Identifying Key Performance Indicators For Upper Gastrointestinal Endoscopy To Reduce Post Endoscopy Upper Gastrointestinal Cancer Rate

By

Umair Kamran

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Dedication

I dedicate this work to my beloved family; to my amazing wife Arooj whose unwavering support, patience and love made this journey possible for me. To my mother who has encouraged me throughout my academic career. To my beautiful daughter Laaibah and son Azaan who have been my source of joy and motivation. And to my mentors, Professor Nigel Trudgill and Dr Nicola J Adderley, whose guidance, insight and encouragement were invaluable.

Thesis Format

This thesis is submitted in accordance with the University of Birmingham guidelines for an alternative thesis submission as detailed in regulation 7.4.1 (g). Therefore published manuscripts or those under submission (chapters 2-6) are inserted directly into this thesis. There is consequently some duplication in terms of methodology among some of the manuscripts and the restrictions of journals in terms of word count and greater detail may have been curtailed. However, chapter 1 (introduction) and chapter 7 (discussion) provide further background and context to the manuscripts.

Contribution statement

This thesis is the product of my own work, supported in conception, analysis and presentation by my supervisors, Professor Nigel Trudgill and Dr Nicola Adderley. Given that the work submitted in this thesis was part of a National Institute for Health and Care Research funded research project, under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number NIHR 201571), the research progress was overseen by a steering committee, members of which included Professor Nigel Trudgill, Dr Nicola Adderley, Professor Matt Rutter, Professor Matthew Brookes, Professor Eva Morris and Ms Mimi Mcccord.

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List of achievements during PhD

Awards and honours

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- "Best endoscopy oral presentation" award at BSG live 2022.
- "Best Oesophageal poster" award at BSG live 2022
- "Abstract of distinction" at BSG 2021
- "Highly commended poster" at BSG 2021

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- Kamran U, Dretzke J, Umar N, Abbasi A, Tahir I, Adderley N, Trudgill N. P172 Systematic review of potential quality indicators for dysplasia and cancer detection at upper gastrointestinal endoscopy. Gut. 2022 Jun 1;71(Suppl 1):A124-.

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- Kamran U, Evison F, Morris EJ, Brookes MJ, Rutter MD, McCord M, Adderley NJ, Trudgill N. The variation in post-endoscopy upper gastrointestinal cancer rates among endoscopy providers in England and associated factors: a population-based study. Endoscopy. 2024 Aug 29.

- Kamran U, King D, Abbasi A, Coupland B, Umar N, Chapman WC, Hebbar S, Trudgill NJ. A root cause analysis system to establish the most plausible explanation for post-endoscopy upper gastrointestinal cancer. Endoscopy. 2023 Feb;55(02):109-18.

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Publications outside this thesis

- Kamran U, Lee PC, Coupland B, Abbasi A, Steed H, Ispoglou S, Varyani F, Trudgill N. Improving 30-day mortality following percutaneous endoscopic gastrostomy tube placement in England from 2007 to 2019: a retrospective national cohort analysis of 87,862 patients.

- Kamran U, King D, Banks M, Nylander D, Shetty S, Hebbar S, Ransford R, Mitchell D, Williams M, Gupta S, Cheung D. Assessment of the role of the Edinburgh dysphagia score in referral triage in a national service evaluation of the urgent suspected upper gastrointestinal cancer pathway. Alimentary Pharmacology & Therapeutics. 2022 May;55(9):1160-8.

- Kamran U, King D, Dosanjh A, Coupland B, Leeds J, Nayar M, Patel P, Trudgill N, Oppong KW. Pancreaticobiliary endoscopic ultrasound in England 2007 to 2016: Changing practice and outcomes. Endoscopy international open. 2021 Nov;9(11):E1731-9.

- Kamran U, Abbasi A, Tahir I, Hodson J, Siau K. Can adjuncts to bowel preparation for colonoscopy improve patient experience and result in superior bowel cleanliness? A systematic review and meta-analysis. United European Gastroenterology Journal. 2020 Dec;8(10):1217-27.

- King D*, Kamran U*, Dosanjh A, Coupland B, Mytton J, Leeds JS, Nayar M, Patel P, Oppong KW, Trudgill NJ. Rate of pancreatic cancer following a negative endoscopic ultrasound and associated factors. Endoscopy. 2022 Nov;54(11):1053-61.
  *(joint first authors)

- Waddingham W, Kamran U, Kumar B, Trudgill NJ, Tsiamoulos ZP, Banks M. Complications of diagnostic upper Gastrointestinal endoscopy: common and rare–recognition, assessment and management. BMJ Open Gastroenterology. 2022 Dec 1;9(1):e000688.

- Waddingham W, Kamran U, Kumar B, Trudgill NJ, Tsiamoulos ZP, Banks M. Complications of colonoscopy: common and rare—recognition, assessment and management. BMJ Open Gastroenterology. 2023 Dec 1;10(1):e001193.

- Goel A, Khanna A, Mehrzad H, Bach S, Karkhanis S, Kamran U, Morgan J, Rajoriya N, Tripathi D. Portal decompression with transjugular intrahepatic portosystemic shunt prior to nonhepatic surgery: a single-center case series. European journal of gastroenterology & hepatology. 2021 Dec 1;33(1S):e254-9.

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Chapter 1: Introduction

Upper gastrointestinal (UGI) cancers refer to the group of cancers which involve the upper portion of the digestive tract. UGI endoscopy is the investigation of choice to detect these cancers. However, it has been previously reported that up to 11% of the patients with UGI cancers had a non diagnostic endoscopy within 3 years prior to their cancer diagnosis, highlighting potentially missed opportunities to diagnose these cancers earlier.[1] The work presented in this thesis seeks to explore the key performance indicators (KPI) for UGI endoscopy to improve the quality of endoscopy and reduce risk of missing cancers during endoscopic examination. This introductory chapter will provide a broad background for the observational studies presented in this thesis. It will seek to broadly describe what is currently known about UGI cancers in terms of aetiology, epidemiology, diagnosis and management. It will also explain the concept of post endoscopy upper gastrointestinal cancers (PEUGIC) and role of KPIs. More focused and detailed introductions are provided in the relevant chapters. This thesis is mainly focused on the role of UGI endoscopy to diagnose oesophageal and gastric cancers. Duodenal cancers are beyond the scope of this research as a standard endoscope may not be able to reach beyond the second part of the duodenum.

1.1 Upper gastrointestinal cancers

UGI cancers mainly comprising malignancies of the oesophagus and stomach represent a significant global burden. According to the World Health Organisation and report from the International Agency for Research on Cancer, around 1.5 million people are diagnosed with cancers of the stomach and oesophagus each year and these were the third and fifth leading causes of cancer related deaths respectively.[2] Both incidence and mortality vary greatly across countries and worldwide regions. Patterns of mortality closely follow those of incidence,

reflecting the poor average prognosis associated with these cancers. Overall five-year survival rates for oesophageal and gastric cancers are only 18% to 23% respectively in England.[3,4]. With no specific symptoms of early UGI cancers, most tumours are diagnosed at a late and rapidly progressing to advanced stage. Efforts to screen for UGI cancers using endoscopy in high-incidence countries such as China, Japan and the Republic of Korea have shown some evidence of a significant reduction in mortality. [5–7] Yet, to-date, population based endoscopic screening in low-risk populations has not proven to be cost effective.

1.1.1 Epidemiology and risk factors for oesophageal cancer

The majority of oesophageal cancers are squamous cell carcinomas (SCC) or oesophageal adenocarcinomas (OAC). Although incidence of oesophageal cancer has decreased in other parts of the world, increasing trends are observed in the historically low-risk population such as the United Kingdom, the Netherlands and the United States white ethnic group. (Figure 1.1)

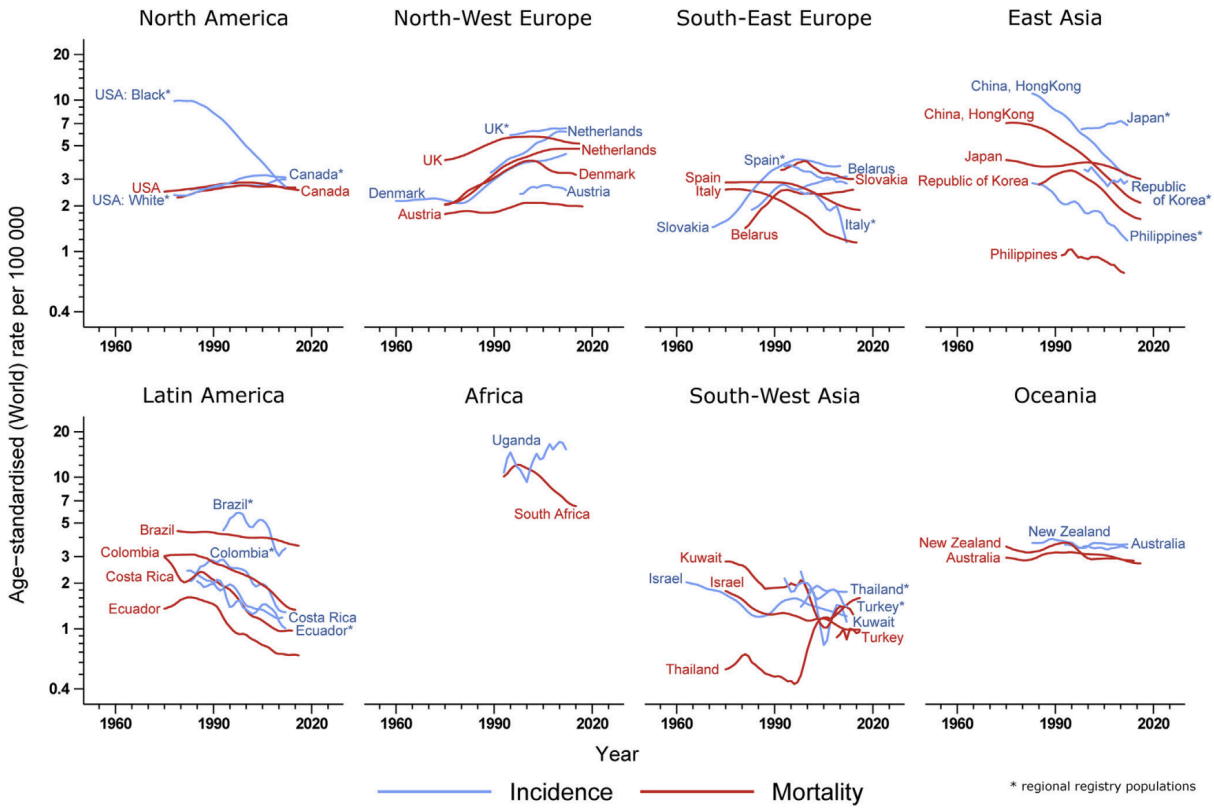


Figure 1 Oesophageal cancer: trends in age-standardised incidence and mortality rates by country. Source: CI5plus and World Health Organization Mortality Database. *(Adapted from Arnold et al. 2020 [2])*

These geographical differences in the trends can partly be explained by the varying distributions of the two histological subtypes of oesophageal cancers. Although incidence of SCC is declining in most countries, rates of OAC appear to be rising in a relatively small number of high income countries including the United Kingdom and the United States. These trends are likely attributable to shifts in the prevalence of risk factors.

SCC arises in the thin, flat cells lining the inside of the oesophagus. This cancer often involves the upper and middle third of the oesophagus but can occur anywhere along the oesophagus. SCC is the most common type of oesophageal cancer globally, particularly in the so-called "central Asian oesophageal cancer belt" and Eastern Africa's "oesophageal cancer corridor".[8,9] Major risk factors in these areas are not well understood, but are thought to include poor nutritional status, low intake of fruits and vegetables, and drinking beverages at high temperatures. In contrast, in low-risk areas for SCC, such as the United States and several Western countries, smoking and excessive alcohol consumption account for approximately 90 percent of the total cases of SCC.[10] Tobacco and alcohol synergistically increase risk.[11] Smoking and alcohol also increase risk of other aerodigestive cancers (head, neck and lung), as a result of field cancerization. Patients with one aerodigestive malignancy have an increased risk of synchronous and second primary tumours of the aerodigestive tract compared with the age-matched general population.[12,13] Chewing of areca nuts and betel quid (areca nuts wrapped in betel leaves), which is widespread in regions of Asia, is implicated in the development of SCC.[14] The mechanism may involve the release of copper, with a resulting induction of collagen synthesis by fibroblasts.[15] The presence of specific preexisting oesophageal diseases such as Achalasia and infection with human papilloma virus (especially type 16 and 18) have also been reported to be associated with the development of SCC.[16,17] Chronic infection of mucosal lining of oesophagus with candidiasis has been reported to increase the risk of SCC due to a gain-of-function mutation in the STAT1 gene.[18]

In contrast to SCC, the OAC arises from the glandular cells in the oesophagus. The glandular cells in the lining of the oesophagus produce and release fluid called mucous. These cancers

usually involve the lower part of oesophagus, near the stomach. For the past three decades, frequency of OAC has increased dramatically. Chronic acid reflux symptoms have been reported to be associated with AC (odds ratio 7.7). Risk was greatest among patients with longstanding (>20 years) and severe symptoms.[19,20] Barrett's oesophagus is a premalignant condition, defined as an oesophagus in which any portion of the normal distal squamous epithelial lining has been replaced by metaplastic columnar epithelium, which is clearly visible endoscopically (>1cm) above the gastro-oesophageal junction.[21] Two European studies have reported a general population prevalence of Barrett's oesophagus of 1.3% and 1.6%.[22,23] A meta-analysis demonstrated a 0.33% annual cancer conversion rate from non-dysplastic Barrett's oesophagus to OAC .[24] Smoking increases the risk of OAC particularly in patients with Barrett's oesophagus.[25] Obesity is also linked to higher risk of OAC and to Barrett's oesophagus.[26] A meta- analysis of case control and cohort studies identified a relative risk of OAC of 1.71 (95% CI 1.51-1.96) for BMI between 25 and 30 kg/m2, and 2.34 (95% CI 1.95-2.81) for BMI ≥30kg/m2.[27] Obesity may represent an indirect risk factor for both OAC and Barrett's oesophagus because it increases the risk of gastro-oesophageal reflux disease by a "mechanical" mechanism (amplified intragastric pressure, disrupted normal oesophageal sphincter function, and increased risk of a hiatal hernia).[28,29] Another possibility is a proinflammatory effect of obesity caused by the secretion of multiple proinflammatory cytokines. A proxy for these obesogenic effects is metabolic syndrome, a constellation of metabolic disorders that includes obesity, impaired fasting glucose, high blood pressure, and dyslipidemia.

1.1.2 Epidemiology and risk factors for gastric cancer

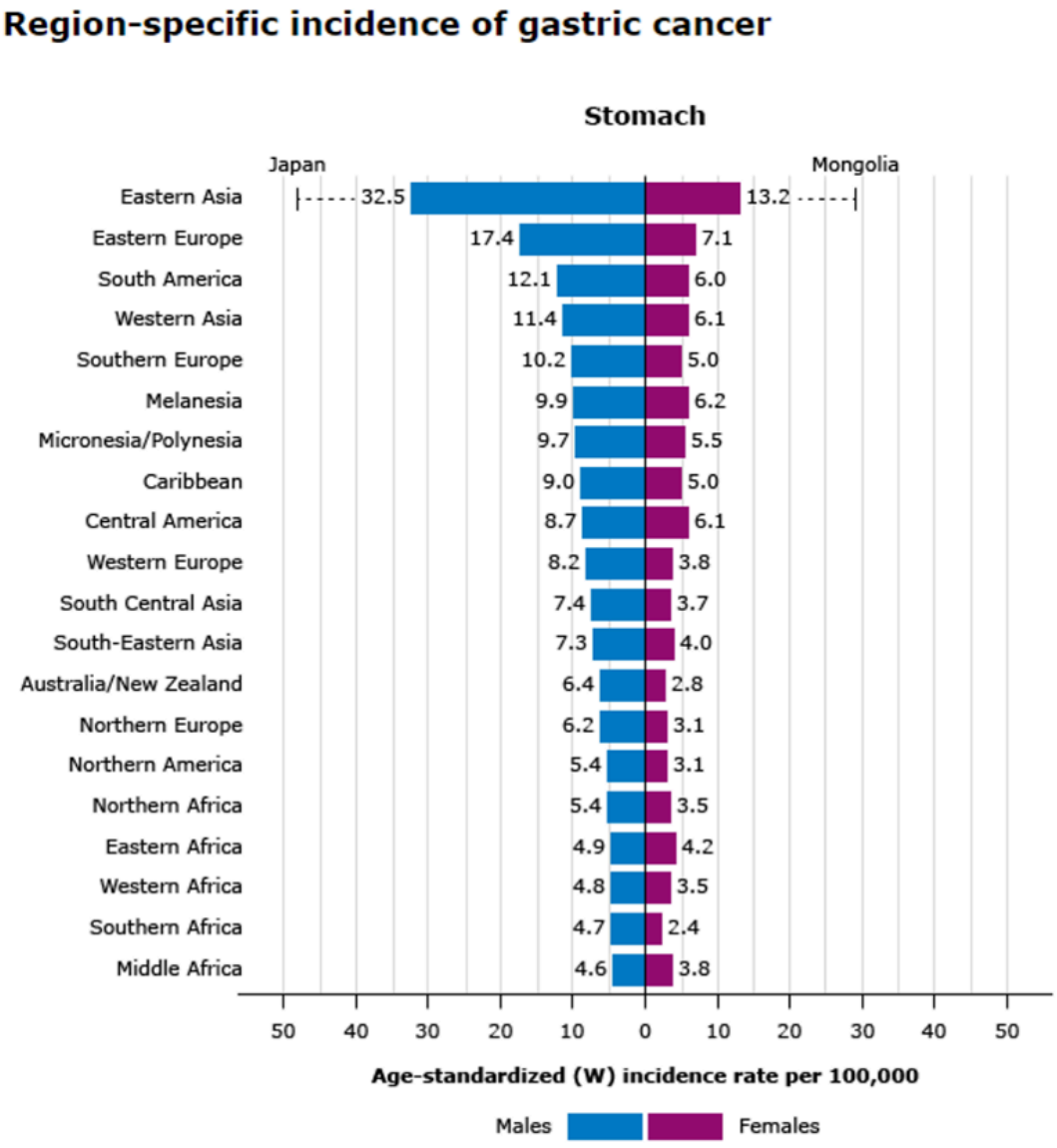
Gastric adenocarcinomas (GAC) account for approximately 90% of all gastric (stomach) cancers. They arise from the mucus-producing cells in the innermost lining of the stomach and can be divided into two main types depending on where they form in stomach:

- Gastric cardia cancers begin in the top inch of the stomach, just below where it meets oesophagus.
- Non cardia cancers are cancers which involve any other part of the stomach.

Histologically, GAC may also be described as intestinal or diffuse type, depending on how the cells look microscopically:

- In intestinal-type tumours, the tumour cells adhere to each other and tend to arrange themselves in tubular or glandular formations, similar to adenocarcinomas arising elsewhere in the intestinal tract (hence their designation as intestinal type). These are more common in males and older age groups and carry better prognosis.
- In the diffuse type or infiltrative type tumours, lack of adhesion molecules due to loss of expression of a key cell surface protein called E-cadherin allows the individual tumour cells to grow and invade neighbouring tissues without gland formation. These are also called poorly cohesive carcinomas and can display various cell types that include neoplastic cells, such as signet ring cells, but also histiocytes as well as lymphocytes. Linitis plastica is a rare diffuse type of cancer which spreads to the muscles of the stomach wall and makes it thicker and more rigid. These cancers show a more equal male:female ratio, are more common in younger age groups and carry worse prognosis than intestinal type.

Incidence rates of GAC are generally 2-fold higher in men relative to women and range from 22 per 100,000 person years in Eastern Asia (Mongolia, China, South Korea and Japan) to fewer than 5 per 100,000 person years in Northern Europe as well as Northern America and Africa (Figure 1.2).



Region-specific incidence age-standardized rates by sex for stomach cancer in 2020. Rates are shown in descending order of the world (W) age-standardized rate among males, and the highest national rates among males and females are superimposed.

Figure 1.2 GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2021. *Adapted from Sung et al. Global cancer statistics 2020[30]*

As gastric cancer is rarely detected early, mortality from this cancer is often high. Geographic and temporal variations in mortality are often closely aligned with the incidence. A steady decline in the incidence and mortality has been observed consistently across world regions in both men and women. Over the last decade, gastric cancer incidence rates have decreased by almost a third (31%) in the UK with a further 12% reduction is expected in the UK between 2023-2025 and 2038-2040.[3] Part of this global decline has been attributed to the better food preservation practices linked to refrigeration during transportation and storage of food. Living conditions have also improved due to economic development leading to reduced overcrowding and better hygiene.

Although several risk factors have been described, Helicobacter pylori (H.Pylori) infection, family history of gastric cancer, especially hereditary diffuse type gastric cancer and pernicious anaemia, have been identified as major risk factors for GAC. The World Health Organization's International Agency for Research on Cancer (IARC) classified H. pylori as a group 1 or definite carcinogen.[31] The canonical model for cancer progression in the stomach is Correa sequence which outlines a stepwise linear progression from chronic gastritis through gastric atrophy, gastric intestinal metaplasia, dysplasia and finally, invasive cancer. The most common cause of chronic gastritis is H. Pylori (Figure 1.3).

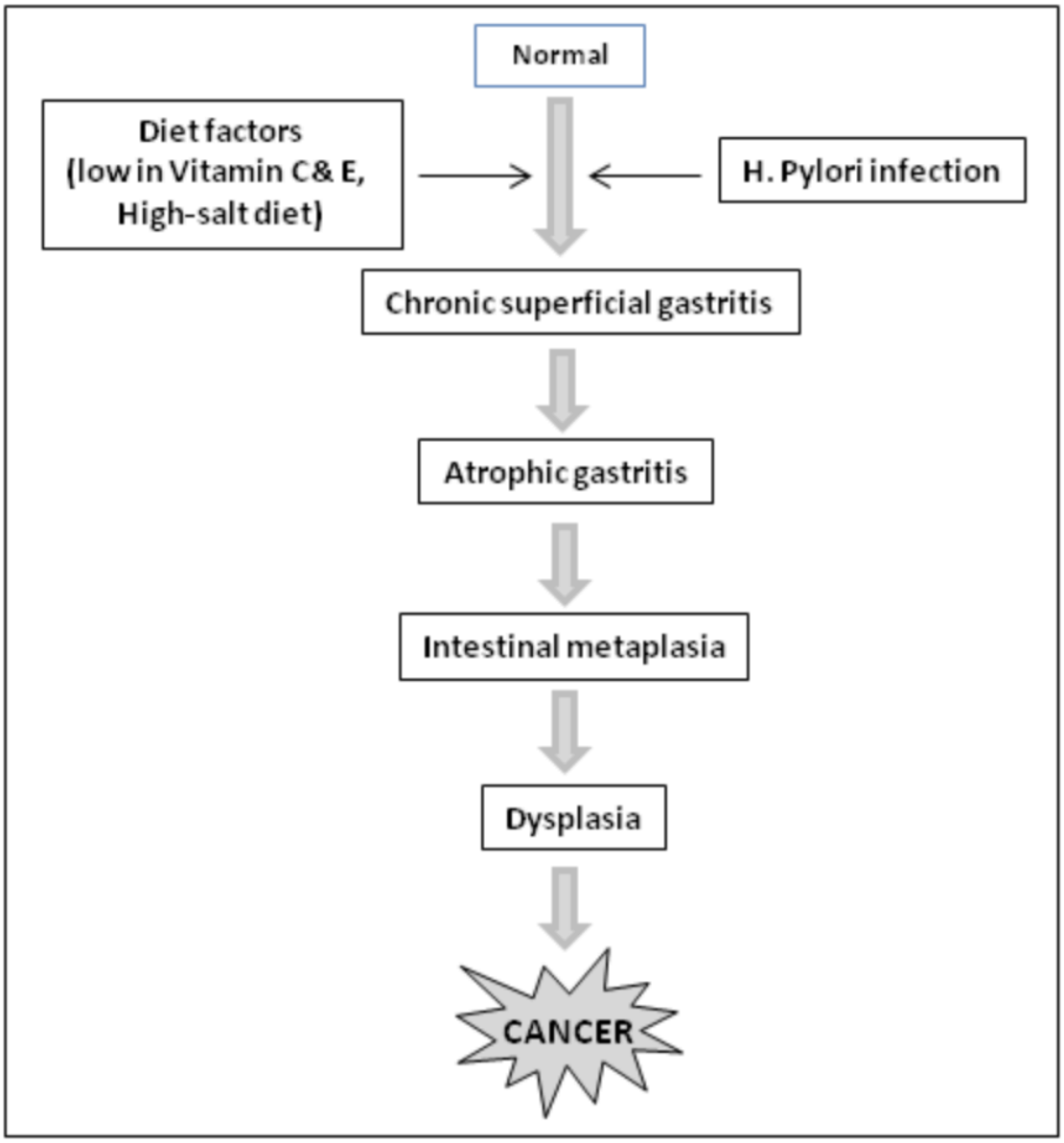


Figure 1.3 Sequence of development of gastric cancer (*Adopted from: Swartz's principles of surgery, 9th edition*)

Epidemiological studies demonstrate a strong correlation between *H. pylori* seropositivity and gastric cancer.[32–34] The EUROGAST study of 17 populations from 13 different countries (11

European countries, the United States, and Japan) found a six-fold increased risk of gastric cancer in *H. pylori*-infected populations compared with uninfected populations.[32] Two meta-analyses of cohort and case control studies found that *H. pylori* infection was associated with a two-fold increased risk for developing gastric adenocarcinoma, especially in younger patients in whom absolute risk is still quite low.[35,36] Long standing chronic superficial gastritis caused by chronic *H. pylori* infection eventually leads to atrophic gastritis which is characterised by progressive atrophy of the glandular epithelium with loss of parietal and chief cells. The loss of the normal exocrine glands of the gastric mucosa causes hypochlorhydria (a decrease in hydrochloric acid) and a resultant increase in gastric pH. An abnormally high pH in the stomach permits microbial colonisation, some of which possess nitrate reductase, allowing nitrosation that is genotoxic. In addition, there is a loss of endocrine cells, which normally secrete epidermal and transforming growth factors, thereby aiding the stomach in regenerating damaged tissue. A Dutch study exploring the follow-up data of 22,365 patients diagnosed with gastric atrophy found the overall annual incidence for the development of gastric cancer in patients was 0.1%. This increased to 0.25% for gastric intestinal metaplasia, 0.6% for low grade dysplasia and 6% for high grade dysplasia within 5 years after diagnosis.[37]

High salt intake and salty food items have been identified as risk factors for gastric cancer.[38,39] Smoking, low socioeconomic status and infection with Epstein-Barr virus have also been reported to be linked with the development of gastric cancer.

Other rare types of UGI cancers include lymphomas, gastrointestinal stromal tumours (formerly classified as either leiomyomas or leiomyosarcomas) and neuroendocrine tumours. As the natural

history of these tumours is not well understood, these cancers are beyond the scope of this thesis.

1.2 Diagnosis and staging of upper gastrointestinal cancers

1.2.1 Oesophago-gastric-duodenoscopy

The diagnosis of UGI cancer requires histological examination of tumour tissue. A diagnostic biopsy can be obtained by the oesophago-gastric-duodenoscopy, also called OGD or UGI endoscopy. Early UGI cancers may appear as plaque, nodule or ulceration. Advanced cancers appear as strictures, ulcerated or circumferential masses, or large ulcerations.

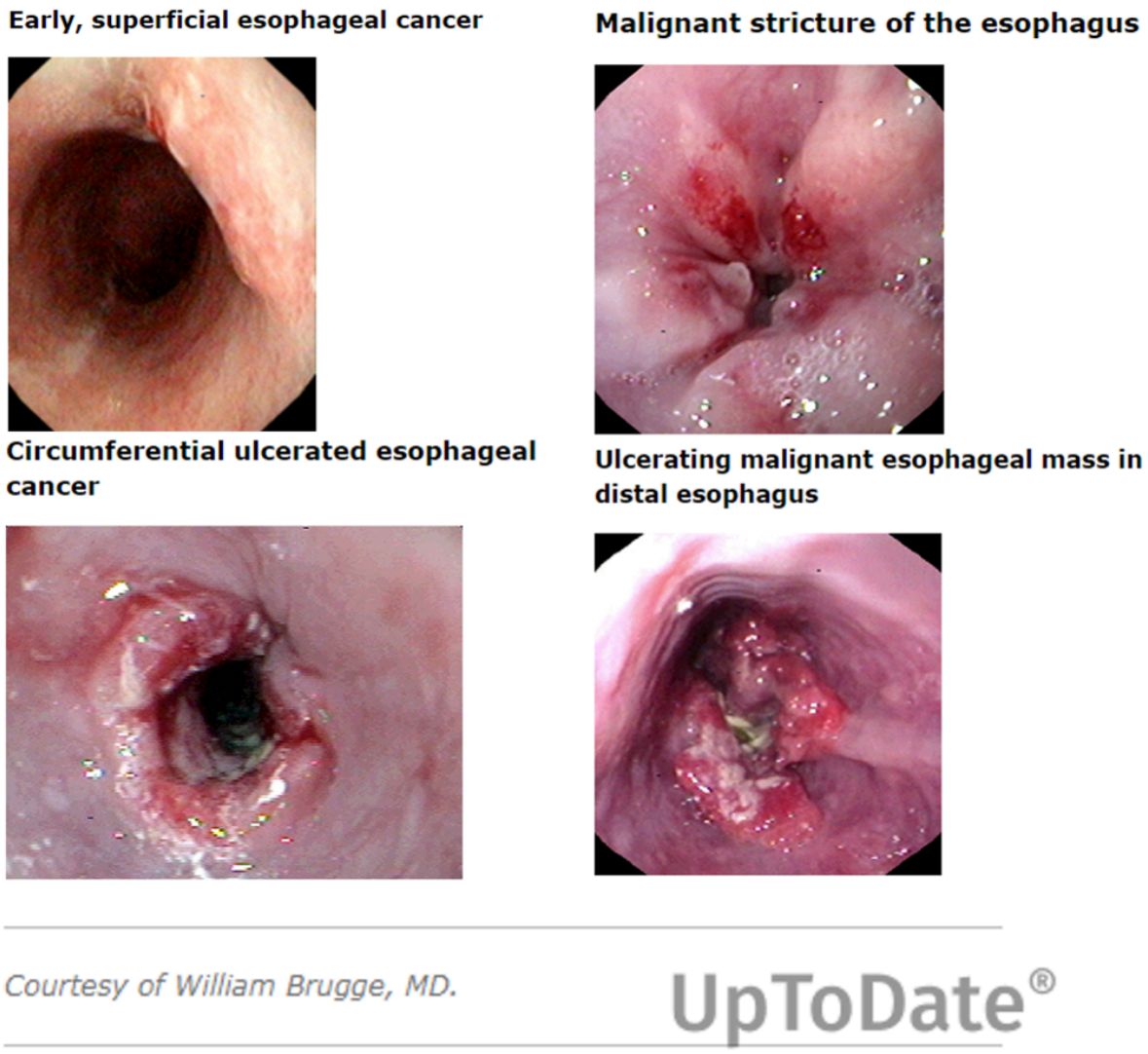


Figure 1.4 Endoscopic images of early and advanced oesophageal cancers (*adapted from © 2024 UpToDate*)

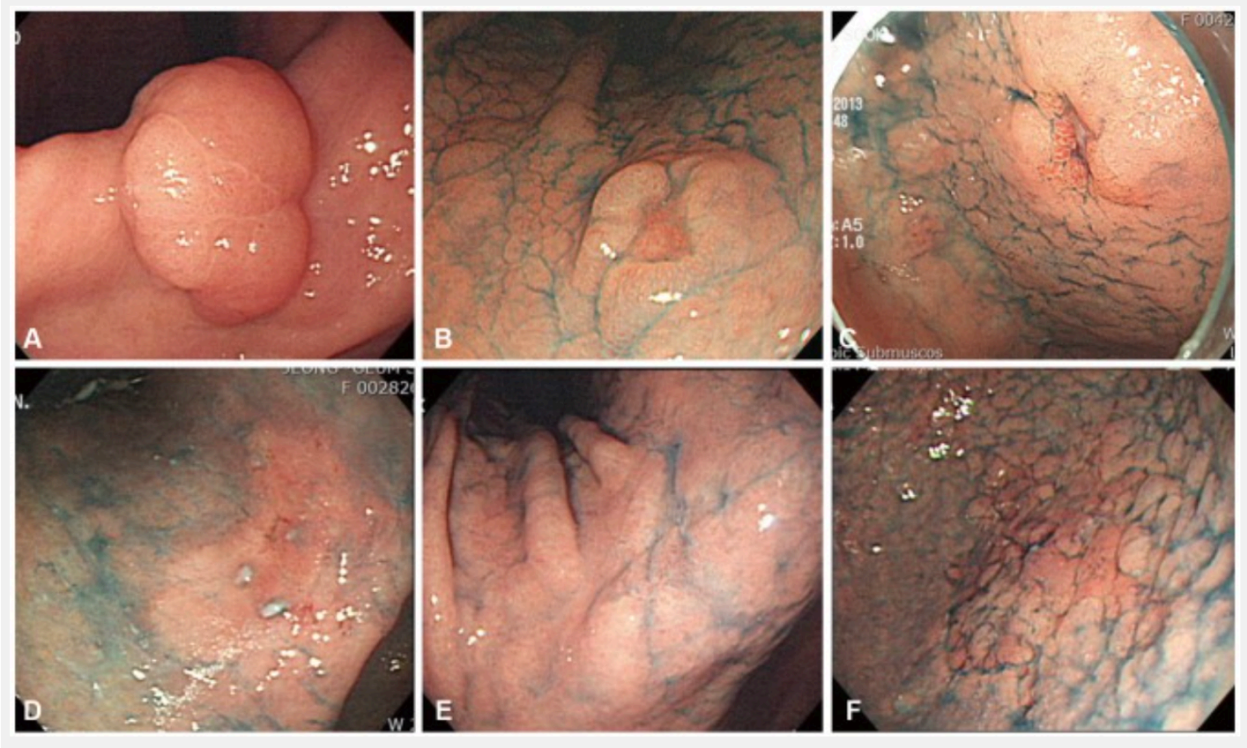


Figure 1.5 Endoscopic images of early gastric cancers. (A) whitish, elevated flat lesion shown at incisura. (B) A doughnut-like elevated lesion in the lesser curvature of the lower body. (C) A reddish depression in the lesser curvature of the antrum. (D) Reddish mucosal changes in the angle. (E) Whitish mucosa changes in the gastric body. (F) Granular mucosal changes in the greater curvature of the lower body. *(Adapted from Moon HS. Improving the endoscopic detection rate in patients with early gastric cancer. Clinical endoscopy. 2015 [40])*

Endoscopy provides information about the exact site of tumour, extension into the oesophagus and stomach, distance from the teeth, length of the lesion, circumferential involvement and presence of obstruction. Endoscopic biopsies also allow histological classification and examination of biomarkers which can guide further treatment and choice of chemotherapy. Since the mucosa can be friable with ulceration a minimum of six biopsies are recommended for histological confirmation. [41]

Various advanced endoscopy imaging techniques have been developed

1.2.2 Barium swallow

A barium swallow is a radiographic (X-ray) examination of the UGI tract, specifically focusing on the pharynx, oesophagus, and stomach. Barium swallow is very sensitive for detecting strictures and intraluminal masses but does not allow staging and biopsy. It is now rarely used, but it may be helpful for studying the distal anatomy in obstructive tumours that are inaccessible by endoscopy.

1.2.3 Cross sectional imaging

Abdominal and chest computed tomography (CT) scans with intravenous contrast are useful for helping to exclude the presence of metastases to the lymph nodes, lungs and liver and may be useful for helping to determine whether adjacent structures have been invaded. Positron emission tomography (PET) is also a useful baseline imaging technique and is increasingly becoming standard in the staging of oesophageal cancer. It may be particularly useful in detecting occult distant lymph node metastases and bone spread. In addition, the intensity of radiopharmaceutical

uptake on PET scans may reflect the biology of the cancer and thus may have prognostic significance.

1.2.4 Endoscopic ultrasound

Endoscopic ultrasonography (EUS) is a sophisticated imaging technique combining endoscopy and ultrasonography to obtain high-resolution images and detailed information about the digestive tract and surrounding tissues. EUS is the most sensitive test for determining the depth of tumour penetration and the presence of enlarged peri-oesophageal lymph nodes.

1.2.5 Diagnostic laparoscopy

Diagnostic laparoscopy is a minimally invasive surgical procedure used to visually examine the abdominal cavity and obtain tissue samples for histological analysis. It provides direct visualisation of the peritoneal cavity, liver, and other intra-abdominal structures. The need for diagnostic laparoscopy for patients who appear to have potentially resectable UGI carcinomas is controversial, and there is no consensus on this issue from expert groups. It is usually reserved for patients who, after conventional pretreatment staging studies, appear to have potentially resectable, locally advanced disease, adenocarcinomas of oesophago-gastric junction, or if there is suspicion of intraperitoneal metastatic disease that cannot otherwise be confirmed.

1.2.6 Staging of UGI cancers

Tumour, node and metastasis (TNM) staging developed jointly by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) is the most common way to stage UGI cancers.[42] TNM staging helps with treatment planning and is closely linked with prognosis (Tables 1 & 2).

Table 1 TNM staging of oesophageal cancer

Primary tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	High-grade dysplasia,* defined as malignant cells confined by the basement membrane
T1	Tumour invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumour invades lamina propria or muscularis mucosae
T1b	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades adventitia
T4	Tumour invades adjacent structures
T4a	Resectable tumour invading pleura, pericardium, azygos vein, diaphragm, or peritoneum
T4b	Unresectable tumour invading other adjacent structures, such as the aorta, vertebral body, and trachea

*High-grade dysplasia includes all non-invasive neoplastic epithelial lesions	
Regional lymph nodes (N)	
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-2 regional lymph nodes
N2	Metastasis in 3-6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Table 2 TNM staging of gastric cancer

Primary tumour (T)	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ: intraepithelial tumour without invasion of the lamina propria
T1	Tumour invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumour invades lamina propria or muscularis mucosae
T1b	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures
T4	Tumour invades serosa (visceral peritoneum) or adjacent structures
T4a	Tumour invades serosa (visceral peritoneum)
T4b	Tumour invades adjacent structures
Regional lymph nodes (N)	
NX	Regional lymph node(s) cannot be assessed

N0	No regional lymph node metastasis
N1	Metastasis in 1-2 regional lymph nodes
N2	Metastasis in 3-6 regional lymph nodes
N3	Metastasis in seven or more regional lymph nodes
N3a	Metastasis in 7-15 regional lymph nodes
N3b	Metastasis in 16 or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

1.3 Overview of upper gastrointestinal cancers management

Multidisciplinary assessment and planning of treatment are mandatory for decision making around treatment of UGI cancers for better outcomes. Treatment is determined together with the patient based on histological subtype, clinical TNM stage, tumour location and the patient's predicted treatment tolerance, which considers performance status and comorbidities, and may be supplemented by functional testing. Correction of malnutrition is often warranted before curative-intent therapy can be started.

1.3.1 Oesophageal cancer treatment

National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) provide detailed guidance on the treatment of oesophageal cancer.[43,44] Treatment options include endoscopic resection, in the form of endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) and ablation of superficial dysplastic cells using radiofrequency energy. EMR is a minimally invasive procedure which involves the removal of a small section of the oesophageal lining (mucosa) where abnormal or cancerous cells are located. ESD is an advanced endoscopic procedure which allows for en bloc resection, meaning the entire lesion is removed in one piece, which is crucial for accurate pathological assessment and reducing the risk of recurrence. EMR, ESD and/or ablation are preferred options for high-grade dysplasia (HGD) or T1a tumours ≤2 cm. Oesophagectomy, which is a major surgical procedure for removal of all or part of the oesophagus, is indicated for patients with extensive HGD or T1a adenocarcinoma with nodular disease that is not adequately controlled by endoscopic resection. Other treatment options are chemotherapy which involves the use of drugs to kill cancer cells or stop them from growing and dividing and radiotherapy which employs high-energy radiation, like X-rays, to target and destroy cancer cells. Chemoradiotherapy can be offered as definitive treatment for patients with early SCC (especially for the tumours involving cervical oesophagus) or early OAC who are not fit for major surgery. In other patients, chemoradiotherapy is offered before or after surgical resection depending on the histology of cancer. SCCs which are completely resected surgically do not require postoperative chemoradiotherapy but all OACs are offered chemotherapy after surgery. Chemoradiation is a preferable option for all non resectable (T4b) tumours. In patients who are not candidates for surgery, because of their clinical condition or advanced disease, palliative care focuses on control of symptoms. For patients with

swallowing difficulty due to obstruction from cancer, palliative treatment options include placement of an oesophageal metal stent or radiological or surgical placement of feeding tube directly into the stomach or small bowel. The goal of palliative care is to prevent and relieve suffering and improve quality of life for patients and their caregivers regardless of the disease stage.

Prognosis of oesophageal cancer varies widely based on the stage at diagnosis and other prognostic factors, including staging, histological type and patient factors. SCC generally has a worse prognosis compared to adenocarcinoma, particularly in Western countries, due to the higher likelihood of presenting at an advanced stage and the association with smoking and alcohol consumption. Five year survival rates for localised (stage 0-I) esophageal cancer is 45-50% , regional (stage II-III) 20%-30% and at advanced stage (stage IV) is <5%.[45]

1.3.2 Gastric cancer treatment

Endoscopic resection is recommended for very early gastric cancers (T1a) if they are clearly (i) confined to the mucosa, (ii) well-differentiated, (iii) ≤2 cm and (iv) non-ulcerated.[46] T1 tumours which do not meet the criteria for endoscopic resection require surgery. For advanced locoregional cancers (T2-T4 with any nodal involvement) peri-operative or postoperative chemotherapy is recommended followed by radical gastrectomy. Locally advanced unresectable or metastatic gastric cancers have very poor prognosis. Systemic chemotherapy and chemoradiotherapy can be offered to the patients with advanced cancers. Targeted immunotherapy in combination with chemotherapy is an option for the cancers with over expression of certain proteins such as HER2 (human epidermal growth factor receptor 2) and PD-L1 (Programmed Death-Ligand 1).[47]

Five year survival rates for early gastric cancers (stage I) are reported as 65% and for regional disease (stage II and III) 25% to 35%. There is no five year survival data for stage IV gastric cancers in the UK as sadly most people do not live for that long after diagnosis. [48]

1.4 Post endoscopy upper gastrointestinal cancer

PEUGIC typically refers to UGI cancers that are diagnosed after an endoscopy in which no cancer was found. The specific time frame most commonly used is 6 to 36 months after a non diagnostic endoscopy. This definition is adapted from the World Endoscopy Organisation's definition of post colonoscopy colorectal cancer (PCCRC) [49] and endorsed by the British Society of Gastroenterology and Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS).[41] PEUGIC can be further categorised as interval and non interval cancers. Interval cancer is defined as the UGI cancer diagnosed after a screening examination or test in which no cancer is detected, and before the date of the next recommended exam. Non interval cancers are defined as those cancers diagnosed at or after the recommended screening or surveillance procedure, or where no subsequent screening or surveillance interval for repeat examination was recommended. While from a screening program perspective, a cancer found at a subsequent screening endoscopy is a screening "success", from an endoscopy quality point of view, study of these procedures is worthwhile, as there might have been a missed opportunity to identify a cancer or identify/fully resect a precancerous lesion at the prior exam. For these reasons, the term *post endoscopy upper gastrointestinal cancer* is recommended as an all-encompassing, overarching term.

Historically, various studies have tried to estimate PEUGIC rates. In a meta-analysis of 10 retrospective studies published in 2014, Menon *et al.* reported that up to 11.3% of patients with

UGI cancers had a non-diagnostic endoscopy within 3 years prior to cancer diagnosis.[1] Marked heterogeneity was found among the studies examined in the meta-analysis given the variety of countries where these studies were conducted, variable endoscopic practices, and differing incidence rates of UGI cancer. More recent studies have reported missed UGI cancer rates ranging from 6% to 8.3%. [50–52]

1.5 Key performance indicators for upper gastrointestinal endoscopy

In a position statement published in 2017, the BSG and AUGIS proposed a list of quality indicators, also called key performance indicators (KPI), and minimum expected standards to improve the quality of endoscopy (Table 3).[41]

Table 3 The minimal expected achievement of upper gastrointestinal endoscopy key performance indicators

Quality indicator	**Minimal standard**	**Aspirational standard**
A minimum number of 100 OGDs per year should be performed to maintain competence	Not applicable	100%
Photo documentation should be made of relevant anatomical landmarks	Not applicable	>90%
Photo documentation should be made of any detected lesions	>90%	100%
Adequate mucosal visualisation should be achieved by a combination of both aspiration and the use of mucosal cleansing techniques	75%	100%
The quality of mucosal visualisation should be reported	Not Applicable	90%
It is suggested that the inspection time during a diagnostic OGD should be recorded for surveillance procedures, such as Barrett's and gastric atrophy/intestinal metaplasia surveillance	Not applicable	>90%
Where a lesion is identified, this should be described using the Paris classification and targeted biopsies taken	>90%	100%

The length of a Barrett's segment should be classified according to the Prague classification	>90%	100%
When no lesions are detected within a Barrett's segment biopsies should be taken in accordance with the Seattle protocol	>90%	100%
Biopsies from two different regions in the oesophagus should be taken to rule out eosinophilic oesophagitis in those presenting with dysphagia/food bolus obstruction, where an alternative cause is not found	>90%	100%
Oesophageal ulcers and oesophagitis that is grade D or atypical in appearance, should be biopsied, with further evaluation in 4–6 weeks of PPI therapy	>90%	100%
Gastric ulcers should be biopsied and re-evaluated after appropriate treatment, including *H. pylori* eradication where indicated, within 6–8 weeks	>90%	100%
The presence of gastric polyps should be recorded, with the number, size, location and morphology described, with representative biopsies taken	>90%	100%
Where there are endoscopic features of gastric atrophy or intestinal metaplasia separate biopsies from the antrum and body should be taken	Not applicable	>90%

Where iron deficiency anaemia is being investigated, separate biopsies from the gastric antrum and body should be taken as well as duodenal specimens if coeliac serology is positive or has not been previously measured	Not applicable	>90%
Where gastric or duodenal ulcers are identified, *H. pylori* should be tested and eradicated if positive	>90%	100%
Where coeliac disease is suspected, a minimum of four biopsies from the second part of the duodenum including a specimen from the duodenal bulb should be taken	>90%	100%
Endoscopy units should audit rates of failing to diagnose upper gastrointestinal cancer on endoscopy	<10%	<5%

Adapted from position statement of the British Society of Gastroenterology (BSG) and Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS) doi:10.1136/gutjnl-2017-314109

Other endoscopy societies have also proposed quality indicators, however, these indicators were mainly focused on the general approach to perform UGI endoscopy and the quality of evidence was graded as weak to moderate due to lack of high quality evidence.[53–55]

1.6 Joint Advisory Group on Gastrointestinal Endoscopy

The Joint Advisory Group on Gastrointestinal Endoscopy (JAG) was initially established in 1994 to standardise endoscopy training across specialties. [56] JAG represents stakeholder organisations, including the Royal Colleges of Physicians, Royal Colleges of Surgeons, Royal Colleges of Radiologists and Royal Colleges of General Practitioners, along with the British Society of Gastroenterology and, more recently, the Association of Coloproctology of Great Britain and Ireland and the Association of Upper GI Surgeons. Over the last two decades, the position of JAG has evolved to meet its current role of quality assuring all aspects of endoscopy in the UK to provide the highest quality, patient-centred care. Over this period, JAG has spearheaded various quality improvement initiatives which have led to the achievement mainly in the three major areas : (1) training, (2) accreditation of services and (3) accreditation of screening endoscopists. The JAG Endoscopy Training System (JETS) was launched in 2009 to provide a structured endoscopy curriculum. It had four main purposes: (1) an electronic record of trainee procedural experience and assessment, (2) a portal for accessing training courses, (3) to provide evidence of trainees meeting JAG standards of competence and (4) to provide feedback to trainers and training course organisers. [57]

JAG accreditation of endoscopy services is a quality assurance program in the UK that promotes quality improvement through highlighting areas of best practice and areas for change. The Global Rating Scale (GRS), a quality improvement tool for endoscopy services was launched by the JAG in 2005 for services to self-assess against, alongside a set of standards which cover four domains: clinical quality, patient experience, clinical workforce, and training. [58] These

standards have recently been updated. [59] Over 50% of services in the UK are currently JAG accredited, with a total of 562 services registered with JAG in the UK and Ireland.

1.7 Thesis rationale, aims and phases of study

Missing oesophageal and gastric cancers at endoscopy and consequent diagnostic delays reduce the chance of cure and survival. Understanding the incidence of PEUGIC in England and associated factors will help to focus future efforts on the patients who are at high risk of PEUGIC. A comprehensive analysis of the reasons for PEUGIC through detailed review of all aspects of the endoscopy and associated clinical care at the hospital where it was undertaken and identifying correctable factors are vital to saving lives from oesophageal and gastric cancer. A standardised root cause analysis system will allow a systematic analysis of PEUGIC cases and missed opportunities which can be addressed at local and national level. A high quality endoscopy can increase chances of identifying cancer at an early or even precancerous stage. Identification of evidence based KPIs for UGI endoscopy will provide measures to improve and monitor quality of endoscopy which can hopefully improve patient outcomes.

1.7.1 Aims

The work in this thesis will aim to (1) summarise existing evidence for the UGI endoscopy KPIs to reduce PEUGIC; (2) identify new evidence for the potential KPIs; (3) develop consensus on the UGI endoscopy KPIs by involving key stakeholders and (4) develop a root case analysis system to investigate PEUGIC in greater depth.

1.7.2 Phases of the study

This project was conducted in 5 phases:

1) Umbrella systematic review of the quality indicators for the detection of dysplasia and cancers on UGI endoscopy (chapter 2);
2) Analysis of national cancer registration and analysis services and hospital episode statistics databases to identify variation in the PEUGIC rates and associated factors (chapter 3);
3) Analysis of the national endoscopy database to identify the differences in endoscopy practices between providers with highest and lowest PEUGIC rates in England (chapter 4);
4) Development of a root cause analysis system to establish the most plausible explanation of PEUGIC by analysing UGI cancer cases at two NHS hospitals (chapter 5);
5) Developing consensus on UGI endoscopy KPIs to reduce PEUGIC by employing modified nominal group technique (chapter 6).

The structure of this thesis, in line with the University of Birmingham guidelines for the alternative format, will take the form of published or publish-ready manuscripts. A final discussion chapter is also presented to summarise the work in this thesis and suggest directions for future research.

Chapter 2: Umbrella systematic review of potential quality indicators for the detection of dysplasia and cancer at upper gastrointestinal endoscopy

In this chapter I present the findings from an umbrella systematic review summarising existing evidence for the UGI endoscopy KPIs for the detection of UGI cancer and dysplasia and comparing it with already published national and international guidelines.

Supplementary material is found in the appendices for this chapter at the end of the thesis.

Manuscript

Kamran U, Abbasi A, Umar N, Tahir I, Brookes MJ, Rutter M, McCord M, Adderley NJ, Dretzke J, Trudgill N. Umbrella systematic review of potential quality indicators for the detection of dysplasia and cancer at upper gastrointestinal endoscopy. Endoscopy International Open. 2023 Sep;11(09):E835-48. DOI: 10.1055/a-2117-8621

2.1 Abstract

2.1.1 Background

Upper gastrointestinal (UGI) endoscopy lacks established quality indicators.

2.1.2 Aims

We conducted an umbrella systematic review of potential quality indicators for the detection of UGI cancer and dysplasia.

2.1.3 Methods

Bibliographic databases were searched until December 2021 for systematic reviews and primary studies. Studies reporting diagnostic accuracy, detection rates or the association of endoscopy or endoscopist related factors with UGI cancer or dysplasia detection were included. AMSTAR2 and JBI checklists used to assess systematic review and primary study quality. Clinical heterogeneity precluded meta-analysis and findings are summarised narratively.

2.1.4 Results

Eight systematic reviews and 9 primary studies were included. Image enhancement, especially narrow band imaging, had high diagnostic accuracy for dysplasia and early gastric cancer (pooled sensitivity 0.87 (95% CI 0.84-0.89) and specificity 0.97 (0.97-0.98)). Higher detection rates with longer endoscopy examination times were reported in three studies, but no difference was observed in one study. Endoscopist biopsy rate was associated with increased gastric cancer detection (odds ratio 2.5 (95% CI 2.1-2.9)). Early oesophageal (0.17% vs 0.14%, p 0.04) and

gastric cancer (0.16% vs 0.12%, p 0.02) detection rates were higher with propofol sedation compared to no sedation.

Endoscopies performed by trained endoscopists on dedicated Barrett's surveillance lists had higher detection rates (8% vs 3%, $p<0.001$). Neoplasia detection rate during diagnostic endoscopies for Barrett's oesophagus was 7 (95% CI 4-10)%.

2.1.5 Conclusions

Image enhancement use, longer examination times, biopsy rate and propofol sedation are potential quality indicators for UGI endoscopy. Neoplasia detection rate and dedicated endoscopy lists are additional potential quality indicators for Barrett's oesophagus.

2.2 Introduction

Endoscopy is the investigation of choice to detect upper gastrointestinal (UGI) cancers and premalignant conditions. However, 7-11% patients with UGI cancer have had an endoscopy within the 3 years prior to their cancer diagnosis which failed to diagnose cancer.[1–4] Improving endoscopy quality can therefore potentially detect UGI cancer at an earlier, or even premalignant, stage enabling organ-preserving endoscopic therapy and improve the often poor prognosis of UGI cancer.

Endoscopic societies have recommended a number of performance measures to optimise endoscopy quality but these are focused predominantly on the overall performance of diagnostic endoscopy, rather than cancer and dysplasia detection.[5–7] However, the recent Asian consensus guideline focused on the early detection of UGI neoplasia [8] and recommended premedications and antispasmodic agents, intravenous sedation, image enhancing techniques and sufficient observation time. Although, limited evidence was noted reporting the association of these factors with the detection of UGI cancer and dysplasia.

We have performed an umbrella review summarising the evidence for the association of potential endoscopic quality indicators with the detection of UGI cancer and dysplasia.

2.3 Methodology

The systematic review protocol was registered with PROSPERO (www.crd.york.ac.uk/prospero/ID=CRD42020225339). The reporting of the review was in accordance with the PRISMA guidelines (Supplementary Table 1). Study selection and data extraction (including quality assessment) was undertaken independently by at least two reviewers (U.K., N.U., A.A or I.T.). Disagreements were resolved through discussion or referral to the senior authors when consensus could not be reached.

2.3.1 Search strategy

A list of potential quality indicators was formulated from scoping searches and published guidelines (Supplementary Table 2). Searches for existing systematic reviews were undertaken in Embase, MEDLINE, MEDLINE In-Process, Cochrane Database of Systematic Reviews and Epistemonikos to December 2021. Supplementary searches for primary studies were undertaken in Embase, MEDLINE and CINAHL for quality indicators not examined by a recent high quality systematic review. Searches combined index terms and text words relating to endoscopy, UGI tract and dysplasia or neoplasm, and used filters for systematic reviews where applicable. There was no restriction by study design in searches for primary studies. Reference lists of included studies and published guidelines were searched for additional primary studies. There were no language restrictions. Examples of search strategies are provided in Supplementary Tables 3 and 4.

2.3.2 Study eligibility and selection

Systematic reviews and primary studies were included if they: (i) reported the detection rate of UGI cancer or dysplasia in relation to one or more endoscopic factors (procedural, endoscopist or endoscopy unit related); (ii) reported diagnostic accuracy of endoscopic factors for UGI cancer or dysplasia detection; or (iii) reported the association between detection rate and endoscopic factors. Eligible populations were adult patients undergoing endoscopy for screening for UGI cancer or dysplasia, to investigate UGI symptoms or for the surveillance of high-risk conditions (e.g. Barrett's oesophagus, gastric atrophy and gastric intestinal metaplasia). Exclusion criteria included narrative (non-systematic) reviews, case reports, conference abstracts and studies with no primary data (e.g. commentaries). A systematic review was defined as a review that at minimum used several data sources to identify studies. Studies which only assessed performance of transnasal or capsule endoscopy, or endoscopic modalities not widely used e.g. artificial intelligence and confocal laser endomicroscopy were also excluded. Where more than one systematic review was identified for an indicator, inclusion was limited to the most recent, comprehensive and/or methodologically robust systematic review. Primary studies of the discarded systematic reviews were cross referenced with the studies included in the most recent systematic review to ensure there were no omissions.

2.3.3 Data extraction and quality assessment

Data extraction was carried out using a piloted data extraction form. Data was collected on study design, population characteristics, sample size, endoscopy indicators, and results (detection rates

or diagnostic accuracy measures). Pooled summary estimates were extracted from systematic reviews.

The AMSTAR 2 tool was used to assess systematic review quality. The quality assessment standards included: multiple databases searched; data extraction and quality assessment performed by more than one reviewer; quality and risk of bias assessment of included studies performed; adequate consideration of heterogeneity of included studies in the synthesis.[9]

The revised Cochrane risk of bias tool (ROB2) was used to assess randomised controlled trial quality and risk of bias arising from the process of randomisation, assignment and adherence to the intervention, missingness of outcome data, measurement of outcome and reporting of results was assessed.[10] A modified JBI (The Joanna Briggs Institute) checklist for cohort studies was used to assess the primary study quality. The quality assessment standard included: criteria to recruit the study population; reliability of measures used to assess the exposure; differences in the experience and training of endoscopists between the groups; strategies to identify and deal with confounding factors; and generalisability of study findings.[11]

2.3.4 Data synthesis

Results are presented for each quality indicator separately. As Barrett's oesophagus is the most common premalignant condition studied, quality indicators associated with the detection of cancer and dysplasia in Barrett's oesophagus were categorised separately. All results were described narratively. For endoscopy examination time, summary estimates were presented in forest plots to show the direction of effect and consistency among studies; pooling of results was

not feasible due to significant heterogeneity due to differences in study population and endoscopist experience. Findings were interpreted in the context of study quality, taking into account whether any associations identified were adjusted for confounders.

2.4 Results

In total, 3,754 studies were screened after removing duplicates and 17 fulfilled the inclusion criteria. These included eight systematic reviews, eight retrospective cohort studies and one randomised controlled trial (Figure 1).[12-28]

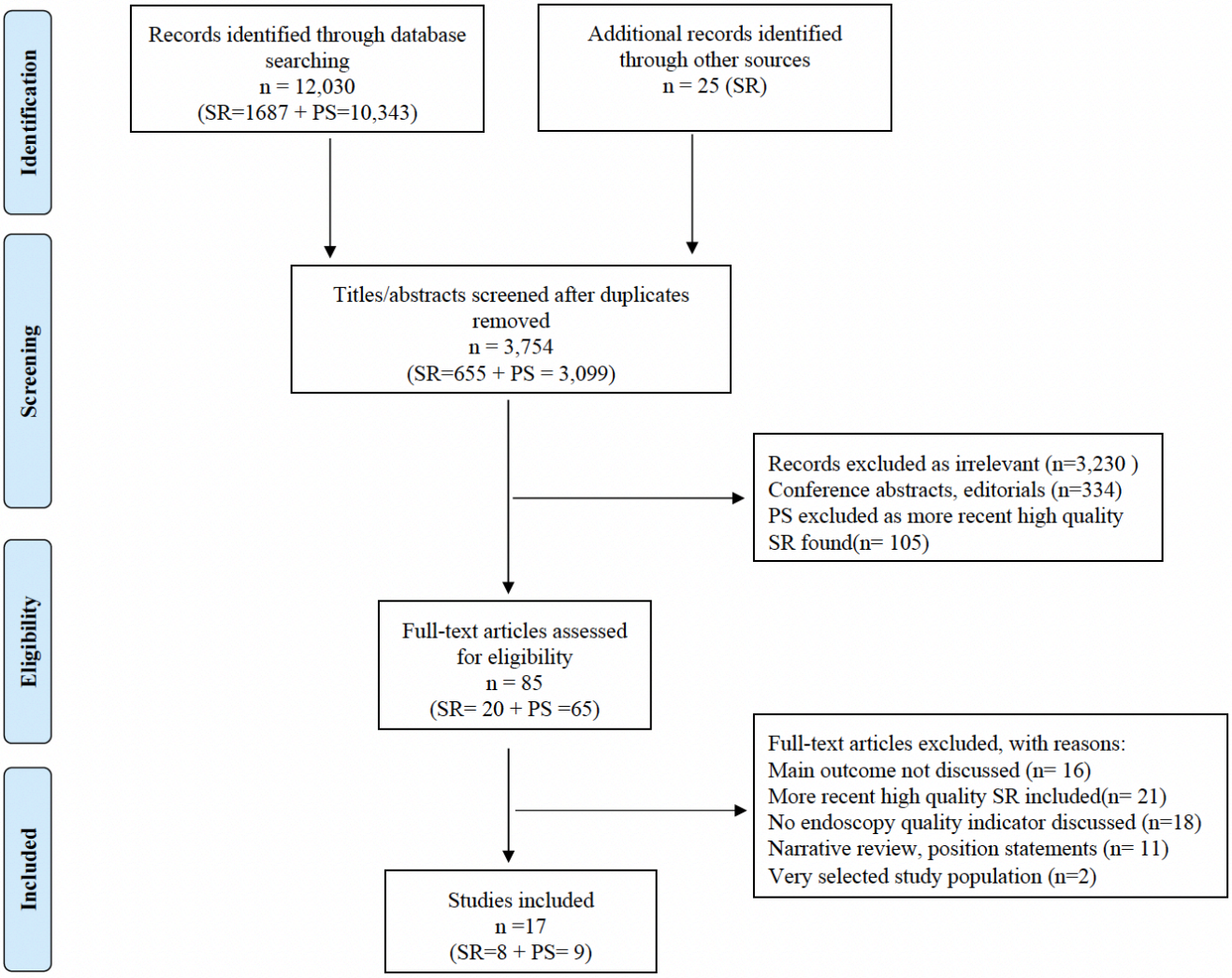


Figure 1 Flow chart of selecting eligible studies

SR, Systematic reviews; PS, Primary studies

List of the studies excluded after full text review and reasons of exclusion are provided in Supplementary Table 5.

The characteristics of the included studies are presented in Tables 1 (systematic reviews) and 2 (primary studies). Results of all meta-analyses included were based on random effect models.

Table 1 The characteristics of the systematic reviews included

Serial number	First Author (Publication year)	Quality indicators examined	Searched years	Number and design of studies included	Population studied	Number of patients	Main risk of bias
1	Parasa, S (2019) [25]	Neoplasia detection rate	2009-2018	11 (7 retrospective, 4 prospective)	Patients with GERD symptoms undergoing screening for Barrett's	10,632	Paucity of data on patient demographics. Pooled results of different study designs (Retrospective and Prospective)
2	Coletta, M (2016) [23]	Acetic acid chromoendoscopy	Inception to 2014	13 (prospective)	Patients with Barrett's oesophagus	1690	Variation in unit of analyses across studies i.e per patient, per area and per procedure analyses
3	Hajelssedig, O (2018) [24]	NBI and targeted biopsies	Inception to 2018	6 (4 RCT, 1 Cross sectional, 1 Single arm cross over)	Patients referred for routine surveillance or were referred for further evaluation of dysplasia in Barrett's oesophagus.	493	Unblinded comparison between NBI and WLE in four studies
4	Qumseya, B (2013)[22]	Advanced imaging techniques	Inception to October 2012	14 (11 RCT, 1 Prospective, 1 Cross sectional, 1 post hoc	Patients undergoing Barrett's surveillance	843	Searches limited to English language

				analysis of images			
5	Rodriguez, M (2020)[13]	Image enhancing techniques	Inception to December 2018	44 (5 RCT, 32 Prospective and 7 Retrospective)	Not specified	10175	52% of studies reported selection bias as highly selected patients/gastric area or lesion type
6	Le, H (2021)[12]	Magnification endoscopy	Inception to March 2020	8 (Prospective)	Not specified	5948	
7	Zhao, Z (2016)[14]	Dye-based chromoendoscopy	Inception to September 2015	10 (9 prospective , 1 retrospective)	Not specified	699	Details of quality assessment not reported
8	Morita, F (2017)[28]	Narrow band imaging	Inception to November 2015	12 (1 Prospective, 11 Cross sectional)	Not specified	1911	False negative rate cannot be assessed as only suspicious lesions were biopsied.

GERD: Gastro oesophageal reflux disease; NBI: Narrow band imaging; WLE: White light endoscopy; RCT: Randomised controlled trial

Table 2 The characteristics of the primary studies included

Serial number	First author (Publication year, country)	Study design	Factor examined	Definition of intervention/ exposure	Comparator arms	Sample size	Target population
1	Park, j (2017, South Korea)[17]	Retrospective, Single centre	Inspection time	Time from duodenal intubation to withdrawal from mouth	Fast (<3 min) vs slow endoscopists (≥ 3 min)	111962	Asymptomatic patients undergoing screening
2	Kawamura, T (2017, Japan)[18]	Retrospective, Single centre	Inspection time	Time from the first image capture in the pharynx or the upper oesophagus to when the exit button was pushed	Fast (<5min) vs moderate (5-7min) vs slow (>7min)	15763	Asymptomatic patients undergoing screening
3	Teh, J (2015, Singapore) [15]	Retrospective, Single centre	Inspection time	Time the endoscope was inserted into the patient's mouth to the time it was withdrawn	Fast <7 min vs Slow >7min	837	Symptomatic patients
4	Yoshimizu, S (2018, Japan)[20]	Retrospective, Single centre	Inspection time	Time from first image capture in the pharynx to scope removal.	Fast (<7min) vs Moderate (≥7min and <10min) vs Slow (≥10min)	3295	Asymptomatic patients undergoing screening
5	Gupta, N (2012, United States)[26]	Retrospective post hoc analysis of Multi centre RCT	Inspection time	Time spent on inspection of Barrett's mucosa on HD WLE (Excluded time spent using image enhancement techniques or for biopsies)	Inspection time > 1min/cm vs ≤1min/cm	112	Patients undergoing Barrett's surveillance or referred to confirm dysplasia
6	Ooi, J (2017, United Kingdom)[27]	Retrospective control vs prospective	Dedicated list by trained endoscopists	Endoscopies performed on dedicated lists by endoscopists trained in Barrett's surveillance	Dedicated lists vs non dedicated lists	729	Patients undergoing Barrett's surveillance

		intervention, multicentre					
7	Januszewicz, W (2019, Poland)[16]	Retrospective cohort, multicentre	Endoscopist biopsy rate	Proportion of endoscopies where at least one biopsy was taken (Biopsies for urease test not included)	Low (22.4% to 36.7%) vs moderate (36.8% to 43.7%) vs high (43.8% to 51.6%) vs very high (51.7% to 65.8%)	12,433 (Derivation cohort) 11,333 (Validation cohort)	Outpatient, Symptomatic and under surveillance
8	Zhou, J (2021, China)[19]	Retrospective, multicentre	Intravenous sedation	Use of propofol without intubation by anaesthesiologist	Propofol vs no sedation (propensity matched groups)	306202	Adults undergoing diagnostic endoscopies
9	Liu, X (2018, China)[21]	Multicentre RCT	Premedications	Use of simethicone and pronase mixed with water	A 100 ml water+20,000 units Pronase+1g NaHCO3 B 100ml water+80mg Simethicone C 100ml water +20,000 units Pronase+1g NaHCO3+ 80mg Simethicone D 100 Water	7143	Patients attending endoscopy for screening

HD- WLE: High definition white light endoscopy; RCT: Randomised controlled trial

2.4.1 Potential quality indicators

The results of the studies reporting potential quality indicators for UGI endoscopy are presented in Table 3.

Table 3 The results of studies reporting potential quality indicators associated with the detection of dysplasia and cancer on upper gastrointestinal endoscopy

Quality indicator	**Systematic review or primary study**	**Outcome**	**Pooled odds ratio**	**Pooled sensitivity**	**Pooled specificity**	**Pooled risk difference**	**Adjusted odds ratio**	**Detection rates**	**Comments**
Image enhancing techniques									
Narrow band imaging	SR and MA[13]	Early gastric cancer or dysplasia		0.87(0.84-0.89)	0.97(0.97-0.98)				Use of magnification associated with higher DOR and specificity. Most studies performed in eastern countries with higher prevalence of gastric cancer

	SR and MA[28]	Squamous cell cancers and HGD of oesophagus		Per lesion: 0.94(0.90-0.97) Per patient: 0.88(0.82-0.93)	Per lesion: 0.65(0.60-0.69) Per patient: 0.88(0.86-0.90)				NBI had higher specificity than Lugol-chromoendoscopy, although sensitivity and area under curve were similar.
Magnification endoscopy	SR and network MA[12]	Early gastric cancer	Overall: 2.97(1.68-5.25) M-NBI: 2.56(2.13-3.13) M-BLI: 3.13(1.85-5.71) M-WLI:1.43(1.12-1.85)						Magnification with NBI and BLI were superior to magnification with WLE. Important confounders e.g endoscopist experience not adjusted for
Dye-based chromoendoscopy	SR and MA[14]	Early gastric cancer and dysplasia		0.90(0.87-0.92)	0.82(0.79-0.86)	Early gastric cancer: 0.36(0.11-0.61) Gastric dysplasia: 0.17(0.07-0.28)			Most studies from Asia. No subgroup analysis based on different dyes

Observation time	Primary study[17]	Oesophageal and gastric cancers						Fast 0.20% vs Slow 0.28%, p=0.005	Endoscopists with examination time >3min detected 8% more small cancers, no difference in detection of large cancers. Screening asymptomatic patients.
	Primary study[18]	Oesophageal and gastric cancers					Moderate 1.90(1.06 –3.40) Slow 1.89(0.98 –3.64)	Fast 0.57% vs moderate 0.97% vs slow 0.94%	Examination time 5-7 minutes was associated with higher cancer detection rate. Factors adjusted for: sex, age, use of sedation, gastric atrophy, type of scope
	Primary study[15]	Gastric cancer and high-risk lesions					Slow 3.42 (1.25-10. 38)	Fast 6.1% vs Slow 14.0%, p<0.01	Examination time >7 min was associated with 3 times increased likelihood of detection of gastric cancer. Factors adjusted for: age, sex,

									endoscopist experience
	Primary study[20]	Oesophageal and gastric cancers						Fast 3.6% vs Moderate 3.3% vs Slow 3.1%, p=0.81	No difference in cancer detection rate. All endoscopists in fast group had intense training, compared to 66% in slow group.
Biopsy rate	Primary study[16]	Gastric cancers and premalignant conditions					Moderate 0.8 (0.5-1.2) High 3.0 (2.4-3.7) Very high 5.6 (3.2-9.8)		Factors adjusted for: age, sex and endoscopy unit. Strong correlation between endoscopist biopsy rate and detection of all UGI premalignant lesions
Intravenous sedation	Primary study[19]	Early oesophageal cancer						Sedation vs No sedation: 0.17% vs 0.14%, p=0.04	Sedation group had higher detection rate of early UGI cancer.

		Early gastric cancer						Sedation vs no sedation: 0.16% vs 0.12%, p=0.02	
Premedications	Primary study[21]	Early oesophageal or gastric cancers						A:1.3%, B:1.4%, C:1.5% D:1.6%, p=0.878	Use of Simethicone and Pronase on their own or as combination did not improve detection rate of cancer or precancerous lesions. All endoscopists had experience of 3000-5000 endoscopies
		Oesophageal and gastric premalignant conditions						A:8.7%, B:8.4%, C:10.0%, D:10.3% p=0.138	

SR: Systematic review; MA: Meta-analysis; HGD: High grade dysplasia; DOR: Diagnostic odds ratio; NBI: Narrow band imaging; WLE: White light endoscopy; BLI: Blue laser imaging; UGI: Upper gastrointestinal

2.4.1.1 Image enhancement techniques

Three systematic reviews reported the role of advanced imaging techniques in the detection of gastric cancer or dysplasia.[12-14] A meta-analysis of 19 studies reported that NBI had a pooled sensitivity of 0.87 (95% confidence interval 0.84-0.89) and pooled specificity of 0.97 (0.97-0.98).[13] Diagnostic accuracy was higher in depressed-type lesions (pooled sensitivity 0.88 (0.80-0.93), pooled specificity 0.96 (0.93-0.97)) than elevated-type lesions (pooled sensitivity 0.88 (0.82-0.92), pooled specificity 0.87 (0.80-0.92)). On subgroup analysis, the use of magnification endoscopy with NBI(ME-NBI) was associated with diagnostic odds ratio of 114.08 (46.30-281.08) compared to 60.34 (9.26-393.14) for non ME-NBI.[13] A network meta-analysis of 8 prospective studies reported that the use of magnification was superior to standard white light endoscopy in detecting early gastric cancer (odds ratio 2.97 (1.68-5.25)).[12]

The use of dye-based chromoendoscopy (including acetic acid, indigo carmine, methylene blue and hematoxylin) favoured detection of early gastric cancer (pooled risk difference 0.36 (0.11-0.61) and pre-malignant conditions (pooled risk difference 0.17 (0.07-0.28)), compared to standard white light endoscopy.[14] No subgroup analyses were performed to examine the diagnostic accuracy of individual dyes and most of the studies (80%) included were conducted in Asian countries with a high prevalence of gastric cancer and associated premalignant conditions.[14]

A systematic review of 18 studies (12 studies included in a meta-analysis) compared NBI with Lugol chromoendoscopy in the detection of oesophageal squamous cell cancer and/or high grade dysplasia.[28] Pathological diagnosis was used as the gold standard. Specificity was higher for

NBI (0.88 (0.86-0.90)) than Lugol chromoendoscopy (0.82 (0.80-0.85)). However, there was no difference in sensitivity and area under receiver operating curve between the two modalities.

2.4.1.2 Endoscopic examination time

Four retrospective studies compared neoplastic detection rates based on the endoscopic examination time.[15,17,18,20] Three studies analysed the detection of all UGI neoplasms[17,18,20], and one analysed detection of gastric malignant and pre-malignant lesions only.[15] There was heterogeneity among studies with regards to the definition of examination time. Three studies recorded the time from endoscope insertion into the mouth or pharynx to the scope withdrawal from the mouth[15,18,20], and one recorded the scope withdrawal time from duodenum to the mouth.[17] Two studies reported that a longer examination time was associated with higher neoplasm detection rate.[15,17] Kawamura et al. reported that the endoscopists with moderate (5-7 minutes) and longer (>7 minutes) examination times had higher UGI cancer detection rates than the endoscopists with shorter (<5 minutes) examination time, however detection rates were similar between endoscopists in moderate and longer examination time groups.[18] One study reported that the oesophageal and gastric cancer detection rates were not statistically different between fast, moderate and slow endoscopists.[20] Although all endoscopists included in this study had an overall experience of performing more than 1000 endoscopies, only 66% of the endoscopists with longer examination times had received intense training in lesion detection, compared to the all endoscopists with shorter examination times.[20] Supplementary Figure 1 shows the forest plot of neoplastic detection rates based on examination time.

2.4.1.3 Biopsy rate

A multicentre retrospective cohort study reported the association of endoscopists' biopsy rates and the rates of both gastric cancer and premalignant diagnoses, and missed gastric cancers (diagnosed between 1 month to 3 years after an endoscopy without a cancer diagnosis).[16] The biopsy rate was calculated as the proportion of endoscopies where at least one biopsy was taken (excluding samples for rapid urease testing). Endoscopists' biopsy rates strongly correlated with gastric premalignant lesions detection (ρ 0.83; P< 0.001). After adjusting for age, sex and endoscopy unit, biopsy rate was strongly associated with gastric cancer detection (OR for highest biopsy rate 5.6 (95% CI 3.2-9.8)). The incidence of missed gastric cancer in the lower biopsy rate group was 49.6 per 100,000 person-years compared to 23.1 per 100,000 person-years in higher biopsy rate.

2.4.1.4 Intravenous sedation

A multicentre retrospective study compared detection rates of early oesophageal and gastric cancers in patients who underwent endoscopic examination under sedation (Propofol without tracheal intubation) with patients who underwent endoscopy without sedation, after propensity matching.[19] Patients in the sedation group had higher early oesophageal cancer (0.17% vs 0.14%, p=0.04) and gastric cancer detection rates (0.16% vs 0.12%, p=0.02). Mean examination time was longer in the sedation group, and more patients in the sedation group were examined using image enhancement and magnification techniques.

2.4.1.5 Mucolytics and defoaming agents

A multicentre randomised control trial examined the effect of defoaming (Simethicone) and mucolytic (Pronase) agents on the detection of early UGI cancers or premalignant lesions (primary endpoint) and mucosal visibility (secondary endpoint). Although premedications improved mucosal visibility at all important anatomical landmarks in the oesophagus and stomach ($p<0.001$), neoplasia detection rates were not statistically different between intervention and control groups.[21]

2.4.2 Potential quality indicators for Barrett's oesophagus

The results of the studies reporting potential endoscopy quality indicators specific to the assessment and surveillance of Barrett's oesophagus are presented in Table 4.

Table 4 Results of studies reporting potential quality indicators associated with the detection of dysplasia and cancer on upper gastrointestinal endoscopy for Barrett's oesophagus

Quality indicator	Systematic review or primary study	Outcome	Pooled prevalence	Pooled sensitivity	Pooled specificity	Pooled risk difference	Detection rates	Comments
Image enhancing techniques								
Narrow band imaging guided targeted biopsies	SR and MA[24]	All grade dysplasia		0.76 (0.61–0.91)	0.99 (0.99–1.00)			NBI targeted biopsies have high diagnostic accuracy for all grade dysplasia but low sensitivity for LGD.
		HGD		0.83 (0.73–0.93)	0.99 (0.99–1.00)			
		LGD		0.60 (0.11–1.00)	0.98 (0.95–1.00)			
Acetic Acid	SR and MA[23]	HGD and early oesophageal cancer		0.92 (0.83-0.97)	0.96 (0.85-0.99)			Median prevalence of HGD/ early oesophageal cancer was 13%, higher than expected in general surveillance population
Virtual and chromoendoscopy	SR and MA[22]	All grade dysplasia				0.34 (0.20 - 0.48)		Heterogenous studies due to use of different imaging modalities

Observation time	Primary study[26]	Endoscopic lesions suspicious of dysplasia					Observation time >1min/cm vs ≤1min/cm: 54.2% vs 13.3%, p=0.04	High prevalence of HGD/ early oesophageal cancer (i.e. 34%) in study population. All endoscopies performed by experienced endoscopists in academic referral centre. Relatively smaller sample size may have resulted in type II error.
		Histologically proven HGD/ early oesophageal cancer					Observation time >1min/cm vs ≤1min/cm: 40.2% vs 6.7%, p=0.06	
Dedicated list by trained endoscopist	Primary study[27]	All grade dysplasia					18% vs 8%, p<0.001	
		HGD/ early oesophageal cancer					8% vs 3% , p<0.001	
Neoplasia detection rate	SR and MA[25]	HGD/ early oesophageal cancer	7 (4-10)%					Higher prevalence in US studies 11(7-16)% vs non US studies 5(3-8)%

2.4.2.1 Image enhancement techniques

Three systematic reviews and meta analyses, including 33 studies, analysed the role of image enhancement techniques in the detection of dysplasia and cancer during Barrett's surveillance.[22-24] Compared to standard white light endoscopy, both virtual and dye-based chromoendoscopy increased the diagnostic yield for dysplasia or cancer by 34(95% CI 20-48)%, however no significant difference was found between virtual and dye-based chromoendoscopy and the findings were not adjusted for important confounding factors e.g. endoscopist experience.[22]

The use of acetic acid with targeted biopsies had a sensitivity of 0.92 (0.83-0.97) and specificity of 0.96 (0.85-0.99) for high grade dysplasia (HGD) and early oesophageal adenocarcinoma.[23] Narrow band imaging (NBI) with targeted biopsies had a high diagnostic accuracy for all grade dysplasia (sensitivity 0.76 (0.61–0.91) and specificity 0.99 (0.99–1.00)) and HGD (sensitivity 0.83 (0.73–0.93) and specificity 0.99 (0.99–1.00)), in comparison to the Seattle protocol biopsies. However, its sensitivity was lower for low grade dysplasia (0.60 (0.11–1.00).[24] Compared to random biopsies, the numbers needed to detect an additional patient with HGD and low grade dysplasia using NBI were 1.95 and 3.95 respectively. None of the studies included in this meta analysis reported data for the median prevalence of dysplasia. No statistically significant difference in the results was observed in a sensitivity analysis of four studies which used magnification.

2.4.2.2 Examination time

In a post hoc analysis of a multicentre clinical trial, a greater proportion of patients were found to have endoscopically suspicious lesions as the total inspection time of Barrett's oesophagus with high definition white light endoscopy increased ($p < 0.001$).[26] This effect persisted even after excluding overtly suspicious lesions. Endoscopists with average inspection times of >1 min per centimetre of Barrett's mucosa had higher detection rates of endoscopically suspicious lesions (54.2% vs 13.3%, $p = 0.04$) but the difference in rates of HGD/early oesophageal adenocarcinoma just failed to reach statistical significance (40.2% vs 6.7%, $p=0.06$).

2.4.2.3 Dedicated endoscopy lists by trained endoscopists

A multicentre study prospectively analysed the dysplasia detection rate of endoscopists trained in lesion recognition, Prague classification and Seattle biopsy protocol technique, undertaking Barrett's surveillance on dedicated lists with extra time for the endoscopies and compared these interventions with historic data of Barrett's surveillance endoscopies.[27] Dedicated sessions had higher detection rates for all grades of dysplasia (18% vs 8%, $p<0.001$) and HGD/early oesophageal adenocarcinoma (8% vs 3% , $p<0.001$).

2.4.2.4 Neoplasia detection rate

A systematic review including 11 studies (10,632 patients) defined the neoplasia detection rate (NDR) as the pooled prevalence of HGD and EAC on the index endoscopy for patients with chronic gastro-oesophageal reflux symptoms undergoing screening for Barrett's oesophagus.[25] NDR was estimated at 7 (95% CI 4-10)% and proposed as a quality measure for such endoscopies.

2.4.3 Other potential quality indicators

No studies have directly examined the association between the detection rate of UGI cancer/dysplasia and the use of antispasmodic medications, photo documentation, endoscopists' specialty or the annual volume of endoscopies.

A summary of the evidence and comparison with published endoscopy society guidelines is presented in Table 5.

Table 5 Summary of quality indicators for upper gastrointestinal endoscopy in national and international guidelines as evidence from this systematic review

Quality indicator	**BSG (2017)[5]**	**ESGE (2016)[6]**	**AGA (2015)[7]**	**Asian consensus (2019)[8]**	**Evidence** (Summary of evidence for the detection of UGI cancer or dysplasia)
Mucolytic and defoaming agents	Recommended	Not specified	Not specified	Recommended	No evidence-one RCT: no difference in the detection rates.
Intravenous sedation	When required	Not specified	Recommended	Recommended	Insufficient evidence- one retrospective study: Sedation (Propofol) improved detection rates
Minimum number of procedures to maintain competence	≥ 100 per year	Not specified	Not specified	Not specified	No evidence

Examination time	≥ 7 minutes	≥ 7 minutes	Not specified	≥ 8 minutes	Insufficient evidence- 3 retrospective cohort studies favour longer observation time, but unable to recommend minimum cut off due to heterogeneity. One study did not find a difference.
Image enhancement techniques	Recommended if squamous neoplasia suspected in oesophagus	Recommended if squamous neoplasia suspected in oesophagus	Not specified	Recommended	Quality indicator recommended as multiple systematic reviews support use of image enhancement techniques
Photo-documentation	Minimum 8 images	Minimum 10 images	Not specified	Minimum 22 images	No evidence

Endoscopist Biopsy rate	Not specified	Not specified	Not specified	Not specified	Insufficient evidence- strong correlation with detection of gastric cancer and all UGI premalignant conditions
Barrett's mucosa inspection time	≥1 min per cm	≥1 min per cm	Not specified	≥1 min per cm	Insufficient evidence- post hoc analysis of RCT: higher rate of endoscopic suspicious lesion but no difference in detection of HGD or cancer
Dedicated list by trained endoscopist for Barrett's surveillance	Not specified	Not specified	Not specified	Not specified	Insufficient evidence-prospective cohort compared with retrospective data showed improved detection rates

Neoplasia detection rate on index endoscopy for Barrett's screening	Not specified	Not specified	Not specified	Not specified	Insufficient evidence- one systematic review reported the prevalence of HGD and oesophageal adenocarcinoma for patients undergoing screening for Barrett's oesophagus.

BSG: British Society of Gastroenterology; ESGE: European Society of Gastrointestinal Endoscopy; AGA: American Gastroenterological Association; UGI: Upper Gastrointestinal; RCT: Randomised Controlled Trial; HGD: High Grade Dysplasia.

2.4.4 Quality assessment

The quality assessment of the systematic reviews is summarised in Supplementary Table 6. Overall, the reviews were of high methodological quality. The main risk of bias was the heterogeneity due to a wide variation in the prevalence of UGI cancer and dysplasia, use of different imaging modalities and non-adjustment for important confounding factors, e.g. endoscopist experience.

The summary of the quality assessment of primary studies is shown in Supplementary Table 7. The main concern in 88% of the studies was that the included study population was not always representative of the standard endoscopy population in terms of underlying risk (of cancer and dysplasia). There was a difference in the endoscopists' training and experience between the two study groups in 50% of studies[17,18,20,27] and confounding factors were not identified in two studies.[26,27] The randomised controlled trial on premedications presented an overall low risk of bias, except for some concern due to the lack of strict adherence to the timing of the mucolytic and defoaming agents.[21]

2.5 Discussion

Gastric and oesophageal cancers are the fourth and fifth leading causes of cancer related deaths worldwide, mainly owing to their typically late presentation.[29] Screening programmes have been developed for some high incidence populations, but they have not been implemented in most parts of the world and endoscopy is generally limited to investigating UGI symptoms and for the surveillance of pre-malignant conditions.[30-32] High quality endoscopy still has a critical role in identifying and monitoring pre-malignant conditions and in the detection of associated cancer and dysplasia, which may be amenable to endoscopic treatment. In this umbrella review we have summarised the evidence for potential quality indicators to improve the diagnostic yield of endoscopy for the detection of UGI cancer and dysplasia.

British and European endoscopic society guidelines recommend white light endoscopy and random biopsies to diagnose premalignant conditions and targeted biopsies for suspected malignant lesions.[5,6] Dye and targeted image enhancement techniques were recommended for better characterisation if squamous dysplasia is suspected in the oesophagus. However, routine use of chromoendoscopy was not recommended due to a lack of robust evidence. The current review found evidence in favour of image enhancement techniques, especially narrow band imaging (NBI; Olympus, Japan). NBI uses filters to enhance microvascular patterns, mainly as a result of the differential optical absorption of light by haemoglobin in the mucosa. NBI, with or without magnification, had a high diagnostic accuracy for the detection of early gastric and oesophageal cancers. However, studies included endoscopists who were experienced in using NBI, or had training in using NBI patterns in enriched populations with a high risk of cancer or dysplasia. This may not be reflective of the routine practice as the majority of endoscopists are

not trained in lesion recognition using NBI. A standardised training programme to use image enhancement techniques can potentially improve endoscopist performance.[33] Several other chromoendoscopy systems are also available, including i-scan (Pentax, Japan), FICE (Flexile spectral imaging colour enhancement; Fujifilm, Japan), SPICE (STORZ professional imaging enhancement system, Storz, Germany) and BLI (Blue laser imaging; Fujifilm, Japan). However, performance of each system has not been compared to date. We recommend from this umbrella systematic review that image enhancement techniques should be considered to enhance the earlier detection and delineation of UGI cancer and dysplastic lesions particularly in high risk patients.

For Barrett's surveillance, chromoendoscopy guided biopsies had high diagnostic accuracy to detect HGD and early oesophageal adenocarcinoma, however, the sensitivity was only 60% for LGD. LGD is the histological or clinical marker associated with the highest risk of progression to HGD or oesophageal adenocarcinoma and there is increasing evidence that LGD can be successfully treated endoscopically, which can halt its progression.[34] Based on current evidence, chromoendoscopy targeted biopsies therefore cannot replace Seattle protocol biopsies, given the low sensitivity for LGD and chromoendoscopy should be used as an adjunct in Barrett's surveillance.

Colonoscopic withdrawal time is a well-established quality indicator for colonoscopy and longer withdrawal times have been shown to be associated with higher adenoma detection rates and a reduced incidence of interval colorectal cancers.[35] Western guidelines have recommended a minimum procedure time of 7 minutes for endoscopy[5,6], but that recommendation was based

on a single retrospective cohort study.[15] The Asian consensus guideline suggested that the systematic observation of the UGI tract should take a minimum of 8 minutes. In the current review, we found three additional retrospective studies. All except one study reported that a longer examination time can increase the diagnostic yield of endoscopy for cancer or dysplasia. Yoshomizu et al. did not find a difference in the UGI cancer detection rates based on the difference in endoscopic examination time.[20] However, all of the endoscopists who had shorter examination times had received ≥ 1 year of intense training in lesion detection, compared to only 66% of the endoscopists with longer examination times in this study, likely introducing performance bias, as the endoscopists with ≥ 1 year of intense training were more likely to find UGI cancers . Longer inspection times of Barrett's mucosa have also been shown to increase the detection rate of endoscopic suspicious lesions. Although the difference in the rate of detection of HGD and oesophageal adenocarcinoma was not statistically significant, the relatively smaller sample size in this study may have resulted in type II error.[26] Although most of the studies favoured longer examination times, it is not possible to comment on the minimum cut off time due to significant heterogeneity among studies and further data in different populations is clearly needed on this important indicator with adjustment for the experience of the endoscopists.

The endoscopist biopsy rate was found to have a strong correlation with the detection of gastric cancer and premalignant conditions and was associated with a lower incidence of missed gastric cancers. However, this observation was based on a single retrospective study from Poland and should be validated in other parts of the world.[16]

The use of sedation can improve patient acceptance and tolerance of endoscopy, which are both important for a high-quality examination. Only one study has investigated impact of sedation on the diagnostic yield and reported that the detection rate for early UGI cancer was higher among patients who received sedation with propofol.[19] However, results in this study were not adjusted for the important confounders e.g. the use of image enhancement and magnifying techniques, observation time and the number of biopsies taken. Furthermore, propofol was used for sedation in this study, in addition to midazolam and opioid, which is not a routine practice in most parts of the world, indicating that the study findings may not be generalisable and warrant further validation.

The neoplasia detection rate at the index or first diagnostic endoscopy has been proposed as a quality indicator for patients undergoing screening for Barrett's oesophagus. Four to ten percent of patients with Barrett's oesophagus are found to have advanced neoplasia on their index endoscopy.[25] Given the relatively low progression rates of non-dysplastic Barrett's oesophagus to advanced neoplasia, this high prevalence rate suggests that a high quality index endoscopy will have the most significant impact in preventing death from neoplasia in Barrett's patients. Similar to the concept of adenoma detection rate in colonoscopy, endoscopists performing high quality Barrett's surveillance endoscopies would be expected to find a higher proportion of patients with advanced neoplasia. However, the association of higher neoplasia detection rates with the outcomes of missed or interval UGI cancers and cancer related mortality have not been studied to date.

For Barrett's surveillance, appropriate time slots and training in the Prague classification, Seattle protocol biopsy regimen and lesion recognition resulted in improvements in the endoscopists' performance and a more than two-fold increase in all grades of dysplasia and oesophageal adenocarcinoma detection. These measures should be investigated in further prospective studies and considered as potential quality indicators for Barrett's surveillance. Previous studies have only examined these measures in dedicated Barrett's surveillance sessions. Future studies should also compare if allocation of appropriate time slots even in non dedicated endoscopy sessions, which are carried out by an appropriately trained endoscopist, would produce similar results.

Some limitations have to be considered. The majority of the studies examined were carried out in Eastern countries where the prevalence of gastric cancer is much higher than in Western countries. There were high levels of heterogeneity among the studies regarding study population, endoscopist experience and the strategies used to measure the exposure of interest e.g. examination time. Due to the retrospective nature of some studies and potential risk of bias due to failure to account for important confounding variables (as summarised in supplementary tables 6 and 7), it was not possible to establish causality. Therefore, the findings are reported as associations rather than causal relationships. The formal assessment of small study effects (including publication bias) was not possible. Interventions such as artificial intelligence and confocal laser endomicroscopy, which could potentially improve the diagnostic yield of endoscopy were not included as they lack published data.

2.6 Conclusion

This review has found evidence for image enhancement techniques, which should be considered to improve the diagnostic yield of UGI endoscopy. Examination time, endoscopist biopsy rate and intravenous sedation are other potential quality indicators, but need further investigation in prospective studies. Neoplasia detection rate and dedicated lists by trained endoscopists were identified as additional quality indicators for Barrett's oesophagus.

2.7 References

1 Menon S, Trudgill N. How commonly is upper gastrointestinal cancer missed at endoscopy? A meta-analysis. *Endosc Int Open* 2014;2:E46–50.

2 Chadwick G, Groene O, Hoare J, *et al.* A population-based, retrospective, cohort study of esophageal cancer missed at endoscopy. *Endoscopy* 2014;46:553–60.

3 Chadwick G, Groene O, Riley S, *et al.* Gastric Cancers Missed During Endoscopy in England. *Clin Gastroenterol Hepatol* 2015;13:1264–70.e1.

4 Pimenta-Melo AR, Monteiro-Soares M, Libânio D, *et al.* Missing rate for gastric cancer during upper gastrointestinal endoscopy. European Journal of Gastroenterology & Hepatology. 2016;28:1041-1049

5 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;66:1886–99. doi:10.1136/gutjnl-2017-314109

6 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;48:843–64.

7 Park WG, Shaheen NJ, Cohen J, *et al.* Quality indicators for EGD. *Am J Gastroenterol* 2015;110:60–71.

8 Chiu PWY, Uedo N, Singh R, *et al.* An Asian consensus on standards of diagnostic upper endoscopy for neoplasia. Gut. 2019;68:186–97. doi:10.1136/gutjnl-2018-317111

9 Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. bmj. 2017 Sep 21;358.

10 Sterne JA, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 366: l4898.

11 Moola S, Munn Z, Tufanaru C, et al. Chapter 7: Systematic reviews of etiology and risk. Joanna briggs institute reviewer's manual. The Joanna Briggs Institute. 2017 Jul 17;5.

12 Le H, Wang L, Zhang L, *et al.* Magnifying endoscopy in detecting early gastric cancer: A network meta-analysis of prospective studies. *Medicine* 2021;100:e23934.

13 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;52:1048–65.

14 Zhao Z, Yin Z, Wang S, *et al.* Meta-analysis: The diagnostic efficacy of chromoendoscopy for early gastric cancer and premalignant gastric lesions. *J Gastroenterol Hepatol* 2016;31:1539–45.

15 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;13:480–7.e2.

16 Januszewicz W, Wieszczy P, Bialek A, *et al.* Endoscopist biopsy rate as a quality indicator for outpatient gastroscopy: a multicenter cohort study with validation. *Gastrointest Endosc* 2019;89:1141–9.

17 Park JM, Huo SM, Lee HH, *et al.* Longer Observation Time Increases Proportion of Neoplasms Detected by Esophagogastroduodenoscopy. *Gastroenterology* 2017;153:460–9.e1.

18 Kawamura T, Wada H, Sakiyama N, *et al.* Examination time as a quality indicator of screening upper gastrointestinal endoscopy for asymptomatic examinees. *Dig Endosc* 2017;29:569–75.

19 Zhou J, Li Z, Ji R, *et al.* Influence of Sedation on the Detection Rate of Early Cancer and Precancerous Lesions During Diagnostic Upper Gastrointestinal Endoscopies: A Multicenter Retrospective Study. *Am J Gastroenterol* 2021;116:1230–7.

20 Yoshimizu S, Hirasawa T, Horiuchi Y, *et al.* Differences in upper gastrointestinal neoplasm detection rates based on inspection time and esophagogastroduodenoscopy training. *Endosc Int Open* 2018;6:E1190–7.

21 Liu X, Guan CT, Xue LY, *et al.* Effect of premedication on lesion detection rate and visualization of the mucosa during upper gastrointestinal endoscopy: a multicenter large sample randomized controlled double-blind study. *Surg Endosc* 2018;32:3548–56.

22 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. Clinical Gastroenterology and Hepatology. 2013;11:1562–70.e2. doi:10.1016/j.cgh.2013.06.017

23 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. Gastrointestinal Endoscopy. 2016;83:57–67.e1. doi:10.1016/j.gie.2015.07.023

24 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. Journal of Gastroenterology and Hepatology. 2021;36:2659–71. doi:10.1111/jgh.15577

25 Parasa S, Desai M, Vittal A, *et al.* Estimating neoplasia detection rate (NDR) in patients with Barrett's oesophagus based on index endoscopy: a systematic review and meta-analysis. Gut. 2019;68:2122–8. doi:10.1136/gutjnl-2018-317800

26 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. Gastrointestinal Endoscopy. 2012;76:531–8. doi:10.1016/j.gie.2012.04.470

27 Ooi J, Wilson P, Walker G, *et al.* Dedicated Barrett's surveillance sessions managed by trained endoscopists improve dysplasia detection rate. Endoscopy. 2017;49:524–8. doi:10.1055/s-0043-103410

28 Morita FHA, Bernardo WM, Ide E, *et al.* Narrow band imaging versus lugol chromoendoscopy to diagnose squamous cell carcinoma of the esophagus: a systematic review and meta-analysis. *BMC Cancer* 2017;17:54.

29 Sung H, Ferlay J, Siegel RL, *et al.* Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021;71:209–49.

30 Gastrointestinal tract (upper) cancers - recognition and referral. https://cks.nice.org.uk/topics/gastrointestinal-tract-upper-cancers-recognition-referral/ (accessed 7 Jun 2022).

31 Fitzgerald RC, di Pietro M, Ragunath K, *et al.* British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. *Gut* 2014;63:7–42.

32 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;68:1545–75.

33 Chiu PW, Sano Y, Uedo N, Singh R, Ng EK, Aang TL, Chiu HM, Ho SH, Banerjee R, Tanaka S, Li XB. Utility of a standardized training program for endoscopic diagnosis of early gastrointestinal neoplasia. Endoscopy international open. 2019 Apr;7(04):E452-8.

34 di Pietro M, Fitzgerald RC, BSG Barrett's guidelines working group. Revised British Society of Gastroenterology recommendation on the diagnosis and management of Barrett's oesophagus with low-grade dysplasia. *Gut* 2018;67:392–3.

35 Shaukat A, Rector TS, Church TR, Lederle FA, Kim AS, Rank JM, Allen JI. Longer withdrawal time is associated with a reduced incidence of interval cancer after screening colonoscopy. Gastroenterology. 2015 Oct 1;149(4):952-7.

Chapter 3: Analysis of national cancer registration and analysis services and hospital episode statistics databases to identify variation in the post endoscopy upper gastrointestinal cancer rates and associated factors

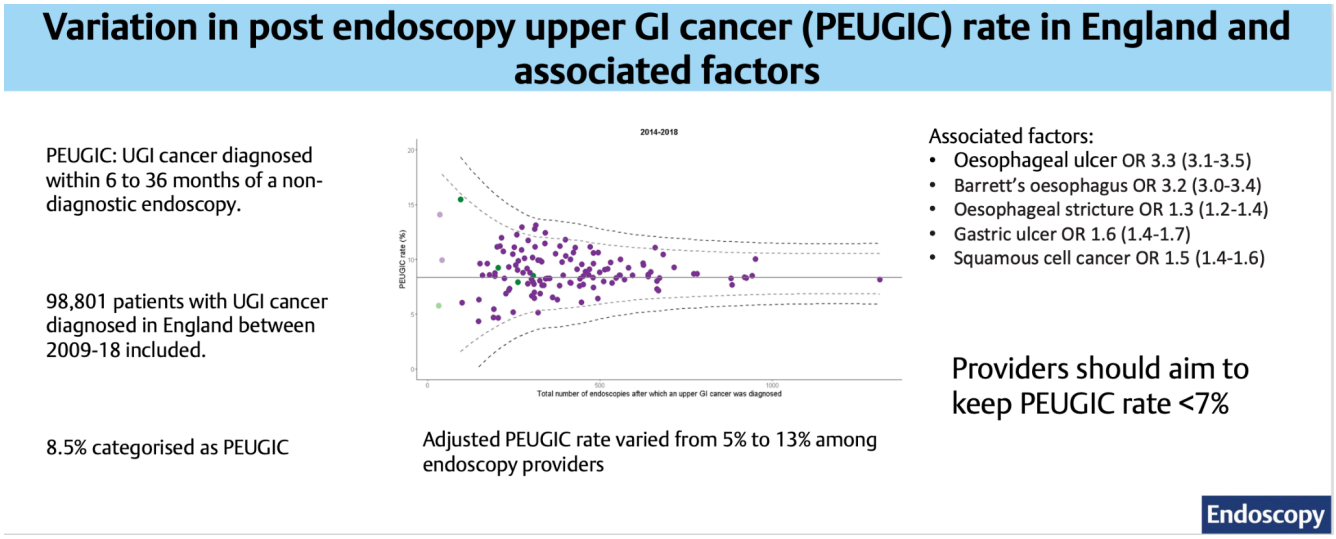
In this chapter I present the findings from a population based retrospective case control study examining variation in PEUGIC rates among endoscopy providers in England and associated factors.

Supplementary material is found in the appendices for this chapter at the end of the thesis.

Manuscript

Kamran U, Evison F, Morris EJ, Brookes MJ, Rutter MD, McCord M, Adderley NJ, Trudgill N. The variation in post-endoscopy upper gastrointestinal cancer rates among endoscopy providers in England and associated factors: a population-based study. Endoscopy. 2024 Aug 29. DOI: 10.1055/a-2378-1464

Graphical abstract



3.1 Abstract

3.1.1 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.

3.1.2 Methods

This 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.

3.1.3 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 oesophagus (OR 3.21 [3.02–3.42]), oesophageal 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]).

3.1.4 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.

3.2 Introduction

In the UK, 16 800 people are diagnosed with upper gastrointestinal (UGI) cancer each year, including cancers in the oesophagus 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.[4–6] 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.

3.3 Methods

3.3.1 Study design and data sources

This was a population-based, retrospective, case–control study. A case-control study design was chosen as patients with the outcome of interest (PEUGIC) were compared to those without: patients were included in the study after they had been diagnosed with UGI cancer and then categorised into cases (PEUGIC) or controls (detected cancers). 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 revision (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]

3.3.2 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 3 years prior to their cancer diagnosis. Patients were excluded if there was no record of an endoscopy within 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 the year of cancer diagnosis.

3.3.3 PEUGIC calculation

We adapted the methods recommended by the World Endoscopy Organization for PCCRC.[13] Endoscopies were categorised 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 false negative or index endoscopy and included in 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.

3.3.4 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 categorised 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 oesophagus (K22.7), oesophageal ulcer (K22.1), oesophageal 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 tumour characteristics: clinical stage – categorised as 1–4, or unknown when data were missing; tumour location – classified as upper, middle, or lower third of the oesophagus, or unspecified site in the oesophagus 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 – categorised 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.

3.3.5 Endoscopy provider characteristics

Healthcare providers were identified using a unique code recorded in HES indicating where the relevant endoscopy was performed. Organisations change over time, for example due to hospital mergers, and therefore historical organisations were mapped to current providers, as they existed on 30 June 2020. Information was collected on whether the provider was an NHS organisation 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 categorised 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 organisations 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 categorised 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.

3.3.6 Statistical analysis

Categorical variables were summarised 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 labelled 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 oesophagus.

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).

3.3.7 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.

3.3.8 Ethics

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

3.4 Results

3.4.1 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) (Figure 1). The PEUGIC rate was 8.8% in patients with oesophageal cancer and 8.0% in patients with gastric cancer (see supplementary Figure 1 and supplementary Figure 2 in the supplementary material). For cancers diagnosed in patients with Barrett's oesophagus, the PEUGIC rate was 21%.

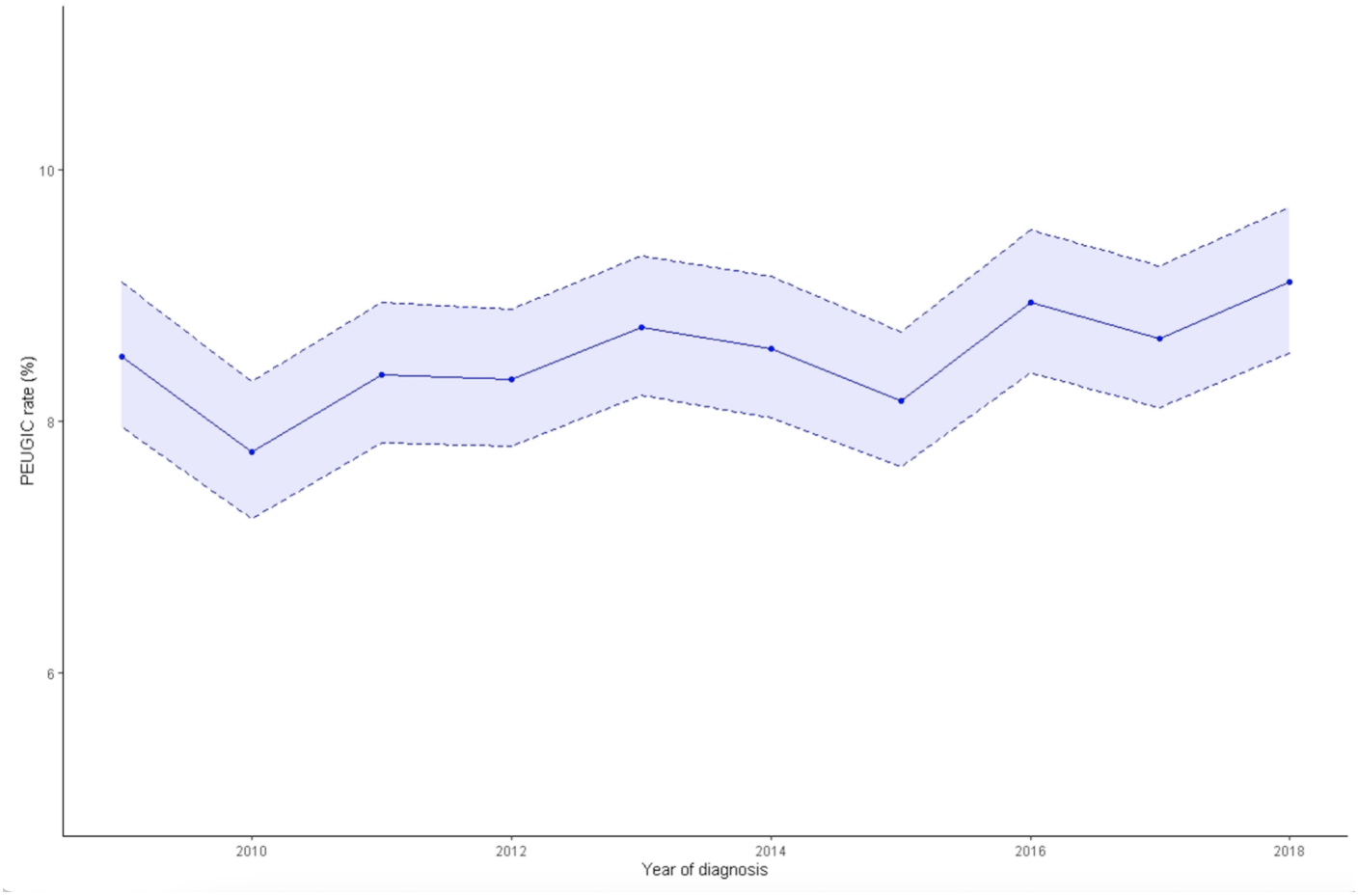


Figure 1 The unadjusted rates of post-endoscopy upper gastrointestinal cancer (PEUGIC) between 2009 and 2018. P value for the difference in rate between 2009 and 2018 = 0.03

Figure. 2 shows a PEUGIC example in a patient with Barrett's oesophagus.

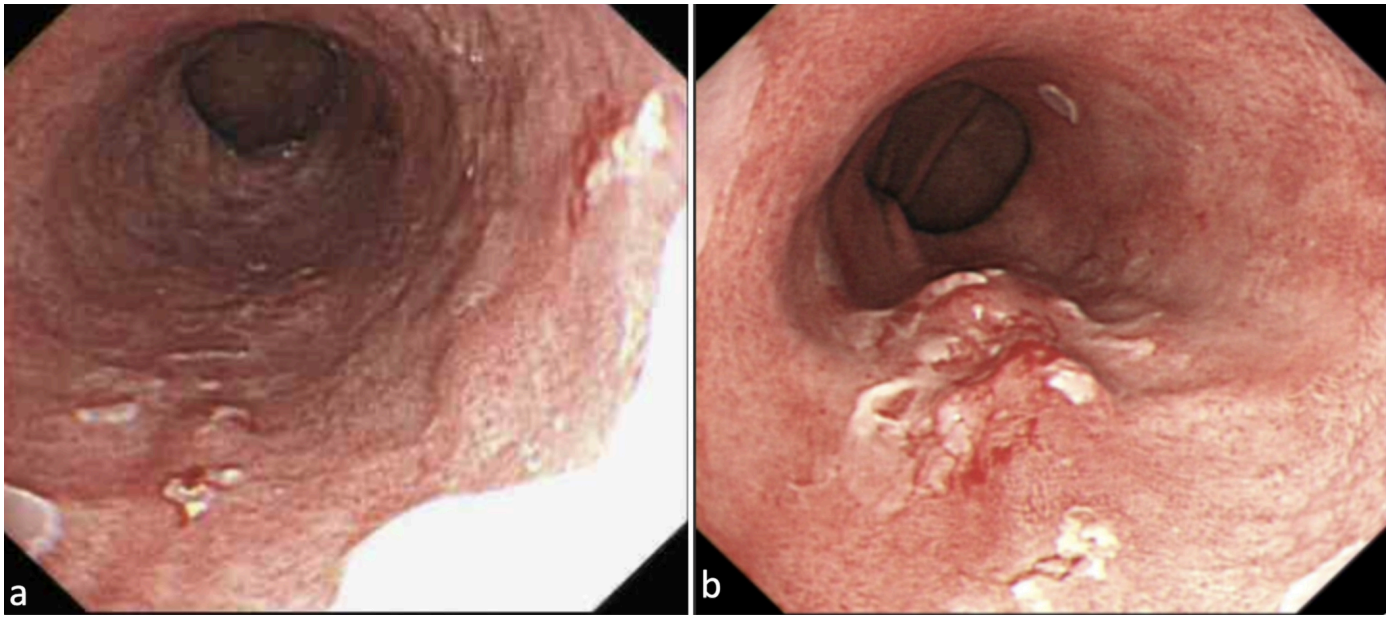


Figure 2 Endoscopic images of a patient with post-endoscopy upper gastrointestinal cancer. a Segment of Barrett's esophagus with an irregular area. Biopsies from this area were indefinite for dysplasia. b Repeat endoscopy 2 years later showed an abnormal area with central depression. Biopsies confirmed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

3.4.2 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), tumour characteristics and endoscopy findings (Table 2), and the characteristics of the providers where the index endoscopy was performed (Table 3).

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.)	25.7

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

Table 2 Previous endoscopic findings and tumour characteristics in patients 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
Previous endoscopic findings					
Oesophageal ulcer	9728	12 307	9467 (9.7)	2840 (31.3)	23.1
Oesophageal stricture	12 466	13 796	12 300 (12.6)	1496 (16.5)	10.8
Barrett's oesophagus	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 oesophagus	2707	2960	2645 (2.7)	315 (3.5)	10.6
Middle third oesophagus	9311	10 121	9235 (9.5)	886 (9.8)	8.8
Lower third oesophagus	32 878	35 300	32 680 (33.5)	2620 (28.9)	7.4
Unspecified site in oesophagus	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.

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, 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
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
Oesophagogastric cancer resection centre					
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.

The PEUGIC rate was higher in younger people, women, people with more comorbidity, and those with a previous oesophageal ulcer, oesophageal stricture, Barrett's oesophagus, gastric ulcer, or gastric atrophy. The PEUGIC rate was lower among those 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 oesophagus. 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 oesophageal cancers, gastric cancers, and Barrett's oesophagus are shown in supplementary tables 1-3 respectively.

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 Tumour factors and previous endoscopy findings associated with post-endoscopy upper gastrointestinal cancer on multivariable logistic regression analysis.

Characteristics	**OR (95%CI)**	***P* value**
Tumour site (vs. upper third oesophagus)		
Middle third oesophagus	0.77 (0.66–0.89)	<0.01
Lower third oesophagus	0.63 (0.55–0.72)	<0.01
Unspecified site in oesophagus	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
Oesophageal ulcer	3.30 (3.11–3.50)	<0.01
Oesophageal stricture	1.28 (1.20–1.37)	<0.01
Barrett's oesophagus	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.

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
Oesophagogastric cancer resection centre	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.

Among patients with gastric adenocarcinoma, PEUGIC was more common with diffuse type (9%), compared with intestinal type (6.7%; $P < 0.001$).

3.4.3 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 (Supplementary table 4). 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 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.

Supplementary table 5 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, Figure 3, and Figure 4 show provider comparisons for each of the time periods.

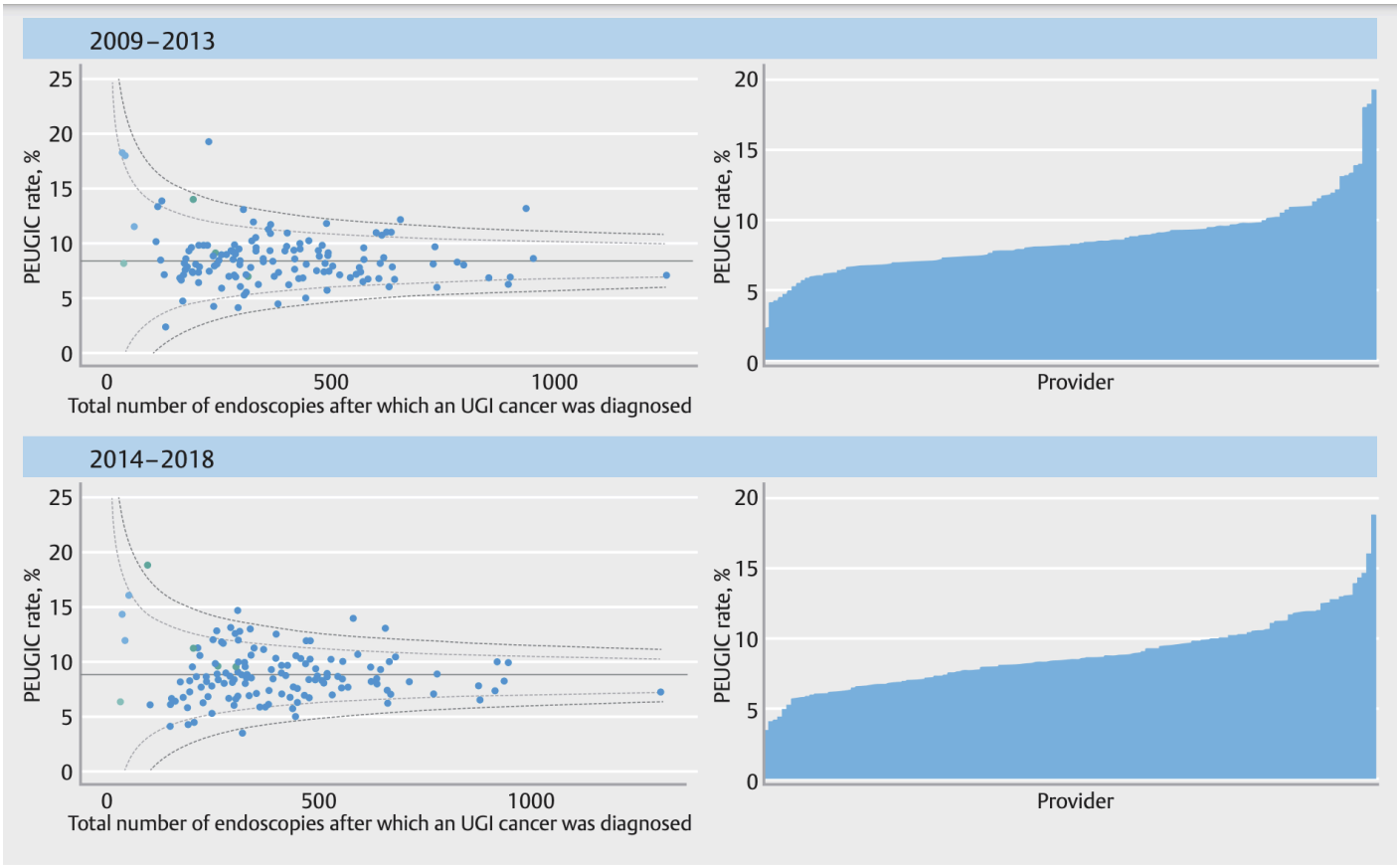


Figure 3 The variation in unadjusted rates of post-endoscopy upper gastrointestinal cancer (PEUGIC) by endoscopy provider for 2009–13 and 2014–18. In the funnel plots, each dot represents an individual provider. Dashed lines represent 95% and 99.8% control limits outside the national PEUGIC rate (solid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

GI,gastrointestinal.

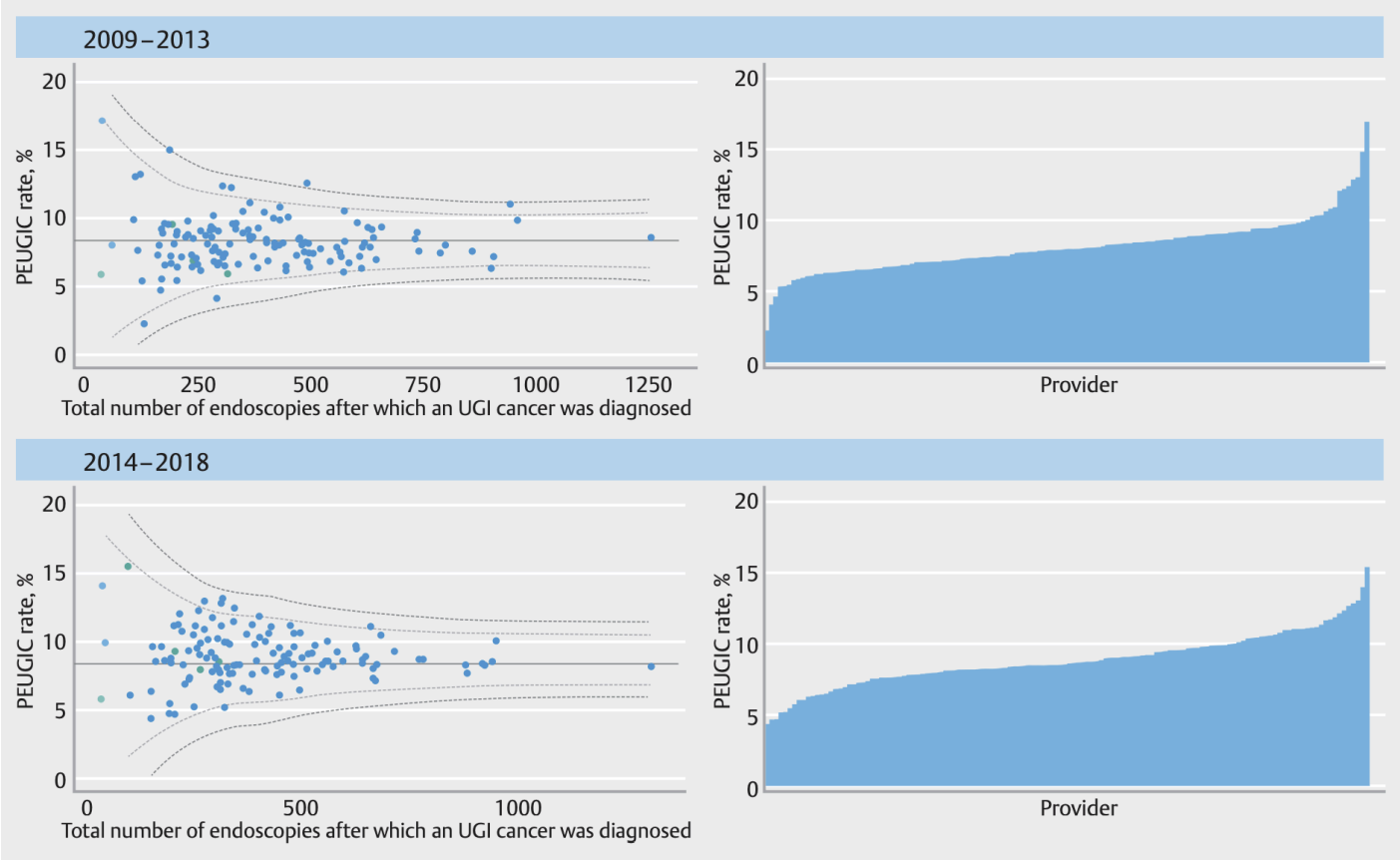


Figure 4 The variation in adjusted rates of post-endoscopy upper gastrointestinal cancer (PEUGIC) by endoscopy provider for 2009–13 and 2014–18. In the funnel plots, each dot represents an individual provider. Dashed lines represent 95% and 99.8% control limits outside the national PEUGIC rate (solid 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.

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. Supplementary Figure 3 shows the results of these estimates.

3.5 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 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 oesophagus 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. Oesophageal adenocarcinoma is more common in Northern and Western Europe than in Central European countries [22], and

surveillance of Barrett's oesophagus 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]

Barrett's oesophagus is the only recognised premalignant condition for oesophageal adenocarcinomas. Guidelines have been developed for the surveillance of Barrett's oesophagus to detect dysplasia or early cancerous changes, so that curative endoscopic treatment can be offered.[23] Despite these guidelines, around one fifth of the incident cancers in patients with Barrett's oesophagus were classified as PEUGIC in the current study. These findings are in line with a previously reported systematic review and meta-analysis which described a missed cancer rate of 25% within one year of index endoscopy in patients with Barrett's oesophagus without dysplasia. [24] These results highlight the importance of adherence to quality standards such as dedicated surveillance lists by the endoscopists with adequate training, which have been shown to improve diagnostic yield[25–27].

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.[28] 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 oesophagus.[6,8,9,24,29] Previous diagnoses of oesophageal and gastric ulcers, oesophageal stricture or gastric atrophy were also found to be associated with PEUGIC. Careful endoscopic examination, follow-up, and surveillance of these high risk conditions is recommended.[7,30] In a multicenter root cause analysis of PEUGIC cases, inadequate surveillance or follow-up plans and administrative delays were important contributing factors to PEUGIC.[29] 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. oesophageal ulcer, oesophageal stricture) and surveillance of premalignant conditions (e.g. Barrett's oesophagus, gastric atrophy, and gastric intestinal metaplasia). Cancer in the upper oesophagus 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 oesophageal 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.[31,32]

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 [33], 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.[34] 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 tumours and gastrointestinal stromal tumours 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.

3.6 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 oesophagus, 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, emphasising 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.

3.7 References

1 Cancer Research UK. Stomach cancer statistics. 2015. Accessed: Aug 23 2022. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/stomach-cancer

2 Cancer Research UK. Oesophageal cancer statistics. 2015. Accessed: Aug 23 2022. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oesophageal-cancer

3 Cancer Research UK. Stomach cancer survival statistics. 2015. Accessed: Aug 23 2022. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/stomach-cancer/survival

4 Menon S, Trudgill N. How commonly is upper gastrointestinal cancer missed at endoscopy? A meta-analysis. Endosc Int Open 2014; 2: E46–50

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 Januszewicz W, Witczak K, Wieszczy P et al. Prevalence and risk factors of upper gastrointestinal cancers missed during endoscopy: a nationwide registry-based study. Endoscopy 2022; 54: 653–660

7 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

8 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

9 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

10 Shenbagaraj L, Thomas-Gibson S, Stebbing J et al. Endoscopy in 2017: a national survey of practice in the UK. Frontline Gastroenterol 2019; 10: 7–15

11 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

12 Joint Advisory Group on GI Endoscopy. Accreditation statuses. Accessed: Aug 10 2022. https://www.thejag.org.uk/RegisteredUnits.aspx

13 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

14 Office for National Statistics. Index of multiple deprivation (IMD) 2007. 2010. Accessed: Aug 9 2022. https://data.gov.uk/dataset/bdc1e1a5-aaf3-4f5a-9988-82a11e341eb8/index-of-multiple-deprivation-imd-2007

15 Nuttall M, van der Meulen J, Emberton M. Charlson scores based on ICD-10 administrative data were valid in assessing comorbidity in patients undergoing urological cancer surgery. J Clin Epidemiol 2006; 59: 265–273

16 National Oesophago-Gastric Cancer Audit. Resources. 2017. Accessed: Aug 10 2022. https://www.nogca.org.uk/resources/?audience%5B%5D=professionals

17 Walker K, Neuburger J, Groene O et al. Public reporting of surgeon outcomes: low numbers of procedures lead to false complacency. Lancet 2013; 382: 1674–1677

18 Chadwick G, Groene O, Riley S et al. Gastric cancers missed during endoscopy in England. Clin Gastroenterol Hepatol 2015; 13: 1264–1270

19 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

20 Spiegelhalter DJ. Funnel plots for comparing institutional performance. Stat Med 2005; 24: 1185–1202

21 Lee TJW, Rutter MD, Blanks RG et al. Colonoscopy quality measures: experience from the NHS Bowel Cancer Screening Programme. Gut 2012; 61: 1050–1057

22 Arnold M, Soerjomataram I, Ferlay J et al. Global incidence of oesophageal cancer by histological subtype in 2012. Gut 2015; 64: 381–387

23 Fitzgerald RC, di Pietro M, Ragunath K et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. Gut 2014; 63: 7–42

24 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.e7; quiz e14–5.

25 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;76:531–8.

26 Ooi J, Wilson P, Walker G, *et al.* Dedicated Barrett's surveillance sessions managed by trained endoscopists improve dysplasia detection rate. *Endoscopy*. 2017;49:524–8.

27 Ratcliffe E, Britton J, Yalamanchili H, *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;15:21–7.

28 Joint Advisory Group on GI Endoscopy. Service accreditation. https://www.thejag.org.uk/about-accreditation (accessed 29 December 2022)

29 Kamran U, King D, Abbasi A, *et al.* A root cause analysis system to establish the most plausible explanation for post-endoscopy upper gastrointestinal cancer. *Endoscopy*. Published Online First: 31 August 2022. doi: 10.1055/a-1917-0192

30 Pimentel-Nunes P, Libânio D, Marcos-Pinto R, *et al.* Management of epithelial precancerous conditions and lesions in the stomach (MAPS II): European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter and Microbiota Study Group (EHMSG), European Society of Pathology (ESP), and Sociedade Portuguesa de Endoscopia Digestiva (SPED) guideline update 2019. *Endoscopy*. 2019;51:365–88.

31 Lin Y, Wimberly MC. Geographic Variations of Colorectal and Breast Cancer Late-Stage Diagnosis and the Effects of Neighborhood-Level Factors. The Journal of Rural Health. 2017;33:146–57.

32 Wrigley H, Roderick P, George S, *et al.* Inequalities in survival from colorectal cancer: a comparison of the impact of deprivation, treatment, and host factors on observed and cause specific survival. *J Epidemiol Community Health*. 2003;57:301–9.

33 Møller H, Richards S, Hanchett N, *et al.* Completeness of case ascertainment and survival time error in English cancer registries: impact on 1-year survival estimates. *Br J Cancer*. 2011;105:170–6.

34 The Quality of Nationally Submitted Health and Social Care Data, England - 2013, Second annual report, Experimental statistics. NHS Digital. https://digital.nhs.uk/data-and-information/publications/statistical/the-quality-of-nationally-submitted-health-and-social-care-data/the-quality-of-nationally-submitted-health-and-social-care-data-england-2013-second-annual-report-experimental-statistics (accessed 4 January 2023)

Chapter 4: Differences between providers with the worst and best post endoscopy upper gastrointestinal cancer rates in England

In this chapter I present findings of a retrospective case control study examining differences in the endoscopy practices between providers with the lowest and highest PEUGIC rates in England using the national endoscopy database and the endoscopy characteristics associated with the best performing providers.

Manuscript

Kamran U, Evison F, Brookes M, Rutter M, McCord M, Morris E, Beaton D, Adderley N, Trudgill N. Differences in endoscopy practices between providers with highest and lowest post endoscopy upper gastrointestinal cancer rates using national endoscopy database.

(Revised manuscript has been resubmitted to the “Clinical Gastroenterology and Hepatology” journal after addressing reviewers’ comments.)

4.1 Abstract

4.1.1 Background & Aims

Post-endoscopy upper gastrointestinal cancer (PEUGIC) rates vary over threefold between endoscopy providers in England. To determine if variations in endoscopy characteristics contribute, providers with the best and worst PEUGIC rates were compared.

4.1.2 Methods

Endoscopy providers were categorised into quartiles based on PEUGIC rates and those in the highest (worst) and lowest (best) quartiles studied. Data for diagnostic upper gastrointestinal (UGI) endoscopies performed between January 2019 and February 2020 extracted from the National Endoscopy Database. Multivariable regression analysis explored the endoscopy characteristics associated with the best PEUGIC rate providers, after adjusting for patient characteristics and indications.

4.1.3 Results

In total, 328,354 diagnostic UGI endoscopies performed by 54 providers were included. Endoscopy characteristics positively associated with the best PEUGIC rate providers included: training schedules (Odds Ratio 1.85 (95% CI 1.81-1.90)); intravenous sedation use (1.09 (1.07-1.11)); endoscopist average UGI endoscopy annual volume 101-200 (1.05 (1.02-1.07) and 201-300 (1.16 (1.13-1.19)). Endoscopy characteristics inversely associated with the best PEUGIC rate providers included: endoscopy schedules with average ≥9 points (0.72 (0.71-0.74)); endoscopists not on nursing, specialty or trainee register (0.83 (0.81-0.85)); and

biopsies during endoscopy (0.84 (0.83-0.86)). Compliance with national quality standards to biopsy high risk conditions was better by providers with best PEUGIC rates.

4.1.4 Conclusions

Training schedules, more endoscopists with minimum annual endoscopy volumes >100, more intravenous sedation, less biopsies and more lower intensity endoscopy schedules were associated with the best PEUGIC rate providers. These findings may help guide efforts to reduce PEUGIC and improve endoscopy quality in future.

4.2 Introduction

In the UK each year, approximately 16,500 people are diagnosed with upper gastrointestinal (UGI) cancer, principally esophageal and gastric cancer, but only one in five survive for more than five years, mainly due to advanced cancer stage at diagnosis.[1] Endoscopy is the investigation of choice to detect UGI cancer. However, studies have reported that 6 to 11% of people with UGI cancer had an endoscopy without a cancer diagnosis within the three years prior to their UGI cancer being found; representing a potential missed opportunity to detect the cancer earlier.[2–4] This is termed post-endoscopy upper gastrointestinal cancer (PEUGIC) and is considered an important key performance indicator of the quality of endoscopy.

A recent population-based study in England has reported substantial unwarranted variation in PEUGIC rates among endoscopy providers.[5] This variation is likely to be due to differences in the quality of UGI endoscopy between providers. However, it was not possible to explore differences in endoscopy characteristics between endoscopy providers from the administrative and cancer registry databases utilised in this study. The National Endoscopy Database (NED) is a novel UK endoscopy registry, overseen by the Joint Advisory Group on Gastrointestinal endoscopy (JAG).[6] It covers >95% of endoscopy providers in the UK and captures anonymised patient-level data automatically and in real-time from routine clinical data entered into each hospital's electronic endoscopy reporting system by endoscopists. This database provides a unique opportunity to examine variations in endoscopy characteristics among providers and to identify quality standards.

We aimed to examine differences in endoscopy characteristics in providers with the highest (i.e. worst) and lowest (i.e. best) PEUGIC rates in England using NED to identify factors which can potentially be addressed to improve endoscopy quality.

4.3 Methods

4.3.1 Post endoscopy upper gastrointestinal cancer rates of endoscopy providers

To calculate PEUGIC rates and performance quartiles for the present study, we used the most recent 4 years of data, between 2015 and 2018, from a previous study in which PEUGIC rates among endoscopy providers in England were estimated.[5] National Cancer Registration and Analysis Service and Hospital Episode Statistics databases were used to calculate PEUGIC rates for all NHS funded endoscopy providers in England. The total number of patients who were diagnosed with UGI cancers between 2015 and 2018 were 39959 with an overall PEUGIC rate of 8.6 (IQR 7.9-9.5)%.

To avoid increased uncertainty due to small sample size, we performed an 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 studies,[7,8] a doubling of this rate to 16% was considered to be unacceptably high. Based on this number and an 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 potentially be a significant outlier and to be included in the study.[5]

PEUGIC rates were adjusted for patient characteristics (age, sex, ethnicity, socioeconomic status, Charlson comorbidity score, a previous diagnosis of oesophageal ulcer, oesophageal stricture, Barrett's oesophagus, gastric ulcer or gastric atrophy), tumour characteristics (tumour histology and site) and endoscopy provider characteristics (accreditation status with the JAG, annual

endoscopy volume and provider type (NHS or independent)). 64% of PEUGIC were esophageal cancers and 36% were gastric cancers. Endoscopy providers were categorised into quartiles based on their adjusted PEUGIC rates. The purpose of this categorization was to allow sufficient providers in each group to detect differences in endoscopy characteristics and to reduce the chances of results being influenced by the extremes. Providers in the quartile with the highest (i.e. worst) PEUGIC rates and providers in the quartile with the lowest (i.e. best) PEUGIC rates were included in this study to allow comparison between providers with highest variability (i.e. those with PEUGIC rates below the 25th centile and those above the 75th centile of the national PEUGIC rate).

4.3.2 National Endoscopy Database

Data for all UGI endoscopies performed in England between January 2019 and February 2020 were obtained from NED. Diagnostic endoscopies performed to investigate UGI symptoms or abnormal findings on previous imaging and for the surveillance of pre-malignant conditions (such as Barrett's oesophagus, gastric atrophy or intestinal metaplasia) or follow up of cancer associated conditions (such as severe esophagitis, oesophageal stricture and esophageal or gastric ulcers) were included. Endoscopies were excluded if a therapeutic procedure was performed during endoscopy. Data for UGI endoscopies were mapped to the previously identified endoscopy providers with the best and worst PEUGIC rates.

4.3.3 Variables examined

Variables included information on patient demographics (age and sex), indications for endoscopy categorised into four groups: alarm symptoms (dysphagia, weight loss and anaemia); non-alarm symptoms (dyspepsia, abdominal pain, nausea or vomiting, reflux symptoms, and duodenal

biopsies for positive tissue transglutaminase antibodies); abnormal findings on barium or CT scan; surveillance or follow up. Data on the use of intravenous sedation during endoscopy included the following variables: Midazolam; Fentanyl; Pethidine; Propofol; and General Anaesthesia. Data for the endoscopy procedures where combined intravenous sedation (i.e. Midazolam + opioid) was also extracted. Procedures were identified when biopsies were taken during endoscopy, except those endoscopies where only a gastric biopsy was taken for rapid urease testing for the detection of Helicobacter pylori.

In the NED, endoscopy schedules were categorised as service or training schedules. Training schedules were those when a trainee doctor or trainee nurse endoscopist were present. Service schedules were those when no trainee was present. In the UK, endoscopy providers use a points system to allocate time for procedures. Usually 15-20 minutes are assigned to one point and an UGI endoscopy or flexible sigmoidoscopy is allocated one point, a colonoscopy is allocated two points.[9] Data for all endoscopies (including colonoscopies and flexible sigmoidoscopies, as many endoscopy schedules included both upper and lower GI procedures) performed by the providers included in study were also extracted from NED to estimate average workload for half day endoscopy sessions for individual providers. We estimated average points allocated to the endoscopy sessions by an individual provider by calculating the total number of points performed over the study period by the provider and dividing them by the number of half day sessions. Average points per schedule were categorised into <9 and ≥ 9 points.

The specialities and grade or roles of endoscopists were identified using their General Medical Council (GMC) or Nursing and Midwifery Council (NMC) numbers and categorised into five

groups: gastroenterologists (including trainees and consultants); surgeons (including trainees and consultants); nurse endoscopists; others (doctors who are not on specialist or training registers); and unknown if GMC or NMC numbers were not available. Consultants were clinicians who had completed either gastroenterology or upper GI surgical training and were on the GMC hospital specialist register. Trainees were those who were registered with the GMC as gastroenterology or surgical trainees during the study period and were training in endoscopy. In the UK, trainees are always supervised by consultants until they achieve accreditation by the JAG. Once they achieve accreditation, trainees can perform independent endoscopies. In this study, consultants and trainees were grouped together according to their registration as either "gastroenterologists" or "surgeons". Nurse endoscopists also need to achieve JAG accreditation in the UK, following which they can work as independent endoscopists. In addition to these, "other" endoscopists were those not registered with the GMC as either consultants or trainees or with the NMC as nurses, during the study period. These endoscopists are usually middle grade doctors who have gone through JAG accreditation in UGI endoscopy but did not undergo formal gastroenterological or surgical training to become independent hospital specialists.

The total number of UGI endoscopies performed by each endoscopist over the study period was calculated to estimate their annual UGI endoscopy volume. The British Society of Gastroenterology (BSG) recommends a minimum annual UGI endoscopy volume of 100.[10] In order to identify the most appropriate threshold, endoscopists were categorised into the following groups based on their average annual UGI endoscopy volume : <100, 101-200, 201-300 and >300).

4.3.4 Outcome measures

The association of the above procedural and endoscopist related characteristics at provider level with the best PEUGIC rate provider quartile was examined. Compliance with the BSG endoscopy quality standards [10] was assessed by comparing the proportion of endoscopies in which at least one biopsy was taken from cancer associated conditions (including oesophageal ulcer, oesophageal stricture and gastric ulcer) and at least six biopsies were taken from a suspected esophageal or gastric cancer.

4.3.5 Statistical analysis

All statistical analyses were carried out using Stata SE v15 (StataCorp., College Station, Texas, USA). Categorical variables were summarised as number and percentages and the chi-squared test was used for comparison. Continuous variables were summarised as median and inter quartile range (IQR).

Univariable and multivariable logistic regression modelling was used to explore the characteristics associated with the best PEUGIC rate provider quartile. Based on the previous studies,[11] clinical experience and availability and accuracy of the data all variables included in the model were determined *a priori.* Patient demographics and indications of endoscopy were considered non-modifiable factors and vary based on geography of the providers. The purpose of the model was to identify potentially modifiable endoscopy characteristics after adjusting for the variation in non-modifiable factors. Age was used as a continuous variable. Other categorical exploratory variables included: sex; indications for endoscopy (alarm symptoms or not);

intravenous sedation use; biopsy taken during endoscopy; endoscopist specialty; endoscopist annual volume; and average points per schedule per endoscopy provider.

Multivariable logistic regression analyses were performed to assess associations between the endoscopies when at least one biopsy was taken and the providers with best PEUGIC rates in the subgroup of endoscopies where a cancer associated condition (oesophageal ulcer, oesophageal stricture or gastric ulcer) was reported during endoscopy. These models were adjusted for patient sex and age.

4.3.6 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 (MM) was also part of the study steering group.

4.3.7 Ethics

Study protocol was approved by London - South East Research Ethics Committee (IRAS project ID # 289695).

4.4 Results

4.4.1 Endoscopies included in the study

A total of 667,435 UGI endoscopies were recorded in NED within the study period. Data for 328,354 diagnostic UGI endoscopies performed by 54 endoscopy providers were included: 175,432 endoscopies performed by the 27 providers with the worst PEUGIC rates (median 10.3% (10.1-11.4)) and 152,922 endoscopies performed by the 27 providers with the best PEUGIC rates (7.2% (7.0-7.5)) (Figure 1).

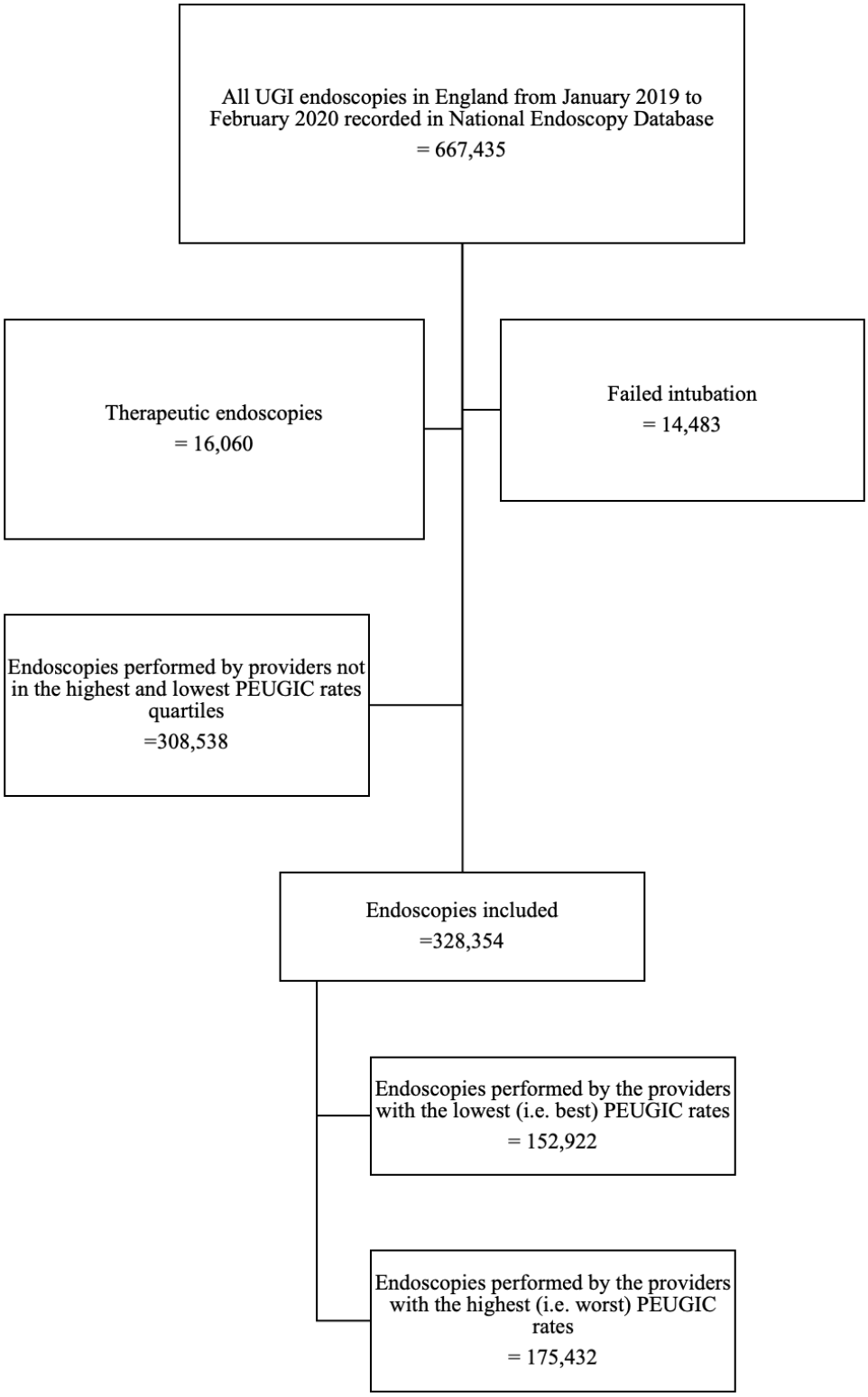


Figure 1 Study flow chart

UGI = Upper gastrointestinal , PEUGIC = Post endoscopy upper gastrointestinal cancer.

Failed intubation was more common in providers with the worst PEUGIC rates (1.9%), compared the best PEUGIC rate providers (1.6%), $p<0.001$. Endoscopies were more commonly performed for female patients and the median patient age was 61 (IQR 47-62) years. Non-alarm symptoms were the commonest indications followed by alarm symptoms and surveillance or follow up endoscopies (Table 1).

Table 1 Demographics of patients and characteristics of endoscopies stratified by the quartiles of providers with the highest (i.e. worst) and lowest (i.e. best) post endoscopy upper gastrointestinal cancer rates. Values are numbers (percentages) unless stated otherwise.

Variables	**Providers with the worst PEUGIC rates**	**Providers with the best PEUGIC rates**
PEUGIC rates* Median (IQR), %	10.3 (10.1-11.4)	7.2 (7.0-7.5)
Endoscopies included	175,432	152,922
Patient age (years)		
Less than 40	26,068 (14.9%)	22,832 (14.9%)
41-50	23,234 (13.2%)	20,188 (13.2%)
51-60	33,766 (19.2%)	29,159 (19.2%)
61-70	35,444 (20.2%)	30,382 (19.9%)
71-80	36,084 (20.6%)	31,440 (20.6%)
>80	19,751 (11.3%)	18,029 (11.8%)
Female patients	93,532 (53.3%)	79,802 (52.2%)
Indications		
Non-Alarm symptoms	128,587 (73.3%)	114,122 (74.6%)
Abnormal imaging	2,247 (1.3%)	1,757 (1.1%)
Surveillance or follow up	11,163 (6.4%)	9,123(6.0%)
Alarm symptoms	33,435 (19.1%)	27,920 (18.3%)
Training schedule	14,685 (8.4%)	22,261 (14.6%)
Use of intravenous sedation	91,869 (52.4%)	81,220 (53.1%)

Use of combined intravenous sedation**	22,866 (13.0%)	23,318 (15.2%)
Biopsy taken***	79,709(45.4%)	64,150 (42.0%)
Endoscopist specialty		
Gastroenterologist	90,919 (51.8%)	77,115 (50.4%)
Nurse endoscopist	28,026 (16.0%)	31,383 (20.5%)
Surgeons	32,192 (18.4%)	27,245 (17.8%)
Other doctors (not on specialist or trainee registers)	23,757 (13.5%)	15,947 (10.4%)
Unknown	538 (0.3%)	1232 (0.8%)
Annual endoscopist volume		
<100	27,157 (15.6%)	24,277 (15.9%)
101-200	37,082 (21.3%)	32,775 (21.4%)
201-300	29,340 (16.8%)	25,831 (16.9%)
>300	80,793 (46.3%)	69,233 (45.3%)
Average points per schedule		
<9	143,878 (82.0%)	132,298 (86.5%)
≥9	31,554 (18.0%)	20,624 (13.5%)

*PEUGIC rates calculated using data between 2015-2018, extracted from our previous study [5]

**Combined use of benzodiazepines and opioids

***At least one biopsy taken (except for rapid urease test)

PEUGIC = Post endoscopy upper gastrointestinal cancer

UGI cancer was suspected in 1% of endoscopies. Gastric ulcers were reported in 1.9%, oesophageal ulcers in 1.2% and oesophageal strictures in 0.6% of endoscopies.

Overall, 11.3% of endoscopies were performed on training schedules and intravenous sedation was used for 52.7% of the procedures. The majority (69.3%) of the procedures were performed by endoscopists registered as specialists (consultants medical or surgical) or specialty trainee doctors. Nurse endoscopists performed 18.1% of endoscopies, and 12.1% were performed by the endoscopists who were neither specialists nor trainees.

4.4.2 Endoscopy characteristics associated with the best PEUGIC rate providers

In multivariable regression analysis after adjusting for patient age, sex and the indications for the procedure, the endoscopy characteristics positively associated with the providers with the best PEUGIC rates included: intravenous sedation use; endoscopies performed on training schedules; endoscopists' average annual UGI endoscopy volume; and endoscopies performed by nurse endoscopists. Endoscopy characteristics inversely associated with providers with the best PEUGIC rates included: endoscopy schedules with average ≥9 points; endoscopies performed by other doctors not on specialist or trainee registers; and biopsies during endoscopy (Table 2). Combined use of intravenous benzodiazepines and opioids was more common among the providers with best PEUGIC rates (15.2% vs 13.0%, $p<0.001$).

Table 2 Univariable and Multivariable regression analysis of factors associated with providers with the best post endoscopy upper gastrointestinal cancer rates

Factors	**Univariable analysis OR (95% CI)**	**Multivariable analysis OR (95% CI)**
Sex of the patient		
Female	Reference	
Male	1.00 (0.98-1.02)	1.01 (0.99-1.02)
Age of the patient (years)		
<40	Reference	
41-50	0.99 (0.97-1.02)	1.01 (0.98-1.04)
51-60	0.98 (0.96-1.01)	1.01 (0.99-1.03)
61-70	0.98 (0.96-1.00)	1.01(0.98-1.03)
71-80	0.99 (0.97-1.02)	1.04 (1.02-1.07)
>80	1.04 (1.01-1.07)	1.11 (1.08-1.14)
Indications for endoscopy		
Non-alarm symptoms	Reference	
Abnormal CT scan	0.88 (0.83-0.94)	0.90 (0.84-0.96)
Surveillance or follow up	0.92 (0.89-0.95)	0.92 (0.90-0.95)
Alarm symptoms	0.94 (0.92-0.96)	0.95 (0.93-0.98)
Schedule type		
Service	Reference	
Training	1.86 (1.82-1.91)	1.85 (1.81-1.90)
Intravenous sedation used		
No	Reference	
Yes	1.03 (1.02-1.04)	1.09 (1.07-1.11)
Biopsies taken		
No	Reference	
Yes	0.87 (0.86-0.88)	0.84 (0.83-0.86)

Endoscopist specialty		
Gastroenterologist	Reference	
Nurse endoscopist	1.32 (1.30-1.35)	1.45 (1.42-1.48)
Surgeon	0.99 (0.98-1.01)	1.00 (0.98-1.02)
Other doctors (not on specialist or trainee registers)	0.79 (0.77-0.81)	0.83 (0.81-0.85)
Annual endoscopist volume		
<100	Reference	
101-200	0.99 (0.97-1.01)	1.05 (1.02-1.07)
201-300	0.98 (0.96-1.01)	1.16 (1.13-1.19)
>300	0.96 (0.94-0.98)	1.09 (1.06-1.11)
Average points per schedule		
<9	Reference	
≥9	0.71 (0.70-0.72)	0.72 (0.71-0.74)

4.4.3 Compliance with quality standards to take biopsies from high-risk conditions

Although the overall biopsy rate was lower in the best PEUGIC rate providers (41.4% vs 44.5%), biopsy rates were higher if a high risk finding was recorded in the endoscopy report, compared to the providers with worst PEUGIC rates: oesophageal ulcers - best PEUGIC rate providers 56.7% vs worst PEUGIC rate providers 51.3% ($p=0.001$); oesophageal strictures - 52.4% vs 48.0% ($p=0.042$); and gastric ulcers - 62.7% vs 58.3% ($p<0.001$). In multivariable regression analyses, biopsies for these high-risk conditions were associated with the best PEUGIC rate provider quartile (Table 3).

However, there was no significant difference between different PEUGIC rate providers in the proportion of endoscopies when at least six biopsies were taken from suspected UGI cancers (best PEUGIC rate 73.9% vs worst 70.7%, $p=0.09$).

Table 3 Multivariable analysis of the association between biopsy rates for oesophageal ulcer, oesophageal stricture and gastric ulcers and providers with the best post endoscopy upper gastrointestinal cancer rates, adjusted for patient age and sex

Subgroups	**Number of patients** N	**Biopsy rate** N (%)	**Association with providers with the lowest PEUGIC rates** Odds ratio (95% confidence interval)
Oesophageal ulcer	3,859	2,090 (54.2)	1.23 (1.08-1.40)
Oesophageal stricture	2,070	1,036 (50.1)	1.19 (1.00-1.42)
Gastric ulcer	6,270	3,792 (60.5)	1.20 (1.09-1.33)

PEUGIC = Post endoscopy upper gastrointestinal cancer

4.5 Discussion

UGI endoscopy lacks well established quality indicators due to a relative paucity of evidence. PEUGIC has been recommended as an important key performance indicator for endoscopy providers [10] but is limited in its impact as it is a relatively infrequent event particularly for individual endoscopists and necessarily retrospective in its application. This study has reported differences in endoscopy characteristics between providers with the best and worst PEUGIC rates in England. More training endoscopy schedules, slightly more intravenous sedation use, annual endoscopist volumes ≥ 100, compliance with national recommendations to biopsy high risk conditions but less biopsies overall and less busy endoscopy schedules were identified as the characteristics associated with the providers with the best PEUGIC rates. These findings can help to reduce variation in endoscopy practice among providers and guide future quality improvement efforts to reduce PEUGIC.

Intravenous sedation is commonly used to improve the tolerability of UGI endoscopy. In England, nearly all UGI endoscopies are performed with local anaesthetic throat spray alone or conscious sedation. Various factors affect patient choice, including previous experience, the ability to resume daily activities or work, the ability to drive home, convenience, the ability to stay in control during the procedure, the absence of an escort, or the perceived discomfort of the procedure. Most sedated endoscopies are carried out using benzodiazepines, with or without opioids. A recent multicentre study from China reported that propofol sedation improved the detection rate of early UGI cancer and high grade dysplasia.[12] These observations are likely to relate to better patient procedural tolerance with sedation, allowing longer and more effective inspection times and easier use of accessory image enhancement techniques to detect early

neoplasia and pre-malignant conditions.[12,13] The current and previous studies suggest that where appropriate based on patient factors, intravenous sedation should be offered to all patients undergoing diagnostic or surveillance endoscopy.

Annual endoscopist UGI endoscopy volume has been proposed as a key performance indicator.[10,14] A recent root cause analysis study of PEUGIC has reported a negative correlation between annual endoscopist volume and the PEUGIC rate.[15] The current study supports the BSG recommendations for minimum annual volumes of >100 UGI endoscopies. There was a marginally stronger association with an endoscopist annual volume of 201-300, suggesting an aspirational standard of >200 UGI endoscopies per year would be appropriate. Most UK endoscopists undertake both upper and lower GI endoscopy. A previous NED analysis reported that only around half of the endoscopists in the UK met the 100 UGI endoscopies per year minimum recommended volume.[16] The present study also found a difference in the failed intubation rate, which could also be used as a potential key performance indicator.

A negative association was found between the number of endoscopies performed by endoscopists not on specialist, trainee or nursing registers and the best PEUGIC rate providers quartile, which reflects a potential impact of endoscopists' specialty and training on the quality of endoscopy. The endoscopists not on a specialist or training register in England may not participate or have the same opportunities for formal training courses or continuous professional development activities to improve their endoscopy and lesion recognition skills. Studies have shown that training in lesion recognition can improve the diagnostic yield of endoscopy and involvement in such training programs should be encouraged for all endoscopists.[17] A positive

association between the number of procedures performed on training schedules and providers with the best PEUGIC rates also suggests a positive impact of the training environment on the quality of endoscopy. Similar results have been reported for colonoscopy, when the involvement of trainees in screening colonoscopies improved adenoma detection rates.[18]

A multicentre cohort study reported a correlation between endoscopist biopsy rate and the detection of malignant and premalignant gastric conditions.[19] Endoscopists with the highest biopsy rates were five times more likely to diagnose gastric cancer and the incidence of the missed gastric cancers was also lower compared to the endoscopists with the lowest biopsy rates. In contrast, the current study found a negative association between overall biopsy rate and the providers with best PEUGIC rates. On further analysis, it was noted that compliance with the national recommendations to take biopsies when a high risk cancer associated lesion was identified[10] was higher by providers with the best PEUGIC rates. These findings suggest that, although in England overall biopsy rate may not be an indicator of endoscopy quality, compliance with national recommendations to take biopsies when assessing high risk cancer associated lesions is an indicator of high quality UGI endoscopy. This issue merits further study and is an opportunity for quality improvement.

The present study identified an association between less intense endoscopy schedules and the best PEUGIC rate provider quartile. Currently there are no benchmarks for how many procedures should be booked on a schedule. The point allocation system is a widely accepted method for scheduling patients for endoscopy in the UK, that is adjusted for case mix, training, endoscopy session length and process factors such as room turnaround time. Busy endoscopy

schedules may result in undue pressure on endoscopists, limiting their ability to spend adequate time examining the UGI mucosa for pre-malignant and early malignant changes. Intense endoscopy schedules may also contribute to operator fatigue, which can affect the quality of endoscopy. Previous studies on colonoscopy have reported that colonoscopist fatigue is associated with reduced adenoma detection.[20–22] Endoscopy providers should ensure that enough time for UGI endoscopy is allocated to allow adequate high quality examination.

The current study has several important limitations. NED data were not exactly contemporaneous with the data which were used to categorise endoscopy providers into quartiles based on PEUGIC rates. It is unlikely that endoscopy characteristics would have significantly changed over this short period of time and affected the results of the study but this cannot be excluded. Severe reflux esophagitis is not coded in HES and therefore PEUGIC rates could not be adjusted for this potential risk factor. Data on important factors such as patient comfort, the quality of views during endoscopy, whether any mucosal cleansing and enhanced imaging techniques were used, procedure time, and the experience and training of endoscopists, number of years out of training and endoscopist sex were not available in the current iteration of NED. Data on some of these factors will be available in the second iteration of NED, which has already been launched in the UK and future studies should analyse these measures in relation to PEUGIC rates. Average points per schedules were calculated by using the points usually allocated to diagnostic procedures. It is possible that some of the endoscopies on these schedules were planned therapeutic procedures and would have been allocated extra points, which could potentially lead to an underestimation of the average points per schedule. However, therapeutic

procedures form a very small proportion of overall endoscopies and this should not affect the results of this study.

4.6 Conclusions

This study has identified important differences in endoscopy characteristics between providers with worst and best PEUGIC rates in England. We therefore suggest endoscopist sedation and failed intubation rates, endoscopy schedule procedure volumes and annual endoscopist UGI endoscopy volumes all merit monitoring and intervention when appropriate. Furthermore, biopsy practice for cancer associated lesions and potentially unnecessary biopsies from minor findings such as gastritis or duodenitis may merit monitoring and intervention.

4.7 References

1 Statistics by cancer type. Cancer Research UK. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/stomach-cancer (accessed 23 Aug 2022). (accessed 2 January 2024)

2 Menon S, Trudgill N. How commonly is upper gastrointestinal cancer missed at endoscopy? A meta-analysis. *Endosc Int Open*. 2014;2:E46–50.

3 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;28:1041–9.

4 Januszewicz W, Witczak K, Wieszczy P, *et al.* Prevalence and risk factors of upper gastrointestinal cancers missed during endoscopy: a nationwide registry-based study. *Endoscopy*. 2022;54:653–60.

5 Kamran U, Evison F, Morris EJA, *et al.* The variation in post-endoscopy upper gastrointestinal cancer rates among endoscopy providers in England and associated factors: a population-based study. *Endoscopy*. Published Online First: 29 August 2024. doi: 10.1055/a-2378-1464

6 About NED. https://jets.thejag.org.uk/ned/about-ned/ (accessed 2 January 2024)

7 Chadwick G, Groene O, Riley S, *et al.* Gastric cancers missed during endoscopy in England. *Clin Gastroenterol Hepatol*. 2015;13:1264–70.e1.

8 Chadwick G, Groene O, Hoare J, *et al.* A population-based, retrospective, cohort study of esophageal cancer missed at endoscopy. *Endoscopy*. 2014;46:553–60.

9 How many points should there be on an endoscopy list? The JAG. https://thejag.zendesk.com/hc/en-us/articles/360000959073-How-many-points-should-there-be-on-an-endoscopy-list- (accessed 10 April 2023)

10 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;66:1886–99.

11 Kamran U, Abbasi A, Umar N, *et al.* Umbrella systematic review of potential quality indicators for the detection of dysplasia and cancer at upper gastrointestinal endoscopy. *Endosc Int Open*. 2023;11:E835–48.

12 Zhou J, Li Z, Ji R, *et al.* Influence of Sedation on the Detection Rate of Early Cancer and Precancerous Lesions During Diagnostic Upper Gastrointestinal Endoscopies: A Multicenter Retrospective Study. *Am J Gastroenterol*. 2021;116:1230–7.

13 McQuaid KR, Laine L. A systematic review and meta-analysis of randomized, controlled trials of moderate sedation for routine endoscopic procedures. *Gastrointest Endosc*. 2008;67:910–23.

14 JAG. https://www.thejag.org.uk/CMS/UploadedDocuments/Scheme/Scheme5/Guidance/191107 (accessed 10 October 2024)

15 Kamran U, King D, Abbasi A, *et al.* A root cause analysis system to establish the most plausible explanation for post-endoscopy upper gastrointestinal cancer. *Endoscopy*. Published Online First: 31 August 2022. doi: 10.1055/a-1917-0192

16 Beaton D, Broughton R, Rogers P, *et al.* PTU-18 Endoscopy procedure volume among the UK endoscopist workforce: Analysis using the national endoscopy database (NED). *Gut*. 2021;70:A50–1.

17 Zhang Q, Chen Z-Y, Chen C-D, *et al.* Training in early gastric cancer diagnosis improves the detection rate of early gastric cancer: an observational study in China. *Medicine* . 2015;94:e384.

18 Peters SL, Hasan AG, Jacobson NB, *et al.* Level of fellowship training increases adenoma detection rates. *Clin Gastroenterol Hepatol*. 2010;8:439–42.

19 Januszewicz W, Wieszczy P, Bialek A, *et al.* Endoscopist biopsy rate as a quality indicator for outpatient gastroscopy: a multicenter cohort study with validation. *Gastrointest Endosc*. 2019;89:1141–9.

20 Lee TJW, Rees CJ, Blanks RG, *et al.* Colonoscopic factors associated with adenoma detection in a national colorectal cancer screening program. *Endoscopy*. 2014;46:203–11.

21 Chan MY, Cohen H, Spiegel BMR. Fewer polyps detected by colonoscopy as the day progresses at a Veteran's Administration teaching hospital. *Clin Gastroenterol Hepatol*. 2009;7:1217–23; quiz 1143.

22 Long MD, Martin C, Sandler RS, et al. Reduced polyp detection as endoscopy shift progresses: experience with screening colonoscopy at a tertiary-care hospital. J Clin Gastroenterol. 2011;45:253–8.

Chapter 5 : A root cause analysis system to establish the most plausible explanation for post endoscopy upper gastrointestinal cancer

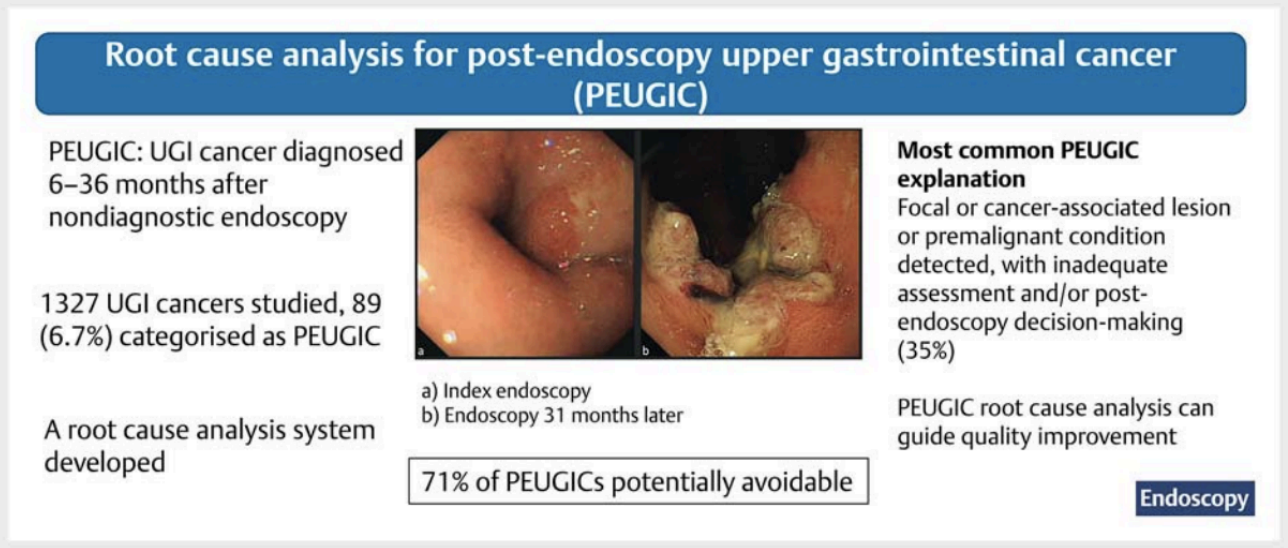
In this chapter, I present findings from retrospective cross sectional study examining data for post endoscopy upper gastrointestinal cancers from two NHS hospitals and development of a root cause analysis system.

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

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GRAPHICAL ABSTRACT



5.1 Abstract

5.1.1 Background

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

5.1.2 Methods

The electronic records of patients with UGIC at two National Health Service providers were examined. PEUGIC were defined as UGIC 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 categorise and identify potentially avoidable PEUGIC.

5.1.3 Results

Of 1327 UGIC studied, 89 (6.7%) were PEUGIC (patient median [IQR] age at endoscopy 73.5 (63.5–81.0); 60.7% men). Of the PEUGIC, 40% were diagnosed in patients with Barrett's oesophagus. PEUGIC were categorised 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 PEUGIC (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).

5.1.4 Conclusion

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

5.2 Introduction

Upper gastrointestinal cancers (UGIC) are usually diagnosed by endoscopy; however, UGIC can be diagnosed after an endoscopy that did not identify the cancer. These are termed post-endoscopy UGIC (PEUGIC). 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 UGIC 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] PEUGIC are less likely to present with alarm symptoms and are more commonly associated with less advanced clinical staging.[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 categorised 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 PEUGIC 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.

5.3 Methods

5.3.1 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.

PEUGIC 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 the 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 judgement of the endoscopist. Data collected included: patient variables (age at endoscopy, sex);

endoscopy variables (indication, photodocumentation, J manoeuvre [gastric retroflexion], view quality in the 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, tumour 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.

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

5.3.2.1 Interval and non-interval cancers

Interval PEUGIC were identified before the next planned surveillance endoscopy.[11] Non-interval PEUGIC 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 Supplementary Table 1.

5.3.2.2 Root cause analysis of the most plausible explanation for PEUGIC

PEUGIC were categorised 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 categorised as "A": lesion detected, adequate assessment and decision-making, but PEUGIC occurred.

If No, PEUGIC categorised 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 categorised as "C": possible missed lesion, endoscopy and decision-making adequate.

If No, PEUGIC categorised 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 time frame), "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 oesophagus, gastric atrophy, or gastric intestinal metaplasia), and focal or cancer-associated lesions (oesophageal 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 categorised 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 manoeuvre 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 manoeuvre, D2, and gastric body were the minimum criteria for adequate photodocumentation.

5.3.3 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 PEUGIC were categorised as unavoidable if they were growing by <5 mm/year, as they would have been unlikely to be detectable during the index endoscopy. PEUGIC 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 PEUGIC were considered potentially avoidable.

5.3.4 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.

5.3.5 Attribution

PEUGIC 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 oesophagus [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.

PEUGIC 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.

5.3.6 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 (categorised as well, moderately, and poorly differentiated) for all PEUGIC and also separately for PEUGIC with and without Barrett's oesophagus. Stata statistical software, release 16, was used for the statistical analysis.

5.3.7 Ethics

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

5.3.8 Patient and public involvement

There was no patient or public involvement in this study.

5.4 Results

5.4.1 Study subjects

A total of 1327 UGIC met the inclusion criteria (Figure 1); 89 (6.7%) were PEUGIC. Of these, 48% were diagnosed 6–18 months after the index endoscopy and 52% were diagnosed 18–36 months after the index endoscopy.

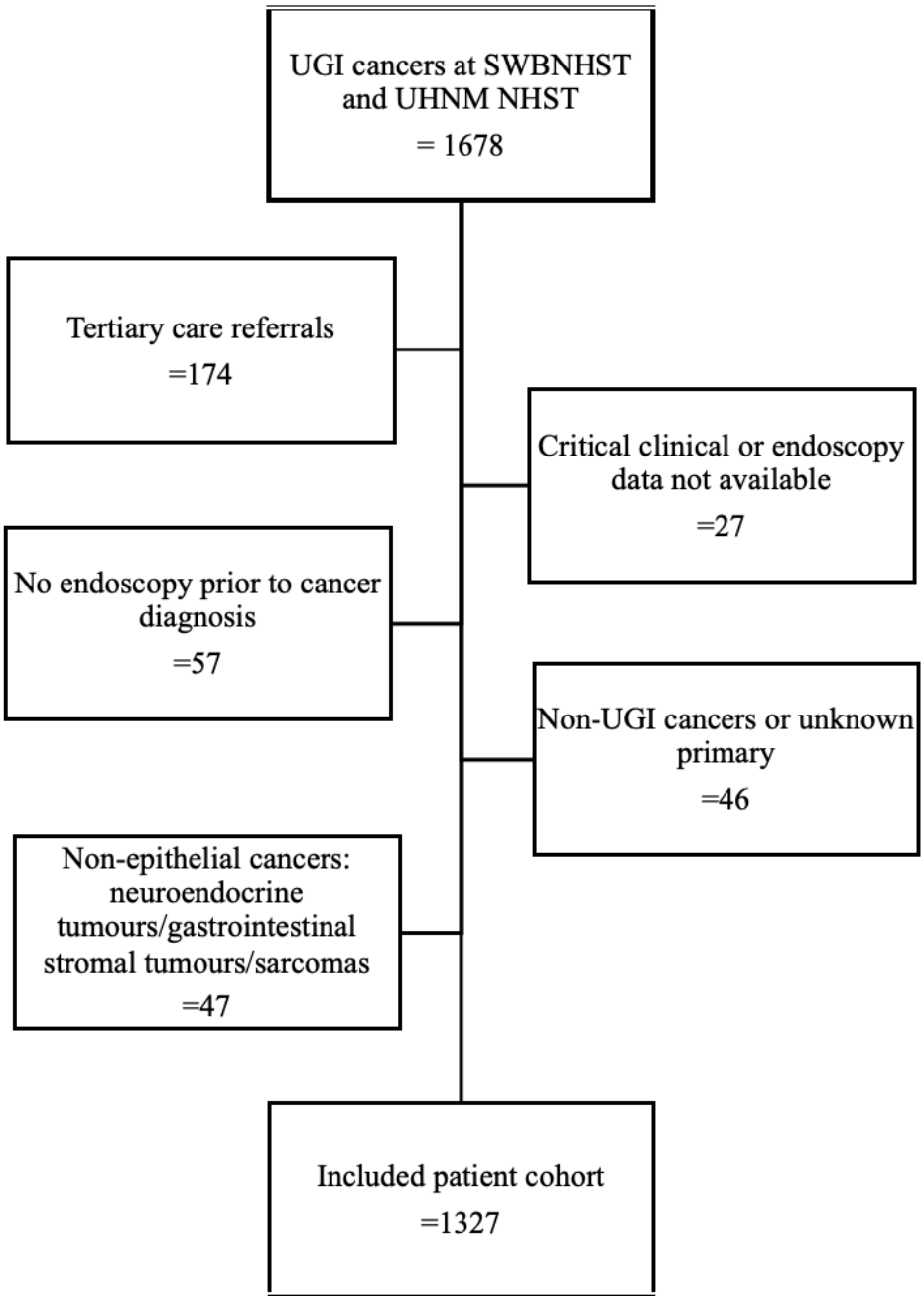


Figure 1 Flow Chart describing reasons for exclusion and selection of study patients.

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

The patient demographic details and characteristics of the index endoscopy for patients with PEUGIC and the UGIC controls are shown in Table 1.

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
Oesophagus	750 (60.6)	74 (83.1)	
Stomach	467 (37.7)	15 (16.9)	
Duodenum	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 oesophagus 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*	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)†	
Barrett's oesophagus	19 (1.5)	36 (40.5)	
Oesophageal ulcer	24 (1.9)	5 (5.6)	
Oesophageal 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)	

* Others comprised consultant physicians other than gastroenterologists.

† Declined curative therapy.

5.4.2 Cancer details

The majority of PEUGIC 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 oesophagus are presented in Table 2. Among the PEUGIC, 57% were early stage (i.e. stage I or II), compared with 22% of the UGIC controls.

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 oesophagus.

		All cancers				**PEUGIC**		
		Total n (%)	UGIC control n (%)	PEUGIC n (%)	P value	Barrett's oesophagus n (%)	No Barrett's oesophagus 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)		1 (2.8)	10 (18.9)	
	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)	0.260	0 (0.0)	6 (11.3)	0.141
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.

No correlation was found between the interval from the index endoscopy to PEUGIC diagnosis and tumour size, staging at diagnosis, or histological differentiation (Supplementary Figure 1). More than half of PEUGIC patients received treatment with curative intent (53%), compared with 29% of the UGIC controls ($P = 0.002$). Patients with PEUGIC were more likely to undergo endoscopic resection than the UGIC controls (31.3% vs. 5.1%; $P = 0.002$).

5.4.3 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).

5.4.4 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 correlation was found between the mean annual UGI endoscopy number 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 (Figure 2). The mean annual number of UGI endoscopies performed by these three endoscopists was 206 (SD 20.6).

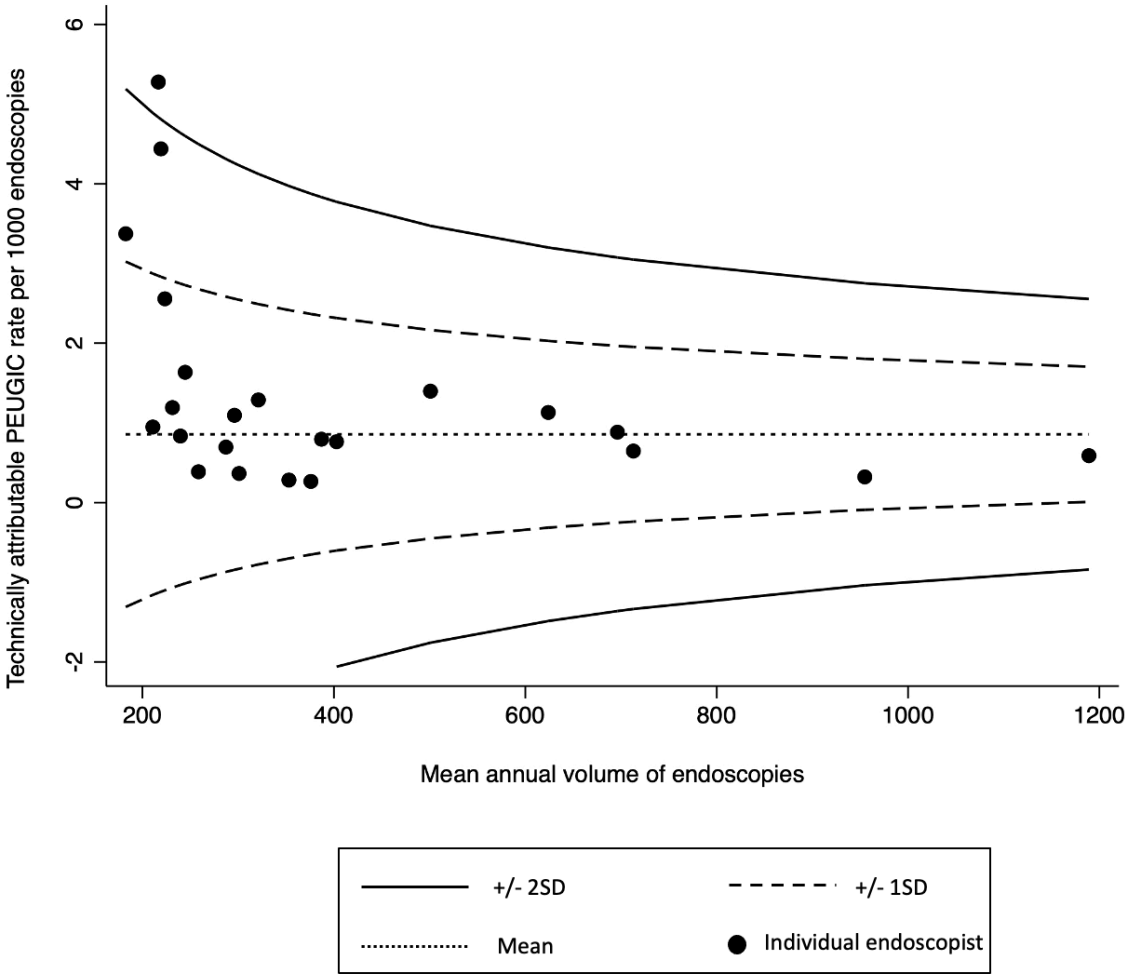


Figure 2 Funnel plot showing the correlation between the annual number of endoscopies performed by individual endoscopists over the study period and the technically attributable post-endoscopy upper gastrointestinal cancer (PEUGIC) rate.

5.4.5 Root cause analysis of the most plausible explanation for PEUGIC

PEUGIC 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 PEUGIC were interval cancers, both of which occurred in patients with Barrett's oesophagus.

Premalignant lesions were identified in 39 patients (43.8%); Barrett's oesophagus 36, gastric adenoma 2, gastric atrophy 1. Focal or cancer-associated lesions were identified in 12 patients (13.5%); oesophageal stricture 4, oesophageal ulcer 2, abnormal esophageal area 3, severe esophagitis 1, cardia inflammation 1, gastroesophageal junction nodule 1. No lesion was found in 38 patients (42.7%) (Figure 3 shows PEUGIC examples).

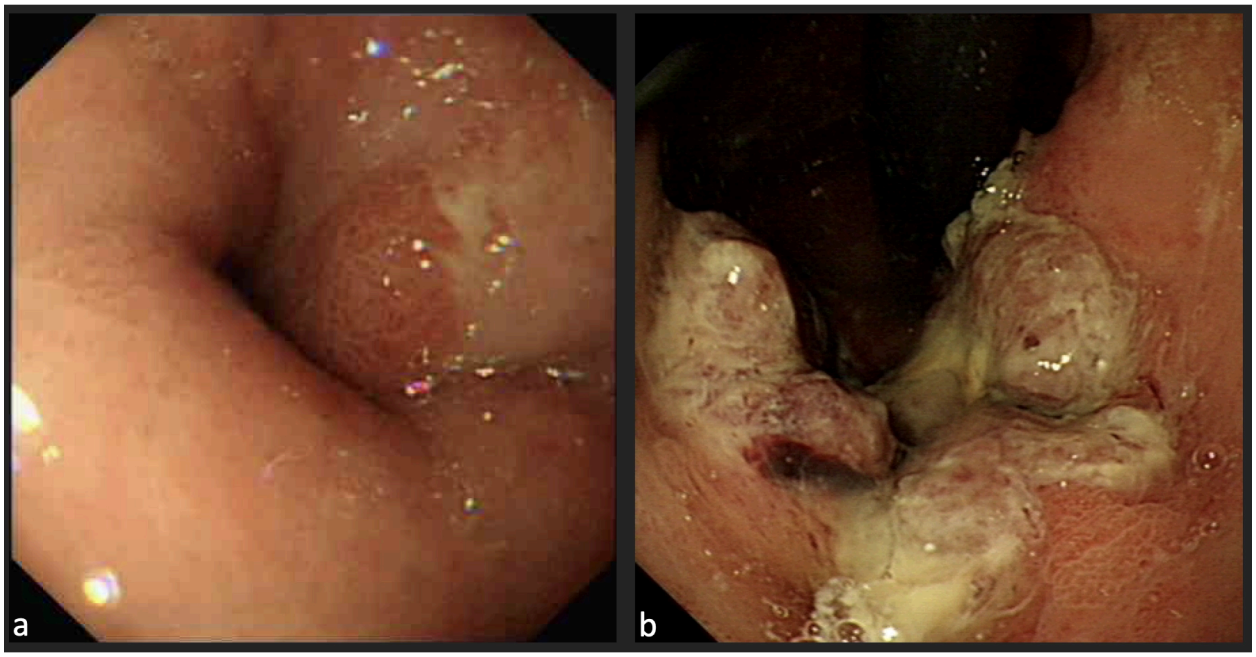


Figure 3 Endoscopic images of a patient with post-endoscopy upper gastrointestinal cancer showing: **a** in the lower esophagus of a patient with a history of chronic reflux, a small ulcer at the gastroesophageal junction that was not biopsied (no follow-up endoscopy was arranged); **b** after the patient 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 Figure 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.

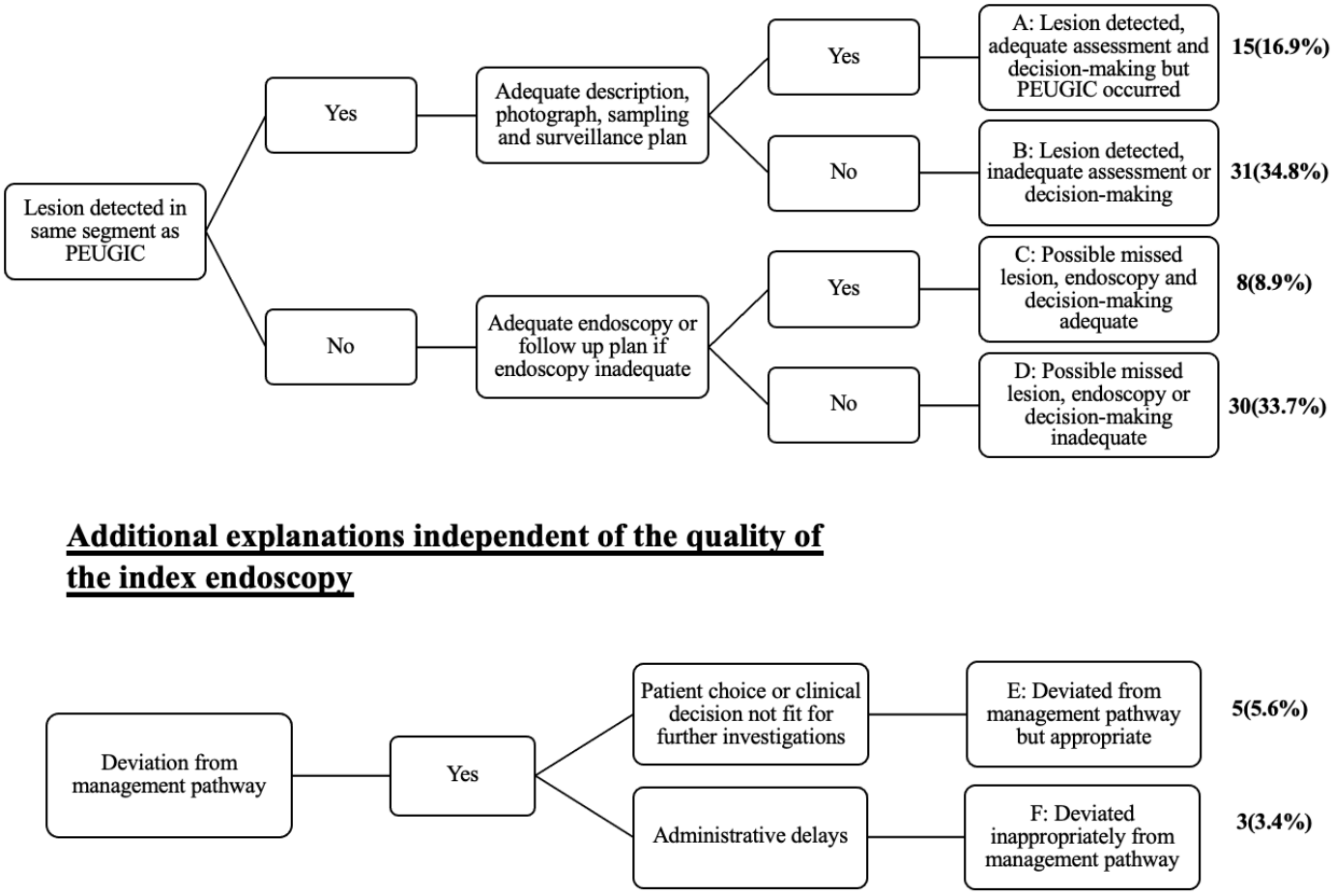


Figure 4 Categorization of post-endoscopy upper gastrointestinal cancers (PEUGIC) based on the most plausible explanation. Lesions included premalignant (e.g. Barrett's esophagus, gastric atrophy, gastric intestinal metaplasia, or gastric adenoma) and focal or cancer-associated lesions (e.g. oesophageal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

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

Type 1	Premalignant lesion noted (e.g. Barrett's oesophagus, gastric intestinal metaplasia or atrophy) in the same segment as the PEUGIC	39 (43.8%)
a	Biopsies adequate and, if Barrett's oesophagus found, segment was adequately measured, and surveillance plan adequate and within correct time frame, 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 time frame but appropriate owing to patient choice or co-morbidity	2 (2.2%)
e	Surveillance not undertaken or not within the correct time frame and inappropriate	3 (3.4%)
Type 2	Focal or cancer-associated lesion noted in the same segment as the PEUGIC (e.g. oesophageal ulcer or stricture, grade C or D reflux oesophagitis, gastric ulcer)	12 (13.5%)
a	Site and morphology described and photographed, adequate biopsy sampling and follow-up undertaken in the correct time frame 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 time frame but appropriate owing to patient choice or co-morbidity	3 (3.4%)
e	Follow-up not undertaken or not within correct time frame 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.

5.4.6 Barrett's oesophagus

Around 40% of PEUGIC were diagnosed in patients with Barrett's oesophagus. 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 PEUGIC in patients with Barrett's oesophagus, 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 PEUGIC, 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.

5.4.7 Avoidability

Of PEUGIC, 71% were categorised as potentially avoidable. The unavoidable PEUGIC included 21 small PEUGIC; 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 frailty.

5.4.8 Impact on clinical outcome

The clinical outcome could potentially have been different for 45% of PEUGIC. 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.

5.5 Discussion

This is the first study to report a detailed root cause analysis of unselected PEUGIC, develop a system of analysis to categorise 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.

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 with Drs. Roland Valori and Nicholas Burr).

Around 40% of PEUGIC occurred in patients with Barrett's oesophagus. A systematic review has also described an esophageal cancer miss rate of 24% in Barrett's oesophagus [18]; however, 89% of the PEUGIC in patients with Barrett's oesophagus 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 tumour staging

and the survival of patients.[19,20] Of the Barrett's PEUGIC, 56% were treated by endoscopic resection and can therefore be regarded as surveillance 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 oesophagus, 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 emphasise 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 oesophagus 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 utilised, 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 consider 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.

5.6 Conclusion

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 UGIC at both endoscopist and institutional level, and guide quality improvement efforts to reduce the PEUGIC rate.

5.7 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;66:1886–99.

2 Menon S, Trudgill N. How commonly is upper gastrointestinal cancer missed at endoscopy? A meta-analysis. *Endosc Int Open*. 2014;2:E46–50.

3 Chadwick G, Groene O, Hoare J, *et al.* A population-based, retrospective, cohort study of esophageal cancer missed at endoscopy. *Endoscopy*. 2014;46:553–60.

4 Chadwick G, Groene O, Riley S, *et al.* Gastric Cancers Missed During Endoscopy in England. *Clin Gastroenterol Hepatol*. 2015;13:1264–70.e1.

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;28:1041–9.

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;61:2674–84.

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;162:1123–35.

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;87:335–9.

9 Raftopoulos SC, Segarajasingam DS, Burke V, *et al.* A cohort study of missed and new cancers after esophagogastroduodenoscopy. *Am J Gastroenterol*. 2010;105:1292–7.

10 Rabeneck L, Paszat LF. Circumstances in which colonoscopy misses cancer. *Frontline Gastroenterol*. 2010;1:52–8.

11 Rutter MD, Beintaris I, Valori R, *et al.* World Endoscopy Organization Consensus Statements on Post-Colonoscopy and Post-Imaging Colorectal Cancer. *Gastroenterology*. 2018;155:909–25.e3.

12 Anderson R, Burr NE, Valori R. Causes of Post-Colonoscopy Colorectal Cancers Based on World Endoscopy Organization System of Analysis. *Gastroenterology*. 2020;158:1287–99.e2.

13 Fitzgerald RC, di Pietro M, Ragunath K, *et al.* British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. *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;131:1392–9.

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;68:1545–75.

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.e7; quiz e14–5.

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;65:548–54.

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;38:162–9.

21 Ooi J, Wilson P, Walker G, *et al.* Dedicated Barrett's surveillance sessions managed by trained endoscopists improve dysplasia detection rate. Endoscopy. 2017;49:524–8.

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. Gastrointestinal Endoscopy. 2012;76:531–8.

23 Park JM, Huo SM, Lee HH, *et al.* Longer Observation Time Increases Proportion of Neoplasms Detected by Esophagogastroduodenoscopy. *Gastroenterology*. 2017;153:460–9.e1.

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. Clinical Gastroenterology and Hepatology. 2013;11:1562–70.e2.

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. Gastrointestinal Endoscopy. 2016;83:57–67.e1.

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;25:778–83.

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 Journal of Gastroenterology. 2019;25:218.

28 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;48:843–64.

29 Chiu PWY, Uedo N, Singh R, *et al.* An Asian consensus on standards of diagnostic upper endoscopy for neoplasia. *Gut*. 2019;68:186–97.

30 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;33:901–3.

31 Rees CJ, Thomas Gibson S, Rutter MD, *et al.* UK key performance indicators and quality assurance standards for colonoscopy. *Gut*. 2016;65:1923–9.

32 The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc*. 2003;58:S3–43.

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. Journal of Gastroenterology and Hepatology. 2021;36:2659–71.

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;52:1048–65.

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;13:480–7.e2.

Chapter 6: Consensus on upper gastrointestinal endoscopy key performance indicators to reduce post endoscopy upper gastrointestinal cancer

In this chapter, I present consensus on the upper gastrointestinal endoscopy key performance indicators which was achieved involving key stakeholders using modified nominal group technique. Minimum standards were also proposed where possible.

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Manuscript

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6.1 Abstract

6.1.1 Background

Upper gastrointestinal (UGI) endoscopy lacks established key performance indicators (KPIs). Up to three fold variation in post endoscopy upper gastrointestinal cancer (PEUGIC) rates has been observed among endoscopy providers in England, highlighting the need for standardisation of UGI endoscopy practices

6.1.2 Objective

We aimed to achieve consensus on evidence-based KPIs to reduce PEUGIC.

6.1.3 Methods

Modified nominal group technique was employed in two consensus workshops, with representation from clinicians, patients and relatives, moderated by James Lind Alliance facilitators. Potential indicators were identified from: umbrella systematic review; English provider PEUGIC rates; and differences in endoscopy practices from the National Endoscopy Database between providers with the highest (worst) and lowest (best) PEUGIC rates. KPIs were categorised as provider or endoscopist/procedure related and ranked as of major or minor importance. Minimum standards were proposed where possible.

6.1.4 Results

Participants included 14 clinicians (gastroenterologists and UGI surgeons), 3 nurse endoscopists, 2 UGI cancer nurse specialists, 14 patients, their relatives and representatives from patient support groups and 4 observers.

Endoscopy provider related major KPIs and proposed standards included: monitoring PEUGIC rates (minimum standard ≤ 7%); less intense endoscopy lists (maximum 10 "points" per list); endoscopy provider accreditation (all providers); and premalignant condition surveillance on dedicated lists by endoscopists with adequate training (>90% surveillance endoscopies).

Endoscopist/procedure related major KPIs included: examination time ≥7 minutes; training in early UGI neoplasia recognition (all endoscopists); mucosal view quality recorded and cleansing agents used if not excellent (>90% endoscopies); intravenous sedation offered to all appropriate patients; recommended number of biopsies from cancer associated or premalignant lesions (>90% endoscopies where such lesions identified); and endoscopists' annual UGI endoscopy volume >100 (all endoscopists).

6.1.5 Conclusion

This study offers a consensus on the KPIs and minimum standards that should be used to improve UGI endoscopy quality and, hence, reduce PEUGIC.

6.2 Key summary

6.2.1 Summarise the established knowledge on this subject

Upper gastrointestinal (UGI) endoscopy lacks established key performance indicators (KPIs). Up to three fold variation in the post endoscopy UGI cancer (PEUGIC) rate has been reported among endoscopy providers in England, indicating significant variation in the quality of UGI endoscopy. Endoscopy societies have proposed a number of recommendations mainly focusing on the general approach to perform UGI endoscopy.

6.2.2 What are the significant and/or new findings of this study?

Current study employed a modified nominal group technique to reach consensus on the KPIs for UGI endoscopy to reduce PEUGIC. Endoscopy provider related major KPIs included monitoring of PEUGIC rate, less intense endoscopy list, external accreditation and premalignant condition surveillance on dedicated lists by endoscopists with adequate training. Endosocpist or procedure related major KPIs included adequate examination time, training in early UGI neoplasia recognition, use of cleansing agents if mucosal views not excellent, offering intravenous sedation to all appropriate patients, recommended number of biopsies from cancer associated or premalignant lesions and endoscopists' annual UGI endoscopy volume.

6.3 Introduction

Upper gastrointestinal (UGI) endoscopy is considered the gold standard investigation to diagnose UGI cancers, and associated premalignant conditions, mainly located in the oesophagus and stomach. 1.2 million UGI endoscopies are performed and approximately 16,500 people are diagnosed with UGI cancer each year in the UK.[1,2] However, more than 8% of patients with UGI cancer in England had an endoscopy which failed to detect cancer in the 3 years before cancer diagnosis, termed post endoscopy UGI cancer (PEUGIC).[3] Given the earlier cancers are diagnosed the better the survival outcomes, reducing rates of PEUGIC is a priority. It is imperative, therefore, to ensure the highest standards and quality in endoscopy to ensure UGI cancers are diagnosed at the earliest stage, or even at a premalignant stage, and so reduce PEUGIC.

The Joint Advisory Group (JAG) on gastrointestinal endoscopy oversees the certification for and assessment of competency in the performance of UGI endoscopy in the UK and the main focus is the technical competence and safety of the procedure. Endoscopy societies, including the British Society of Gastroenterology (BSG), the European Society of Gastrointestinal Endoscopy (ESGE) and the American Gastroenterological Association (AGA) have proposed UGI endoscopy quality standards, but these are mainly focused on the general approach to diagnostic endoscopy.[4–6] An Asian statement on the endoscopy quality standards to detect early upper gastrointestinal (UGI) neoplasia was published in 2019, however, the quality of evidence for most of the standards was poor and based on expert opinion.[7]

6.4 Aims and scope

We aimed to develop consensus on key performance indicators (KPI) to be used to enhance the quality of UGI endoscopy diagnosis and reduce the risk of PEUGIC.

The consensus process focused on the following domains:

a) Identification of potential KPIs

b) Ranking of KPIs as major and minor quality indicators

c) Suggestion of minimum target standards where possible

The following aspects were not included:

- Therapeutic endoscopy
- Transnasal endoscopy

6.5 Materials and methods

6.5.1 Evidence synthesis

Potential KPIs for UGI endoscopy were identified from the following resources:

a) Systematic review

Bibliographic databases were searched up to December 2021 and evidence for endoscopy and endoscopist related factors associated with the detection of dysplasia and UGI cancer was summarised.[8]

b) National Cancer Registry and Hospital Episode Statistics database analysis

Using linked National Cancer Registry and Analysis Services (NCRAS) and Hospital Episode Statistics (HES) databases, data for 98,801 patients were analysed who were diagnosed with UGI cancer within 3 years of an endoscopy without a cancer diagnosis in England between 2009 and 2018. The variation in PEUGIC rates among endoscopy providers in England was examined.[3]

c) National Endoscopy Database analysis

Using the UK National Endoscopy Database (NED), endoscopy practices were compared between providers with the best and worst PEUGIC rates in England and endoscopy practices associated with the providers with the best PEUGIC rates identified.

KPIs were categorised as endoscopist/procedure-related and endoscopy provider-related.

6.5.2 Consensus workshops

We employed the modified Nominal Group Technique to develop consensus on the KPIs. This rigorous, yet flexible approach facilitates generation and prioritisation of ideas from a diverse group of participants, ensuring a democratic and inclusive process.[9] This was conducted in the

form of two online workshops moderated by James Lind Alliance facilitators. The James Lind Alliance is a non-profit making initiative dedicated to bringing together clinicians, patients and carers to discuss research priorities. The National Institute for Health and Care Research funds their infrastructure.

In each workshop, the participants were divided into three groups with balanced clinician and patient/relative representation. A summary of the evidence and list of potential KPIs and minimum standards were circulated to participants in advance. The first workshop focused on identifying candidate KPIs. Participants were asked to provide their opinion on the list of potential KPIs. This was followed by a ranking exercise within each of three groups. Additional KPIs were added to the list based on participants' opinions. Facilitators provided a summary of ranking scores from each small group session. In the second workshop, participants confirmed the ranking of the KPIs and consensus was reached by combining the ranking scores.

6.5.3 Ranking of indicators

The ranking system prioritised KPIs based on their relative importance to reducing PEUGIC. Ranking scores from the small group sessions were combined and the geometric mean was calculated by multiplying the ranks together, and then taking the nth root, where "n" was the number of groups. This produces a geometric average which is better at respecting outlier ranks. The ranking system was designed such that a lower score denotes a more important indicator. The top 10 KPIs were considered major indicators and the remaining ones minor. The level of evidence for each KPI is reported using GRADE methodology. (Table 1)[10]

Table 1 The quality of evidence and definitions according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system

Quality of evidence	**Definition**
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

6.5.4 Funding and ethics

This project was funded by the National Institute for Health and Care Research (NIHR) under its Research for Patient Benefit (RfPB) Programme (Grant Reference Number NIHR 201571). The study was approved by London - South East Research Ethics Committee (IRAS project ID # 289695).

6.6 Results

6.6.1 Participants

Participants included 14 clinicians (consultant gastroenterologists, UGI surgeons and trainees), 3 nurse endoscopists, 2 UGI cancer nurse specialists, 14 patients, their relatives and representatives from patient support groups, and 4 observers.

6.6.2 Key Performance Indicators

A list of KPIs, proposed minimum standards and the quality of evidence for each is provided in Table 2.

Table 2 List of proposed key performance indicators for upper gastrointestinal endoscopy and their quality of evidence

Quality indicators	**Minimum standards**	**Quality of evidence**
Major Indicators		
Endoscopy provider related		
1. Monitoring of PEUGIC rate	≤ 7%	Moderate
2. Less intense endoscopy lists	< 10 points per list	Low
3. External accreditation of endoscopy providers	All providers	Low
4. Surveillance of high-risk conditions performed on dedicated lists by endoscopists with adequate training.	>90% of surveillance UGI endoscopies	Moderate
Endoscopist or procedure related		
5. Adequate examination time	≥7 minutes	Moderate
6. Endoscopists should have dedicated training in the recognition of early UGI neoplasia	All endoscopists	Low
7. Quality of mucosal views recorded and mucosal cleaning agents employed if not excellent mucosal views	>90% of diagnostic endoscopies	Moderate
8. Intravenous sedation offered to all patients	Unable to suggest	Moderate

9. If a cancer associated or premalignant lesion is identified, recommended number of biopsies taken	>90% of endoscopies where a cancer associated, or premalignant lesion is identified	Low
10. Endoscopists' annual Upper Gastrointestinal endoscopy volume	>100 Upper GI endoscopies/ year	Moderate
Minor Indicators		
1. Neoplasia detection rate	Unable to suggest	Low
2. Detection rate for premalignant conditions	Unable to suggest	Low
3. Image enhancement techniques used especially in high-risk patients	Unable to suggest	High
4. Photo documentation of important anatomical sites	>90% of diagnostic Upper GI endoscopies	Low
5. Artificial intelligence	Unable to suggest	Low

PEUGIC - Post Endoscopy Upper Gastrointestinal Cancer

Mean ranking scores for each KPI are reported in Table 3.

Table 3 Mean ranking scores for the key performance indicators for upper gastrointestinal endoscopy

Key performance indicators	**Mean ranking score**
1. Monitoring of endoscopy provider PEUGIC rate	2.0
2. Less intense endoscopy lists	2.1
3. External accreditation of endoscopy providers	2.3
4. Surveillance of high-risk conditions performed on dedicated lists by endoscopists with adequate training	2.5
5. Minimum examination time ≥7 minutes	2.0
6. Endoscopists should have dedicated training in recognition of early UGI neoplasia	2.2
7. Mucosal cleaning agents used to achieve good mucosal views	3.1
8. Intravenous sedation offered to all patients	4.0
9. If a cancer associated or premalignant lesion is identified, recommended number of biopsies taken	4.3

10. Minimum annual Upper Gastrointestinal endoscopy volume >100	4.9
11. Neoplasia detection rate monitored	12.2
12. Detection rate for premalignant conditions monitored	7.2
13. Image enhancement techniques used, especially in high-risk patients	9.6
14. Photo documentation of important anatomical sites	10.2
15. Artificial intelligence	13.7

PEUGIC - Post Endoscopy Upper Gastrointestinal Cancer

6.6.2.1 Endoscopy provider related

Four provider related KPIs were identified, all ranked as major and included: monitoring of PEUGIC rate (minimum standard ≤ 7%); less intense endoscopy lists (less than 10 points per list); external accreditation of endoscopy providers (all providers); and surveillance of upper gastrointestinal premalignant conditions performed on dedicated lists by endoscopists with appropriate training (>90% of surveillance endoscopies). The level of evidence for these KPIs was graded as low to moderate. Monitoring of PEUGIC rates and less intense endoscopy lists were ranked as the most important KPIs.

6.6.2.2 Endoscopist or procedure related

In total, 11 endoscopist or procedure related KPIs were identified, six of these ranked as major and included: adequate examination time (at least 7 minutes); endoscopists should have dedicated training in the recognition of early UGI neoplasia (all endoscopists); the quality of mucosal views recorded and mucosal cleansing agents employed if not excellent mucosal views (>90% of diagnostic endoscopies); intravenous sedation offered to all patients (unable to suggest minimum standard); if a cancer associated or premalignant lesion is identified, the recommended number of biopsies taken (>90% of endoscopies where a cancer associated or premalignant lesion identified); endoscopists' annual UGI endoscopy volume (>100 UGI endoscopies/year). The level of evidence for these KPIs was graded as low to moderate. Adequate examination time and endoscopist training in lesion recognition were ranked as the most important KPIs by all three groups.

Five KPIs were ranked as minor and included: use of image enhancement techniques in high risk patients; photo documentation of important anatomical sites; neoplasia detection rate; detection rate for premalignant conditions; and use of artificial intelligence.

6.7 Discussion

This study employs a unique methodology to take into account patient perspectives in addition to the current evidence and experts' opinion, in order to identify the KPIs which can improve endoscopy quality and reduce PEUGIC. Up to three fold variation in PEUGIC rates has been observed among endoscopy providers in England, highlighting the need for standardisation of UGI endoscopy practices.[3] Adoption of the proposed recommendations can contribute to minimising the variation among providers.

Monitoring of PEUGIC rates and less intense endoscopy lists were considered the most important provider level KPIs. The BSG and JAG recommend that endoscopy providers should audit their PEUGIC rates and aim to keep PEUGIC rates below 10%.[4] However, our recent analysis of NCRAS and HES databases for all UGI cancers diagnosed between 2009-2018 in England reported that the national PEUGIC rate was 8.5%, with the 25th centile rate 7%.[3] It was estimated that if the national PEUGIC rate can be reduced to the 25th centile rate, there would be 162 fewer patients with PEUGIC each year. A recent multicentre root cause analysis of PEUGIC cases reported that up to 70% of PEUGIC were potentially avoidable.[11] Based on these reports, the panel agreed with a new benchmark rate of 7%. Some patients may be diagnosed with UGI cancer at a different provider from the provider where they had their initial endoscopy. Therefore, relying on local data will underestimate the PEUGIC rate. In order to overcome this, a national reporting system is being developed in England. PEUGIC will be identified nationally and providers where the patient had an endoscopy within the 3 years before diagnosis are alerted. Providers will then perform root cause analysis to identify missed opportunities in potentially avoidable cases.

Endoscopy providers should ensure that enough time for UGI endoscopy is allocated to allow high quality examinations. In the UK, endoscopy providers use a points system to allocate time for procedures. Although there is provider-level variation, in general, 15-20 minutes are assigned for one point and an UGI endoscopy or flexible sigmoidoscopy is allocated one point and a colonoscopy two points. In the NED analysis, a negative association was found between more intense endoscopy lists (average points per list >9) and the best PEUGIC rate providers.[12]

In the UK, the JAG provides external accreditation of endoscopy providers. This is a quality assurance programme and providers are assessed against a set of standards covering four domains: clinical quality, patient experience, clinical workforce and training. Providers which did not participate in the JAG accreditation process and those which were assessed and required improvement had higher PEUGIC rates compared to those which were awarded and maintained JAG accreditation.[3] These findings suggest that external accreditation can improve the quality of endoscopy. In the UK, all endoscopy providers should aim to achieve and maintain JAG accreditation.

Premalignant conditions (including Barrett's oesophagus, gastric atrophy and gastric intestinal metaplasia) were strongly associated with PEUGIC.[3] Retrospective studies have shown that the diagnostic yield of dysplasia was higher if Barrett's surveillance was performed by endoscopists trained in its assessment and on dedicated lists where extra time was allocated.[13–15] Although no data is available on the impact of dedicated lists on dysplasia detection for other premalignant conditions (e.g. gastric atrophy and intestinal metaplasia), the

panel recommended that similar expertise and dedicated lists were required for such surveillance endoscopies.

Examination time is an important operator dependent aspect of endoscopy. A multicentre study reported that lengthening the Barrett's inspection time (>1 minute/cm) resulted in better diagnostic yield for suspicious lesions.[13] Three other studies have reported that longer examination times were associated with higher neoplasia detection rates.[16–18] Kwamura et al. examined data for 15,763 screening endoscopies and reported that the UGI cancer detection rates were higher for endoscopists with average examination times over 7 minutes.[18] It was agreed that an UGI endoscopy should take a minimum of 7 minutes.[4,5]

Currently the JAG endoscopy curriculum in the UK is focused on acquiring technical skills with insufficient emphasis on training in the identification of early UGI neoplastic changes. A structured learning programme can increase the knowledge and recognition skills of endoscopists to detect early UGI cancer. A randomised controlled trial that enrolled 335 endoscopists from 35 countries around the world investigated the value of an e-learning programme to detect early gastric cancer and found higher test scores in the e-learning group compared to the control group.[19] An observational study from China reported that a lesion recognition training programme in a real world clinical setting resulted in increased detection of early gastric cancer.[20] Dedicated training modules should therefore be incorporated into the endoscopy curriculum to improve endoscopic detection and characterisation of pre-malignant and early malignant changes.

Defoaming (e.g Simethicone) and mucolytic agents (e.g. N-Acetylcysteine and Pronase) have been investigated in randomised controlled trials.[21–26] The use of Simethicone, in combination or alone provides significantly better mucosal views.[21–24] N-Acetylcysteine did not improve mucosal visibility if Simethicone was given beforehand[22,27], although a significantly smaller number of patients required flushing during endoscopy. A randomised controlled trial from South Korea reported that pronase can improve mucosal visibility and the negative predictive value of NBI at endoscopy.[28] The consensus panel agreed that mucosal cleansing techniques should be routinely used to achieve good mucosal views.

In the NED analysis, it was noted that use of intravenous sedation was more common among providers with the best PEUGIC rates.[12] Concomitant use of opioids and benzodiazepines was also more common among providers with lowest PEUGIC rates. A multicentre study from China reported higher UGI cancer and high grade dysplasia detection rates with Propofol.[29] These observations are likely related to better patient tolerance with sedation, allowing adequate examination time and use of image enhancement techniques as required. Where appropriate, considering patient factors, intravenous sedation should be offered to all patients undergoing UGI endoscopy. The panel was not able to recommend a minimum standard for use of IV sedation but the rate, benchmarked against national data, can be used as an auditable outcome.

In the NCRAS analysis, premalignant (e.g. Barrett's oesophagus) and cancer associated lesions (oesophageal ulcer/stricture, severe oesophagitis and gastric ulcer) were found to be strongly associated with PEUGIC.[3] Inadequate assessment of high risk lesions and decision making on surveillance or follow up was one of the most common reason for missing the cancers on

PEUGIC root cause analysis.[11] National recommendations e.g. from the BSG should be followed when assessing these lesions and endoscopy providers should audit compliance with these recommendations.[4,30,31]

The BSG proposes that the endoscopists should aim to perform a minimum of 100 procedures annually to maintain their proficiency and endoscopy providers are required to monitor the annual volume of UGI endoscopies performed by endoscopists.[4,32] A NED analysis reported that around half of the endoscopists in the UK met the 100 UGI endoscopies per year minimum recommended volume.[33] A multicentre root cause analysis of PEUGIC described a negative correlation between annual UGI endoscopy volume and the PEUGIC rates of individual endoscopists.[11] In a recent NED analysis, a positive association was found between annual endoscopist volume >100 and providers with the best PEUGIC rates, supporting the BSG recommendation.[12]

Provider level KPIs offer granular insights that are essential for detailed performance assessment and can be used to compare the performance of different healthcare providers. For the first time, intensity of endoscopy lists, external accreditation and dedicated lists for surveillance were proposed as KPIs to assess the efficacy and quality of services provided. A new benchmark was also proposed for the PEUGIC rate. These KPIs can be instrumental in identifying best practices and areas of improvement when comparing different providers.

Current study used modified nominal group technique which is different from the more commonly used Delphi consensus process. Both are established techniques to develop

consensus. The nominal group technique entails face-to-face discussion in small groups, to explore views from both patients and clinicians, provides a prompt result and was ideally suited to the current study.[34] The Delphi consensus technique is more commonly used to develop guidelines, mainly involving healthcare professionals. It is a more detailed process, involving multiple rounds of voting and it can be time consuming to reach consensus. The current project was part of an NIHR funded study and required equal involvement of patients and their carers to identify and assess the measures. Therefore, the nominal group technique was considered more appropriate and chosen in advance.

This study has a number of limitations. Due to lack of well designed trials, most of the evidence examined was graded as low to moderate quality. As the group of experts and participating patients were all from the UK, there is a potential bias that these recommendations may be more applicable to UK endoscopy practice. We expect that the current study provides a framework for further research in other healthcare systems to corroborate or refute our recommendations. Due to the paucity of evidence in the field, it was not possible to suggest minimum standards for some measures. However, assessment of those KPIs was considered important. Such KPIs are sometimes described as "auditable outcomes" and it is hoped that future research will help determine appropriate standards.[35] We recognise that bias may be evident in consensus statements receiving higher ranking, as major KPIs with only weak evidence. We allowed discordantly high ranking when the consensus group determined a particular KPI was integral to assessing the quality of endoscopy. While this leaves these recommendations open to criticism, we hope that by setting these standards, high quality research can be undertaken to validate these findings.

6.8 Conclusions

This consensus provides a list of major and minor KPIs to improve the quality of endoscopy and reduce PEUGIC. This framework will enable endoscopy providers to monitor their performance and ensure provision of a high quality UGI endoscopy service for their patients.

6.9 References

1 Shenbagaraj L, Thomas-Gibson S, Stebbing J, *et al.* Endoscopy in 2017: a national survey of practice in the UK. *Frontline Gastroenterol*. 2019;10:7–15.

2 Stomach cancer statistics. Cancer Research UK. 2015. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/stomach-cancer (accessed 21 January 2024)

3 Kamran U, Evison F, Morris EJA, *et al.* The variation in post-endoscopy upper gastrointestinal cancer rates among endoscopy providers in England and associated factors: a population-based study. *Endoscopy*. Published Online First: 29 August 2024. doi: 10.1055/a-2378-1464

4 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;66:1886–99.

5 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;48:843–64.

6 Park WG, Shaheen NJ, Cohen J, *et al.* Quality indicators for EGD. *Am J Gastroenterol*. 2015;110:60–71.

7 Chiu PWY, Uedo N, Singh R, *et al.* An Asian consensus on standards of diagnostic upper endoscopy for neoplasia. *Gut*. 2019;68:186–97.

8 Kamran U, Abbasi A, Umar N, *et al.* Umbrella systematic review of potential quality indicators for the detection of dysplasia and cancer at upper gastrointestinal endoscopy. *Endosc Int Open*. 2023;11:E835–48.

9 Jones J, Hunter D. Consensus methods for medical and health services research. *BMJ*. 1995;311:376–80.

10 Guyatt GH, Oxman AD, Vist GE, *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924–6.

11 Kamran U, King D, Abbasi A, *et al.* A root cause analysis system to establish the most plausible explanation for post-endoscopy upper gastrointestinal cancer. *Endoscopy*. Published Online First: 31 August 2022. doi: 10.1055/a-1917-0192

12 Kamran U, Evison F, Brookes M, *et al.* P176 Differences in endoscopy practices between providers with highest and lowest post endoscopy upper gastrointestinal cancer rates using national endoscopy database. *Gut*. 2023;72:A146–7.

13 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;76:531–8.

14 Ooi J, Wilson P, Walker G, *et al.* Dedicated Barrett's surveillance sessions managed by trained endoscopists improve dysplasia detection rate. *Endoscopy*. 2017;49:524–8.

15 Ratcliffe E, Britton J, Yalamanchili H, *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;15:21–7.

16 Park JM, Huo SM, Lee HH, *et al.* Longer Observation Time Increases Proportion of Neoplasms Detected by Esophagogastroduodenoscopy. *Gastroenterology*. 2017;153:460–9.e1.

17 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;13:480–7.e2.

18 Kawamura T, Wada H, Sakiyama N, *et al.* Examination time as a quality indicator of screening upper gastrointestinal endoscopy for asymptomatic examinees. *Dig Endosc*. 2017;29:569–75.

19 Yao K, Uedo N, Muto M, *et al.* Development of an E-learning System for the Endoscopic Diagnosis of Early Gastric Cancer: An International Multicenter Randomized Controlled Trial. *EBioMedicine*. 2016;9:140–7.

20 Zhang Q, Chen Z-Y, Chen C-D, *et al.* Training in early gastric cancer diagnosis improves the detection rate of early gastric cancer: an observational study in China. *Medicine* . 2015;94:e384.

21 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;25:778–83.

22 Chang W-K, Yeh M-K, Hsu H-C, *et al.* Efficacy of simethicone and N-acetylcysteine as premedication in improving visibility during upper endoscopy. *J Gastroenterol Hepatol*. 2014;29:769–74.

23 Song M, Kwek ABE, Law NM, *et al.* Efficacy of small-volume simethicone given at least 30 min before gastroscopy. *World J Gastrointest Pharmacol Ther*. 2016;7:572–8.

24 Basford PJ, Brown J, Gadeke L, *et al.* A randomized controlled trial of pre-procedure simethicone and N-acetylcysteine to improve mucosal visibility during gastroscopy - NICEVIS. *Endosc Int Open*. 2016;4:E1197–202.

25 Lee GJ, Park SJ, Kim SJ, *et al.* Effectiveness of Premedication with Pronase for

Visualization of the Mucosa during Endoscopy: A Randomized, Controlled Trial. *Clin Endosc*. 2012;45:161–4.

26 Liu X, Guan CT, Xue LY, *et al.* Effect of premedication on lesion detection rate and visualization of the mucosa during upper gastrointestinal endoscopy: a multicenter large sample randomized controlled double-blind study. *Surg Endosc*. 2018;32:3548–56.

27 Chen H-W, Hsu H-C, Hsieh T-Y, *et al.* Pre-medication to improve esophagogastroduodenoscopic visibility: a meta-analysis and systemic review. *Hepatogastroenterology*. 2014;61:1642–8.

28 Cha JM, Won KY, Chung I-K, *et al.* Effect of pronase premedication on narrow-band imaging endoscopy in patients with precancerous conditions of stomach. *Dig Dis Sci*. 2014;59:2735–41.

29 Zhou J, Li Z, Ji R, *et al.* Influence of Sedation on the Detection Rate of Early Cancer and Precancerous Lesions During Diagnostic Upper Gastrointestinal Endoscopies: A Multicenter Retrospective Study. *Am J Gastroenterol*. 2021;116:1230–7.

30 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;68:1545–75.

31 Fitzgerald RC, di Pietro M, Ragunath K, *et al.* British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. *Gut*. 2014;63:7–42.

32 JAG. https://www.thejag.org.uk/CMS/UploadedDocuments/Scheme/Scheme5/Guidance/191107%20-%20guidance%20-%20JAG%20quality%20and%20safety%201.0%20final (accessed 12 June 2024)

33 Beaton D, Broughton R, Rogers P, *et al.* PTU-18 Endoscopy procedure volume among the UK endoscopist workforce: Analysis using the national endoscopy database (NED). *Gut*. 2021;70:A50–1.

34 McMillan SS, King M, Tully MP. How to use the nominal group and Delphi techniques. *Int J Clin Pharm*. 2016;38:655–62.

35 Rutter MD, Senore C, Bisschops R, *et al.* The European Society of Gastrointestinal Endoscopy Quality Improvement Initiative: developing performance measures. *Endoscopy*. 2016;48:81–9.

Chapter 7: Discussion

A study specific discussion is contained within each of the chapters presented above. Here I will summarise key findings from the work undertaken, future directions and implications for this body of work.

7.1 Summary of key findings

Several key findings from this thesis will inform future research priorities.

7.1.1 Findings from Umbrella systematic review

In the umbrella systematic review (chapter 2), I examined existing evidence for the potential key performance indicators (KPIs) for upper gastrointestinal (UGI) endoscopy. I found strong evidence in the form of high quality systematic reviews and meta analyses [60–65] that image enhancement techniques, especially narrow band imaging (NBI), can improve the diagnostic yield of endoscopy for dysplasia and UGI cancers. However, most studies included in these systematic reviews involved endoscopists who were experienced in using NBI, or had training in using NBI patterns in enriched populations with a high risk of cancer or dysplasia which may not be reflective of the routine practice as the majority of endoscopists are not trained in lesion recognition using NBI. A standardised training programme to use image enhancement techniques can potentially improve endoscopist performance. Insufficient evidence in the form of retrospective studies was found for examination time, endoscopist biopsy rate and intravenous sedation use.[66–72] Neoplasia detection rate and dedicated lists by trained endoscopists were identified as additional quality indicators for Barrett's oesophagus. [73,74]

7.1.2 Outcomes from Hospital Episode Statistics and National Cancer Registration and Analysis Services databases analysis

In chapter three, I examined linked Hospital Episode Statistics (HES) and National Cancer Registration and Analysis Services (NCRAS) databases to explore the factors associated with post endoscopy UGI cancer (PEUGIC). PEUGIC rate was estimated to be 8.5% and no improvement was observed between 2009 and 2018. These rates were similar to those reported in 2014/2015. [50,51] My study confirmed a number of factors with an established association with PEUGIC including younger age, female sex, increasing comorbidity, and Barrett's oesophagus. [52,75–77] For cancers diagnosed in patients with Barrett's oesophagus, the PEUGIC rate was 21%. This study reported additional factors associated with higher PEUGIC rates including history of oesophageal ulcer, oesophageal stricture, gastric ulcer or gastric atrophy. These findings highlight the importance of careful endoscopic examination, follow-up, and surveillance of these high risk conditions following national guidelines.[21,41,78] This is the first study which reported up to three-fold variation in PEUGIC rates among endoscopy providers in England, even after adjusting for differences in case mix and tumour related factors. These findings demonstrate unwarranted variation in the quality of UGI endoscopy performed across the country and the need for standardisation of endoscopy practices. I explored endoscopy provider related factors and identified that endoscopy provider accreditation status by the Joint Advisory Group on GI Endoscopy (JAG) was associated with PEUGIC: endoscopies performed by both the providers which were assessed by JAG during the study period and required improvement to achieve accreditation status and by the providers which never had an assessment during the study period were more likely to be false negative. These results suggest that external accreditation of endoscopy providers can potentially improve the quality of endoscopy.

7.1.3 Outcomes from National Endoscopy Database analysis

In chapter four, I compared endoscopy practices between providers with highest and lowest PEUGIC rates in England using the National Endoscopy Database (NED). Endoscopy characteristics associated with providers with the best (lowest) PEUGIC rates included: less intense (maximum 10 points per list) and training endoscopy sessions; intravenous sedation use; and endoscopists' average annual UGI endoscopy volume > 100, suggesting these factors can potentially improve the quality of endoscopy. There was a marginally stronger association with an endoscopist annual volume of 201-300, suggesting an aspirational standard of >200 UGI endoscopies per year would be appropriate. A negative association was found between the number of endoscopies performed by endoscopists not on specialist, trainee or nursing registers and the best PEUGIC rate providers quartile. This reflects a potential impact of endoscopists' specialty and training on the quality of endoscopy as the endoscopists not on a specialist or training register in England may not participate or have the same opportunities for formal training courses or continuous professional development activities to improve their endoscopy and lesion recognition skills. Although the overall biopsy rate was lower in the best PEUGIC rate providers, compliance with the national recommendations to take biopsies when a high risk cancer associated lesion was identified was higher by providers with the best PEUGIC rates.

7.1.4 Development of root cause analysis of post endoscopy upper gastrointestinal cancers

An algorithm based on the World Endoscopy Organization post-colonoscopy colorectal cancer algorithm [49,79] was developed to categorise and identify potentially avoidable PEUGIC (chapter 5). Possible missed lesions, inadequate assessment or decision-making were identified

as the most common plausible explanation on a root cause analysis of 89 PEUGIC cases at two NHS providers. Interestingly, a negative correlation was found between the mean annual UGI endoscopy number performed by endoscopists and the technically attributable PEUGIC rate, providing additional evidence that annual volume can be an important KPI to monitor endoscopists' performance, as suggested by the British Society of Gastroenterology (BSG) and JAG. [41,80] No correlation was found between the interval from the index endoscopy to PEUGIC diagnosis and tumour size, staging at diagnosis, or histological differentiation. This research estimated that the cancer outcome could have been different in 45% of PEUGIC cases if it had been diagnosed on the initial endoscopy.

7.1.5 Outcomes from the consensus workshops

In chapter six, I presented findings from consensus workshops where all above findings (reported in chapters 2-5) were presented to key stakeholders including clinicians (gastroenterologists and UGI surgeons), nurse endoscopists, UGI cancer nurse specialists, patients, their relatives and representatives from patient support groups. Consensus on the UGI endoscopy KPIs was developed using modified nominal group technique. Endoscopy provider related major KPIs and proposed standards included: monitoring PEUGIC rates (minimum standard ≤ 7%); less intense endoscopy lists (maximum 10 "points" per list); endoscopy provider accreditation (all providers); and premalignant condition surveillance on dedicated lists by endoscopists with adequate training (> 90% surveillance endoscopies).

Endoscopist/procedure related major KPIs included: examination time ≥7 minutes; training in early UGI neoplasia recognition (all endoscopists); mucosal view quality recorded and cleansing agents used if not excellent (>90% endoscopies); intravenous sedation offered to all appropriate patients; recommended number of biopsies from cancer associated or premalignant lesions (>90% endoscopies where such lesions identified); and endoscopists' annual UGI endoscopy volume >100 (all endoscopists).

7.2 Implications and future directions

Results from this thesis have been presented at regional, national and international conferences as described on pages 14 and 15. The recommendations from this thesis gained substantial recognition in the form of national awards and were well received reflecting a broad consensus among professionals in the domain.

7.2.1 National PEUGIC root cause analysis project

Based on the root cause analysis system which I developed (chapter 5), NIHR funding, and the lessons learned from the recent Post Colonoscopy Colorectal Cancer Audit,[81] a national online portal has been developed by Health Data Insight, which is a social enterprise overseen by the *Office of the Regulator of Community Interest Companies*.[82] This portal contains an online form to capture the data items required to undertake a comprehensive root cause analysis of PEUGIC. PEUGIC cases were identified from final or provisional registrations in the National Cancer Registration and Hospital Episode Statistics Datasets held by the National Cancer Registration and Analysis Service. Endoscopy providers were informed of each PEUGIC soon after the patient was diagnosed with cancer and the need for a root cause analysis. Rigorous hospital review of the endoscopy performed within 3-36 months prior to cancer diagnosis and decision making around it was undertaken locally and data were uploaded on the secure online portal. The results will be captured centrally to enable collation and analysis of the reasons for PEUGIC at a national level.

In the first phase, this system has been piloted at 13 NHS hospitals in England involving 220 PEUGICs.[83] In the second phase, the PEUGIC root cause analysis portal was rolled out to all

NHS providers in England with the aim to review over 2500 cases. This system not only provides a systematic method to analyse PEUGIC, but the intelligence generated will also then be used to suggest interventions to reduce the incidence of PEUGIC through local and national quality improvement efforts.

7.2.2 New benchmark PEUGIC rate

I estimated the potential benefit if the PEUGIC rate was reduced to the 25th centile rate (chapter 3). If the PEUGIC rate was reduced to 7% between 2009 and 2017, there would have potentially been 162 fewer patients with PEUGIC each year. PEUGIC root cause analysis study which was conducted at two NHS trusts (chapter 5), 71% of PEUGIC cases were considered avoidable. Based on these findings, I recommend a new benchmark PEUGIC rate of <7% which is lower than the current BSG recommendation of <10%.[41] This recommendation was well received at national conferences, leading to productive dialogue and interest from experts in the field.

7.2.3 Update of National Endoscopy Database (iteration two) analysis

NED allows KPI data available to endoscopists and services to be provided in a consistent format. In the first iteration, data was captured for a small number of UGI endoscopy KPIs including procedure count, intravenous sedation dose, intubation rate into the second part of duodenum and J manoeuvre (retroflexion in the stomach to examine upper part of stomach and gastro-oesophageal junction) rate. Recently the second iteration of NED has been launched which will allow monitoring data for additional KPIs for which evidence was found in our systematic review (chapter 2). These include examination time, mucosal visualisation quality, use of image enhancement techniques and mucosal cleaning techniques and adequate number of biopsies for Barrett's oesophagus and gastric atrophy. I am involved in the planning of the next

phase of NED analysis which will use data from the second iteration to compare providers with the best and worst PEUGIC outcomes including these additional KPIs. These studies will provide more robust KPI data to guide future efforts to improve the quality of endoscopy.

7.2.4 Monitoring surveillance and follow up rates of premalignant and cancer associated conditions

Endoscopy providers are required to monitor the follow up rates for gastric ulcer within 12 weeks as part of their JAG accreditation process as an indicator of their performance.[84] Based on the findings from this thesis, we recommend that endoscopy providers should also monitor follow up and surveillance rates of other premalignant (e.g. Barrett's oesophagus, gastric atrophy and gastric intestinal metaplasia) and cancer associated conditions (e.g. oesophageal ulcer and oesophageal stricture) which have been found to be strongly associated with PEUGIC (chapter 3). Endoscopy reporting systems should be developed and updated to measure performance at the endoscopy provider level of these KPIs.

7.2.5 Dedicated training of endoscopists in lesion recognition

Currently there is a lack of structured or formal training system in the UK to train endoscopists in recognition of early cancer changes in UGI tract. Dedicated training modules should therefore be developed and incorporated into the endoscopy curriculum to improve endoscopic detection and characterisation of pre-malignant and early malignant changes. Summative assessment of proficiency in lesion recognition should be included in the UGI endoscopy sign off for trainee endoscopists. Upskilling courses should be developed and delivered at regional endoscopy academy level to refresh the recognition of pre-malignant and early malignant changes for established endoscopists and update them on endoscopy techniques such as image enhancement.

7.2.6 Less intense endoscopy lists

For the first time, this thesis has provided evidence that less intense endoscopy lists can result in better quality endoscopy (chapter 4). I presented these results in the clinical endoscopists' annual meeting and the participants agreed that overloaded endoscopy sessions negatively impact the ability of the operator to spend enough time during the procedure to perform high quality endoscopic examination. It was also highlighted that there is huge variation in the country with regards to allocation of points per procedure and per session. There is ongoing discussion to develop a national guidance on appropriate time allocation by the BSG and JAG and increasing time allocation for a diagnostic UGI endoscopy to 30 minutes (currently 15-20 minutes) and for a surveillance endoscopy to 40 minutes (currently no specific recommendation). This would allow endoscopists to spend more time and look for subtle lesions which could represent early cancers or precancerous conditions, use advanced imaging techniques and take an adequate number of biopsies. In future, studies can examine how these changes in time allocation impact other KPIs including dysplasia and cancer detection rates.

7.2.7 Artificial intelligence

Although currently there is limited data on the use of artificial intelligence (AI) in UGI endoscopy, there is emerging evidence that AI assistance has a promising role in early detection of UGI cancer. Studies have reported that deep learning based AI systems can detect early cancerous changes in patients undergoing Barrett's oesophagus surveillance [85–87] and also improve diagnostic yield for early oesophageal squamous cell cancers [88,89] and gastric cancers [90–92], with a diagnostic accuracy comparable to expert endoscopists. The movement towards adoption of AI in endoscopy is inevitable as the technology has gained popularity in

other industries. AI will likely improve the ability of general endoscopists for better detection and more accurate optical diagnosis, potentially closing the gap between generalists and experts. The biggest limitation of image-based AI is the requirement for high-quality images for both training, validation, and real-life application. In future, data on the use of AI assistance can potentially be captured in NED which would allow future studies to further refine and expand the role of AI in endoscopy, contributing to a deeper understanding of its potential and limitations and optimising its integration into diagnostic and therapeutic procedures.

7.2.8 Cluster randomised controlled trials

Endoscopy practices vary across the country. This provides an opportunity to compare the effect of various interventions suggested in this thesis on endoscopy quality. Future work, including controlled trials with cluster randomisation of endoscopy providers to test bundle interventions (e.g. training endoscopists in lesion recognition, dedicated lists for surveillance and follow up endoscopies of high risk conditions, use of premedications, less intense endoscopy lists and minimum examination time >7 minutes) and compare it with standard care, should be considered to look at the impact of these interventions on cancer and dysplasia detection rates.

7.2.9 Implications for patients

Findings from this thesis can potentially have significant implications on patient care and outcomes. Patients and carers who kindly participated in the consensus workshops (chapter 6) were particularly interested in the proposals to develop early cancer recognition training modules for endoscopists which would ensure that patients get the best possible opportunity to have early diagnosis of cancer. Patient comfort is critical during endoscopy to allow a high quality examination and also to make it less traumatic, especially for those who need repeated

endoscopies and intervention. Recommendation from this thesis to offer intravenous sedation to all patients was therefore considered very important from patients' perspective. Monitoring of PEUGIC rates and external accreditation of endoscopy providers will provide objective measures to monitor and compare performance at national level, which will improve patients' confidence in the system.

7.3 Conclusions

This thesis has examined variation in the endoscopy practices in the country and identified the factors which are associated with missing a cancer on endoscopy. This work also identified new evidence for UGI endoscopy KPIs to improve the quality of endoscopy. Consensus was developed on the role of these measures involving key stakeholders. A novel root cause analysis system has been developed to systematically examine the most plausible explanation of potentially missed cancers on endoscopy and identify the correctable factors. The findings from this work also provide research priorities for future quality improvement efforts which I hope will result in earlier detection of UGI cancer and hence improved patient outcomes.

References for Introduction and Discussion

1 Menon S, Trudgill N. How commonly is upper gastrointestinal cancer missed at endoscopy? A meta-analysis. *Endosc Int Open*. 2014;2:E46–50.

2 Arnold M, Abnet CC, Neale RE, *et al.* Global Burden of 5 Major Types of Gastrointestinal Cancer. *Gastroenterology*. 2020;159:335–49.e15.

3 Stomach cancer statistics. Cancer Research UK. 2015. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/stomach-cancer (accessed 9 July 2024)

4 Oesophageal cancer survival statistics. Cancer Research UK. 2015. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/oesophageal-cancer/survival (accessed 9 July 2024)

5 Wei W-Q, Chen Z-F, He Y-T, *et al.* Long-Term Follow-Up of a Community Assignment, One-Time Endoscopic Screening Study of Esophageal Cancer in China. *J Clin Oncol*. 2015;33:1951–7.

6 Jung K-W, Won Y-J, Kong H-J, *et al.* Cancer Statistics in Korea: Incidence, Mortality, Survival, and Prevalence in 2016. *Cancer Res Treat*. 2019;51:417–30.

7 Matsuda T, Saika K. Cancer burden in Japan based on the latest cancer statistics: need for evidence-based cancer control programs. *Ann Canc Epidemiol*. 2018;2:2–2.

8 Semnani SH, Besharat S, Abdolahi N, *et al.* Esophageal cancer in northeastern Iran. *Indian J Gastroenterol*. 2005;24:224.

9 Van Loon K, Mwachiro MM, Abnet CC, *et al.* The African Esophageal Cancer Consortium: A Call to Action. *J Glob Oncol*. 2018;4:1–9.

10 Engel LS, Chow W-H, Vaughan TL, *et al.* Population attributable risks of esophageal and gastric cancers. *J Natl Cancer Inst*. 2003;95:1404–13.

11 Prabhu A, Obi KO, Rubenstein JH. The synergistic effects of alcohol and tobacco consumption on the risk of esophageal squamous cell carcinoma: a meta-analysis. *Am J Gastroenterol*. 2014;109:822–7.

12 Erkal HS, Mendenhall WM, Amdur RJ, *et al.* Synchronous and metachronous squamous cell carcinomas of the head and neck mucosal sites. *J Clin Oncol*. 2001;19:1358–62.

13 Petit T, Georges C, Jung GM, *et al.* Systematic esophageal endoscopy screening in patients previously treated for head and neck squamous-cell carcinoma. *Ann Oncol*. 2001;12:643–6.

14 Akhtar S, Sheikh AA, Qureshi HU. Chewing areca nut, betel quid, oral snuff, cigarette

smoking and the risk of oesophageal squamous-cell carcinoma in South Asians: a multicentre case-control study. *Eur J Cancer*. 2012;48:655–61.

15 Trivedy C, Baldwin D, Warnakulasuriya S, *et al.* Copper content in Areca catechu (betel nut) products and oral submucous fibrosis. *Lancet*. 1997;349:1447.

16 Zagari RM, Marasco G, Tassi V, *et al.* Risk of Squamous Cell Carcinoma and Adenocarcinoma of the Esophagus in Patients With Achalasia: A Long-Term Prospective Cohort Study in Italy. *Am J Gastroenterol*. 2021;116:289–95.

17 Petrelli F, De Santi G, Rampulla V, *et al.* Human papillomavirus (HPV) types 16 and 18 infection and esophageal squamous cell carcinoma: a systematic review and meta-analysis. *J Cancer Res Clin Oncol*. 2021;147:3011–23.

18 Koo S, Kejariwal D, Al-Shehri T, *et al.* Oesophageal candidiasis and squamous cell cancer in patients with gain-of-function STAT1 gene mutation. *United European Gastroenterol J*. 2017;5:625–31.

19 Lagergren J, Bergström R, Lindgren A, *et al.* Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med*. 1999;340:825–31.

20 Rubenstein JH, Taylor JB. Meta-analysis: the association of oesophageal adenocarcinoma with symptoms of gastro-oesophageal reflux. *Aliment Pharmacol Ther*. 2010;32:1222–7.

21 Fitzgerald RC, di Pietro M, Ragunath K, *et al.* British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. *Gut*. 2014;63:7–42.

22 Ronkainen J, Aro P, Storskrubb T, *et al.* Prevalence of Barrett's esophagus in the general population: an endoscopic study. *Gastroenterology*. 2005;129:1825–31.

23 Zagari RM, Fuccio L, Wallander M-A, *et al.* Gastro-oesophageal reflux symptoms, oesophagitis and Barrett's oesophagus in the general population: the Loiano–Monghidoro study. *Gut*. 2008;57:1354–9.

24 Desai TK, Krishnan K, Samala N, *et al.* The incidence of oesophageal adenocarcinoma in non-dysplastic Barrett's oesophagus: a meta-analysis. *Gut*. 2012;61:970–6.

25 Cook MB, Kamangar F, Whiteman DC, *et al.* Cigarette smoking and adenocarcinomas of the esophagus and esophagogastric junction: a pooled analysis from the international BEACON consortium. *J Natl Cancer Inst*. 2010;102:1344–53.

26 Thrift AP, Shaheen NJ, Gammon MD, *et al.* Obesity and risk of esophageal adenocarcinoma and Barrett's esophagus: a Mendelian randomization study. *J Natl Cancer Inst*. 2014;106. doi: 10.1093/jnci/dju252

27 Turati F, Tramacere I, La Vecchia C, *et al.* A meta-analysis of body mass index and esophageal and gastric cardia adenocarcinoma. *Ann Oncol*. 2013;24:609–17.

28 Cook MB, Greenwood DC, Hardie LJ, *et al.* A Systematic Review and Meta-Analysis of the Riskof Increasing Adiposity on Barrett's Esophagus. *Official journal of the American College of Gastroenterology | ACG*. 2008;103:292.

29 Chen C-C, Hsu Y-C, Lee C-T, *et al.* Central Obesity and H. pylori Infection Influence Risk of Barrett's Esophagus in an Asian Population. *PLoS One*. 2016;11:e0167815.

30 Sung H, Ferlay J, Siegel RL, *et al.* Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021;71:209–49.

31 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, International Agency for Research on Cancer, World Health Organization. *Schistosomes, Liver Flukes and Helicobacter Pylori*. IARC 1994.

32 An international association between Helicobacter pylori infection and gastric cancer. The EUROGAST Study Group. *Lancet*. 1993;341:1359–62.

33 Parsonnet J, Friedman GD, Vandersteen DP, *et al.* Helicobacter pylori infection and the risk of gastric carcinoma. *N Engl J Med*. 1991;325:1127–31.

34 Hansen S, Melby KK, Aase S, *et al.* Helicobacter pylori infection and risk of cardia cancer and non-cardia gastric cancer. A nested case-control study. *Scand J Gastroenterol*. 1999;34:353–60.

35 Huang JQ, Sridhar S, Chen Y, *et al.* Meta-analysis of the relationship between Helicobacter pylori seropositivity and gastric cancer. *Gastroenterology*. 1998;114:1169–79.

36 Eslick GD, Lim LL, Byles JE, *et al.* Association of Helicobacter pylori infection with gastric carcinoma: a meta-analysis. *Am J Gastroenterol*. 1999;94:2373–9.

37 de Vries AC, van Grieken NCT, Looman CWN, *et al.* Gastric cancer risk in patients with premalignant gastric lesions: a nationwide cohort study in the Netherlands. *Gastroenterology*. 2008;134:945–52.

38 Tsugane S, Sasazuki S. Diet and the risk of gastric cancer: review of epidemiological evidence. *Gastric Cancer*. 2007;10:75–83.

39 Peleteiro B, Lopes C, Figueiredo C, *et al.* Salt intake and gastric cancer risk according to Helicobacter pylori infection, smoking, tumour site and histological type. *Br J Cancer*. 2011;104:198–207.

40 Moon HS. Improving the Endoscopic Detection Rate in Patients with Early Gastric Cancer. *Clin Endosc*. 2015;48:291–6.

41 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;66:1886–99.

42 Amin MB, Edge SB, Greene FL, *et al. AJCC Cancer Staging Manual*. Springer International Publishing 2018.

43 Ajani JA, D'Amico TA, Bentrem DJ, *et al.* Esophageal and Esophagogastric Junction Cancers, Version 2.2023, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2023;21:393–422.

44 Obermannová R, Alsina M, Cervantes A, *et al.* Oesophageal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2022;33:992–1004.

45 Website. Wang Y, Mukkamalla SKR, Singh R, et al. Esophageal Cancer. [Updated 2024 Aug 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459267/

46 Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, *et al.* Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy*. 2015;47:829–54.

47 Lordick F, Carneiro F, Cascinu S, *et al.* Gastric cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆. *Annals of*. Published Online First: 2022.

48 Survival for stomach cancer. https://www.cancerresearchuk.org/about-cancer/stomach-cancer/survival (accessed 27 March 2025)

49 Rutter MD, Beintaris I, Valori R, *et al.* World Endoscopy Organization Consensus Statements on Post-Colonoscopy and Post-Imaging Colorectal Cancer. *Gastroenterology*. 2018;155:909–25.e3.

50 Chadwick G, Groene O, Riley S, *et al.* Gastric Cancers Missed During Endoscopy in England. *Clin Gastroenterol Hepatol*. 2015;13:1264–70.e1.

51 Chadwick G, Groene O, Hoare J, *et al.* A population-based, retrospective, cohort study of esophageal cancer missed at endoscopy. *Endoscopy*. 2014;46:553–60.

52 Januszewicz W, Witczak K, Wieszczy P, *et al.* Prevalence and risk factors of upper gastrointestinal cancers missed during endoscopy: a nationwide registry-based study. *Endoscopy*. 2022;54:653–60.

53 Park WG, Shaheen NJ, Cohen J, *et al.* Quality indicators for EGD. *Gastrointest Endosc*. 2015;81:17–30.

54 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;48:843–64.

55 Chiu PWY, Uedo N, Singh R, *et al.* An Asian consensus on standards of diagnostic upper endoscopy for neoplasia. *Gut*. 2019;68:186–97.

56 JAG. https://www.thejag.org.uk/ (accessed 17 October 2024)

57 How does certification work? https://jets.thejag.org.uk/eportfolio/how-does-certification-work/ (accessed 17 October 2024)

58 Our history. https://www.thejag.org.uk/our-history (accessed 17 October 2024)

59 https://www.thejag.org.uk/Downloads/JAG/Accreditation (accessed 17 October 2024)

60 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;52:1048–65.

61 Zhao Z, Yin Z, Wang S, *et al.* Meta-analysis: The diagnostic efficacy of chromoendoscopy for early gastric cancer and premalignant gastric lesions. *J Gastroenterol Hepatol*. 2016;31:1539–45.

62 Le H, Wang L, Zhang L, *et al.* Magnifying endoscopy in detecting early gastric cancer: A network meta-analysis of prospective studies. *Medicine* . 2021;100:e23934.

63 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;11:1562–70.e1–2.

64 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.e1.

65 Hajelssedig OE, Zorron Cheng Tao Pu L, 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;36:2659–71.

66 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;13:480–7.e2.

67 Park JM, Huo SM, Lee HH, *et al.* Longer observation time increases proportion of neoplasms detected by esophagogastroduodenoscopy. *Gastroenterology*. 2017;153:460–9.e1.

68 Kawamura T, Wada H, Sakiyama N, *et al.* Examination time as a quality indicator of screening upper gastrointestinal endoscopy for asymptomatic examinees. *Dig Endosc*. 2017;29:569–75.

69 Yoshimizu S, Hirasawa T, Horiuchi Y, *et al.* Differences in upper gastrointestinal neoplasm detection rates based on inspection time and esophagogastroduodenoscopy training. *Endosc Int Open*. 2018;6:E1190–7.

70 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;76:531–8.

71 Januszewicz W, Wieszczy P, Bialek A, *et al.* The endoscopists' biopsy rate as a quality indicator for outpatient gastroscopy: a multicenter cohort study with validation. *Gastrointest Endosc*. 2019;89:1141–9.

72 Zhou J, Li Z, Ji R, *et al.* Influence of sedation on the detection rate of early cancer and precancerous lesions during diagnostic upper gastrointestinal endoscopies: A multicenter retrospective study. *Am J Gastroenterol*. 2021;116:1230–7.

73 Parasa S, Desai M, Vittal A, *et al.* Estimating neoplasia detection rate (NDR) in patients with Barrett's oesophagus based on index endoscopy: a systematic review and meta-analysis. *Gut*. 2019;68:2122–8.

74 Ooi J, Wilson P, Walker G, *et al.* Dedicated Barrett's surveillance sessions managed by trained endoscopists improve dysplasia detection rate. *Endoscopy*. 2017;49:524–8.

75 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;162:1123–35.

76 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;61:2674–84.

77 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.e7; quiz e14–5.

78 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;68:1545–75.

79 Anderson R, Burr NE, Valori R. Causes of post-colonoscopy colorectal cancers based on World Endoscopy Organization system of analysis. *Gastroenterology*. 2020;158:1287–99.e2.

80 JAG. https://www.thejag.org.uk/CMS/UploadedDocuments/Scheme/Scheme5/Guidance/191107%20-%20guidance%20-%20JAG%20quality%20and%20safety%201.0%20final (accessed 17 October 2024)

81 PCCRC Audit. healthdatainsight.org.uk. 2020.

https://healthdatainsight.org.uk/project/pccrc-audit/ (accessed 29 September 2024)

82 PEUGIC Root Cause Analysis. healthdatainsight.org.uk. 2022. https://healthdatainsight.org.uk/project/peugic-root-cause-analysis/ (accessed 17 October 2024)

83 Srinivasa A, Fiadeiro R, Rahman T, *et al.* O53 The causes of post endoscopy upper gastrointestinal cancer: pilot results from the national root cause analysis project. *Oral Presentations*. BMJ Publishing Group Ltd and British Society of Gastroenterology 2024:A32.2–A33.

84 JAG. https://www.thejag.org.uk/CMS/UploadedDocuments/Scheme/Scheme5/Guidance/191107 (accessed 17 October 2024)

85 Hashimoto R, Requa J, Dao T, *et al.* Artificial intelligence using convolutional neural networks for real-time detection of early esophageal neoplasia in Barrett's esophagus (with video). *Gastrointest Endosc*. 2020;91:1264–71.e1.

86 de Groof AJ, Struyvenberg MR, van der Putten J, *et al.* Deep-learning system detects neoplasia in patients with Barrett's esophagus with higher accuracy than endoscopists in a multistep training and validation study with benchmarking. *Gastroenterology*. 2020;158:915–29.e4.

87 Ebigo A, Mendel R, Probst A. Real-time use of artificial intelligence in the evaluation of cancer in Barrett's oesophagus. *Gut*. 2020;69:615–6.

88 Fukuda H, Ishihara R, Kato Y, *et al.* Comparison of performances of artificial intelligence versus expert endoscopists for real-time assisted diagnosis of esophageal squamous cell carcinoma (with video). *Gastrointest Endosc*. 2020;92:848–55.

89 Cai S-L, Li B, Tan W-M, *et al.* Using a deep learning system in endoscopy for screening of early esophageal squamous cell carcinoma (with video). *Gastrointest Endosc*. 2019;90:745–53.e2.

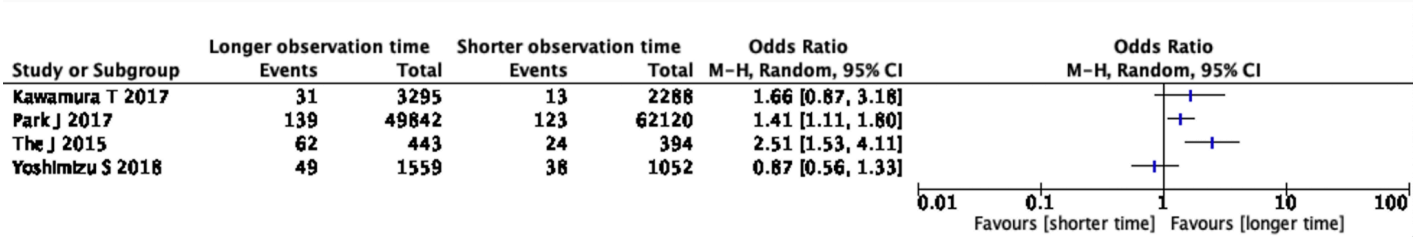
90 Kanesaka T, Lee T-C, Uedo N, *et al.* Computer-aided diagnosis for identifying and delineating early gastric cancers in magnifying narrow-band imaging. *Gastrointest Endosc*. 2018;87:1339–44.

91 Hirasawa T, Aoyama K, Tanimoto T, *et al.* Application of artificial intelligence using a convolutional neural network for detecting gastric cancer in endoscopic images. *Gastric Cancer*. 2018;21:653–60.

92 Luo H, Xu G, Li C, *et al.* Real-time artificial intelligence for detection of upper gastrointestinal cancer by endoscopy: a multicentre, case-control, diagnostic study. *Lancet Oncol*. 2019;20:1645–54.

Supplementary material

Supplementary material for chapter 2



Supplementary Figure 1 Forest plot of studies reporting impact of examination time on upper gastrointestinal cancer detection rate

Supplementary Table 1 PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page #37
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page #37
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pages #39
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page #38
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page #38, Supplementary Tables 3, 4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page #38
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if	Pages #38, 39

		applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pages #39, 40
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pages #39, 40
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page #40
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Pages #40
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Pages #40, 41
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Pages #40, 41
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pages #40, 41
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pages #40, 41

	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Pages #40, 41
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page #42, Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Supplementary Table 5
Study characteristics	17	Cite each included study and present its characteristics.	Page #42, Table 1 and Table 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplementary Tables 6 & 7
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Tables 3 & 4
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Tables 3 & 4
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Tables 3 & 4
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Tables 3 & 4
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA

Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Tables 3 & 4
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pages #67-71
	23b	Discuss any limitations of the evidence included in the review.	Page #71
	23c	Discuss any limitations of the review processes used.	Page #71
	23d	Discuss implications of the results for practice, policy, and future research.	Pages #67-71
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page #38
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page #38
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Title page
Competing interests	26	Declare any competing interests of review authors.	Title page
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Can be provided on request

Supplementary Table 2 List of potential endoscopy quality indicators included in searches.

Endoscopy measures		
Procedure related	Sedation	Throat spray Conscious sedation (Midazolam/Fenta-nyl/Combination) Propofol General anaesthesia
	Antispasmodic agents	Hyoscine Glucagon injection Topical spray of peppermint oil/L-menthol
	Mucosal clearing agents	Simethicone Pronase N-acetylcysteine Water other
	Photo documentation of anatomical landmarks	Number of images
	J-manoeuvre	
	Image enhancing techniques	Virtual chromoendoscopy
		Dye-based chromoendoscopy
	Inspection time	Overall Oesophageal inspection time Gastric inspection time
	Biopsy rate	
	Patient discomfort score	

Endoscopist related	Number of procedures per year	
	Specialty	Gastroenterologist (consultant/trainee) Upper gastrointestinal surgeon (consultant/trainee) Nurse endoscopist Others (e.g. GP, acute medicine consultants)
Endoscopy provider related	Tertiary Vs Secondary care	
	Volume of procedures	

Supplementary Table 3 Search strategy for systematic reviews in Embase

1.	exp endoscopy/
2.	endoscopy.ti,ab.
3.	esophagogastroduodenoscop*.ab,ti.
4.	exp esophagogastroduodenoscopy/
5.	oesophagogastroduodenoscop*.ab,ti.
6.	oesophagogastroduodenoscop*.mp.
7.	exp gastroscopy/
8.	gastroscop*.ti,ab.
9.	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10.	esophagus.ti,ab.
11.	esophageal.ti,ab.
12.	oesophageal.ti,ab.
13.	oesophagus.ti,ab.
14.	exp esophagus/
15.	exp upper gastrointestinal tract/ or exp gastrointestinal tract/
16.	stomach.ti,ab.
17.	gastric.ti,ab.
18.	exp stomach/
19.	duoden*.ab,ti.
20.	upper gastrointestin*.ab,ti.
21.	cancer*.ti,ab.
22.	exp malignant neoplasm/di, ep [Diagnosis, Epidemiology]
23.	carcinom*.ti,ab.
24.	exp carcinoma/
25.	tumour.ti,ab.
26.	exp neoplasm/

27.	neoplasm.ti,ab.
28.	dysplas*.ti,ab.
29.	exp dysplasia/
30.	malignan*.ti,ab.
31.	exp malignant neoplasm/
32.	pre cancer*.ti,ab.
33.	exp precancer/ or exp "precancer and cancer-in-situ"/
34.	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
35.	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
36.	9 and 34 and 35
37.	limit 36 to "reviews (maximizes specificity)"
38.	exp esophagus cancer/
39.	exp stomach cancer/ or exp stomach tumor/ or exp linitis plastica/ or exp stomach carcinogenesis/ or exp stomach carcinoid/ or exp stomach carcinoma/ or exp stomach lymphoma/
40.	exp duodenum cancer/ or exp duodenum tumor/ or exp small intestine cancer/ or exp duodenum carcinoma/
41.	(esophag$ adj3 cancer).ti,ab.
42.	(oesophag$ adj3 cancer).ti,ab.
43.	(oesophag$ adj3 tumour).ti,ab.

44.	(esophag$ adj3 tumour).ti,ab.
45.	(esophag$ adj3 carcinom$).ti,ab.
46.	(oesophag$ adj3 carcinom$).ti,ab.
47.	(esophag$ adj3 malignan$).ti,ab.
48.	(oesophag$ adj3 malignan$).ti,ab.
49.	(esophag$ adj3 neoplas$).ti,ab.
50.	(oesophag$ adj3 neoplas$).ti,ab.
51.	(stomach adj3 cancer).ti,ab.
52.	(gastric adj3 cancer).ti,ab.
53.	(stomach adj3 tumour).ti,ab.
54.	(gastric adj3 tumour).ti,ab.
55.	(stomach adj3 carcinom$).ti,ab.
56.	(gastric adj3 carcinom$).ti,ab.
57.	(stomach adj3 malignan$).ti,ab.
58.	(gastric adj3 malignan$).ti,ab.
59.	(stomach adj3 neoplas$).ti,ab.
60.	(gastric adj3 neoplas$).ti,ab.
61.	(esophag$ adj2 dysplas$).ti,ab.
62.	(oesophag$ adj2 dysplas$).ti,ab.
63.	(stomach adj2 dysplas$).ti,ab.
64.	(gastric adj2 dysplas$).ti,ab.
65.	(duoden$ adj3 neoplas$).ti,ab.
66.	(duoden$ adj3 cancer).ti,ab.
67.	(duoden$ adj3 carcinom$).ti,ab.
68.	(duoden$ adj3 malignan$).ti,ab.
69.	(duoden$ adj3 dysplas$).ti,ab.

70.	38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69
71.	9 and 70
72.	limit 71 to "reviews (maximizes specificity)"
73.	37 or 72

Supplementary Table 4 Search strategy for primary studies in Embase

1.	exp endoscopy/
2.	endoscopy.ti,ab.
3.	esophagogastroduodenoscop$.ti,ab.
4.	oesophagogastroduodenoscop$.ti,ab.
5.	exp esophagogastroduodenoscopy/
6.	exp gastroscopy/
7.	gastroscop$.ti,ab.
8.	1 or 2 or 3 or 4 or 5 or 6 or 7
9.	oesophagus.ti,ab.
10.	oesophageal.ti,ab.
11.	esophagus.ti,ab.
12.	esophageal.ti,ab.
13.	exp esophagus/
14.	exp upper gastrointestinal tract/
15.	exp gastrointestinal tract/
16.	stomach.ti,ab.
17.	gastric.ti,ab.
18.	exp stomach/
19.	duoden$.ti,ab.
20.	upper gastrointestin$.ti,ab.
21.	9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22.	cancer$.ti,ab.
23.	exp malignant neoplasm/di, ep
24.	carcinom$.ti,ab.
25.	exp carcinoma/
26.	tumour$.ti,ab.
27.	exp neoplasm/

28.	neoplasm$.ti,ab.
29.	dysplas$.ti,ab.
30.	exp dysplasia/
31.	malignan$.ti,ab.
32.	pre-cancer$.ti,ab.
33.	precancer$.ti,ab.
34.	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35.	8 and 21 and 34
36.	exp standard/
37.	exp professional standard/
38.	quality.ti,ab.
39.	indicator$.ti,ab.
40.	performance.ti,ab.
41.	standard$.ti,ab.
42.	(detect$ adj3 rate$).ti,ab.
43.	(proportion adj3 detect$).ti,ab.
44.	(increas$ adj3 detect$).ti,ab.
45.	(improv$ adj3 detect$).ti,ab.
46.	36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45
47.	35 and 46
48.	dedicated list.ti,ab.
49.	(number$ adj4 list$).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]
50.	exp training/

51.	(train$ adj2 list$).ti,ab.
52.	photodocumentation.ti,ab.
53.	photo-documentation.ti,ab.
54.	retroflexion.ti,ab.
55.	(photo$ adj2 fund$).ti,ab.
56.	j manoeuvre.ti,ab.
57.	(endoscop$ adj3 diagnos$).ti,ab.
58.	endoscopy/ or exp diagnosis/
59.	(patient$ adj2 comfort$).ti,ab.
60.	(patient adj2 discomfort).ti,ab.
61.	discomfort score.ti,ab.
62.	toleran$.ti,ab.
63.	number of endoscop$.ti,ab.
64.	exp endoscopist/
65.	endoscopist.ti,ab.
66.	per year.ti,ab.
67.	yearly.ti,ab.
68.	annual$.ti,ab.
69.	exp experience/
70.	experience.ti,ab.
71.	(procedur$ adj2 volume).ti,ab.
72.	(endoscop$ adj2 volume).ti,ab.
73.	centre.ti,ab.
74.	(endoscop$ adj2 provider$).ti,ab.
75.	tim$.ti,ab.
76.	duration.ti,ab.
77.	48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76

78.	47 and 77

Supplementary Table 5 List of studies excluded after full text review and reasons of exclusion

Excluded studies	Reasons of exclusion
Dhaliwal L, Codipilly DC, Gandhi P, et al. Neoplasia detection rate in Barrett's esophagus and its impact on missed dysplasia: results from a large population-based database. Clinical Gastroenterology and Hepatology. 2021 May 1;19(5):922-9.	Association with upper gastrointestinal cancer or dysplasia not discussed
Singh S, Manickam P, Amin AV, et al. Incidence of esophageal adenocarcinoma in Barrett's esophagus with low-grade dysplasia: a systematic review and meta-analysis. Gastrointestinal endoscopy. 2014 Jun 1;79(6):897-909.	Endoscopy quality indicators not discussed
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 Mar 1;150(3):599-607.	Endoscopy quality indicators not discussed
Visrodia K, Singh S, Krishnamoorthi R, et al. Systematic review with meta‐analysis: prevalent vs. incident oesophageal adenocarcinoma and high‐grade dysplasia in Barrett's oesophagus. Alimentary pharmacology & therapeutics. 2016 Oct;44(8):775-84.	Endoscopy quality indicators not discussed
Sharma P, Brill J, Canto M, et al. White paper AGA: advanced imaging in Barrett's esophagus. Clinical Gastroenterology and Hepatology. 2015 Dec 1;13(13):2209-18.	Endoscopy quality indicators not discussed
Lv X, Wang C, Xie Y, et al. Diagnostic efficacy of magnifying endoscopy with narrow-band imaging for gastric neoplasms: a meta-analysis. PloS one. 2015 Apr 9;10(4):e0123832.	White paper on advanced imaging in Barrett's oesophagus
Hu YY, Lian QW, Lin ZH, et al. Diagnostic performance of magnifying narrow-band imaging for early gastric cancer: a meta-analysis. World Journal of Gastroenterology: WJG. 2015 Jul 7;21(25):7884.	More recent high quality review included
Zhang Q, Wang F, Chen ZY, et al. Comparison of the diagnostic efficacy of white light endoscopy and magnifying endoscopy with narrow band imaging for early gastric cancer: a meta-analysis. Gastric Cancer. 2016 Apr;19(2):543-52.	More recent high quality review included
TENG L. Diagnostic Value of White Light Endoscopy and Magnifying Endoscopy With Narrow-band Imaging for Distinguishing	More recent high quality review included

Intestinal-type Gastric Adenoma and Early Gastric Cancer. Chinese Journal of Gastroenterology. 2019:389-94.	
Yoshimizu S, Yamamoto Y, Horiuchi Y, et al. Diagnostic performance of routine esophagogastroduodenoscopy using magnifying endoscope with narrow‐band imaging for gastric cancer. Digestive Endoscopy. 2018 Jan;30(1):71-8.	More recent high quality review included
Dobashi A, Goda K, Furuhashi H, et al. Diagnostic efficacy of dual-focus endoscopy with narrow-band imaging using simplified dyad criteria for superficial esophageal squamous cell carcinoma. Journal of Gastroenterology. 2019 Jun;54(6):501-10.	More recent high quality review included
Zheng HW, Xue HG, Yang AH, et al. Comparison between narrowband imaging combined with magnifying endoscopy and gastric biopsy for diagnosis of early gastric cancer. [Chinese]. World Chinese Journal of Digestology. 2015;23(24):3917-22.	More recent high quality review included
Sha J, Wang P, Zhu B, et al. Acetic acid enhanced narrow band imaging for the diagnosis of gastric intestinal metaplasia. PloS one. 2017 Jan 30;12(1):e0170957.	More recent high quality review included
Zhou F, Wu L, Huang M, et al. The accuracy of magnifying narrow band imaging (ME-NBI) in distinguishing between cancerous and noncancerous gastric lesions: A meta-analysis. Medicine. 2018 Mar;97(9).	More recent high quality review included
Desai M, Boregowda U, Srinivasan S, et al. Narrow band imaging for detection of gastric intestinal metaplasia and dysplasia: A systematic review and meta‐analysis. Journal of Gastroenterology and Hepatology. 2021 Aug;36(8):2038-46.	More recent high quality review included
Huang LY, Cui J, Wu CR, et al. Narrow-band imaging in the diagnosis of early esophageal cancer and precancerous lesions. Chinese medical journal. 2009 Apr 5;122(07):776-80.	More recent high quality review included
Yokoyama A, Ohmori T, Makuuchi H, et al. Successful screening for early esophageal cancer in alcoholics using endoscopy and mucosa iodine staining. Cancer. 1995 Sep 15;76(6):928-34.	Very selected population, more recent review included
Lopes AB, Fagundes RB. Esophageal squamous cell carcinoma-precursor lesions and early diagnosis. World journal of gastrointestinal endoscopy. 2012 Jan 1;4(1):9.	Narrative review
Panteris V, Nikolopoulou S, Lountou A, et al. Diagnostic capabilities of high-definition white light endoscopy for the diagnosis of gastric intestinal metaplasia and correlation with histologic and clinical data. European Journal of Gastroenterology & Hepatology. 2014 Jun 1;26(6):594-601.	Association with upper gastrointestinal cancer or dysplasia not discussed

McQuaid KR, Laine L. A systematic review and meta-analysis of randomized, controlled trials of moderate sedation for routine endoscopic procedures. Gastrointestinal endoscopy. 2008 May 1;67(6):910-23.	Association with upper gastrointestinal cancer or dysplasia not discussed
Meining A, Semmler V, Kassem AM, et al. The effect of sedation on the quality of upper gastrointestinal endoscopy: an investigator-blinded, randomized study comparing propofol with midazolam. Endoscopy. 2007 Apr;39(04):345-9.	Association with upper gastrointestinal cancer or dysplasia not discussed
Song KH, Hwang JA, Kim SM, et al. Acetic acid chromoendoscopy for determining the extent of gastric intestinal metaplasia. Gastrointestinal Endoscopy. 2017 Feb 1;85(2):349-56.	Association with upper gastrointestinal cancer or dysplasia not discussed
Emura F, Sharma P, Arantes V, et al. Principles and practice to facilitate complete photodocumentation of the upper gastrointestinal tract: World Endoscopy Organization position statement. Digestive Endoscopy. 2020 Jan;32(2):168-79.	Association with upper gastrointestinal cancer or dysplasia not discussed
Bretthauer M, Aabakken L, Dekker E, et al. Requirements and standards facilitating quality improvement for reporting systems in gastrointestinal endoscopy: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. Endoscopy. 2016 Mar;48(03):291-4.	Association with upper gastrointestinal cancer or dysplasia not discussed
Zhang Q, Chen ZY, Liu T, et al. Training in early gastric cancer diagnosis improves the detection rate of early gastric cancer: an observational study in China. Medicine. 2015 Jan;94(2).	Endoscopy quality indicators not discussed
Chiu PW, Sano Y, Lau J, et al. Standardized training program for diagnosis of early gastrointestinal cancers in Asia. United European Gastroenterology Journal. 2015;3(5):A97.	Endoscopy quality indicators not discussed
Basford PJ, Brown J, Gadeke L, et al. Sa1458 Nicevis-Results of a Randomised Controlled Trial of Simeticone and N-Acetylcysteine As a Pre-Procedure Drink to Improve Mucosal Visibility During Diagnostic Gastroscopy. Gastrointestinal Endoscopy. 2015 May 1;81(5):AB224.	Association with upper gastrointestinal cancer or dysplasia not discussed
Mahawongkajit P, Kanlerd A. A prospective randomized controlled trial comparing simethicone, N-acetylcysteine, sodium bicarbonate and peppermint for visualization in upper gastrointestinal endoscopy. Surgical Endoscopy. 2021 Jan;35(1):303-8.	Association with upper gastrointestinal cancer or dysplasia not discussed
Swager A, Curvers WL, Bergman JJ. Diagnosis by endoscopy and advanced imaging. Best Practice & Research Clinical Gastroenterology. 2015 Feb 1;29(1):97-111.	Narrative review
Lee JWJ, Lim LG, Yeoh KG. Advanced endoscopic imaging in gastric neoplasia and preneoplasia. BMJ Open Gastroenterol 2017; 4: e000105	Narrative review

Mashimo H, Gordon SR, Singh SK. Advanced endoscopic imaging for detecting and guiding therapy of early neoplasias of the esophagus. Ann N Y Acad Sci 2020; 1482: 61–76	Narrative review
Hoffman A, Manner H, Rey JW, et al. A guide to multimodal endoscopy imaging for gastrointestinal malignancy — an early indicator. Nature Reviews Gastroenterology & Hepatology 2017; 14: 421–434	Narrative review
Teh J-L, Shabbir A, Yuen S, et al. Recent advances in diagnostic upper endoscopy. World Journal of Gastroenterology 2020; 26: 433–447	Only one database searched
Januszewicz W, Kaminski MF. Quality indicators in diagnostic upper gastrointestinal endoscopy. Therapeutic Advances in Gastroenterology 2020; 13: 175628482091669	Narrative review
VeitVeitch AM, Uedo N, Yao K, et al. Optimizing early upper gastrointestinal cancer detection at endoscopy. Nat Rev Gastroenterol Hepatol 2015; 12: 660–667	Narrative review
Fernández-Esparrach G, Marín-Gabriel JC, Redondo PD, et al. Quality in diagnostic upper gastrointestinal endoscopy for the detection and surveillance of gastric cancer precursor lesions: Position paper of AEG, SEED and SEAP. Gastroenterología y Hepatología (English Edition) 2021; 44: 448–464	Spanish position statement
Mountford RA, Brown P, Salmon PR, et al. Gastric cancer detection in gastric ulcer disease. Gut 1980; 21: 9–17	Endoscopy quality indicators not discussed
Seli Silenger CP, Cochrane R, Thanaraj S, et al. Gastric ulcers: malignancy yield and risk stratification for follow-up endoscopy. Endosc Int Open 2016; 4: E709–E714	Endoscopy quality indicators not discussed
Lupano F, Sategna-Guidetti C. Endoscopic Follow-up of Patients with Gastric Ulcer. Journal of Clinical Gastroenterology 1986; 8: 430–434	Endoscopy quality indicators not discussed
Hopper AN, Neil Hopper A, Stephens MR, et al. Relative value of repeat gastric ulcer surveillance gastroscopy in diagnosing gastric cancer. Gastric Cancer 2006; 9: 217–222	Endoscopy quality indicators not discussed
Yeh JM, Ho W, Hur C. Cost-effectiveness of endoscopic surveillance of gastric ulcers to improve survival. Gastrointestinal Endoscopy 2010; 72: 33–43	Endoscopy quality indicators not discussed
Koeppe AT, Lubini M, Bonadeo NM, et al. Comfort, safety and quality of upper gastrointestinal endoscopy after 2 hours fasting: a randomized controlled trial. BMC Gastroenterology 2013; 13	Association with upper gastrointestinal cancer or dysplasia not discussed

Silva APD, De Silva AP, Amarasiri L, et al. One-hour fast for water and six-hour fast for solids prior to endoscopy provides good endoscopic vision and results in minimum patient discomfort. Journal of Gastroenterology and Hepatology 2009; 24: 1095–1097	Association with upper gastrointestinal cancer or dysplasia not discussed
Hikichi T, Irisawa A, Sato M, et al. Utility of peppermint oil for endoscopic diagnosis of gastric tumors. Fukushima J Med Sci 2011; 57: 60–65	Very selected population
Hiki N, Kurosaka H, Tatsutomi Y, et al. Peppermint oil reduces gastric spasm during upper endoscopy: a randomized, double-blind, double-dummy controlled trial. Gastrointest Endosc 2003; 57: 475–482	Association with upper gastrointestinal cancer or dysplasia not discussed
Hiki N, Kaminishi M, Yasuda K, et al. Multicenter phase II randomized study evaluating dose-response of antiperistaltic effect of L-menthol sprayed onto the gastric mucosa for upper gastrointestinal endoscopy. Dig Endosc 2012; 24: 79–86	Association with upper gastrointestinal cancer or dysplasia not discussed
Hiki N, Kaminishi M, Yasuda K, et al. Antiperistaltic effect and safety of L-menthol sprayed on the gastric mucosa for upper GI endoscopy: a phase III, multicenter, randomized, double-blind, placebo-controlled study. Gastrointest Endosc 2011; 73: 932–941	Association with upper gastrointestinal cancer or dysplasia not discussed
Vajravelu RK, Kolb JM, Thanawala SU, et al. Sa1197 RATE AND CORRELATES OF PREVALENT, INTERVAL, AND INCIDENT ESOPHAGEAL CANCER (EC) AFTER DIAGNOSIS OF BARRETT'S ESOPHAGUS (BE): A POPULATION-BASED COHORT STUDY. Gastroenterology 2020; 158: S – 308	Endoscopy quality indicators not discussed
Mannath J, Subramanian V, Hawkey C, et al. Narrow band imaging for characterization of high grade dysplasia and specialized intestinal metaplasia in Barrett's esophagus: a meta-analysis. Endoscopy 2010; 42: 351–359	Most recent high quality review included
Song J, Zhang J, Wang J, et al. Meta-analysis of the effects of endoscopy with narrow band imaging in detecting dysplasia in Barrett's esophagus. Diseases of the Esophagus 2015; 28: 560–566	Most recent high quality review included
Sharma P. Magnification chromoendoscopy for the detection of intestinal metaplasia and dysplasia in Barrett's oesophagus. Gut 2003; 52: 24–27	Most recent high quality review included
Beg S, Mensa M, Fullard M, et al. Impact of advanced endoscopic imaging on Barrett's esophagus in daily clinical practice. Gastrointestinal Endoscopy 2018; 87: 1189–1194	Most recent high quality review included

Thota PN, Lee H-J, Goldblum JR, et al. Risk Stratification of Patients With Barrett's Esophagus and Low-grade Dysplasia or Indefinite for Dysplasia. Clinical Gastroenterology and Hepatology 2015; 13: 459–465.e1	Endoscopy quality indicators not discussed
Tholoor S, Bhattacharyya R, Tsagkournis O, et al. Acetic acid chromoendoscopy in Barrett's esophagus surveillance is superior to the standardized random biopsy protocol: results from a large cohort study (with video). Gastrointestinal Endoscopy 2014; 80: 417–424	Most recent high quality review included
Sawas T, Majzoub AM, Haddad J, et al. Magnitude and Time-Trend Analysis of Postendoscopy Esophageal Adenocarcinoma: A Systematic Review and Meta-analysis. Clinical Gastroenterology and Hepatology 2022; 20: e31–e50	Endoscopy quality indicators not discussed
Sikk Sikkema M, de Jonge PJF, Steyerberg EW, et al. Risk of Esophageal Adenocarcinoma and Mortality in Patients With Barrett's Esophagus: A Systematic Review and Meta-analysis. Clinical Gastroenterology and Hepatology 2010; 8: 235–244	Endoscopy quality indicators not discussed
Thomas T, Abrams KR, de Caestecker JS, et al. Meta analysis: cancer risk in Barrett's oesophagus. Alimentary Pharmacology & Therapeutics 2007; 26: 1465–1477	Endoscopy quality indicators not discussed
Bhat S, Coleman HG, Yousef F, et al. Risk of Malignant Progression in Barrett's Esophagus Patients: Results from a Large Population-Based Study. JNCI Journal of the National Cancer Institute 2011; 103: 1049–1057	Endoscopy quality indicators not discussed
Zagari RM, Marasco G, Tassi V, et al. Risk of Squamous Cell Carcinoma and Adenocarcinoma of the Esophagus in Patients With Achalasia: A Long-Term Prospective Cohort Study in Italy. American Journal of Gastroenterology 2021; 116: 289–295	Endoscopy quality indicators not discussed
Ponds FA, Moonen A, Smout AJP, et al. Screening for Dysplasia With Lugol Chromoendoscopy in Longstanding Idiopathic Achalasia. American Journal of Gastroenterology 2018; 113: 855–862	Very selected population
Zheng H-W, Xue H-G, Yang A-H, et al. Comparison between narrow-band imaging combined with magnifying endoscopy and gastric biopsy for diagnosis of early gastric cancer. World Chinese Journal of Digestology 2015; 23: 3917	Most recent high quality review included
Gossner L, Pech O, May A, et al. Comparison of methylene blue-directed biopsies and four-quadrant biopsies in the detection of high-grade intraepithelial neoplasia and early cancer in Barrett's oesophagus. Dig Liver Dis 2006; 38: 724–729	Most recent high quality review included

Diaz LI, Mony S, Klapman J. Narrative review of the role of gastroenterologist in the diagnosis, treatment and palliation in gastric and gastroesophageal cancer. Ann Transl Med 2020; 8: 1106	Narrative review
GorrGorrepati VS, Sharma P. How Should We Report Endoscopic Results in Patient's with Barrett's Esophagus? Digestive Diseases and Sciences 2018; 63: 2115–2121	Narrative review
Curvers WL, van den Broek FJC, Reitsma JB, et al. Systematic review of narrow-band imaging for the detection and differentiation of abnormalities in the esophagus and stomach (with video). Gastrointest Endosc 2009; 69: 307–317	Most recent high quality review included
Kikuste I, Marques-Pereira R, Monteiro-Soares M, et al. Systematic review of the diagnosis of gastric premalignant conditions and neoplasia with high-resolution endoscopic technologies. Scandinavian Journal of Gastroenterology 2013; 48: 1108–1117	Most recent high quality review included
Yu T, Geng J, Song W, et al. Diagnostic Accuracy of Magnifying Endoscopy with Narrow Band Imaging and Its Diagnostic Value for Invasion Depth Staging in Esophageal Squamous Cell Carcinoma: A Systematic Review and Meta-Analysis. BioMed Research International 2018; 2018: 1–11	Association with upper gastrointestinal cancer or dysplasia not discussed
Bretthauer M, Aabakken L, Dekker E, et al. Requirements and standards facilitating quality improvement for reporting systems in gastrointestinal endoscopy: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. Endoscopy 2016; 48: 291–294	Association with upper gastrointestinal cancer or dysplasia not discussed

Supplementary Table 6 Summary of quality assessment of systematic reviews using AMSTAR2

	Zhao Z[14]	Le H[12]	Parasa S[25]	Morita F[28]	Coletta M[23]	Qumseya B[22]	Hajelssedig O[24]	Rodriguez M[13]
Did the research questions and inclusion criteria for the review include the components of PICO?								
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?								
Did the review authors explain their selection of the study designs for inclusion in the review?								
Did the review authors use a comprehensive literature search strategy?								
Did the review authors perform study selection in duplicate?								
Did the review authors perform data extraction in duplicate?								
Did the review authors provide a list of excluded studies and justify the exclusions?								

Did the review authors describe the included studies in adequate detail?								
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?								
Did the review authors report on the sources of funding for the studies included in the review?								
If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?								
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?								
Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?								
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?								

If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?								
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?								

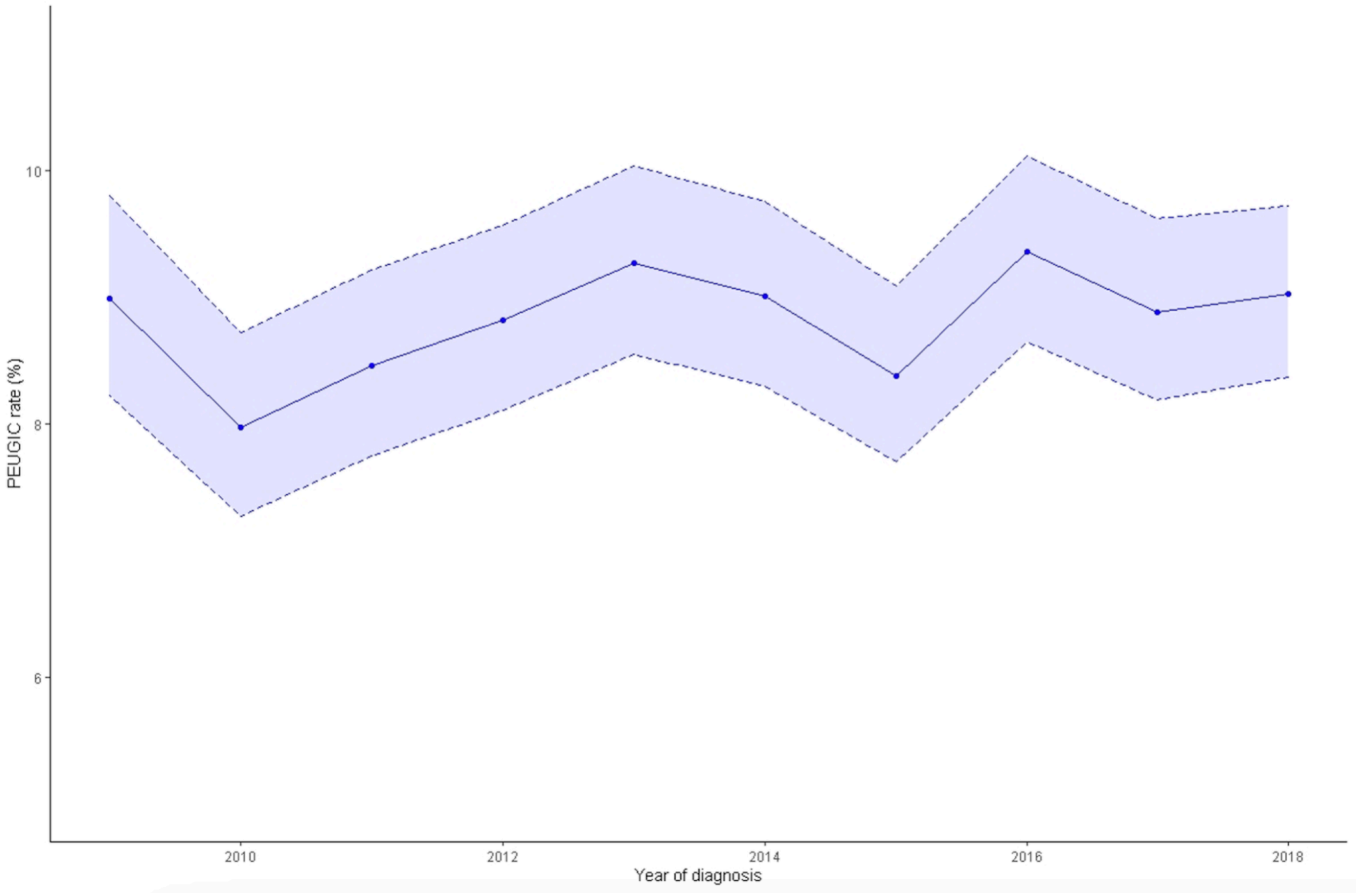
Yes	
No	
Partial yes	

Supplementary Table 7 Summary of quality assessment of primary studies (based on modified JBI checklist).

	Gupta N[26]	Park J[17]	Yoshimizu S[20]	Ooi J[27]	Kawamura T[18]	The J[15]	Zhou J[19]	Januszewicz W[16]
Were the two groups similar and recruited from the same population?								
Were the exposures measured similarly to assign people to both exposed and unexposed groups?								
Was the exposure measured in a valid and reliable way?								
Were the endoscopists similar (training/experience) between groups?								
Were confounding factors identified?								
Were strategies to deal with confounding factors stated?								
Were the outcomes measured in a valid and reliable way?								
Are results generalisable?								

Yes	
No	
Unclear	
Not applicable	

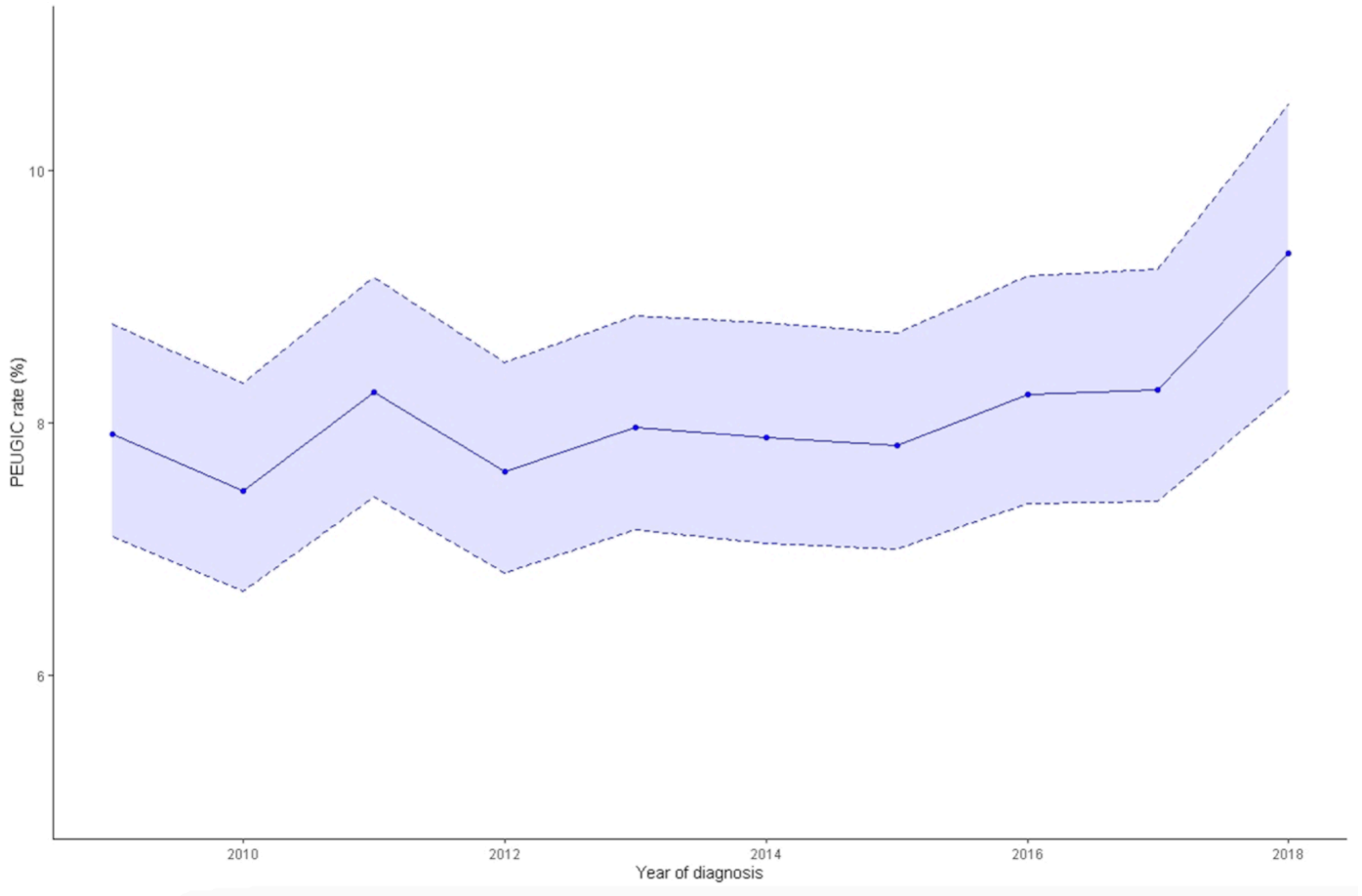
Supplementary material for chapter 3



Supplementary Figure 1 The unadjusted rates of post endoscopy oesophageal cancer over the study period

p value for the difference in rate between 2010 and 2018 = 0.16

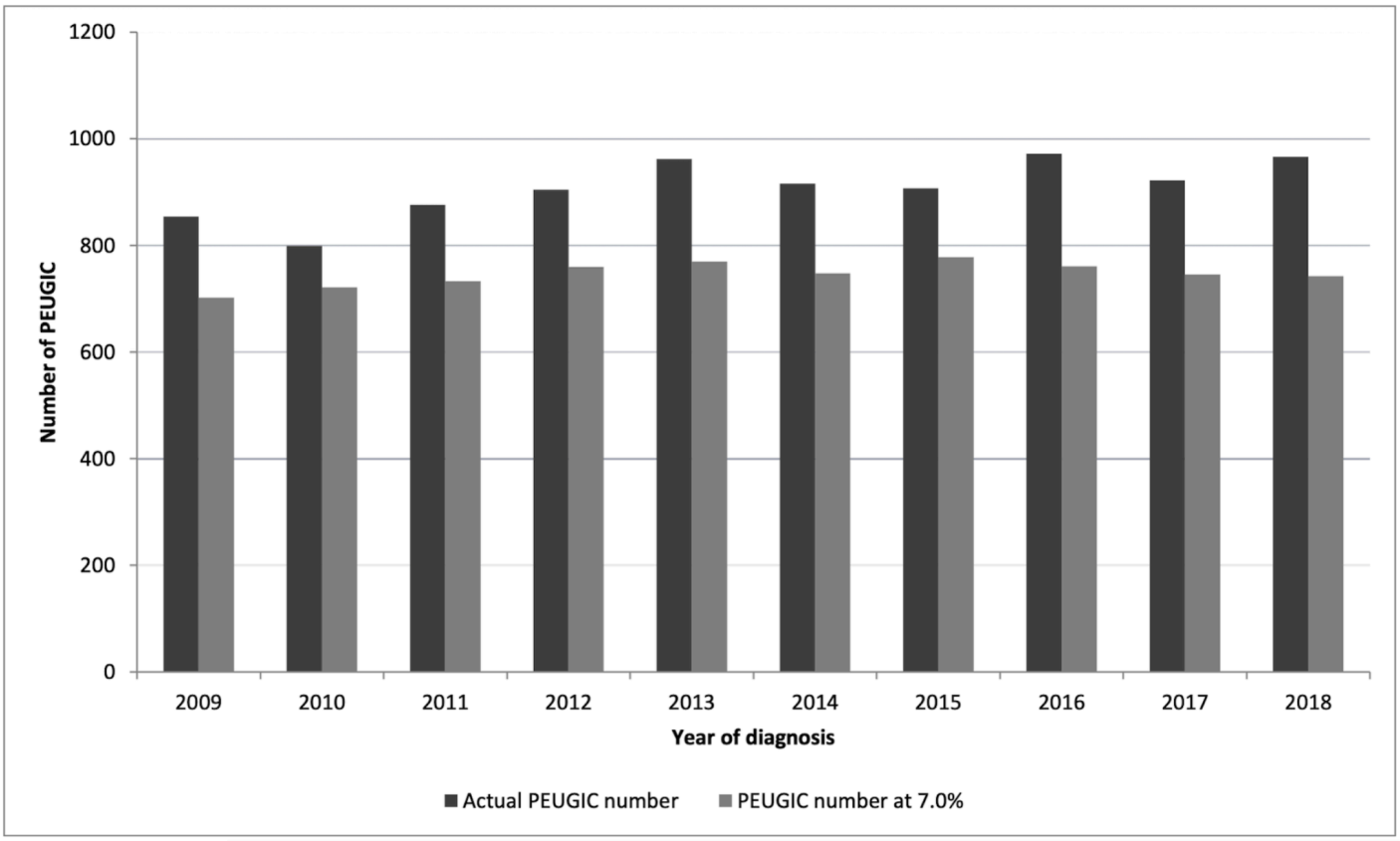
PEUGIC = Post endoscopy upper gastrointestinal cancer



Supplementary Figure 2 The unadjusted rates of post endoscopy gastric cancer over the study period

p value for the difference in rate between 2010 and 2018 = 0.28

PEUGIC = Post endoscopy upper gastrointestinal cancer



Supplementary Figure 3 The number of post endoscopy upper gastrointestinal cancers observed and expected if the rate were reduced to the 25th centile (i.e. 7%) for the whole study period

PEUGIC = Post endoscopy upper gastrointestinal cancer

Supplementary Table 1 Factors associated with post endoscopy upper gastrointestinal cancer on multivariable logistic regression analysis in people with oesophageal cancer

Characteristics	**Odds ratio (95%CI)**	**p-value**
Age group		
60 and under	Reference category	
61-69	0.85 (0.78 to 0.93)	<0.01
70-75	0.79 (0.72 to 0.87)	<0.01
76-80	0.73 (0.66 to 0.81)	<0.01
Over 80	0.56 (0.51 to 0.62)	<0.01
Sex		
Male	Reference category	
Female	1.25 (1.17 to 1.33)	<0.01
Ethnicity		
White	Reference category	
Black	1.25 (0.90 to 1.71)	0.15
South Asian	0.91 (0.70 to 1.19)	0.50
Chinese	0.34 (0.08 to 1.41)	0.14
Mixed	0.94 (0.44 to 2.02)	0.88
Other minority ethnicity	0.87 (0.57 to 1.33)	0.53
Unknown	0.74 (0.58 to 0.93)	0.01
Tumour site		
Upper third of oesophagus	Reference category	
Middle third of oesophagus	0.77 (0.66 to 0.89)	<0.01
Lower third of oesophagus	0.63 (0.55 to 0.73)	<0.01
Unspecified site in oesophagus	0.91 (0.79 to 1.04)	0.17
IMD category		
1 - Least deprived	Reference category	

2	0.92 (0.84 to 1.01)	0.07
3	0.93 (0.85 to 1.02)	0.14
4	0.91 (0.82 to 1.00)	0.04
5 - Most deprived	0.88 (0.80 to 0.97)	0.01
Charlson comorbidity score		
0	Reference category	
1-4	2.70 (2.54 to 2.87)	<0.01
≥ 5	4.41 (3.71 to 5.24)	<0.01
Histology		
Adenocarcinoma	Reference category	
Squamous cell carcinoma	1.61 (1.49 to 1.74)	<0.01
Histology unknown	2.55 (2.29 to 2.85)	<0.01
Oesophageal ulcer		
No	Reference category	
Yes	3.53 (3.30 to 3.77)	<0.01
Oesophageal stricture		
No	Reference category	
Yes	1.24 (1.15 to 1.33)	<0.01
Barrett's oesophagus		
No	Reference category	
Yes	3.46 (3.23 to 3.71)	<0.01
Diagnosis route		
Urgent outpatient	Reference category	
Routine outpatient	3.15 (2.89 to 3.43)	<0.01
Emergency admission	2.60 (2.35 to 2.88)	<0.01
Missing	2.45 (2.19 to 2.74)	<0.01
Previous endoscopy prior to false negative or true positive endoscopy		
No	Reference category	

Yes	0.75 (0.70 to 0.81)	<0.01
Provider type		
Independent	Reference category	
NHS provider	0.90 (0.69 to 1.17)	0.43
Annual endoscopy volume per provider		
<3974	Reference category	
3974-6374	0.94 (0.84 to 1.05)	0.29
>6374	0.99 (0.89 to 1.10)	0.88
Oesophago-gastric cancer resection centre		
No	Reference category	
Yes	1.01 (0.93 to 1.10)	0.74
National accreditation status		
Accredited	Reference category	
Assessed and improvements required	1.18 (1.07 to 1.30)	<0.01
Assessed and accreditation not awarded	1.03 (0.95 to 1.12)	0.46
Not assessed	1.29 (1.05 to 1.58)	0.01
Adjusted PCCRC rate		
<5.55%	Reference category	
5.55%-6.35%	0.99 (0.89 to 1.11)	0.89
6.36%-6.95%	0.99 (0.88 to 1.11)	0.82
6.96%-8.02%	1.05 (0.94 to 1.18)	0.37
>8.02%	1.02 (0.91 to 1.15)	0.74
No data	0.94 (0.69 to 1.29)	0.71

IMD= Index of multiple deprivation; PCCRC=post-colonoscopy colorectal cancer

Supplementary Table 2 Factors associated with post endoscopy upper gastrointestinal cancer on multivariable logistic regression analysis in people with gastric cancer

Characteristics	**Odds ratio (95%CI)**	**p-value**
Age group		
60 and under	Reference category	
61-69	0.88 (0.77 to 1.00)	0.04
70-75	0.77 (0.68 to 0.88)	<0.01
76-80	0.60 (0.53 to 0.68)	<0.01
Over 80	0.47 (0.42 to 0.54)	<0.01
Sex		
Male	Reference category	
Female	1.29 (1.19 to 1.39)	<0.01
Ethnicity		
White	Reference category	
Black	0.95 (0.75 to 1.21)	0.67
South Asian	0.85 (0.66 to 1.10)	0.23
Chinese	0.80 (0.40 to 1.59)	0.52
Mixed	0.61 (0.30 to 1.22)	0.16
Other minority ethnicity	1.00 (0.71 to 1.41)	0.98
Unknown	0.67 (0.49 to 0.91)	0.01
Tumour site		
Proximal stomach	Reference category	
Distal stomach	0.96 (0.86 to 1.08)	0.52
Unspecified site in stomach	1.30 (1.20 to 1.42)	<0.01
IMD category		
1 - Least deprived	Reference category	
2	0.95 (0.84 to 1.08)	0.42

3	0.98 (0.87 to 1.11)	0.77
4	0.91 (0.81 to 1.03)	0.14
5 - Most deprived	0.84 (0.74 to 0.95)	0.01
Charlson comorbidity score		
0	Reference category	
1-4	3.38 (3.12 to 3.66)	<0.01
≥ 5	6.47 (5.35 to 7.84)	<0.01
Histology		
Adenocarcinoma	Reference category	
Squamous cell carcinoma	1.40 (1.03 to 1.90)	0.03
Histology unknown	2.27 (2.02 to 2.55)	<0.01
Gastric ulcer		
No	Reference category	
Yes	1.47 (1.35 to 1.60)	<0.01
Gastric atrophy		
No	Reference category	
Yes	2.54 (2.05 to 3.16)	<0.01
Diagnosis route		
Urgent outpatient	Reference category	
Routine outpatient	2.33 (2.08 to 2.61)	<0.01
Emergency admission	2.01 (1.78 to 2.26)	<0.01
Missing	2.09 (1.77 to 2.46)	<0.01
Previous endoscopy prior to false negative or true positive endoscopy		
No	Reference category	
Yes	0.85 (0.78 to 0.93)	<0.01
Provider type		
Independent	Reference category	
NHS provider	0.95 (0.69 to 1.30)	0.75

Annual endoscopy volume per provider		
<3974	Reference category	
3974-6374	1.05 (0.93 to 1.19)	0.42
>6374	1.05 (0.93 to 1.18)	0.45
Oesophago-gastric cancer resection centre		
No	Reference category	
Yes	1.07 (0.98 to 1.17)	0.13
National accreditation status		
Accredited	Reference category	
Assessed and improvements required	0.97 (0.87 to 1.08)	0.60
Assessed and accreditation not awarded	1.04 (0.95 to 1.14)	0.34
Not assessed	1.10 (0.85 to 1.41)	0.48
Adjusted PCCRC rate		
<5.55%	Reference category	
5.55%-6.35%	0.96 (0.85 to 1.09)	0.53
6.36%-6.95%	1.04 (0.92 to 1.18)	0.55
6.96%-8.02%	1.00 (0.88 to 1.14)	0.95
>8.02%	1.01 (0.88 to 1.15)	0.94
No data	1.79 (1.25 to 2.57)	<0.01

IMD= Index of multiple deprivation; PCCRC=post-colonoscopy colorectal cancer

Supplementary Table 3 Factors associated with post endoscopy upper gastrointestinal cancer on multivariable logistic regression analysis in people with Barrett's oesophagus

Characteristics	**Odds ratio (95%CI)**	**p-value**
Age group		
60 and under	Reference category	
61-69	0.85 (0.73 to 0.98)	0.02
70-75	0.77 (0.67 to 0.90)	<0.01
76-80	0.67 (0.57 to 0.79)	<0.01
Over 80	0.49 (0.42 to 0.58)	<0.01
Sex		
Male	Reference category	
Female	1.20 (1.07 to 1.36)	0.02
Ethnicity		
White	Reference category	
Black	0.79 (0.26 to 2.41)	0.68
South Asian	1.10 (0.59 to 2.08)	0.76
Other minority ethnicity	0.60 (0.23 to 1.58)	0.30
Unknown	0.93 (0.66 to 1.30)	0.67
Tumour site		
Upper third of oesophagus	Reference category	
Middle third of oesophagus	0.71 (0.50 to 1.01)	0.06
Lower third of oesophagus	0.59 (0.42 to 0.83)	<0.01
Unspecified site in oesophagus	0.71 (0.51 to 1.00)	0.05
IMD category		
1 - Least deprived	Reference category	
2	0.98 (0.85 to 1.13)	0.79
3	0.95 (0.82 to 1.10)	0.46

4	0.87 (0.75 to 1.01)	0.07
5 - Most deprived	0.90 (0.77 to 1.05)	0.19
Charlson comorbidity score		
0	Reference category	
1-4	1.95 (1.76 to 2.15)	<0.01
≥ 5	2.38 (1.78 to 3.19)	<0.01
Histology		
Adenocarcinoma	Reference category	
Squamous cell carcinoma	1.61 (1.49 to 1.74)	<0.01
Histology unknown	1.27 (1.03 to 1.55)	0.02
Oesophageal ulcer		
No	Reference category	
Yes	2.73 (2.47 to 3.03)	<0.01
Oesophageal stricture		
No	Reference category	
Yes	1.14 (1.00 to 1.30)	0.05
Diagnosis route		
Urgent outpatient	Reference category	
Routine outpatient	3.83 (3.22 to 4.56)	<0.01
Emergency admission	2.51 (2.01 to 3.12)	<0.01
Missing	3.91 (3.22 to 4.76)	<0.01
Previous endoscopy prior to false negative or true positive endoscopy		
No	Reference category	
Yes	0.49 (0.44 to 0.54)	<0.01
Provider type		
Independent	Reference category	
NHS provider	1.16 (0.76 to 1.77)	0.50
Annual endoscopy volume per		

provider		
<3974	Reference category	
3974-6374	0.85 (0.71 to 1.01)	0.07
>6374	0.98 (0.83 to 1.15)	0.77
Oesophago-gastric cancer resection centre		
No	Reference category	
Yes	0.88 (0.77 to 1.01)	0.06
National accreditation status		
Accredited	Reference category	
Assessed and improvements required	1.06 (0.93 to 1.21)	0.40
Assessed and accreditation not awarded	1.11 (0.95 to 1.29)	0.20
Not assessed	1.28 (0.89 to 1.84)	0.18
Adjusted PCCRC rate		
<5.55%	Reference category	
5.55%-6.35%	0.99 (0.82 to 1.18)	0.89
6.36%-6.95%	0.99 (0.82 to 1.18)	0.90
6.96%-8.02%	1.04 (0.88 to 1.25)	0.63
>8.02%	1.10 (0.92 to 1.33)	0.30
No data	0.82 (0.49 to 1.39)	0.46

IMD= Index of multiple deprivation; PCCRC=post-colonoscopy colorectal cancer

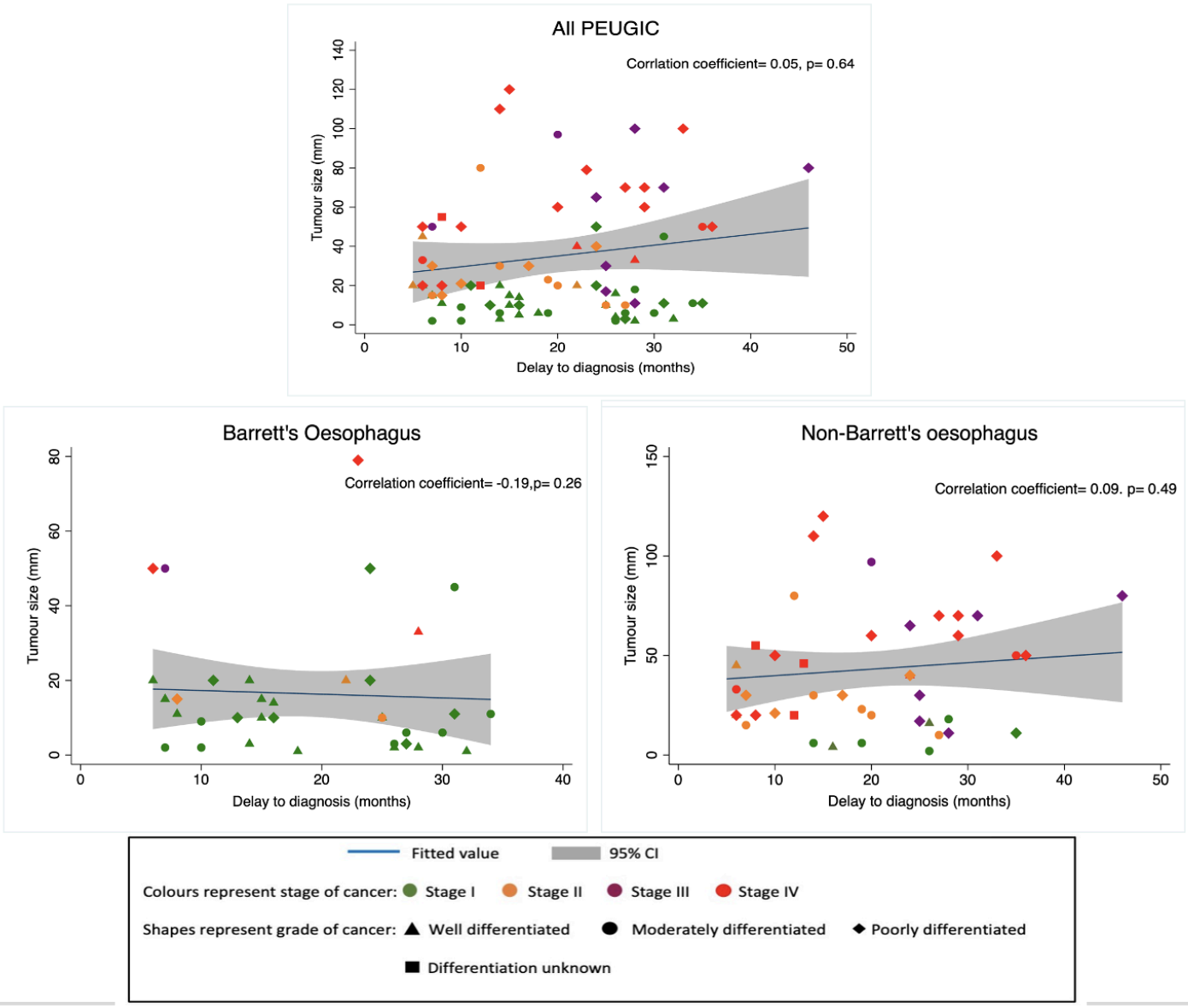
Supplementary Table 4 Change in post endoscopy upper gastrointestinal cancer rate for endoscopy providers between the periods 2009-2013 and 2014-2018

	Adjusted analyses		**Unadjusted Analyses**	
	Number of providers	%	Number of providers	%
No change	32	25.0%	38	29.7%
No change or movement of one quintile (in either direction)	78	60.9%	87	68.0%
1 quintile lower	22	17.2%	24	18.8%
2 quintiles lower	15	11.7%	13	10.2%
3 quintiles lower	7	5.5%	6	4.7%
4 quintiles lower	4	3.1%	2	1.6%
1 quintile higher	24	18.8%	25	19.5%
2 quintiles higher	12	9.4%	14	10.9%
3 quintiles higher	9	7.0%	4	3.1%
4 quintiles higher	3	2.3%	2	1.6%

Supplementary Table 5 Percentiles showing spread of unadjusted post endoscopy upper gastrointestinal cancer rates for each five-year study period

Percentile	2009-2013	2014-2018	Whole cohort
1%	4.1	4.1	5.2
5%	5.3	5.7	6.0
10%	6.1	6.0	6.5
25%	7.0	7.0	7.3
50%	8.1	8.4	8.2
75%	9.4	9.9	9.6
90%	10.9	11.9	10.8
95%	12.0	12.7	11.7
99%	13.9	14.4	15.0

Supplementary material for chapter 5



Supplementary Figure 1 Correlation between delay in diagnosis and tumour size, staging at diagnosis and histological differentiation

PEUGIC: Post endoscopy upper gastrointestinal cancer, CI: Confidence Interval

Supplementary Table 1 Examples of post endoscopy upper gastrointestinal cancer (PEUGIC)

	Interval cancers	**Non interval cancers**		
		Type I	Type II	Type III
	Detected before recommended surveillance interval	Detected at recommended surveillance interval	Detected after recommended surveillance interval	Where no surveillance/ follow up had been recommended
Index OGD findings	Barrett's oesophagus maximum length 2cm, no dysplasia on histology	Barrett's oesophagus maximum length 5cm, no dysplasia on histology	Gastric atrophy and non-visible low grade dysplasia in stomach	Normal OGD
Recommendation	Surveillance in 3 years	Surveillance in 3 years	Surveillance in 1 year	No Surveillance
Outcome	30 months later develops dysphagia; diagnosis oesophageal cancer	Oesophageal cancer found at surveillance OGD	Patient misses appointment, returns 2 years later with gastric cancer	Attends 28 months later with weight loss, repeat OGD reveals gastric cancer

Possible cause	The recommended interval may be too long or missed lesion	The recommended interval may be too long or missed lesion	Patient failed to adhere to recommended interval or missed lesion	Fast growing cancer or missed lesion