 2020;21(8):1035-44.
18. Kamran U, Evison F, Morris EJA, Brookes MJ, Rutter MD, McCord M, et al. The variation in post-endoscopy upper gastrointestinal cancer rates among endoscopy providers in England and associated factors: a population-based study. Endoscopy. 2025;57(1):17-28.
19. Kamran U, King D, Abbasi A, Coupland B, Umar N, Chapman WC, et al. A root cause analysis system to establish the most plausible explanation for post-endoscopy upper gastrointestinal cancer. Endoscopy. 2023;55(2):109-18.
20. Rutter MD, Beintaris I, Valori R, Chiu HM, Corley DA, Cuatrecasas M, et al. World Endoscopy Organization Consensus Statements on Post-Colonoscopy and Post-Imaging Colorectal Cancer. Gastroenterology. 2018;155(3):909-25 e3.
21. Offman J, Pesola F, Fitzgerald RC, Hamilton W, Sasieni P. Impact of Barrett oesophagus diagnoses and endoscopies on oesophageal cancer survival in the UK: A cohort study. Cancer Med. 2022;11(4):1160-71.
22. Bae JM, Shin SY, Kim EH. Mean sojourn time of preclinical gastric cancer in Korean men: a retrospective observational study. J Prev Med Public Health. 2014;47(4):201-5.
23. Reid BJ, Paulson TG, Li X. Genetic Insights in Barrett's Esophagus and Esophageal Adenocarcinoma. Gastroenterology. 2015;149(5):1142-52 e3.
24. Srinivasa A, Fiadeiro R, Rahman T, Burr N, Banks M, Healey C, et al. The causes of post endoscopy upper gastrointestinal cancer: pilot results from the national root cause analysis project. Gut. 2024;73:A1–A309.
25. Wani S, Yadlapati R, Singh S, Sawas T, Katzka DA, Post-Endoscopy Esophageal Neoplasia Expert Consensus P. Post-Endoscopy Esophageal Neoplasia in Barrett's Esophagus: Consensus Statements from an International Expert Panel. Gastroenterology. 2021.
26. Desai M, Lieberman D, Srinivasan S, Nutalapati V, Challa A, Kalgotra P, et al. Post-endoscopy Barrett's neoplasia after a negative index endoscopy: a systematic review and proposal for definitions and performance measures in endoscopy. Endoscopy. 2022;54(9):881-9.
27. Beck M, Bringeland EA, Qvigstad G, Fossmark R. Gastric Cancers Missed at Upper Endoscopy in Central Norway 2007 to 2016—A Population-Based Study. Cancers. 2021;13:5628.
28. Bloomfeld RS, Bridgers DI, 3rd, Pineau BC. Sensitivity of upper endoscopy in diagnosing esophageal cancer. Dysphagia. 2005;20(4):278-82.
29. Chadwick G, Groene O, Hoare J, Hardwick RH, Riley S, Crosby TD, et al. A population-based, retrospective, cohort study of esophageal cancer missed at endoscopy. Endoscopy. 2014;46(7):553-60.
30. Chadwick G, Groene O, Riley S, Hardwick R, Crosby T, Hoare J, et al. Gastric Cancers Missed During Endoscopy in England. Clin Gastroenterol Hepatol. 2015;13(7):1264-70 e1.
31. Cheung D, Menon S, Hoare J, Dhar A, Trudgill N. Factors Associated with Upper Gastrointestinal Cancer Occurrence After Endoscopy that Did Not Diagnose Cancer. Dig Dis Sci. 2016;61(9):2674-84.
32. Cho YS, Chung IK, Kim JH, Jung Y, Lee TH, Park SH, et al. Risk factors of developing interval early gastric cancer after negative endoscopy. Dig Dis Sci. 2015;60(4):936-43.
33. Delgado Guillena PG, Morales Alvarado VJ, Jimeno Ramiro M, Rigau Canardo J, Ramirez Salazar C, Garcia Rodriguez A, et al. Gastric cancer missed at esophagogastroduodenoscopy in a well-defined Spanish population. Dig Liver Dis. 2019;51(8):1123-9.
34. Dhaliwal L, Codipilly DC, Gandhi P, Johnson ML, Lansing R, Wang KK, et al. Neoplasia Detection Rate in Barrett's Esophagus and Its Impact on Missed Dysplasia: Results from a Large Population-Based Database. Clin Gastroenterol Hepatol. 2021;19(5):922-9 e1.
35. Gavric A, Hanzel J, Zagar T, Zadnik V, Plut S, Stabuc B. Survival outcomes and rate of missed upper gastrointestinal cancers at routine endoscopy: a single centre retrospective cohort study. Eur J Gastroenterol Hepatol. 2020;32(10):1312-21.
36. Hamashima C, Shabana M, Okamoto M, Osaki Y, Kishimoto T. Survival analysis of patients with interval cancer undergoing gastric cancer screening by endoscopy. PLoS One. 2015;10(5):e0126796.

37. Hernanz N, Rodriguez de Santiago E, Marcos Prieto HM, Jorge Turrion MA, Barreiro Alonso E, Rodriguez Escaja C, et al. Characteristics and consequences of missed gastric cancer: A multicentric cohort study. Dig Liver Dis. 2019;51(6):894-900.
38. Hosokawa O, Hattori M, Douden K, Hayashi H, Ohta K, Kaizaki Y. Difference in accuracy between gastroscopy and colonoscopy for detection of cancer. Hepatogastroenterology. 2007;54(74):442-4.
39. Hosokawa O, Watanabe K, Hatorri M, Douden K, Hayashi H, Kaizaki Y. Detection of gastric cancer by repeat endoscopy within a short time after negative examination. Endoscopy. 2001;33(4):301-5.
40. Iida T, Yamashita K, Ohwada S, Ohkubo Y, Hirano T, Miyake T, et al. Natural history of gastric cancer from a retrospective review of endoscopic images of older patients with interval gastric cancer. Geriatr Gerontol Int. 2018;18(7):997-1002.
41. Januszewicz W, Wieszczy P, Bialek A, Karpinska K, Szlak J, Szymonik J, et al. Endoscopist biopsy rate as a quality indicator for outpatient gastroscopy: a multicenter cohort study with validation. Gastrointest Endosc. 2019;89(6):1141-9.
42. Januszewicz W, Witczak K, Wieszczy P, Socha M, Turkot MH, Wojciechowska U, et al. Prevalence and risk factors of upper gastrointestinal cancers missed during endoscopy: a nationwide registry-based study. Endoscopy. 2021.
43. Jin S, Jeon SW, Kwon Y, Nam SY, Yeo SJ, Kwon SH, et al. Optimal Endoscopic Screening Interval for Early Detection of Gastric Cancer: a Single-Center Study. J Korean Med Sci. 2018;33(23):e166.
44. Leung WK, Ho HJ, Lin JT, Wu MS, Wu CY. Prior gastroscopy and mortality in patients with gastric cancer: a matched retrospective cohort study. Gastrointest Endosc. 2018;87(1):119-27 e3.
45. Raftopoulos SC, Segarajasingam DS, Burke V, Ee HC, Yusoff IF. A cohort study of missed and new cancers after esophagogastroduodenoscopy. Am J Gastroenterol. 2010;105(6):1292-7.
46. Rodriguez de Santiago E, Hernanz N, Marcos-Prieto HM, De-Jorge-Turrion MA, Barreiro-Alonso E, Rodriguez-Escaja C, et al. Rate of missed oesophageal cancer at routine endoscopy and survival outcomes: A multicentric cohort study. United European Gastroenterol J. 2019;7(2):189-98.
47. Tai FWD, Wray N, Sidhu R, Hopper A, McAlindon M. Factors associated with oesophagogastric cancers missed by gastroscopy: a case–control study. Frontline Gastroenterology. 2019;0:1-8.
48. Vajravelu RK, Kolb JM, Thanawala SU, Scott FI, Han S, Singal AG, et al. Characterization of Prevalent, Post-Endoscopy, and Incident Esophageal Cancer in the United States: A Large Retrospective Cohort Study. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2021.
49. van Putten M, Johnston BT, Murray LJ, Gavin AT, McManus DT, Bhat S, et al. 'Missed' oesophageal adenocarcinoma and high-grade dysplasia in Barrett's oesophagus patients: A large population-based study. United European Gastroenterol J. 2018;6(4):519-28.
50. Wang YR, Loftus EV, Jr., Judge TA, Peikin SR. Rate and Predictors of Interval Esophageal and Gastric Cancers after Esophagogastroduodenoscopy in the United States. Digestion. 2016;94(3):176-80.
51. Yalamarthi S, Witherspoon P, McCole D, Auld CD. Missed diagnoses in patients with upper gastrointestinal cancers. Endoscopy. 2004;36(10):874-9.
52. Burr NE, Derbyshire E, Taylor J, Whalley S, Subramanian V, Finan PJ, et al. Variation in post-colonoscopy colorectal cancer across colonoscopy providers in English National Health Service: population based cohort study. BMJ. 2019;367:l6090.
53. Beaton DR, Sharp L, Lu L, Trudgill NJ, Thoufeeq M, Nicholson BD, et al. Diagnostic yield from symptomatic gastroscopy in the UK: British Society of Gastroenterology analysis using data from the National Endoscopy Database. Gut. 2024;73(9):1421-30.
54. Hadjinicolaou A, Modolell I, Vishwanathan S, Ortiz Fernández-Sordo J, Patel K, Morris D, et al. P159 The prevalence of premalignant upper GI conditions is underestimated based on endoscopic diagnosis: interim data from a multicentre, prospective study. Gut. 2024;73.
55. Anderson R, Burr NE, Valori R. Causes of Post-Colonoscopy Colorectal Cancers Based on World Endoscopy Organization System of Analysis. Gastroenterology. 2020;158(5):1287-99 e2.

56. Trudgill N. Improving the diagnosis of oesophageal and gastric cancers by system-wide identification and analysis of missed diagnoses of oesophageal and gastric cancers during endoscopy 2022 [Available from: https://fundingawards.nihr.ac.uk/award/NIHR203599.
57. Srinivasa A, Fiadeiro R, Rahman T, Burr N, Banks M, Healey C, et al. O53 The causes of post endoscopy upper gastrointestinal cancer: pilot results from the national root cause analysis project. Gut. 2024;73.
58. Joint Advisory Group on GI Endoscopy, participating services 2023 [Available from: https://www.thejag.org.uk/RegisteredUnits.aspx.
59. Siau K, Green JT, Hawkes ND, Broughton R, Feeney M, Dunckley P, et al. Impact of the Joint Advisory Group on Gastrointestinal Endoscopy (JAG) on endoscopy services in the UK and beyond. Frontline Gastroenterol. 2019;10(2):93-106.
60. Kang JH, Evans N, Singh S, Samadder NJ, Lee JK. Systematic review with meta-analysis: the prevalence of post-colonoscopy colorectal cancers using the World Endoscopy Organization nomenclature. Alimentary pharmacology & therapeutics. 2021;54(10):1232-42.
61. Corley DA, Jensen CD, Marks AR, Zhao WK, Lee JK, Doubeni CA, et al. Adenoma detection rate and risk of colorectal cancer and death. N Engl J Med. 2014;370(14):1298-306.
62. Kaminski MF, Regula J, Kraszewska E, Polkowski M, Wojciechowska U, Didkowska J, et al. Quality indicators for colonoscopy and the risk of interval cancer. The New England journal of medicine. 2010;362(19):1795-803.
63. Simmons DT, Harewood GC, Baron TH, Petersen BT, Wang KK, Boyd-Enders F, et al. Impact of endoscopist withdrawal speed on polyp yield: implications for optimal colonoscopy withdrawal time. Aliment Pharmacol Ther. 2006;24(6):965-71.
64. Barclay RL, Vicari JJ, Doughty AS, Johanson JF, Greenlaw RL. Colonoscopic withdrawal times and adenoma detection during screening colonoscopy. The New England journal of medicine. 2006;355(24):2533-41.
65. Burr N, Beaton D, Trudgill N, Rutter M, Morris E, Valori R. 027 English national root-cause analysis of post-colonoscopy colorectal cancers. Gut. 2023;72.
66. Rees C, Penman I. Has the COVID-19 pandemic changed endoscopy in the UK forever? Lancet Gastroenterol Hepatol. 2023;8(1):6-8.
67. Bisschops R, Areia M, Coron E, Dobru D, Kaskas B, Kuvaev R, et al. Performance measures for upper gastrointestinal endoscopy: a European Society of Gastrointestinal Endoscopy (ESGE) Quality Improvement Initiative. Endoscopy. 2016;48(9):843-64.
68. Ratcliffe E, Britton J, Yalamanchili H, Rostami I, Nadir SMH, Korani M, et al. Dedicated service for Barrett's oesophagus surveillance endoscopy yields higher dysplasia detection and guideline adherence in a non-tertiary setting in the UK: a 5-year comparative cohort study. Frontline Gastroenterol. 2024;15(1):21-7.
69. Ooi J, Wilson P, Walker G, Blaker P, DeMartino S, O'Donohue J, et al. Dedicated Barrett's surveillance sessions managed by trained endoscopists improve dysplasia detection rate. Endoscopy. 2017;49(6):524-8.

Table 1

PEUGIC categorisation	Explanation
A	Lesion detected, adequate assessment and decision-making but PEUGIC still occurred
B	Lesion detected, inadequate assessment or decision-making
C	Possible missed lesion, endoscopy and decision-making adequate
D	Possible missed lesion, endoscopy or decision-making inadequate
E	Deviated from management pathway but appropriate (patient choice or clinical decision was not fit for further investigations)
F	Deviated inappropriately from management pathway (administrative delays)

Table 2

Endoscopist
Awareness and concern for PEUGIC
Heightened vigilance with lower threshold to expect premalignant / malignant disease
Slow down, take time to complete high-quality examination
Clean mucosa and remove bubbles (e.g. suction, water, simethicone or n-acetyl cysteine)
Appreciate mucosal and vascular detail (e.g high definition WLE, image enhancement, e.g. NBI)
Meticulous photodocumentation
Upskilling in lesion recognition (e.g. early squamous and Barrett's neoplasia, and premalignant stomach)
Upskilling in lesion delineation and classification
Optimise sedation
Generous biopsies from oesophageal strictures and oesophageal / gastric ulcers
Strict endoscopic follow-up of oesophageal and gastric ulcers, and grade C or D oesophagitis
Very low threshold for repeat endoscopy if poor tolerance or inadequate views
Consider sampling error – low threshold for early repeat endoscopy and biopsies if clinical concern (oesophageal stricture, oesophageal / gastric ulcer, consider linitis plastica, confirmed Barrett's low-grade dysplasia)
Service
Triage to enrich lists with pathology and avoid low yield endoscopy
Reduce the number of procedures per list and allow sufficient time to focus on quality for both diagnostic and surveillance procedures
Strict endoscopic follow-up of oesophageal and gastric ulcers (robust administration support)
Dedicated Barrett's surveillance lists
Regular PEUGIC root cause analysis – inform endoscopists concerned and wider team, with emphasis on shared learning

Abbreviations: NBI, Narrow band imaging; PEUGIC, post endoscopy upper gastrointestinal cancer; WLE, white light endoscopy

Practice points

- Post-endoscopy upper gastrointestinal cancer (PEUGIC) accounts for ~ 11% of upper GI malignancies nationally
- PEUGIC represent missed opportunities for prevention and early detection
- Avoidable delays in diagnosis are common
- Sub-optimal assessment and management of premalignant upper GI disease and cancer-related lesions, and administrative delays are contributory
- A focus on endoscopy quality improvement and decision-making is key to prevention of PEUGIC
- Endoscopy units should audit PEUGIC rates routinely and undertake root cause analysis

Research agenda

- Influence of endoscopy quality metrics on PEUGIC occurrence need to be evaluated
- Interventions to prevent PEUGIC need to be developed and evaluated
- Further research is needed to establish mechanisms underpinning differences in PEUGIC rates (by sex, morbidity and deprivation)

Post-Endoscopy Upper Gastrointestinal Cancer: Emerging Data and Opportunities to improve Early Detection

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