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ORIGINAL ARTICLE

Pancreas exocrine replacement therapy is associated with increased survival following pancreatoduodenectomy for periampullary malignancy

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Abstract

Background: Although many patients undergoing pancreatoduodenectomy (PD) for cancer have pancreatic exocrine insufficiency, pancreatic enzyme replacement therapy (PERT) is not routinely used, and effects upon post-operative survival are unclear.

Methods: This review of patients undergoing PD for periampullary malignancy sought to test for an association between PERT and overall survival, with post-hoc subgroup analysis performed after stratifying patients by the year of surgery, pancreatic duct width and tumour type.

Results: Some 202/469 (43.1%) patients received PERT. After accounting for pathological variables and chemotherapy, PERT use was found to be independently associated with improved survival on multivariable analysis [HR 0.72 (95% CI: 0.52–0.99), p = 0.044] and on propensity matched analysis (p = 0.009). The effect of PERT upon improved survival was predominantly observed amongst patients with a dilated pancreatic duct (≥3 mm).

Discussion: PERT use was independently associated with improved survival following PD for cancer. The validity of this observation is supported by an effect largely confined to those patients with a dilated pancreatic duct. The nutritional status of patients undergoing PD for cancer needs further investigation and the effects of PERT require verification in further clinical studies.

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Introduction

Periampullary malignancy is associated with a poor prognosis, with only a minority of patients able undergo potentially curative surgery. Pancreatic adenocarcinoma is a particularly lethal tumour, where survival is lower than any other common malignancy and has not changed over the past 40 years.[1] Adjuvant chemotherapy can be beneficial in these patients, although is only associated with modest improvements in survival.[2] Strategies to resect borderline resectable tumours with associated venous resection are becoming mainstream in large volume centres,[3] as is downstaging chemotherapy for patients with limited involvement of local vascular structures.[4] However, these aggressive strategies come at the cost of increased morbidity, are only applicable to small groups of well selected patients and are therefore unlikely to affect overall survival of the whole patient group. New avenues for research and treatment options are urgently needed to improve the outcomes of this disease.

Pancreatic exocrine insufficiency (PEI) is a manifestation of many pancreatic diseases. A large proportion of patients with chronic pancreatitis suffer from PEI,[5] leading to deficiencies of micronutrients, lipid soluble vitamins[6] and ultimately decreased bone density and fractures.[7,8] Survival also appears to be adversely affected amongst patients undergoing surgery for chronic pancreatitis, where pancreatic enzyme replacement therapy (PERT) is associated with significantly greater survival than those patients not receiving PERT.[9] The consequences of PEI upon cancer related outcomes are, however, unknown. Evidence for a potential association is however seen, particularly if

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the role of vitamin D is considered. Amongst patients with pancreatic cancer, vitamin D deficiency is common at presentation.[10] The above evidence thus provides a platform to investigate a potential effect of PERT upon survival following resection of periampullary malignant tumours.

This study reviewed the outcomes of a cohort of patients undergoing pancreatoduodenectomy (PD), with the aim of assessing the effect of PERT upon survival. For this observational study, patients with pancreatic adenocarcinoma were identified, as well as patients undergoing PD for other carcinomas (cholangiocarcinoma, ampullary carcinoma and duodenal carcinoma), as these lesions have a different histological profile (i.e. no associated stroma), may also obstruct the pancreatic duct, and these patients may receive PERT and thus provide further opportunities to review the role of PERT in a similar setting.

Methods

This was a retrospective review of consecutive adult patients undergoing pancreatoduodenectomy at University Hospitals Birmingham NHS Trust between February 2007 and December 2015. Patients were identified from a departmental registry after institutional approval for the study. The team has a dedicated data manager that reviews patients every day prior to discharge. Post-operative complications such as pancreatic fistula, delayed gastric emptying and haemorrhage were defined using the International Study Group for Pancreatic Surgery definitions. Post-operative infections were defined as superficial or deep surgical site infection, as defined by the Centre for Disease Control and Infection. Missing data were dealt with via case note review and by contacting referring hospitals to identify which patients received chemotherapy. Otherwise, due to the nature of prospective data collection, there was very little missing data. Of the variables analysed in this study, just two had less than 100% complete data (smoking history, 92.8% and body mass index, 97.9% complete data).

Patients with a pathological diagnosis other than pancreatic ductal adenocarcinoma, cholangiocarcinoma, ampullary carcinoma or duodenal carcinoma were excluded, as were patients who either died (n = 36) or were lost to follow up (n = 7) within 90 days of surgery, to avoid effects of immortal time bias.

Patients were considered to be receiving PERT if this was prescribed at the time of discharge and/or at the first outpatient appointment following surgery. The dose and frequency of PERT was recorded where possible. The allocation of PERT was based upon clinical features and patient symptoms. Laboratory testing using faecal elastase 1 was not routinely used and ^{13}C breath testing for PEI was not available.

Following surgery, patients were discussed at a multidisciplinary meeting and offered chemotherapy in line with patient fitness, tumour type and standard practice at that time. Patients were reviewed in outpatient clinic every 3–6 months for the first two years and then annually until five years.

Data analysis

Initially, the associations between PERT usage and range of factors were assessed. Continuous variables were reported as medians and interquartile ranges (IQRs), with comparisons between cohorts made using Mann–Whitney tests. Ordinal variables were also compared using Mann–Whitney tests, with Fisher's exact tests used for categorical variables. Relationships between each factor and overall survival were then tested using univariable Cox regression models. A multivariable Cox regression model was then produced, in order to assess the relationship between PERT and OS, after accounting for other potentially confounding factors. A backwards stepwise approach was used, in order to identify independent predictors of overall survival.

Adjustment for confounding factors was also performed using a propensity matched analysis. Propensity scores were produced based on a binary logistic regression model including all potentially confounding factors. Patients from the two cohorts were then matched 1:1 without replacement on the resulting scores. The factors from the matched cohorts were then compared using Wilcoxon's tests for ordinal and continuous variables, McNemar's test for dichotomous variables, and Fisher's exact tests for the remainder. The overall survival in the two groups was then compared using a stratified Cox regression model, to account for the pairing of patients.

Subgroup analyses were also performed on the cohort as a whole in order to identify the groups where PERT had the greatest potential benefit. These used Cox regression models considering PERT usage, the factor of interest and an interaction term, to test whether the effect of PERT differed across various patient groups.

All analyses were performed by a medical statistician (JH) using IBM SPSS Statistics 22 (IBM Corp. Armonk, NY). Patients with missing data were excluded on a per-analysis basis. A p-value < 0.05 was deemed to be indicative of statistical significance throughout.

Results

Amongst 469 patients, the median age at the time of surgery was 68 years (IQR 61–73) and there were 256 males (54.6%). Some 250 (53.3%) tumours were considered to be pancreatic ductal adenocarcinomas, 126 (26.6%) ampullary carcinomas, 64 (13.6%) cholangiocarcinomas and 29 (6.2%) duodenal carcinomas. The median BMI at the time of surgery was 25 (IQR 22–28). The Kaplan Meier estimated median duration of potential follow up was 42 months (95% CI: 34–50). At the last follow up some 185 (39.4%) patients were alive and disease free, 33 (7.0%) were alive but with disease, 197 (42.0%) had died of disease, 24 (5.1%) had died of another cause and 30 (6.4%) had died of an unknown cause.

Pancreatic enzyme replacement therapy (PERT)

The only PERT used was Creon (Mylan pharmaceuticals). Some 202 patients (43.1%) were prescribed PERT, a proportion which

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Table 1 Factors associated with PERT use

	Valid N	PERT at/after discharge		p-Value
		No	Yes	
Age (Years)	469	67.3 (61.4–73.3)	68.4 (61.5–73.5)	0.579
BMI	459	24.8 (22.2–27.9)	25.0 (22.0–28.2)	0.873
Gender				**0.039**
Male	256	157 (58.8%)	99 (49.0%)	
Female	213	110 (41.2%)	103 (51.0%)	
Smoking status				**0.043**
No	256	139 (56.3%)	117 (62.2%)	
Ex	119	65 (26.3%)	54 (28.7%)	
Yes	60	43 (17.4%)	17 (9.0%)	
Year of surgery				**<0.001***
2007–2009	125	95 (35.6%)	30 (14.9%)	
2010–2011	107	55 (20.6%)	52 (25.7%)	
2012–2013	101	59 (22.1%)	42 (20.8%)	
2014–2015	136	58 (21.7%)	78 (38.6%)	
Tumour type				0.262
PDAC	250	132 (49.4%)	118 (58.4%)	
Cholangiocarcinoma	64	41 (15.4%)	23 (11.4%)	
Duodenal cancer	29	17 (6.4%)	12 (5.9%)	
Ampullary cancer	126	77 (28.8%)	49 (24.3%)	
Duct width (mm)	469	4.0 (1.6–6.7)	4.0 (1.3–6.2)	0.845
T stage				0.201*
1	30	19 (7.1%)	11 (5.4%)	
2	52	34 (12.7%)	18 (8.9%)	
3	357	197 (73.8%)	160 (79.2%)	
4	30	17 (6.4%)	13 (6.4%)	
N stage				0.210
0	129	67 (25.1%)	62 (30.7%)	
1	340	200 (74.9%)	140 (69.3%)	
R status				0.391
0	387	224 (83.9%)	163 (80.7%)	
1	82	43 (16.1%)	39 (19.3%)	
Venous resection				0.184
No	402	234 (87.6%)	168 (83.2%)	
Yes	67	33 (12.4%)	34 (16.8%)	
Wound infection				0.204
No	425	246 (92.1%)	179 (88.6%)	
Yes	44	21 (7.9%)	23 (11.4%)	
POPF				0.473*
No	392	221 (82.8%)	171 (84.7%)	
Grade A	34	16 (6.0%)	18 (8.9%)	
Grade B	30	21 (7.9%)	9 (4.5%)	
Grade C	13	9 (3.4%)	4 (2.0%)	

(*continued on next page*)

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Table 1 (*continued*)

	Valid N	PERT at/after discharge		p-Value
		No	Yes	
Intra-abdominal collection				0.313
No	430	248 (92.9%)	182 (90.1%)	
Yes	39	19 (7.1%)	20 (9.9%)	
Adjuvant chemotherapy				0.251
No	179	108 (40.4%)	71 (35.1%)	
Yes	290	159 (59.6%)	131 (64.9%)	

Continuous data reported as: "median (quartiles)", with p-values from Mann–Whitney tests. Categorical data reported as: "N (column %)", with p-values from Fisher's exact test or *Mann–Whitney tests, as applicable. Bold p-values are significant at $p < 0.05$. PERT, pancreas enzyme replacement therapy; BMI, body mass index; PDAC, pancreatic ductal adenocarcinoma; POPF, postoperative pancreatic fistula.

did not differ significantly by tumour type ($p = 0.262$). In the 117 patients where the daily dose was recorded, the median dose was 75,000 units (IQR 60,000–150,000). The associations between PERT use and a range of variables are reported in Table 1.

PERT usage increased significantly over the period of the study ($p < 0.001$), from being used in 24.0% of cases in 2007–2009, to 57.4% in 2014–2015. Of the patient demographic factors considered, PERT usage was found to be significantly less common in males and those patients that smoked. There were no pre-existing health conditions that were significantly associated with PERT usage (Supplementary Table 1).

Survival

On univariable analysis, overall survival was found to be significantly improved in those patients that received PERT ($p = 0.034$, Fig. 1), with median survival of 33.1 vs. 26.7 months, resulting in a hazard ratio of 0.76 (95% CI: 0.59–0.98). The association between other factors and survival are reported in Table 2. Tumour stage, resection margin status, presence of nodal metastases and tumour type were all significantly related to survival (all $p < 0.001$). Patients undergoing venous resection also had reduced survival ($p = 0.019$), although this was related to the higher proportion of patients with pancreatic adenocarcinoma undergoing venous resection compared to patients with other tumour types (22.0% vs. 5.5%, $p < 0.001$).

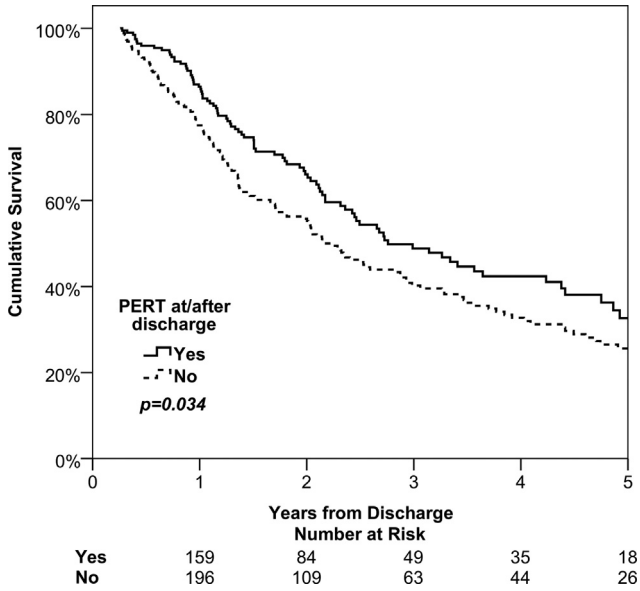

Figure 1 Survival of the whole cohort grouped by the use of pancreatic enzyme replacement therapy (PERT) or not

On multivariable analysis, diagnosis of pancreatic adenocarcinoma, increasing T-stage and presence of nodal metastases were found to be significant independent predictors of shorter survival (all $p < 0.001$), whilst adjuvant chemotherapy ($p < 0.001$) and having surgery in the final years of the study ($p = 0.022$) were independent predictors of improved survival. After accounting for these factors, the effect of PERT remained significant ($p = 0.046$), with a hazard ratio of 0.75 (95% CI: 0.57–0.99).

A propensity matched analysis was also performed, as an alternative approach to account for potentially confounding factors. A propensity score for treatment with PERT was produced, based on all factors in Table 1, and N = 129 pairs of patients were able to be matched based on this score. None of the factors included in the propensity score were found to differ significant between the two groups after matching (Table 3). For these matched patients, overall survival remained significantly improved in the PERT group, with a hazard ratio of 0.57 (95% CI: 0.38–0.87, $p = 0.009$) relative to controls.

A range of subgroup analyses were then performed on the cohort as a whole, in order to identify any groups of patients where PERT conferred a greater survival benefit (Fig. 2). The association between PERT and overall survival was not found to differ significantly by either the year of the study ($p = 0.740$), or the tumour type ($p = 0.457$). Analysis of the duct width also found no significant interaction with PERT ($p = 0.104$). However, there was a trend for the benefit of PERT to be greater in those with larger ducts (Fig. 3), with PERT conferring a significant survival benefit in patients with duct widths of 3+ mm (HR: 0.64, 95% CI: 0.47–0.89, $p = 0.006$) but not for ducts of <3 mm (HR: 1.01, 95% CI: 0.66–1.55, $p = 0.970$).

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Table 2 Factors associated with overall survival

	Univariable		Multivariable	
	Hazard ratio (95% CI)	**p-Value**	**Hazard ratio(95% CI)**	**p-Value**
PERT at/after discharge	0.76 (0.59–0.98)	**0.034**	0.75 (0.57–0.99)	**0.046**
Age (Years)		0.702	–	*NS*
<60	–	–	–	–
60–66	0.90 (0.63–1.30)	0.583	–	–
67–74	1.10 (0.79–1.54)	0.582	–	–
75+	1.04 (0.70–1.54)	0.841	–	–
BMI		0.123	–	*NS*
≤25	–	–	–	–
26–30	0.73 (0.55–0.97)	0.030	–	–
31–35	0.72 (0.46–1.15)	0.168	–	–
>35	0.78 (0.41–1.48)	0.441	–	–
Gender (Female)	0.89 (0.69–1.14)	0.359	–	*NS*
Smoking status		0.109	–	*NS*
No	–	–	–	–
Ex	1.03 (0.77–1.38)	0.818	–	–
Yes	1.46 (1.02–2.08)	0.039	–	–
Year of surgery		0.093		**0.022**
2007–2009	–	–	–	–
2010–2011	0.78 (0.57–1.06)	0.111	0.97 (0.69–1.36)	0.854
2012–2013	1.03 (0.73–1.44)	0.874	1.34 (0.93–1.94)	0.111
2014–2015	0.65 (0.42–1.01)	0.055	0.59 (0.36–0.97)	**0.038**
Tumour type		**<0.001**	–	**<0.001**
PDAC	–	–	–	–
Cholangiocarcinoma	0.81 (0.56–1.15)	0.239	0.66 (0.44–1.00)	**0.050**
Duodenal cancer	0.32 (0.17–0.64)	**0.001**	0.21 (0.10–0.45)	**<0.001**
Ampullary cancer	0.41 (0.30–0.56)	**<0.001**	0.51 (0.34–0.76)	**<0.001**
Duct width (3+ mm)	1.24 (0.95–1.61)	0.108	–	*NS*
T stage		**<0.001**	–	**<0.001**
1	–	–	–	–
2	1.79 (0.70–4.59)	0.222	1.39 (0.49–3.91)	0.531
3	5.87 (2.60–13.23)	**<0.001**	3.09 (1.17–8.16)	**0.022**
4	5.95 (2.36–15.01)	**<0.001**	5.38 (1.86–15.58)	**0.002**
N stage (1)	4.17 (2.89–6.00)	**<0.001**	2.95 (1.98–4.40)	**<0.001**
R status (1)	1.66 (1.23–2.24)	**<0.001**	–	*NS*
Venous resection	1.48 (1.07–2.06)	**0.019**	–	*NS*
Wound infection	1.19 (0.79–1.80)	0.403	–	*NS*
POPF		0.643	–	*NS*
No	–	–	–	–
Grade A	0.83 (0.51–1.37)	0.473	–	–
Grade B	1.10 (0.67–1.81)	0.696	–	–
Grade C	0.64 (0.26–1.55)	0.321	–	–
Adjuvant chemotherapy	1.09 (0.84–1.41)	0.516	0.59 (0.43–0.80)	**<0.001**

Results are from uni- and multi-variable Cox regression models. The multivariable analysis used a backwards stepwise approach to select factors, with all factors in the table considered for inclusion, and is based on the N = 427 with data available for all factors. NS = factors that were not selected for the final multivariable model due to non-significance. Bold p-values are significant at $p < 0.05$. PERT, pancreas enzyme replacement therapy; BMI, body mass index; PDAC, pancreatic ductal adenocarcinoma; POPF, postoperative pancreatic fistula.

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Table 3 Cohort after propensity matching

	PERT at/after discharge		p-Value
	No	Yes	
Age (Years)	67.6 (59.8–73.3)	68.4 (61.9–73.3)	0.335
BMI	24.7 (22.3–28.4)	24.9 (22.0–27.8)	0.794
Gender (Male)	73 (56.6%)	72 (55.8%)	1.000
Smoking Status			0.878**
No	76 (58.9%)	77 (59.7%)	
Ex	33 (25.6%)	35 (27.1%)	
Yes	20 (15.5%)	17 (13.2%)	
Year of surgery			1.000*
2007–2009	24 (18.6%)	24 (18.6%)	
2010–2011	42 (32.6%)	42 (32.6%)	
2012–2013	33 (25.6%)	33 (25.6%)	
2014–2015	30 (23.3%)	30 (23.3%)	
Tumour type			0.100**
PDAC	81 (62.8%)	66 (51.2%)	
Cholangiocarcinoma	17 (13.2%)	17 (13.2%)	
Duodenal cancer	11 (8.5%)	10 (7.8%)	
Ampullary cancer	20 (15.5%)	36 (27.9%)	
Duct width (mm)	4.0 (1.0–6.2)	4.0 (1.0–6.2)	0.384*
T stage			0.161*
1	4 (3.1%)	9 (7.0%)	
2	11 (8.5%)	14 (10.9%)	
3	105 (81.4%)	97 (75.2%)	
4	9 (7.0%)	9 (7.0%)	
N stage (1)	102 (79.1%)	92 (71.3%)	0.203
R status (1)	25 (19.4%)	23 (17.8%)	0.860
Venous resection	21 (16.3%)	20 (15.5%)	1.000
Wound infection	8 (6.2%)	8 (6.2%)	1.000
POPF			0.269*
No	112 (86.8%)	108 (83.7%)	
Grade A	10 (7.8%)	9 (7.0%)	
Grade B	5 (3.9%)	9 (7.0%)	
Grade C	2 (1.6%)	3 (2.3%)	
Intra-abdominal collection	12 (9.3%)	13 (10.1%)	1.000
Adjuvant chemotherapy	91 (70.5%)	82 (63.6%)	0.272

Continuous data reported as: "median (quartiles)", with p-values from Wilcoxon's tests. Categorical data reported as: "N (column %)", with p-values from McNemar's tests, * Wilcoxon's tests or **Fisher's exact tests, as applicable. Bold p-values are significant at $p < 0.05$. PERT, pancreas enzyme replacement therapy; BMI, body mass index; POPF, postoperative pancreatic fistula.

Discussion

This was a retrospective review of risk factors related to survival amongst patients following PD for pancreatic adenocarcinoma or other periampullary tumours, with a focus on the effect of PERT. The main findings were that survival was related to expected variables such as tumour type, T stage, N stage and chemotherapy, but also to the use of PERT. This observation remained significant even after accounting for the effects of potentially confounding factors using both multivariable adjustment and a propensity matched analysis. Accounting for these factors was particularly important, since the use of PERT increased during the study period, during which time adjuvant chemotherapy regimens have changed, with significant improvement in survival with combination chemotherapy observed within the ESPAC-4 study.[11]

The reason for the increased survival amongst patients with PERT is likely to relate to whether PEI was treated or not. It seems likely that PEI was under diagnosed and therefore poorly treated. If all patients with PEI were treated, then it would be expected that the BMI and pancreatic duct width would be different to those patients without PEI. However, at the time of surgery, PERT usage was not significantly associated with either BMI or duct width. This explanation is likely, as the majority of patients with tumours of the head of the pancreas have PEI.[12] However, less than half of the present cohort received PERT. This is further supported by the fact that PERT usage had no significant effect upon survival when only patients with narrow pancreatic ducts were considered, as these patients retain capacity to produce endogenous enzymes.

PERT was prescribed in response to patient symptoms, as biochemical analysis of PEI was not performed. To assess the appropriateness of allocation of PERT, this study used surrogate markers of PEI (BMI and pancreatic duct width). This is based upon the classic picture, which includes weight loss and muscle wasting. Furthermore, pancreatic duct width has been used to assess PEI.[13] This approach is not ideal, as weight loss in the setting of cancer is multifactorial and duct width is an indirect measurement of PEI. However, problems surround the optimal method of diagnosing PEI. The gold standard test of PEI requires patients to maintain a strict diet to include 100 g of fat per day for three days, together with quantification of three days' worth of faecal fat.[14] This is unpleasant for patients and laboratory staff alike and is consequently very rarely used.[15] Faecal elastase 1 (FE-1) is widely used to diagnose PEI. However, following pancreatic resection, the ratio of faecal fat to FE-1 levels are higher, which reduces the sensitivity of FE-1 to diagnose PEI in this setting.[16,17] The ^{13}C-mixed triglycerides breath test[18] measures the degradation of triglycerides, which has the advantage over FE-1 testing that it is not testing exocrine insufficiency but functional insuf-

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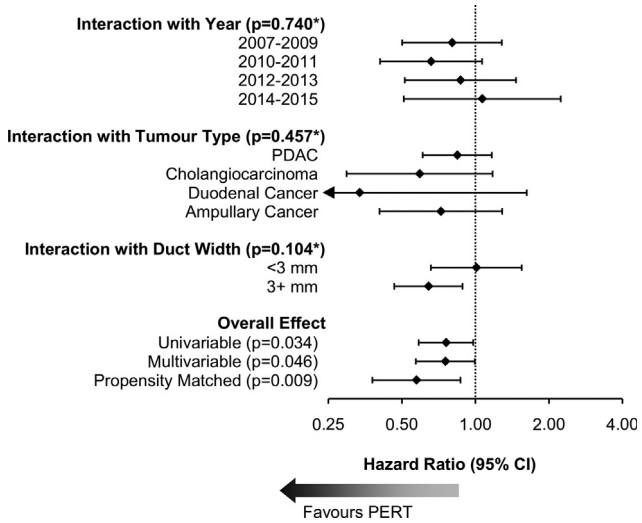

Figure 2 Forest plot of pancreatic enzyme replacement therapy (PERT) subgroup survival analyses. Plotted values are hazard ratios from Cox regression models within the subgroups of cases, with the overall effects from the analysis in Table 2. *p-Values are for the interaction terms from Cox regression models, with PERT usage, the factor of interest and an interaction as factors

ficiency: it is possible to have normal pancreatic exocrine function but for some other failure of the intestinal tract to prevent fat absorption. The drawback is that this test is confined to a few highly specialised centres. Thus, there is no widely used reliable laboratory test to diagnose PEI following pancreatic resection. Studies reviewing the natural history of PEI after pancreatoduodenectomy demonstrate that it affects most patients at the time of surgery and the vast majority after several months. In addition, it is not confined to those with pancreatic adenocarcinoma, also affecting those with resected periampullary tumours.[19,20]

The deleterious effects of nutritional failure and untreated PEI have been explored previously. Weight loss amongst patients with advanced pancreatic cancer is associated with reduced survival and quality of life.[21] Untreated PEI is associated with a negative impact upon quality of life.[22] Patients with the greatest amount of weight loss are more likely to be unresectable at surgery and have a greater burden of metastatic disease and, thus, it could be argued that weight loss simply reflects this relationship.[23] However, PERT appears able to reverse nutritional failure to some degree. In a randomised trial of patients with inoperable pancreatic cancer, patients on PERT gained weight during the study period, whilst those not on PERT lost weight.[24] The effect of PERT on survival was however not assessed. Amongst a non-randomised cohort of patients with advanced pancreatic cancer, PERT, along with palliative chemotherapy, were independent factors associated with increased survival.[25] The relationship between FE-1 levels and survival has recently been explored, and patients with the lowest levels of FE-1 had the worst survival.[26] The experience of historic cohorts of patients with cystic fibrosis presents an opportunity to understand the effects of untreated PEI upon mortality. This classical observation was made by Corey et al., who reviewed the outcomes of two cohorts of patients with cystic fibrosis from similar backgrounds in 1988.[27] One cohort was managed with a traditional low fat diet with limited or no PERT, whilst the other received high dose PERT and high fat and calorie intake. The median age of death was 30 years amongst the patients receiving high dose PERT and

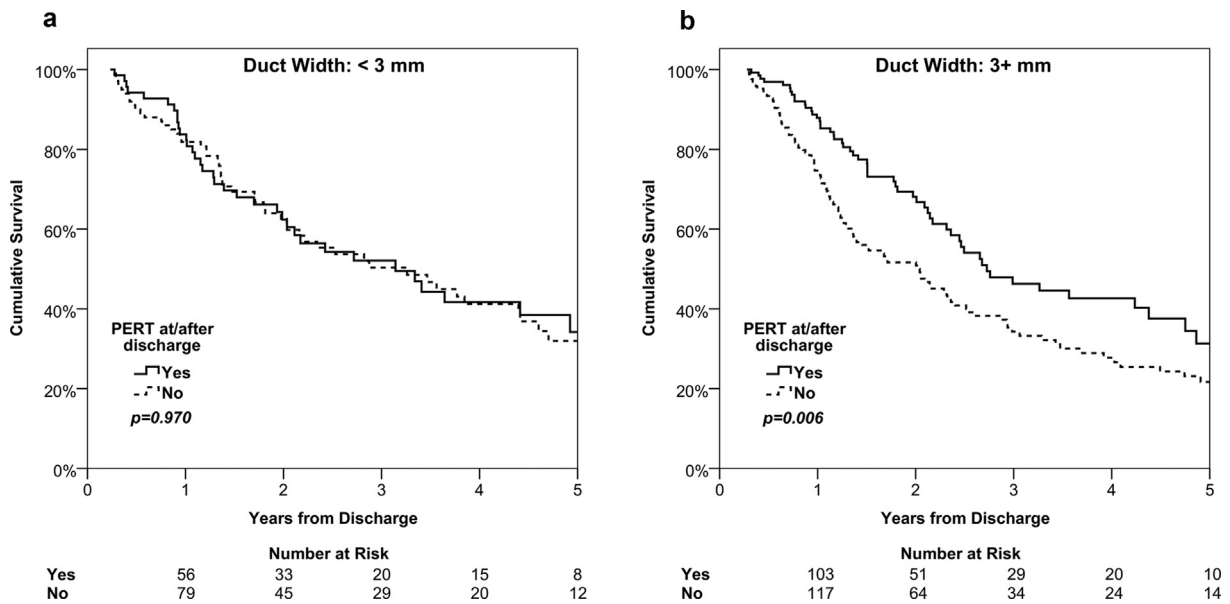

Figure 3 Effect of pancreatic duct width upon overall survival among patients who did or did not receive pancreatic enzyme replacement therapy (PERT). Patients with a dilated duct (3+ mm) had reduced survival if they did not receive supplemental PERT

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21 in the group with traditional low fat diet. In the setting of major pancreatic surgery followed by adjuvant chemotherapy (and for most patients recurrent cancer), it is not a difficult assumption to make that untreated PEI will reduce a patients duration of survival.

Increased caloric intake, weight stabilisation and improved nutritional profile through optimised absorption of fats, proteins and carbohydrates are the postulated mechanisms by which PEI and PERT are thought to relate to the above observations. A further link between PEI and adverse outcomes comes from an assessment of the potential role for fat soluble vitamins. Vitamin D deficiency is indirectly linked to adverse outcomes amongst patients with pancreatic adenocarcinoma. Vitamin D deficiency is prevalent amongst patients with pancreatic adenocarcinoma[10] and associated with a worse prognosis amongst patients with stage 3 or 4 disease. Furthermore, a key regulator of the tumour stroma which characterises pancreatic adenocarcinoma is the vitamin D receptor.[28] Stimulation of the receptor by vitamin D analogues remodels the stroma via pancreatic stellate cells, reducing tumour volume and increasing intratumoural gemcitabine. Calcitriol, a vitamin D analogue, has been shown to inhibit growth of pancreas cancer cells *in-vitro*,[29] whilst a study of calcitriol combined with docetaxel demonstrated improved survival compared to historical controls treated with docetaxel only.[30] These observations provide a mechanism by which PERT may be beneficial in a method partly independent of PEI and amongst patients with pancreatic adenocarcinoma. The vitamin D receptor has been demonstrated in cholangiocarcinoma where treatment with vitamin D reduces cell proliferation in-vitro[31] and in a murine model.[32] Vitamin E intake has been demonstrated to be inversely related to risk of pancreatic cancer in epidemiological studies.[33] Nutritional effects and roles of vitamin therapy are less clear amongst patients with ampullary or duodenal cancer. However, duodenal cancer shares similar genetic homology with colorectal carcinoma.[34] Epidemiological studies demonstrate vitamin D[35] and E[36] deficiency with colorectal carcinoma.

Whilst the relationship between PERT use and increased survival following PD for cancer has not been made before, this observation is not without precedent. Recently a cohort of patients who had undergone surgery for chronic pancreatitis were demonstrated to have improved survival if they were on PERT at the time of surgery.[9]

In summary, this study demonstrates a remarkable observation – a relationship between PERT use and increased survival amongst patients undergoing PD for cancer. Furthermore, this relationship was temporal and, importantly, the benefit was limited to those patients with (indirect) biologic evidence for PEI, a dilated pancreatic duct. An understanding of the nutritional profile of patients undergoing PD, the harmful consequences of PEI and potential benefits of PERT provide a plausible biological explanation for this observation. A simple observational study, however cannot prove causation. Thus, the final factor to consider in proving causation is a strong research design. A randomised trial appears warranted on the basis of the results of this study.

Conflict of interest

None to declare.

Disclosures

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.hpb.2017.05.009.

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