Rate of pancreatic cancer following a negative endoscopic ultrasound and associated factors

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Abstract:	Background and Study aims: Data are limited regarding pancreatic cancer diagnosed following a pancreatobiliary endoscopic ultrasound (EUS) that does not diagnose pancreatic cancer. We have studied the frequency and factors associated with post EUS pancreatic cancer (PEPC) and one year mortality. Methods: Between 2010 and 2017, subjects with pancreatic cancer and a preceding pancreatobiliary EUS were identified in a national cohort using Hospital Episode Statistics. Subjects with a pancreatobiliary EUS 6-18 months before a later pancreatic cancer diagnosis were PEPC cases and controls those with pancreatic cancer diagnosed within 6 months of pancreatobiliary EUS. Multivariable logistic regression models examined factors associated with PEPC and a Cox regression model examined factors associated with one year cumulative mortality. Results: 9,363 pancreatic cancer subjects studied; 93.5% identified as controls (median age 68 (IQR 61-75), male 53.2%)); 6.5% PEPC cases (median age 69 (61-77), male 58.2%)). PEPC was associated with older age group (i.e ≥75 years, odds ratio 1.42 (95% CI 1.15-1.76) compared to <65 years), increasing comorbidity (Charlson comorbidity score >5, 1.90 (1.49-2.43)), chronic pancreatitis (3.13 (2.50-3.92)) and diabetes mellitus (1.58 (1.31-1.90)). Metal biliary stents (0.57 (0.38-0.86)) and EUS-FNA (0.49 (0.41-0.58)) were inversely associated with PEPC. PEPC

	was associated with increased cumulative mortality at one year (Hazard ratio 1.12 (95% CI 1.02-1.24)), with only 14(95% CI 12-17)% having a surgical resection, compared with 21(20-22)% of controls Conclusions: PEPC occurred in 6.5% of subjects and was associated with chronic pancreatitis, older age, more comorbidities and diabetes mellitus. PEPC was associated with a worse prognosis and lower surgical resection rates.

Comments for Production Editor

Figure 2

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Background: Data are limited regarding pancreatic cancer diagnosed following a pancreaticobiliary endoscopic ultrasound (EUS) that does not diagnose pancreatic cancer. We have studied the frequency of, and factors associated with, post-EUS pancreatic cancer (PEPC) and 1-year mortality.

Methods: Between 2010 and 2017, patients with pancreatic cancer and a preceding pancreaticobiliary EUS were identified in a national cohort using Hospital Episode Statistics. Patients with a pancreaticobiliary EUS 6–18 months before a later pancreatic cancer diagnosis were the PEPC cases; controls were those with pancreatic cancer diagnosed within 6 months of pancreaticobiliary EUS. Multivariable logistic regression models examined the factors associated with PEPC and a Cox regression model examined factors associated with 1-year cumulative mortality.

Results: 9363 pancreatic cancer patients were studied; 93.5% identified as controls (men 53.2%; median age 68 [interquartile range (IQR) 61–75]); 6.5% as PEPC cases (men 58.2%; median age 69 [IQR 61–77]). PEPC was associated with older age (≥75 years compared with <65 years, odds ratio [OR] 1.42, 95%CI 1.15–1.76), increasing co-morbidity (Charlson co-morbidity score >5, OR 1.90, 95%CI 1.49–2.43), chronic pancreatitis (OR 3.13, 95%CI 2.50–3.92), and diabetes mellitus (OR 1.58, 95%CI 1.31–1.90). Metal biliary stents (OR 0.57, 95%CI 0.38–0.86) and EUS-FNA (OR 0.49, 95%CI 0.41–0.58) were inversely associated with PEPC. PEPC was associated with a higher cumulative mortality at 1 year (hazard ratio 1.12, 95%CI 1.02–1.24), with only 14% of PEPC patients (95%CI 12%–17%) having a surgical resection, compared with 21% (95%CI 20%–22%) of controls

Conclusions: PEPC occurred in 6.5% of patients and was associated with chronic pancreatitis, older age, more co-morbidities, and specifically diabetes mellitus. PEPC was associated with a worse prognosis and lower surgical resection rates.

Introduction

Pancreatic cancer is the seventh leading cause of cancer death worldwide [1]. Prognosis in pancreatic cancer is poor, with an overall 5-year survival rate in England and Wales of only 3.3% [2], and globally of between 2% and 9% [1,3,4]. Surgical resection provides the only curative therapy, but presenting with potentially resectable disease is uncommon (only 15%–20% of pancreatic cancer patients). Survival, even in this potentially curative group, remains disappointing however, with only 10%–27% survival at 5 years in high-volume surgical centers [5].

Pancreaticobiliary endoscopic ultrasound (EUS) has an established role in the investigation, diagnosis, and staging of pancreatic disease [6]. Pancreaticobiliary EUS with fine-needle aspiration (FNA) has both high sensitivity (89%) and high specificity (96%) for pancreatic cancer diagnosis [7]. Fine-needle biopsy (FNB) with second-generation core biopsy needles has recently been shown to have superior diagnostic performance to FNA [8]. EUS is superior to cross-sectional imaging for diagnosing pancreatic cancer, particularly for small tumors [9,10], with the added benefit of offering the ability to sample the tumor.

Despite the accuracy and versatility of pancreaticobiliary EUS in the diagnosis and investigation of pancreatic cancer, there remains a risk of missing significant pathology. Cancer diagnosis following a colonoscopy that did not diagnose colonic cancer is known as post-colonoscopy colorectal cancer (PCCRC) and following an endoscopy that did not diagnose upper gastrointestinal (GI) cancer as post-endoscopy upper GI cancer (PEUGIC) [11–13]. PCCRC and PEUGIC have become established quality standards for colonoscopy and endoscopy [11,12]. Efforts to improve pancreaticobiliary EUS diagnostic accuracy are required, along with the development

of similar quality standards for pancreaticobiliary EUS, given that potential failings in detecting pancreatic cancer have been described [14,15].

The primary aim of this study was to examine the rate of post-EUS pancreatic cancer (PEPC) and the possible associations of patient and procedural characteristics and provider pancreaticobiliary EUS volume with PEPC. We have also examined 1-year cumulative mortality following pancreatic cancer diagnosis in patients with a preceding pancreaticobiliary EUS and the variables associated with 1-year cumulative mortality.

Methods

Data source

Hospital Episode Statistics (HES) is a database that gathers information on all elective and emergency care episodes in National Health Service hospitals in England. Individual patients can be followed through their hospital admissions and outpatient attendances through a unique identifier. Records include data on diagnoses, procedures, demographics, and geographical information. Diagnostic data are coded using the International Classification of Diseases, version 10 (ICD-10). Procedure data are coded using the Office of Population Censuses and Surveys Classification of Interventions and Procedures, 4th revision (OPCS-4). Office of National Statistics (ONS) data are linked to HES and allow the date and cause of death information to be examined [16]. The codes used in this study are listed in **Appendix 1s**, see online-only Supplementary material.

Inclusion criteria

All adult patients over the age of 18 with a diagnosis of pancreatic cancer between 2010 and 2017 who had undergone pancreaticobiliary EUS within the preceding 18 months were examined for the study. Patients diagnosed with pancreatic cancer 6–

18 months following a pancreaticobiliary EUS were included in the PEPC cohort. This chosen timeframe was different from the timeframe suggested for PCCRC (diagnosis within 6–36 months of colonoscopy) as the natural history of pancreatic cancer is not well understood and less is known about the precancerous stage of pancreatic cancer than is known about the adenoma–carcinoma sequence in CRC. Pancreatic cancer is often an aggressive disease and EUS is focused on identifying cancer and not its precancerous conditions. We sought to strike a balance between falsely including new cancers that developed within the timeframe (i.e. having too long a timeframe) and falsely excluding cancers missed at EUS (having too short a timeframe). A control cohort was established consisting of those patients diagnosed with pancreatic cancer within 6 months of a pancreaticobiliary EUS.

Exclusion criteria

Patients were excluded if they were under the age of 18, had a prior diagnosis of pancreatic cancer, were resident outside of England, or had incomplete demographic data. Patients were also excluded if they underwent pancreaticobiliary EUS at a provider undertaking less than one pancreaticobiliary EUS per year to minimize miscoding of EUS data.

Data validation

To assess the validity of pancreaticobiliary EUS coding in HES, the electronic medical records at three hospital sites in England were examined between 2010 and 2016. The number of pancreaticobiliary EUS procedures recorded on endoscopy reporting systems were compared with the number of pancreaticobiliary EUS procedures recorded in HES for each site for the same time period.

Demographic data

Demographic data including age, sex, ethnicity, and deprivation level were extracted from the hospital admission coding. Age was included as a categorical variable and grouped into tertiles (<65, 65–74, and ≥75 years). Ethnicity was classified into White, Asian, Black, mixed ethnicity, and other minority ethnicities. Deprivation level was calculated using an aggregate score for English Lower Layer Super Output Areas (LSOA), based on employment status, income, crime levels, and living environment [17]. Deprivation was categorized into quintiles, with 1 the most deprived and 5 the least deprived. A modified Charlson co-morbidity score was calculated using ICD-10 codes for secondary diagnoses, excluding any form of cancer or diabetes mellitus. The Charlson co-morbidity score has previously been validated in HES [18].

Healthcare providers

Pancreaticobiliary EUS providers were stratified based on their number of procedures over the study period. Centers with an ultralow volume of pancreaticobiliary EUS activity (<8 procedures over the study period) were excluded. 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 centers in each tertile.

Outcome measures

By adapting the World Endoscopy Organization methodology to calculate the unadjusted PCCRC rate, the unadjusted rate of PEPC was calculated by dividing the number of PEPCs by the total of the number of PEPCs and the number of detected pancreatic cancers within 6 months of pancreaticobiliary EUS [19]. The unadjusted PEPC rate has the advantage of being clinically relevant and is unaffected by the prevalence of pancreatic cancer in the population undergoing pancreaticobiliary EUS. Odds ratios (ORs) were calculated for the factors associated with PEPC and hazard

ratios (HRs) for the factors associated with 1-year all-cause mortality from the date of cancer diagnosis. The rates of patients undergoing surgical resection, chemotherapy, and no active pancreatic cancer treatment were reported for the two groups.

Statistical analysis

All statistical analyses were carried out using STATA SE v15 (StataCorp., College Station, Texas, USA). Categorical variables were summarized as number and percentages and the chi-squared test was used for comparison. The unadjusted PEPC rate was calculated by dividing the number of PEPCs by the total of the number of patients in the control group plus the number of PEPCs.

Uni- and multivariable logistic regression models explored the association of variables with the main outcome of a PEPC diagnosis. All exploratory variables were used as categorical variables and included age, sex, deprivation quintile, ethnicity, modified Charlson score, presence of a biliary stent (coded as metal or other [presumed plastic]), chronic pancreatitis, diabetes mellitus, FNA, and total provider volume of pancreaticobiliary EUSs over the study period. Diabetes mellitus was considered an independent variable owing to its known association with pancreatic cancer [20]. Further uni- and multivariable logistic regression analyses were performed for an outcome of PEPC following exclusion of patients with chronic pancreatitis, given its recognized impact on the diagnostic accuracy of pancreaticobiliary EUS [15] and included the same exploratory variables. Missing data were treated as complete case analysis, any observation with a missing value for the variable of interest was excluded and only complete observations were included in the logistic regression analysis. All associations were reported as crude and adjusted ORs.

Funnel plots were produced to examine the variation in PEPC rate. Funnel plots are constructed as scatter plots representing individual providers, with superimposed control limits that represent two and three standard deviations from the mean.

Finally, survival analysis was undertaken using a multivariable Cox regression model and HRs of the factors associated with cumulative mortality at 1 year following pancreatic cancer diagnosis after pancreaticobiliary EUS were examined. The model included the following categorical variables: age, sex, deprivation quintile, ethnicity, modified Charlson score, presence of a biliary stent (coded as metal or other [presumed plastic]), chronic pancreatitis, diabetes mellitus, FNA, PEPC, and total provider volume of pancreaticobiliary EUSs over the study period. Kaplan–Meier survival curves were produced to examine mortality in pancreatic cancer patients with and without PEPC. *P* values of <0.05 were considered statistically significant.

Ethics

Data from HES are available under a data-sharing agreement with NHS Digital for the purposes of service evaluation and their use does not require ethical approval. This study was registered locally at University Hospitals Birmingham NHS Foundation Trust. Numbers of patients less than six are censored from publication to protect patient anonymity.

Results

Validation data

Sandwell and West Birmingham NHS Trust performed 153 pancreaticobiliary EUSs in the validation period and 139 were coded within HES for the same period – an accuracy rate of 90.8%. Newcastle upon Tyne Hospitals NHS Foundation Trust performed 6444 pancreaticobiliary EUSs, with an accuracy rate within HES of 92.9%. Finally,

University Hospitals Birmingham NHS Foundation Trust performed 6672 pancreaticobiliary EUSs, with an accuracy rate within HES of 97.4%.

Patient demographic characteristics

A total of 9519 cases of pancreatic cancer were identified within 18 months of pancreaticobiliary EUS. Of these, 9363 patients were included in the study for analysis (**Fig. 1**). There were 8753 patients (93.5%) who had their pancreatic cancer diagnosed within 6 months of pancreaticobiliary EUS; median age 68 years (interquartile range [IQR] 61–75) and 53% were men. The remaining 610 pancreatic cancer patients (6.5%) were diagnosed within 6–18 months following pancreaticobiliary EUS (PEPC). The median age in this group was 69 years (IQR 61–77) and 58% were men.

Chronic pancreatitis was coded in 122 PEPC cases (20%) compared with 577 of the pancreatic cancer controls (6.6%) diagnosed within 6 months of EUS ($P < 0.001$). A total of 738 pancreaticobiliary EUS procedures were performed on 610 patients in the PEPC group and FNA was performed in 55% of these EUS procedures compared with 76.4% in controls ($P < 0.001$). Diabetes mellitus was coded among 31% of PEPC patients compared with 20% of controls ($P < 0.001$).

In the PEPC group, 28% of pancreatic cancers were coded as being in the head; 13% in the body, tail, or neck; 2% in both the head and body, tail, or neck; while in 57% the location was unspecified. In the control group, 44% of pancreatic cancers were in the head; 23% in the body, tail, or neck; 4% in both the head and body, tail, or neck; and in 29% the location was unspecified.

The baseline demographic characteristics of the two groups are shown in **Table** 1. There was no change in the rate of PEPC over the study period, despite an increase in pancreaticobiliary EUS activity (**Table 1s**).

Logistic regression analysis of factors associated with post-EUS pancreatic cancer

The uni- and multivariable logistic regression analyses examining factors associated with PEPC are shown in **Table 2**. Data on either age, sex, or region of residence were missing for 44 patients (43 controls; 1 PEPC) who were excluded from the regression analyses. The following factors were associated with PEPC: age >74 years (adjusted OR 1.42, 95%CI 1.15–1.76), co-morbidity score >5 (adjusted OR 1.90, 95%CI 1.49–2.43), diabetes mellitus (adjusted OR 1.58, 95%CI 1.31–1.90), and chronic pancreatitis (adjusted OR 3.13, 95%CI 2.50–3.92). The presence of a metal stent compared with no stent (adjusted OR 0.57, 95%CI 0.38–0.86) and performance of FNA (adjusted OR 0.49, 95%CI 0.41–0.58) were associated with reduced odds of PEPC. There was no evidence for an association of PEPC with pancreaticobiliary EUS provider volume for the whole study cohort. **Fig. 1s** shows a funnel plot of the PEPC rate by pancreaticobiliary EUS annual provider volume.

Owing to the very strong association between chronic pancreatitis and PEPC, a further multivariable regression analysis was undertaken, excluding patients with chronic pancreatitis, to examine the influence of other factors. Factors associated with PEPC in those without chronic pancreatitis are shown in **Table 3** and include age >74 years (OR 1.42, 95%CI 1.13–1.79), co-morbidity score >5 (OR 2.15, 95%CI 1.64–2.82), and diabetes mellitus (OR 1.43, 95%CI 1.16–1.78). Performance of an FNA (OR 0.49, 95%CI 0.41–0.60) and the presence of metal stent (OR 0.60, 95%CI 0.38–0.93) were inversely associated with PEPC in this cohort.

Pancreatic cancer therapy

Patients diagnosed with pancreatic cancer following an EUS received no active treatment in 35% of cases. This was significantly more common in the PEPC group (54.9%, 95%CI 50.9%–58.9%) compared with the controls diagnosed within 6 months

of EUS (34.7%, 95%CI 33.7%–35.7%). Surgical resection was performed in 14.4% (95%CI 11.8%–17.4%) of PEPC cases, compared with 20.7% (95%CI 19.9%–21.6%) of controls. Chemotherapy alone was given to 30.7% (95%CI 27.0%–34.5%) of PEPC cases and 44.6% (95%CI 43.6%–45.7%) of controls.

Mortality

There were 59% of patients in the PEPC cohort who had died by 1 year and 56% in the control cohort. A Kaplan–Meier unadjusted survival curve is presented in **Fig. 2**.

A multivariable Cox regression model examining factors associated with cumulative mortality at 1 year after pancreatic cancer diagnosis in the study cohort is shown in **Table 4**. A PEPC diagnosis was associated with a higher cumulative mortality at 1 year (HR 1.12, 95%CI 1.02–1.24). Older age (age ≥75 years compared with <65 years, HR 1.50, 95%CI 1.41–1.59) and increased co-morbidity (Charlson co-morbidity score >5, HR 1.23, 95%CI 1.13–1.33) were associated with higher cumulative mortality as expected, but a pancreaticobiliary EUS volume effect was also identified, with patients who had a pancreaticobiliary EUS in the lowest and middle volume providers having a 35% and 12% increased risk of cumulative mortality, respectively, at 1 year compared with those having pancreaticobiliary EUS in the highest volume centers. The presence of a metal stent (HR 1.25, 95%CI 1.15–1.36) and performance of an FNA (HR 1.13, 95%CI 1.06–1.18) were associated with higher mortality; patients in the least deprived quintile (HR 0.86, 95%CI 0.80–0.93) had lower cumulative mortality at 1 year compared with those in the most deprived quintile.

Discussion

Pancreatic cancer remains one of the malignancies with the worst outcomes due to the majority of patients presenting either at a late stage or with incurable locally advanced

disease. Additionally, there is significant morbidity and only a modest survival benefit associated with surgical resection [21]. EUS has a key role in the assessment and diagnosis of pancreatic cancer and the use of pancreaticobiliary EUS has rapidly expanded over the last 10 years [22]. With the increasing use of this modality, the need to ensure quality is paramount. In the UK, guidance on training in EUS seeks to ensure that, for a relatively new procedure, this is consistent with the established high standards required for other forms of endoscopy. Although, as of yet, there is no EUS certification for independent practice in the UK, as is required for endoscopy and colonoscopy.

In the present study, 21% of the control pancreatic cancer group and 14% of the PEPC group underwent surgical resection for pancreatic cancer. This is higher than reported in England overall for pancreatic cancer and will relate to the fact that, to merit undergoing an invasive diagnostic EUS procedure, the patients studied should have been potentially fit enough for surgical or oncological therapy of their cancer [23]. PEPC patients were also less likely to receive chemotherapy. One-third of patients diagnosed with pancreatic cancer received no active treatment. The nature of the study precludes definite reasons for this to be advanced; however, it likely reflects the nature of the disease, whereby the majority of cancers are not resectable and a significant proportion of patients may deteriorate, such that they are not fit for chemotherapy when they are subsequently seen by an oncologist, or decline therapy. A recent Dutch study also reported infrequent use of chemotherapy in unresectable pancreatic cancer patients [24]. A PEPC diagnosis was associated with a higher 1-year cumulative mortality. Lead time bias will potentially have contributed to this association but differences in surgical resection and chemotherapy rates are also likely to have contributed.

This study has established, for the first time, the key factors associated with PEPC. Chronic pancreatitis is known to reduce the sensitivity of EUS [15], and this was the

factor most strongly associated with PEPC. Significantly, diabetes mellitus was also associated with PEPC, particularly in those without chronic pancreatitis; an important finding, given that diabetes mellitus can be an early consequence of pancreatic cancer but may also be a risk factor for pancreatic cancer [25]. It is noteworthy that mortality was lower among patients undergoing pancreaticobiliary EUS in higher volume providers. Potential causes for this association include better case selection for this invasive procedure in higher volume providers or other factors associated with cancer care in higher volume pancreatic cancer centers. The presence of metal biliary stents was inversely associated with PEPC. The presence of a metal stent may make a small pancreatic cancer more difficult to diagnose; however, the presence of a metal biliary stent and biliary obstruction also implies a higher risk of pancreatic cancer when undertaking EUS, and this may be the explanation for this association.

Improvements in needle technology enabling core biopsies for histological assessment have recently improved diagnostic performance in EUS tissue sampling; however, we believe that such technological advances are unlikely to have a significant impact on the PEPC rate. The inverse association of FNA with PEPC suggests that the issue is less related to tissue sampling and more to finding a lesion to sample at pancreaticobiliary EUS.

This study has used the now well-established methodology for measuring the rates of and predictive factors for not diagnosing GI cancer at diagnostic endoscopy [26]. The minimization of PCCRC and PEUGIC rates is a feasible aim, given the established precancerous phases of many cases of GI cancer [27]. The precancerous phase in pancreatic cancer is however less well understood, and early stage pancreatic cancer diagnoses are rare owing to a lack of symptoms and there being currently no suitable screening modality [28]. Incidentally found pancreatic cancer has been reported to have

a better median survival [29]. This is not however strictly analogous to the present study, given that undertaking an EUS implies a suspicion of pancreaticobiliary disease and the increased use of axial imaging is likely to be responsible for such incidental pancreatic cancer cases [28]. Nevertheless, some data suggest that the progression of pancreatic cancer in its early stages may be slower than previously thought [30], emphasizing the importance of minimizing the rate of PEPC to improve outcomes for pancreatic cancer patients.

Work continues to establish the biological basis and timelines involved in the progression of pancreatic cancer from an intraepithelial precursor to pancreatic cancer [31]. This is important to try and establish screening to aid in the early detection of pancreatic cancer before it becomes inoperable. In the absence of a robust and satisfactory screening test for precancerous changes or early pancreatic cancer, continuing efforts to improve early detection of pancreatic cancer through improved EUS performance has a vital role to play in improving outcomes for pancreatic cancer patients. With EUS having higher spatial resolution than axial imaging, EUS has the potential to enable the preclinical diagnosis of early stage, potentially curable pancreatic cancer, but requires a high degree of suspicion.

Large observational studies are powerful tools to identify risks and associations within populations. There are however a number of limitations to the present study. Data relevant to variables such as body mass index, performance status, staging details, and size of the pancreatic cancer are unavailable in the HES dataset. Unfortunately, the indications for each pancreaticobiliary EUS are also not available in HES and we were unable to differentiate patients undergoing FNA for tissue sampling prior to chemotherapy and patients undergoing potentially more challenging diagnostic pancreaticobiliary EUS.

EUS reports including procedural details were not available in HES so it is not possible to comment on how many of the PEPCs were related to overlooking the tumor or to procedural factors, such as the experience of the endoscopist, or the sampling techniques and their false negative rate. It was also not possible to ascertain the exact location of the cancer in 57% of PEPCs, coded as "unspecified," so the location of the cancer could not be included in the regression analyses. We would suggest that root cause analysis of PEPCs should be performed at provider level to identify the association of such factors with PEPC. Small numbers of patients were excluded from the regression analysis because of missing data, but it is unlikely that these exclusions would have led to the introduction of significant selection bias.

Although validation of the EUS codes has ensured that coding bias is reduced, the link between a pancreatic cancer diagnosis and a pancreaticobiliary EUS in the present study is through coding, rather than directly from cancer registry data. The study did not use case note review and relied on the temporal association of a pancreatic cancer diagnosis and procedural coding. The PEPC definition of 6–18 months following an EUS is different from that used for PCCRC and PEUGIC [12,19]. This was intended to mitigate the risk of exaggerating the number of PEPC diagnoses in those patients where there is a delay in diagnosis of a few weeks or months related to coding, rather than a true failure to diagnose pancreatic cancer. Given that the natural history of pancreatic cancer is not well understood, we chose a shorter timeframe than those for PCCRC and PEUGIC to avoid including, as PEPC, newly developed pancreatic cancers that would not plausibly have been detectable at EUS 3 years before diagnosis. A large-scale prospective multicenter study allowing careful case ascertainment, validation, and EUS report analysis would be required to better determine the most appropriate timeframe for PEPC.

In conclusion, PEPC occurred in 6.5% of patients with pancreatic cancer who underwent pancreaticobiliary EUS, a rate not dissimilar to PCCRC [27]. PEPC patients were less likely to undergo curative surgery or chemotherapy and had a worse prognosis. PCCRC is established as a key performance indicator or quality standard for colonoscopy, with clear definitions and a methodology for investigating the cause through root cause analysis [27]. We found similar associations in PEPC to those identified in PCCRC (i.e. older age group, increasing co-morbidity, and endoscopic performance) [26]. The results of this study indicate the need for the development of a similar methodological framework for defining, investigating, and categorizing PEPC cases, to establish PEPC as a key performance indicator or quality standard for EUS.

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Fig. 1 Study flow chart.

EUS, endoscopic ultrasound; PEPC, post-EUS pancreatic cancer.

Fig. 2 Kaplan–Meier survival curve of post-endoscopic ultrasound pancreatic cancer (PEPC) patient survival compared with controls.

Numbers <6 were censored from publication to protect patient confidentiality.

Table 1 Baseline demographic characteristics of the 9363 patients included in the study.

Demographics	Post-EUS pancreatic cancer patients	Control patients (pancreatic cancer diagnosed within 6 months of EUS)
Total number of patients, n (%)	610 (6.5)	8753 (93.5)
Age, median (IQR), years	69 (61–77)	68 (61–75)
Sex, male, n (%)	355 (58.2)	4656 (53.2)
Deprivation level, n (%)		
1 (most)	116 (19.0)	1474 (16.8)
2	107 (17.5)	1594 (18.2)
3	120 (19.7)	1882 (21.5)
4	136 (22.3)	1977 (22.6)
5 (least)	131 (21.5)	1822 (20.8)
Unknown	0 (0.0)	4 (0.0)
Ethnicity, n (%)		
White	570 (93.4)	8025 (91.7)
Asian / Asian British	10 (1.6)	208 (2.4)
Black / Black British	8 (1.3)	143 (1.6)
Mixed	1 (0.2)	35 (0.4)

Other minority ethnicities	14 (2.3)	147 (1.7)
Unknown	7 (1.1)	195 (2.2)
Charlson co-morbidity score, n (%)		
<1	438 (71.8)	7103 (81.1)
1–5	74 (12.1)	1007 (11.5)
>5	98 (16.1)	643 (7.3)
Chronic pancreatitis, n (%)	122 (20.0)	577 (6.6)
Diabetes mellitus, n (%)	189 (31.0)	1738 (19.9)
Stent, n (%)		
No stent	490 (80.3)	6831 (78.0)
Plastic	93 (15.2)	1282 (14.6)
Metal	27 (4.4)	640 (7.3)
Provider volume of pancreaticobiliary EUSs, n (%)		
8–172	28 (4.6)	292 (3.3)
173–897	114 (18.7)	1825 (20.8)
>897	468 (76.7)	6636 (75.8)

EUS, endoscopic ultrasound; IQR, interquartile range.

Table 2 Multivariable logistic regression analysis of factors associated with post-endoscopic ultrasound pancreatic cancer.

	Odds ratios		95%CIs	*P* value
	Crude	Adjusted		
Age, years				
<65	Reference			
65–74	0.87	0.87	0.71–1.08	0.21
≥75	1.41	1.42	1.15–1.76	0.001
Sex				
Male	Reference			
Female	0.82	0.87	0.74–1.04	0.12
Deprivation quintile				
1 (most)	Reference			
2	0.85	0.85	0.64–1.12	0.25
3	0.81	0.85	0.65–1.12	0.25
4	0.87	0.95	0.73–1.24	0.71
5 (least)	0.91	0.97	0.74–1.28	0.85
Ethnic group				

White	Reference			
Asian	0.68	0.68	0.35–1.30	0.24
Black	0.79	0.72	0.35–1.51	0.39
Mixed	0.40	0.34	0.05–2.57	0.30
Other minority ethnicities	1.34	1.34	0.76–2.37	0.32
Unknown	0.51	0.63	0.29–1.36	0.24
Charlson co-morbidity score				
0	Reference			
1–5	1.19	1.10	0.84–1.42	0.49
>5	2.47	1.90	1.49–2.43	<0.001
Stent				
None	Reference			
Metal	0.59	0.57	0.38–0.86	0.007
Plastic	1.01	0.95	0.75–1.20	0.68
Diabetes mellitus				
No	Reference			
Yes	1.81	1.58	1.31–1.90	<0.001
Fine-needle aspiration/biopsy				

No	Reference			
Yes	0.46	0.49	0.41–0.58	<0.001
Chronic pancreatitis				
No	Reference			
Yes	3.54	3.13	2.50–3.92	<0.001
Provider volume of pancreaticobiliary EUSs				
8–172	1.36	1.33	0.89–2.01	0.17
173–897	0.89	0.88	0.71–1.10	0.26
>897	Reference			

EUS, endoscopic ultrasound.

Table 3 Multivariable logistic regression analysis of factors associated with post-endoscopic ultrasound pancreatic cancer in patients without chronic pancreatitis.

	Odds ratios		95%CIs	*P* value
	Crude	Adjusted		
Age, years				
<65	Reference			
65–74	0.93	0.89	0.70–1.12	0.31
≥75	1.57	1.42	1.13–1.79	0.003
Sex				
Male	Reference			
Female	0.86	0.90	0.74–1.08	0.26
Deprivation quintile				
1 (most)	Reference			
2	0.87	0.86	0.63–1.18	0.35
3	0.87	0.88	0.64–1.19	0.40
4	1.03	1.04	0.78–1.40	0.78
5 (least)	0.99	0.99	0.73–1.34	0.95

Ethnicity				
White	Reference			
Asian	0.67	0.70	0.34–1.43	0.32
Black	1.00	0.98	0.47–2.05	0.96
Mixed	0.52	0.47	0.06–3.51	0.46
Other minority ethnicities	1.35	1.43	0.76–2.67	0.27
Unknown	0.60	0.68	0.32–1.47	0.33
Charlson co-morbidity score				
0	Reference			
1 to 5	1.09	1.05	0.78–1.41	0.77
>5	2.60	2.15	1.64–2.82	<0.001
Stent				
None	Reference			
Metal	0.61	0.60	0.38–0.93	0.02
Plastic	1.08	1.02	0.79–1.31	0.90
Diabetes mellitus				
No	Reference			
Yes	1.54	1.43	1.16–1.78	0.001

Fine-needle aspiration/biopsy				
No	Reference			
Yes	0.49	0.49	0.41–0.60	<0.001
Provider volume of pancreaticobiliary EUSs				
8–172	1.27	1.16	0.74–1.83	0.52
173–897	0.84	0.81	0.63–1.03	0.08
>897	Reference			

EUS, endoscopic ultrasound.

Table 4 Multivariable Cox regression of factors associated with all-cause mortality at 1 year following a diagnosis of pancreatic cancer after pancreaticobiliary endoscopic ultrasound.

	Hazard ratio	95%CIs	P value
Age, years			
<65	Reference		
65–74	1.28	1.21–1.35	<0.001
≥75	1.50	1.41–1.59	<0.001
Sex			
Male	Reference		
Female	0.95	0.91–0.99	0.02
Deprivation quintile			
1 (most)	Reference		
2	0.93	0.87–1.01	0.05
3	0.95	0.88–1.02	0.06
4	0.88	0.82–0.95	0.001
5 (least)	0.86	0.80–0.93	<0.001
Ethnic group			

White	Reference		
Asian	0.74	0.63–1.03	0.12
Black	0.69	0.57–0.84	<0.001
Mixed	0.70	0.48–1.03	0.07
Other	0.68	0.56–0.82	<0.001
Unknown	0.86	0.73–1.01	0.07
Modified Charlson co-morbidity score			
0	Reference		
1 to 5	1.09	0.97–1.12	0.26
>5	1.23	1.13–1.33	<0.001
Stent			
None	Reference		
Metal	1.25	1.15–1.36	<0.001
Plastic	1.09	1.03–1.17	0.004
Diabetes mellitus			
No	Reference		
Yes	1.05	1.00–1.11	0.07
Chronic pancreatitis			

No	Reference		
Yes	0.98	0.90–1.07	0.63
Provider volume tertile			
8–172	1.35	1.19–1.52	<0.001
173–897	1.12	1.06–1.18	<0.001
>897	Reference		
Post-EUS pancreatic cancer			
No	Reference		
Yes	1.12	1.02–1.24	0.02
Fine-needle aspiration/biopsy			
No	Reference		
Yes	1.13	1.06–1.18	<0.001

EUS, endoscopic ultrasound.

In brief

In a nationwide cohort of 9363 patients with pancreatic cancer and a preceding pancreaticobiliary EUS, 6.5% had cancer diagnosed within 6–18 months of EUS, thereby meeting the definition of post-EUS pancreatic cancer (PEPC). Compared with

patients with cancer diagnosed within 6 months of EUS, those with PEPC were less likely to undergo curative surgery and had a worse prognosis. PEPC was more frequently associated with chronic pancreatitis, older age, co-morbidities, and specifically diabetes mellitus.

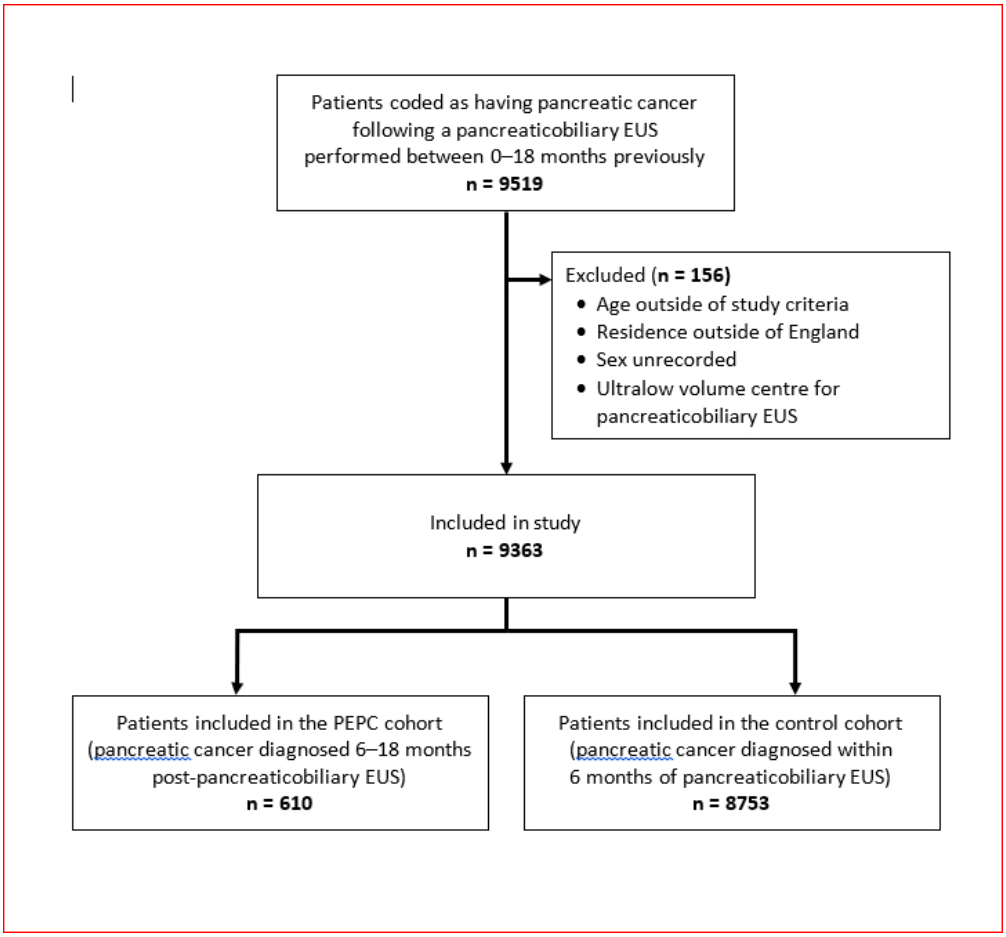

Figure 1. Study flow chart
EUS: Endoscopic ultrasound

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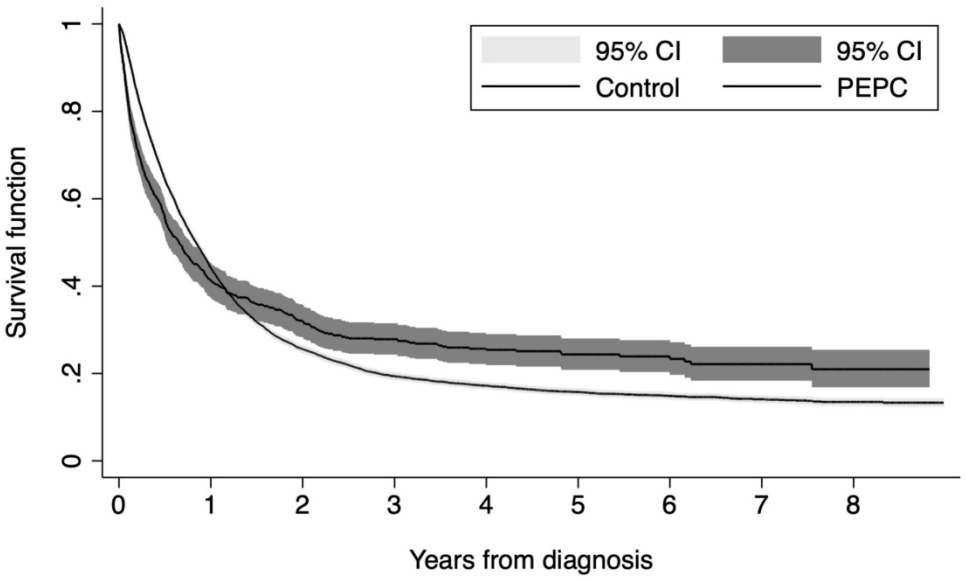


	Numbers at risk								
Category	0 years	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years
Controls	8753	3857	2235	1393	971	667	434	272	120
PEPC	610	250	193	138	91	62	41	27	8

Figure 2. Kaplan-Meier survival curve – Post endoscopic ultrasound pancreatic cancer subject survival compared to controls
Numbers <6 were censored from publication to protect patient confidentiality.
PEPC: Post EUS pancreatic cancer

174x138mm (300 x 300 DPI)

Rate of pancreatic cancer following a negative endoscopic ultrasound and associated factors

Dominic King, Umair Kamran, Amandeep Dosanjh, Ben Coupland, Jemma Mytton, John S. Leeds, Manu Nayar, Prashant Patel, Kofi W. Oppong, Nigel J. Trudgill

Appendix 1s

Pancreatic Cancer

C25 Malignant neoplasm of the pancreas

PB EUS

J74 Endoscopic ultrasound examination of pancreas
J74.1 Endoscopic ultrasound examination of pancreas and biopsy of lesion of pancreas
J74.8 Other specified endoscopic ultrasound examination of pancreas
J74.9 Unspecified endoscopic ultrasound examination of pancreas
J53 Endoscopic ultrasound examination of bile duct
J53.1 Endoscopic ultrasound examination of bile duct and biopsy of lesion of bile duct
J53.8 Other specified endoscopic ultrasound examination of bile duct
J53.9 Unspecified endoscopic ultrasound examination of bile duct
J17 Endoscopic ultrasound examination of liver
J17.1 Endoscopic ultrasound examination of liver and biopsy of lesion of liver
J17.8 Other specified endoscopic ultrasound examination of liver
J17.9 Unspecified endoscopic ultrasound examination of liver

Pancreatic cancer resection

J55 Total excision of pancreas
J55.1 Total pancreatectomy and excision of surrounding tissue
J55.2 Total pancreatectomy NEC
J55.8 Other specified total excision of pancreas
J55.9 Unspecified total excision of pancreas
J56 Excision of head of pancreas
J56.1 Pancreaticoduodenectomy and excision of surrounding tissue
J56.2 Pancreaticoduodenectomy and resection of antrum of stomach
J56.3 Pancreaticoduodenectomy NEC
J56.4 Subtotal excision of head of pancreas with preservation of duodenum and drainage HFQ
J56.8 Other specified excision of head of pancreas
J56.9 Unspecified excision of head of pancreas
J57 Other partial excision of pancreas
J57.1 Subtotal pancreatectomy
J57.2 Left pancreatectomy and drainage of pancreatic duct
J57.3 Left pancreatectomy NEC
J57.4 Excision of tail of pancreas and drainage of pancreatic duct
J57.5 Excision of tail of pancreas NEC

J57.8 Other specified other partial excision of pancreas
J57.9 Unspecified other partial excision of pancreas
J58 Extirpation of lesion of pancreas
J58.2 Excision of lesion of pancreas NEC
J58.8 Other specified extirpation of lesion of pancreas
J58.9 Unspecified extirpation of lesion of pancreas

Chemotherapy codes

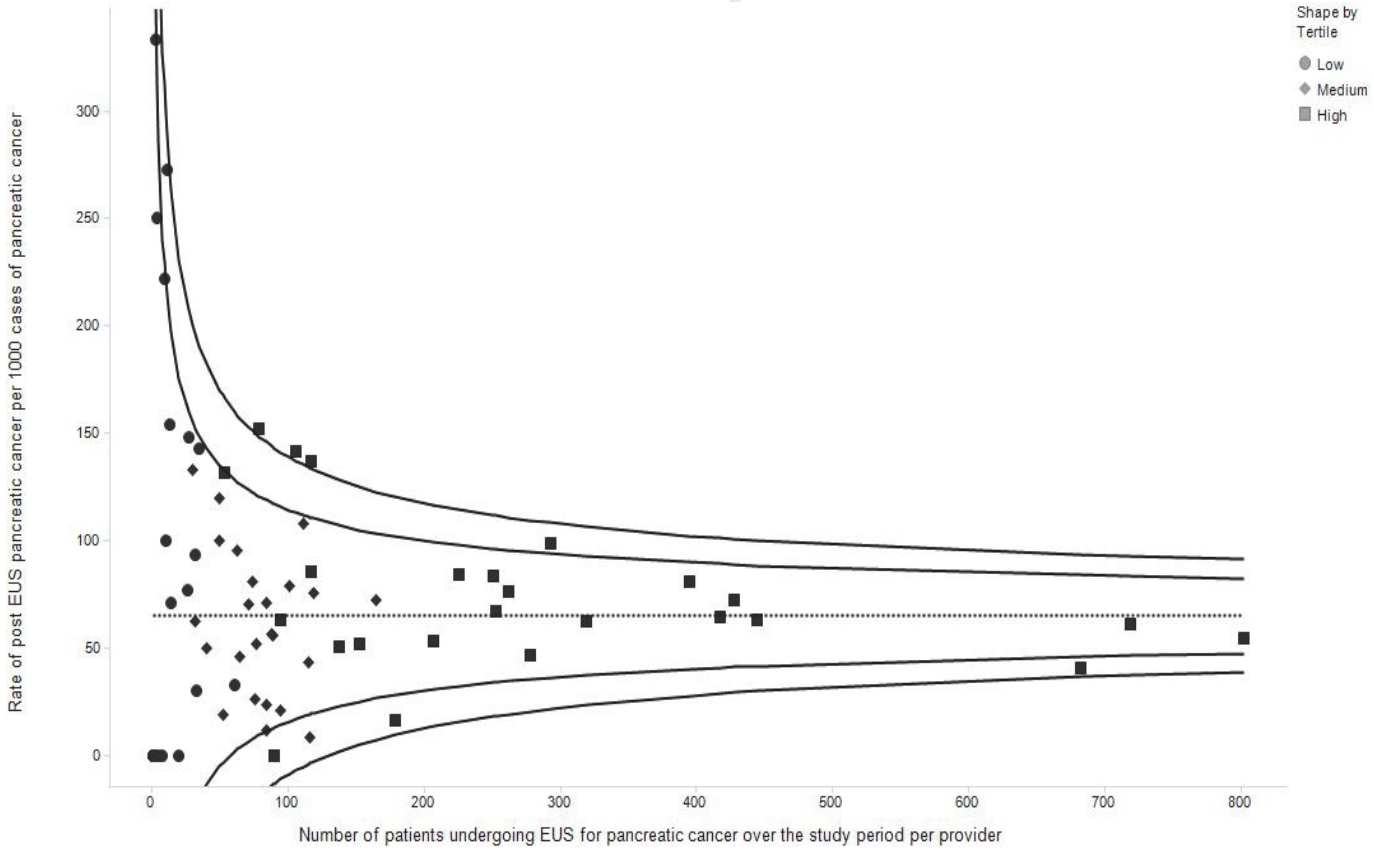
X70.1 Procurement of drugs for chemotherapy for neoplasm for regimens in Band 1
X70.2 Procurement of drugs for chemotherapy for neoplasm for regimens in Band 2
X70.3 Procurement of drugs for chemotherapy for neoplasm for regimens in Band 3
X70.4 Procurement of drugs for chemotherapy for neoplasm for regimens in Band 4
X70.5 Procurement of drugs for chemotherapy for neoplasm for regimens in Band 5
X70.8 Other specified NCCS
X70.9 Unspecified
X71.1 Procurement of drugs for chemotherapy for neoplasm for regimens in Band 6
X71.2 Procurement of drugs for chemotherapy for neoplasm for regimens in Band 7
X71.3 Procurement of drugs for chemotherapy for neoplasm for regimens in Band 8
X71.4 Procurement of drugs for chemotherapy for neoplasm for regimens in Band 9
X71.5 Procurement of drugs for chemotherapy for neoplasm for regimens in Band 10
X71.8 Other specified
X71.9 Unspecified 'X352'
X37.3 Intramuscular chemotherapy
X38.4 Subcutaneous chemotherapy
X72.1 Delivery of complex chemotherapy for neoplasm including prolonged infusion treatment at first attendance
X72.2 Delivery of complex parenteral chemotherapy for neoplasm at first attendance
X72.3 Delivery of simple parenteral chemotherapy for neoplasm at first attendance
X72.4 Delivery of subsequent element of cycle of chemotherapy for neoplasm NCCS
X72.8 Other specified
X72.9 Unspecified NCCS
X73.1 Delivery of exclusively oral chemotherapy for neoplasm NCCS
X73.8 Other specified
X73.9 Unspecified
X74 Other chemotherapy *drugs*
X74.8 Other specified NCCS
X74.9 Unspecified NCCS

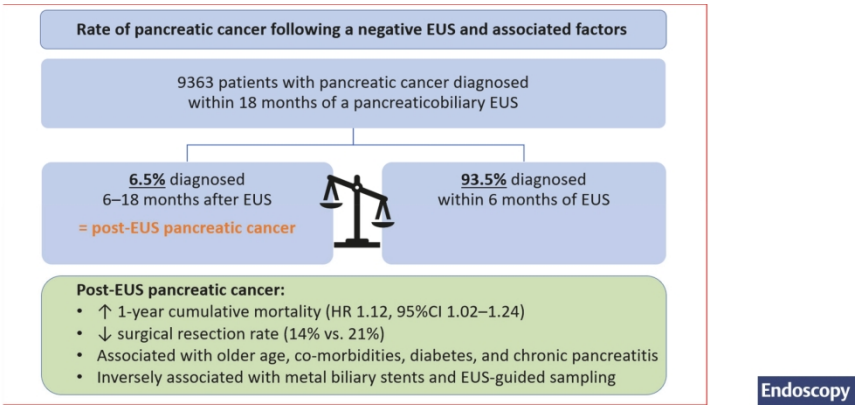
Table 1s, The annual rates of post endoscopic ultrasound pancreatic cancer over the study period

Pancreatic cancer diagnosis year	PEPC cases (%)	Pancreatic cancer controls (%)	Total
2010	43 (4.8)	857 (95.2)	900
2011	72 (6.6)	1015 (93.4)	1087
2012	78 (6.7)	1089 (93.3)	1167
2013	102 (7.7)	1219 (92.3)	1321
2014	104 (6.9)	1409 (93.1)	1513
2015	114 (6.9)	1540 (93.1)	1654
2016	97 (5.6)	1624 (94.4)	1721
Total	610 (6.5)	8753 (93.5)	9363

EUS: endoscopic ultrasound; PEPC: post EUS pancreatic cancer

Figure 1s. Funnel plot of post EUS pancreatic cancer rates by provider volume of patients with pancreatic cancer undergoing endoscopic ultrasound during the study period
EUS: Endoscopic ultrasound





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