Research Article

Prevalence of symptomatic pancreatic exocrine insufficiency in patients with pancreatic malignancy: nutritional intervention may improve survival.

Lynne McCallum[1][*][Δ], Angela Lamarca[1][*], Juan W Valle[1,2]

[1] Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester M20 4BX, Manchester, United Kingdom
[2] Institute of Cancer Sciences, University of Manchester, Manchester Academic Health Science Centre, Manchester M20 4BX, Manchester, United Kingdom
*Lynne McCallum and Angela Lamarca contributed equally to this work.

[Δ] **Corresponding author**: Lynne McCallum, Medical Oncology Department, The Christie NHS Foundation Trust, Wilmslow Road, M20 4BX, Manchester, UK. Telephone: +44 (0)1614468106; Fax number: +44 (0)1614463468. Email: Lynne.McCallum@christie.nhs.uk.

ABSTRACT

Patients diagnosed with pancreatic cancer (PC) will often present with symptoms affecting their nutritional wellbeing. We aimed to assess the nutritional support provided to patients with PC in an oncology reference centre. We undertook a single-centre retrospective analysis of all consecutive patients (Jan'13 - Jan'14) diagnosed with PC [both pancreatic ductal adenocarcinoma (PDAC) and neuroendocrine tumours (pNETs) were included]. The primary end-point was to assess the prevalence of pancreatic exocrine insufficiency (PEI)-related symptoms/signs and the nutritional support provided. Secondary objectives included analysis of the impact of nutritional intervention on overall survival (OS). A total of 183 patients were eligible; most (78%) of the patients were diagnosed with PDAC and had been referred for palliative chemotherapy (83%). Sixty-three percent of patients (n=115) had symptoms/signs in keeping with PEI (weight loss, abdominal pain and / or diarrhoea). Seventy-nine patients (43%) received nutritional intervention defined as pancreatic enzyme replacement therapy (PERT) (93%), nutritional supplements (4%) or referral to a dietician (4%). Patients who received a nutritional intervention were more likely to receive chemotherapy treatment (65.8% vs. 50%; p-value 0.03). Nutritional intervention was shown to be an independent factor associated with longer survival (10.2 months (95% Confidence Interval (CI) 7.5-13.3) vs. 6.9 months (95% CI 5.5-9.9); Hazard Ratio (HR) 0.6 (95% CI 0.4-0.9), p-value 0.015) when adjusted for other variables in a multivariable analysis. Our data highlight the importance of nutritional assessment and support to all patients diagnosed with PC, particularly due to its potential impact on ability to deliver chemotherapy and its effect on survival.

INTRODUCTION

A pancreatic malignancy poses many nutritional challenges, for the patient, their family and the health care professionals delivering their care (1). Due to the anatomical localization of disease and the important endocrine and exocrine (digestive) regulatory function of the pancreas, patients will often present with systemic symptoms/signs affecting their nutritional wellbeing, which include anorexia (83%), asthenia (86%) and weight loss

(85%) (2). In addition to the impact of these symptoms on quality of life, their presence may impair the patient's performance status (Eastern Cooperative Oncology Group Performance Status score (ECOG-PS) which, in turn, may preclude active treatment options (e.g. receipt of palliative chemotherapy).

When discussing pancreatic malignancy, it is important to define the two main types, namely pancreatic ductal adenocarcinoma (PDAC) and pancreatic neuroendocrine tumours (pNETs). Differences in prognosis and treatment options make the differentiation between them crucial.

The outlook for individuals diagnosed with a PDAC remains poor, with the 1-year survival of this patient group being around 20% and the 5-year survival rate around 3% (3). There are approximately 20% of patients diagnosed with disease amenable to curative surgery; these patients undergo a pancreatic resection followed by adjuvant chemotherapy (with a fluoropyrimidine or gemcitabine) (4, 5); unfortunately, despite surgery and chemotherapy, 80% of patients will develop disease relapse. Good nutritional status before and after surgery is essential; in addition, nutritional stability is a necessity before embarking on adjuvant treatment as it potentially impacts on the completion of adjuvant chemotherapy which, in turn, has been shown to impact on survival (6).

Due to this low percentage of patients diagnosed with potentially resectable disease, most patients will receive treatment (often systemic chemotherapy) with palliative intent. The aim of palliative chemotherapy is to improve quality of life and prolong overall survival (OS). Single-agent gemcitabine has been considered the standard of care for many years, with a median OS of six months in patients receiving treatment (7). Recent chemotherapy combinations have shown improved results, achieving a median OS of 8.5 months (nab-paclitaxel / gemcitabine) (8) and 11 months (5-FU, oxaliplatin and irinotecan combination) (9).

Pancreatic NETs are considered rare tumours (incidence of approximately 1 per 100,000 individuals per year) and represent approximately 3% of all pancreatic primary neoplasms (10, 11). Due partly to improvements in diagnostic methods, the prevalence of pNETs is increasing; these cancers often, but not wholly, present a more indolent malignant behaviour (12, 13). Approximately 90% of pNETs present as non-functioning tumours which can delay the early detection of disease. The remaining 10% are functional tumours characterised by secretion of active peptides, causing a variety of specific hormonal syndromes often leading to an earlier diagnosis (14, 15). Surgery is also the treatment of choice for patients with early-stage disease. In the advanced setting, although chemotherapy has been the cornerstone of treatment for patients with advanced pNETs over many decades (16), emerging targeted therapies such everolimus (17) and sunitinib (18) have changed the management of patients with (well-differentiated) pNETs, achieving median OS around 2 to 3 years even for patients diagnosed with metastatic disease. In addition, patients may be considered for other treatment modalities, such as liver-directed therapy, somatostatin analogues or peptide-receptor radiotherapy.

Although they represent different disease profiles, PDAC and pNET present similar nutritional challenges: pancreatic exocrine insufficiency (PEI) is one such challenge. PEI, described as *"a reduction in pancreatic enzyme activity in the intestinal lumen to a level that is below the threshold required to maintain normal digestion"* (1), leads to mal-digestion, steatorrhoea and malnutrition. It is postulated to be one of the reasons for the high rate of "unfit" (poor performance status) patients diagnosed with a pancreatic malignancy (19). A high prevalence of PEI has been described both in resected (>80% showed evidenced of PEI) and advanced disease patients (92% showed evidence of PEI) and it has been shown to have a detrimental impact on quality of life (20-22). Even though healthcare professionals seem to be aware of the importance of the diagnosis and treatment of PEI in patients who have undergone a pancreatic resection, this aspect is often overlooked in patients diagnosed with advanced disease, where the focus is often on anti-tumour therapy. The under-recognition and under-treatment of PEI in patients with advanced pancreatic malignancy is an on-going issue that needs urgent action (23). Several guidelines for the management of PEI are available (24, 25). Implementation of nutritional intervention (defined as pancreatic exocrine replacement

Table 1: Baseline characteristics of the patients included in this retrospective study

Patient characteristics			Overall		With int.*		With no int**.		P***
			n(183)	%	n(79)	%	n(104)	%	
Gender	Male/Female		87/96	47/53	37/42	47/53	50/54	48/52	0.868
Age at diagnosis (years)	Median (range)		68.3 (16.2-88.9)		68.1 (16.2-87.2)		68.4 (35.6-88.9)		0.713
ECOG-PS (baseline)	0		36	20	11	14	25	24	
	1		79	43	41	52	38	37	
	2		39	21	17	22	22	21	0.151
	3		27	15	10	13	17	16	
	4		2	1	0	0	2	2	
Comorbidities	None		57	31	24	30	33	32	
	Mild		87	48	36	46	51	49	0.862
	Moderate		32	18	16	20	16	15	
	Severe		7	4	3	4	4	4	
Pathology subtype	Adenocarcinoma		142	78	68	86	74	71	
	Neuroendocrine tumours		20	11	6	8	14	13	
		Grade 1	12	60	4	67	8	57	0.116
		Grade 2	8	40	2	33	6	43	
	Other		4	2	1	1	3	3	
	Not biopsied		17	8	4	5	13	13	
Tumour location	Pancreatic head		109	60	61	77	48	46	
	Pancreatic body		49	27	15	19	34	33	<0.001
	Pancreatic tail		25	13	3	4	22	21	
Diabetes when patient was referred to our centre	No		129	71	51	65	78	75	
	Diabetes on oral medication		26	14	10	13	16	15	0.051
	Diabetes on insulin		21	11	12	15	9	9	
	Diabetes on oral medication and insulin		7	4	6	8	1	1	
Stage at diagnosis	Localized (resected)		32	18	19	24	13	13	
	Locally advanced (unresectable)		56	4	20	25	36	35	0.094
	Metastatic		95	52	40	51	55	53	
Referred for consideration of	Adjuvant treatment		31	17	17	22	14	13	0.238
	Palliative treatment		152	83	62	78	90	87	
Further follow-up after the first visit	Yes		130	71	64	81	66	63	0.012
Chemotherapy	Yes		104	57	52	66	52	50	0.032
		Capecitabine monotherapy	8	8	6	12	2	4	
		Gemcitabine monotherapy	37	35	18	34	19	37	
		Gemcitabine and Capecitabine	37	35	18	34	19	37	
		FOLFIRINOX	11	11	3	6	8	15&	0.243
		Gemcitabine + vandetanib/placebo (26)	8	8	6	12	2	4	
		Irinotecan (26)	1	1	1	2	0	0	
		Streptozocin and Capecitabine	2	2	0	0	2	4	

*Patients <u>with</u> nutritional intervention

**Patients <u>with no</u> nutritional intervention

*** P-value for the comparison of baseline characteristics between cohort of patients with and without nutritional intervention. ECOG-PS: Eastern Cooperative Oncology Group Performance Status score.

&This column sums 101 rather that 100% due to rounding.

therapy (PERT), nutritional supplementation or assessment by specialised dietician) is essential for an adequate management of PEI. Such nutritional intervention should be a continuous approach with frequent reassessment of symptoms and dose adjustment according to each individual.

The aim of this study was to assess the prevalence of PEI and the impact of nutritional intervention in an unselected population of patients with pancreatic cancer (either PDAC or pNET).

MATERIAL AND METHODS
We undertook a single-centre retrospective analysis of all consecutive patients diagnosed with a pancreatic malignancy, referred to our institution for oncological assessment between January 2013 and January 2014 (the timeframe was selected in order to provide meaningful follow-up data). Patients were identified from local electronic records. Eligible patients were those with histological, cytological or radiological confirmation of a pancreatic malignancy (both PDAC and pNET patients were included) with at least one clinic appointment. The local audit committee approved this study (CE13/1216).

Baseline symptoms, ECOG-PS, cancer subtype, location and stage, comorbidities and on-going medication data were collected for all patients, with additional special interest placed on PEI symptoms/signs. Baseline weight and albumin (as a surrogate of malnutrition) were collected. Estimation of weight loss since first cancer-related symptoms and our baseline visit was based on patient-provided information collected during the first appointment. Body mass index (BMI) for each patient was calculated using weight (kg) and height (cm). Diagnosis of PEI was assessed by the treating clinician (mainly based on symptoms/signs in keeping with PEI, such as abdominal discomfort, flatulence, steatorrhoea, diarrhoea, weight loss). Implemented nutritional intervention and its duration were collected from case notes. Comorbidity severities were classified according to the Adult Comorbidity Evaluation (ACE)-27 index (26). For patients with a diagnosis of pNET, the grade was specified according to the ENETS / WHO classification (27). Staging was performed according to AJCC 7th Edition (28). Weight loss and serum albumin (which is systematically performed in all patients attending our centre) were monitored

during follow-up; clinician's annotations were reviewed, looking for statements regarding weight loss during follow-up (using the weight at the first appointment as baseline). Chemotherapy treatment and survival data were also collected when available.

The primary end-point of this study was to assess the prevalence of PEI-related symptoms/signs and the nutritional support provided. Secondary objectives included analysis of the impact of the nutritional intervention on OS.

The OS was measured from the date of diagnosis of pancreatic malignancy until the date of death of the patient or censored at the date of last follow-up without death. All patients were followed until discharge from the clinic or death. Time on follow-up was defined as the time from first appointment to date of last follow-up available or death. Student T-test and Chi square tests were employed when appropriate. Pearson correlation test was employed for correlative analyses. Median OS was estimated by the Kaplan-Meier method. Prognostic factors were identified by log-rank test and Cox regression. Multivariable analysis (Cox regression method) was performed, including those variables, which were positive in the univariate analysis (defined as p-value <0.05), and those variables that were previously identified as variable of interest (chemotherapy, stage at diagnosis, nutritional intervention, ECOG-PS and pathologic subtype of pancreatic malignancy). All patients with data available were included in the survival analyses.

The statistical analysis was performed with Stata version 12.0 package. Two-sided significance test with a p-value of <0.05 was considered significant.

RESULTS
A total of 436 patients diagnosed with hepato-pancreato-biliary and neuroendocrine tumours were referred to our centre between January 2013 and January 2014. Of these, 183 patients met the inclusion criteria for this study; the remaining 253 patients were excluded due to not been patients with pancreatic cancer primary tumours. The median time of follow-up was 8.7 months; by the end of the follow-up 75% of the patients had died.

PATIENT DEMOGRAPHICS
The median age at the time of diagnosis of pancreatic malignancy was 68.3 years (range 16.2-

Table 2: Prevalence of weight loss and its severity, together with other PEI symptoms at patients' first visit to our institution

PEI-related symptoms		Overall		Patients with nutritional intervention		Patients with no nutritional intervention	
		n (183)	%	n (79)	%	n (104)	%
Weight loss before attending our department	No	99	54	40	51	59	57
	Yes	84	46	39	49	45	43
	Not specified	46	55	22	56	24	53
	<5%$	16	19	5	13	11	24
	5-10%£	12	14	5	13	7	16
	>10%#	10	12	7	18	3	7
Other PEI symptoms	No	120	66	42	53	78	75
	Yes	63	34	37	47	26	25
	Abdominal pain	45	71	22	59	23	88
	Diarrhoea	18	29	15	41	3	12
BMI baseline	Overweight	64	35	28	35	36	35
	Normal	70	38	36	46	34	33
	Underweight	10	6	3	4	7	7
	Severely underweight	2	1	1	1	1	1
	Unknown	37	22	11	14	26	25

BMI: body mass index. PEI: pancreatic exocrine insuficiency. $ weight loss of <5% between first symptom presentation and first appointment; £ weight loss 5-10% between symptom presentation and first appointment; # weight loss of >10% between symptom presentation and first appointment.

88.9). Most of the patients were diagnosed with PDAC (78%), while only 11% of patients had a diagnosis of pNETs (see **Table 1** for demographic characteristics). Out of the 183 patients included in the study, most of them (83%) were referred for consideration of treatment with a palliative intent; 130 patients had further follow-up appointments, with 104 (57%) receiving chemotherapy. Details of the chemotherapy received by patients are given in **Table 1**.

PANCREATIC EXOCRINE INSUFICIENCY-RELATED SYMPTOMS
Overall, 115 (63%) patients had symptoms/signs in keeping with a diagnosis of PEI. This data is summarised in **Table 2** and **Table 3**. Diagnosis of PEI was based on PEI-related symptoms/signs in all patients (79 out of 79 patients; 100%); no faecal elastase or other screening was performed. Eighty-

four patients (46%) had self-reported weight loss when they were referred to our department: of these, only 38 patients (45%) had the amount of self-reported weight loss quantified within the case notes. Moreover, 63 patients (34%) had other PEI-related symptoms such as abdominal pain (45 patients; 71%) or diarrhoea (18 patients; 29%). The BMI at baseline was normal in 38% of the patients. Median albumin levels at the first appointment were 41 g/L (range 28-51).

NUTRITIONAL INTERVENTION
Overall, 79 patients (43%) received nutritional intervention: PERT (93%), nutritional supplements (4%) or referral to dietician (4%). Demographic characteristics and symptom/sign profile for this subgroup of patients are specified in **Table 1** and **Table 2**. Out of the 79 patients with nutritional intervention, 41 patients (52%) started the

Table 3: Summary of the prevalence of PEI symptoms/signs at the time of the first appointment. PEI: pancreatic exocrine insufficiency.

		Other PEI symptoms		
		Yes	No	Total
Weight loss at first appointment	Yes	32 (18%)	52 (28%)	84 (46%)
	No	31 (17%)	68 (37%)	99 (54%)
Total		63 (35%)	120 (65%)	183 (100%)

nutritional intervention before the referral to our centre; in the remaining 38 patients (48%) the nutritional support was started after being seen in our department.

In the remaining 104 patients (60 of whom had symptoms/signs compatible with PEI (33% of all our study population)); no nutritional intervention was documented at any point. Demographic characteristics and symptom/sign profile for this subgroup of patients are specified in **Table 1** and **Table 2**.

FOLLOW-UP
From the total of 130 patients with further follow-up in our centre, the percentage of patients with no diabetes (71% at baseline) was reduced to 54% at the end of the follow-up. See **Table 4** for more detail. Glucose monitoring was performed in 77% of the patients on follow-up in our institution (64% monthly, 36% less frequently).
According to clinician's notes, 14 patients (11%) had weight loss greater than 10% during follow-up in our institution. However, when serial weights were retrospectively reviewed, only 12 patients (9%) had such a weight loss. Moreover, when cross-referencing these lists of patients, clinicians identified incorrectly patients with weight loss of greater than 10%. The sensitivity shown by the clinicians to identify these patients in the daily practice was 42% (5 out of 12 patients).
By the end of follow-up, the rate of underweight patients increased from 5% to 11%; however, there was no significant drop either in the median weight, or BMI (p-values >0.1; full data not shown). The median percentage weight change during the follow up was -0.9% (loss of 0.9% compared with baseline)

(range -33.1 to +20.9). A significant drop in albumin levels was shown between baseline and the last follow-up albumin levels (mean albumin 41.5 g/L (95% Confidence Interval (CI) 40.7-42.2) (baseline) vs. 37.9.5 g/L (95% CI 36.9-39.1) (end of follow-up); p-value <0.001).
Our series showed a significant correlation (r 0.3; p-value 0.002) between the levels of absolute loss of albumin and the percent of body weight loss during follow-up suggesting that albumin is a good surrogate of weight loss; see **Figure 1** for more detail.

IMPACT OF NUTRITIONAL INTERVENTION ON SURVIVAL AND CHEMOTHERAPY ADMINISTRATION
Patients who received nutritional intervention were more likely to receive chemotherapy treatment (65.8% vs. 50%; univariate p-value 0.03).
The estimated median OS for all patients was 8.7 months (95% CI 6.9-10.7). Survival was longer in the cohort of patients referred for adjuvant treatment (median overall survival not reached at the time of the analysis) when compared with those patients referred for palliative treatment (median OS 6.9 months (95% CI 6-8.3)); differences were statistically significant (p-value <0.001). Variables such as pathologic type of pancreatic cancer (pNETs), stage at diagnosis (localised stage), ECOG-PS (0-1), chemotherapy and nutritional intervention were shown to be independent factors related with longer OS in our series. See **Table 5** for full details of the univariate and multivariable analysis.
As detailed above, receiving nutritional intervention was associated with improved OS: for the cohort of patients with no nutritional intervention, the estimated median survival was 6.9 months (95% CI 5.5-9.9)), compared with 10.2 months (95% CI 7.5-

Table 4: Diabetic status of our cohort at the beginning and the end of the follow-up period.

Diabetes	Baseline		End of follow-up	
	n (183)	%	n (130)	%
No diabetes	129	71	70	54
Rising glucose with no definitive diagnosis of diabetes	0	0	19	15
Diabetes	54	29	36	27
Unknown	0	0	5	4

13.3) in the cohort of patients who had nutritional support (see **Figure 2**). As shown in **Table 5** these differences were statistically significant when corrected for other prognostic factors in the multivariable analysis (Hazard Ratio (HR) 0.6 (95% CI 0.4-0.9), p-value 0.015) such as chemotherapy, showing that both chemotherapy and nutritional intervention were independent prognostic factors (**Figure 3**). In contrast, there were no differences in OS when looking at the time of starting the nutritional intervention: the subgroup of patients who started treatment before being referred to our centre (median OS 10.7 months (95% CI 6.5-19.1)) had similar survival to those who commenced nutritional intervention during the follow-up in our department (median OS 9.3 months (95% CI 7.2-13.3)); p-value 0.5252. Differences in the impact of nutritional intervention between the cohort treated with palliative and adjuvant intent could not be analysed due to a low rate of events in the adjuvant cohort.

DISCUSSION
While many publications have addressed the issue of pancreatic enzyme insufficiency in patients with benign pancreatic diseases (e.g. acute or chronic pancreatitis), this is, to our knowledge, one of the largest series focusing on pancreatic cancer patients only.

There is a widely-accepted view that patients with a pancreatic malignancy will have some degree of weight loss prior to diagnosis (29); a pancreatic malignancy can pose a daunting assault on the patient's nutritional status from the psychological impact of the diagnosis itself through to disease-related factors. However, compared with other aspects of symptomatic care associated with a pancreatic malignancy (obstructive jaundice, vomiting due to gastroparesis or gastric outlet obstruction and pain) patients' nutritional status and wellbeing may be considered "less important" and may be neglected (30, 31). Some authors advocate screening for PEI and subsequent use of PERT in all patients with a pancreatic malignancy regardless of their symptoms/signs or the location of their tumour (32-35).

Our study highlights a number of these aspects: although nearly half of all patients (46%) reported weight loss at the time of initial referral, this was quantified by the attending clinician in a minority (45%) of them. Clinicians and patients are often focused on systemic therapy (chemotherapy) and it is easy to overlook nutritional status. In addition, PEI is often associated with steatorrhoea; in fact this is a late sign of severe insufficiency and diarrhoea and cramping abdominal pain were only present in a minority of patients; weight loss was the commonest feature and one which is easy to quantify. Interventions will usually align with their respective availability; thus in the 43% of patients who did go on to receive nutritional intervention, nearly all (93%) were prescribed PERT; referral to a dietician (not routinely available at out institution) only occurred 4% of the time. Although nutritional supplements are readily available, they were also used in a minority; this may have been sourced by some from their general practitioner.

Some authors highlight the importance of being trained in the assessment and diagnosis of PEI and advocate an early assessment of exocrine function in all patients diagnosed with a pancreatic malignancy (18). In our study no patients were routinely "screened" for PEI; the diagnosis of PEI is considered

Table 5: Univariate and multivariable analysis for factors related with overall survival

Overall survival (COX regression)	Univariate analysis P-value	Multivariable analysis HR (IC 95%)	P-value
Gender	0.220	-	-
Age	0.001	1.01 (0.9-1.04)	0.235
Pancreatic location of the tumour	0.871	-	-
Pathologic subtype	< 0.001		
Neuroendocrine		1 (Ref)	
Adenocarcinoma		15.9 (4.6-54.9)	**< 0.001**
Others		6.6 (1.01-43.5)	**0.048**
Not biopsied		20.7 (5.5-77.8)	**< 0.001**
PEI symptoms/signs	0.002		
No		1 (Ref)	
Yes		1.14 (0.7-1.7)	0.551
Stage	< 0.001		
Localised		1 (Ref)	
Locally advanced		1.6 (0.7-3.6)	0.267
Metastatic		4.5 (2.1-9.6)	**< 0.001**
ECOG-PS	< 0.001		
0-1		1 (Ref)	
≥2		1.6 (1.02-2.7)	**0.040**
Comorbidities	0.588	-	-
Diabetic status at diagnosis	0.603	-	-
Albumin level at the first appointment	0.001	0.9 (0.9-1.04)	0.779
Baseline BMI	0.089	-	-
Nutritional Intervention $	0.141		
No		1 (Ref)	
Yes		0.6 (0.4-0.9)	**0.015**
			Figure 2
Chemotherapy received	0.058		
No		1 (Ref)	
Yes	0.058	0.5 (0.3-0.8)	**0.003**

BMI: body mass index. PEI: pancreatic exocrine insuficiency. ECOG-PS: Eastern Cooperative Oncology Group Performance Status score; HR: hazard ratio; 95% CI: 95% confidence interval. $Nutritional intervention was considered as a variable of interest (See Methods) at the design of the study and therefore was included in the multivariable analysis even though the p-value in the univariate analysis was not statistically significant.

burdensome to perform: the three-day faecal fat quantification (the gold-standard diagnostic tool) is challenging in clinical practice (1). Therefore, other diagnostic techniques such as faecal elastase (36), ^{13}C-mixed breath test (37) or nutritional panel assessment have been proposed (38). However, the most effective method for the diagnosis and monitoring of PEI in patients with pancreatic
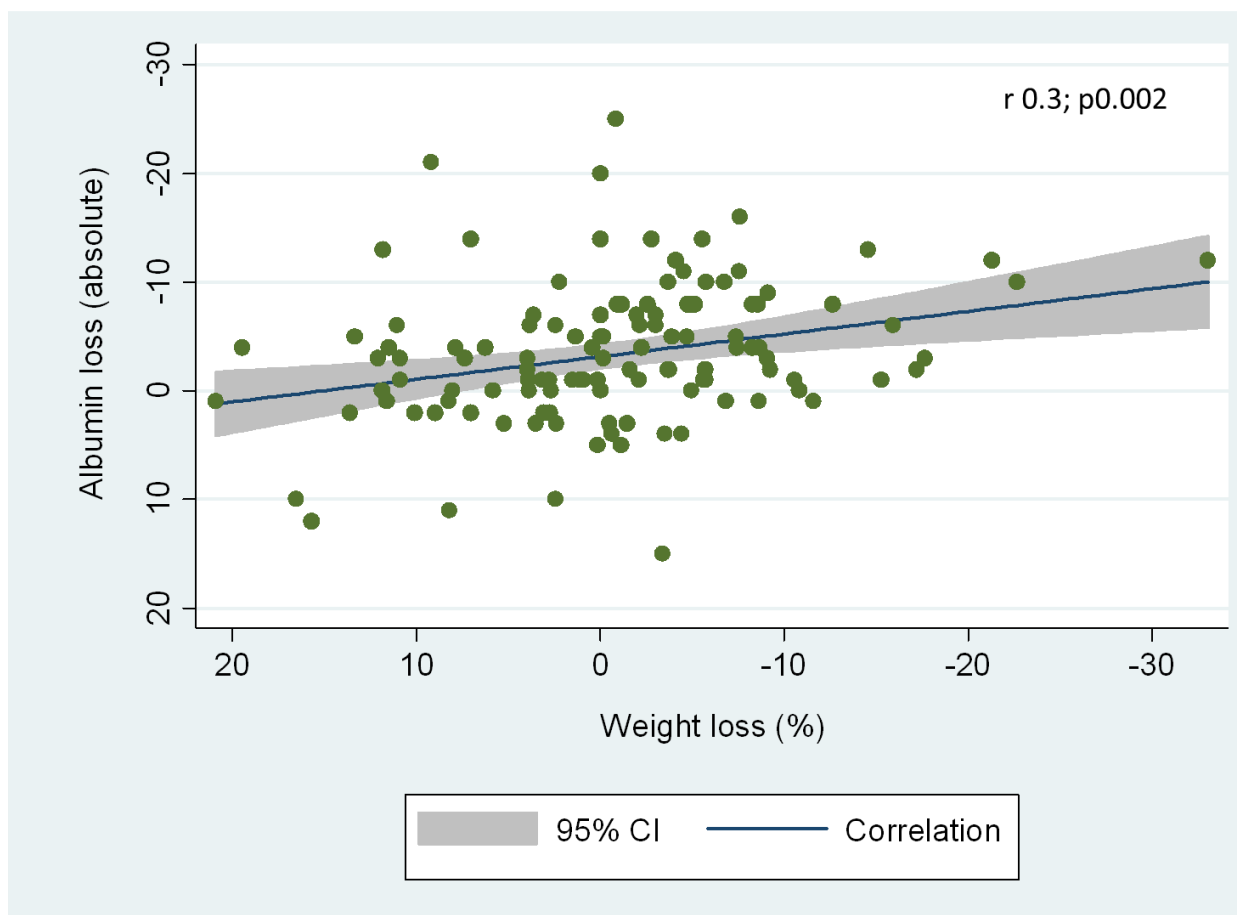
Figure 1: Correlation between albumin drop and weight loss. Our data support a significant correlation, suggesting albumin as a surrogate marker of weight loss.

malignancy remains undefined and is an area for further research.

In our study around 40% of the patients were deemed not fit enough (poor ECOG-PS) for chemotherapy treatment. We showed that patients who received nutritional intervention were more likely to receive active systemic treatment supporting the premise that paying special attention to nutritional wellbeing (not only during oncology follow-up but even prior to patients being referred to oncology services) could potentially expand treatment options for this patient group. Moreover, it may open up additional therapeutic options (e.g. 2nd or 3rd line palliative treatment choices). What is difficult to conclude from our study is what the potential is for improving individual patient's ECOG-PS with specialist nutritional focus earlier in the

disease trajectory. This study suggests that relying on clinicians alone to identify, quantify and treat weight loss may be challenging. In fact, with a sensitivity of only 42%, we have shown that clinicians did not readily identify patients with significant (>10%) weight loss during follow-up, further validating the development of PEI detection "tools" for use in clinical practice.

Albumin may be an objective surrogate biomarker of malnutrition; this is supported by the significant correlation shown in our study between albumin and weight loss. We showed that during the follow-up period there were no statistically significant changes seen in weight loss or BMI; however, decreasing albumin may be a useful biomarker in identification of patients at high risk of weight loss and malnutrition. How early in the process of weight loss
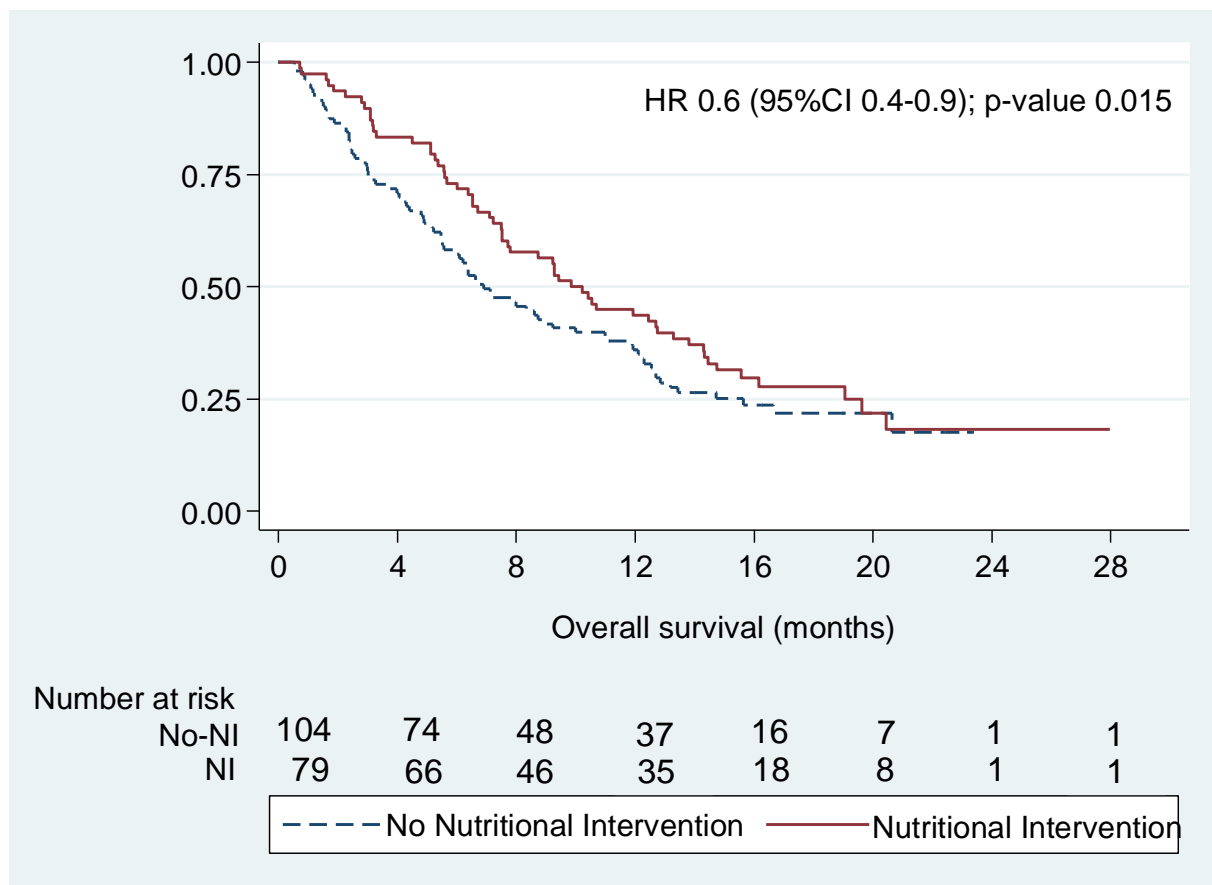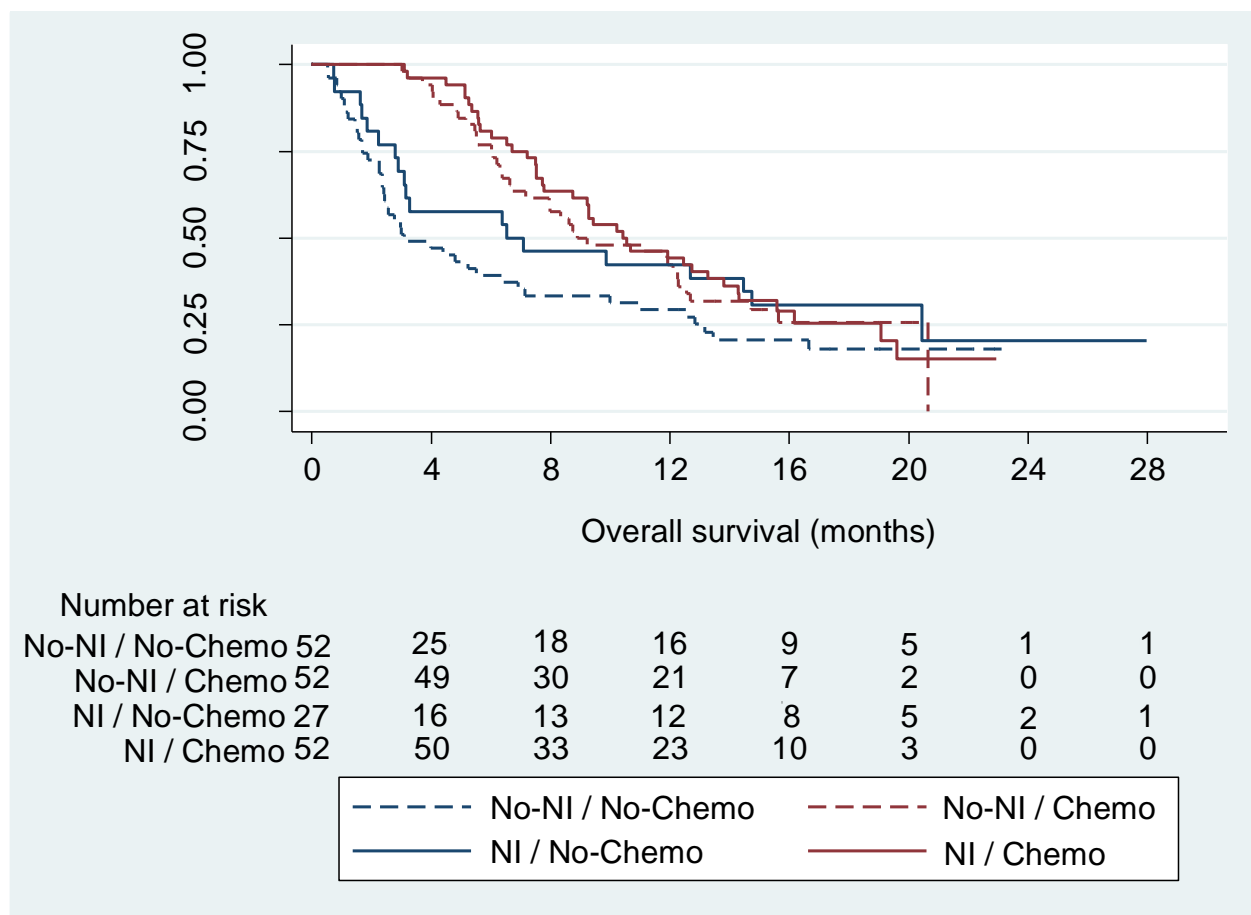
Figure 2: Impact of nutritional intervention on overall survival (Kaplan Meier curve). Reported HR and p-value corresponde to adjusted analysis (multivariable analysis, as summarised in Table 5) NI: Nutritional intervention; No-NI: no nutritional intervention; HR: hazard ratio; 95%: 95% confidence interval

the albumin is useful is not known from our study due to the relatively advanced cancer stage of the majority of patients.

We identified a beneficial impact in OS from patients receiving nutritional intervention, even though our results need to be interpreted carefully due to the multiple biases applicable to any retrospective study (especially selection bias). Moreover, we found that the presence of PEI symptoms/signs *per se* did not impact survival (HR 1.14 (95% CI 0.7-1.7); p-value 0.5), supporting the conclusion that nutritional intervention was not measuring a group of patients with a different natural tumour behaviour. Demographic characteristics comparison between the cohort of patients with and without nutritional intervention showed that PDAC (compared to pNETs) and resected patients (compared to locally advanced patients) had more nutritional support

(**Table 1**). Clinicians appear to pay more attention to these patient populations in regards to nutritional support while locally advanced patients and pNETs remain, probably, underdiagnosed regarding PEI.

A number of limitations apply. This study is a single-centre experience, however, we believe that the data presented is indicative to UK practice and potentially further afield. Publications looking specifically at issues raised in this study are scant; this is most likely due to the poor prognosis of pancreatic cancer, which limits the time to collect meaningful data. However the link between nutritional wellbeing and quality of life is well documented and should not be neglected when providing cancer care for this patient group, regardless of life expectancy (20). Due to the retrospective nature of this study, we do not have prospective evaluation of nutritional wellbeing and

Figure 3: Impact of nutritional intervention (NI) and chemotherapy (Chemo) on overall survival (Kaplan Meier curve). Administration of chemotherapy and nutritional intervention were both independent prognostic factors prolonging survival (see multivariable analysis, Table 5). This graphic shows how nutritional intervention benefitted patients regardless whether they were or not treated with chemotherapy and how chemotherapy prolonged survival regardless whether they received or not nutritional intervention. Estimated median overall survival were as follows: No-NI / No-Chemo 3.1 months (95% CI 2.4-6.9), NI / No-Chemo 7.1 months (2.9-20.4), No-NI / Chemo 8.9 months (6.7-12.3), NI / Chemo 10.4 months (7.8-13.8). Some of these confidence intervals overlap due to small sample size for subgroup analyses, however multivariable analysis confirmed the trend of the data showed in this graphic. 95%CI: 95% confidence interval.

a measure of its influence on the patient and their care-givers. The expected prognostic factors were confirmed in our series (pathological type, stage, ECOG-PS), confirming that our series was representative of the pancreatic cancer population. Limitations of any retrospective analysis apply; the impact of selection bias was minimised by the inclusion of all consecutive patients. First, a retrospective analysis may not be the most suitable design for looking at PEI; prospective studies with specific criteria for definition of PEI are advisable for future studies. Our data relied on recorded information with the bias that this implies (for example, the clear omission of one of the key symptoms of PEI: steatorrhoea, which was mostly recorded as diarrhoea). In addition, dose of PERT was missing for most patients and could therefore not be included within the reported results. Potential reporting bias needs to be acknowledged, mainly due to the weight loss at baseline, which was self-reported by the patients. Other limitations include the lack of a subgroup analysis by

pathological subtype (PDAC and pNETs); this is due to the small number of patients with pNETs and the difficulties in extrapolation of any results that this implies. Finally, diagnosis of PEI was assessed mainly by identification of weight loss and clinical symptoms (some of them unspecific, such as abdominal pain, which very frequent in patients with pancreatic malignancies) which may be considered a weakness since no diagnostic techniques such as faecal elastase or breath test were systematically implemented.

We did not address the impact of nutritional support on patients' ability to tolerate treatment or the dose intensity of chemotherapy achieved; however, this is a worthwhile point to be addressed in future pancreatic cancer studies. We did not find differences with respect to timing of initiation of the nutritional intervention, suggesting that the factor impacting survival was the receipt of nutritional intervention rather than the time this was instituted. This study suggests that the early recognition of weight loss and/or PEI and its treatment presents a valid method of improving outcomes for this patient group; however, from this work there is clear indication that starting nutritional intervention at any point in the patient pathway can, in itself, influence patient outcomes.

Elements from this study have identified points for consideration to improve the patients' nutrition in practice; the under-recognition and under-treatment of PEI in patients with a pancreatic malignancy is an on-going issue that warrants urgent attention. Recommendations from this study are:
➢ Patients should undergo routine PEI assessment
➢ There is a need for clearly-defined diagnostic criteria of PEI
➢ Management protocols should be developed as a guide to clinical staff
➢ Future studies should explore the link between optimal supportive care (including nutritional assessment and management) and reduced morbidity

An essential part of improving care for this patient group is the input of specialist dieticians; dieticians should be considered as essential members of the pancreatic cancer Multidisciplinary Teams (MDTs). It was disappointing that only 4% of our patient group, with a documented nutritional need had access to a dietician (usually a community dietician). This is unsatisfactory however not surprising given that there is generally a lack of dietetic provision in the hospital outpatient setting. It is recognized that all pancreatic cancer patients, regardless of whether they are treated at a specialist (tertiary care) or in secondary care, should have their case reviewed by a dietician and this should be reflected in any pancreatic cancer guidelines (39) there are no similar recommendations for those patients affects by pNET however this study suggests that this group is potentially as affected nutritionally, and certainly with regards to PEI.

CONCLUSIONS
This study highlights the high prevalence of PEI-related symptoms/signs in two-thirds of patients diagnosed with pancreatic malignancies. It also shows that patients are not always adequately managed; with one third of the whole population constituting patients with PEI-related symptoms/signs who did not receive any nutritional support. The fact that patients who received nutritional intervention were more likely to receive life-extending chemotherapy treatment and had a longer survival highlights the importance of our results. We identified that the nutritional wellbeing of this patient group continues to be complex and, in particular, the common nutritional challenge of pancreatic enzyme insufficiency may be overlooked. However, we have demonstrated that with nutritional attention those affected with a pancreatic malignancy are able to undergo more treatment and this, in turn, may favourably influence overall survival. Our findings highlight the importance of a dietician been involved in the care of all pancreatic cancer patients.

Institutional review board statement: The study was reviewed and approved by The Christie NHS Foundation Trust (Manchester, United Kingdom); institutional approval number CE13/1216.

ABBREVIATIONS:
ACE: adult comorbidity evaluation
BMI: body mass index

Chemo: chemotherapy

CI: confidence cnterval

ECOG-PS: Eastern Cooperative Oncology Group performance status score

HR: hazard ratio

MDTs: multidisciplinary teams

NI: nutritional intervention

OS: overall survival

PC: pancreatic cancer

PDAC: pancreatic ductal adenocarcinoma

PEI: pancreatic exocrine insufficiency

PERT: pancreatic enzyme replacement therapy

pNETs: pancreatic neuroendocrine tumours

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