Pancreatic enzyme replacement therapy in patients with pancreatic cancer: a national prospective study

*The RICOCHET Study Group on behalf of the West Midlands Research Collaborative**

*Collaborating authors are listed in Supplemental Material

Correspondence: Richard Wilkin, West Midlands Research Collaborative, Open Plan East, Second Floor, Institute for Translational Medicine, University of Birmingham, Edgbaston, Birmingham, B15 2TH, UK. Email: r.wilkin@bham.ac.uk

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ABSTRACT

OBJECTIVE

UK national guidelines recommend pancreatic enzyme replacement therapy (PERT) in pancreatic cancer. Over 80% of pancreatic cancers are unresectable and managed in non-surgical units. The aim was to assess variation in PERT prescribing, determine factors associated with its use and identify potential actions to improve prescription rates.

DESIGN

RICOCHET was a national prospective audit of malignant pancreatic, peri-ampullary lesions or malignant biliary obstruction between April and August 2018. This analysis focuses on pancreatic cancer patients and is reported to STROBE guidelines. Multivariable regression analysis was undertaken to assess factors associated with PERT prescribing.

RESULTS

Rates of PERT prescribing varied among the 1,350 patients included. 74.4% of patients with potentially resectable disease were prescribed PERT compared to 45.3% with unresectable disease.

PERT prescription varied across surgical hospitals but high prescribing rates did not disseminate out to the respective referring network. PERT prescription appeared to be related to the treatment aim for the patient and the amount of clinician contact a patient has.

PERT prescription in potentially resectable patients was positively associated with dietitian referral(p=0.001) and management at hepaticopancreaticobiliary(p=0.049) or pancreatic

unit(p=0.009). Prescription in unresectable patients also had a negative association with Charlson comorbidity score 5-7(p=0.045) or >7(p=0.010) and a positive association with clinical nurse specialist review(p=0.028).

CONCLUSION

Despite national guidance, wide variation and under-treatment with PERT exists. Given that most patients with pancreatic cancer have unresectable disease and are treated in non-surgical hospitals, where prescribing is lowest, strategies to disseminate best practice and overcome barriers to prescribing are urgently required.

INTRODUCTION

Despite the challenges presented by pancreatic cancer, after decades of lack of improvement in very poor outcomes, there is now reason for cautious optimism[1]. Systematic improvements across pathways such as improved outcomes with surgery, strategies to treat borderline or locally advanced pancreatic cancer, multimodal chemotherapy and a focus upon improving the patient experience are some of the causes for this optimism[2].

One consequence of pancreatic cancer is pancreatic exocrine insufficiency (PEI), which is highly prevalent and progressive[3-5]. The malabsorptive state results in weight loss and progressive frailty, while symptoms are unpleasant and impair quality of life. Treatment with pancreatic enzyme replacement therapy (PERT) improves quality of life, reverses malabsorption and maintains weight[6-7]. While the size of the treatment effect and it's influence on outcomes is not fully understood, there is evidence that PERT is independently associated with a survival advantage [8-9]. Despite the fundamental importance of correcting malnutrition, there is, however, evidence of widespread under treatment with PERT among pancreatic cancer patients across the United Kingdom (UK)[8]. In our opinion, there can be no doubt that PERT is an important part of 'best medical care' for patients with pancreatic cancer.

Consequently, in February 2018, the National Institute for Health and Care Excellence (NICE) in the UK recommended PERT for all patients with pancreatic cancer[10]. Following publication of the NICE guidelines, a prospective audit of pancreatic cancer care was conducted across the UK: "ReceIpt of Curative resection Or palliative Care for HEpatopancreaticobiliary Tumours - The RICOCHET Study"[11]. Given the fundamental

importance of treating PEI, the aim of the present study was to assess variation in PERT prescribing, determine factors associated with its use in order to identify potential interventions to improve the care of pancreatic cancer patients.

METHODS

Study design and subjects

RICOCHET was a nationwide, prospective observational audit of all patients presenting with pancreatic cancer or malignant biliary obstruction across the UK[11]. This manuscript represents an analysis of patients with a final diagnosis of pancreatic cancer. Data collection took place over a 16 week period from April to July 2018. Patients were followed up for 90 days from presentation and the data was collected via the Research Electronic Data Capture (REDCap) platform[12].

The study was disseminated via established trainee and medical student collaborative networks, presentation at regional teaching days, regional collaborative meetings and national conferences[11].

Patients diagnosed with pancreatic cancer at any of the hospitals in the RICOCHET study were included in the analysis for the present study. A diagnosis of pancreatic cancer was made on the basis of either histology and radiology, or radiology alone, as determined by the local multidisciplinary team. Any patient under the age of 16, with gallbladder or intrahepatic malignant lesions was excluded, as was any patient subsequently found to have benign disease.

Each patient's treatment cohort was based upon the local definition of a patient being either potentially resectable or unresectable as assessed at MDT meeting along with any treatment undertaken or awaited. Patients being investigated for suitability for surgery, waiting for surgery or who had surgery were included in the 'potentially resectable' cohort, whilst patients not on a pathway to surgery were in the 'unresectable'cohort. Full details of

identification, recruitment and follow-up can be found in the protocol[11]. Patients that died within 14 days of their first MDT discussion were excluded from this analysis on the basis that it may have not been appropriate for them to receive PERT.

Outcome measures

The primary outcome of this analysis was the proportion of pancreatic cancer patients receiving PERT. Secondary outcomes were factors associated with PERT prescription.

For this analysis, the Charlson comorbidity score was calculated for each patient[13]. Jaundice was defined as a bilirubin greater than 35 umol/L or biliary obstruction identified at the time of MDT and performance status was assessed according to the ECOG Performance Status assessment[14].

Record linkage between sites

Patients treated at more than one site (typically at the local non-surgical hospital first and then referred to the regional surgical hospital) were identified through the use of anonymised patient identifiers. This enabled secure patient identification while meeting the needs of information governance, given that this was an audit. For this purpose, the OpenPseudonymiser programme was used[15]. The programme was distributed on USB sticks and is described in detail in the study protocol[11].

Statistical analysis

Patients with missing PERT prescription data were excluded from all analyses. A table comparing the details of those with missing and available PERT data is provided in

Supplementary Table 1. Data items were compared using the Chi squared tests or students t-tests for categorical or continuous numerical items respectively.

Multivariable logistic regression models were constructed with PERT prescription as the dependent variable. Models were constructed for patients with resectable cancer and patients with unresectable cancer. Pearson's test was applied to confirm goodness of fit.

Statistical analysis was undertaken in Stata version 15[16]. P values of <0.05 were considered to be statistically significant. Missing data were reported in the complete cohort. Any variable with >2.5% of data items missing was subsequently reported with a missing data variable. The results have been reported in accordance with the STROBE guidelines for cohort studies.

Patient involvement

Patients were involved during the design stage of the study. The study protocol was disseminated to a group of patients contacted through Pancreatic Cancer UK. Patients provided valuable review and constructive criticism of the protocol and data points resulting in various alterations to both.

Ethical approval

RICOCHET is an audit and service evaluation and therefore research ethics committee approval was not required. This was confirmed using the national UK decision-making tool of the NHS Health Research Authority and the Medical Research Council[17]. RICOCHET was registered as an audit or service evaluation and given prospective approval prior to data collection at all participating hospitals.

RESULTS

Study subjects

Across 84 NHS hospitals (59 non-surgical and 25 surgical hospitals) data on 1350 patients was collected for analysis. The consort diagram showing how cases were selected for analysis is shown in Figure 1. Overall, 54.5% of patients were prescribed PERT. 429 patients were diagnosed with a potentially resectable and 921 patients with an unresectable pancreatic cancer. The characteristics of the study population according to whether they were prescribed PERT are shown in Table 1.

Variation across centres

There was marked variation of PERT prescription across centres in the UK. Overall, pancreato-biliary (PB) and combined hepato-pancreato-biliary (HPB) surgical hospitals had higher rates of prescription than non-surgical centres (84.6% vs 55.2% vs 42.3%). In addition, teams within surgical PB hospitals were more likely to prescribe PERT, compared to those within surgical HPB hospitals, to patients with resectable (93.0% vs 76.3%, $p=0.001$) and unresectable (79.3% vs 40.5%, $p<0.001$) cancer.

Surgical centres that had a higher rate of prescription for resectable patients also had a higher rate amongst their unresectable patients. However, this did not disseminate beyond the surgical hospital to the networked non surgical hospitals. There was no correlation between a surgical centre's prescribing rate and it's network of non-surgical referring centres. (Figure 2)

Patients with potentially resectable pancreatic cancer

Overall, 74.4% of patients with potentially resectable cancer were prescribed PERT (Table 2). PERT prescribing varied widely depending on which pathway or stage of treatment patients were on. Prescribing was highest among patients who had undergone resectional surgery (96.9%) and was lower among those who had been planned for curative surgery but in whom a resection could not be performed (74.5%). It was lowest in patients waiting for surgery (40.5%), but slightly higher among those undergoing neoadjuvant therapy (63.7%). 112 patients were initially considered potentially resectable, but following specialist review or further investigation, they did not undergo surgery and PERT prescribing among this cohort was 63.4%. In all groups these differences were statistically significant compared to patients that underwent a resection (all $p<0.001$). Further data on these patient groups are shown in Supplementary Table 2.

On multivariable analysis, resectable patients prescribed acid suppression medication (OR 5.21 (95%CI 2.73-9.94)) or nutritional supplements (OR 2.87, (1.36- 6.07)) or who had a dietitian referral (OR 3.78, (1.73- 8.29)) were more likely to be prescribed PERT (Table 2). Patients treated in surgical PB and HPB hospitals were also more likely to receive PERT than those treated in non-surgical hospitals (PB- OR 5.18, (1.50- 17.80), HPB OR 2.07, (1.00- 4.27)). Patients undergoing neoadjuvant therapy were also more likely to be prescribed PERT if they had seen a clinical nurse specialist ($p<0.001$) or were treated at a surgical hospital ($p=0.04$) (Supplementary Table 2). Low volume resectional hospitals were less likely to prescribe PERT in patients who had been resected ($p=0.021$) (Supplementary Table 2).

Patients with unresectable pancreatic cancer

PERT was prescribed in 45.3% of patients with unresectable cancer (Table 3). On univariable analysis, PERT prescribing was associated with younger age, male sex, lower performance

status, less comorbidity, clinical nurse specialist review, dietician referral, acid suppression and nutritional supplement prescription and surgical PB hospitals (all $p<0.001$). Data comparing PERT prescribing among patients with unresectable cancer stratified by whether they were treated at surgical or non-surgical hospital sites are shown in Supplementary Table 3.

On multivariable analysis, patients with increasing comorbidity were less likely to receive PERT (OR 0.36, (0.17- 0.78)) (Table 3). Those patients who were reviewed by a clinical nurse specialist (OR 1.68, (1.06- 2.68)) or a dietician (OR 3.43, (2.14- 5.50)), and those prescribed acid suppression medication (OR 5.18, (3.52- 7.63)) or nutritional supplements (OR 2.29, (1.38- 3.80)) were more likely to be prescribed PERT. PERT prescribing was associated with care in a surgical PB hospital compared with HPB and non-surgical hospitals (OR 2.62, (1.37- 5.00)).

DISCUSSION

This was a prospective evaluation of PERT prescribing among patients with pancreatic cancer in the United Kingdom. The main finding was of widespread variation in PERT prescribing, despite national guidelines recommending this treatment. This is the first national study of it's type from anywhere in the world, but the identification of low PERT prescription is consistent with other studies within the literature[17-18]. This analysis is the first to include all types of pancreatic cancer (resectable and unresectable) from both surgical and non-surgical centres and to follow patients across centres.

The variation in prescribing appeared to be more strongly associated with organisational factors and treatment pathways rather than with patient characteristics. Prescribing of PERT was higher when patients were treated within surgical hospitals, regardless of whether the patient had resectable or unresectable cancer. In 2001, centralisation of pancreatic cancer surgery across the UK resulted in a small number of surgical hospitals (tertiary centres that provide surgery to a network of referring hospitals) and a larger number of non-surgical hospitals (secondary centres that refer patients for surgery/ specialist opinion). Diagnostic pathways and treatment decisions are common to both types of hospital and are defined by multidisciplinary teams (MDT's). MDT members within non-surgical hospitals tend to cover a broad set of diseases and cancer types while teams within surgical centres commonly treat cancers of the liver and pancreas (HPB) or may be limited to pancreatobiliary disease (PB). Within surgical hospitals, prescribing rates were highest when patients were treated by teams providing pancreato-biliary surgery, suggesting that there was a culture within those organisations not limited to the surgical teams which supported PERT prescribing. However, that culture did not appear to extend outside of the organisations, as there was no correlation

in prescribing rates between the surgical hospital and their network of referring hospitals (Figure 2). It was hypothesised that outreach to multi-disciplinary team meetings in non-surgical hospitals or local education events would have helped share good practice, but that does not appear to be the case from this evaluation.

An important factor associated with PERT prescription is the treatment aim for the patient. There was a significant difference in the rate of prescription between potentially resectable and unresectable patients (74.4% vs 45.3%, $p<0.001$). Despite our analysis excluding patients that died within 14 days of first MDT, there may be some patients within the unresectable group that would not benefit from PERT due to severe frailty and limited life expectancy. However, these reasons do not explain the difference in PERT prescription between patients that have undergone a curative resection versus patients that have undergone a palliative resection (96.9% vs 74.5%, $p<0.001$). Both groups of patients were fit enough for a planned major operation and the lack of PERT cannot be explained by frailty or reduced benefit. This indicates an inequality of healthcare where patients that are being aimed for cure are more likely to receive optimised treatment, while those patients being managed palliatively are significantly less likely to have all the treatments from which they may benefit.

Within the potentially resectable cohort, there is an increase in the rate of prescription as patients progress along their curative treatment pathway. If a patient is awaiting surgery, they are prescribed PERT 40.5% of the time. This is the lowest rate within the resectable cohort of patients. 63.7% of patients being managed with neoadjuvant chemotherapy had PERT prescribed while 90.8% of patients that had surgery were prescribed PERT. It may be that the amount of contact with clinicians is an important factor in PERT prescribing in the UK. This is supported by the multivariable analysis which identified referral to a dietician and clinical

nurse specialist contact as important factors increasing the likelihood that a patient would be prescribed PERT.

Lack of an accurate, point of care diagnostic test of PEI may be a major barrier to its treatment. The present diagnostic test, faecal elastase, is unpleasant, has relatively low accuracy and typically results are not available for several days after a sample is provided. Relying on symptoms of PEI, such as weight loss, abdominal pain and discomfort, to triage patients in need of PERT is a very poor strategy as they are often mistaken for those of the underlying cancer[10]. For these reasons, UK national guidance recommends PERT for all patients with pancreatic cancer, and there is no mention of diagnostic testing. Despite this pragmatic solution to issues surrounding the diagnosis of PEI there is clearly a failure of implementation of the guidelines. This may relate in part to the short timeframe between publication of the guidelines (February 2018) and the period of data collection (Summer 2018), although under treatment with PERT in pancreatic cancer has been reported from other European countries and Australia[20-22].

Given the poor compliance with a national guideline and the clear benefits of PERT, strategies are needed to improve the situation. We believe that both national and local initiatives are required to improve prescribing rates. It is important to identify local reasons for failing to comply with the national guidance and guide quality improvement efforts. While centralisation of pancreatic surgery has improved the safety of surgery[23], it may have led to unintended consequences of clinicians outside of surgical units perceiving a lack of ownership of, and focus upon, pancreatic cancer management as evidenced by PERT under-prescribing[2]. The labelling of some clinicians as “non-specialists” is potentially harmful and

may be a disservice to those who are responsible for the delivery of care to the majority of patients with pancreatic cancer.

In view of the association between both a referral to a dietician and clinical nurse specialist input, and an increased probability of PERT prescription, we suggest that pancreatic services in both surgical and non-surgical hospitals should ensure more patients have contact with these clinicians. A surprisingly high number of patients were not referred to a dietician (512/1213, 42.2%) or receive input from a clinical nurse specialist (312/1334, 23.4%). While not every patient can, or should, be managed in a surgical centre, the teams within these centres should increase links with and dissemination of best practice to their referring network. Further work is needed to identify the practices that lead to PB centres having high rates of PERT prescription and the barriers that exist within non-surgical hospitals, along with exploration of reasons why certain groups, such as those with unresectable disease and higher Charlson comorbidity scores have lower prescription rates.

This study has some limitations. This analysis is based upon Ricochet which was an observational study and therefore the results show an association between PERT prescription and the factors included rather than causation. Patient classification for this analysis was according to MDT outcomes. This included any patient that was on a curative pathway as potentially curative regardless how long they were managed as this. This will have inevitably included some patients that were eventually on a palliative treatment pathway in the 'potentially resectable' group. One of the drawbacks of any largescale, multicentre audit is including all eligible patients. While collaborators are clearly asked to include all eligible patients, it is never possible to be sure that this occurs. Our identification of 1609 patients in just over three months in 84 centres across the UK approximately corresponds to 10000

pancreatic cancer diagnoses each year[24]. This study was also performed soon after the publication of UK national guidelines and many centres may not have changed their practice before this study commenced. The results of this study increases the number of further questions around PERT prescription and the current study has not assessed these. We do not assess the amount of enzyme that is prescribed, whether it is actually taken by the patient and if they do not have a prescription of PERT, and whether this had been discussed with the patient at any point. We also do not attempt to collect race/ethnicity data.

In conclusion, given that untreated PEI leads to weight loss, reduced quality of life and survival, strategies to diminish variation and barriers to prescribing PERT are urgently required. In a landscape where funders have pledged huge sums for research to improve pancreatic cancer outcomes and where progress is desperately needed but seldom seen[1] under treatment with PERT is a major inequality in pancreatic cancer care and immediate action is required to rectify it.

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RW is guarantor of the article. The article is published under corporate authorship with all collaborators contributing to the project.

Competing interests

KR has received honoraria and research funding from Mylan pharmaceuticals. There are no other competing interests to declare.

Data availability

We will consider requests to make anonymised data available to interested researchers upon request and following a formal data use agreement. Data use requests should be forwarded to the corresponding author. The mailing address is: Mr R Wilkin, Academic Department of Surgery, Room 29, Fourth Floor, Heritage Building, University of Birmingham, Mindelsohn Drive, Edgbaston, Birmingham, B15 2TT (phone number +44-121-371-8910).

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Table 1. The characteristics of all study patients by PERT prescription

			Total	PERT prescribed	PERT not prescribed	p value
All			1350	736 (54.5%)	614 (45.5%)	
Patient characteristics	**Mode of presentation**	Emergency	457	245 (53.6%)	212 (46.4%)	0.629
		Elective	891	490 (55%)	401 (45%)	
		Missing	2	1 (50%)	1 (50%)	
	Age quintile	<63	278	175 (62.9%)	103 (37.1%)	<0.001
		63-70	292	183 (62.7%)	109 (37.3%)	
		71-75	290	172 (59.3%)	118 (40.7%)	
		76-81	249	117 (47%)	132 (53%)	
		>81	241	89 (36.9%)	152 (63.1%)	
		Missing	0			
	Sex	Male	698	406 (58.2%)	292 (41.8%)	0.005
		Female	652	330 (50.6%)	322 (49.4%)	
		Missing	0			
	Charlson comorbidity score	<5	368	243 (66%)	125 (34%)	<0.001
		5-7	754	399 (52.9%)	355 (47.1%)	
		>7	122	94 (41.2%)	94 (41.2%)	
		Missing	0			
	Performance status	0	551	336 (61%)	215 (39%)	<0.001
		1	411	232 (56.4%)	179 (43.6%)	
		2	224	115 (51.3%)	109 (48.7%)	
		>2	142	49 (34.5%)	93 (65.5%)	
		Missing	22	7 (31.8%)	15 (68.2%)	
Disease factors	**Resectable**	Yes	429	319 (74.4%)	110 (25.6%)	<0.001
		No	921	417 (45.3%)	504 (54.7%)	
		Missing	0			
	Jaundice	Yes	522	324 (62.1%)	198 (37.9%)	<0.001
		No	828	412 (49.8%)	416 (50.2%)	
		Missing	0			
Management	**Surgery performed**	Resection	157	152 (96.8%)	5 (3.2%)	<0.001
		Bypass	45	33 (73.3%)	12 (26.7%)	
		Missing	0			
	CNS review	Yes	1022	662 (64.8%)	360 (35.2%)	<0.001
		No	312	66 (21.1%)	246 (78.9%)	
		Missing	16	8 (50.0%)	8 (50.0%)	
		Yes	803	607 (75.6%)	196 (24.4%)	<0.001

	Acid suppression	No	513	104 (20.3%)	409 (79.7%)	
		Missing	34	25 (73.5%)	9 (26.4%)	
	Dietitian referral	Yes	701	538 (76.7%)	163 (23.3%)	<0.001
		No	512	102 (19.9%)	410 (80.1%)	
		Missing	137	96 (70.1%)	41 (29.9%)	
	Nutritional supplements prescribed	Yes	609	475 (78%)	134 (22%)	<0.001
		No	586	148 (25.3%)	438 (74.7%)	
		Missing	155	113 (72.9%)	42 (27.1%)	
Healthcare provider	**Hospital type**	Non Surgical	487	206 (42.3%)	281 (57.7%)	<0.001
		Surgical HPB	681	376 (55.2%)	305 (44.8%)	
		Surgical PB	182	154 (84.6%)	28 (15.4%)	
		Missing	0			
	Provider volume (Surgical HPB and PB hospital only)	Low	236	124 (52.5%)	112 (47.5%)	0.004
		Mid	255	165 (64.7%)	90 (35.3%)	
		High	337	219 (65%)	118 (35%)	
		Missing	35	22 (62.9%)	13 (37.1%)	

PERT - Pancreatic enzyme replacement therapy

CNS – Clinical Nurse Specialist

HPB - Hepato-pancreato-biliary

PB - Pancreato-biliary

Table 2. The characteristics of patients with potentially resectable pancreatic cancer disease by PERT prescription, including multivariable logistic regression analysis of factors associated with PERT prescription

					Logistic regression model			
		Total	PERT prescribed (%)	P value	Odds ratio	95% CI		P value
All		429	319 (74.4%)					
Age quintile	<63	111	84 (75.7%)	0.262	ref			
	63-70	119	92 (77.3%)		1.21	0.46	3.20	0.699
	71-75	89	70 (78.7%)		1.85	0.50	6.82	0.356
	76-81	73	49 (67.1%)		0.95	0.26	3.46	0.939
	>81	37	24 (64.9%)		0.96	0.22	4.25	0.952
Sex	Male	223	173 (77.6%)	0.112	ref			
	Female	206	146 (70.9%)		0.62	0.33	1.13	0.120
Charlson comorbidity score	<5	159	123 (77.4%)	0.128	Ref			
	5-7	231	172 (74.5%)		0.71	0.25	2.01	0.515
	>7	39	24 (61.5%)		0.31	0.08	1.25	0.101
Performance status	0	232	173 (74.6%)	0.608	ref			
	1	120	92 (76.7%)		0.83	0.40	1.74	0.627
	2	56	40 (71.4%)		1.18	0.46	3.04	0.733
	>2	19	12 (63.2%)		0.76	0.16	3.60	0.732
Jaundice	Yes	221	176 (79.6%)	0.010	1.73	0.95	3.17	0.076
	No	208	143 (68.8%)		ref			
CNS review	Yes	372	298 (80.1%)	0.001	2.26	0.96	5.32	0.062
	No	52	18 (34.6%)		ref			
Acid suppression	Yes	332	285 (85.8%)	<0.001	5.21	2.73	9.94	<0.001
	No	95	34 (35.8%)		ref			
Dietitian referral*	Yes	285	245 (87.0%)	<0.001	3.78	1.73	8.29	0.001
	No	92	32 (34.8%)		ref			
	Missing	52	42 (80.8%)		1.47	0.32	6.76	0.620
Nutritional supplements prescribed*	Yes	237	209 (88.2%)	<0.001	2.87	1.36	6.07	0.006
	No	128	55 (43.0%)		Ref			
	Missing	64	55 (85.9%)		4.67	1.10	19.78	0.037
Hospital type	Non surgical	79	40 (50.4%)	<0.001	Ref			
	Surgical HPB	279	213 (76.3%)		2.07	1.00	4.27	0.049
	Surgical PB	71	66 (93.0%)		5.18	1.50	17.80	0.009

PERT - Pancreatic enzyme replacement therapy

CNS – Clinical Nurse Specialist

HPB - Hepato-pancreato-biliary

PB - Pancreato-biliary

*missing data >2.5%.

Table 3. The characteristics of patients with unresectable pancreatic cancer by PERT prescription, including multivariable logistic regression analysis of factors associated with PERT prescription

					Logistic regression model			
		Total	PERT prescribed (%)	P value	Odds ratio	95% CI		p value
All		921	417 (45.3%)					
Mode of presentation	Emergency	309	134 (43.4%)	0.396				
	Elective	611	283 (46.3%)					
Age quintile	<63	167	91 (54.5%)	<0.001	Ref category			
	63-70	173	91 (52.6%)		1.25	0.66	2.37	0.501
	71-75	201	102 (50.6%)		1.89	0.87	4.11	0.111
	76-81	176	68 (38.6%)		1.18	0.53	2.62	0.680
	>81	204	65 (31.9%)		0.80	0.36	1.79	0.587
Sex	Male	475	233 (49.1%)	0.018	Ref category			
	Female	546	284 (52%)		1.04	0.72	1.50	0.826
Charlson comorbidty score	<5	209	120 (57.4%)	<0.001	Ref category			
	5-7	523	227 (43.4%)		0.50	0.26	0.98	0.045
	>7	189	70 (37.0%)		0.36	0.17	0.78	0.010
Performance status	0	319	163 (51.1%)	0.001	Ref category			
	1	291	140 (48.1%)		1.08	0.69	1.69	0.749
	2	168	75 (44.6%)		1.32	0.75	2.33	0.341
	>2	123	37 (30.1%)		0.55	0.29	1.05	0.071
Jaundice	Yes	301	148 (49.2%)	0.098	1.35	0.92	1.96	0.130
	No	620	269 (43.4%)		Ref category			
CNS review	Yes	650	364 (56%)	<0.001	1.68	1.06	2.68	0.028
	No	260	48 (18.5%)		Ref category			
Acid suppression	Yes	471	322 (68.4%)	<0.001	5.18	3.52	7.63	<0.001
	No	418	70 (16.6%)		Ref category			
Dietitian referral*	Yes	416	293 (70.4%)	<0.001	3.43	2.14	5.50	<0.001
	No	420	70 (16.7%)		Ref category			
	Missing	85	54 (63.5%)		3.42	1.37	8.54	0.008
Nutritional supplements prescribed*	Yes	372	266 (71.5%)	<0.001	2.29	1.38	3.80	0.001
	No	458	93 (20.3%)		Ref category			
	Missing	91	58 (63.7%)		1.19	0.48	2.96	0.704
Hospital type	Non surgical	408	166 (40.7%)	<0.001	Ref category			
	Surgical HPB	402	163 (40.5%)		1.45	0.98	2.14	0.065
	Surgical PB	111	88 (79.3%)		2.62	1.37	5.00	0.003

Provider volume (Surgical HPB+PB only)	Low	182	91 (50%)	0.662	
	Mid	145	75 (51.7%)		
	High	167	78 (46.7%)		

PERT - Pancreatic enzyme replacement therapy

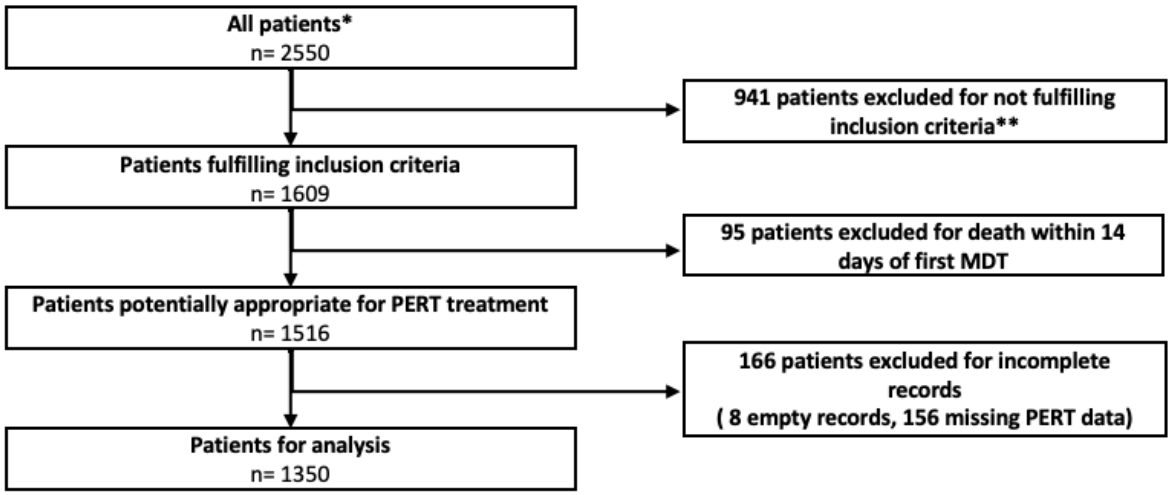
CNS – Clinical Nurse Specialist

HPB - Hepato-pancreato-biliary

PB - Pancreato-biliary

*missing data >2.5%.

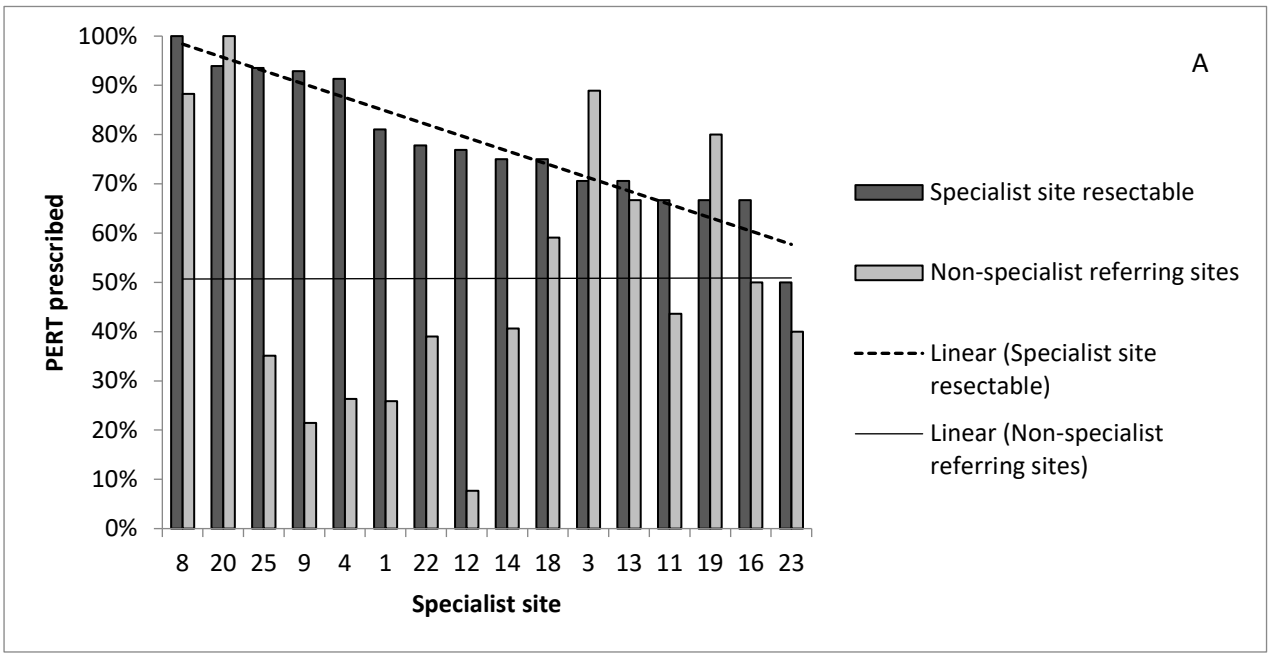
Figure 1. Consort diagram

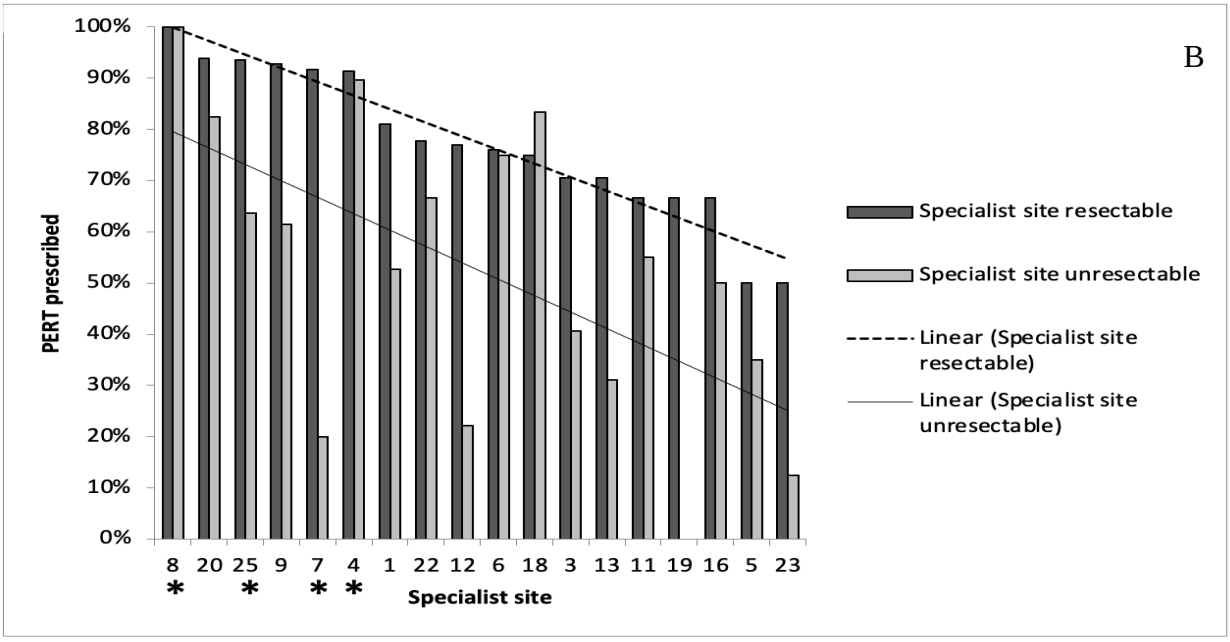


*All patients refers to the total number of patients included in the Ricochet study.

**941 patients did not fulfil the inclusion criteria for this analysis of Ricochet, for example, they had cholangiocarcinoma etc.

Figure 2. Variation in PERT prescribing in pancreatic cancer patients within referral networks and within surgical hospitals.





Graphs showing the patterns of PERT prescribing. Figure A illustrates a lack of correlation between the prescription rates within surgical sites and their network of referring non-surgical sites. Sites are ranked by PERT prescribing compliance in resectable patients with 'lines of best fit' shown for the rate of PERT prescription for resectable patients managed in specialist sites (dotted line) and the rate of PERT prescription in each specialist site's referral network (solid line). Figure B shows the correlation between prescribing for both resectable and unresectable patients in surgical centres. Surgical and non-surgical sites with n<8 cases were excluded.

Supplementary Material 1

Authorship

Writing Group

**denotes joint first author*

*Harvey PR, *McKay SC, Wilkin RJW, Layton GR, Powell-Brett S, Okoth K, Trudgill N, Roberts KJ.

Steering Committee

Baker G, Brom MK, Brown Z, Farrugia A, Haldar D, Harvey PR, Kalisvaart M, Layton GR, Marley A, McKay SC, Pande R, Patel R, Roberts, KJ, Stephenson BTF, Trudgill N, Wilkin RJW.

Regional Leads

Baillie C, Croitoru C, Eddowes PJ, Elshaer M, Farhan-Alanie MM, Laing R, Mann K, Materacki L, Nandi S, Pericleous S, Prasad P, Rinkoff S, Selvaraj E, Shah J, Sheel ARG, Szatmary P, Williams P.

Local Teams

**Local lead consultants*

***Local lead trainees*

Aberdeen Royal Infirmary: *Milburn J,**Bekheit M,**Ghazanfar M, Curry H, Persson P, Rollo A, Thomson R. Addenbrooke's Hospital, Cambridge: *Harper S, *Varghese S,**Collins J,**Stupalkowska W, Afzal Z, Badran A, Barker J, Hakeem A, Kader R, Saji S, Sheikh S, Smith ACD, Stasinos K, Steinitz H. Aintree University Hospital, Liverpool: *Malik H, Burston C, Carrion-Alvarez L. Barnsley District General Hospital: *Shiwani M, Ahmad G, Allen T, Darley E, Patil S. Basingstoke & North Hampshire Hospital: *Brooks C, *Cresswell B, *Welsh F,**Cook C,**Smyth R, Booth R, West M. Birmingham Heartlands Hospital: *King A, *Tucker O,**Phelan L, Burahee A, Devogel C, Javed A, Kay R, Khan S, Leet F, Troth T, Ward A. Borders General Hospital, Melrose: *Young J,**Murray E, Gray T, Johnson R. Bradford Royal Infirmary: *Lockwood S,**Young R, Zhou G. Bristol Royal Infirmary: *Portal J, *Rees J,**Arnold B,**Scroggie D, Abeysekera KWM, Asif A, Hay F, Maccabe T, Pathak S, Robertson H, Sandberg C, Woodland H. Broomfield Hospital: *Charalabopoulos A,**Kordzadeh A. Cheltenham General Hospital: *Anderson J,**Napier D, Hodges P, Jones G, Sheiybani G. Chesterfield Royal Hospital: **Archer T, Khan A, Kirk S, Walker N, Hassam U, Wong I. Churchill Hospital, Headington: *Silva M,**Jones K, Allen J, Abbas SH. City Hospital, Birmingham: **Harborne M, Majid Z. Countess of Chester Hospital: *Eardley N, *Reilly I,**Wadsworth P, Bell C, Holloway K, Stockton W. Croydon University Hospital: *Thomas R,**Williams KJ. Cumberland Infirmary, Carlisle: *Canelo R,**Tay Y, Adnan M. Derriford Hospital, Plymouth: *Aroori S,**Rajaretnam N. Diana Princess of Wales Hospital, Grimsby: *Rekhraj S,**Wilkins A, Nelapatia R, Verebcean M, Braithwaite S. Dumfries & Galloway Royal Infirmary: *Apollos J,**Robertson N. East Surrey Hospital, Redhill: *Belgaumkar A, Brant A, Shahdoost A.

Freeman Hospital, Newcastle: *French JJ, *Sen G,**Thakkar R, Kanwar A, Klaptocz J, Rodham P. Glangwili General Hospital, Carmarthen: *O'Riordan B,**Maharaj G, Davies M. Gloucestershire Royal Hospital: *Higgs S,**Cutting J. Great Western Hospital, Swindon: *Joseph M,**Backhouse L, Butler J, Cooper J, O'nions T. Hinchingbrooke Hospital, Huntingdon: *Shaukat S,**Kumar A, George V, Ingmire J. Huddersfield Royal Infirmary: *Saha A,**Coe P, Noor R. Hull Royal Infirmary: *Lykoudis P,**Elshaer A, Andreou A, Clarke T, Davies O, Rimmer P. James Cook University Hospital, Middlesbrough: *Kanakala V, *Mitra V, Akol G, Burgess M, Elzubier M, Jones R, Majumdar D, Wescott H. John Radcliffe Hospital, Oxford: *Bailey A, Gomez M, Herman O. Kingston Hospital: *Deguara J, **Whitehead-Clarke T, Gorard L, Law R, Leung LY. Luton & Dunstable Hospital: *Whitelaw D, Adil M, Krivan S. Maidstone Hospital: *Waters J,**Fernandes R, Mealey L, Merh R, Okaro A, Shepherd J. Manchester Royal Infirmary: *O'Reilly D, **Pilkington J, Hussain Z, Ingram S, Stott MC. Manor Hospital, Walsall: *Abbott S, Bhamra N, Hirri F, Lee K, Murrell J, Resool S. Mater Hospital, Belfast: *Taylor M, King M. Milton Keynes University Hospital: *Madhotra R,**Ayubi H, Ali J, Chander N, Mckune G, Wothers T. Morriston Hospital, Swansea: *Shingler G,**Mortimer M, Dykes K, Edwards H. New Cross Hospital, Wolverhampton: *Menon S,**Gautham A, Ali I, Anjum R, Brookes M, Wilkinson B. Ninewells Hospital, Dundee: *Tait I, **Noaman I,**Wilson M. Norfolk and Norwich University Hospital: *Mogan S, *Rushbrook S,**Hyde S, Baker S, Hall P, Lucas H, Pease J. North Middlesex University Hospital: *Millar A,**Tariq Z, Blad W, Cunningham M, Hall M, Luthra P. North Tyneside General Hospital, North Shields: *Seymour, K,**Aawsaj Y,**Jones M, Elliott D. Northampton General Hospital: *Finch JG,**Rajjoub Y, Gupta A, Molloy P, Mykoniatis I. Nottingham University Hospitals Trust: **Atallah E, Albraba E, Asimba V, Baxter A, Chin A, Vojtekova K. Peterborough City Hospital: *Ong L,**Modi HN, Muscara F. Pilgrim Hospital, Boston: *Perry M,**Katz C,**Shaban N, Dichmont L,

Dissanayake T, Mostafa W. Princess Alexandra Hospital, Harlow: *Ghosh D,**Hwang S, Bajomo O, Lloyd T, Wye J. Queen Elizabeth Hospital, Bimingham: *Holt A,**Pathanki A,**Townsend S, Babar N, Giovinazzo F, Kennedy L, Kandathil M, King D, Pillai M. Queen Elizabeth University Hospital, Glasgow: *Glen P,**Holroyd D, Drozdzik S, Kourounis G, Thompson, J. Raigmore Hospital: *McNally S,**Thomas I. Royal Blackburn Hospital: *Reddy Y, *Subar D,**Heywood N, Khoo E. Royal Derby Hospital: *Austin A, *Awan A,**Tan H, Kasi M. Royal Devon & Exeter Hospital: *Prasad S,**Baqai M, Abd Alkoddus M, Al-Allaf O, Mitchell K, Mole S, Yoong A. Royal Free Hospital: *Fusai G, Brown S, Bulathsinhala S, Gilliland J, Lykoudis P. Royal Gwent Hospital, Newport: *Boyce T,**Al-Ardah M, Matthews E. Royal Hampshire County Hospital, Winchester: *Wakefield C, Hou D, Smyth R, West M. Royal Infirmary of Edinburgh: *Thomasset S,**Guest R, Cambridge WA, Falconer S, Hughes M, Johnston C, Kung JWC, Lee E, McNally E, Sherif AE, Stutchfield B. Royal Liverpool University Hospital: *Baron RD, *Dunne DFJ,**Jones R, Dickerson LD, Exarchou KE, Knight E, Whelan P. Royal London Hospital: *Hutchins R, *Wilson P, **Phillpotts S, Badrulhisham F ,Dawes A, Derwa Y, Rajagopal S, Ramoutar S, Vaik T. Royal Marsden Hospital: *Bhogal RH, McLaren N, Policastro T. Royal Shrewsbury Hospital: *Butterworth J, *Riera, M,**Ismail A, Ahmed A, Alame R, Alford, K, Banerjee S, Bull C, Kirby G. Royal Stoke University Hospital: *Athwal T, *Hebbar S,**Ishtiaq J,**Kamran U, Abbasi A, Kamarul-bahrin M, Banks A, Khalil A. Royal Surrey County Hospital, Guildford: *Karanjia N,**Trivedi D, Chakravaratty S, Frampton A, Gabriella J, Pinn G. Royal United Hospital, Bath: *Colleypriest B, Betteridge F, Murugiah D, Rossiter A, Yong K. Russells Hall Hospital, Dudley: *Sellahewa C, Chui K, Ehsan A, Fisher N, Iyer S. Salford Royal Hospital: *McMurtry H, Garbutt G. Sandwell General Hospital, West Bromwich: **Mahgoub S, Alleyne L,Harvey J, Johnson K, Richards E. Sherwood Forest Hospitals NHS Foundation Trust: **Palaniyappan N, Bowler C, Inumerable R, Tan H.

Southampton General Hospital: *Abu M,**Giovinazzo F, Suhool A, Talbot T, Westwood J, Zumbo G. Southmead Hospital, Bristol: *Osborne A,**Botes A, Dyer S, Thomas-Jones I, Merker L, Przemioslo R, Roderick M, Valverde J, Zerafa A. St George's Hospital, Tooting: *Barker S, *Wan A,**Lalani R, Barrett C, Kapirial N, McCarthney K, Ramamoorthy R, Yalchin M. St James's University Hospital, Leeds: *Huggett M, *Macutkiewicz C, *Smith A,**Buchanan A, Burke J. University College Hospital, London: Goodchild G, Keane MG, Potts J. University Hospital Coventry and Warwickshire: *Disney B, **McFarlane M, Baker E, Bullock S, Coleman S, Mcardle C, Morgan J, Mozdiak E, Obisesan A, O'Flynn L. University Hospital of Wales, Cardiff: *O'Reilly D,**Mowbray N, de Berker HT. Victoria Hospital, Kirkcaldy: *Driscoll P,**Noaman I. West Suffolk Hospital, Bury St Edmunds: *Alberts JC,**Sadien ID, Webb K. Wishaw General Hospital: *Bryce G,**McCormack K, Jamieson W, Mitchell L. Worcestershire Royal Hospital: *Cheung D,**Hicken B, Abbas N, Kurian A, McFarlane M, Tahir I. Yeovil District Hospital: *Spearman J, Johnston T, Jones C.

Supplementary Table 1. Comparison of cases included with those missing PERT prescription

		PERT completed	Percentage	PERT missing	Percentage
All		1350		161	
Mode of presentation	Emergency	457	33.9	37	23.0
	Elective	891	66.0	124	77.0
	Missing	2	0.1	0	0.0
Age quintile	<63	278	20.6	34	21.1
	63-70	292	21.6	32	19.9
	71-75	290	21.5	26	16.1
	76-81	249	18.4	34	21.1
	>81	241	17.9	35	21.7
	Missing	0	0.0	0	0.0
Sex	Male	698	51.7	74	46.0
	Female	652	48.3	87	54.0
	Missing	0	0.0	0	0.0
Charlson score	<5	368	27.3	44	27.3
	05-Jul	754	55.9	98	60.9
	>7	122	9.0	19	11.8
	Missing	0	0.0	0	0.0
Performance status	0	551	40.8	66	41.0
	1	411	30.4	46	28.6
	2	224	16.6	26	16.1
	>2	142	10.5	15	9.3
	Missing	22	1.6	8	5.0
Resectable	Yes	429	31.8	57	35.4
	No	921	68.2	104	64.6
	Missing	0	0.0	0	0.0
Jaundice at any time	Yes	522	38.7	47	29.2
	No	828	61.3	114	70.8
	Missing	0	0.0	0	0.0
Surgery performed	Resection	157	11.6	13	8.1
	Bypass	45	3.3	1	0.6
	Missing	0	0.0	0	0.0
CNS review	Yes	1022	75.7	66	41.0
	No	312	23.1	11	6.8
	Missing	16	1.2	84	52.2

Acid suppression	Yes	803	59.5	3	1.9
	No	513	38.0	2	1.2
	Missing	34	2.5	156	96.9
Dietitian referral	Yes	701	51.9	4	2.5
	No	512	37.9	2	1.2
	Missing	137	10.1	155	96.3
Nutritional supplements prescribed	Yes	609	45.1	8	5.0
	No	586	43.4	15	9.3
	Missing	155	11.5	138	85.7
Hospital type	Non Surgical	487	36.1	34	21.1
	Surgical HPB	681	50.4	98	60.9
	Surgical PB	182	13.5	29	18.0
	Missing	0	0.0	0	0.0
Provider volume (Surgical HPB and PB hospital only)	Low	236	17.5	21	13.0
	Mid	255	18.9	62	38.5
	High	337	25.0	43	26.7
	Missing	35	2.6	21	13.0

PERT - Pancreatic enzyme replacement therapy

CNS – Clinical Nurse Specialist

HPB - Hepato-pancreato-biliary

PB - Pancreato-biliary

Supplementary Table 2. The characteristics of patients with potentially resectable pancreatic cancer split by resection status and use of neoadjuvant chemotherapy

		Neoadjuvant Chemotherapy			Awaiting Resection			Resection		
		Total	PERT prescribed	P value	Total	PERT prescribed	P value	Total	PERT prescribed	P value
All		91	58 (63.7%)		37	15 (40.5%)		207	188 (90.8%)	
Age quintile	**<63**	24	15 (62.5%)	0.298	14	4 (28.6%)	0.222	62	58 (93.6%)	0.258
	63-70	30	20 (66.7%)		9	2 (22.2%)		60	56 (93.3%)	
	71-75	21	16 (76.2%)		4	3 (75%)		48	44 (91.7%)	
	76-81	14	6 (42.9%)		7	4 (57.1%)		31	25 (80.7%)	
	>81	2	1 (50%)		3	2 (66.7%)		6	5 (83.3%)	
Sex	**Male**	49	31 (63.3%)	0.904	17	9 (52.9%)	0.157	112	105 (93.8%)	0.113
	Female	42	27 (64.3%)		20	6 (30%)		95	83 (87.4%)	
Charlson comorbidity score	**<5**	34	23 (67.7%)	0.57	17	4 (23.5%)	0.107	93	87 (93.6%)	0.263
	5-7	52	33 (63.5%)		17	10 (58.8%)		107	94 (87.9%)	
	>7	5	2 (40.0%)		3	1 (33.3%)		7	7 (100%)	
Performance status	**0**	47	26 (55.3%)	0.186	22	5 (22.7%)	0.014	137	126 (92%)	0.257
	1	27	22 (81.5%)		10	5 (50%)		53	45 (84.9%)	
	2	15	9 (60%)		4	4 (100%)		12	12 (100%)	
	>2	2	1 (50%)		1	1 (100%)		4	4 (100%)	
Jaundice	**Yes**	45	31 (68.9%)	0.184	15	9 (60%)	0.047	117	109 (93.2%)	0.183
	No	46	27 (58.7%)		22	6 (27.3%)		90	79 (87.8%)	
CNS review	**Yes**	78	57 (73.1%)	<0.001	32	15 (46.9%)	0.047	194	177 (91.2%)	0.295
	No	12	1 (8.3%)		5	0 (0%)		11	9 (81.8%)	
Acid suppression	**Yes**	58	49 (84.5%)	<0.001	21	12 (57.1%)	0.018	194	179 (92.3%)	0.005
	No	31	9 (29%)		16	3 (18.8%)		13	9 (69.2%)	
Dietitian referral	**Yes**	60	47 (78.3%)	<0.001	21	13 (65%)	0.002	166	157 (94.6%)	<0.001
	No	22	4 (18.2%)		16	2 (12.5%)		19	10 (52.6%)	
	Missing	9	7 (77.8%)		0	0 (0%)		22	21 (95.5%)	
Nutritional supplement	**Yes**	44	35 (79.6%)	<0.001	14	10 (71.4%)	0.008	145	138 (95.2%)	<0.001
	No	32	11 (34.4%)		21	4 (19.1%)		37	26 (70.3%)	
	Missing	15	12 (80.0%)		2	1 (50.0%)		25	24 (96.0)	
Resection type	**Resection**	X	X		X	X (%)		162	157 (96.9%)	<0.001
	Bypass	X	X		X	X (%)		47	35 (74.5%)	

Hospital type	**Surgical HPB**	47	29 (61.7%)		17	10 (58.8%)	0.099	155	138 (89%)	0.098
	Non surgical	24	12 (50%)	0.04	19	5 (26.3%)		15	13 (86.7%)	
	Surgical PB	17	15 (88.2%)		1	0 (0%)		37	37 (100%)	
Provider volume (HPB + PB only)	**Low**	9	7 (77.8%)	0.84	2	2 (100%)	0.351	38	30 (79%)	0.021
	Mid	15	10 (66.7%)		5	3 (60%)		67	63 (94%)	
	High	39	27 (69.2%)		11	5 (45.5%)		76	71 (93.4%)	

PERT - Pancreatic enzyme replacement therapy

CNS – Clinical Nurse Specialist

HPB - Hepato-pancreato-biliary

PB - Pancreato-biliary

Supplementary Table 3. The characteristics of patients with unresectable pancreatic cancer in non-surgical and surgical sites

		Non-surgical sites			HPB + PB sites		
		Total	PERT prescribed (%)	P value	Total	PERT prescribed (%)	P value
All		408	166 (40.7%)		513	251 (48.9%)	
Mode of presentation	**Emergency**	171	71 (41.5%)	0.771	138	63 (45.7%)	0.354
	Elective	237	95 (40.1%)		374	188 (50.3%)	
Age quintile	**<63**	63	30 (47.6%)	0.002	104	61 (58.7%)	0.011
	63-70	76	39 (51.3%)		97	52 (53.6%)	
	71-75	85	42 (49.4%)		116	60 (51.7%)	
	76-81	81	26 (32.1%)		95	42 (44.2%)	
	>81	103	29 (28.2%)		101	36 (35.6%)	
Sex	**Male**	213	97 (45.5%)	0.037	262	136 (51.9%)	0.168
	Female	195	69 (35.4%)		251	115 (45.8%)	
Charlson comorbidity score	**<5**	80	39 (48.8%)	0.258	129	81 (62.8%)	<0.001
	5-7	228	89 (39.0%)		295	138 (46.8%)	
	>7	100	38 (38.0%)		89	32 (36.0%)	
Performance status	**0**	135	64 (47.4%)	0.005	184	99 (53.8%)	0.034
	1	123	47 (38.2%)		168	93 (55.4%)	
	2	85	40 (47.1%)		83	35 (42.2%)	
	>2	62	14 (22.6%)		61	23 (37.7%)	
Jaundice	**Yes**	156	76 (48.7%)	0.009	145	72 (49.7%)	0.836
	No	252	90 (35.7%)		368	179 (48.6%)	
CNS review	**Yes**	325	142 (43.7%)	0.012	325	222 (68.3%)	0.001
	No	78	22 (28.2%)		182	26 (14.3%)	
Acid suppression	**Yes**	218	127 (58.3%)	<0.001	253	195 (77.1%)	0.001
	No	182	34 (18.7%)		236	36 (15.3%)	
Dietitian referral	**Yes**	191	121 (63.4%)	<0.001	225	172 (76.4%)	<0.001
	No	197	33 (16.8%)		223	37 (16.6%)	
	Missing	20	12 (60.0%)		65	42 (64.6%)	
Nutritional supplements	**Yes**	178	117 (65.7%)	<0.001	194	149 (76.8%)	<0.001
	No	210	41 (19.5%)		248	52 (21.0%)	
	Missing	20	8 (40.0%)		71	50 (70.4%)	
Hospital type	**HPB**	X	X (X%)		402	163 (40.5%)	<0.001
	PB only	X	X (X%)		111	88 (79.3%)	
Provider volume (HPB + PB only)	**Low**	X	X (X%)		182	91 (50%)	0.662
	Mid	X	X (X%)		145	75 (51.7%)	
	High	X	X (X%)		167	78 (46.7%)	