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

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Keyword:	05 Endoscopic Ultrasonography, Pancreas < 05 Endoscopic Ultrasonography, Tissue diagnosis < 05 Endoscopic Ultrasonography, Epidemiology < 10 Other focus
Abstract:	<p>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.</p> <p>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.</p> <p>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</p>

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	<p>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.</p>



Comments for Production Editor**Figure 2**

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3 **Background:** Data are limited regarding pancreatic cancer diagnosed following a
4 pancreaticobiliary endoscopic ultrasound (EUS) that does not diagnose pancreatic
5 cancer. We have studied the frequency of, and factors associated with, post-EUS
6 pancreatic cancer (PEPC) and 1-year mortality.
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12 **Methods:** Between 2010 and 2017, patients with pancreatic cancer and a preceding
13 pancreaticobiliary EUS were identified in a national cohort using Hospital Episode
14 Statistics. Patients with a pancreaticobiliary EUS 6–18 months before a later pancreatic
15 cancer diagnosis were the PEPC cases; controls were those with pancreatic cancer
16 diagnosed within 6 months of pancreaticobiliary EUS. Multivariable logistic regression
17 models examined the factors associated with PEPC and a Cox regression model
18 examined factors associated with 1-year cumulative mortality.
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29 **Results:** 9363 pancreatic cancer patients were studied; 93.5% identified as controls
30 (men 53.2%; median age 68 [interquartile range (IQR) 61–75]); 6.5% as PEPC cases
31 (men 58.2%; median age 69 [IQR 61–77]). PEPC was associated with older age
32 (≥ 75 years compared with < 65 years, odds ratio [OR] 1.42, 95%CI 1.15–1.76),
33 increasing co-morbidity (Charlson co-morbidity score > 5 , OR 1.90, 95%CI 1.49–2.43),
34 chronic pancreatitis (OR 3.13, 95%CI 2.50–3.92), and diabetes mellitus (OR 1.58,
35 95%CI 1.31–1.90). Metal biliary stents (OR 0.57, 95%CI 0.38–0.86) and EUS-FNA
36 (OR 0.49, 95%CI 0.41–0.58) were inversely associated with PEPC. PEPC was
37 associated with a higher cumulative mortality at 1 year (hazard ratio 1.12, 95%CI 1.02–
38 1.24), with only 14% of PEPC patients (95%CI 12%–17%) having a surgical resection,
39 compared with 21% (95%CI 20%–22%) of controls
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55 **Conclusions:** PEPC occurred in 6.5% of patients and was associated with chronic
56 pancreatitis, older age, more co-morbidities, and specifically diabetes mellitus. PEPC
57 was associated with a worse prognosis and lower surgical resection rates.
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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

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3 of similar quality standards for pancreaticobiliary EUS, given that potential failings in
4
5 detecting pancreatic cancer have been described [14,15].
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8 The primary aim of this study was to examine the rate of post-EUS pancreatic cancer
9 (PEPC) and the possible associations of patient and procedural characteristics and
10 provider pancreaticobiliary EUS volume with PEPC. We have also examined 1-year
11 cumulative mortality following pancreatic cancer diagnosis in patients with a preceding
12 pancreaticobiliary EUS and the variables associated with 1-year cumulative mortality.
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20 21 **Methods**

22 *Data source*

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

52 All adult patients over the age of 18 with a diagnosis of pancreatic cancer between
53 2010 and 2017 who had undergone pancreaticobiliary EUS within the preceding
54 18 months were examined for the study. Patients diagnosed with pancreatic cancer 6–
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3 18 months following a pancreaticobiliary EUS were included in the PEPC cohort. This
4
5 chosen timeframe was different from the timeframe suggested for PCCRC (diagnosis
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7 within 6–36 months of colonoscopy) as the natural history of pancreatic cancer is not
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9 well understood and less is known about the precancerous stage of pancreatic cancer
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11 than is known about the adenoma–carcinoma sequence in CRC. Pancreatic cancer is
12
13 often an aggressive disease and EUS is focused on identifying cancer and not its
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15 precancerous conditions. We sought to strike a balance between falsely including new
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17 cancers that developed within the timeframe (i.e. having too long a timeframe) and
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19 falsely excluding cancers missed at EUS (having too short a timeframe). A control
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21 cohort was established consisting of those patients diagnosed with pancreatic cancer
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23 within 6 months of a pancreaticobiliary EUS.
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30 *Exclusion criteria*

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

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

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3 ratios (HRs) for the factors associated with 1-year all-cause mortality from the date of
4 cancer diagnosis. The rates of patients undergoing surgical resection, chemotherapy,
5 and no active pancreatic cancer treatment were reported for the two groups.
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10 11 *Statistical analysis*

12 All statistical analyses were carried out using STATA SE v15 (StataCorp., College
13 Station, Texas, USA). Categorical variables were summarized as number and
14 percentages and the chi-squared test was used for comparison. The unadjusted PEPC
15 rate was calculated by dividing the number of PEPCs by the total of the number of
16 patients in the control group plus the number of PEPCs.
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25 Uni- and multivariable logistic regression models explored the association of variables
26 with the main outcome of a PEPC diagnosis. All exploratory variables were used as
27 categorical variables and included age, sex, deprivation quintile, ethnicity, modified
28 Charlson score, presence of a biliary stent (coded as metal or other [presumed plastic]),
29 chronic pancreatitis, diabetes mellitus, FNA, and total provider volume of
30 pancreaticobiliary EUSs over the study period. Diabetes mellitus was considered an
31 independent variable owing to its known association with pancreatic cancer [20].
32 Further uni- and multivariable logistic regression analyses were performed for an
33 outcome of PEPC following exclusion of patients with chronic pancreatitis, given its
34 recognized impact on the diagnostic accuracy of pancreaticobiliary EUS [15] and
35 included the same exploratory variables. Missing data were treated as complete case
36 analysis, any observation with a missing value for the variable of interest was excluded
37 and only complete observations were included in the logistic regression analysis. All
38 associations were reported as crude and adjusted ORs.
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3 Funnel plots were produced to examine the variation in PEPC rate. Funnel plots are
4 constructed as scatter plots representing individual providers, with superimposed
5 control limits that represent two and three standard deviations from the mean.
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10 Finally, survival analysis was undertaken using a multivariable Cox regression model
11 and HRs of the factors associated with cumulative mortality at 1 year following
12 pancreatic cancer diagnosis after pancreaticobiliary EUS were examined. The model
13 included the following categorical variables: age, sex, deprivation quintile, ethnicity,
14 modified Charlson score, presence of a biliary stent (coded as metal or other [presumed
15 plastic]), chronic pancreatitis, diabetes mellitus, FNA, PEPC, and total provider volume
16 of pancreaticobiliary EUSs over the study period. Kaplan–Meier survival curves were
17 produced to examine mortality in pancreatic cancer patients with and without PEPC.
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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,

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3 University Hospitals Birmingham NHS Foundation Trust performed 6672
4 pancreaticobiliary EUSs, with an accuracy rate within HES of 97.4%.
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9 *Patient demographic characteristics*

10 A total of 9519 cases of pancreatic cancer were identified within 18 months of
11 pancreaticobiliary EUS. Of these, 9363 patients were included in the study for analysis
12 (**Fig. 1**). There were 8753 patients (93.5%) who had their pancreatic cancer diagnosed
13 within 6 months of pancreaticobiliary EUS; median age 68 years (interquartile range
14 [IQR] 61–75) and 53% were men. The remaining 610 pancreatic cancer patients (6.5%)
15 were diagnosed within 6–18 months following pancreaticobiliary EUS (PEPC). The
16 median age in this group was 69 years (IQR 61–77) and 58% were men.
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27 Chronic pancreatitis was coded in 122 PEPC cases (20%) compared with 577 of the
28 pancreatic cancer controls (6.6%) diagnosed within 6 months of EUS ($P < 0.001$). A
29 total of 738 pancreaticobiliary EUS procedures were performed on 610 patients in the
30 PEPC group and FNA was performed in 55% of these EUS procedures compared with
31 76.4% in controls ($P < 0.001$). Diabetes mellitus was coded among 31% of PEPC
32 patients compared with 20% of controls ($P < 0.001$).
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42 In the PEPC group, 28% of pancreatic cancers were coded as being in the head; 13% in
43 the body, tail, or neck; 2% in both the head and body, tail, or neck; while in 57% the
44 location was unspecified. In the control group, 44% of pancreatic cancers were in the
45 head; 23% in the body, tail, or neck; 4% in both the head and body, tail, or neck; and in
46 29% the location was unspecified.
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53 The baseline demographic characteristics of the two groups are shown in **Table 1**.
54 There was no change in the rate of PEPC over the study period, despite an increase in
55 pancreaticobiliary EUS activity (**Table 1s**).
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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

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3 of EUS (34.7%, 95%CI 33.7%–35.7%). Surgical resection was performed in 14.4%
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5 (95%CI 11.8%–17.4%) of PEPC cases, compared with 20.7% (95%CI 19.9%–21.6%)
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7 of controls. Chemotherapy alone was given to 30.7% (95%CI 27.0%–34.5%) of PEPC
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9 cases and 44.6% (95%CI 43.6%–45.7%) of controls.

14 *Mortality*

15 There were 59% of patients in the PEPC cohort who had died by 1 year and 56% in the
16
17 control cohort. A Kaplan–Meier unadjusted survival curve is presented in **Fig. 2**.

20 A multivariable Cox regression model examining factors associated with cumulative
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22 mortality at 1 year after pancreatic cancer diagnosis in the study cohort is shown in
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24 **Table 4**. A PEPC diagnosis was associated with a higher cumulative mortality at 1 year
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26 (HR 1.12, 95%CI 1.02–1.24). Older age (age ≥ 75 years compared with < 65 years,
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28 HR 1.50, 95%CI 1.41–1.59) and increased co-morbidity (Charlson co-morbidity score
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30 > 5 , HR 1.23, 95%CI 1.13–1.33) were associated with higher cumulative mortality as
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32 expected, but a pancreaticobiliary EUS volume effect was also identified, with patients
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34 who had a pancreaticobiliary EUS in the lowest and middle volume providers having a
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36 35% and 12% increased risk of cumulative mortality, respectively, at 1 year compared
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38 with those having pancreaticobiliary EUS in the highest volume centers. The presence
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40 of a metal stent (HR 1.25, 95%CI 1.15–1.36) and performance of an FNA (HR 1.13,
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42 95%CI 1.06–1.18) were associated with higher mortality; patients in the least deprived
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44 quintile (HR 0.86, 95%CI 0.80–0.93) had lower cumulative mortality at 1 year
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46 compared with those in the most deprived quintile.
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54 **Discussion**

55 Pancreatic cancer remains one of the malignancies with the worst outcomes due to the
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57 majority of patients presenting either at a late stage or with incurable locally advanced
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3 disease. Additionally, there is significant morbidity and only a modest survival benefit
4 associated with surgical resection [21]. EUS has a key role in the assessment and
5 diagnosis of pancreatic cancer and the use of pancreaticobiliary EUS has rapidly
6 expanded over the last 10 years [22]. With the increasing use of this modality, the need
7 to ensure quality is paramount. In the UK, guidance on training in EUS seeks to ensure
8 that, for a relatively new procedure, this is consistent with the established high standards
9 required for other forms of endoscopy. Although, as of yet, there is no EUS certification
10 for independent practice in the UK, as is required for endoscopy and colonoscopy.
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22 In the present study, 21% of the control pancreatic cancer group and 14% of the PEPC
23 group underwent surgical resection for pancreatic cancer. This is higher than reported
24 in England overall for pancreatic cancer and will relate to the fact that, to merit
25 undergoing an invasive diagnostic EUS procedure, the patients studied should have
26 been potentially fit enough for surgical or oncological therapy of their cancer [23].
27 PEPC patients were also less likely to receive chemotherapy. One-third of patients
28 diagnosed with pancreatic cancer received no active treatment. The nature of the study
29 precludes definite reasons for this to be advanced; however, it likely reflects the nature
30 of the disease, whereby the majority of cancers are not resectable and a significant
31 proportion of patients may deteriorate, such that they are not fit for chemotherapy when
32 they are subsequently seen by an oncologist, or decline therapy. A recent Dutch study
33 also reported infrequent use of chemotherapy in unresectable pancreatic cancer patients
34 [24]. A PEPC diagnosis was associated with a higher 1-year cumulative mortality. Lead
35 time bias will potentially have contributed to this association but differences in surgical
36 resection and chemotherapy rates are also likely to have contributed.
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57 This study has established, for the first time, the key factors associated with PEPC.
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59 Chronic pancreatitis is known to reduce the sensitivity of EUS [15], and this was the
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3 factor most strongly associated with PEPC. Significantly, diabetes mellitus was also
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5 associated with PEPC, particularly in those without chronic pancreatitis; an important
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7 finding, given that diabetes mellitus can be an early consequence of pancreatic cancer
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9 but may also be a risk factor for pancreatic cancer [25]. It is noteworthy that mortality
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11 was lower among patients undergoing pancreaticobiliary EUS in higher volume
12
13 providers. Potential causes for this association include better case selection for this
14
15 invasive procedure in higher volume providers or other factors associated with cancer
16
17 care in higher volume pancreatic cancer centers. The presence of metal biliary stents
18
19 was inversely associated with PEPC. The presence of a metal stent may make a small
20
21 pancreatic cancer more difficult to diagnose; however, the presence of a metal biliary
22
23 stent and biliary obstruction also implies a higher risk of pancreatic cancer when
24
25 undertaking EUS, and this may be the explanation for this association.
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31 Improvements in needle technology enabling core biopsies for histological assessment
32
33 have recently improved diagnostic performance in EUS tissue sampling; however, we
34
35 believe that such technological advances are unlikely to have a significant impact on
36
37 the PEPC rate. The inverse association of FNA with PEPC suggests that the issue is
38
39 less related to tissue sampling and more to finding a lesion to sample at
40
41 pancreaticobiliary EUS.
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46 This study has used the now well-established methodology for measuring the rates of
47
48 and predictive factors for not diagnosing GI cancer at diagnostic endoscopy [26]. The
49
50 minimization of PCCRC and PEUGIC rates is a feasible aim, given the established
51
52 precancerous phases of many cases of GI cancer [27]. The precancerous phase in
53
54 pancreatic cancer is however less well understood, and early stage pancreatic cancer
55
56 diagnoses are rare owing to a lack of symptoms and there being currently no suitable
57
58 screening modality [28]. Incidentally found pancreatic cancer has been reported to have
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3 a better median survival [29]. This is not however strictly analogous to the present
4 study, given that undertaking an EUS implies a suspicion of pancreaticobiliary disease
5 and the increased use of axial imaging is likely to be responsible for such incidental
6 pancreatic cancer cases [28]. Nevertheless, some data suggest that the progression of
7 pancreatic cancer in its early stages may be slower than previously thought [30],
8 emphasizing the importance of minimizing the rate of PEPC to improve outcomes for
9 pancreatic cancer patients.

10
11 Work continues to establish the biological basis and timelines involved in the
12 progression of pancreatic cancer from an intraepithelial precursor to pancreatic cancer
13 [31]. This is important to try and establish screening to aid in the early detection of
14 pancreatic cancer before it becomes inoperable. In the absence of a robust and
15 satisfactory screening test for precancerous changes or early pancreatic cancer,
16 continuing efforts to improve early detection of pancreatic cancer through improved
17 EUS performance has a vital role to play in improving outcomes for pancreatic cancer
18 patients. With EUS having higher spatial resolution than axial imaging, EUS has the
19 potential to enable the preclinical diagnosis of early stage, potentially curable pancreatic
20 cancer, but requires a high degree of suspicion.

21
22 Large observational studies are powerful tools to identify risks and associations within
23 populations. There are however a number of limitations to the present study. Data
24 relevant to variables such as body mass index, performance status, staging details, and
25 size of the pancreatic cancer are unavailable in the HES dataset. Unfortunately, the
26 indications for each pancreaticobiliary EUS are also not available in HES and we were
27 unable to differentiate patients undergoing FNA for tissue sampling prior to
28 chemotherapy and patients undergoing potentially more challenging diagnostic
29 pancreaticobiliary EUS.

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3 EUS reports including procedural details were not available in HES so it is not possible
4
5 to comment on how many of the PEPCs were related to overlooking the tumor or to
6
7 procedural factors, such as the experience of the endoscopist, or the sampling
8
9 techniques and their false negative rate. It was also not possible to ascertain the exact
10
11 location of the cancer in 57% of PEPCs, coded as “unspecified,” so the location of the
12
13 cancer could not be included in the regression analyses. We would suggest that root
14
15 cause analysis of PEPCs should be performed at provider level to identify the
16
17 association of such factors with PEPC. Small numbers of patients were excluded from
18
19 the regression analysis because of missing data, but it is unlikely that these exclusions
20
21 would have led to the introduction of significant selection bias.
22
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27 Although validation of the EUS codes has ensured that coding bias is reduced, the link
28
29 between a pancreatic cancer diagnosis and a pancreaticobiliary EUS in the present study
30
31 is through coding, rather than directly from cancer registry data. The study did not use
32
33 case note review and relied on the temporal association of a pancreatic cancer diagnosis
34
35 and procedural coding. The PEPC definition of 6–18 months following an EUS is
36
37 different from that used for PCCRC and PEUGIC [12,19]. This was intended to mitigate
38
39 the risk of exaggerating the number of PEPC diagnoses in those patients where there is
40
41 a delay in diagnosis of a few weeks or months related to coding, rather than a true failure
42
43 to diagnose pancreatic cancer. Given that the natural history of pancreatic cancer is not
44
45 well understood, we chose a shorter timeframe than those for PCCRC and PEUGIC to
46
47 avoid including, as PEPC, newly developed pancreatic cancers that would not plausibly
48
49 have been detectable at EUS 3 years before diagnosis. A large-scale prospective
50
51 multicenter study allowing careful case ascertainment, validation, and EUS report
52
53 analysis would be required to better determine the most appropriate timeframe for
54
55 PEPC.
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3 In conclusion, PEPC occurred in 6.5% of patients with pancreatic cancer who
4 underwent pancreaticobiliary EUS, a rate not dissimilar to PCCRC [27]. PEPC patients
5 were less likely to undergo curative surgery or chemotherapy and had a worse
6 prognosis. PCCRC is established as a key performance indicator or quality standard for
7 colonoscopy, with clear definitions and a methodology for investigating the cause
8 through root cause analysis [27]. We found similar associations in PEPC to those
9 identified in PCCRC (i.e. older age group, increasing co-morbidity, and endoscopic
10 performance) [26]. The results of this study indicate the need for the development of a
11 similar methodological framework for defining, investigating, and categorizing PEPC
12 cases, to establish PEPC as a key performance indicator or quality standard for EUS.
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4 **Fig. 1** Study flow chart.
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7 EUS, endoscopic ultrasound; PEPC, post-EUS pancreatic cancer.
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11 **Fig. 2** Kaplan–Meier survival curve of post-endoscopic ultrasound pancreatic
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15 cancer (PEPC) patient survival compared with controls.
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18 Numbers <6 were censored from publication to protect patient confidentiality.
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For Peer Review

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				

1					
2					
3					
4	White	Reference			
5					
6	Asian	0.68	0.68	0.35–1.30	0.24
7					
8					
9	Black	0.79	0.72	0.35–1.51	0.39
10					
11					
12	Mixed	0.40	0.34	0.05–2.57	0.30
13					
14					
15	Other minority ethnicities	1.34	1.34	0.76–2.37	0.32
16					
17					
18	Unknown	0.51	0.63	0.29–1.36	0.24
19					
20					
21					
22	Charlson co-morbidity score				
23					
24					
25	0	Reference			
26					
27					
28	1–5	1.19	1.10	0.84–1.42	0.49
29					
30					
31	>5	2.47	1.90	1.49–2.43	<0.001
32					
33					
34	Stent				
35					
36					
37	None	Reference			
38					
39					
40	Metal	0.59	0.57	0.38–0.86	0.007
41					
42					
43	Plastic	1.01	0.95	0.75–1.20	0.68
44					
45					
46					
47	Diabetes mellitus				
48					
49					
50	No	Reference			
51					
52					
53	Yes	1.81	1.58	1.31–1.90	<0.001
54					
55					
56	Fine-needle aspiration/biopsy				
57					
58					
59					
60					

1					
2					
3					
4	No	Reference			
5					
6	Yes	0.46	0.49	0.41–0.58	<0.001
7					
8					
9					
10	Chronic pancreatitis				
11					
12					
13	No	Reference			
14					
15					
16	Yes	3.54	3.13	2.50–3.92	<0.001
17					
18					
19	Provider volume of pancreaticobiliary EUSs				
20					
21					
22	8–172	1.36	1.33	0.89–2.01	0.17
23					
24					
25	173–897	0.89	0.88	0.71–1.10	0.26
26					
27					
28	>897	Reference			
29					
30					

EUS, endoscopic ultrasound.

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

	Odds ratios		95% CIs	<i>P</i> 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.

For Peer Review

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			

1				
2				
3				
4	White	Reference		
5				
6	Asian	0.74	0.63–1.03	0.12
7				
8				
9	Black	0.69	0.57–0.84	<0.001
10				
11				
12	Mixed	0.70	0.48–1.03	0.07
13				
14				
15	Other	0.68	0.56–0.82	<0.001
16				
17				
18	Unknown	0.86	0.73–1.01	0.07
19				
20				
21				
22	Modified Charlson co-morbidity score			
23				
24				
25	0	Reference		
26				
27				
28	1 to 5	1.09	0.97–1.12	0.26
29				
30				
31	>5	1.23	1.13–1.33	<0.001
32				
33				
34	Stent			
35				
36				
37	None	Reference		
38				
39				
40	Metal	1.25	1.15–1.36	<0.001
41				
42				
43	Plastic	1.09	1.03–1.17	0.004
44				
45				
46				
47	Diabetes mellitus			
48				
49				
50	No	Reference		
51				
52				
53	Yes	1.05	1.00–1.11	0.07
54				
55				
56	Chronic pancreatitis			
57				
58				
59				
60				

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

1
2
3 patients with cancer diagnosed within 6 months of EUS, those with PEPC were less
4
5 likely to undergo curative surgery and had a worse prognosis. PEPC was more
6
7 frequently associated with chronic pancreatitis, older age, co-morbidities, and
8
9 specifically diabetes mellitus.
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For Peer Review

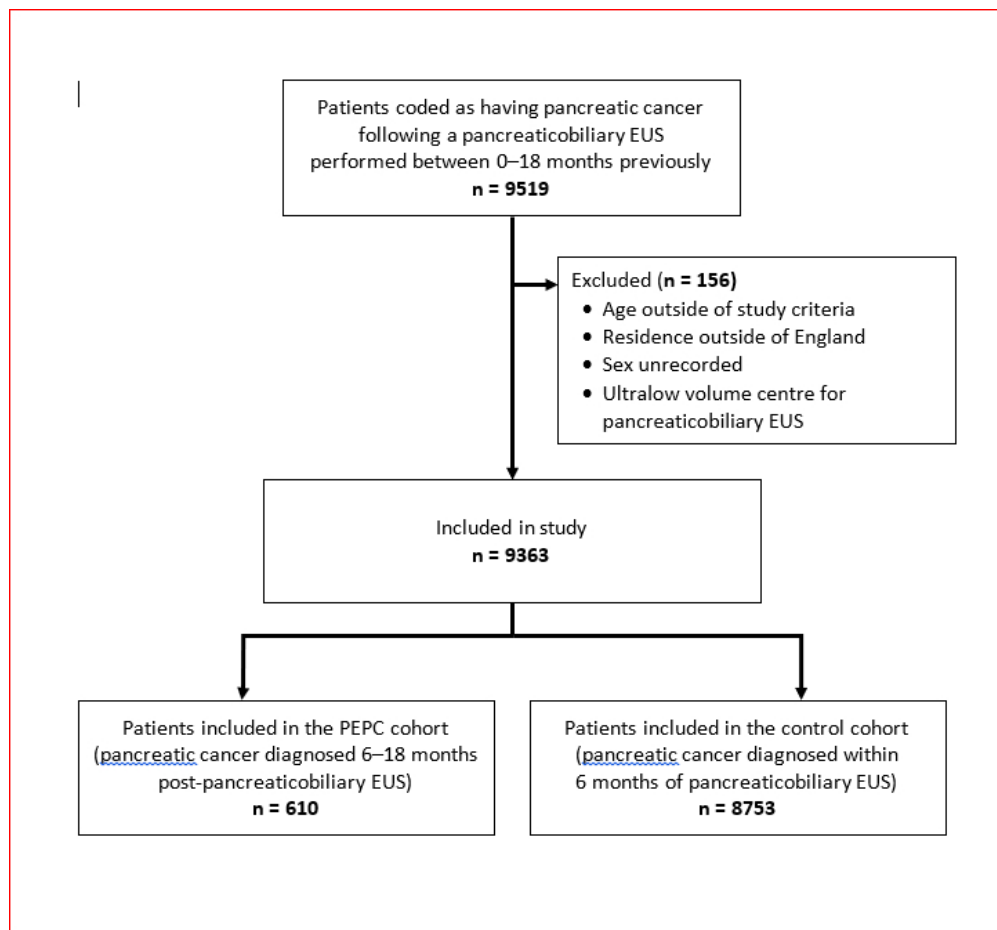
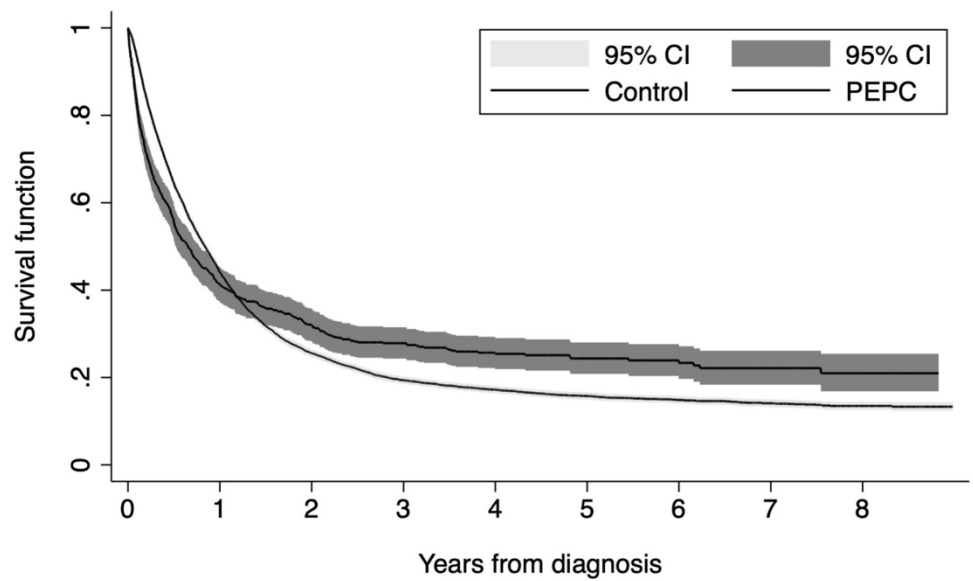


Figure 1. Study flow chart
EUS: Endoscopic ultrasound

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Category	Numbers at risk									
	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)

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3 Rate of pancreatic cancer following a negative endoscopic ultrasound and associated
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5 factors
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9 Dominic King, Umair Kamran, Amandeep Dosanjh, Ben Coupland, Jemma Mytton,
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11 John S. Leeds, Manu Nayar, Prashant Patel, Kofi W. Oppong, Nigel J. Trudgill
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For Peer Review

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

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3 J57.8 Other specified other partial excision of pancreas

4 J57.9 Unspecified other partial excision of pancreas

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6 J58 Extirpation of lesion of pancreas

7 J58.2 Excision of lesion of pancreas NEC

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9 J58.8 Other specified extirpation of lesion of pancreas

10 J58.9 Unspecified extirpation of lesion of pancreas

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14 **Chemotherapy codes**

15 X70.1 Procurement of drugs for chemotherapy for neoplasm for regimens in Band 1

16 X70.2 Procurement of drugs for chemotherapy for neoplasm for regimens in Band 2

17 X70.3 Procurement of drugs for chemotherapy for neoplasm for regimens in Band 3

18 X70.4 Procurement of drugs for chemotherapy for neoplasm for regimens in Band 4

19 X70.5 Procurement of drugs for chemotherapy for neoplasm for regimens in Band 5

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21 X70.8 Other specified NCCS

22 X70.9 Unspecified

23 X71.1 Procurement of drugs for chemotherapy for neoplasm for regimens in Band 6

24 X71.2 Procurement of drugs for chemotherapy for neoplasm for regimens in Band 7

25 X71.3 Procurement of drugs for chemotherapy for neoplasm for regimens in Band 8

26 X71.4 Procurement of drugs for chemotherapy for neoplasm for regimens in Band 9

27 X71.5 Procurement of drugs for chemotherapy for neoplasm for regimens in Band 10

28 X71.8 Other specified

29 X71.9 Unspecified 'X352'

30 X37.3 Intramuscular chemotherapy

31 X38.4 Subcutaneous chemotherapy

32 X72.1 Delivery of complex chemotherapy for neoplasm including prolonged infusion treatment at first attendance

33 X72.2 Delivery of complex parenteral chemotherapy for neoplasm at first attendance

34 X72.3 Delivery of simple parenteral chemotherapy for neoplasm at first attendance

35 X72.4 Delivery of subsequent element of cycle of chemotherapy for neoplasm NCCS

36 X72.8 Other specified

37 X72.9 Unspecified NCCS

38 X73.1 Delivery of exclusively oral chemotherapy for neoplasm NCCS

39 X73.8 Other specified

40 X73.9 Unspecified

41 X74 Other chemotherapy drugs

42 X74.8 Other specified NCCS

43 X74.9 Unspecified NCCS

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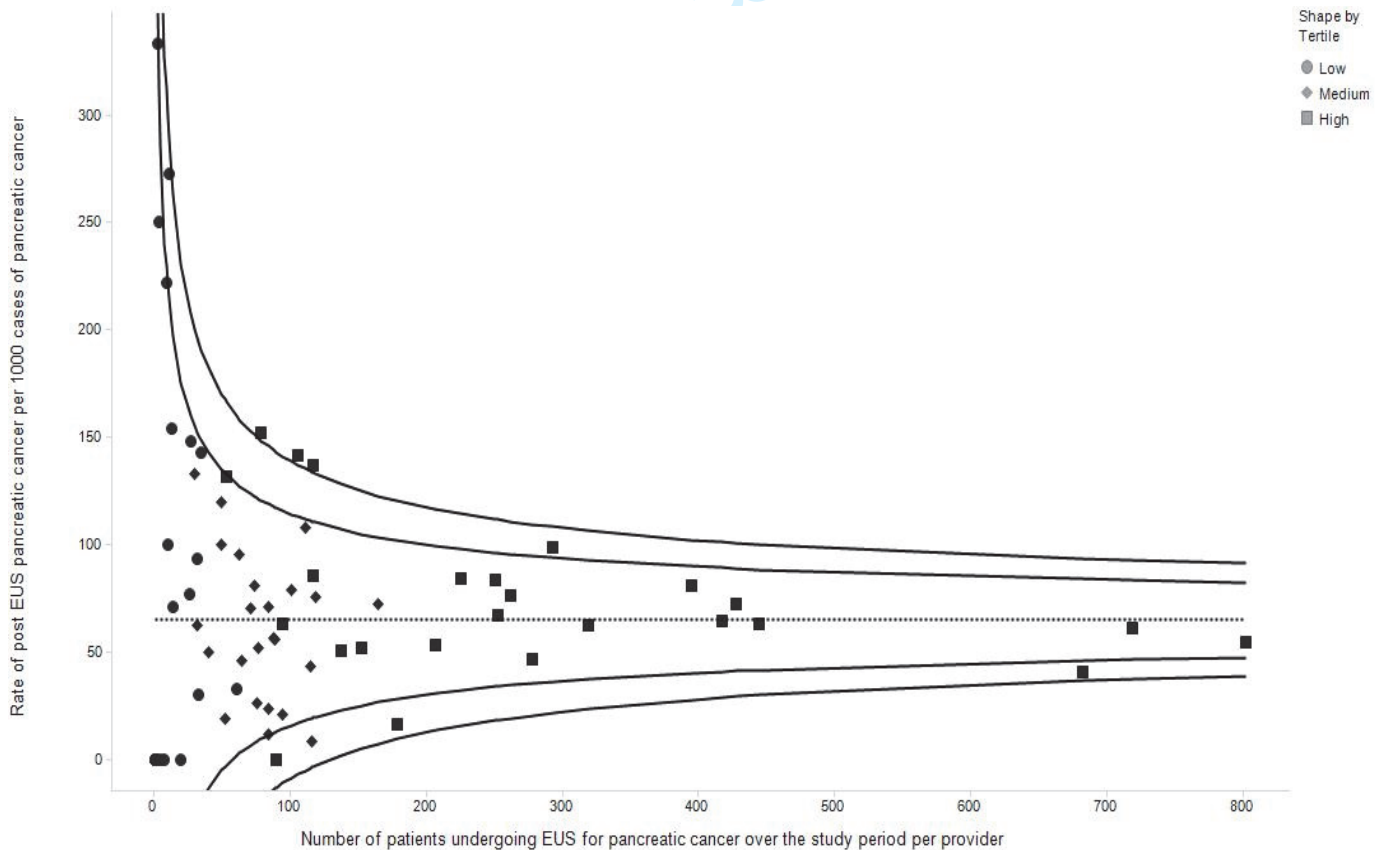
Table 1s, The annual rates of post endoscopic ultrasound pancreatic cancer over the study period

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

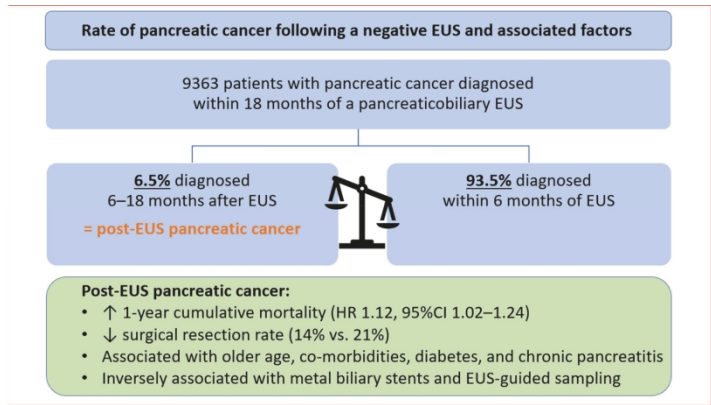
EUS: endoscopic ultrasound; PEPC: post EUS pancreatic cancer

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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Endoscopy

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