Investigating the impact of body composition and nutritional intervention strategies in pancreatic cancer

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Declaration

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Summary

Pancreatic cancer remains a significant oncological challenge. Unlike other cancers which have seen improving outcomes in recent years, this challenging cancer has seen minimal meaningful change in five- year survival rates over the last 30 years. Curative resection is only available as a treatment strategy for the minority of patients (<20%). Despite increasing recognition that pancreatic cancer is a systemic disease, conventional chemotherapy agents have limited effect in the treatment of the disease, and any potential benefit is often outweighed by unmanageable treatment toxicity and /or side effects. The consequential physical decline and weight loss associated with pancreatic cancer is debilitating for patients, and often assumed to be an inevitable component of the disease and associated cachexia. The application of CT as a tool for body composition assessment allows opportunistic in-depth evaluation of body composition parameters without subjecting patients to additional investigations. The emergence of neoadjuvant therapy for BRPC provides a discrete window of opportunity to evaluate a nutritional intervention, delivered concurrently, without necessitating treatment delay or modification.

The dual aims of this thesis were to investigate the impact of body composition and nutritional intervention strategies in pancreatic cancer.

Chapter 5, a systematic review and meta-analysis, examined the prevalence of sarcopenia in patients with resectable and borderline

resectable cancer. The findings of this meta-analysis demonstrated that 40% of patients have low muscle indices at diagnosis.

A retrospective cohort study (Chapter 6) evaluated the impact of sarcopenia on post-operative morbidity and mortality in patients with resectable pancreatic cancer and demonstrated similar prevalence. Low muscle indices were associated with increased post-operative morbidity and reduced overall survival. Chapter 7 evaluated the impact of sarcopenia and low muscle quality in patients who underwent neoadjuvant therapy and demonstrated similar negative prognostic effects.

The final study (Chapter 8) evaluated the feasibility of a multi-modal nutritional intervention study designed for patients undergoing neoadjuvant chemotherapy for pancreatic cancer. Systematic nutritional evaluation of these patients highlighted a high prevalence of cancer cachexia and pancreatic insufficiency. The primary outcome found that the study was feasible as designed for most patients, with many opting to continue the intervention beyond the 12-week study period. Weight maintenance and improvement of functional parameters were achieved by most participants

The findings of this thesis highlight the need to incorporate the impact of body composition into future pancreatic cancer research. These results add to our understanding of the impact of malnutrition in pancreatic cancer and have treatment implications for patients undergoing neoadjuvant chemotherapy.

Permission

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Oonagh Mary Griffin

Date

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Dedication

This thesis is dedicated to the memory of my late father, Jimmy Griffin.

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Abbreviations

5FU	Fluorouracil
AHBPA	American-Hepato-Pancreato-Biliary Association
ASCO	American Association of Clinical Oncology
ATP	Adenosine triphosphate
BIA	Bio-impedance analysis
BMI	Body mass index
BRPC	Borderline resectable pancreatic cancer
BSA	body surface area
CA	Coeliac Axis
CA19-9	Carbohydrate antigen 19-9
CAP	College of American Pathologists
CFA	Co-efficient of fat absorption
CHA	Common hepatic artery
CI	Confidence interval
Cm	Centimetre
CRP	C-reactive protein
CT	computed tomography
DEXA	Dual-energy x-ray absorptiometry
DGE	Delayed gastric emptying
DHA	Docosahexaenoic acid
DM	Diabetes mellitus
DP	Distal pancreatectomy
DP & S	Distal pancreatectomy & splenectomy
EN	Enteral Nutrition
EPA	Eicosapentanoic acid
ERCP	Endoscopic retrograde cholangio-pancreatography
ESPEN	European Society for Clinical Nutrition and Metabolism
EUS	Endoscopic ultrasonography
FE-1	Faecal elastase
FFM	Fat-free mass
FM	Fat mass
G	Gram
GF	Growth Factor
HbA1C	Glycated haemoglobin
HGS	Hand grip strength
Hk	Hexokinase
HPB	Hepatobiliary
HR	Hazard ratio

HRB	Health Research Board
HU	Hounsfield Unit
IGF-1	Insulin growth factor
IL-6	Interleukin 6
IMAT	Intra-muscular adipose tissue
IPAQ	International physical activity questionnaire
ISGPS	International Study Group for Pancreatic Surgery
IU	International Units
IVC	inferior vena cava (IVC)
KG	Kilogram
L3	3rd lumbar vertabrae
L4	4th lumbar vertabrae
L5	5th lumbar vertabrae
LAPC	Locally advanced pancreatic cancer
LSMI	Lumbar skeletal muscle index
M	Metre
MA	Muscle attenuation
MDA	MD Anderson
MDT	Multi-disciplinary team
MET	Metabolic equivalent
mGPS	modified Glasgow prognostic score
Mm	Millimetre
MRCP	Magnetic resonance cholangiopancreatography (MRCP)
MRI	Magnetic resonance imaging
N	Sample size
N-3 PUFA	Omega -3 Polyunsaturated fatty acids
NCCN	National Comprehensive Cancer Network
ng	Nanogram
NSCPC	National surgical centre for pancreatic cancer
OHA	Oral hypoglycaemic agents
OR	Odds ratio
PanIN	pancreatic intraepithelial neoplasia
PD	Pancreaticoduodenectomy
PDAC	Pancreatic adenocarcinoma
PEI	Pancreatic exocrine insufficiency (PEI
PERT	Pancreatic enzyme replacement therapy
pg	Picogram
PN	Parenteral nutrition
POPF	Post-operative pancreatic fistula
POPH	Post-operative pancreatic haemorrhage

PPPD	Pylorus preserving pancreaticoduodenectomy
PV	Portal vein
QOL	Quality of life
R/BRPC	Resectable/borderline resectable pancreatic cancer
R0	Complete macroscopic resection
REE	Resting energy expenditure
RR	Relative risk
SARMS	Selective androgen receptor molecules
SAT	Subcutaneous tissue
SM	Skeletal muscle
SMA	Superior mesenteric artery
SMI	Skeletal muscle index
SMV	Superior mesenteric vein
SSAT	Society for Surgery of the Alimentary Tract
SSO	Society of Surgical Oncology
SVPH	St Vincent's Private Hospital
SVUH	St Vincent's University Hospital
TAMA	Total abdominal muscle area
TEE	Total energy expenditure
TNF	Tumour- necrosis factor
TNF-α	Tumour- necrosis factor alpha
TP	Total pancreatectomy
TUG	Timed-Up and Go
U	Unit
UK	United Kingdom
US	United States
VAT	Visceral adipose tissue

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Chapter 1 Pancreatic cancer

Pancreatic adenocarcinoma (PDAC), while often described a rare or neglected cancer, is the fourth cause of cancer-related mortality in the US and Europe (1). The 5-year survival rate remains less than 10%, with minimal improvements observed in the treatment of the disease over the last 20 years (2). Curative resection is only available as a treatment strategy for the minority of patients (<20%), and the risk of recurrence remains significant. The insidious nature of the disease and vagueness of associated symptoms mean that most patients present locally advanced or metastatic disease at the time of diagnosis, excluding safe or complete surgical excision of the disease. Despite increasing recognition that pancreatic cancer is a systemic disease, conventional chemotherapy agents have limited effect in the treatment of the disease, and any potential benefit is often outweighed by unmanageable treatment toxicity and /or side effects. For many patients, the advanced nature of the disease at diagnosis will limit their treatment options to supportive and palliative care. Patient performance status and clinical condition often deteriorates rapidly, resulting in a sense of nihilism outside of specialist centres. The average life expectancy for patients diagnosed in the UK is limited to 3-6 months (3).

1.1 Risk factors for the development of PDAC

Pancreatic cancer typically presents in the seventh decade of life, with most patients developing pancreatic cancer aged 65 and above. Cigarette smoking is thought to be the most important modifiable risk factor for the development of pancreatic cancer (4). Multiple PDAC case control studies show that smokers have twice the risk of developing the disease than non-smokers (4). Smoking is also implicated in the pathogenesis of pancreatitis. The chronic inflammation associated with chronic pancreatitis is thought to contribute to the initiation of pre-malignant pancreatic lesions and their progression to PDAC, and metastatic spread. Longstanding diabetes mellitus (DM), both types 1 and 2, have also been shown to double the risk of developing pancreatic cancer. Newly diagnosed, unstable or brittle DM in the older adult may be an early sign of PDAC, and patients may have prolonged hyperglycaemia and insulin resistance which has limited response to oral hypoglycaemic agents (OHA) and exogenous insulin therapy. Insulin resistance is also observed in patients with obesity and excessive abdominal adiposity which are both implicated as risk factors for the development of PDAC. Obesity (body mass index (BMI) ≥ 30 kg/m^2) has been shown to increase the risk of developing PDAC; a meta-analysis of 23 prospective cohort studies reported a 10% higher risk associated with a 5 kg/m^2 increase in adult BMI (RR 1.1,1.07-1.14) (5). Abdominal adiposity, defined by a high waist hip ratio, was shown to increase relative risk of developing PDAC by 1.34-1.71(6). Increased visceral adiposity is characterised by chronic inflammation and insulin

resistance, both of which support the pro-inflammatory conditions which are necessary for tumour genesis and progression.

A familial history of pancreatic cancer affects up to 10% of patients with PDAC, and for these high-risk individuals, early detection and screening is crucial to detect premalignant lesions. The International Cancer of the Pancreas Screening guidelines suggested individuals with at least two blood relatives with the disease, where at least one affected first- degree relative should be considered for screening (7). Genetic alterations implicated in familial PDAC include BRCA2, p16, cationic trypsinogen, and serine/threonine kinase 11 genes. Familial syndromes with characteristic mutations include Peutz-Jegher Syndrome, melanoma-pancreatic-cancer - syndrome, familial adenomatous polyposis and hereditary breast and ovarian cancer (6). In patients with a known genetic alteration or familial syndrome, screening should occur in those with at least one first degree relative diagnosed with PDAC (with the exception of those with Peutz-Jegher Syndrome who should be routinely screened)(7).For an individual with three or more affected first-degree relatives, their risk of developing pancreatic cancer is increased by an estimated 32-fold.

1.2 Pathogenesis of PDAC

Adenocarcinomas comprise the majority of pancreatic cancers, with PDAC accounting for 90% of cancer types. PDAC typically develops from precursor lesions known as pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasms (IPMNs) and/ or mucinous cystic neoplasms. These are initially graded histologically as low- or high-grade dysplasia, with high-grade dysplasia considered carcinoma in situ.

Pancreatic carcinogenesis is characterised by accumulation of cancer-promoting mutations, primarily the activation of the KRAS2 oncogene, and inactivation of tumour suppressor genes CDKN2A and TP53 (8). KRAS is the most common mutation in pancreatic cancer, occurring in 90% of patients (9). Mutated KRAS genes produce RAS proteins. While RAS proteins are normally responsible for cell signalling to control growth, this mutation leads to continual activation of cell proliferation and survival pathways, promoting pancreatic cancer development. Inactivation of CDKN2A, which is responsible for the production of tumour suppressor proteins p16 and p14, is seen in 95% of pancreatic cancers. When mutations are present in TP53, cells are capable of bypassing checkpoints which normally control DNA damage, leading to propagation of aberrant cell lines. SMAD4 inactivation is a late event observed in 50-60% of cases and may be characteristic of more aggressive disease. As these mutations develop, high grade dysplasia gives rise to invasive carcinoma. A complex series of signalling cascades involving pro-inflammatory cytokines,

facilitates pancreatic cancer cell proliferation and migration. Dysbiosis may play a role in this; higher levels of *Porphyromonas gingivalis,* the main micro-organism involved in periodontal disease, have been implicated in the development of PDAC (10, 11). It is thought that periodontal disease is linked to carcinogenesis due to an abnormal inflammatory response, rather than by having a direct mutagenic effect (10, 12). A protective microenvironment composed of a dense collagenous stroma forms which encapsulates the developing tumour, creating a hypoxic and hypo-vascular environment that continues to promote tumour growth but which limits penetration of tumour by systemic chemotherapy agents. In addition, emerging evidence suggest that pancreatic tumours contain an average of 63 genetic alterations. This heterogeneity partially explains the resistance of pancreatic cancer to chemotherapy.

1.3 Clinical presentation and diagnosis.

Presenting symptoms of pancreatic cancer depend on the location of the tumour, and are often non-specific in nature; nausea, early satiety, weight loss, diarrhoea and steattorhoea. Tumours in the head of the pancreas may cause biliary obstruction, with the resulting jaundice allowing earlier detection and diagnosis compared to tumours located in the body and/or tail of the gland where the most common symptom is epigastric pain. This pain, which radiates to the back, is caused by compression of the coeliac, splanchnic and mesenteric plexi. Cancers of the body and tail tend to

present later in the disease trajectory, when metastatic disease has already developed. Irrespective of tumour site, weight loss is a prominent feature of PDAC, with cachexia-induced muscle wasting frequently described as a hallmark feature of the disease. The nutritional implications of PDAC are discussed in further detail in Chapter 2.

Diagnosis of pancreatic cancer is largely reliant on imaging, with a pancreas protocol computed tomography (CT) utilising both non-contrast-enhanced, and late arterial plus portal venous phases after contrast injection and reconstruction deemed the modality of choice. Magnetic resonance imaging (MRI) may be used in patients with renal impairment where contrast administration required for CT visualisation is prohibited. MRI allows characterisation of indeterminate liver lesions detected by CT, and magnetic resonance cholangiopancreatography (MRCP) is valuable for the diagnosis and assessment of pancreatic cystic lesions.

Endoscopic ultrasonography (EUS) is used in tertiary centres where operator expertise allows and provides an additional assessment of small lesions which may not be fully characterised on CT. EUS also provides an opportunity for tumour biopsy via fine-needle aspiration, allowing histological confirmation of disease which is essential in patients requiring neo-adjuvant treatment. Endoscopic retrograde cholangio-pancreatography (ERCP) is used for endoscopic bile duct brushing and biliary stent placement in patients with unresectable or metastatic disease.

Carbohydrate antigen 19-9 (CA19-9), a sialylated Lewis antigen, is often elevated in PDAC, and has a diagnostic sensitivity and specificity in symptomatic patients of 80% and 82-90% respectively. Levels may be falsely elevated in patients with pancreatitis, obstructive jaundice and DM, limiting the use of CA19-9 as a screening tool for PDAC.

1.4 Treatment of pancreatic cancer.

The treatment and management of pancreatic cancer depend on the extent of the disease at the time of presentation. Surgery is limited to those with localised disease without contact with any of the nearby critical vascular structures. More frequently, patients present with more locally advanced or metastatic disease. The most prominent definitions of pancreatic cancer resectability are (a) the joint consensus guidelines of the American-Hepato-Pancreato-Biliary Association (AHPBA), the Society of Surgical Oncology (SSO), and the Society for Surgery of the Alimentary Tract (SSAT); and (b) the MD Anderson Classification (Table 1.1)(13).

Table 1. 1 The AHPBA/SSO/SSAT Classification and the MD Anderson Classification defining resectability

AHPBA/SSO/SSAT Classification				**MD Anderson Classification**		
Localisation	Potentially Resectable	Borderline Resectable	Locally advanced	Potentially resectable	Borderline resectable	Locally advanced
SMV/PV	No abutment[a] or encasement[b]	Abutment, encasement, or occlusion	Not reconstructible	Abutment or encasement without occlusion	Short-segment occlusion	Not reconstructible
SMA	No abutment or encasement	Abutment	Encasement	No abutment or encasement	Abutment	Encasement
CHA	No abutment or encasement	Abutment or short-segment	Long-segment encasement	No abutment or encasement	Abutment or short-segment encasement	Long-segment encasement
Coeliac Trunk	No abutment or encasement	No abutment or encasement	Abutment	No abutment or encasement	Abutment	Encasement

SMV, superiormesenteric vein; PV, portal vein; SMA, superior mesenteric artery; CHA, common hepatic artery
a < 180° of vascular circumference; b > 180° of vascular circumference

(Adapted with permission from (13))

The AHPBA/SSO/SSAT guidelines form the basis of the National Comprehensive Cancer Network (NCCN) Guidelines which have been endorsed by the International Study Group for Pancreatic Surgery (ISGPS)(14), (Table 1.2) and have been adopted by our centre. Less than 20% of patients present with resectable disease, characterised by the absence of any involvement with any of the following structures, assessed on cross-sectional imaging; the coeliac axis (CA), superior mesenteric artery (SMA), superior mesenteric vein (SMV) and/or portal vein (PV).

Surgical treatment options are limited for patients with borderline resectable (BRPC) or locally advanced disease (LAPC) due to the increased likelihood of incomplete tumour clearance, and positive resection margins. There is increasing recognition that these patients often have distant occult micro-metastases, requiring systemic treatment to control and treat their disease. Similarly, the high rates of metastatic recurrence within a relatively short time following surgery for seemingly resectable disease highlight the limitations of current staging modalities in identifying aggressive tumour biology.

Table 1. 2 NCCN Guidelines Version 1.2019 Pancreatic Adenocarcinoma

Resectability Status	Arterial	Venous
Resectable	No arterial tumour contact (coeliac axis (CA), superior mesenteric artery (SMA), or common hepatic artery (CHA).	No tumour contact with superior mesenteric vein (SMV) or portal vein (PV) or ≤ 180° contact without vein contour irregularity
Borderline Resectable	Pancreatic head/uncinate process: Solid tumour contact with CHA without extension to CA or hepatic artery bifurcation allowing for safe and complete resection and reconstruction Solid tumour contact with the SMA ≤180° Solid tumour contact with the variant arterial anatomy and the presence and degree of tumour contact should be noted if present, as it may affect surgical planning. Pancreatic body/tail Solid tumour contact with CA of ≤180° Solid tumour contact with the CA >180 without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby allowing an Appleby procedure	Solid tumour contact with the SMV or PV >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with the suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. Solid tumour contact with the inferior vena cava (IVC)
Unresectable	Distant metastasis (including non-regional lymph node metastasis) Head/uncinate process: Solid tumour contact with SMA >180° Solid tumour contact with the CA >180° Body and tail: Solid tumour contact of >180° with the SMA or CA Solid tumour contact with the CA and aortic involvement	Head/uncinate process: Unreconstructible SMV/PV due to tumour involvement or occlusion (can be due to tumour or bland thrombus) Contact with most proximal draining jejunal branch into SMV Body and tail: Unreconstructible SMV/PV due to tumour involvement or occlusion (can be due to tumour or bland thrombus)

(adapted from (15))

1.4.1 Surgery

The goal of surgical resection of pancreatic cancer is to achieve complete macroscopic resection with clear margins on pathological examination(R0). A pancreaticoduodenectomy (PD), which includes resection of the gallbladder, bile duct, head of the pancreas and peri-pancreatic lymph nodes, is the standard approach for a tumour located in the head of the pancreas. This may be performed as an open, laparoscopic and more recently robotic procedure, and may involve an antrectomy (Classic Whipple or Radical Pancreaticoduodenectomy – Figure 1.1) or preservation of the pylorus (pylorus preserving pancreaticoduodenectomy (PPPD) – Figure 1.2). Where the tumour is located in the neck or body of the gland, a distal pancreatectomy is indicated, alongside a splenectomy if the splenic vessels are sacrificed during the procedure (Figure 1.3).

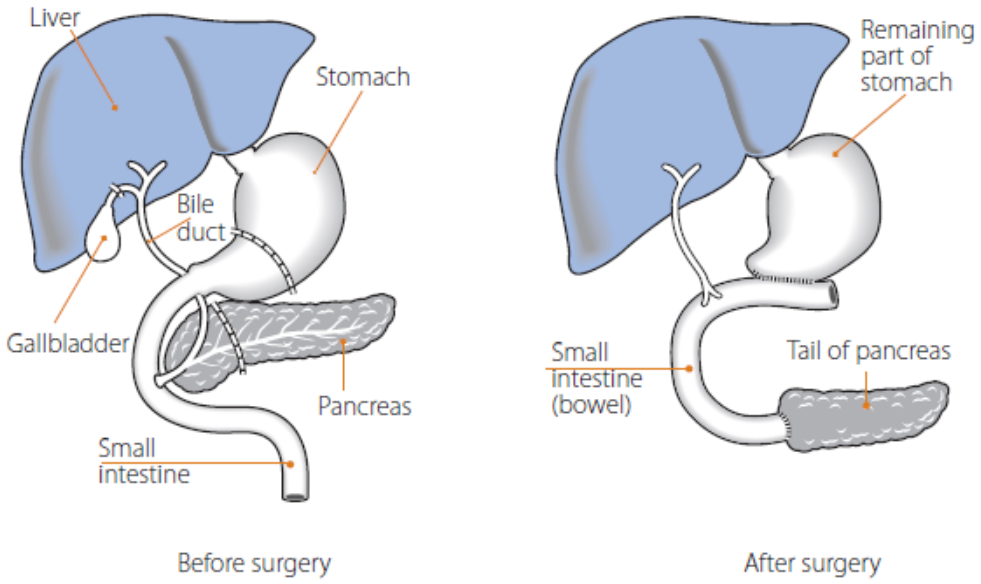


Figure 1. 1 Pancreaticoduodenectomy (Classic Whipple's Procedure)

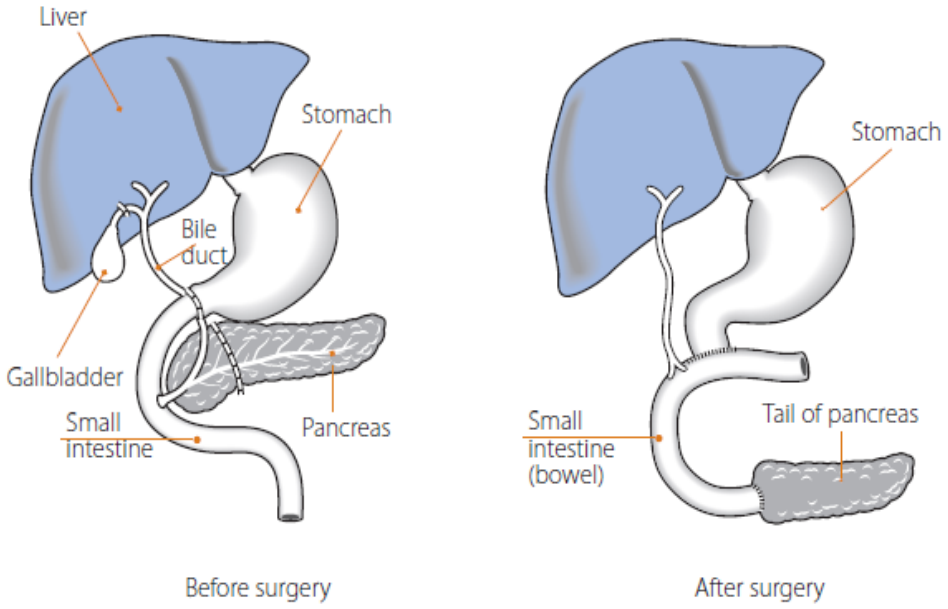


Figure 1. 2 Pylorus -Preserving Pancreaticoduodenectomy

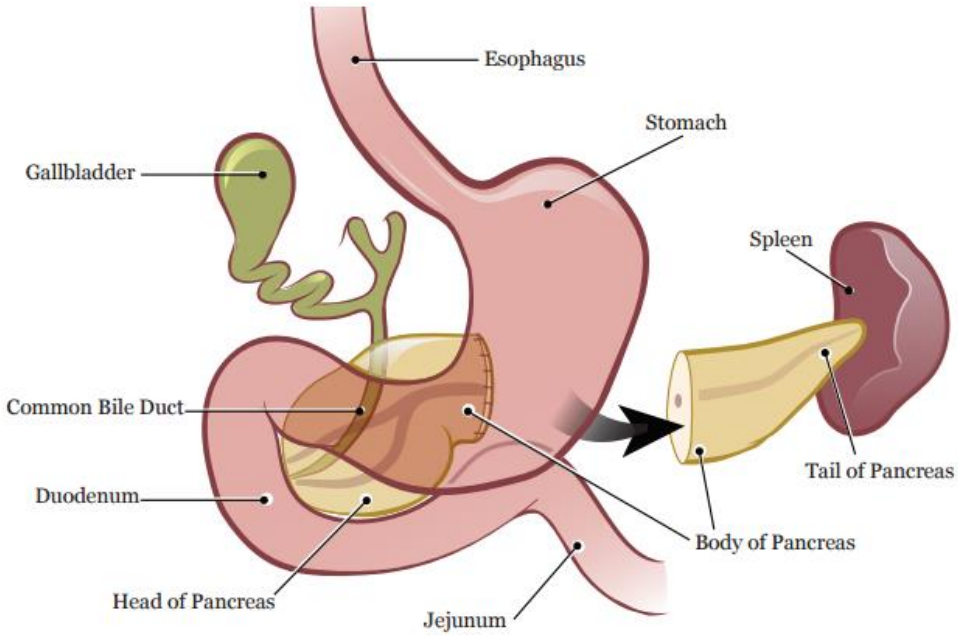


Figure 1. 3 Distal Pancreatectomy and Splenectomy

Pancreatic surgery is associated with a significant risk of post-operative morbidity and mortality, and the improvement of post-operative outcomes have been studied extensively in recent decades. Centralisation of pancreatic cancer surgery to high-volume, tertiary level academic centres across Europe has shown a reduction in post-operative mortality and complications, improved overall survival and, in some cases, an increase in the number of patients being offered surgery for their disease (16). These improvements are due to both surgeon volume and skill, and the specialist multidisciplinary infrastructure present in large academic centres. Recent work has shown that the ability to rescue patients who endure post-

operative complications, rather than the incidence of major complications, was an important predictor of post-operative mortality rates (17).

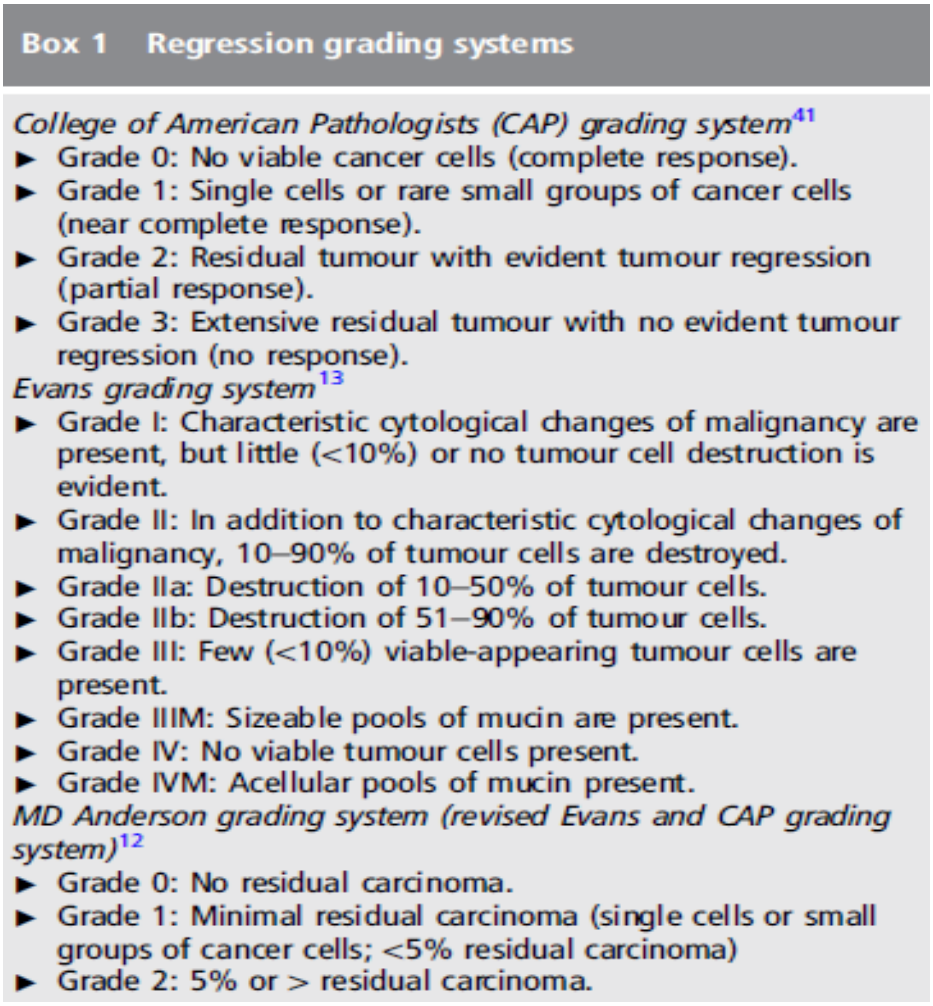
The ISGPS has developed a number of consensus definitions for the identification and classification of common post-operative complications which occur after pancreatic surgery, and are associated with prolonged hospital stay, critical care readmissions, and the need for emergency surgical exploration (outlined in further detail in Chapter 5). Delayed gastric emptying (DGE) has been reported in approximately 15% of patients following PD, impairing oral intake and necessitating prolonged hospital admission for enteral nutrition (EN) and/or parenteral nutrition (PN) (18). Post-operative pancreatic fistula (POPF), when severe, carries the most significant risk of procedure-related mortality following PD, and often requires radiological drainage as well as supportive care (19). Post-operative pancreatic haemorrhage (POPH) can occur early (< 24 hours of surgery) or late (>24 hours post procedure), and most frequently results from bleeding from the gastroduodenal artery stump (20). Other complications include biliary anastomotic breakdown, strictures, chyle leaks (21), pancreatitis, abscesses and portal/superior mesenteric vein thrombosis. Necessary adjuvant treatment may need to be postponed or even abandoned in the context of significant post-operative morbidity, with post-operative recovery taking up to 6 months following surgery.

1.4.2 Chemotherapy and/or chemoradiotherapy

Neoadjuvant therapy, in the form of chemotherapy and/or chemoradiotherapy, is recommended by the NCCN for all patients with BRPC. Tissue diagnosis is necessary prior to commencing treatment, and patient fitness and performance status are key to agent selection, once histological diagnosis has been confirmed. FOLFIRINOX combination therapy, consisting of 5 FU/leucovorin plus oxaliplatin and irinotecan has been shown to allow complete (R0) resection in up to 64% of patients with BRPC (22). A recent systematic review and meta-analysis evaluating the impact of neoadjuvant treatment in PDAC included over 5,000 patients and reported R0 resection rates of 23%- 60%, dependent on initial disease staging, on an intention-to-treat basis (23). However, a pragmatic observational cohort study from Verona recently suggested that these data may be optimistic; in 680 patients treated between 2013 and 2015, predominantly with FOLIFIRINOX or gemcitabine combined with albumin-bound paclitaxel, only 15.1% of patients achieved resection (24% BRPC, 9% LAPC) (24). While FOLFIRINOX has been shown to be superior to gemcitabine-based chemotherapy regimens in achieving resectability in patients with LAPC (25), patient performance status often prohibits its use in clinical practice. More recently gemcitabine combined with albumin-bound Paclitaxel has emerged as a therapeutic option in the neoadjuvant setting for both BRPC and LAPC, largely due to improved toxicity profile compared to FOLFIRINOX, and on the basis of data supporting its efficacy as a palliative therapy in patients with metastatic disease.

Many centres have adopted neoadjuvant treatment for patients with resectable disease, reasoning that it allows identification of patients who have rapid disease progression due to adverse tumour biology, avoiding surgery in patients where resection is unlikely to confer any benefit. While no randomised controlled trials to date have conferred a survival benefit for neoadjuvant therapy for PDAC, several non-randomised studies have reported median survival times ranging from 15 to 35 months (13). Difficulty in accrual is a common feature across studies, despite multicentre design, with most terminating early before the primary endpoint (most often survival) is reached. Reasons given for this include the frequent finding of unexpected metastatic disease at the time of surgery, questioning the original disease staging (26), and declining performance status during the study period, limiting the delivery of the trial regimen being evaluated. Despite the limited evidence to date, the NCCN recommends either FOLFIRINOX or gemcitabine with albumin- bound paclitaxel, followed by chemoradiation in the neoadjuvant setting(15). In clinical practice the duration of radiotherapy largely depends on the patient's response to chemotherapy. Where tumour bulk has decreased, short course (30 Gray delivered over 10 fractions) is recommended, while long course (50.4 Gray over 28 fractions) is given where limited response, persistent vascular involvement, or stable disease is seen. Where the patient has a known BRCAA1/2 or PALB 2 mutation, FOLFIRINOX or gemcitabine combined with Cisplatin is preferred.

The NCCN encourages participation in clinical trials by all patients and recommends treatment delivery is at least co-ordinated through a high-volume centre. Where patients achieve resectability following neoadjuvant therapy, a number of regression grading systems are used to assess response to treatment (Evans, the College of American Pathologists (CAP), and the MD Anderson (MDA) grading systems) Figure 1.4 (27). Concordance between the three most common grading systems has been shown to be poor(27). As a consequence of this poor concordance the pathologists in our centre utilise both the Evans and CAP systems when assessing and reporting the impact of preoperative therapy on pathology on resected pancreatic cancer specimens.



Box 1 Regression grading systems

College of American Pathologists (CAP) grading system[41]

- Grade 0: No viable cancer cells (complete response).
- Grade 1: Single cells or rare small groups of cancer cells (near complete response).
- Grade 2: Residual tumour with evident tumour regression (partial response).
- Grade 3: Extensive residual tumour with no evident tumour regression (no response).

Evans grading system[13]

- Grade I: Characteristic cytological changes of malignancy are present, but little (<10%) or no tumour cell destruction is evident.
- Grade II: In addition to characteristic cytological changes of malignancy, 10–90% of tumour cells are destroyed.
- Grade IIa: Destruction of 10–50% of tumour cells.
- Grade IIb: Destruction of 51–90% of tumour cells.
- Grade III: Few (<10%) viable-appearing tumour cells are present.
- Grade IIIM: Sizeable pools of mucin are present.
- Grade IV: No viable tumour cells present.
- Grade IVM: Acellular pools of mucin present.

MD Anderson grading system (revised Evans and CAP grading system)[12]

- Grade 0: No residual carcinoma.
- Grade 1: Minimal residual carcinoma (single cells or small groups of cancer cells; <5% residual carcinoma)
- Grade 2: 5% or > residual carcinoma.

Figure 1. 4 Regression grading in neoadjuvant treated pancreatic cancer

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Adjuvant chemotherapy is recommended for most patients following pancreatic resection, chemoradiotherapy may be recommended for patients who did not receive radiotherapy as part of a neoadjuvant regimen or who present with microscopically positive margins at the time of surgery. The CONKO-001 trial was the first to demonstrate the benefits of adjuvant therapy in pancreatic cancer with the addition of single agent gemcitabine

improving both progression free- and overall survival compared to observation alone (28). The American Association of Clinical Oncology (ASCO) recommends that patients should ideally commence treatment within 8 weeks of surgery (29), however evidence from the ESPAC–3 trial suggests that delaying treatment to allow adequate recovery from surgery up until 12 weeks is safe as long as the patients receives the full course (6 cycles) of treatment (30).

Currently ASCO recommend that patients who did not receive pre-operative therapy should be considered for modified FOLFIRINOX in the adjuvant setting (31). This recommendation follows the findings of a recent multicentre randomised trial, PRODIGE 24/CCTG PA.6) across France and Canada (32), and concur with recent NCCN recommendations (33). Researchers compared adjuvant modified FOLFIRINOX (mFOLFIRINOX) (with the bolus of 5 FU omitted) with gemcitabine in patients who had a successful R0 resection, were aged less than 80 years and good performance status (ECOG 0/1) (32). Nearly 500 patients were randomised to receive either 12 cycles of mFOLFIRINOX given every 14 days, or 6 cycles of gemcitabine given day 1, 8 and 15 over 28 days. Significantly longer survival was seen in the patients who received mFOLFIRINOX (median survival 54.4 months compared to 33.6 months). Despite a higher incidence of grade 3 or 4 toxicities in the patients who received mFOLFIRINOX, the median survival observed is the longest ever reported to date, suggesting that, where patient performance status allows,

it should be considered as the new standard of care for patient receiving adjuvant chemotherapy for pancreatic cancer.

Performance status and significant post-operative complications remain limiting factors to the delivery of chemotherapy in the adjuvant setting for pancreatic cancer. A recent Dutch study highlighted that one-third of patients did not receive chemotherapy following resection (34). Where there are concerns about excessive toxicity or difficulties with tolerance either gemcitabine in combination with capecitabine where performance status allows, or monotherapy using gemcitabine are also recommended as potential adjuvant therapy by ASCO (31). Gemcitabine combined with capecitabine in the adjuvant setting was shown to improve median survival in the ESPAC-4 trial compared to single agent gemcitabine, with the combined regimen considered to have a tolerable adverse effect profile (35). Recent secondary analysis of this patient cohort has shown no difference in progression free survival rates, or the location of disease recurrence, with the authors concluding that pancreatic cancer is a systemic disease which warrants effective systemic therapy (36).

ASCO currently recommends either FOLFIRINOX or Gemcitabine with albumin-bound Paclitaxel for patients with metastatic disease, if their performance status and underlying medical history allows(37). Both FOLFIRINOX and gemcitabine combined with albumin-bound paclitaxel have been shown to improve overall survival for patients with metastatic pancreatic cancer when compared to gemicitabine alone (38, 39). The

evidence for patients with locally advanced, unresectable disease is less clear however. While chemotherapy and or chemoradiotherapy may be considered, ASCO does not promote the use of one regimen over another (40). For both cohorts, goals of care, patient preferences, psychological status, symptom burden and support systems should guide decisions for treatment (37, 40), and referral to palliative care should be made at initial consultation. Patients will frequently require the placement of a biliary stent to relieve obstructive jaundice prior to commencing treatment and may also require palliative bypass surgery or duodenal stent placement to deal with gastric outlet obstruction.

1.5 Conclusion and future directions

The impact of regionalisation of pancreatic cancer surgery over the last decade has led to improved outcomes for patients with resectable pancreatic cancer(16). The advent of FOLFIRINOX and gemcitabine with albumin- bound paclitaxel has allowed improved survival for patients following resection (32), and in those with metastatic disease (38, 39). The role of neoadjuvant therapy has emerged as an important focus for future study, with initial data suggesting that it may allow improved resectability prospects for patients with BRPC (22).

Recent progress with genomic sequencing has identified specific molecular subtypes of PDAC (36), suggesting opportunities for therapeutic

targets (36, 41). Earlier this year NCCN recommended germline testing for all patients with pancreatic cancer, due to potential familial and therapeutic implications on an individual patient basis. Molecular profiling of all patients with pancreatic cancer has also been recommended by NCCN as it may allow enhanced therapeutic options which may not be evident without profiling, and they argue that is may be crucial to improving disease outcome (33).

The lack of research funding compared to other cancers, along with poor accrual to previous randomised controlled trials, has limited progress in the treatment of PDAC (3, 13). While there have been considerable attempts to target tumour– related factors, little attention has been paid to the impact of PDAC on the host's nutritional and functional capacity, and digestive function (further discussed in chapter 2). Despite performance status frequently being the deciding factor for treatment decision-making, few formal, objective measurements are made as part of patient assessment. Failure to address malnutrition and functional decline in pancreatic cancer will both limit the translation of successful research findings into clinical practice and delay future evaluation of new therapies.

Chapter 2 Nutrition and PDAC

2.1 Weight loss and PDAC

Unintentional weight loss is a prominent feature in pancreatic cancer; over 80% of patients report weight loss at the time of their diagnosis, with more than one third experiencing weight loss in excess of 10% of their initial body weight (42). It is thought to affect up to half of patients with early stage disease (43), and continued, persistent weight loss during treatment has been shown to be an adverse prognostic factor (44), impacting both overall survival and patient-reported quality of life (45).Progressive and intractable weight loss has been described as one of the most distressing and intractable features of PDAC (46). Despite this, the occurrence and extent of weight loss may be missed or under-reported; patients with pancreatic cancer are increasingly presenting with a normal BMI despite experiencing significant weight loss. delaying diagnosis and treatment.

Weight loss and malnutrition in pancreatic cancer is caused by a number of factors, which often occur in combination, including anorexia, cancer cachexia, pancreatic exocrine insufficiency, obstructive jaundice and gastric outlet obstruction. For many patients these will be further amplified by treatment-related side effects.

Table 2. 1 Aetiology of Malnutrition in Pancreatic Cancer

Inadequate nutritional intake	**Maldigestion/Malabsorption**	**Impaired utilisation of nutrients**
Anorexia	Pancreatic Exocrine insufficiency	Cancer Cachexia and inflammation
Pain	Biliary obstruction	Type 3c/Pancreaticogenic / Secondary Diabetes
Early satiety, nausea & vomiting	Post-operative anatomy and physiological changes	Vitamin and mineral deficiency
Psychological distress and anxiety		Refeeding syndrome
Treatment side effects		
Increased nutritional requirements e.g. sepsis		

2.2 Impact of PDAC on nutrient metabolism

Nutrients in the form of carbohydrates, amino acids and lipids are used by cells to maintain energy balance, assist in detoxification, and support biosynthesis. Pancreatic cancer cells rewire these intermediary metabolic pathways to support different energetic and biosynthetic demands compared to normal cells (47), with most of this re-programming driven by mutations in the oncogene KRAS (48). Oncogenic KRAS signalling promotes extracellular glucose avidity and capture via upregulation of the glucose transport (GLUT-1) and hexokinase (HK) pathways respectively (49). Glucose is a principle metabolic and biosynthetic nutrient, which when used by normal cells is completely oxidised to carbon dioxide in the mitochondria to produce ATP. In contrast to normal cells, cancer cells predominantly use glucose-derived carbon for the biosynthesis of ribose, glycosylation precursors, amino acids and lipids (50). Downstream of HK, mutant KRAS also activates expression of glycolytic enzymes. Oncogenic KRAS is implicated in the increased entry of glucose derived carbon into the pentose phosphate pathway, the predominant pathway by which proliferating cells make ribose- 5-phosphate for DNA and RNA synthesis (47).

The PDAC tumour environment is a source of intense physical and oxidative stress, with the resulting pressure leading to vascular collapse and tumour hypo-perfusion. To deal with the resultant hypo-vascular and nutrient-deprived microenvironment (51), PDAC cells activate pathways

which enable recycling of intra-cellular nutrients (through elevated basal macroautophagy), allow access to non-traditional extracellular nutrients by scavenging extracellular space (RAS-mediated macropinosome formation), and engage in metabolic cross-talk with non-malignant cells in the tumour micro-environment (evolved cross-feeding mechanisms where metabolites from one population can be used to fuel growth of another) (51-53) (Figure 2.1). These adaptive nutrient acquisition pathways essentially allow PDAC to thrive in an environment where hypoxia and hypo-perfusion are limiting factors to the successful delivery of drug therapies.

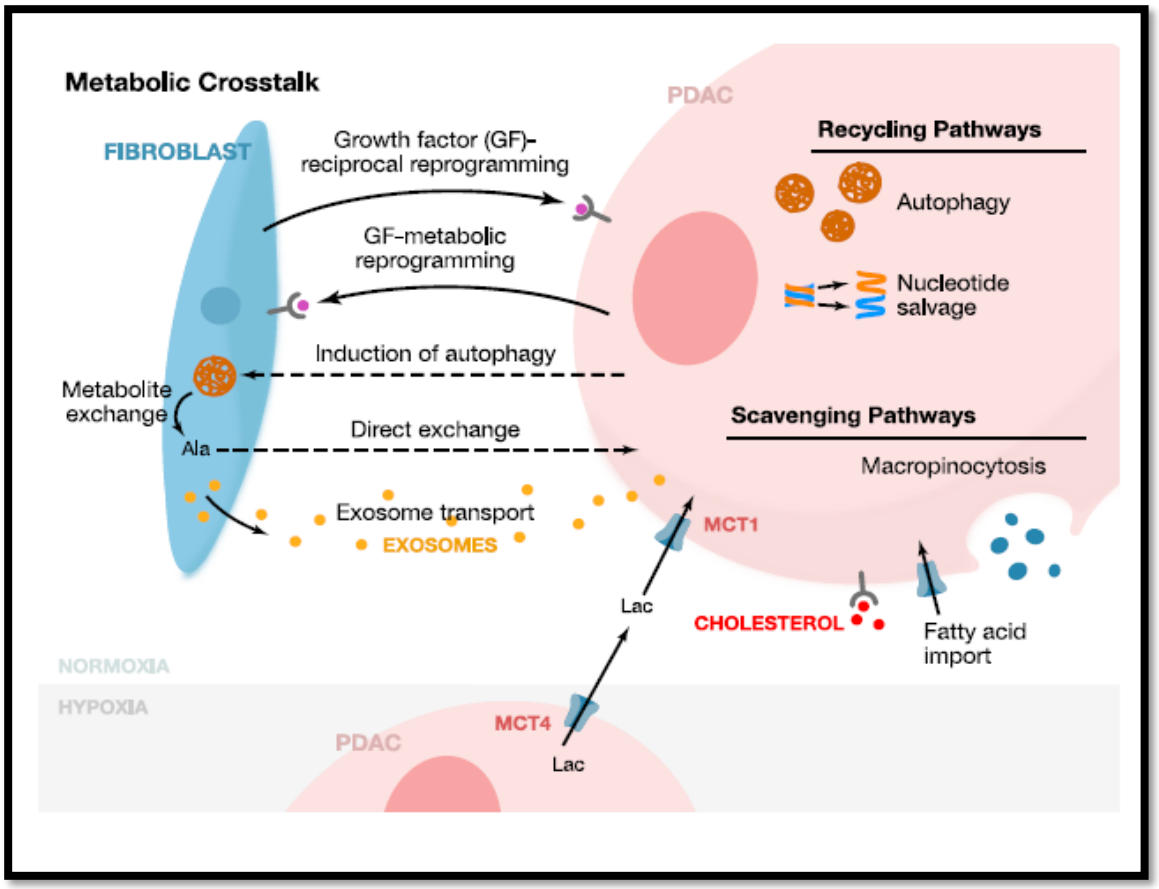

Figure 2. 1 Methods of nutrient acquisition utilised by PDAC

(Reprinted with permission (47))

Increased glucose oxidation, protein turnover and lipolysis are widely observed metabolic disturbances in patients with cancer cachexia (54). Carbohydrate metabolism is altered in patients with cancer cachexia, and is characterised by insulin resistance, glucose intolerance, and gluconeogenesis from amino acids and lactate (55) Muscle protein metabolism is disrupted, with increased catabolism, and a blunted anabolic response to muscle protein synthesis (56). Tumours may also cause

increased mobilisation and oxidation of lipids, resulting in increased energy expenditure and inefficient futile browning of adipose tissue in an attempt to release energy (57).Despite the resultant increase in resting energy expenditure (REE) associated with cancer- induced inflammation and cachexia, declining physical activity levels limit any increase in total energy expenditure (TEE) (58, 59). Estimation of REE using predictive equations is difficult in clinical practice, even if body composition is measured (60).

The European Society for Clinical Nutrition and Metabolism (ESPEN) recommend a daily energy provision of 25-30 calories/kg body weight/ day for cancer patients, in line with healthy individuals (61), reasoning that overfeeding may aggravate metabolic derangements without increasing body weight or body composition. With regards to protein intake, ESPEN advocates for at 1-1.5g protein/kg body weight/day, highlighting old age, inactivity and systemic inflammation associated anabolic resistance necessitating a higher protein intake to stimulate muscle protein synthesis.

2.2 Pancreatic exocrine insufficiency

Pancreatic exocrine insufficiency (PEI), a functional limitation of pancreatic enzyme secretion (62), is a common complication of PDAC which results in malabsorption and malnutrition, and affects 80-90% of patients. PEI is more likely when the tumour is encroaching on the duodenum, post pancreatic surgery, and in head of pancreas lesions with pancreatic duct obstruction. Pancreatic atrophy secondary to tumour-induced main pancreatic duct obstruction and pancreatic fibrosis can lead to PEI prior to pancreatic resection. In addition resection of exocrine tissue, extensive denervation following lymph node dissection, and surgically altered anatomy contribute further to PEI following surgery (63). PEI negatively impacts quality of life (64), and is associated with poor survival (65). Patients with PEI experience significant, often debilitating, diarrhoea, steattorhoea, post prandial abdominal pain and nausea. Awareness of PEI by many clinicians is poor outside of high volume HPB centres(66) and symptoms are often overlooked or accepted as unavoidable, treatment-related side effects. Failure to treat PEI with pancreatic enzyme replacement therapy (PERT) causes detrimental effects on nutritional status (67) and quality of life (68).

2.2.1 Diagnosing PEI

Confirmation of PEI in clinical practice usually relies on faecal elastase (FE-1) testing despite its limitations as an indirect test of pancreatic function, and limited sensitivity detecting mild insufficiency (69). While quantification of the co-efficient of fat malabsorption (CFA) is deemed the gold standard method for the diagnosis of fat maldigestion, it has several disadvantages which limit its use in clinical practice (62). Patients must consume a standard diet containing 100g fat daily for a five-day period, and have their stool collected for at least three days for analysis. Patient compliance and laboratory processing are significant barriers for the use of this test. A mixed 13C-triglyceride (MTG) breath test was developed as an alternative to CFA for the diagnosis of PEI (70). This test measures carbon dioxide expiration after the ingestion of a test meal containing a labelled substrate which requires intraduodenal hydrolysis by pancreatic enzymes before hepatic metabolism (62). Both CFA and MTG breath test assess fat malabsorption, but cannot quantify the influence of extra-pancreatic factors (71). The advantages and disadvantages of pancreatic function tests are shown in table 2.1.

Table 2. 2 Advantages and disadvantages of available pancreatic function tests

Pancreatic Function Test	Advantages	Disadvantages
Faecal fat excretion/ Coefficient of fat absorption	• Clinically Relevant • It detects other cause of maldigestion • Useful for monitoring response to treatment	• Very cumbersome and difficult to perform • Not widely available
Faecal elastase-1	• Very easy to preform • Widely available	• Does not detect other causes of maldigestion • Not useful for monitoring response to treatment • Low correlation with faecal fat excretion in operated patients •
13C-labeled mixed triglyceride breath test	• Theoretically detects other causes of maldigestion • Probably useful for monitoring response to treatment	• Not properly validated • Expensive • Scarcely available • Time-consuming

(reprinted with permission from (72))

An international expert consensus group commissioned by the Spanish Association of Pancreatology concluded that pancreatic function tests have limited clinical value post pancreatic surgery, and an empirical trial of PERT should be initiated where there is any suspicion of PEI (72).

2.2.2 Incidence of PEI in pancreatic cancer

Sikkens and colleagues prospectively evaluated the incidence of PEI in a cohort of patients with unresectable pancreatic cancer located in the head of the gland. Two-thirds of patients had PEI at diagnosis (on the basis of FE-1 assessment), increasing to 89% on re-evaluation two months later (73). Two other studies examined the incidence of PEI in patients with unresectable pancreatic cancer. Perez et al reported an incidence of 75% utilising the 72-hour faecal fat test (74), while Partelli detected PEI in 60% of patients using FE-1, reporting that low FE-1 correlated with reduced survival(65).

A recent review of the incidence of PEI in patients undergoing pancreatic surgery found that 42-45% of patients undergoing PD had PEI pre-operatively, whilst the post-operative incidence was 56-98% after PD, and 12-80% following distal and central pancreatectomy (71). The choice of pancreatic anastomosis (i.e pancreaticojejunostomy versus pancreaticogastrostomy) appears to have no effect (63). Despite this high incidence, a recent study evaluating 4,554 UK patients with pancreatic cancer found that only one-fifth of patients had been prescribed PERT(75), and observed that patients who did receive PERT had a significantly longer survival.

2.2.3 Treatment of PEI

Management of PEI involves replacing the lack of adequate pancreatic enzymes, which should be used to maintain weight and improve the

symptoms of maldigestion (76). PERT should begin when PEI is diagnosed or when there is the clinical suspicion for PEI(72). Therapy should start with doses of 40,000 – 50,000 units of lipase with meals, and 10,000 – 25,000 units with every snack (77, 78). Dose escalation and inhibition of gastric acid secretion may be warranted according to response; in patients who fail to respond to treatment, extra-pancreatic causes should be evaluated (77) (Figure 2.2).

The first study to evaluate the impact of PERT as a treatment for PEI was the randomised double-blind trial led by Bruno et al, which studied patients with unresectable pancreatic cancer. PERT (median daily dose ~200,000 IU daily) was shown to prevent weight loss, increase body weight, improve dietary energy and protein intakes, and reduce fat malabsorption (67). More recently, PERT use was shown to improve survival in patients post resection in a post -hoc subgroup analysis, particularly in those with pancreatic ductal dilation (main pancreatic duct > 3mm) (79). A prospective, placebo- controlled study evaluating the impact of PERT on weight loss in patients with unresectable pancreatic cancer failed to show any benefit(80); however, these patients were prescribed a fixed dose of PERT with no dose adjustment for individualised portion size or food type.

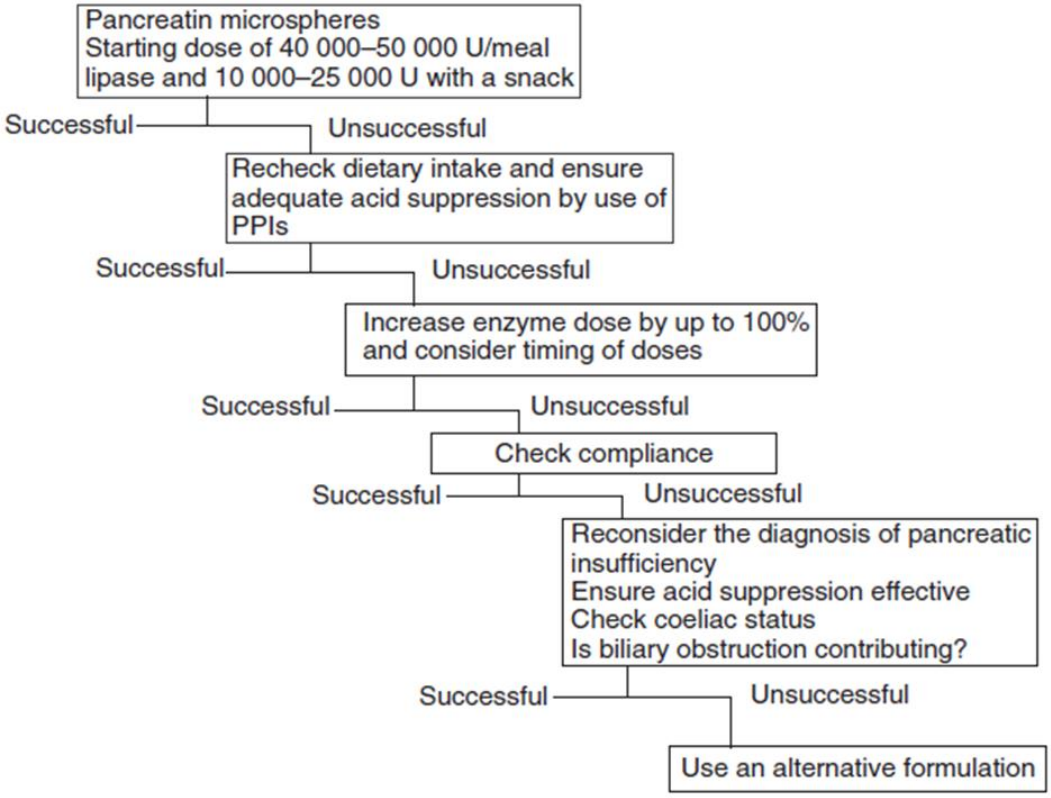

Figure 2. 2 Suggested algorithm for the treatment of PEI

(reprinted with permission from (77))

Dietary intake and nutritional status should be monitored regularly to maximise patient compliance and specialist dietetic assessment sought in patients with underlying malnutrition (71) (table 2.2). Untreated, PEI may lead to multiple micronutrient deficiencies and weight loss, and the consequential gastrointestinal symptoms may be mis-attributed to food intolerances, leading to unnecessary restrictions. Pancreatic cancer patients with PEI warrant routine specialist dietetic assessment and intervention to address the significant symptom burden associated with

PEI to improve patient quality of life and to maximise performance status(46).

Table 2. 3 Summary of dietetic assessment parameters in pancreatic cancer

(adapted for pancreatic cancer from (71))

Anthropometric	Biochemical	Clinical symptoms	Dietary	Medical history	Medication
Weight changes assessed in context to energy intake **Function assessment** • Grip strength • Chair stand test • Exercise tolerance/fatigue **Body Composition Assessment**	**Fat soluble vitamin status** • Vitamin A • Vitamin D • Vitamin E • Prothrombin time (or other markers of vitamin K status if available) **Electrolytes** • Magnesium • Potassium **Bone profile** • Calcium • Phosphate • Parathyroid hormone **Anaemia screen** • Iron studies • Ferritin and C-reactive protein • Vitamin B12 • Folate • Haemoglobin **Other micronutrients** • Zinc & Selenium **Glycaemic control** • Random Glucose • Oral Glucose Tolerance Test • Glycosolated haemoglobin (HbA1c) • Incidence of hypoglycaemia in a known diabetic	**Abdominal symptoms** • Diarrhoea (frequency; consistency; colour; buoyancy; urgency) • Bloating • Flatulence • Post prandial abdominal pain **Symptoms influencing dietary intake** • Nausea • Vomiting • Indigestion • Post prandial pain • Anorexia • Early satiety • Taste changes • Sore mouth • Oral thrush **Systemic Inflammation** • C-reactive protein • Albumin **Psychological distress**	**Dietary adequacy** • Identification of missing food groups • Quantification/adequacy of energy and protein composition of diet • Assessment of micronutrient intake/is dietary intake adequate/well balanced **Food avoidances** • Cultural dietary restriction • Identification of foods the patient associates with worsening symptoms • History of food allergies/intolerances	**Previous surgery** • Gastrointestinal surgery • Extent of resection • Type of reconstructionl surgery **Endocrine function** • History and type of diabetes **Diseases affecting bowel function** • Coeliac disease • Irritable bowel syndrome • Inflammatory bowel diseases • Food allergies/intolerances **Conditions influencing dietary intake** • Heart disease • Renal disease • Alcohol intake • Eating disorders • Exocrine function **Extent and type of pancreatic disease** • Location of disease (head/body/tail) • Duration of disease • Pancreatic duct dilation • Pancreatic atrophy • Pancreatic function test results	**Presence of medication that influence gut function** • Chemotherapy regimen • Anti-diarrhoeals • Laxatives • Gastric acid suppression • Somatostatin • Iron Supplements • Pro-kinetics • Opiates • Antibiotics • Probiotics **Medication that influence weight** • Anti-obesity drugs • Steroids • Diuretics • Insulin • Metformin **Recent changes in medication which may suggest reduced absorption** • Discontinuation of cholesterol lower medication • Reduction in Insulin doses

2.3 Cancer cachexia and PDAC

Cancer cachexia is a multifactorial syndrome characterised by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment (81). Cancer cachexia affects the majority of patients with advanced cancer, and is driven by a variable combination of anorexia and reduced oral intake, altered macronutrient metabolism, inflammation and muscle wasting (57).Pancreatic cancer patients have the highest prevalence of cancer cachexia of all cancer patients, experiencing the most severe weight loss (Figure 2.3)(82). Weight loss and cachexia predict poor outcomes in PDAC (43, 83, 84). Most patients with PDAC will die with cachexia, and it is estimated that 30% will die of cachexia (46, 85, 86).

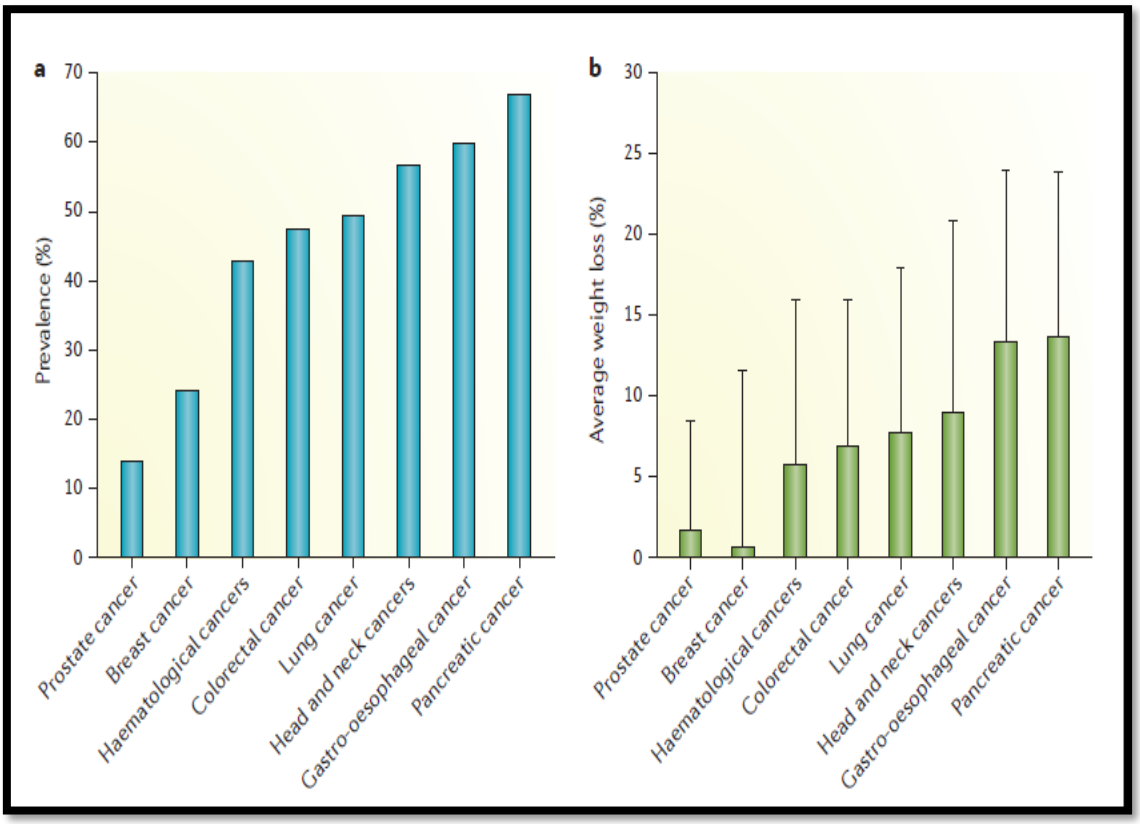

Figure 2. 3 Cancer cachexia by tumour site.

The prevalence of cachexia (defined as >5% weight loss in previous 6 months) by cancer site (part A) and the average percentage of weight loss and its variation (error bars) by cancer site (part B) are shown (Reprinted with permission from (57).

2.3.1 Diagnosing cancer cachexia

A number of diagnostic criteria exist for cancer cachexia, with two most frequently in use

1. Weight loss in excess of five percent over the preceding six months (in the absence of simple starvation), or low BMI (<20kg/m^2) combined with weight loss greater than two percent or evidence of sarcopenia (81).
2. Weight loss greater than five percent or BMI<20kg/m^2, plus three of the following criteria: decreased muscle strength, fatigue, anorexia, low fat-free mass and or abnormal biochemistry (increased inflammatory markers or low haemoglobin) (87).

The development of the international consensus definition for cancer cachexia introduced the concept of a cancer cachexia spectrum, recommended that future research targets pre- cachexia and cachexia (81).

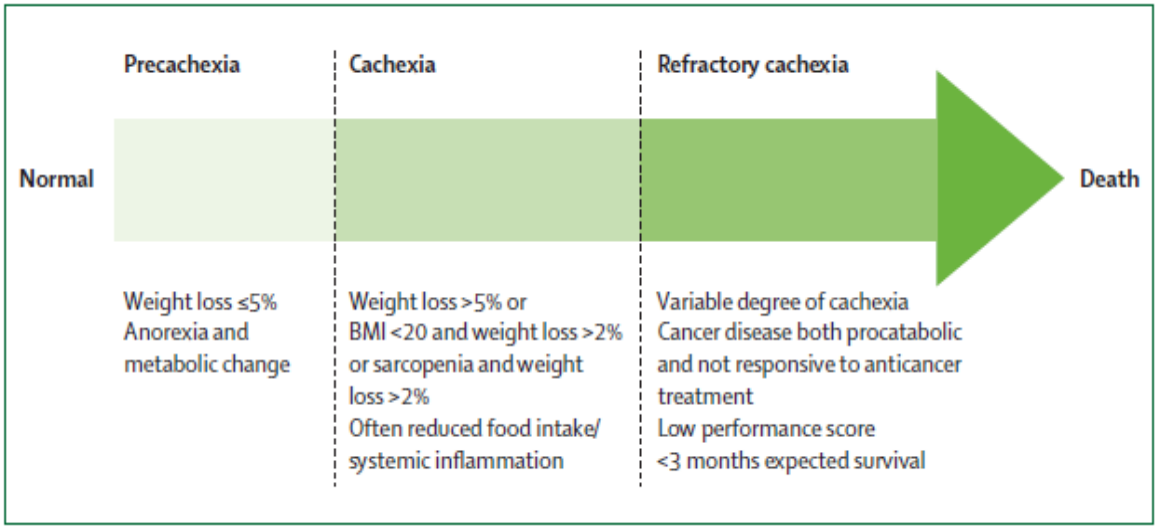

Figure 2. 4 Cancer cachexia continuum

(Reprinted with permission from (81))

Cachexia is prevalent in pancreatic cancer, with the resulting muscle loss or sarcopenia often described as a hallmark feature of the condition (82). Cachectic PDAC patients have reduced survival, regardless of their disease stage at diagnosis (88). Despite this high prevalence and potential for mortality, PDAC–associated cachexia is diagnosed and treated in a minority of patients (46), and there is no established treatment (89).

Sarcopenia, commonly described as the age-associated loss of muscle, is accelerated in patients with poor nutritional intake, physical inactivity and inflammation (90). Pancreatic cancer typically presents in the seventh decade of life, and the associated anorexia, cancer cachexia-induced inflammation, and physical decline combine to increase the risk and rate of sarcopenia.

A consensus statement published by the ISGPS highlighted the prognostic significance of inflammatory markers in pancreatic cancer, and recommended the routine inclusion of the modified Glasgow Prognostic Score (based on serum albumin and C-reactive protein (CRP)) in pre-operative assessment (14). Pro-inflammatory cytokines are implicated in the aetiology of cancer cachexia, either secreted by the tumour itself, or by the host in response to the tumour (91). Tumour-derived cytokines have been shown to induce an acute phase response in the liver via an interleukin-6 (IL-6) dependent mechanism. The host response to this inflammatory insult prolongs this acute phase response, activating trans signalling IL-6 pathways, secreting soluble receptors to increase the potential range of IL-6 target tissues beyond those inherently expressing a receptor (hepatocytes, white blood cells, myoblasts). This sustained inflammatory response leads to prolonged catabolism and muscle atrophy, increasing resting energy expenditure.

Intracellular protein degradation in muscle relies on four potential proteolytic pathways that depend on calpains, caspases, lysosomes, and proteasome (92), with multiple studies demonstrating that those involving lysosomes and proteasomes are over-activated in cancer. Muscle breakdown via the ubiquitin-dependent proteolytic pathway is partly mediated by tumour necrosis factor- alpha (TNF-α). Lysosomal proteolysis is caused by overactivation of autophagy (92).

Assessment of body composition, a direct recommendation of the international consensus group as part of cancer cachexia assessment, has highlighted high levels of sarcopenic obesity (a condition with co-existing low muscle mass and increased adipose tissue levels) among patient with PDAC. Sarcopenic obesity is a negative prognostic factor for patients with PDAC, regardless of disease stage(85), and may be obscured unless body composition assessment is routinely adopted as part of disease staging and assessment (82). The increased incidence of obesity and reduced physical activity levels in the general population, both potential risk factors for the development of pancreatic cancer, may result in pre-cancer obesity that masks the loss of lean body mass, leading to a the occurrence of sarcopenic obesity in many PDAC patients (93).

With the advances in chemotherapy in recent years, and the availability of more potent, toxic agents, body composition and nutritional status should be considered in treatment planning, as poor nutritional status may be a limiting factor in chemotherapy (94). Most chemotherapy agents are hydrophilic, dispersed and metabolised in lean tissue. Conventional chemotherapy dose prescribing is based on body surface area (BSA), which like BMI, is based on a ratio of weight and height, and cannot identify individual patient variation in body composition (Figure 2.5). Changes in BMI and weight history may highlight patient risk of malnutrition; however both are crude measurements of nutritional status, and neither quantify the extent or type of tissue lost.

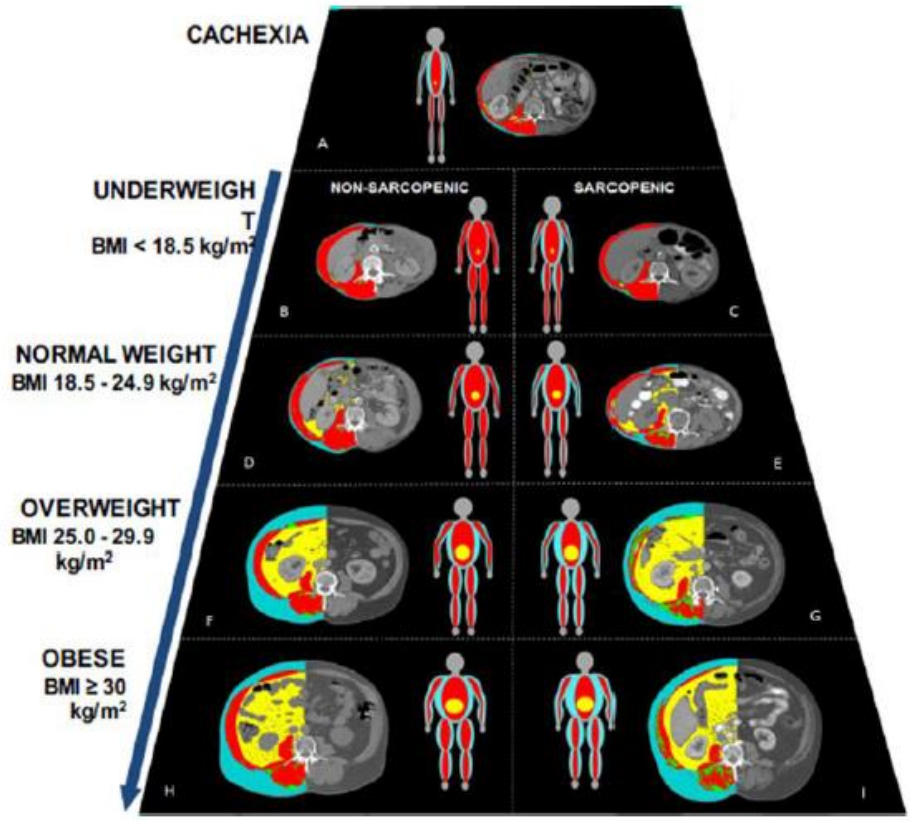

Figure 2. 5 Body Composition Variability in Cancer Patients

(Adapted with permission from (95))

2.3.2 Body composition assessment methods in PDAC

Body composition can be assessed using a variety of methods, including anthropometry (lengths, circumference and skinfold thickness), bioimpedance analysis (BIA) and imaging/x-ray attenuation with dual–energy x-ray absorptiometry (DEXA), CT, MRI and ultrasound (96). CT measurement of body composition at the level of the third lumbar vertebrae (L3) has been validated for total body muscle and fat estimation in oncology patients (97). Pancreatic cancer patients undergo numerous abdominal investigations in order to correctly stage their disease and identify optimal therapy options, presenting an ideal opportunity for body composition assessment and monitoring.

X-ray attenuation is measured by a computer software programme (e.g. Tomovision Slice-O-Matic™) that reconstructs cross-sectional images. Pixels are given a numerical value (Hounsfield Units) based on their tissue attenuation related to electron density. Bone, skeletal muscle, adipose tissue and visceral organs all have specific HU ranges, allowing identification in cross-sectional images.

L3 was identified as a landmark of interest in body composition assessment in 2004 when 320 healthy individuals were evaluated by Shen et al with the aim of identifying the region at which cross-sectional area in a single image was the best correlate of whole-body muscle volume. The best correlate was seen 5 centimetres above L4/L5, at the level of L3 (98).

Following on from Shen's work, a study was undertaken in Canada by Mourtzakis et al which compared CT assessment at the level of L3 to Body BIA and DEXA in 50 patients with advanced cancer (97). BIA was shown to grossly under and overestimate fat free mass (by up to 10kg) and was unable to detect significant changes over time. Regional analysis at L3 using either DEXA or CT strongly predicted total body fat and fat free mass. Mourtzakis et al subsequently developed prediction equations to estimate whole body fat and fat-free mass using CT assessed L3 measurements in oncology patients.

While there is high radiation exposure associated with CT, opportunistic use of scans acquired as part of routine cancer diagnosis and monitoring provide a chance for accurate body composition quantification. CT also offers a distinct advantage over DEXA in cancer patients by allowing discrimination of lean tissue at the tissue organ level. This is important for sequential measurements in cancer patients as peripheral wasting and solid organ hypertrophy through tumour metastases, for example liver metastases often occur simultaneously as disease progresses.

2.3.3 Treatment of cancer cachexia

While weight and muscle loss caused by cancer cachexia cannot be reversed by the provision of nutritional support (81), patients still benefit from individualised assessment to ensure that modifiable nutrition impact symptoms are addressed, and dietary protein intake and dose distribution optimised (99).

The therapeutic potential of exercise as a treatment strategy has been suggested by some authors (100, 101); both endurance or aerobic activity to modulate inflammation, and progressive resistance training to maximise muscle mass and function. No pharmacological agent has to date shown efficacy in counteracting depletion of muscle strength and in attenuating cancer cachexia symptoms (102), Anamorelin, a ghrelin receptor agonist, has shown the most promise, improving patient quality of life and muscle mass in phase three studies (103). No improvement was seen in muscle strength however, and as a consequence the drug failed to get regulatory approval. Pharmacological approaches to cancer cachexia are summarised in Table 2.4.

Two nutrients have shown promise in the treatment of cancer cachexia; omega -3 polyunsaturated fatty acids and L-carnitine

2.3.3.1 Omega -3 Polyunsaturated fatty acids (N-3 PUFA)

N-3 PUFA include alpha-linolenic acid, eicosapentoic acid (EPA), docosapantoic acids (DPA) and docosohexanoic acid (DHA). Both in vitro and in vivo studies have suggested that n-3 PUFA have anti-tumour effects in pancreatic cancer cell lines and animal models (104, 105). EPA has been shown to downregulate pro-inflammatory cytokines (106, 107), and ameliorate elevated REE in pancreatic cancer patients with cachexia (58).

A systematic review by Ma et al evaluated the impact of N-3 PUFA in unresectable pancreatic cancer. Eleven studies were included in the meta-analysis. Consumption of n-3 PUFA increased weight, reduced REE and increased median survival. Heterogeneity was significant however, which the authors attributed to small sample size (n=259) and publication bias(108). Lack of compliance to a daily N-3 PUFA supplement, and differing supplement content and type and heterogenous cancer populations have been highlighted as additional barriers to the systematic evaluation of the impact of N-3 PUFA in cancer cachexia (109, 110). Recent studies have highlighted the potential of N-3 PUFA to act as sensitising agents to chemotherapy, particularly in chemoresistant cancer cells, suggested their potential as an adjuvant in the treatment of drug resistant cancers (111, 112).

2.3.3.2 L- Carnitine.

Deficiency of L- Carnitine has been proposed as a contributing cause of cancer cachexia (113) and fatigue (114). One prospective double-blinded randomised trial of L- carnitine supplementation in patients with unresectable pancreatic cancer demonstrated both improved body weight and quality of life (114).

2.3.4 Multi-modal therapy for cancer cachexia

While multiple anti-inflammatory substrates have been proposed as a mechanism to overcome the pro-inflammatory, hyper-catabolic effects of cancer cachexia, there is increasing awareness that a multi-modal approach is necessary to counteract the multi-factorial aetiology of malnutrition in pancreatic cancer (115, 116). The MENAC study, an international multi-centre randomised study, targeting patients with unresectable cancer receiving palliative chemotherapy is currently underway. The six-week intervention comprises nutritional counselling, an n-3 PUFA-enriched nutritional supplement, non-steroidal anti-inflammatory medications, and an exercise target. Preliminary results have highlighted feasibility and patient acceptance (117).

2.4 Treatment strategies for malnutrition in pancreatic cancer.

It has been suggested that all patients with pancreatic cancer should be referred to a specialist dietitian (46). Dietetic led interventions in pancreatic cancer have been shown to improve weight (45), quality of life (118), and survival (45). Moreover, the delay or lack of dietetic referral has been highlighted as the primary unmet supportive care need among patients and/or their carers (68). Recent ESPEN consensus guidelines for nutrition in cancer patients recommend daily energy intakes between 25 and 30 kcal/kg/day, and a minimum protein intake of at least 1g/kg/day, ideally aiming for 1.5g/kg/day (119). Individualised patient counselling regarding meal frequency, food choice, distribution and use of PERT and nutritional supplements is needed to achieve this in the context of multiple barriers to adequate nutritional intake and/or absorption.

Table 2. 4 Pharmacological agents for cancer cachexia

Drug type	Mechanism of action	Positive effects	Limitations/risks
Corticosteroids	Inhibition of prostaglandin activity Suppression of IL-6 and TNF-α	Central effects; improved nausea, appetite, euphoria and sense of wellbeing	Time limited benefit (2-4 weeks) Increased protein losses Hyperglycaemia Immunosuppression
Anamorelin			
Progesterone	Appetite stimulant Cytokine antagonist	Increased appetite	Oedema Thrombolic effects Death
Selective androgen receptor molecules (SARMS)	Activate skeletal muscle androgen receptors	Minimal systemic effects Improved lean mass and function	Limited study to date
Canniboids	Appetite stimulant	Increased appetite ? improve nausea	Hallucinations & psychosis Vertigo
NSAIDs	Downregulate inflammation Inhibit prostaglandin synthesis	Improvement in weight Improved quality of life Improved function	Small sample size Multiple contraindications
TNF- inhibitors	Downregulate TNF-α production		Limited study/ effect in cancer patients
Statins	Anti-inflammatory		Data limited to epidemiological studies

2.4.1 Locally Advanced and/or Metastatic Disease

It can be argued that all patients with advanced pancreatic cancer should receive individualised nutritional assessment and advice. This patient cohort endures a significant symptom burden, requiring routine assessment and monitoring to identify and address any unnecessary suffering as consequence of modifiable disease or treatment-related factors and nutrition impact symptoms. PERT has been shown to improve overall survival in patients with unresectable pancreatic cancer in multiple, non-randomised studies (120, 121). Moreover, studies evaluating PERT in pancreatic cancer highlighted that the use of PERT led to improved symptom control and quality of life (67).

2.4.2 Resectable Pancreatic Cancer

2.4.2.1 Pre-operative considerations

While the centralisation of pancreatic cancer surgery has led to a reduction in mortality associated with the procedure, post-operative morbidity remains significant, affecting up to 50% of patients. Pre-operative sarcopenic obesity has been shown to increase the risk of failure to rescue patients who developed major post-operative complications following pancreaticoduodenectomy (122). Pre-operative malnutrition may limit or delay the patient's ability to undergo resection, with some patients

requiring a period of pre-operative artificial nutritional support. Where surgery is delayed to allow improvement of nutritional status, the placement of an enteral feeding tube during surgery for post-operative support should be considered. Numerous studies evaluating the effect of prehabilitation (comprising nutritional counselling and/or individualised exercise advice) prior to pancreatic cancer surgery or during neoadjuvant chemotherapy are currently underway. (https://www.clinicaltrials.gov NCT03688867, NCT03466593, NCT03244683, NCT03706963, NCT02295956).

2.4.2.2 Post-operative nutritional support

Whilst some patients recover well from pancreatic resection, the complication rate is significant, and many complications have either a direct impact on nutrition or require alteration in nutrient provision as part of their management. Whilst it is generally accepted that pre-operative malnutrition is associated with worse surgical outcomes (123) direct data examining these risks following pancreaticoduodenectomy (PD) is sparse. These data are limited by the difficulty determining malnutrition. Probst et al prospectively applied 11 different nutritional screening tools to determine malnutrition in 279 patients undergoing elective pancreatic resection. The incidence of malnutrition, as defined by each of these tools, varied from 1.1% to 79.6% and none of the risk tools predicted outcome when subjected to multivariable regression analysis (124).

More recently research has focused on the impact of sarcopenic obesity, and this has been identified as an important factor in both predicting post-operative complications (125) and survival from major complications (122). As all nutritional risk scores incorporate weight and weight loss as a factor within each score, the validity of these as a predictor of sarcopenia is now disputed (126).

In the immediate post-operative setting EN is preferred over the PN, however as experience of enhanced recovery programmes develops, a focus on oral rather than enteral nutrition is apparent (127). In those patients who do not experience a post-operative complication, progression onto oral diet appears to be sufficient, although there has been no study examining nutritional adequacy post operatively, and there is a lack of observational data on factors that impact post-operative rehabilitation.

The evidence for early oral nutrition in the post-operative setting is derived predominantly from colorectal and orthopaedic surgery, but adapted into many pancreatic surgery pathways, with observational data suggesting relative tolerance (128, 129). However concern remains that although many patients benefit from EN in the pre and post-operatively, the implementation of enhanced recovery after surgery (ERAS) pathways has led to a reduction in the insertion of intra-operative feeding tube insertion, that were previously inserted routinely (130). Routine use of PN is not recommended (131), but in the absence of intra-operatively inserted feeding tubes, the use of PN will continue, especially in those patients with

DGE. Studies looking at outcomes in patients receiving EN via different routes are limited by small sample sizes, and retrospective trial design (132). More research is required to determine the efficacy of post-operative nutritional support, especially with regard to progression onto and tolerance of adjuvant chemotherapy.

Post-operative pancreatic fistula (POPF) is the most significant complication following PD, with the risk of haemorrhage and subsequent mortality. The incidence of pancreatic fistulae does not appear to be influenced by pre-operative malnutrition (133), but sarcopenic obesity is a predictor for pancreatic fistula (134). The incidence has been shown to be lower in those patients who receive post-operative EN, possibly due to improved mesenteric perfusion (135). However high drain amylase, soft pancreatic glands and narrow ducts, gender, pre-operative stenting, surgical technique and presence of PDAC remain the most reliable predictors of pancreatic fistulae (136, 137). There are mixed opinions on the nutritional management of this complication. The option to continue with distal jejunal feeding theoretically should prevent ongoing stimulation of the pancreas (138) thus complimenting the use of somatostatin analogues. However pancreatic fistulae are often associated with ileus, and in this instance PN is required.

EN via the jejunal route is of most benefit when DGE occurs. The aetiology is multifactorial but vagal nerve damage has been proposed as a possible factor (139), alongside the development of a peripancreatic collection. The

incidence of DGE in the literature varies significantly between 2.2% and 37% (139). The discrepancy is likely due to the use of variable definitions of DGE. Managing gastric secretions with a naso-gastric tube on drainage should allow full rate EN via a jejunal feeding tube. When gastric emptying improves and gastric drainage is no longer required patients can be managed in the outpatient setting with jejunal feeding until restoration of full oral intake occurs. One small study (n=30 patients receiving EN) suggested that EN resulted in prolonged DGE (140). The incidence of DGE within this study was much higher (57%) than in other studies where routine EN was not assessed (140).

Chyle leaks can be successfully managed with medium chain triglyceride-based enteral feeds (141). Whilst questions have been raised as the role of early EN in the development of chyle leaks, one small study reported a higher incidence of chyle leak (total chyle leak = 7) in those with early EN, but chyle leaks occurred more than 2 weeks post operatively and in the absence of early EN (142) , and the degree of lymphatic clearance remains the most likely predictor for chyle leaks (141).

2.4.2.3 Post discharge nutrition

The most common cause of readmission following pancreatico-duodenectomy is malnutrition and dehydration(143), but there are a paucity of data surrounding long term nutritional status.

Resection of the duodenum and use of the first part of the jejunum for reconstruction results in reduction of the absorptive capacity of the proximal small bowel with particular regard to micronutrients and several case reports have highlighted nutrient deficiencies in post-operative patients (144, 145). One observational study identified lower levels of iron, selenium, vitamin D, vitamin E in patients 6 months after pancreatic resection (146). There are limited data in this patient group due to poor long-term survival, but many units opt to supplement with micronutrients in those undergoing treatment with a curative intent.

2.4.2.4 Survivorship

Long term nutritional management of pancreatic cancer following resection is based on symptom management, and largely experience-based due to a lack of clinical studies. Sarcopenia is a predictor of long-term survival, with worse survival in those losing skeletal muscle in the 12 months following surgery (147). Chronic pancreatitis and bariatric surgery patients present with similar long-term nutritional complications as seen following pancreatic

resection, and many units extrapolate data from studies in these cohorts to support long term observation (76).

Quality of life is impacted predominantly by abdominal symptoms in the post-operative setting (148). PEI is common - affecting up to 98% of patients following PD and at least 20% of patients following distal pancreatectomy (71). Guidelines support routine administration of pancreatic enzymes in patients with pancreatic cancer (149). Other causes of long term bowel symptoms have been identified, such as small intestinal bacterial overgrowth or bile acid diarrhoea (71).

2.5 Conclusion

The nutritional management of pancreatic cancer is complex. Nutrition plays a significant role in all stages of the disease pathway, and the impact should not be underestimated. Early referral and the development of specialist nutritional services with experienced dietitians working within the surgical and oncology teams is important for optimal patient care. Weight loss and BMI should no longer be considered a stand-alone marker of pre-operative nutritional status, and research should focus on more accurate methods of quantifying nutritional status, identification and treatment of sarcopenia, especially in the obese population. The role of pre-habilitation is emerging as the most significant change in practice to enhance pre and post-operative nutritional status and ultimately improve survival.

Chapter 3 Thesis outline

This chapter describes the background to this body of work along with the rationale and specific objectives of each study.

3.1 Thesis context and study setting

Pancreatic cancer surgery was centralised to the National Surgical Centre for Pancreatic Cancer (NSCPC) at St Vincent's University Hospital (SVUH) in 2010, and a full-time dedicated senior dietetic post was funded in anticipation of a highly malnourished, underweight patient group. When appointed as senior dietitian for the service in 2011, I conducted an audit of the nutritional status of the first 150 patients referred. While patients presented with significant weight loss at diagnosis (mean 7.5%), the average BMI of patients was in the overweight range.

The centre formally adopted routine use of neoadjuvant therapy for patients with BRPC in 2013, and we subsequently observed that patients undergoing resection following neo-adjuvant chemotherapy appeared frail and deconditioned, with a prolonged post-operative length of stay, when compared to patients deemed immediately resectable. These clinical observations led me to design a number of studies on this topic, under the supervision and guidance of the PhD supervisors.

Several principles underpin this work. There is a paucity of evidence evaluating body composition or nutritional needs in BRPC patients. The emergence of FOLFIRINOX offers a new treatment strategy for pancreatic cancer, but access in the real-life clinic setting is limited by performance status, often based on subjective assessment parameters. CT scans used for cancer diagnostic and monitoring purposes offer an opportunity for body composition assessment and may allow more objective assessment to aid decision making. Variations in individual patient body composition may impact the delivery of chemotherapy or influence post-operative outcomes. Whether sarcopenia and muscle loss are modifiable factors for all patients with pancreatic cancer is yet to be determined.

3.2 The Health Research Board Training Fellowship

This work is funded by the Health Research Board (HRB), Ireland by means of a Research Training for Health Professionals Fellowship (HPF-2015-977).

The objective of this Fellowship programme was to enable health and social care professionals to undertake advanced research training leading to a research doctorate. This training plays a critical role in preparing recipients to inform, undertake, support and implement research and evidence in their clinical careers to improve patient care and service user experience, and to support innovations in health and social care. Findings

must have a realistic potential of being applied in practice and have relevance to health and social gain. Finally, the Fellowship is a personal research training scholarship and not just a means of funding a project.

3.3 Overall thesis aims

This thesis had four main aims, outlined in Table 3.1

Table 3. 1 Thesis aims with corresponding chapters

Research questions	**Thesis Chapter**
1. What is the prevalence of sarcopenia in early stage pancreatic cancer? Objectives • To conduct a systematic review and meta-analysis evaluating the prevalence of sarcopenia in resectable and borderline resectable pancreatic cancer • To describe body composition methods used in pancreatic cancer patients	5
2. Does body composition influence post-operative outcome in pancreatic cancer? Objectives • To examine the prevalence of sarcopenia in patients undergoing pancreatic surgery • To investigate the impact of body composition on post-operative morbidity and mortality	6
3 What happens to body composition during neoadjuvant chemotherapy for pancreatic cancer Objective • To characterise body composition change during neoadjuvant chemotherapy using CT- based body composition analysis	7
4 Is a multi-modal nutritional intervention feasible and acceptable to patients undergoing neoadjuvant chemotherapy for pancreatic cancer? Objective • To assess the feasibility of combining early nutritional, prescriptive exercise, and pancreatic enzyme replacement therapy for patients undergoing neoadjuvant chemotherapy • To assess health-related quality of life, body composition, functional and inflammatory status at both diagnosis and completion of chemotherapy	8

Chapter 4 General Methodology

This chapter describes common methodologies used throughout the research studies and includes details on my role as lead investigator. It details the acquisition of ethical approval, study design, study sponsorship, recruitment, patient assessments, and statistical analyses. Specific additional details pertaining to individual studies are provided in the relevant chapters, where appropriate.

4.1 Investigator and data collection

I conducted all aspects of the research throughout this thesis including literature reviews, study design, data collection, data entry, body composition assessment, provision of dietetic care to participants in the FEED Study, initial preparation of cytokine samples prior to cold storage, statistical analyses, and writing of research papers, conference abstracts, and the final thesis.

The research studies were conducted between October 2015 and March 2019.

Some aspects of the research required assistance of clinical nurse specialists, librarians, statisticians, and specialists, detailed below:

- Mr Joseph Peakin and Ms Jean McMahon, Medical Librarians at Tallaght University Hospital provided assistance with the systematic review in Chapter 4, specifically by devising the search strategy
- Mr Donal O' Connor and Mr Yasir Bashir acted as second independent reviewers for the systematic review (Chapter 5)
- Dr Carla Prado, Dr Jingjie Xiao and Ms Taiwo Olobatuyi at the University of Alberta provided body composition analysis training and examination and were available for consultation and advice throughout (Chapters 6-8).
- Ms Deirdre Burke, Ms Gillian Stewart, Ms Marie O'Brien, Ms Mary Donohoe, Ms Kate Sheanon and Professor Raymond McDermott assisted with the identification and recruitment of suitable patients and with patient recruitment for the intervention study in Chapter 8
- Mr Karl McAuley, Senior research Laboratory technician provided guidance and training with cytokine sample preparation for freezing, and undertook the final cytokine analysis for the study outlined in Chapter 8
- Dr Ronan Ryan, Dr Eric Heffernan and Dr Rory O' Donohoe for their practical assistance with acquisition of CT images for body composition analysis, and ongoing advice and support with quality control elements (Chapter 6, 7 and 8).
- Phlebotomy was undertaken by trained Phlebotomists from the Phlebotomy Departments of SVUH and St Vincent's Private Hospital for Chapter 8

For all studies, all three thesis supervisors provided guidance, feedback and support in implementation of study design,statistical analysis and writing.

4.2. Ethical approval

4.2.1. Informed consent

Ethical approval was obtained from St Vincent's Healthcare Group Ethics and Medical Research Committee prior to undertaking these studies. Letters of ethical approval are included in the appendices.

A waiver of consent was granted for both retrospective cohort studies (Chapter 6 and 7). Prior to inclusion in the prospective feasibility study (Chapter 8), patients were provided with patient information leaflets detailing the study in full and given the opportunity to consider and ask any questions prior to deciding to be included. Prior to inclusion, written signed informed consent forms were obtained from all patients only after a minimum cool-off period of 24 hours. Patients were provided with a signed copy of the patient information leaflet/consent form and supplied with relevant contact details enabling them to contact the investigator. Patients were advised that their participation was entirely voluntary, that they may choose not to take part, and that they may remove themselves at any time during the study, without prejudice or discrimination. Access to dietetic support during treatment was not restricted to participation in the study, and all eligible patients were assured of this. Where patients declined to

take part in the study, they were offered an appointment with the clinical dietetic team within one week.

4.2.2. Data Storage

I collected patient data from patient recruitment, data collection and face-to-face interviews including demographic data and questionnaires. Confidential patient information, notes and charts were stored in a locked filing cabinet in a locked office in a security monitored building in SVUH which required swipe card access. All electronic information was coded and stored on password protected hospital computers. CT images were fully anonymised and downloaded onto a dedicated, encrypted hard drive to allow body composition analysis in Trinity College Dublin. Care was taken not to disclose any information that could identify or connect any of the participants to the study.

4.2.3. Vulnerable subjects

The study included only adults above 18 years of age. Intellectually impaired adults, people with brain injuries, or otherwise incapacitated were not included, due to risk of lack of comprehension of the study or inability to provide informed consent. Women of child bearing age were not excluded, but those who were pregnant at the time of the study were not included. Elderly / aged persons >65 years were not excluded, as

pancreatic cancer typically presents in the seventh decade of life, and elderly patients are particularly vulnerable to sarcopenia. Any person who was unable to provide informed written consent or who did not willingly volunteer for inclusion in the studies was not included.

4.2.4 Study sponsorship

This research is funded by the HRB, Ireland by means of a Research Training for Health Professionals Fellowship (HPF-2015-977), the purpose of which is outlined in Chapter 3. St Vincent's Foundation provided additional funding by means of an unrestricted research grant to allow continued recruitment of patients to the intervention study outlined in chapter 8. This grant comprised monies donated specifically for pancreatic cancer research within the hospital. No constraints were exerted on any of the studies. Neither sponsor was involved in study design, advertisement, recruitment, analysis, or in the write-up of manuscripts for publication. Neither I nor any other investigator involved in the studies had any conflicts of interest.

4.2.5 Reimbursement

Participation in the prospective study (Chapter 8) was voluntary and no payment (monetary or otherwise) was provided for participation. Where possible all appointments coincided with diagnostic, clinic and/or

chemotherapy unit attendance, unless an alternative was specifically requested by the patient. All costs relating to assessments, investigations and procedures relevant to the study were met, and no monies sought from patients and/or their health insurance companies. Both the PERT and N-3 PUFA enriched nutritional supplement selected for the intervention were approved for reimbursement under the General Medical Scheme (GMS) for pancreatic cancer patients. If patients were not medical card holders and entitled to free GMS listed medications or were not already reaching the maximum monthly threshold amount on the Drug Payment Scheme (€144 2017/€134 2018), they were provided with N-3 PUFA supplement free-of-charge.

4.3. Study design

To fulfil the aims of this thesis, several methodological and scientific approaches were adopted, and specific details pertaining to each study methodology are detailed in the relevant study chapters (chapters 5-8).

4.3.1 Study recruitment

Patients were recruited to the study utilising the following approaches:

1. For both retrospective cohort studies (Chapters 6 and 7): patients were identified from a prospectively maintained database

2. For the prospective study (Chapter 8) patients were identified at the weekly pancreatic cancer MDT meeting if their treatment recommendation was neoadjuvant therapy. The patient attended a surgical or oncology clinic where they were informed of the MDT meeting outcome. Eligible patients (those who opted to receive their chemotherapy at either SVUH or SVPH) were made aware of the study by their consultant before being contacted after their consultation by me and invited to particpate in the study.

4.3.2 Questionnaires

Questionnaires, data collection forms, and assessment forms were utilised for all recruitment studies, and are discussed within each individual study chapter. All such documentation is included in the Appendices.

4.3.3. Assessment and equipment

General assessment techniques, methods, reference ranges and equipment used during the studies are described here. Additional specific

parameters, and technical information are detailed within each individual chapter as appropriate.

4.3.3.1 Nutritional Assessment (weight, height and BMI*)*

Weight was obtained on a Class III or above scales and recorded to one decimal place. Height was measured using a stadiometer, with the patient standing straight and stretched. Heels were flush against the wall and measurement was taken with the head in the Frankfort plane. Percentage weight loss was calculated by subtracting actual weight from usual or previous weight, divided by the usual weight and multiplied by 100. BMI was obtained by dividing actual weight by height squared, and the WHO classification used for interpretation (Table 4.1) (150)

Table 4. 1 WHO classification of obesity

WHO class	**Body Mass Index Kg/M²**
Underweight	<18.5
Normal weight	18.5-24.9
Overweight: Pre-obese Obese class I Obese class II Obese class III	 25.0-29.9 30.0-34.9 35.0-39.9 >40.0

4.3.3.2 Body Composition Analysis

Following training at the University of Alberta and meeting the necessary standard required for certification (co-efficient of variance <1%) on examination, I conducted all body composition analysis. Existing CT scans, acquired for cancer diagnosis and restaging, were analysed using a validated programme (Slice-O-Matic version 5.0 Tomovision, Montreal, Canada).

The relevant, sequential, axial CT images which clearly visualised the L3 vertebrae were landmarked, anonymised and downloaded in DICOM format. Where sequential measurements were taken on the same patient, image selection was controlled for the use of contrast and phase of CT. The surface area of skeletal muscle tissue (psoas, erector spinae, quadratus lumborum, transversus abdominus, external and internal obliques and rectus abdominus structures) and adipose tissue (visceral, intra-muscular and subcutaneous) were measured using established radio-density cut-offs (Table 4.2) (94). The Hounsfield unit (HU) scale is a linear transformation of the linear attenuation coefficient measurement in which the radiodensity of distilled water at standard pressure and temperature is defined as zero Hounsfield units and the radiodensity of air at standard pressure and temperature is defined as -1000 HU.

Table 4. 2 Radiodensity thresholds used for body composition analysis

Body composition parameter	**HU range between**
Skeletal muscle	-29 and 150
Visceral adipose tissue	-150 and -50
Subcutaneous and intramuscular adipose tissue	-190 and -30

Lumbar skeletal muscle index (LSMI) was calculated by normalising skeletal muscle area for height, and subsequently compared values to the Martin gender- and BMI-specific references (151). Muscle attenuation (MA) was quantified by measuring average skeletal muscle radio-density and defined as per BMI–specific (151) (Table 4.3).

Table 4. 3 Threshold values used for body composition analysis

	LSMI (cm^2/m^2) ¥		Skeletal muscle Attenuation (HU) §	
BMI Category (kg/m^2)	Men	Women	Men	Women
Underweight (<20)	<43	<41	<41	<41
Normal weight (20.0 to 24.9)	<43	<41	<41	<41
Overweight (25 to 29.9)	<53	<41	<33	<33
Obese (≥30)	<53	<41	<33	<33

BMI, body mass index; LSMI, lumbar skeletal muscle index; HU, hounsfield units

¥ Sarcopenia defined as LSMI below these values

§ Low muscle attenuation defined as HU below these values

(adapted with permission from Martin 2013)

Validated regression equations(97) were then applied to estimate whole body fat and fat-free mass:

Total body fat mass (FM) (kg) = 0.042 x [total adipose area at L3] + 11.2

Total body (FFM) (kg)= 0.3 x [skeletal muscle area at L3] + 6.06.

Total body skeletal muscle volume was then estimated using the regression equation developed by Shen and colleagues(98).

Skeletal muscle volume= 0.166[skeletal muscle area at L3) +2.142

A density of 1.04g/ml was subsequently applied to estimate skeletal muscle mass from volume(152).

Cancer cachexia was defined using the Fearon definition; either(81):

1. Involuntary weight loss > 5% in the last 6 months in the absence of simple starvation

or

2. Weight loss > 2% if BMI was < 20 kg/m²or sarcopenia was present.

4.3.3.3 Functional Assessment

4.3.3.3.1 Handgrip strength

Handgrip strength (HGS) was selected for functional assessment as it is both a simple method for clinical practice (153), and advocated as the preferred muscle strength assessment method by the European Working Party on Sarcopenia in Older People (EWSOP)(90).

HGS was assessed using a Jamar hydraulic-dynanometer, using the non-dominant arm. Participants were seated with their elbow flexed at 90°, and their forearm resting on arm rest, with their wrist just over the end of the chair arm, in a neutral position. The handle was adjusted as necessary for individual hand size to ensure optimal fit. Three measurements were taken with one-minute intervals in between to avoid muscle fatigue, and the results averaged. The value obtained was compared to gender- and age-specific reference values (154).

Figure 4. 1 Handgrip strength assessment using a Jamar dynanometer

4.3.3.3.2 Timed Up and Go Test

The Timed Up and Go (TUG) test was used as a physical performance test. This test observes the time a patient needs to rise from an armed chair, to walk 3 metres (equivalent to 10 feet), turn and walk back to the same chair and sit down again(155). If a walking aid was used routinely by the patient, this was used during the assessment, and patients were advised to wear comfortable clothing and flat shoes for the appointment.

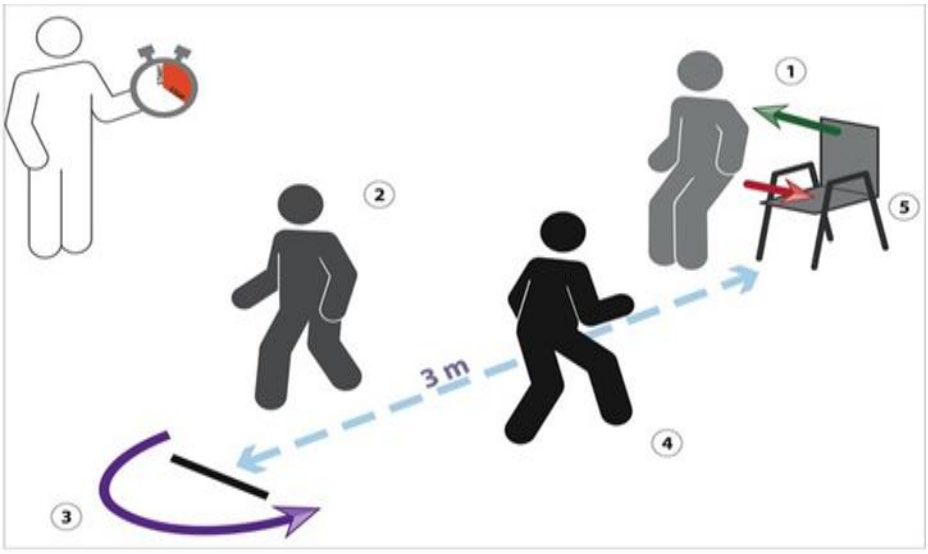

Figure 4. 2 Timed-Up and Go Test

(reprinted with permission from (156))

4.3.5. Biochemistry

Blood samples for the interventional study (Chapter 8) were taken in the Phlebotomy Department in either St Vincent's University Hospital or St Vincent's Private Hospital and processed according to standard protocols in SVUH Pathology Manual. The biochemical assays used in these studies are summarised in Table 4.4

Table 4. 4 Biochemical assays, methods and reference Ranges

	Unit	Method of measurement	Range	Site of Assessment
CA19-9	kU/L	Chemiluminescent microparticle assay	0-37	SVUH/SVPH
Albumin	g/L	Chemistry-immunoturbidimetry	35-50	SVUH/SVPH
CRP	mg/L	Chemistry-Spectrophotometry	0-5	SVUH/SVPH
Vitamin B12	ng/L	Chemiluminescent microparticle assay	197-771	SVUH/SVPH
Folate	µg/L	Chemiluminescent microparticle assay	>3	SVUH/SVPH
Vitamin D	nmol	Chemiluminescent microparticle assay	≥50	SVUH
Glucose	mmol/L	Hexokinase/G-6-PDH	4.0-6.0 (fasting)	SVUH/SVPH
HbA1c	mmol/mol	Chemistry-immunoturbidimetry	20-42	SVUH
Vitamin A	µmol/l	High Performance Liquid Chromatography	1.28-1.91	Eurofins Biomnis Ireland
Retinol Binding Protein	mg/L	Nephelometry	30-60	Eurofins Biomnis Ireland
Vitamin E	µmol/l	High Performance Liquid Chromatography	9.87-30.59	Eurofins Biomnis Ireland
Cholesterol	mmol/L	Chemistry-Spectrophotometry	<5	SVUH/SVPH
Iron	µmol/L	Chemistry-Spectrophotometry	5.8-34.5	SVUH/SVPH
Ferritin	µg/l	Chemiluminescent microparticle assay	13-150 (female) 30-400 (male)	SVUH/SVPH

CA19.9, Carbohydrate antigen 19.9; CRP, c-reactive protein; HbA1c, glycosylated haemoglobin;SVUH, St Vincent's University Hospital; SVPH, St Vincent's Private Hospital. G6P-DH, Glucose 6-Phosphate Dehyrodgenase

4.3.6 Pancreatic Exocrine Function Assessment,

Stool samples obtained for faecal elastase testing were frozen within 2 hours of receipt of sample before being transferred to an external laboratory (Eurofins Biomnis Ireland) for processing using a monoclonal enzyme-linked immunosorbent assay (ELISA; ScheBo Tech, Giessen, Germany) as per routine hospital practice. The results obtained were interpreted as per Table 4.5 details below

Table 4. 5 Interpretation of faecal elastase-1 results.

Elastase-1 concentration (µg/g of faeces)	**Interpretation**
>200	Normal
100-200	Slight to moderate pancreatic exocrine insufficiency
<100	Severe pancreatic exocrine insufficiency

4.4 Follow-up and aftercare of patients post study participation.

All patients enrolled in the prospective interventional study (Chapter 8) were provided with ongoing fortnightly dietetic monitoring for the duration of their chemotherapy. When they proceeded to radiotherapy, patients were referred to the specialist oncology dietitians in the radiotherapy treatment centre. Following resection and/or treatment completion, all

patients were referred to the specialist pancreatic dietitian at SVUH for long-term monitoring and follow up.

4.5 Copyright and permissions

All published works which are quoted throughout this thesis are appropriately referenced. Where tables, figures or illustrations are replicated, or where the author's own work from a scientific journal is included, relevant licence agreements for copyrighted material was obtained through Rightslink®. Where necessary, authors were contacted directly for permission.

4.6 Statistical analysis

The thesis author conducted the statistical analysis for the studies, with assistance and guidance from the research supervisors where necessary. Two medical statisticians from The Centre for Support and Training in Analysis and Research (CSTAR, University College Dublin) was consulted at the outset, and their advice sought on appropriate statistical methodologies. In addition, I undertook a post-graduate certificate in statistics as part of this scholarship.

The statistical software packages used were the Statistical Package for

Social Sciences (SPSS Version 24 Chicago, IL, USA, 2015) and MetaXL (Epigear, version 5.3, Queensland, Australia, 2016). Data analysis was conducted at Trinity College Dublin on a Toshiba personal computer and Mac computer using the institutional licenced software access. Specific analyses techniques employed in the studies are detailed in their relevant chapters. In all cases, unless otherwise specified, a P value of <0.05 was deemed to be statistically significant.

Chapter 5: Measurement of body composition in pancreatic cancer: a systematic review and meta-analysis and recommendations

5.1 Introduction

Malnutrition and weight loss affect up to 80% of patients with pancreatic cancer at the time of diagnosis (157). Anorexia and early satiety are induced by tumour–derived cytokines, and are aggravated by pancreatic exocrine insufficiency and increased inflammation, leading to reduced nutritional intake, malabsorption and increased resting energy expenditure (89). Developments in body composition assessment methodologies (97, 98) have highlighted the prognostic importance of sarcopenic obesity in advanced pancreatic cancer (85) and other solid tumours (94), supporting the argument that formal body composition assessment should be routine in clinical practice (158).

Pancreatic cancer surgery carries significant risk of post-operative morbidity despite centralisation to high volume centres and the refinement of surgical technique. More active chemotherapy agents can deliver a meaningful survival advantage to patients in the adjuvant setting (32). However, reduced patient performance status is a limiting factor for the successful delivery of chemotherapy agents, and there are few objective assessments to aid clinical decision-making. Recently there has been increasing interest in evaluating the prognostic significance of body composition parameters in gastrointestinal malignancies (94, 159-161)

However, the impact of sarcopenia and cachexia in pancreatic cancer has been described as ‘understudied’, and the heterogeneity in study techniques limits the potential for comparison (159).

5.1.1 Study aims and objectives

By conducting a meta-analysis, this study sought to determine the prevalence of sarcopenia in patients with R/BRPC. The secondary aims were to compare the prevalence of sarcopenia in patients with R/BRPC according to the assessment technique employed, and to determine if sarcopenia was associated with increased mortality and survival. Finally, recommendations for assessment of body composition in this population were developed, applicable for the design of future studies and for clinical practice.

5.2 Methods

5.2.1 Search Strategy

A search strategy was devised for Ovid MEDLINE (1946 – May 2018) and translated for Elsevier EMBASE by two independent librarians. Tables 5.1 and 5.2 outline the search protocols for Medline and EMBASE respectively. A combination of MeSH, or EMTREE terms where appropriate, and keywords were then used to identify published studies regarding the prevalence of sarcopenia in adults with R/BRPC. Subject headings and keywords related to pancreatic cancer, pancreatic malignancy, sarcopenia, sarcopenic obesity, pancreatic surgery, cachexia, skeletal muscle, muscle atrophy, and weight loss were searched. Language, geographical and date restrictions were not applied. Additional studies were identified by reference searching. The search was conducted on the 31st of May 2018.

Table 5. 1 Medline search

#21	#10 AND #20
#20	#17 OR #18 OR #19
#19	Search borderline resectable
#18	Search resectable
#17	Search #11 OR #12 OR #13 OR #14 OR #15 Or #16
#16	Search adenocarcinoma [MeSH Term] OR adenocarcinoma [Text Word]
#15	Search pancreaticoduodenectomy [MeSH Term] OR pancreaticoduodenectomy [Text Word]
#14	Search pancreatectomy [MeSH Term] OR pancreatectomy [Text Word]
#13	Search pancreas surgery [MeSH Term] OR pancreas surgery [Text Word]
#12	Search pancreas cancer [MeSH Term] OR pancreas cancer [Text Word]
#11	Search pancreas neoplasm [MeSH Term] OR pancreas neoplasm [Text Word]
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
#9	Search body mass [MeSH Term] OR body mass [Text Word]
#8	Search body weight loss [MeSH Term] OR body weight loss [Text Word]
#7	Search lean body weight [MeSH Term] OR lean body weight [Text Word]
#6	Search lean tissue [MeSH Term] OR lean tissue [Text Word]
#5	Search muscle atrophy [MeSH Term] OR muscle atrophy [Text Word]
#4	Search cachexia [MeSH Term] OR cachexia [Text Word]
#3	Search skeletal muscle [MeSH Term] OR skeletal muscle [Text Word]
#2	Search sarcopenic obesity [MeSH Term] OR sarcopenic obesity[Text Word]
#1	Search Sarcopenia [MeSH Terms] OR sarcopenia [Text Word]

Table 5. 2. Embase search

#24	#11 AND #23
#23	#20 OR #21 OR #22
#22	borderline resectable
#21	Resectable
#20	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#19	adenocarcinoma */exp OR adenocarcinoma
#18	Pancreaticoduodenectomy */exp OR pancreaticoduodenectomy
#17	Pancreatectomy */exp OR pancreatectomy
#16	Pancreas surgery */exp OR pancreas surgery
#15	Pancreas neoplasms*/exp OR pancreas neoplasms
#14	Pancreas carcinoma */exp OR pancreas carcinoma
#13	Pancreas cancer*/exp OR pancreas cancer
#12	Pancreas tumour */exp OR pancreas tumour
#11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#10	Lean tissue mass */exp OR lean tissue mass
#9	Body mass*/exp OR body mass
#8	Body weight loss */exp OR body weight loss
#7	Lean body weight*/exp OR lean body weight
#6	Lean tissue*/exp OR lean tissue
#5	Muscle atrophy */exp OR muscle atrophy
#4	Cachexia */exp OR cachexia
#3	Skeletal muscle */exp OR skeletal muscle
#2	Sarcopenic obesity*/exp OR sarcopenic obesity
#1	Sarcopenia */exp OR sarcopenia

5.2.2 Inclusion and exclusion criteria

Studies in the English language which evaluated the prevalence of sarcopenia in adult subjects with R/BRPC were included. Conference proceedings and abstracts were included if they contained the necessary data. Exclusion criteria were: (1) studies evaluating acute pancreatitis, chronic pancreatitis, metastatic pancreatic cancer, and/or pancreatic neuroendocrine tumours; (2) publications with mixed populations where the prevalence of sarcopenia for mixed tumour site or stage cohorts could not be separated from those with R/BRPC; and (3) case reports, review articles and studies which did not specify details of body composition/function assessment.

5.2.3 Definitions

The condition of interest was sarcopenia or low muscle mass, sarcopenic obesity, muscle loss, lean tissue, lean body mass, fat free mass, skeletal muscle index, myosteatosis, decline in physical function diagnosed by any accepted means; appendicular skeletal muscle mass, grip strength, skinfold thickness, bioimpedance, phase angle, lumbar skeletal muscle index, psoas muscle index, and/or muscle attenuation.

5.2.4 Study Outcomes

The primary outcome measure was prevalence (with percentages) and corresponding 95% CI. Pooled estimates were computed using a random-effects model in MetaXL to provide the most conservative estimate of prevalence allowing for the likely variation between studies. Statistical heterogeneity was be calculated as I^2 (presented as 0-100%). Values <40% were considered relatively unimportant, 40–60 % were considered to indicate moderate heterogeneity and >60% indicated substantial heterogeneity. The Meta-Analysis Of Observational Studies in Epidemiology (MOOSE) guidelines were adhered to throughout.(162). P values less than 0.05 were considered statistically significant.

5.2.5 Data Extraction

This study is reported according to guidelines set out by the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement. The software programme Covidence (Victoria, Australia, www.covidence.org) was used as management tool. After excluding duplicates, I, along with a second researcher, independently reviewed the titles and abstracts and identified relevant studies for full paper assessment. I and a second researcher independently carried out data extraction for each study. Data were recorded on a pre-defined extraction form with the following information extracted: Authors, year of publication,

study type, and characteristics of population. Reference lists of each individual paper were hand-checked.

The risk of bias was assessed using the Cochrane Risk of Bias Comparison and study quality was formally assessed using the Newcastle Ottawa Score (NOS) which uses a star rating system to measure the quality of observational studies. Conference proceedings were not amenable to quality assessment. We assigned scores of 0 to 3, 4 to 6, and 7-9 for low-, moderate-, and high-quality studies respectively.

5.3 Results

5.3.1 Study characteristics.

The literature search identified 33 studies, reported according to the PRISMA guidelines (Figure 5.1). Characteristics of included studies including study quality are described in Table 5.3. The majority of studies (n=25) evaluated patients with resectable pancreatic cancer undergoing surgery (134, 163-187), while eight studies investigated patients undergoing neo-adjuvant treatment (188-194). Thirteen studies represented Asian cohorts, while 11 were from North America, seven were from Europe and one was from Australia. All studies evaluated adult patients only, and none employed an upper age cut-off. The majority reported that the median age of their cohort fell between 60 and 70 years, as is typical for the age of onset of pancreatic cancer. All studies assessed body composition parameters, with none utilising functional parameters to measure sarcopenia.

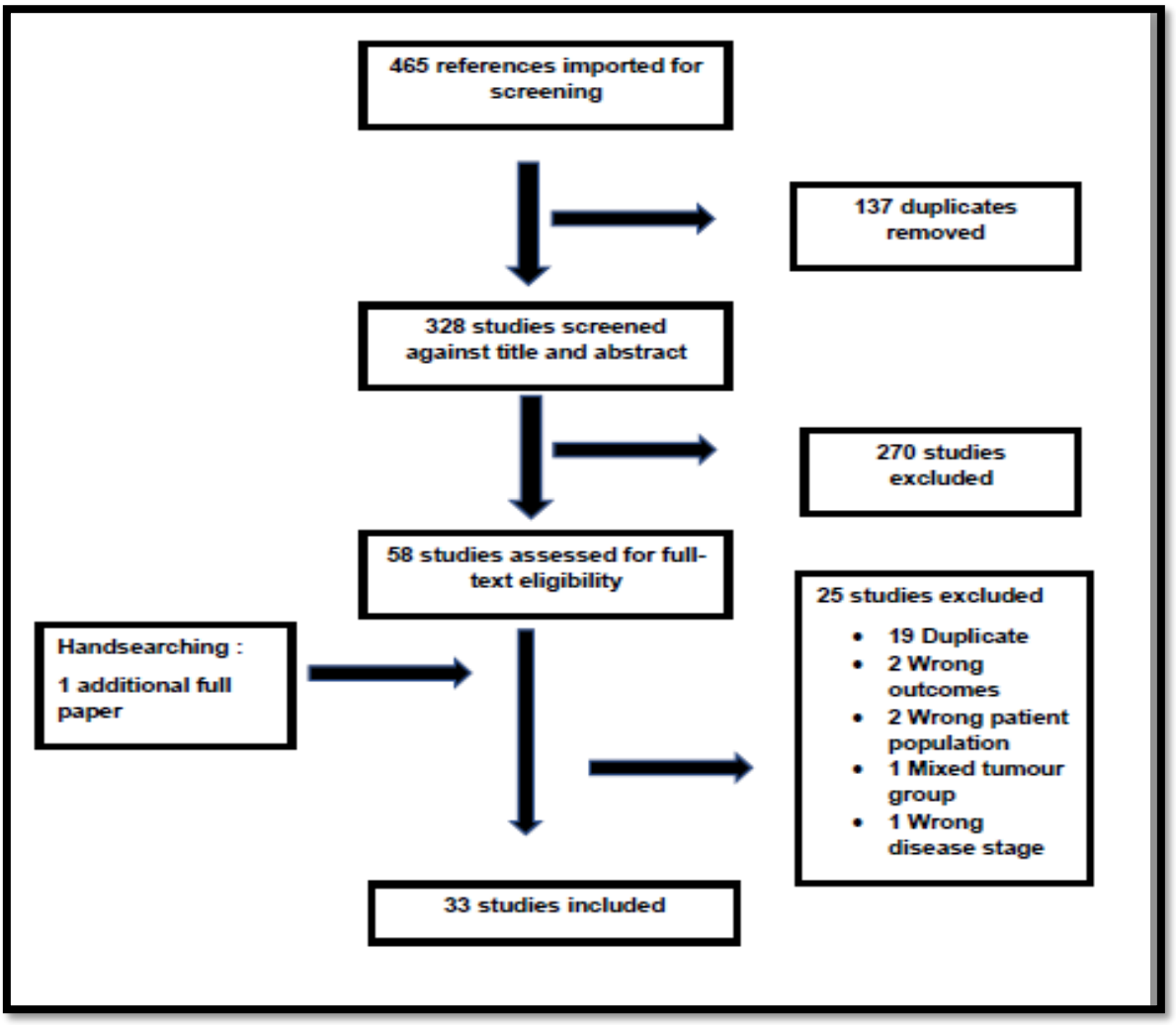

Figure 5. 1 Flowchart illustrating the process for the assessment of eligible studies for analysis.

Table 5. 3 Characteristics of included studies for assessment of prevalence

Study Author & Year	Publication Type	Method of assessment	Site of assessment	Definition and cut-offs used	N	Age (years)	Gender (% male)	Sarcopenia prevalence	Country	NOS
Akahori 2015	Paper	CT	L3	Muscle attenuation – HU Lowest quartile (sex-specific)	83	Low HU "MA" 69 Non MA 64	55.4	24% MA	Japan	7
Amini 2015	Paper	CT	L3	Total Psoas Area (TPA) (mm^2/m^2) <414.5 (F) <564.2 (m) Total Psoas Volume (TPV) (cm^3/m^2) <12.0 (F) <17.2 (M)	763	67 (58-74)	55	TPA 25.2% TPV 19.9%	USA	7
Asare 2012 [40]	Abstract	CT	L3	TAMA (mm^2/m^2) Median <143.9 (M) <97.7 (F)	132			52.3% (42% RPC) (69% BRPC)	USA	X
Aslani 2010	Paper	BIA	Seca Hand & foot unilateral	Total body Nitrogen Nutrition Index	36	71.4 (41-81.6)	41.7	13.9%	Australia	7
Carrara 2016	Paper	CT	L3	LSMI <52.4cm/m^2 (M) <38.5cm/m^2 (F)	273	66.6 (10.9)	55.7	64.5%	Italy	8
Chakedis 2018	Abstract	CT	L3	Psoas Lowest quintile	99	___	___	21%	USA	X
Choi 2018	Paper	CT	L3	LSMI – lowest tertiles (sex-specific)	180	64 (9.3)	54	33%	Korea	8
Cloyd 2017	Paper	CT	L3	LSMI <55.4cm/m^2 (M) <38.9cm/m^2 (F)	127	64.6 (8.9)	53.5	63%	USA	7

Study Author & Year	Publication Type	Method of assessment	Site of assessment	Definition and cut-offs used	N	Age (years)	Gender (% male)	Sarcopenia prevalence	Country	NOS
Coe 2014	Abstract	CT	____	Skeletal muscle area/height Skeletal muscle Density Lowest tertile	85	____	____-	33%	UK	X
Cooper 2015	Paper	CT	L3	LSMI <55.4cm/m² (M) <38.9cm/m² (F)	89	63 (38 -79)	55	55%	USA	7
Delitto 2016	Paper	CT	L3	Psoas muscle/L3 vertebrael body Median level	73	50% < 65 31% 65-74 19%>75	58.9	50.6%	USA	7
Furukawa 2016	Abstract	CT	L3	LSMI – lowest quartile (sex-specific)	223	____	64.7	27.3%	Japan	x
Jin 2018	Paper	CT	L4	Psoas Area (mm²/m²) cut-off:500	183	68 (sarco)	51.9	33%	USA	9
Joglekar 2015	Paper	CT	L3	Total Psoas Index Psoas Density (HUAC) (lowest quartile)	118	____	63.6	26.3% TPI 24.6% HUAC	USA	7

Study Author & Year	Publication Type	Method of assessment	Site of assessment	Definition and cut-offs used	N	Age (years)	Gender (% male)	Sarcopenia prevalence	Country	NOS
Miyamoto 2017	Abstract	BIA	Whole body bilateral	SMI <6.87kg/m² (M) <5.46 kg/m² 9F)	122	____	____	42.6%	Japan	x
Namm 2013	Abstract	CT	L3	Total Psoas Area (cm²/m²) lowest tertile	58	67 (36-87)	_____	32.7	USA	X
Ninomoya 2017[7]	Paper	CT	L3	LSMI <43.75cm/m²(M) <38.5cm/m² (F)	265	M 65(10.5) F 66(9.3)	61.9%	64.2%	Japan	8
Nishida 2016	Paper	CT	L3	LSMI <43cm/m² (M) BMI <25kg/m² <53cm/m² (M <41 cm/m² (F)	266	69(27-87)	68%	49.6%	Japan	8
Okumura 2017	Paper	CT	L3	LSMI <47.1cm/m² (M) <36.6cm/m² (F)	301	68 (61-74)	55.8%	39.9%	Japan	8
Pecorelli 2018	Paper	CT	L3	LSMI <43cm/m² (M) where BMI <25kg/m² <53cm/m² (M) where BMI >25kg/m² <41 cm/m² (F) Sarcopenic obese VFA/TAMA ratio>3.2	120	62.5 (aged over 70)	62.5%	55.8% Sarcopenia 52.5% sarcopenic obese.	Italy	7
Sagnotta 2015	Abstract	CT	L3	LSMI <52.4cm/m² (M) <38.9cm/m² (F)	144	67.15	49%	74.5%	Italy	X

Study Author & Year	**Publication Type**	**Method of assessment**	**Site of assessment**	**Definition and cut-offs used**	N	**Age (years)**	**Gender (% male)**	**Sarcopenia prevalence**	**Region**	**NOS**
Sandini 2018	Paper	CT	L3	LSMI <43cm/m² (M) where BMI <25kg/m² <53cm/m² (M) where BMI >25kg/m² <41 cm/m² (F)	193	64(	50.3	43.5%	USA/ Italy	8
Sandini 2016	Paper	CT	L3	LSMI <43cm/m² (M) where BMI <25kg/m² <53cm/m² (M) where BMI >25kg/m² <41 cm/m² (F)	124	72	50.8%	24.2	Italy	7
Stretch 2018	Paper	CT	L3	LSMI Lowest 40th percentile <47.7cm/m² (M) <36.5cm/m² (F)	119	Sarcopenic 68.5 Non-sarcopenic: 66.1	61.8%	44	Canada	6
Sugimoto 2018	Paper	CT	L3	LSMI <55.4cm/m² (M) <38.9cm/m² (F)	323	65	54.4%	61.9% 24.7%	USA	8
Sui 2018	Paper	CT	L3	LSMI – quartiles <40.5cm/m² (M) <33.5cm/m² (F)	168 /354		57.3%	31.5%	Asia	8
Takagi 2017	Paper	CT	L3	TAMA/BSA = SBI (cm²/m²) Lowest quartile	86/ 219	65.9	65.3%	29%	Asia	8
Takahashi 2017	Abstract	CT	L3	LSMI Median: 40.79	43	____	_____	51%	Asia	X

Study Author & Year	Publication Type	Method of assessment	Site of assessment	Definition and cut-offs used	N	Age (years)	Gender (% male)	Sarcopenia prevalence	Region	NOS
van Dijk 2017	Paper	CT	L3	LSMI (tertile) Muscle attenuation (HU) Lowest tertile <33.9 HU (M) <30.9 HU (F)	73/ 186	66.5	54.8	LSMI 33 HU 28.8	The Netherlands	9
Wagner 2018	Paper	CT	L3	Total Psoas Index – lowest quartile <14..65cm²/m² (F) <20.74 cm²/m² (M) Psoas Density (HUAC) <15.69(F)/<16.29 (M)	424	63	47.9	TPI 34% HUAC 34.2%	Austria	7
Wu 2018	Paper	CT	L3	LSMI Western <52.4cm/m² (M) <38.9cm/m² (F) LSMI Eastern <36.2cm/m² (M) <29.6cm/m² (F)	57 /146	65.5	56.8	61.4% Western cut-off 7% Eastern cut-off	Taiwan	7
Yamamura 2017	Abstract	CT	L3	LSMI <42cm²/m² (M) <38cm²/m² (F)	130	_____	_____	31.5%	Japan	X
Yamane 2018	Paper	CT	L3	LSMI <43cm/m² (M) where BMI <25kg/m² <53cm/m² (M) where BMI >25kg/m² <41 cm/m² (F)	99	55.6%>70	69.7%	40.4%	Japan	6

5.3.2 Body composition assessment in pancreatic cancer

Only two studies utilised BIA (163, 172) as an assessment method, while the remainder used a variety of CT-derived measurements. Twenty-three studies measured skeletal muscle at the level of the L3, and normalised for height to report as LSMI (134, 164, 168, 170, 174-187, 190, 191, 193, 194) or Total Abdominal Muscle Area (189). One study normalised muscle area by Body Surface Area(193). Seven studies evaluated psoas muscle only, with some reporting Psoas Index (area normalised for patient's height) (165, 166, 171, 173, 183, 192), and one reported psoas area divided by L3 vertebral body (169).

Methods of assessment varied from manual tracing of muscle structure to the application of a number of different software programmes using established radiodensity cut-offs, specifically Slice-O-Matic™, Osirix, Image- J, Synapse Vincent Fujifilm, and Aquarius iNtuition Server. Studies utilising LSMI as a proxy for sarcopenia either applied a variety of previously reported, pre-defined gender specific cut-offs, or defined their individual population-specific cut-offs, such as the lowest gender specific quartile or median level. Five studies applied previously reported gender- and BMI-specific cut-offs (134, 151, 174, 176, 178, 194). A number of studies included the assessment of muscle density assessment when evaluating body composition (168, 171, 182, 183, 188), while three studies considered the impact of co-existing obesity/adiposity (134, 176, 178).

5.3.3 Prevalence of Sarcopenia – Meta- analysis

Over five thousand patients from thirty-three studies were included in this meta-analysis. The reported prevalence of sarcopenia in patients with R/BRPC varied between 14 and 74 %. Based on the random-effects model, the pooled prevalence rate of sarcopenia was 39% (95% CI 38-40%) (Figure 5.2). Including studies which used CT- derived LSMI alone, the pooled prevalence was 47% (Figure 5.3), while assessment using psoas index yielded a pooled prevalence of 28% (Figure 5.4). The pooled prevalence of sarcopenia was 35% in studies assessing sarcopenia using muscle radiodensity. Heterogeneity was considerable however (I^2 *93*%) and did not improve significantly when controlling for assessment method (CT derived LSMI 93%, psoas index 72%, muscle density or attenuation 84%), and/or pre-defined gender and BMI- specific cut-offs (Figure 5.5).

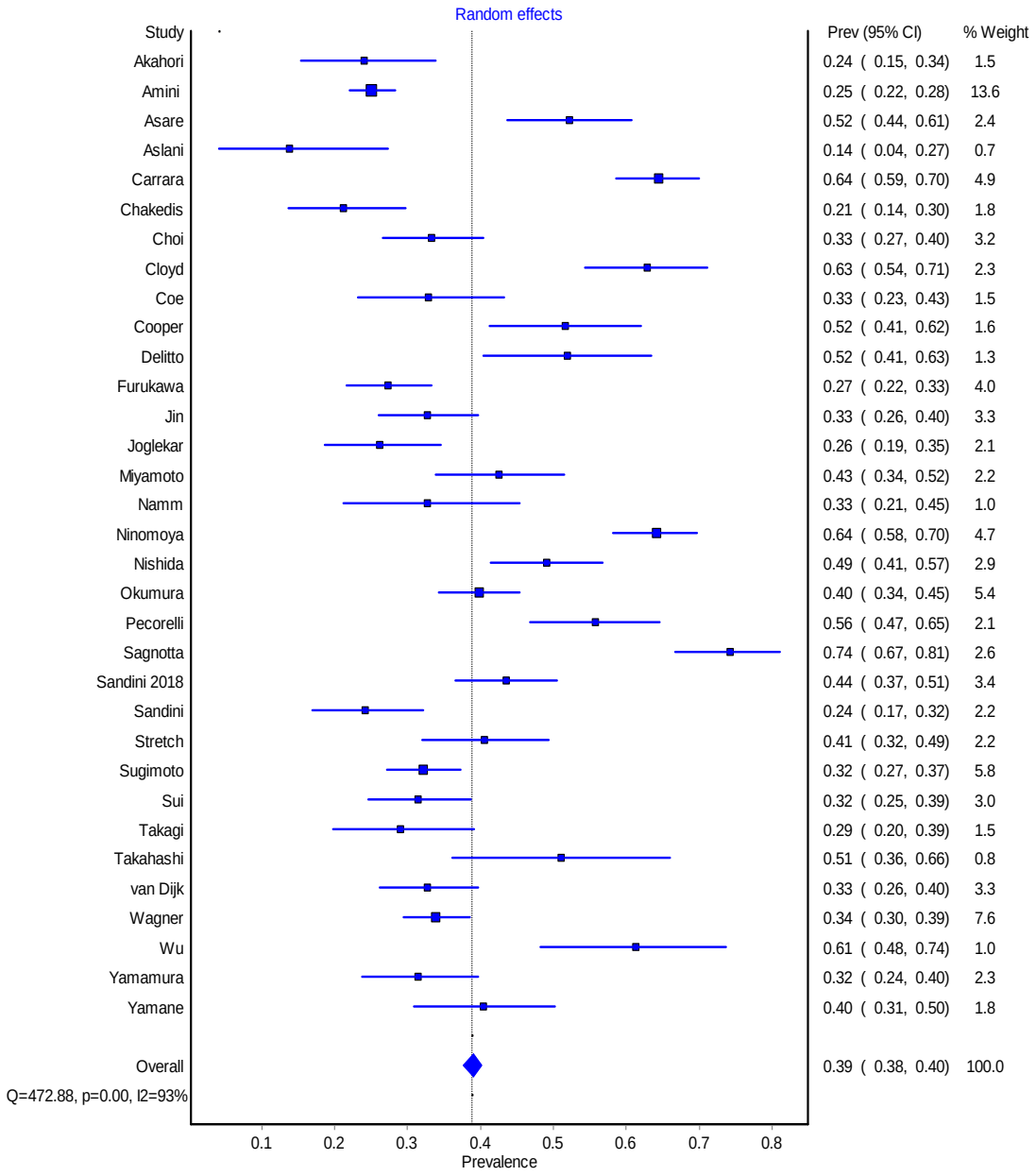

Figure 5. 2 Prevalence of sarcopenia, all studies, all methods (n=5,593)

CI confidence interval

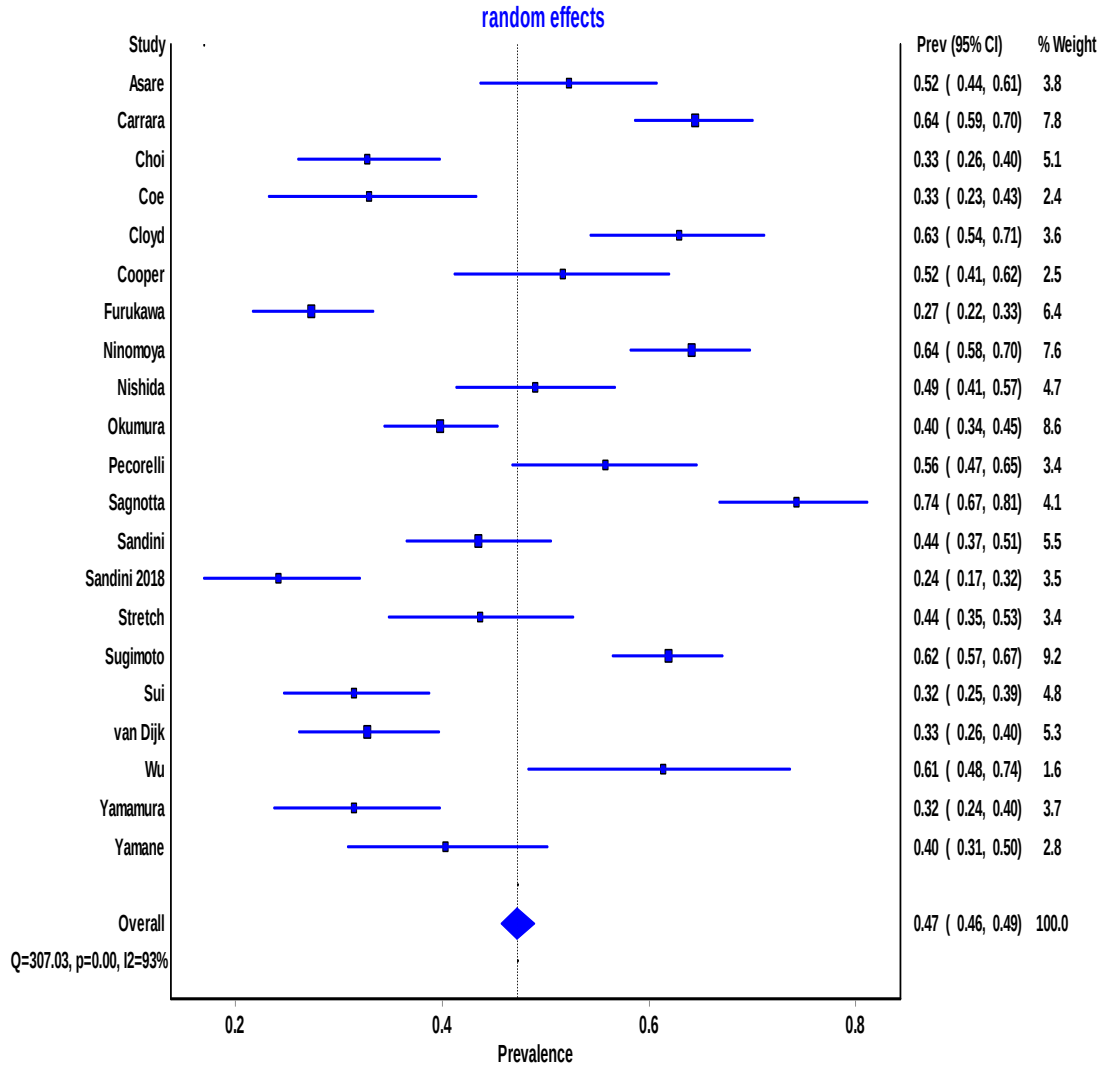

Figure 5. 3 Prevalence of sarcopenia when assessed by Computed Tomography at L3 (LSMI)

L3 third lumbar vertebrae; LSMI lumbar skeletal muscle index; CI confidence interval

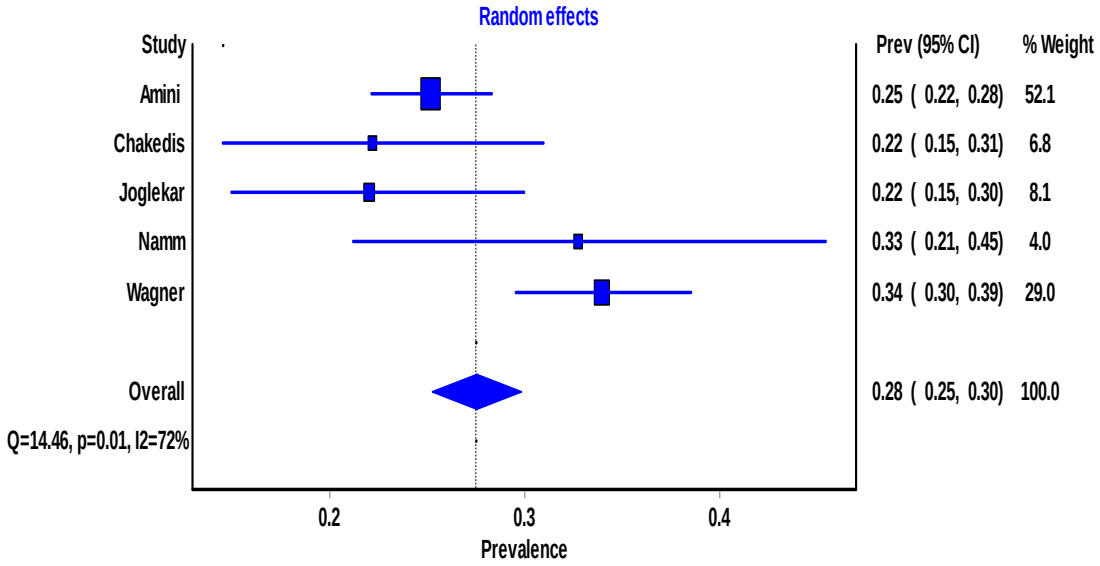

Figure 5. 4 Prevalence of sarcopenia when assessed by Psoas Muscle Index

CI confidence interval

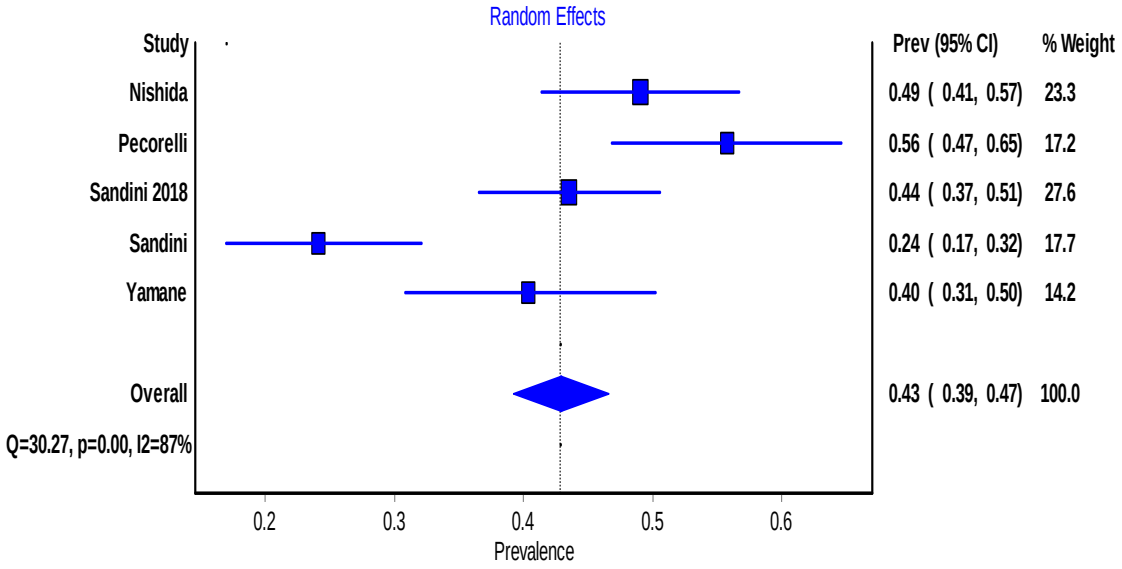

Figure 5. 5 Prevalence of sarcopenia, assessed by CT using Martin gender and BMI- specific cut-offs (151)

CT computed tomography; BMI body mass index; CI confidence intervals

5.3.4 Post-operative morbidity and mortality

Two studies evaluated body composition using BIA, and neither found that protein deficiency or reduced skeletal muscle index had any effect of post-operative morbidity or mortality (163, 172).

Seven studies evaluated LSMI and the impact of sarcopenia on post-operative morbidity and mortality. One study found that sarcopenia had no effect on post-operative morbidity (167), and two studies found sarcopenia was associated with an increased risk of infection (171, 181). Four studies found an associated between sarcopenia and post-operative complications. Nishida et al reported that sarcopenia was independently associated with increased risk of clinically significant POPF, OR 2.869 (95% CI 1.329-6.197), p=0.007 (174). In a multicentre study, Pecorelli et al evaluated found that sarcopenic obesity, but not sarcopenia itself, was independently associated with 90-day mortality (OR 5.7(95% CI 1.6-20.7) P=0.008) (176). Similarly Yamane et al found that sarcopenic obesity rather than sarcopenia was independently associated with increased risk of POPF, HR 5.353 (95% CI 1.534 -18.68), P=0.009 (134, 174). A cohort study from Italy also reported that sarcopenic obesity, rather than sarcopenia itself, was associated with an increased risk of major post-operative complications (OR 3.2(95% CI 1.35-7.6) P=0.008) (178).

5.3.5 Treatment tolerance and delivery

Six studies evaluated the impact of pre-treatment muscle indices on the tolerance and delivery of treatment, three of which concluded that sarcopenia at baseline had an adverse effect on treatment tolerance. Two studies found that pre-treatment sarcopenia was associated with a higher incidence of treatment toxicity for patients undergoing gemcitabine-based chemotherapy (193) and stereotactic body radiation therapy (192). A mixed cohort of patients with R/BRPC found that sarcopenia at diagnosis was a negative prognostic indicator for successful completion of neo-adjuvant therapy, OR 2.57 (95%CI 1.06-6.10) P=0.03 (189). Three studies found that while sarcopenia at diagnosis had no effect on treatment delivery (188, 190, 194), improvements in muscle indices during treatment were associated with improved patient outcomes(188, 194).

5.3.6 Long-term survival

The impact of sarcopenia on the overall survival for patients with R/BRPC was assessed in 13 studies (165, 167, 169, 175, 177, 180, 182, 184, 186, 188, 190-192). Five studies reported that baseline muscle indices had no effect on overall survival (177, 188, 190-192). Of the remaining nine studies, two utilising psoas muscle measurement methodologies found that sarcopenia was an independent prognostic indicator (165, 169). Similarly, low muscle attenuation was independently associated with reduced survival (175, 182) in two studies utilising this technique. Only two studies

evaluated the impact of sarcopenia on recurrence-free survival, both of which reported that sarcopenia, assessed by LSMI, was independently associated with reduced recurrence-free survival (175, 180).

5.4 Discussion

This systematic review and meta-analysis of 33 studies comprised 5,593 patients with R/BRPC and demonstrated that sarcopenia is prevalent in patients with early stage disease, affecting nearly 40% of patients prior to treatment. Previously described as understudied (159), this review has shown that interest in body composition in pancreatic cancer is increasing. Of the 33 studies included in the meta-analysis, almost 9 in 10 were published in the three years preceding the search.

Multiple studies reported that sarcopenia, assessed by a variety of body composition methodologies, was associated with increased post-operative complications, treatment toxicities and reduced overall and recurrence-free survival. Conventional chemotherapy prescription is based on body surface area calculation, which like BMI, fails to take body composition into account. Variation in body composition may result in increased chemotherapy drug toxicity and intolerance.

As reported, the majority of studies utilised CT for body composition assessment, and only two studies used BIA. CT- based assessment offers the advantage of discriminating at the tissue-organ level when compared to DEXA or BIA and is particularly important in the setting of malignant disease where tumour metastases and peripheral wasting can occur simultaneously. BIA has been shown to be inferior to CT when evaluating the body composition of cancer patients (97, 195). Application is typically restricted to opportunistic assessment of the scans acquired as part of cancer treatment planning and review however, making it difficult to optimise timing of assessment, or control for the use of contrast. Both phase of CT, and the use of contrast have previously been shown to influence body composition parameters, in particular muscle radiodensity or attenuation, and adipose tissue values (196). Similarly the choice of body composition analysis software programmes may lead to disparity in measures (197), and therefore the same software should be used for sequential measurements.

The advent of CT- based body composition assessment has led to the popularisation of numerous methods and techniques as seen in the studies included in this systematic review. While lumbar muscle area correlates with whole body muscle/lean tissue (98), the use of single muscle measurement (such as psoas measurement) to diagnose sarcopenia or to estimate total body muscle has not been validated or approved by any expert group (198). An expert consensus group recently reviewed the validity of body composition assessment methods in clinical populations,

and concluded that the use of DEXA, BIA or ultrasound for the assessment of lean body mass could not be recommended. However, while CT was used as a reference for many of the studies included for evaluation of DEXA as a method of assessment, the expert consensus group did not comment on or address the validity of the optimal method of CT-based body composition assessment (199).

Although loss of muscle mass and myosteatosis occur as physiological consequences of aging (200), age has not been included in the development CT-derived cut-offs for sarcopenia and low muscle attenuation (whether population-specific or predefined). There is a clear need for normative data values for LSMI across the life span. Additionally, there should be international, collaborative efforts to evaluate variation in body composition across geographical regions and ethnicities(161). One study from Japan evaluated ethnicity- specific criteria for the assessment of sarcopenia in pancreatic cancer patients undergoing surgery. The authors applied pre-defined gender specific LSMI cut-offs from so called ‘eastern’ and ‘western’ populations, and reported a disparity in the prevalence of sarcopenia according to the definition used (7% vs 61.4%)(184), with only the Eastern cut-offs showing a prognostic effect.

5.4.1 Study limitations

The limitations of this study relate to the inherent limitations of the individual studies included. Specifically, while authors reported the prevalence of sarcopenia for patients with pancreatic cancer separately in

mixed cohorts, most studies also included patients with other cancers (cholangiocarcinomas, ampullary adenocarcinoma, neuroendocrine and duodenal cancers) when subsequently evaluating the impact of sarcopenia on post-operative morbidity and overall survival. This confounds the ability to extract the data for pancreatic cancer patients.

A further limitation of published studies was the failure to include any functional measurement in the assessment of sarcopenia, particularly in the context of the recently updated expert consensus diagnostic criteria for sarcopenia which focuses on low muscle strength as a key characteristic of sarcopenia(201). Similarly, while half of the studies included in this meta-analysis reported blinding of individuals carrying out body composition analysis to patient outcome to reduce the risk of bias, none reported inter or intra-observer variability. Furthermore, considerable heterogeneity of studies limited the potential to carry out sub-group analyses to evaluate the impact on specific outcomes.

5.5 Conclusions and Recommendations for Practice

This systematic review and meta-analysis highlighted that sarcopenia, defined by low muscle mass or low muscle quality assessed by CT, is common at diagnosis in patients with cancer/BRPC.

Future studies evaluating the impact of sarcopenia in pancreatic cancer should recognise the importance of muscle strength and physical performance alongside assessment of muscle quantity/ quality. While there has been increasing interest in the assessment of sarcopenia in cancer patients, no specific guidelines exist for optimal assessment technique. Therefore, recommendations for the use of CT-based techniques for future studies are suggested in Table 5.4. International collaboration is essential to achieve these necessary advances in body composition assessment methodology of cancer patients. While welcome progress has been made in the development of chemotherapy agents targeting pancreatic cancer, malnutrition and poor performance status remain limiting factors to their successful delivery in practice.

Table 5. 4 Recommendations for the design of studies using computed tomography for body composition assessment

Recommendations for the design of studies using CT for body composition assessment
1. To measure body composition, use a technique which has been validated for the estimation of total body composition rather than measuring a single muscle in isolation(198). 2. For sequential measurements, both software, CT-phase and use of contrast enhanced images should be consistent and controlled (196, 197) 3. Measure physical performance such as gait speed, and/or handgrip strength as well as muscle quality/quantity(201). 4. If devising population-specific cut-offs, use ROC analysis to determine whether dichotomous variable from the population being studied has predictive ability and external reproducibility regarding outcome of interest(202). 5. Those conducting the assessment should be trained in the technique, and inter- and /or intra-observer variance reported.

ROC, Receiver-operating characteristics; CT, computed tomography.

Chapter 6: Investigating the prevalence and impact of sarcopenia on post-operative morbidity and mortality in pancreatic cancer surgery

This chapter describes a retrospective cohort study which evaluated the association between sarcopenia and post-operative outcomes in patients undergoing pancreatic cancer surgery.

6.1 Rationale for study

As highlighted in Chapters 1 and 2, curative surgery for pancreatic cancer is limited to less than one-quarter of patients diagnosed with the disease. Given the high morbidity and mortality associated with pancreatic resection, international efforts have focused on centralisation of pancreatic surgery to high volume centres in an attempt to improve outcomes. Despite this, post-operative morbidity remains significant, and may delay or limit the delivery of post-operative adjuvant oncological treatment.

The negative impact of pre-operative weight loss on post-operative outcome in pancreatic cancer surgery is well established (43, 88), however weight loss maybe missed in an overweight or obese patient. A prospective survey of practice among oncology dietitians in Ireland highlighted the problem of late referral and multiple missed opportunities for nutritional assessment, particularly in patients with pre-existing obesity(203). Conventional nutritional screening tools have demonstrated

limited sensitivity in identifying sarcopenia in cancer patients (126).The emergence of sarcopenic obesity as a negative prognostic factor in advanced cancer (85, 94) has stimulated multiple researchers to retrospectively evaluate body composition in patients with pancreatic cancer (159, 204). The previous study, detailed in Chapter 4, highlighted ongoing disparity in assessment methods used in these studies. This heterogeneity limits the potential to evaluate the impact of body composition on post-operative outcome.

Multiple systematic reviews have identified the benefits of prehabilitation prior to major abdominal surgery, reporting reduced post-operative complications (respiratory and cardiac) in patients who underwent pre-operative prehabilitation (205, 206). However, delaying surgery for pre-operative patient optimisation in the context of pancreatic malignancy is not a risk-free strategy, and concern regarding disease progression during the period of prehabilitation may be a limiting factor in both clinical practice and the research setting.

6.2 Aim

This study sought to examine the prevalence of sarcopenia in patients undergoing pancreatic surgery**,** and to investigate the impact of sarcopenia on post-operative morbidity and mortality.

6.3 Methods

6.3.1 Subjects

All patients who underwent pancreatic resection at SVUH for suspected pancreatic malignancy between 1st January 2010 and 31st December 2013 were identified from a prospectively maintained database. Additional inclusion criteria were the availability of a pre-operative CT scan for body composition analysis along with necessary anthropometric details for interpretation.

6.3.2 Data collection

Individual patient charts were reviewed to allow extraction of relevant procedure details and post-operative course. Major post-operative morbidity was defined as per Clavien-Dindo (>3) grading (207) (Table 6.1) , while individual complications were defined as per ISGPS consensus definitions (DGE, Chyle leaks, POPH, POPF)(18-21) (Table 6.2,6.3,6.4 and 6.5). Patient status was censored on 31th December 2018 to allow a minimum of five-year follow up for all patients.

Table 6. 1 Clavien-Dindo classification

Grades	Definition of grades	Modes of therapy
Grade I	Any deviation from the normal postoperative course.	No pharmacological or surgical treatment, endoscopic or radiological interventions were required. Acceptable therapeutic regimens are drugs such as anti-emetics, antipyretics, analgesics, diuretics, and electrolytes and physiotherapy. Wound infections or small abscess requiring incision at bedside is within this category
Grade II	Normal course altered	Pharmacological management other than in Grade 1. Blood transfusions and total parenteral nutrition are also included.
Grade III	Complications that require intervention of various degrees	Sub-classified into: Grade 111a – complications that require an intervention performed under local anaesthesia Grade 111b – interventions that require general or epidural anaesthesia.
Grade IV	Complications threatening life of patients (including CNS complications), requiring ITU support	Further sub-classified into: Grade IVa – single organ dysfunction (including dialysis) Grade IVb – multi-organ dysfunction
Grade V	Death of a patient	

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Table 6. 2 ISGPS consensus DGE definition

DGE Grade	NGT required	Unable to tolerate solid oral intake by POD	Vomiting/gastric distention	Use of prokinetics
A	4-7 days or reinsertion > POD 3	7	±	±
B	8-14 days or reinsertion > POD 7	14	+	+
C	>14 days or reinsertion > POD 14	21	+	+

ISGPS International study group for pancreatic surgery; DGE Delayed gastric emptying; POD Postoperative day; NGT Nasogastric tube

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Table 6. 3 ISGPS consensus chyle leak definition and grading

	Grade A	Grade B	Grade C
Therapeutic consequence	None or oral dietary restrictions*	Nasoenteral nutrition with dietary restriction* and/or TPN, percutaneous drainage by IR, maintenance of surgical drains, or drug (eg. Octreotide) treatment	Other invasive in-hospital treatment, admission to the intensive care unit, and/or mortality
Discharge with (surgical) drain or readmission	No	Possibly	Possibly
Prolonged hospital stay	No	Yes	Yes

Chyle leak is defined as the output of milky-coloured fluid from a drain, drain site, or wound, on or after postoperative day 3, with a triglyceride content $\geq$110mg/dL or $\geq$1.2 mmol/L.

*No-fat diet with/without medium-chain-triglyceride.
TPN. total parenteral nutrition: *IR*. interventional Radiology
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Table 6. 4 ISGPS classification of post-pancreatic haemorrhage

Grade	Time of onset, location, severity and clinical impact of bleeding	Clinical condition	Diagnostic consequence	Therapeutic consequence
A	Early, intra- or extraluminal, mild	Well	Observation, blood count, ultrasonography and, if necessary, computed tomography	No
B	Early, intra- or extraluminal, severe	Often well/intermediate, very rarely life-threatening	Observation, blood count, ultrasonography, computed tomography, angiography, endoscopy	Transfusion of fluid/blood, intermediate care unit (or ICU), therapeutic endoscopy embolisation, relaparotomy for early PPH
C		Severely impaired, life- threatening	Angiography, computed tomography, endoscopy	Localization of bleeding, angiography and embolisation *or* relaparotomy, ICU

ISGPS International Study Group for Pancreatic Surgery; PPH post-operative pancreatic haemorrhage; ICU Intensive care unit

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Table 6. 5 ISGPS consensus definition and checklist for POPF

Event	BL (No POPF)	Grade B POPF*	Grade C POPF*
☐	☐	☐	☐
☐ Increased amylase activity >3 times Upper limit institutional normal serum value	☐ Yes	☐ Yes	☐ Yes
☐ Persisting peripancreatic drainage > 3 weeks	☐ No	☐ Yes	☐ Yes
☐ Clinically relevant change in management of POPF*	☐ No	☐ Yes	☐ Yes
☐ POPF percutaneous or endoscopic specific interventions for collections	☐ No	☐ Yes	☐ Yes
☐ Angiographic procedures for POPF related bleeding	☐ No	☐ Yes	☐ Yes
☐ Reoperation for POPF	☐ No	☐ No	☐ No
☐ Signs of infection related to POPF	☐ No	☐ Yes, without organ failure	☐ Yes, with organ failure
☐ POPF related organ failure	☐ No	☐ No	☐ Yes
☐ POPF related death	☐ No	☐ No	☐ Yes

ISGPS International Study Group on Pancreatic Surgery; BL biochemical leak; POPF postoperative pancreatic fistula.

*A clinically relevant POPF is defined as a drain output of any measurable volume of fluid with amylase level greater than 3 times the upper Institutional normal serum amylase level, associated with a clinically relevant development/condition related directly to the POPF

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6.3.3 Body composition analysis

Body composition analysis was carried out using the methodology outlined in Chapter 4, with the Martin gender and BMI-specific cut-offs used to define sarcopenia and low muscle attenuation.

6.3.4 Statistical analysis

Statistical analysis was conducted using SPSS (IBM SPSS Statistics version 24, Chicago, Illinois, USA) as described in Chapter 4. Overall survival (OS) was calculated from the date of surgery until the date of death or censor (December 31st 2018). Associations between relevant clinical and anthropometric variables were assessed using Cox proportional hazard models or binary logistic regression as appropriate. Results were reported as either hazard ratios (HR) or odds ratios (OR) with 95% Confidence Intervals. Kaplan-Meier survival curves were generated using dichotomised defined cut-off values and evaluated using the log-rank (or Mantel-Cox test).

6.4 Results

In total, 344 patients underwent pancreatic resection at SVUH between 2010 and 2013 for suspected malignancy. Of these, the majority were male (62%, n=214), and the median age was 65 years (interquartile range 54-70 years). Over two-thirds (n=235) had malignant pathology on pathological examination. The 30-day mortality was 1.7% (n=6) while 4.6% (n=16) patients died within 90 days of their surgery. Major post-operative morbidity, defined as per Clavien-Dindo >3, was 26.2% (n=90). Most patients (73%, n=251) underwent PD (with or without pylorus preservation), and the median overall survival was 61 months.

N=276 patients had both a pre-operative CT available for analysis and the necessary anthropometry for interpretation, and these patients comprised the study population. The patient demographics and clinicopathologic parameters of this patient cohort are summarised in Table 6.6. Sarcopenia was observed in 46% of this patient cohort (n=127), while low muscle attenuation was present in 51.8% of patients (n=143).

Table 6. 6 Patient cohort demographics and clinicopathologic parameters

BASELINE (n=344) (median or %)			
Age (years)	63	**CA 19-9 (IU/L)**	73.5
Male gender (n,%)	156 (56.5%)	**mGPS >2 (n, %)**	40 (36.7)
Body Mass Index (kg/m²)	25	**Sarcopenia**	127 (46%)
Weight loss at diagnosis (%)	4.6	**Low muscle attenuation**	143 (51.8%)
ASA classification >2 (n,%)	88 (32%)		
PATHOLOGY, n (%)			
Pancreatic adenocarcinoma	107 (54.9)	**Tumour stage ≥3**	141 (74.6)
Cholangiocarcinoma	31 (11.2)	**Positive margin (R1)**	60 (30.6)
Ampullary adenocarcinoma	27 (13.8)	**Node positive disease**	119 (60)
Pancreatic metastases	4 (1.4)		
Neuroendocrine cancer	26 (9.4)		
Benign/pre-malignant	80 (29)		
PROCEDURE	**n (%)**	**MORBIDITY**	**n (%)**
Pancreaticoduodenectomy	140 (50.7)	**Clavien- Dindo >3**	73 (26.5)
Pylorus- preserving pancreaticoduodenectomy	62 (22.5)	**POPF**	32 (11.6)
Distal pancreatectomy	31 (11.2)	**POPH**	15 (5.4)
Distal pancreatectomy & Splenectomy	35 (12.7)	**Chyle leak**	16 (5.8)
Total pancreatectomy	3 (1.1)	**DGE**	35 (12.7)
Other (ventral pancreatectomy, Izbicki)	5 (1.8)	**Need for re-laporotomy**	22 (8)
OUTCOME (median or %)			
LOS (days)	14	30-day mortality	3 (1%)
Survival (months)	60	90-day mortality	11 (4%)

ASA, American Society of Anaesthesiologists; mGPS, modified Glasgow Prognostic Score; POPF, Post-operative pancreatic fistula; POPH, Post-operative pancreatic haemorrhage; DGE, delayed gastric emptying; LOS, length of stay.

6.4.1 Post-operative morbidity

Significant post-operative morbidity occurred in 26.5% of patients (n= 73), and led to a more prolonged median length of stay compared to patients who did not experience complications (31 vs 14 days respectively, $p<0.0001$). Those with higher post-operative morbidity had lower muscle attenuation than those with lower post-operative morbidity (34.7 vs 37.5 HU $p=0.05$). Sarcopenia, in contrast, did not appear to predict post-operative morbidity (Table 6.7). Low muscle attenuation predicted major post-operative morbidity (OR 1.6, 95%CI1.07-2.19, $p=0.029$) and the occurrence of post-operative pancreatic haemorrhage (OR 3.97, 95% CI1.1-14.4, $p=0.036$). The full results of binary logistic regression analysis are detailed in Table 6.7

Table 6. 7 Logistic regression analysis of muscle variables and post-operative morbidity

Complication	Muscle variable	Odds ratio (95% CI)	P
Clavien-Dindo >3	Sarcopenia Low muscle attenuation	1.02 (0.6-1.75) 1.6 (1.07-2.19)	0.94 0.029
Post-operative pancreatic fistula	Sarcopenia Low muscle attenuation	0.96 (0.46-2.01) 1.41 (0.67-2.99)	0.92 0.36
Post-operative pancreatic haemorrhage	Sarcopenia Low muscle attenuation	0.55 (0.19 -1.6) 3.97 (1.1-14.4)	0.27 0.036
Delayed gastric emptying	Sarcopenia Low muscle attenuation	0.89 (0.437-1.81) 0.6 (0.29-1.24)	0.745 0.16
Chyle leak	Sarcopenia Low muscle attenuation	1.11 (0.4-3.07) 0.834	0.841 0.73
90-day mortality	Sarcopenia Low muscle attenuation	0.31 (0.08-1.18) 4.4 (093-20.7)	0.085 0.061

CI Confidence interval

6.4.2 Overall survival

The median overall survival for this cohort was 60 months. Mortality risk was significantly higher in those with sarcopenia (HR 1.657, 95% CI 1.15-2.4, p=0.007), and sarcopenic patients had reduced median survival (41 months compared to 62 months, log-rank test =0.036, Figure 6.1). Having normal muscle attenuation was associated with lower mortality (HR 0.473, 95% CI 0.34-0.664, p=0.0001), while low muscle attenuation was associated with reduced overall survival (29 months vs 61 months, log rank test p<0.0001, Figure 6.2).

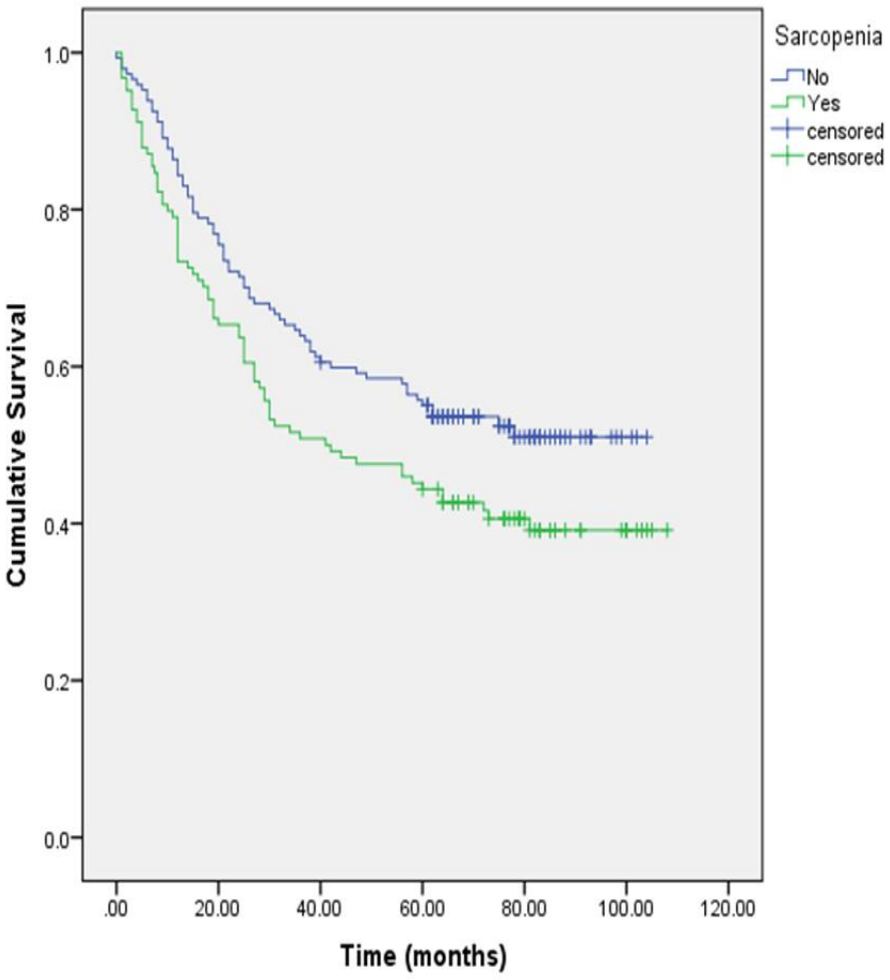

Figure 6. 1 Kaplan-Meier survival curves showing survival in patients with sarcopenia (green line) and without sarcopenia (blue line)

N=276, Log-rank test p=0.016

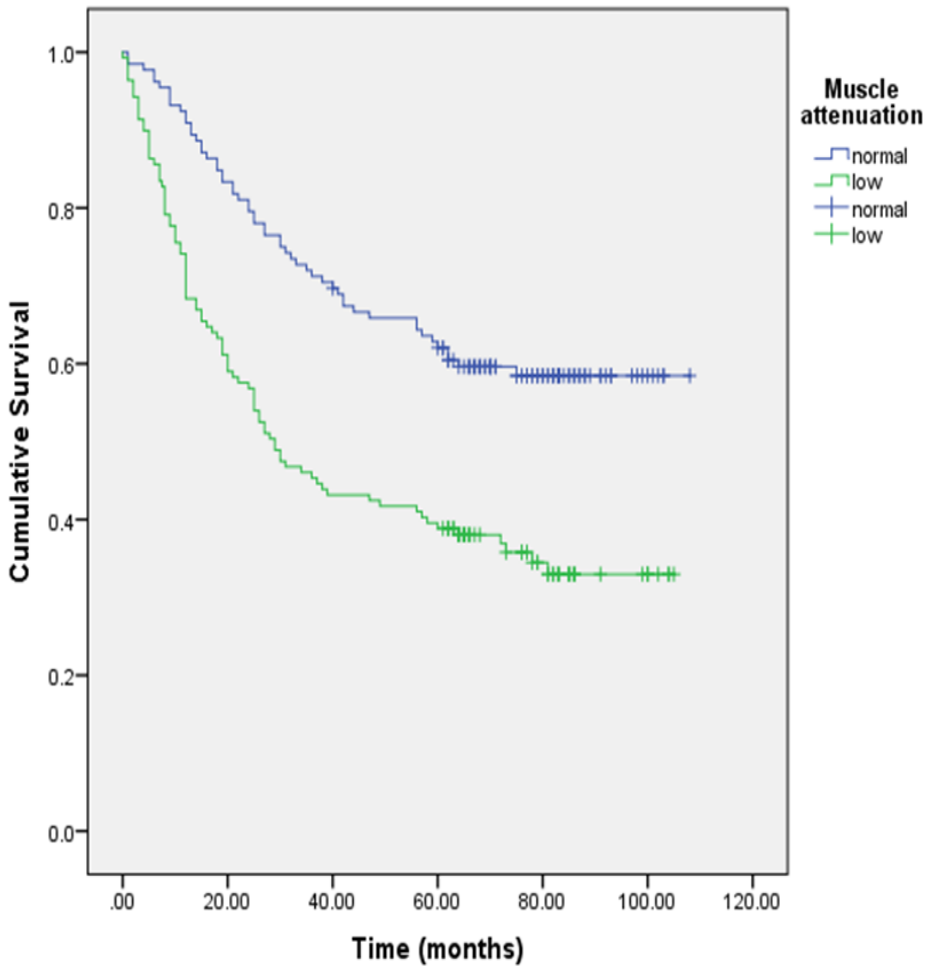

Figure 6. 2 Kaplan-Meier survival curves showing survival in patients with normal muscle attenuation (blue line) compared to low muscle attenuation (green line)

n=276, log-rank test p<0.0001

When the patients with PDAC (n=107) were examined separately, both pre-operative sarcopenia and low muscle attenuation were associated with reduced overall survival. The 5-year survival for patients who underwent surgery for PDAC was 15% (n=16), and the median survival was 20.5 months (IQR 10.75 -40.25). Median survival was 16 months for those with sarcopenia compared to 26 months for those without (p=0.017), (Figure 6.3). Median survival was 12 months for those with low muscle attenuation compared to 30 months for patients with normal muscle attenuation (p=0.016) (Figure 6.4).

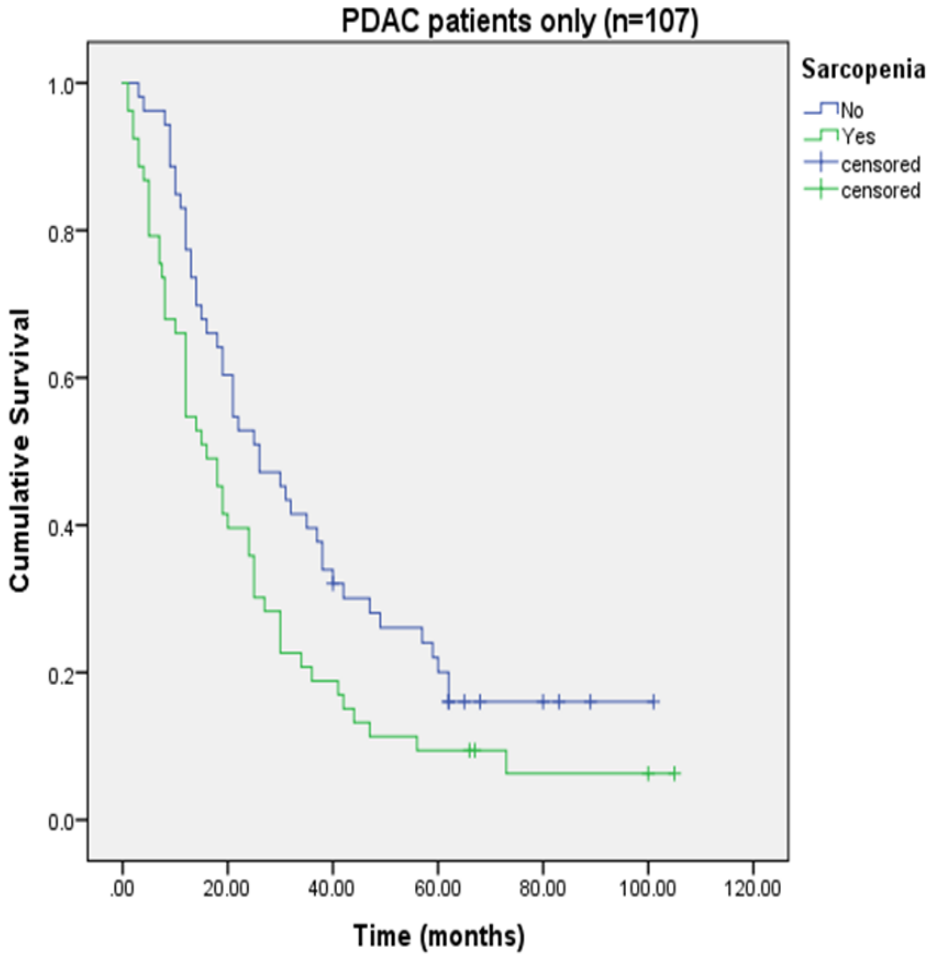

Figure 6. 3 Kaplan-Meier curves showing survival in patients with sarcopenia (green line) compared to no sarcopenia (blue line) in the PDAC only patient cohort

N=107, log-rank test p=0.017

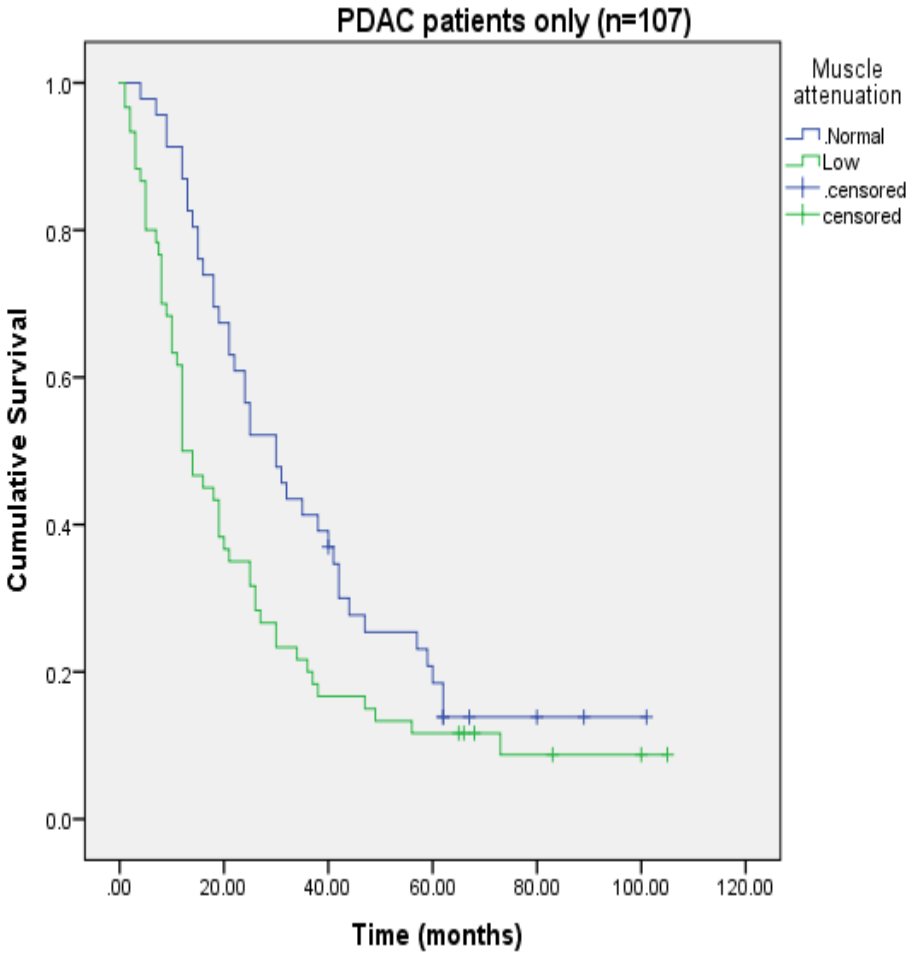

Figure 6. 4 Kaplan-Meier survival curves showing survival for patients with low muscle attenuation (green line) compared to those with normal muscle attenuation (blue line) in the PDAC only patient cohort

N=107, log rank test p=0.016.

6.5 Discussion

This study found that both low muscle attenuation and sarcopenia were prevalent in patients with suspected pancreatic malignancy prior to surgery. Both factors were associated with increased mortality risk and reduced overall survival, while low muscle attenuation was associated with higher major post- operative morbidity.

The most recent consensus definition for primary sarcopenia advocates the use of functional assessment to diagnosis sarcopenia (201). They recommend that assessment of muscle mass (regardless of body composition assessment method) should only be used to confirm the diagnosis (201). Muscle attenuation may be superior to measurement of mass in predicting functional and strength assessment (208). Muscle attenuation or radiodensity is reduced by adipose tissue infiltration of muscle, a known consequence of aging. Increased accumulation of lipid within muscle has also been demonstrated in patients with increased inflammation associated with cachexia (209), and is associated with reduced muscle contractility and power (208). Transcriptomic analysis of rectus abdominal muscle biopsies taken from patients with pancreatic cancer at the time of resection highlighted that sarcopenia and myosteatosis are distinct biological profiles; increased inflammation and decreased muscle synthesis were observed in patients with sarcopenia while disruption of oxidative phosphorylation and lipid accumulation were seen in patients with low muscle radiodensity (210). Unlike most reports

evaluating muscle radiodensity in pancreatic cancer patients to date, in this study muscle attenuation in muscle only was measured, by isolating and measuring intra-muscular adipose tissue separately. This approach was also adopted in a recent Dutch cohort study evaluating pancreatic cancer patients who underwent surgery where low muscle attenuation at diagnosis was also associated with reduced survival (211).

Multiple studies have evaluated the impact of sarcopenia on post-operative morbidity (134, 167, 171, 174, 176, 178, 181) with conflicting results. In contrast, studies investigating the effect of sarcopenia combined with obesity (either low muscle mass with an elevated BMI, or arbitrary visceral adipose to muscle mass ratios) have consistently shown a predictive prognostic effect (134). Studies investigating the impact of sarcopenia on long-term survival following pancreatic resection have also shown contradictory results (as described in Chapter 4). To the best of my knowledge this is the first study to evaluate the impact of muscle indices on five-year survival using both a validated method of body composition assessment and validated gender- and BMI- specific cut-offs for sarcopenia and muscle attenuation. These findings demonstrate that either muscle mass or radiodensity predicts prognosis following pancreatic resection, irrespective of indication for surgery or pathological findings.

Probability nomograms are frequently used to predict post-operative outcome in cancer. The nomogram most commonly used in pancreatic cancer utilises a number of disease-related variables, applied after

resection, to predict 1-, 2- and 3-year survival (212-214). A recent international multicentre study evaluated both the addition of a novel molecular biomarker to this existing nomogram and a newly derived nomogram utilising variables only available pre-operatively, and demonstrated that high expression of these biomarkers were independent negative prognostic factors for death within one year of resection (215). The authors proposed that this nomogram could improve patient selection for surgery, highlighting patients with aggressive tumour biology who are less likely to benefit from resection.

6.4.1 Study limitations

This study has some limitations. The retrospective nature carries an inherent risk of bias. Individual patient charts were interrogated and standardised consensus definitions for post-operative complications were used rather than discharge summaries to try to minimise this. CT scans were anonymised and analysed off site in an attempt to minimise this risk of bias further. The limited number of patients with PDAC surviving beyond five years highlights the need to validate these observations on larger scale cohorts.

6.5 Conclusions and recommendations for practice.

These findings highlight the potential need for routine assessment of body composition in line with cancer staging to accurately identify patients with sarcopenia.

Our findings highlight the prognostic effect of the patient or host, rather than tumour- or disease-related factors. The observed effects of muscle indices on long-term survival are striking, and if demonstrated in a pharmacological study in pancreatic cancer, warrants further investigation and potential practice changes.

Almost all patients undergo routine CT assessment prior to resection, providing the opportunity for body composition assessment in parallel with disease evaluation and staging. Whether a therapeutic strategy such as prehabilitation has the potential to increase a patient's muscle mass and quality to reduce their risk of post-operative morbidity and mortality is yet to be established. Opportunistic use of CT acquired for diagnostic purposes for body composition analysis (by trained investigators, using validated methods) could add value to pre-operative patient evaluation.

Chapter 7 Characterising body composition change during neoadjuvant chemotherapy for cancer

This chapter details a retrospective cohort study examining body composition in patients undergoing neoadjuvant chemotherapy for pancreatic cancer.

7.1 Introduction

Pancreatic cancer is currently the fourth leading cause of cancer related mortality in Europe (216), with median 5-year survival rates largely remaining static over the last 40 years (217). Patients frequently present with advanced disease at the time of diagnosis, limiting their potential for curative resection. Recent developments in the management of this disease include an evolving international consensus for disease staging and classification, and the advent of neo-adjuvant therapy for patients with borderline resectable disease (218).

Malnutrition and cachexia affect up to 80% of patients at diagnosis(219), and remain limiting factors to successful treatment delivery and tolerance (85, 220). Increasing pre-morbid obesity levels increase the risk of developing pancreatic cancer. Additionally, pre-morbid obesity may delay diagnosis as initial unintentional weight loss may be overlooked as a symptom of the disease or misperceived as advantageous. Furthermore, excess adiposity and obesity may mask underlying sarcopenia, an

established adverse prognostic factor for patients with advanced pancreatic cancer(85).

The prevalence and prognostic significance of cachexia, sarcopenia and sarcopenic obesity in cancer have gained recognition in recent years (94, 151). There has, however, been considerable disparity in the methods used in various studies regarding muscle measurement as well as in the definition of sarcopenia used (159). As highlighted in Chapter 4 these disparities preclude adequate comparison of studies and create a degree of uncertainty around the true impact of sarcopenia on clinical outcomes in pancreatic cancer (160). Recent attempts to evaluate the impact of sarcopenia on survival in pancreatic cancer concluded that future studies evaluating body composition in pancreatic cancer should utilise the international consensus definition for cachexia(81, 159) and include a direct measurement of muscle mass (DEXA, CT or MRI).

7.1.1 Study Aims

Given the uncertainty to date, this study was to determine the prevalence of sarcopenia and low muscle mass in pancreatic cancer patients undergoing neoadjuvant chemotherapy. Specifically, the study had three aims. Firstly, it sought to determine the prevalence and degree of cachexia, sarcopenia and low muscle attenuation at baseline for patients with BRPC. Secondly, it sought to investigate changes in body composition between baseline (diagnosis) and post-chemotherapy. Finally, the study

evaluated the impact of both baseline body composition characteristics, and changes experienced during treatment, on survival.

7.2 Methods

7.2.1 Patient selection and management

Consecutive patients with pancreatic adenocarcinoma who were referred for neoadjuvant chemotherapy between 2012 and 2015 were identified from a prospectively maintained database and comprised the study population. Additional inclusion criteria included the availability of the digital CT images required for body composition analysis, along with necessary anthropometric data for interpretation.

Patients were referred to the NSCPC, at diagnosis for specialist multidisciplinary discussion. Following discussion patients underwent neo-adjuvant chemotherapy either at SVUH or their local cancer centre. Tumour staging was defined as per current National Comprehensive Cancer Network criteria(218). Chemotherapy agent selection was decided by the local treating oncologist, and in some instances, individual patient private health insurance policy cover influenced the choice of chemotherapy agent. Upon completion of chemotherapy patients underwent a restaging CT scan which was submitted to the NSCPC to assess their response to treatment and potential for resectability before proceeding to radiotherapy.

7.2.2 Body Composition Assessment

Body composition analysis was carried out using the assessment methods described in Chapter 4. The relevant, sequential, axial CT images which clearly visualised the L3 vertebrae were landmarked, anonymised and downloaded in DICOM format. LSMI was calculated by normalising skeletal muscle area for height, and subsequently compared values to gender- and BMI-specific references (151). MA was quantified by measuring average skeletal muscle radio-density and defined as per BMI–specific values (151). Validated regression equations(97) were then applied to estimate whole body fat and fat-free mass and skeletal muscle (98). Changes in total skeletal mass are expressed in changes per hundred days to account for any potential variation in the timing of CT imaging between patients. Cancer cachexia was staged using the International Consensus Classification as either(81). BMI was categorised as per WHO classification (150).

7.2.3 Statistical Analysis

Statistical analysis was conducted using SPSS (IBM SPSS Statistics version 24, Chicago, Illinois, USA). Data were expressed using mean +/- SD or median +/- interquartile range (IQR) as appropriate. Paired t-tests were used to examine sequential changes in body composition measurement. Overall survival (OS) was calculated from the date of MDT decision to treat until the date of death or censor (December 31st 2017).

Associations between relevant clinical and anthropometric variables was assessed using Cox proportional hazard models. Backward stepwise selection was used to identify variables for the multivariable model, and results were reported as HR with 95% Confidence Intervals.

7.3 Results

Of n=100 patients diagnosed with BRPC between 2012 and 2015, n=78 had both a CT suitable for body composition analysis, and necessary anthropometric details required for inclusion. Baseline characteristics and treatment-related variables are described in Table 7.1. Following neo-adjuvant therapy n=67 patients were re-staged. N=25 (32%) were considered to have a either a clinical response or stable disease and underwent resection. There was one case of in-hospital mortality due to multi-organ failure caused by intra-abdominal sepsis (day 59).

Table 7. 1 Patient characteristics and treatment variables (n=78)

	N (%) or mean (SD) / median (IQR)		**N (%) or mean (SD) / median (IQR)**
Baseline demographics		**Treatment outcome**	
Age (years)[1]	64.2 (7.9)	Resectable (n=67)	25 (32%)
Male Gender	37 (47%)	Dose-limiting toxicity (n=63)	20 (25.6%)
Biliary Obstruction	60 (78%)	Crisis admission required (n=63)	30 (47.6%)
Pancreatitis	5 (6%)	Survival (days)	475 days (300-819)
Diabetes	19 (24%)	Survival (months)	14.6 (10-24.8)
CA19-9 (IU/L) (n=64)	323 (141-973)	**Nutrition Parameters at Diagnosis**	
CRP(mg/L) (n=56)	9 (5-24.5)	Body Mass Index	26.4 (4.9)
Albumin (g/L) (n=67)	34 (30-39)	Percentage weight loss	7. (0-13)
Glasgow Prognostic Score >2 (n=56)	16 (29%)	Sarcopenia	39(50%)
Chemotherapy Agent		Low muscle attenuation	40(51%)
None (Patient declined/rapid deterioration)	3 (4)	Cachexia	43(55%)
FOLFIRINOX	34 (44)		
Gemcitabine + Nab-Paclitaxel	15 (19)	**Resected Patients (n=25)**	
Gemcitabine (single agent)	9 (11)	Tumour stage 1/2/3/4	6 (24%)/2 (8%)/17(68%)/0
Gemcitabine + Oxaliplatin	10(13)	Nodal stage 0/1/2	13(52%)/12 (48%)/0
Gemcitabine + Cis/Carboplatin	3 (4)	Resection margin 0/1/2	19 (76%)/6 (24%)/0
5FU	4 (5)	Adjuvant chemotherapy	48%

Half of the patients had low muscle mass at the time of diagnosis. Sarcopenia occurred across all BMI categories, with over half occurring in patients with an elevated BMI (Figure 7.1). Over half (55%) of the patients were cachectic at diagnosis.

Forty-five percent of patients with BRPC were referred for specialist dietetic intervention during chemotherapy. Patients with higher baseline mean weight loss (11.42% vs 3.74%, p=0.0001), lower BMI (24.7 kg/m² vs 27.8kg/m², p=0.015) and lower total mean fat mass (23.8kg vs 27.3kg, p=0.026) were more likely to be referred for intervention. There was no difference in baseline muscle indices among patients referred for dietetic intervention compared to those not seen (LSMI 44.2 vs 45.6, p=0.467, fat-free mass 44.2 kg vs 43.7kg p=0.862, skeletal muscle 24.1kg vs 24.2 kg p=0.93, muscle attenuation 35.8 HU vs 33.6 HU P=0.234). Fewer than half (43%) of the study group had been prescribed PERT to treat PEI. Patients who had been prescribed PERT had presented with a higher baseline weight loss (10 % vs 5.3%, P=0.011), while there was no difference in baseline body composition.

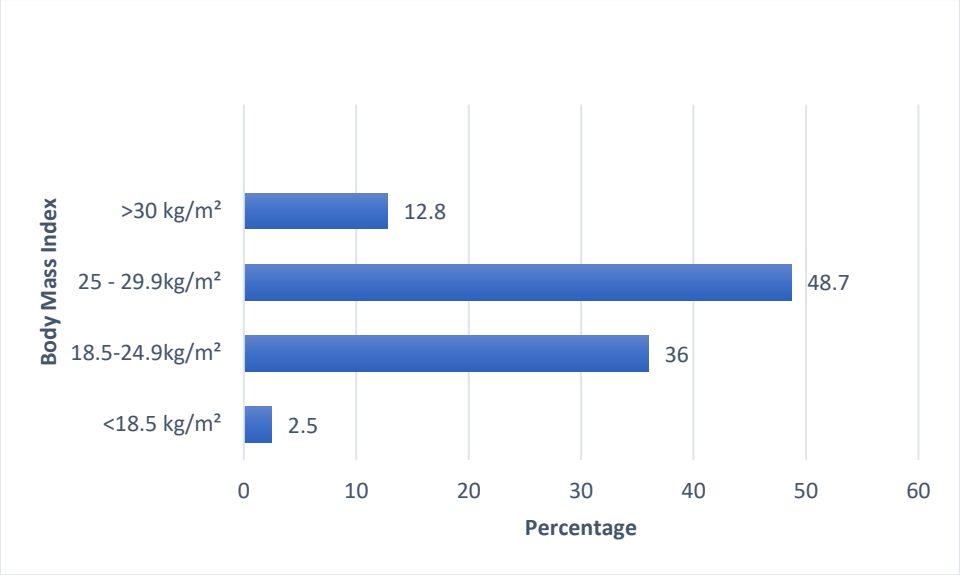

Figure 7. 1 Body mass index distribution of sarcopenic patients (%)

The change in body composition from baseline to post-chemotherapy treatment in the n=67 patients with an available post-treatment CT scan was assessed. The median (IQR) interval between CT scans was 182 days (72-316), and the median (IQR) muscle loss per hundred days was 1.3kg (-8.3 – +4.0). All body composition parameters, except muscle attenuation deteriorated during treatment (Table 7.2). The majority of patients (73%) experienced loss of lean tissue (SMI, fat- free mass, skeletal muscle mass) during treatment.

Table 7. 2: Body composition changes during neo-adjuvant chemotherapy

	Diagnostic CT	Post-chemotherapy CT	p- value
Skeletal Muscle (cm^2)	128.4 (32.7)	120 (33.7)	<0.0001*
Intra- muscular adipose tissue(cm^2)	9.3 (7.5)	7.9 (6.3)	0.003*
Visceral adipose tissue (cm^2)	143.5 (93.7)	111.5 (70.3)	<0.0001*
Sub-cutaneous adipose tissue (cm^2)	191.2 (91.6)	158.5 (81.9)	<0.0001*
Lumbar Skeletal Muscle Index (cm^2/m^2)	45.6 (8.7)	42.3 (9.3)	<0.0001*
Muscle attenuation (HU)	34.6(8.2)	34.4 (8.1)	0.803
Estimated fat free mass (kg)[1]	44.3 (9.7)	41.7 (10)	<0.0001*
Estimated fat mass (kg)[1]	25.7 (6.6)	22.8 (5.7)	<0.0001*
Estimated skeletal muscle mass (kg)	24.4(5.6)	22.93(5.8)	<0.0001*

Neither the presence of cancer cachexia nor sarcopenia at diagnosis had an impact on ultimate resectability or survival (cachexia HR 0.799, 95% CI 0.795-1.684, p=0.447, sarcopenia HR 0.841 95% 0.51 -1.386, p=0.497). Half of the patient group had low MA at diagnosis, and this was associated with an increased mortality risk (median survival for normal MA vs low MA group, 19 months vs 14 months (HR 0.53, 95% CI 0.313 -0.88, p=0.015) (Figure 7.2).

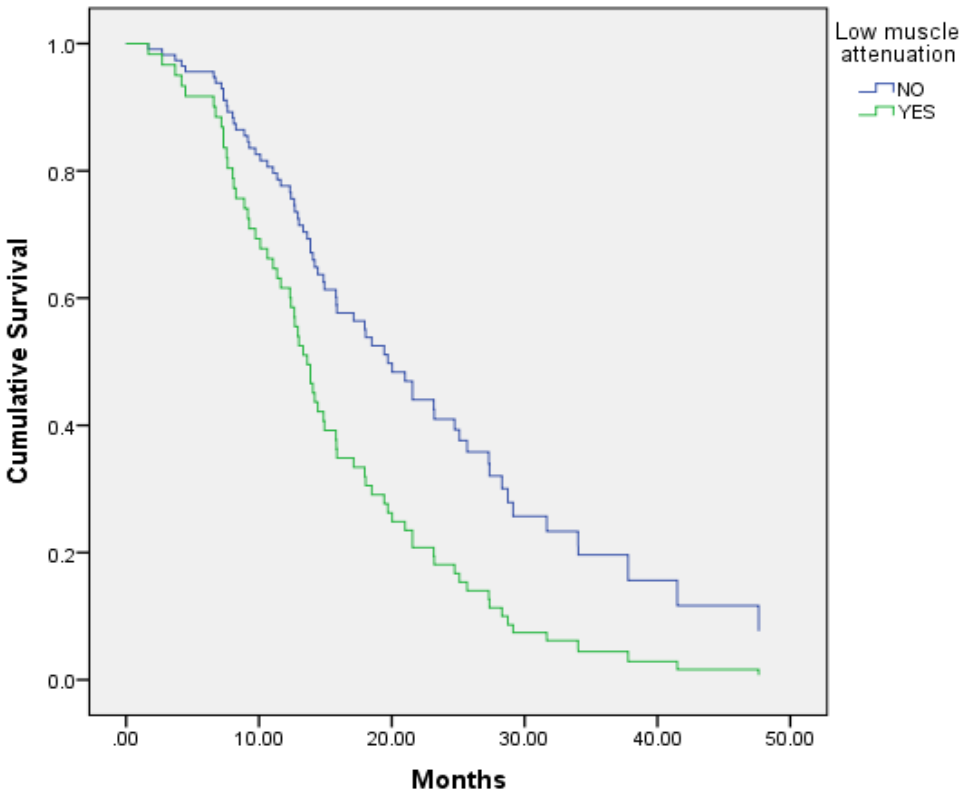

Figure 7. 2 Impact of low muscle attenuation at diagnosis on mortality risk

Loss of lean tissue during neoadjuvant chemotherapy was also associated with a higher risk of mortality (mean fat-free mass loss 2.6kg, HR 1.1, 95%CI 1.03-1.17, p=0.003, mean skeletal muscle mass loss 1.5kg, HR 1.21, 95% CI 1.08-1.35, p=0.001) (Figure 7.3a and 7.3b).

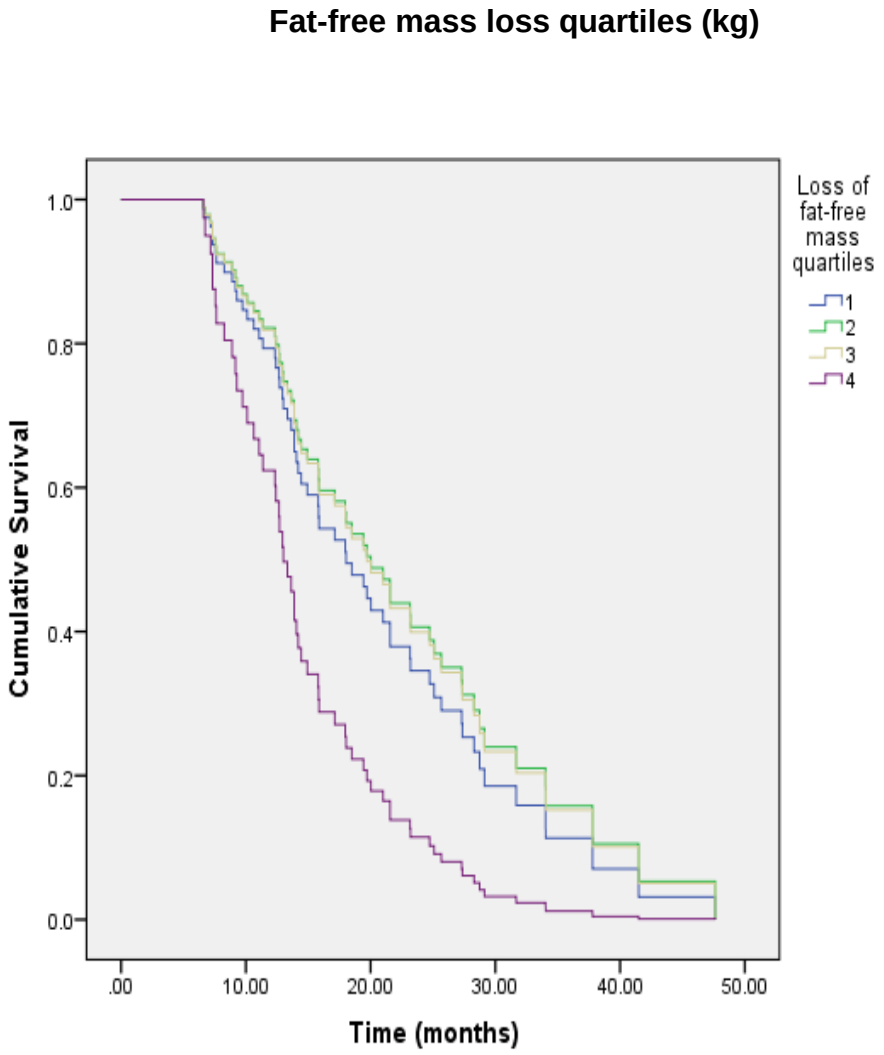

Figure 7. 3 Impact of fat-free mass loss (kg) during chemotherapy

The patients who experienced the most extreme loss of lean tissue (quartile 4, Figure 7.3 and 7.4) had the shortest survival, losing 15% of their muscle mass between diagnosis and their restaging scan (median time of 18 weeks).

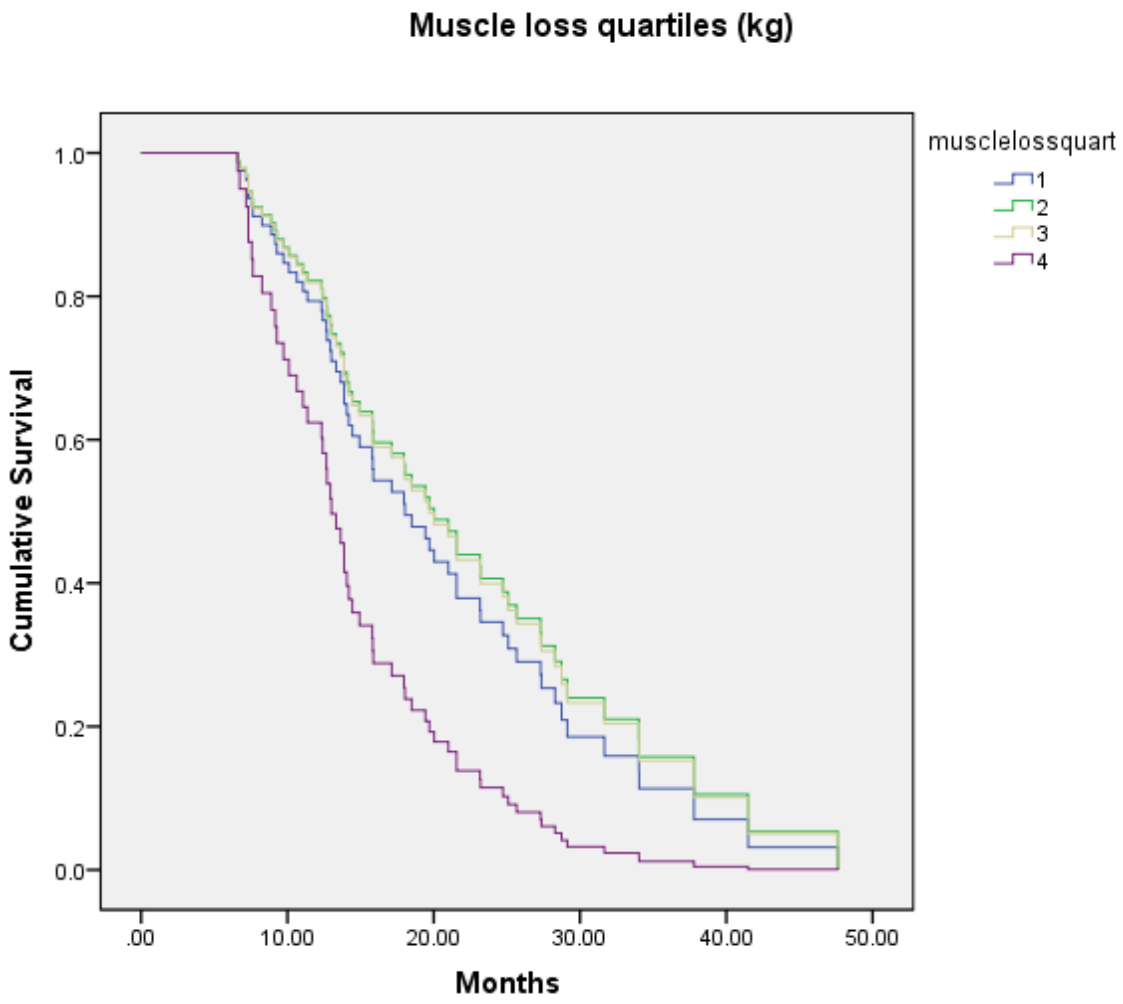

Figure 7. 4 Impact of Skeletal Muscle Mass Loss during chemotherapy

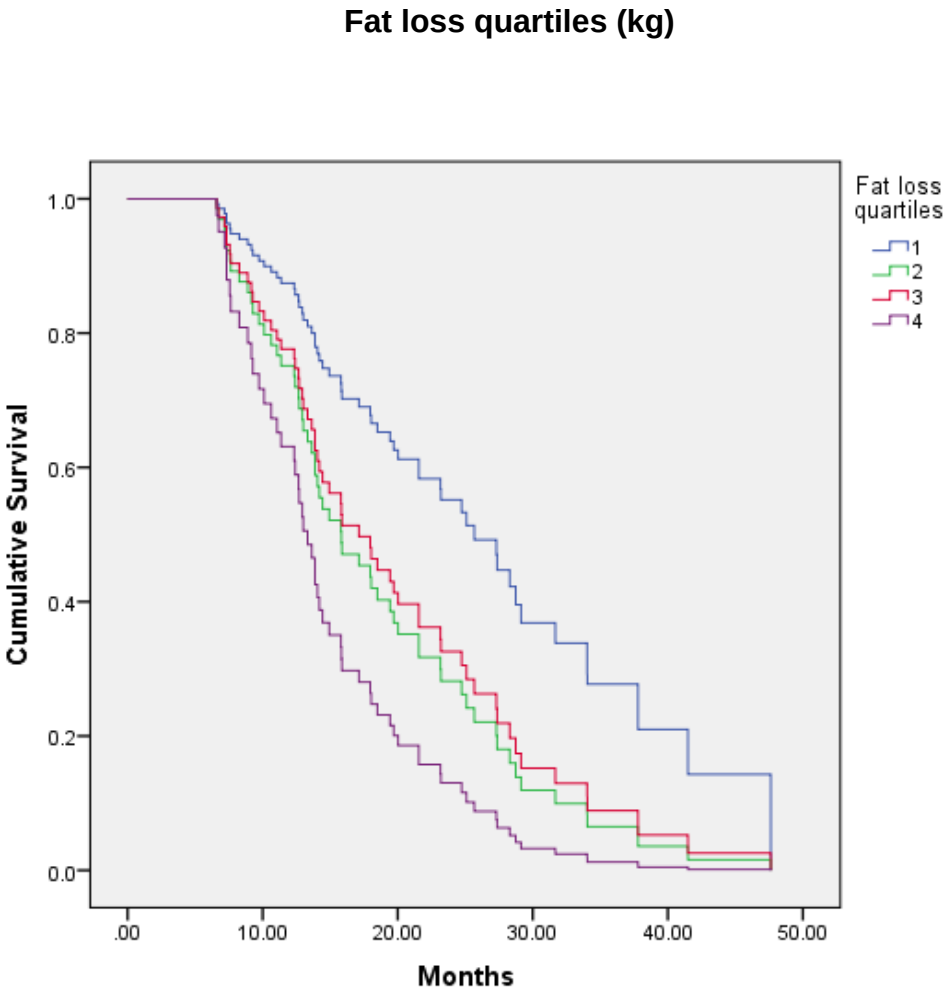

Figure 7. 5 Impact of fat loss during chemotherapy

Loss of fat mass during neoadjuvant chemotherapy was also associated with a higher mortality risk (mean loss 2.8kg HR 1.09, 95% CI 1.03- 1.16, p=0.004) (Figure 7.4).

In a multivariable model, the following indices remained predictive of longer survival; administration of radiotherapy as part of neoadjuvant therapy, normal muscle attenuation at baseline, and preservation of muscle during therapy. No other factors remained significant (Table 7.3).

Table 7. 3 Univariable and Multivariable Analysis of Survival

	Univariable		Multivariable	
	HR (95%CI)	P value	HR (95%CI)	P value
Baseline				
Glasgow Prognostic Score ≥2	0.62 (0.25-1.56)	0.31		
CA19-9 ≥323 IU/L (median)	0.67 (0.39-1.14)	0.14		
Weight loss at diagnosis	1.02 (0.98-1.04)	0.43		
Body mass index	0.98 (0.93-1.03)	0.409		
Treatment factors				
FOLFIRINOX vs Gemcitabine -based treatment	0.90 (0.53-1.52)	0.685		
Full chemotherapy dose delivered	0.5 (0.28-0.88)	0.016		
Radiotherapy delivery	2.82 (1.57-5.1)	0.001	3.49 (1.82-6.71)	<0.0001
Resectable disease following neoadjuvant treatment	1.62 (0.97-2.72)	0.067		
Body Composition				
Cachexia (pre-treatment)	0.79 (0.47-1.35)	0.4		
Sarcopenia (pre-treatment)	0.84 (0.51-1.39)	0.47		
Normal muscle attenuation	0.53 (0.31-0.88)	0.011*	0.36 (0.19-0.69)	0.002*
Loss of fat-free mass during chemotherapy	1.1 (1.03-1.17)	0.003		
Loss of muscle during chemotherapy	1.19 (1.07-1.33)	0.002	1.21 (1.02-1.42)	0.025
Loss of fat mass during chemotherapy	1.09 (1.03 -1.16)	0.004		

HR hazard ratio

Nearly one-third of patients showed radiological response to neoadjuvant treatment, and subsequently underwent resection. Table 7.4 compares patient characteristics and treatment details between resected and non-resected patients. There were no statistical differences in baseline characteristics, treatment factors, body composition parameters, or survival between those who achieved resectability and those who did not.

Table 7. 4 Comparison of Resected versus Non-Resected Patients

	Resected	Non-Resected	P value
Baseline Characteristics			
Age (years) [a]	68 (59-70)	65.5(56.8-69.2)	0.68
CA19-9 at presentation (I.U./L) [a]	292(165-845)	323 (102-1061)	0.8
Body Mass Index(kg/m²) [a]	26 (22.3-30.2)	26.3 (22.7-28.8)	0.6
Weight loss at presentation (%) [a]	0(0-10)	8 (0-15)	0.18
Sarcopenia [b]	14 (56%)	32 (56%)	0.48
Low muscle attenuation [b]	13 (52%)	29 (55%)	0.64
Cachexia (%) [b]	60	52	0.51
Treatment factors			
FOLFIRINOX chemotherapy (%) [b]	52	38	0.48
Pre-operative radiotherapy (%) [b]	75	76	0.77
Body Composition Change during chemotherapy			
Skeletal muscle loss (kg) [a]	0.8 (+0.2-1.74)	1.4(0-3.2)	0.46
Fat-free mass loss (kg) [a]	1.5 (+0.4-4.1)	2.5(0-5.5)	0.36
Fat mass (kg) loss [a]	2.1 (0-4.6)	2.8(0.9-6.8)	0.36
Outcome			
Survival (months)	17.6 (12.7-27.5)	13.5(8.2-23.2)	0.1

[a] Median (IQR), [b] Chi-square test

7.4 Discussion

This study found that low muscle attenuation or radiodensity at diagnosis, along with further muscle depletion during chemotherapy was associated with a higher risk of death in patients with BRPC. Furthermore, it highlighted the high occurrence of cancer cachexia and sarcopenia at diagnosis for patients with BRPC, with more than half being affected.

While previous studies showed that cancer cachexia affects between 40-80% of patients with pancreatic cancer, I believe this to be the first study to evaluate the incidence using the Fearon classification (81) in a BRPC cohort. This work has shown that cancer cachexia is an early feature of the disease. Despite this, no association was found between cachexia at diagnosis and resectability, treatment tolerance, treatment delivery or overall survival. While this may be surprising, it is consistent with the findings of a another recent study which evaluated the impact of baseline body composition on survival in nearly 800 patients with untreated pancreatic cancer (221). They also reported that sarcopenia and depleted adipose tissue stores were early features of the disease but did not impact survival.

While sarcopenia and cachexia at diagnosis were not associated with treatment outcome, this study demonstrated that low MA at the time of diagnosis was found to double mortality risk. This finding is consistent with

the findings of the previous study outlined in Chapter 6. A previous cohort study of Japanese pancreatic cancer patients found that low muscle attenuation prior to neoadjuvant chemotherapy was not significant, however post treatment muscle attenuation was a negative prognostic indicator (222).

Only three studies have sought to quantify body composition change during neoadjuvant chemotherapy for pancreatic cancer to date. The first study evaluated body composition change in 89 patients who received neoadjuvant Gemcitabine combined with Cisplatin followed by short-course radiotherapy and concurrent Gemcitabine as part of a phase II study (223). The majority (64%) achieved resectability following treatment. A significant loss of skeletal muscle, visceral and subcutaneous adipose tissue were observed, and the degree of muscle loss correlated with disease-free survival, while visceral adipose loss was associated with overall and progression-free survival. Another longitudinal study from that institution evaluated 127 patients who achieved resectability following neoadjuvant therapy (224). Similar to this work, a variety of chemotherapy regimens was used. Unlike their earlier findings only minimal changes in body composition during neoadjuvant therapy were observed. In contrast, post-operative skeletal muscle increase during the first year following resection was associated with improved survival. More recently, a retrospective cohort of 193 patients who were treated across four institutions over three-year period were evaluated (225). Nearly two thirds of patients received FOLFIRINOX chemotherapy, and the majority (71%) achieved

resectability. A significant loss of both visceral and subcutaneous adipose tissue was observed while skeletal muscle increased. An increase in skeletal muscle during neoadjuvant chemotherapy was associated with resectability.

Muscle attenuation or intramuscular adipose tissue measurement were not measured in these three studies, precluding direct comparison with our findings. In addition, all three studies reported that most patients achieved resectability which contrasts with the findings of a recent meta-analysis where 40% of patients with borderline resectable and locally advanced pancreatic cancer had resectable disease following neoadjuvant treatment(226). This may be due to differences in centre practice; while some units commit to surgically exploring all patients who complete the proposed treatment, the unit where this work was carried out only surgically explores in patients who have achieved partial or complete response (assessed by RECIST criteria) following chemotherapy. A common finding among all four studies is that sarcopenia was prevalent at baseline among patients who undergo neoadjuvant treatment. In addition, the data suggest that preservation of body composition parameters, especially muscle indices, during treatment is a positive prognostic feature. The observed rate of muscle depletion per hundred days is higher than in a previously reported advanced disease cohort (152), but was consistent with another recent study on patients with foregut cancers, where accelerated muscle depletion was observed among patients receiving

neoadjuvant chemotherapy compared to those receiving palliative treatment (227).

Most patients with sarcopenia were overweight or obese, potentiating the risk of excess adiposity masking underlying muscle depletion (151). Sarcopenic obesity has previously been shown to significantly increase the mortality risk and dose-limiting toxicity in patients receiving palliative chemotherapy (85). Despite malnutrition being an established feature of pancreatic cancer, fewer than half of patients in this study were referred for specialist nutritional assessment/intervention at any point during their treatment. Timing of referral varied across centres due to disparity in dietetic resourcing, with some patients only receiving a one-off assessment when chemotherapy dose reduction was required, due to weight loss. Other centres offered routine assessment and monitoring throughout by a specialist oncology dietitian. This lack of standardisation limits the potential to evaluate the impact of dietetic intervention in this study.

7.4.1 Study limitations

This study has some limitations. Pain was not formally assessed at diagnosis and could be not be reported. The small sample size reduces the power of the survival analyses which warrant verification in a larger study. The opportunistic use of existing CT scans for body composition assessment means that controlling for contrast enhancement and CT phase was limited to an individual patient basis. In addition, a variety of

chemotherapy agents were delivered, prohibiting assessment of individual regimen effects which should be considered in future studies.

7.5 Conclusions.

These findings highlight the need for routine assessment of body composition in line with cancer staging to accurately identify patients with muscle depletion and ongoing monitoring of body composition throughout treatment. Where agent choice is still largely determined by patient fitness and perceived ability to tolerate treatment, muscle mass or attenuation measure may offer an objective parameter to aid clinician decision-making. These findings add strength to the argument for multimodal interventions to address malnutrition and cachexia during treatment (61, 228). The recent progress with characterising pancreatic cancer (36), and developments with chemotherapeutics for patients with BRPC provide hope for future treatment of the disease(226). However, failure to recognise the impact of sarcopenia and malnutrition to the successful delivery of treatments, and the necessary advancement of supportive care for these patients will both limit the success of these and prolong unnecessary suffering in a cohort of patients who already endure a significant symptom burden.

Chapter 8: The feasibility of an intensive nutrition and exercise supportive care intervention for patients undergoing neo-adjuvant chemotherapy for pancreatic cancer: The FEED Study (Fish oil, Enzyme Replacement, Exercise and Diet).

8.1 Background and rationale for study

Surgery is the mainstay of curative treatment for pancreatic cancer, however fewer than a quarter of patients have resectable disease at the time of their diagnosis. Up to a further 20% have either BRPC or LAPC when diagnosed (13). The NCCN recommends that patients with BRPC undergo neoadjuvant chemotherapy rather than going straight to surgery (229). New chemotherapy agents offer therapeutic options for patients diagnosed with borderline resectable disease, however the delivery of, and access to these agents in clinical practice is limited by individual patient performance status(158, 230).

8.1.1 Impact of body composition on treatment tolerance during neoadjuvant therapy for pancreatic cancer

In Chapter 4 I described how prevalent sarcopenia and low muscle quality are in patients with R/BRPC. Studies have demonstrated that the degree of skeletal muscle loss experienced during neoadjuvant treatment correlated with disease- free survival (223) and overall survival (44). Conversely preservation of muscle indices during neoadjuvant treatment has been associated with achieving resectability (194). The study described in

Chapter 7 confirmed that loss of lean tissue indices (either fat-free mass or skeletal muscle) during neoadjuvant chemotherapy were independently associated with increased risk of mortality. A novel finding from the same study was that low muscle attenuation at the time of diagnosis, rather than muscle quantity, increased mortality risk for patients with BRPC. Low muscle radiodensity or attenuation has been shown to be a superior predictor of muscle function and performance when compared to muscle mass (208).

8.1.2 Nutritional management of patients with pancreatic cancer

Current nutritional management of pancreatic cancer in clinical practice includes dietary assessment and counselling; however access to specialised dietetic assessment and support is not universal, and patients only tend to be referred in response to treatment-disrupting weight loss and necessitating admission (203, 231). The intervention focus is on increasing or preserving calorie and protein intake and may include advice tailored at improving symptom control e.g. early satiety, anorexia. The overall goal of nutritional management is generally weight preservation, as weight loss in excess of 10% necessitates chemotherapy dose reduction and/or regimen modification. Similarly weight preservation has previously been shown to be advantageous in pancreatic cancer (45), improving survival and patient quality of life in patients living with unresectable disease. Whilst evidence supports the role of dietetic counselling and oral

nutritional supplementation in improving nutritional intake and quality of life in cancer patients (232), a systematic reviews and meta-analysis did not proven any survival benefit (233). Following on from the publication of international consensus guidelines for the classification and diagnosis of cancer cachexia (as described in Chapter 2) (81), there is a need to re-visit these strategies, targeting the intervention more appropriately, at cachectic and pre-cachectic patients, much earlier in the disease trajectory.

Administration of omega-3 polyunsaturated fatty acids (n-3 PUFA), specifically eicosapentoic acid (EPA) and docosahexanoic acid (DHA) found in fish oil, has re-emerged as a potential anti-cachexia intervention (110). The proposed mechanisms of action of EPA include;

1. Improving protein synthesis; supporting anabolic potential of skeletal muscle by sensitising muscle to insulin, and increasing both energy and protein intake
2. Inhibiting proteolysis; decreasing production of pro-inflammatory cytokines (IL-6 and TNF-α), effectively normalising the elevated energy expenditure induced by cancer cachexia.

Previous studies have demonstrated elevated serum levels of IL-6 and TNF-α in patients with pancreatic cancer. A key component of pancreatic cancer cachexia- induced muscle loss is attributable to the inflammatory response in the liver(234). This inflammation- induced acute phase response is characterised by the production of pro-inflammatory cytokines, including IL-6 and TNF-α. These cytokines are also secreted by or in response to pancreatic cancer cells, disrupting normal homeostasis, and leading to a prolonged, sustained catabolic acute phase response.

Prolonged elevated pro-inflammatory cytokine secretion also impacts the central nervous system, leading to increased fatigue and reduced appetite or anorexia(89). N-3 PUFA are thought to mediate TNF-α – induced proteolysis in pancreatic cancer (106).

Inhibition of IGF/IGF receptors have been proposed as a potential therapeutic target in pancreatic cancer (235). IGF are essential for cell proliferation and energy homeostasis (236), and IGF-1 is thought to mediate exercise-induced muscle hypertrophy (237), particularly in aging muscle (238) and influence injury-triggered regeneration in skeletal muscle (239). A previous American study evaluating the impact of a IGFR inhibitor in patients with metastatic pancreatic cancer found that the quantity of muscle lost during treatment, rather than response to treatment, was predictive of overall survival (235).

A recent systematic evaluation of the impact of n-3 PUFA in pancreatic cancer highlighted a positive effect on body weight, lean body mass, a significant decrease in resting energy expenditure and an increase in overall survival in patients with unresectable pancreatic cancer (108). No study to date has evaluated the impact of n- 3 PUFA in patients with resectable or borderline resectable disease, a considerable research gap.

PEI in pancreatic cancer patients is under-recognised in non-specialist centres (66), and endocrine insufficiency in non-diabetic patients is rarely considered unless the patient presents with significant glycaemic control

issues. PEI has been detected in up to 93% of patients with head of pancreas cancers prior to surgery, particularly in patients with co-existing biliary obstruction (70). A recent review of PEI in pancreatic cancer highlighted the increased likelihood of PEI where main pancreatic ductal obstruction exceeded 60%, and concluded the need to consider PERT in conjunction with chemotherapy agents such as FOLFIRINOX to optimize performance status and treatment potential (63).

8.1.3 Physical activity

Little is known about physical activity levels among patients with pancreatic cancer, and the lack of failure to include exercise in cachexia studies has been recognised as a limitation (102). One study of patients with cancer cachexia, many of whom had pancreatic cancer, demonstrated physical activity levels similar to community dwelling patients with spinal cord injuries (91). Exercise has been shown to reduce fatigue and improve QOL in cancer patients. (116), and is thought to decelerate loss of muscle strength and physical function. The need for multi-modal interventions for cancer cachexia has been recognised, and there are a of number large international multicentre study in patients with advanced cancer already underway (116). When surveyed, pancreatic cancer survivors reported that there is interest exercise and diet interventions, specifically shortly after diagnosis. They also highlighted that survivors prioritised future research outcomes pertaining to supportive care and quality of life(240).

8.1.4 The need for a study with a multimodal approach

A common criticism of sarcopenia assessment in cancer cachexia trials is an over reliance on muscle mass measurement, without considering muscle function or strength. In fact, the latest international consensus for the diagnosis of sarcopenia advocates the use of functional measurement for assessment, with muscle mass estimation only used to confirm the diagnosis (201). While cachexia is likely to be a major contributor to skeletal muscle degradation in pancreatic cancer, sarcopenia is not a unifactorial process, and the potential for other aetiologies (nutritional, physical activity related) need to be evaluated. Studies have evaluated individual treatment options for cancer cachexia and have shown only minor benefits to date. There has been a lack of consistency in defining cancer cachexia (241), and a failure to recognise the need for a multimodal approach (242). Moreover, malabsorption was not formally considered in previous studies evaluating omega-3 PUFA supplements in pancreatic cancer. This is likely to have limited patient compliance due to side effects, and the accurate quantification of the therapeutic dose required. Dietary counselling and nutritional supplementation have been shown to increase overall weight rather than lean body mass. Finally, a failure to combine physical activity advice with an enhanced protein intake impairs the net utilisation of protein, further limiting anabolic potential.

8.2 Research hypotheses.

To reflect the multifactorial aetiology of malnutrition and weight loss in pancreatic cancer, I led the design of this multi-modal interventional study, drawn from the broad base of evidence to date. The research hypothesis was that the multi-modal approach would allow for clinically-significant improvements in indices of sarcopenia and malnutrition, whilst being feasible for patients and reflective of real-world clinical practice.

8.2.1 Research questions

1. To systematically evaluate the aetiology of malnutrition and weight loss in patients undergoing neo-adjuvant chemotherapy for pancreatic cancer.
2. To investigate the feasibility of a prospective multi-modal intervention for patients with pancreatic cancer undergoing neo-adjuvant chemotherapy.

8.2.2 Aims / Objectives

8.2.2.1 Primary objective

To determine the feasibility (defined as 60% acceptance) of a combined intervention comprising 1) individualised dietary advice, 2) PERT, 3) an omega-3 enriched oral nutritional supplement, and 4) individualised daily physical activity target. The primary objective of this study was to ascertain if the multimodal intervention was feasible in this patient group (target accrual n=20). Specifically I sought to determine to following(243):

A. To evaluate recruitment cabability
B. To evaluate the acceptability and suitability of the intervention and the study procedures
C. To evaluate the resources and ability to manage the study
D. To evaluate the participants response to the intervention.

Secondary objectives

As the primary objective was feasibility, the study was not powered a priori to detect differences in the secondary outcomes. Nevertheless, it was deemed imperative to measure additional clinically-relevant outcomes to gain full value from the study in this particular patient group.

1. To quantify dietary intake, functional status, QOL, exocrine and endocrine function in pancreatic cancer patients prior to commencing chemotherapy

2. To measure body composition utilising CT scans acquired for diagnosis and restaging of cancer.
3. To assess activity levels and sedentary behaviour
4. To investigate serum cytokine levels prior to and following chemotherapy
5. To determine functional status and quality of life at diagnosis and following 12 weeks of intervention.

8.3 Patient and methods

8.3.1 Study design

This was a clinical research study, using a prospective descriptive real world observational approach. We used a consecutive sampling method, and any patient with a diagnosis of pancreatic cancer referred for neo-adjuvant chemotherapy on the St Vincent's Campus, that met the specified inclusion criteria were approached and invited to participate in the study.

8.3.2 Research Subjects / Participants

Diagnosis of pancreatic cancer was based on clinical and radiological data with histological confirmation as per international guidelines (NCCN). Treatment recommendation was based on multi-disciplinary team consensus. Since 2013 the MDT recommends neo-adjuvant chemotherapy for patients with BRPC, and occasionally for selected patients with Locally Advanced Pancreatic Cancer where the primary tumour size, extent of

nodal and vessel involvement might be amenable to resection if significant tumour downstaging occurred. Individual surgeon and patient preference dictated whether patients with resectable disease at the outset underwent chemotherapy prior to surgery.

8.3.3 Treatment details

Patients received one of two chemotherapy regimens as decided by their treating oncologist; either FOLFIRINOX given fortnightly, or Gemcitabine combined with Nab-Paclitaxel. The sequencing of drug administration of the latter regimen was on an individual basis with patients either receiving treatment on day 1 and 8 of a 21-day cycle, or day 1 and 15 of a 28-day cycle. Individual chemotherapy dose was prescribed on body surface area, calculated using the DuBois method. All patients were prescribed anti-emetic cover routinely, including 3 days of Dexamethasone. G-CSF was used prophylactically in all patients who received FOLFIRINOX. Where patients experienced weight loss in excess of 10% between chemotherapy cycles, their chemotherapy dose was reduced.

All patients received a re-staging contrast-enhanced CT scan following 12 weeks of treatment to assess their response to treatment, defined as per RECIST criteria (244). Patients with complete response at this point were referred for short course radiotherapy (30 Gray, 10 fractions) prior to surgical exploration. Patients with partial response or stable disease received additional chemotherapy following which they were restaged and considered for radiotherapy (either short course therapy as outlined above,

or long course with concomitant weekly chemotherapy (50.4Gray, 28 # and 5FU). Patients with disease progression at this point were either referred for palliative care or second line chemotherapy, as per their performance status and individual preference. Patients with evidence of disease response were listed for surgical exploration unless individual patient factors precluded the possibility of surgery.

8.3.4 Recruitment

Inclusion criteria:

1. Patients with pancreatic cancer who underwent neoadjuvant chemotherapy at St Vincent's, and who consented to take part
2. CT scan available for body composition analysis
3. Age >18 years.

Exclusion criteria:

1. Inability to give informed consent
2. Patients who could/would not consume fish/pork products
3. Blood clotting disorders/liver cirrhosis
4. Unstable hypertension
5. Patients with muscle wasting disorders e.g. paraplegia
6. Pregnancy

8.4 Study Part A: Assessment

Given the lack of studies evaluating the aetiology of malnutrition in patients with pancreatic cancer, and the findings of Chapter 6 where muscle loss experienced during treatment was shown to impact survival. I sought to carry out a comprehensive systematic nutritional assessment of patients. The assessment took place in all patients prior to commencing chemotherapy, or on attendance for their first cycle of chemotherapy, and comprised the following:

8.4.1 Dietary assessment

Dietary intake was initially assessed using an interview administered diet history to establish usual eating pattern over a 1-week period, followed by a food frequency questionnaire to obtain further information regarding protein and omega-3 PUFA sources. Throughout the study a 24-hour dietary recall was be used to monitor dietary intake as is routine in clinical dietetic practice.

8.4.2 Nutritional assessment

Weight, height and BMI were assessed using the methods outlined in Chapter 4. Body composition was assessed using CT analysis as described in Chapter 4. Images from both diagnostic and restaging CT were landmarked together to ensure consistency and anonymised for analysis. Using Slice-O-Matic™ and pre-defined radiodensity thresholds,

skeletal muscle, intramuscular, visceral and subcutaneous adipose tissue were measured following which Lumbar Skeletal Muscle Index was calculated by normalising the skeletal muscle area for height. Total muscle, fat-free mass and fat were calculated using validated regression equations for cancer patients (97, 98).

8.4.4 Functional Assessment

Handgrip strength (HGS) was selected for functional assessment as it is both a simple method for clinical practice(153), and advocated as muscle strength assessment method by the European Working Party on Sarcopenia in Older People (EWSOP)(90).

HGS was assessed using a Jamar hydraulic-dynanometer, using the methods described in Chapter 4. Three measurements were taken with one-minute intervals in between to avoid muscle fatigue, and the results averaged. The value obtained was compared to gender and age specific reference values(154).

The Timed Up and Go (TUG) test was used as a physical performance test, and the methodology outlined in Chapter 4 applied. A previous systematic review and meta-analysis evaluating the prognostic value of physical performance measures in cancer patients found that the TUG was significantly correlated with survival, and may also be associated with treatment-related complications and functional decline(245).

8.4.5 Pancreatic function assessment

Exocrine function was assessed using the faecal elastase-1 test. Patients were also questioned regarding GI function and symptoms, specifically steatorrhoea, urgency, diarrhoea, constipation, dyspepsia and flatulence. Endocrine function was assessed by measuring Haemoglobin A1c (HbA1c) and pre-chemotherapy fasting serum blood glucose levels. Where the serum blood glucose levels were increased on 2 consecutive attendances, or where the patient continued to lose weight after week 4 of the intervention, patients were trained to check their blood glucose levels using a glucometer. Patients were asked to check their levels four times daily, including a fasting level, for a minimum of 5 days.

8.4.6 Micronutrient and cytokine assessment

Micronutrients were assessed prior to the patient initiating chemotherapy, using methods described in Chapter 4. Insulin-growth factor (IGF), Interleukin – 6 (IL-6), tumour necrosis factor- α (TNF-α) were measured along with serum insulin levels. Fasting samples acquired for cytokine and insulin measurement in tubes containing a specific, gel- containing serum separator. After a minimum of 30 minutes following venepuncture and sample acquisition, serum was isolated by centrifugation for ten minutes at 1200 RPM using an Eppendorf Centrifuge 5810 R (Hamburg, Germany). The isolated serum was frozen in 250μml aliquots and stored in research

laboratory temperature- controlled freezers at minus 80 degrees Celsius before being analysed together at the end of the study by a senior labaratory technician.

8.4.6.1 Cytokine measurement methodology

A chemiluminescent microparticle immunoassay (CMIA) was used for the quantitative determination of Insulin using the Abbott Architect i1000sr. The electrochemiluminescence immunoassay (ECLIA) was used for the quantitative determination of IL-6 using the Roche cobas e411. The QuantiGlo Human TNF-alpha Chemiluminscent Immunoassay was used to measure TNF-α. Serum Quantikine® Human IGF-I/IGF-1 Immunoassay was used to measure IGF (REF: DG100; R&D Systems, Minneapolis, MN)

Results were validated by the use of quality control material provided by the manufacturer. Quality control results that fell within +/- 2SD of the manufacturers mean were deemed successful.

8.4.7 Health related Quality of Life assessment

Quality of Life was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30). This QLQ-C30 questionnaire was designed to measure cancer patients' physical, psychological and social function in clinical trials, and was subsequently validated in multicultural clinical research settings. It is composed of five multi-item scales (pain, fatigue, financial impact, appetite

loss, nausea/vomiting, diarrhoea, constipation, sleep disturbance and quality of life) (246). I adminstered the questionnaire to patients at the beginning and end of the 12- week intervention. Results obtained were processed as per the EORTC specified scoring manual(246).

8.4.8 Physical activity

Physical activity levels were measured for each patient. Self- assessment of physical activity was carried out using the long form of the International Physical Activity Questionnaire (IPAQ), a self-administered questionnaire which has been validated for adults between 18 and 65 years (247). The IPAQ was specifically designed to measure health-related physical activity in clinical populations (248). It consists of four domains: (a) during transportation, (b) at work, (c) during household and gardening tasks, and (d) during leisure time, including exercise and sports. The long form of the questionnaire was used as it has been shown to have acceptable validity properties for assessing the different domains of physical activity, physical activity intensities and total physical activity in adult populations (248)

The metabolic equivalent task (MET), or simply metabolic equivalent, is a physiological measure expressing the energy cost of physical activity, and is defined as the ratio of metabolic rate (and therefore the rate of energy consumption) during a specific activity to a reference metabolic rate, set by convention to 3.5 ml O2·kg−1·min−1 or equivalently (249). MET describes the intensity of activities in a way comparable among persons of different

weight. However actual EE (e.g., in kilocalories) during an activity depends on the person's body mass and composition.

MET was calculated by IPAQ evaluation as follows: MET values and formula for computation of MET-minutes/week

1. Walking MET-minutes/week = ×3.3 walking minutes × walking days
2. Moderate MET-minutes/week = ×4.0 moderate-intensity activity minutes × moderate days
3. Vigorous MET-minutes/week = ×8.0 vigorous-intensity activity minutes × vigorous-intensity days
4. Total PA MET-minutes/week = sum of walking + moderate + vigorous MET-minutes/week scores.

After calculation of the total MET score, the participants were divided into various categories as follows:

• Category 1 (low): <600 MET-minutes/week

• Category 2 (moderate): ≥600 to <3000 MET-minutes/week

• Category 3 (high): ≥3000 MET-minutes/week.

Following on from physical assessment using the IPAQ, accelerometry was used to objectively assess physically activity levels. Patients were provided with a pre-programmed activPal micro accelerometer (PAL Technologies, Glasgow UK, Figure 8.1) which they were asked to wear on the front of their mid-thigh for a consecutive 7-day period (except when bathing or showering). Accelerometry rather a simple pedometer was selected to examine the duration of sedentary behaviour daily, as well as minimise any alteration in patient behaviour which might occur if patients

were able to monitor steps with a pedometer. Patients were asked to wear for 1 week at the outset of the study. On return of the accelerometer, activity was analysed using the specified manufacturer software. Individual patient steps were averaged, and this value was taken as a minimum step target, but participants were asked to aim for 10% above this on a daily basis

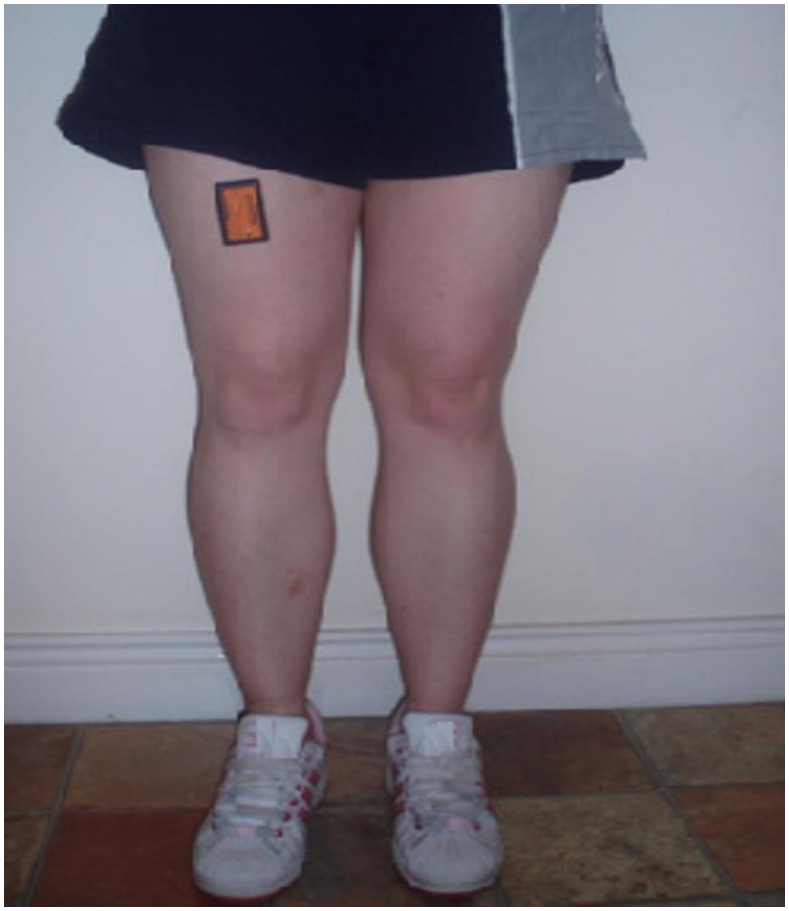

Figure 8. 1 ActivPal accelerometer

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The IPAQ provided information about the patient's perception of their physical activity levels, while the accelerometer both verified this and quantified the duration of sedentary behaviour, daily steps taken, as well as the number of sit to stand transitions taken on a daily basis. The addition of the accelerometer was deemed necessary to evaluate the daily distribution of physical activity, to include an objective assessment of physical activity, and to account for the lack of a validated physical activity questionnaire for elderly cancer patients above the age of 65.

8.5 Part B: 12-week intervention

On completion of the assessment patients were then invited to take part in 12-week intervention comprising the following;

8.5.1 Dietary counselling.

Patients received fortnightly individualised dietary counselling, the goal of which was to maximise energy and protein intake, to ensure adequate nutrient provision and prevent weight and muscle loss caused by caloric/ protein deficits.

Targets for both energy and protein intake were based on recent European consensus guidelines for nutrition in cancer patients (energy 25-30kcal/kg/day, protein 1-1.5g/kg/day) (119). Diet sheets and recipe booklets routinely used for oncology patients in clinical practice were provided. Individual dietary counselling focused on maximising energy and protein intake to achieve the specified energy and protein targets.

8.5.2 PERT

Patients were prescribed PERT, starting dose of 50,000 IU with meals and 10-25,000 IU with snacks and oral nutritional supplements, and escalated as necessary on an individual basis(77)

Creon was used as first line (due to its GMS reimbursable status), with a switch to an alternative dose if required on an individual patient basis. All patients were provided with pillboxes to aid compliance.

8.5.3 N-3 enriched nutritional supplement.

A daily dose of 2g of EPA was administered as Prosure 2 x 200 ml (GMS approved omega-3 PUFA enriched oral nutritional supplement for patients with pancreatic cancer). Serving suggestions and recipe ideas were provided to encourage compliance.

The supplement was commenced only when enzyme replacement therapy was established, and any necessary biliary stenting perfomed. Patients were provided with a 60ml medicine cup and advised to start with 30ml shots four times daily, escalating as able, to the maximum dose of 400mls daily over the course of 2 weeks (Table 8.1). The suggested protocol (table 8.1) was provided to patients with a one-week supply of the product and medicine cups for administration. Where the patient felt any nausea, whether they felt it was supplement or chemotherapy induced, they were advised to revert to the volume they previously tolerated

Table 8. 1 Suggested dose escalation strategy for Prosure

Day	Prosure dose
1-2	30 mls three times daily
3-4	60 mls three times daily
5-6	90 mls three times daily
7-8	120mls three times daily
9-10, and onwards	220mls twice daily

8.5.4 Exercise target

Once individual physical activity levels were quantified using the accelerometer, patients were provided with a Medicare pedometer and advised to aim for a daily step target defined by own individual baseline level. To encourage increased physical activity patients were advised to aim for a step target 10% above their own baseline level.

8.5.5 Monitoring

Dietary intake was monitored via 24-hour recall during dietetic review appointments, as is routine in clinical practice. Patients were asked to verify that this account of dietary recall was representative of the preceding two weeks and asked to describe their worst day in terms of oral intake to allow comparison, along with identification and estimation of any cumulative caloric deficit. Nutrition impact symptoms were routinely assessed and graded prior to each chemotherapy treatment using the National Cancer Institute Grading Common Toxicity Criteria Patient Assessment Form, as per routine hospital practice (251).

Patients were asked to complete a self – monitoring form daily throughout the duration of the 12-week intervention, detailing supplement volume taken, number of enzyme capsules and steps taken. At each visit patients were reminded that the purpose of the study was to assess feasibility of each of the components of the intervention. Prescriptions for both the N-3 PUFA supplement and PERT were issued monthly, and the amounts dispensed verified with the individual patient's community pharmacy.

Functional, QOL and cytokine measurements were repeated at the end of the 12-week period, and body composition assessment was repeated using the restaging scans acquired to assess disease response following 12 weeks of chemotherapy.

8.5.6 Data Analysis

Statistical analysis was carried out using Microsoft Excel and SPSS (Version 24.0 © IBM 2016). The primary objective of this study was to assess feasibility rather than treatment effect, and as such no sample size calculation was required. I sought to recruit 15-20 patients for assessment of feasibility. As the primary focus of this study was to assess feasibility, descriptive tests were primarily used for statistical analysis, including frequencies, percentages, mean and standard deviations and/or median and interquartile ranges. Paired t-tests and/or Wilcoxon rank tests were used as appropriate (selected following assessment of normality using the Shapiro-Wilk test) to examine changes in sequential measurements. Spearman rank correlations were used to assess any bivariate association between parameters. In all cases unless otherwise specified, a *P* value of <0.05 was taken as statistically significant.

8.6 Results

8.6.1 Primary objective

8.6.1.1 Recruitment capability

Between September 2017 and November 2018, twenty patients were recruited to the study, representing 100% accrual.

A total of 28 patients met the eligibility criteria for this study, with eight patients declining to take part. Half of these patients required a gastrojejunostomy bypass procedure for gastric outlet obstruction prior to commencing chemotherapy. The predominant reason for declining was fear of recurrent nausea associated with nutritional supplements (n=4). Others reported that they did not wish to participate (n=4).

The majority (71%) of patients opted to take part in the study. Most reported concerns regarding their ability to maintain their strength during treatment to allow surgery was their main motivation for enrolling. Two-thirds reported confusion regarding the optimal diet and nutrition for treatment, along with persistent gastrointestinal symptoms, and cited their concerns with both as reasons to participate. All of the patients expressed a wish to try and improve care and treatment for other patients suffering with the disease.

8..6.2 Patient characteristics and treatment variables

The baseline patient characteristics, and treatment details are summarised in tables 8.2 and 8.3.

Table 8. 2 Baseline Patient Characteristics

	N (%)/ **Median (Interquartile range)**
Male gender	12 (60%)
Age (years)	68 (41-80)
Presenting symptom	
Jaundice	12 (60%)
Pain	6 (30%)
New onset/worsening Diabetes	2 (10%)
Disease Staging & Burden	
Borderline Resectable	14 (70%)
Locally Advanced	6 (30%)
CA19-9 (IU/L)	207 (2-21,729)
Modified Glasgow Prognostic Score>2	6 (30%)
ECOG Score 0-1	17 (85%)
Nutritional Parameters	
Body Mass Index (kg/m²)	24.9 (20.4 -35.5)
Weight loss (%)	6 (0-30)

The median age of this patient cohort was 68 years and the majority were male (60%). Most patients presented with jaundice and/or pain, while two patients were diagnosed with the disease following investigations due to newly diagnosed DM. the majority of patients enrolled in this study had BRPC rather than LAPC (70% vs 30%). Seventy percent (n=14) had weight loss prior to diagnosis, with a median percentage weight loss of 6% (0-30) for the whole cohort. Despite this weight loss, half of the cohort had a normal BMI while the other half were overweight or obese (median BMI 24.9 kg/m^2, 20.4-35.5). No patients were underweight.

Table 8. 3 Treatment details.

	N (%)/Median (Interquartile range)
Chemotherapy	
FOLFIRINOX	11 (55%)
Gemcitabine combined with Nab-Paclitaxel	9 (45%)
Number of cycles delivered	6 (3-12)
Dose reduction required	5 (25%) (2 FOLFIRINOX, 3 Gemcitabine combined with Nab- Paclitaxel)
Weight loss-induced dose reduction	3 (15%)
Crisis admission	8 (40%)
Crisis admission length of stay	7 (5-10)
Radiotherapy	
Yes	18 (90%)
Short	7 (35%)
Long	11 (55%)
Treatment Outcome at 12 weeks	
Complete/Partial Response	6 (30%)
Stable disease	7 (35%)
Disease progression	7 (35%)
Resectability	
Resectable following treatment	9 (45%)
Resected	7 (35%)

Over half of the patients received FOLFIRINOX chemotherapy, and the median number of cycles delivered was 6 (4-12). Only two patients did not receive radiotherapy as planned; one patient died unexpectedly (with disease progression) while another refused it.

Five patients (25%) required a dose reduction during chemotherapy due to neutropenia (n=1), weight loss (n=3) and intractable vomiting and diarrhoea (n=1) respectively. Where dose reduction was required, it occurred by cycle 4 for all patients. 40% of this cohort required crisis admission during the 12-week intervention. Four patients had recurrent biliary sepsis, with three patients requiring stent changes (all received FOLFIRINOX). One patient was diagnosed with neutropenic sepsis following their first cycle of treatment (Gemcitabine combined with Nab-Paclitaxel), while two patients were admitted with dehydration due to intractable vomiting and diarrhoea following their second cycle of treatment (both received FOLFIRINOX).

Nearly half (45%) of these patients were deemed to have resectable disease following completion of their neo-adjuvant chemotherapy. Two of these patients did not pass pre-operative assessment however due to the development of a thrombus in their left ventricle (n=1), and significant pre-existing cardiac failure in another. Ultimately a third of patients under went resection

8.6.3 Assessment of pancreatic function.

8.6.3.1 Exocrine function.

Ninety percent of patients had exocrine insufficiency (figure 8.2) Only half of these patients reported noticeable steattorhoea and/or post prandial bloating on enrolment to the study, but all reported improvements following initiation of PERT. The remaining two patients had normal exocrine function on the basis of faecal elastase testing. Both of these patients reported intermittent steattorhoea, and/ or post- prandial abdominal pain and bloating on stopping PERT, suggesting they had some degree of PEI. Both patients opted to continue taking the prescription.

Assessment of micronutrient status revealed nearly 50% of patients had a vitamin D deficiency. No other micronutrient deficiencies were observed.

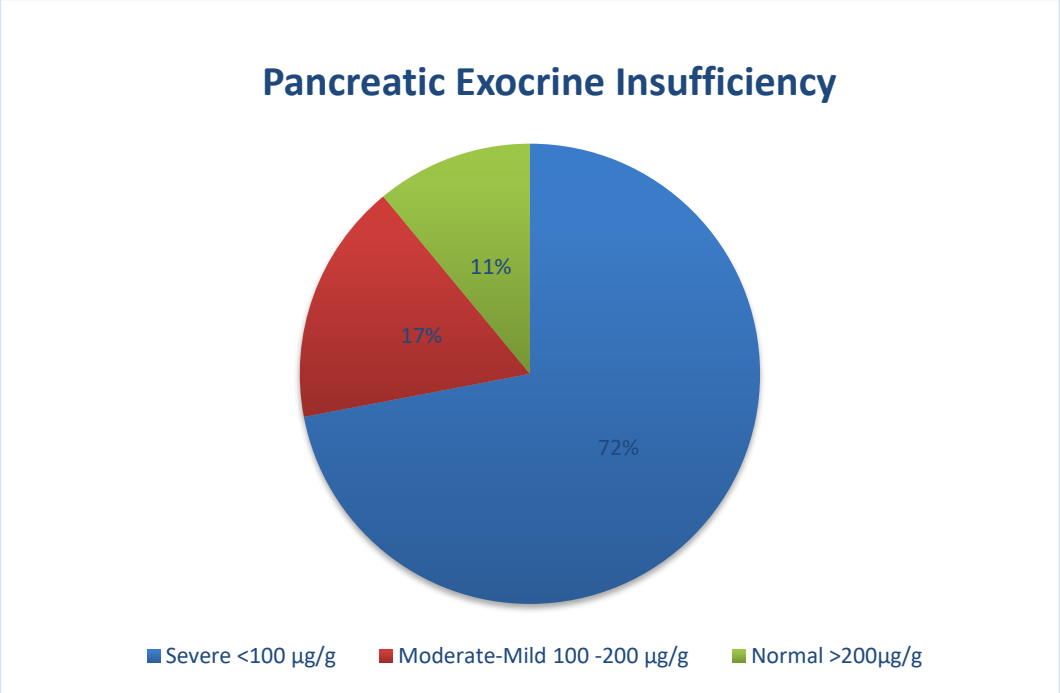

Figure 8. 2 Assessment of exocrine insufficiency

8.6.3.2 Assessment of endocrine function.

One-quarter of patients (n=5) included in this study were known to have DM at the outset of this study, either long-term (n=3), or as the presenting sign of their pancreatic cancer (n=2). A further five patients were diagnosed during the study period. Most had a normal HbA1c level, however symptoms suggesting endocrine dysfunction; such as nocturia, persistent weight loss after one month of the study intervention and polydipsia were reported. These patients reporting these symptoms was trained to assess the blood glucose level using a glucometer and asked to monitor their blood glucose levels four times daily for a minimum of one week. To discriminate between any transient hyperglycaemia induced by

steroid therapy, patients were asked to continue testing for five days after cessation of steroid therapy. These findings are summarised in figure 8.3.

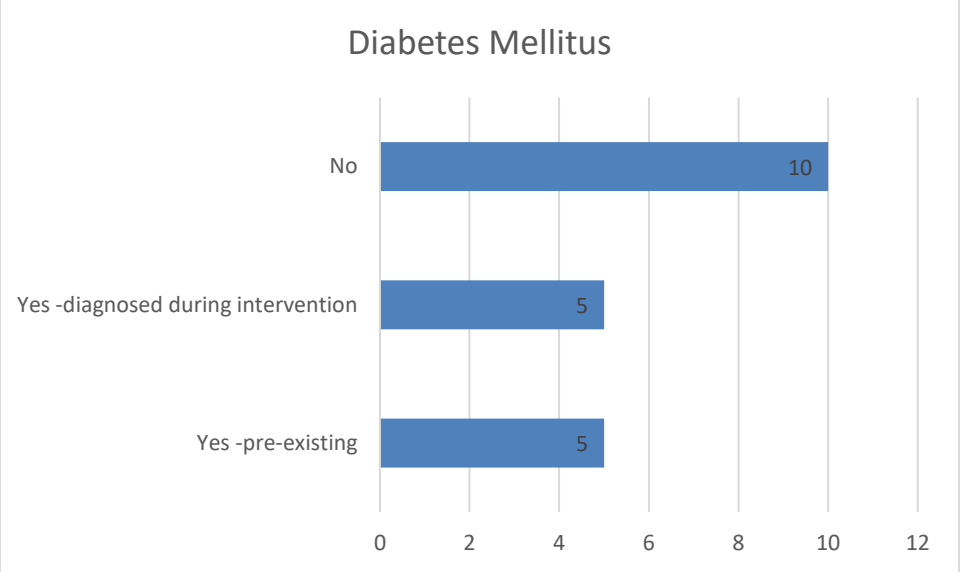

Figure 8. 3 The prevalence and timing of diabetes mellitus among patients who completed the intervention.

8.6.4 Acceptability and suitability of the intervention and the study procedures

Twenty patients opted to participate in this study. Two patients did not complete the intervention; one patient was excluded as they developed gastric outlet obstruction and required parenteral nutrition, while the other withdrew three days after enrolling, stating that they were overwhelmed with their diagnosis and the prospect of chemotherapy. The remaining 18 patients completed the intervention.

The majority (11/18) of patients found that the intervention was deliverable as designed. Compliance with dietetic appointment attendance was 100% with most preferring to be seen during their attendance for chemotherapy. Only one patient opted to attend outside their scheduled chemotherapy appointments, stating that the cold cap treatment worn to minimise their risk of alopecia, and the anxiety it induced, were barriers to engaging with healthcare staff whilst receiving chemotherapy. Following restaging CT scan after 12 weeks of treatment, 13 patients required further chemotherapy, and all opted to continue with the intervention whilst receiving this. The feasibility of all components of this intervention is summarised in Table 8.5.

8.6.4.1 Energy and protein targets

Half the patients exceeded the maximum daily 30 calories per kg, largely due to compliance with the oral nutritional supplement prescription. Only four patients were unable to consistently achieve a minimum daily energy intake in excess of 25 kcal/kg body weight. Anorexia was a persistent symptom for all four patients, while three of the four reported cumulative calorie deficits of 1800-3500 calories per cycle due to nausea and vomiting between days 3 and 7.

Achieving adequate protein intake was a challenge for over a third of patients. Where patients achieved the minimum daily target of 1 gram/kg body weight, they had even distribution of protein throughout the day, reported an estimated 15- 35 g protein/meal, and described minimal nutrition impact symptoms. Only two patients were able to achieve the maximum 1.5g/kg body weight/day, consuming two full bottles of Prosure daily in addition to protein-rich diet.

Nausea and vomiting following treatment and persistent early satiety were prominent in the patients who did not achieve the minimum protein target. Their meal frequency and portion size were also reduced, and they disliked all nutritional supplements offered (either Prosure or any alternative preparations). One patient reported an aversion to meat products following the initiation of treatment, reporting that ingesting any meat product worsened and prolonged dysgeusia.

8.6.4.2 Pancreatic Enzyme Replacement Therapy.

PEI was present in 90% of patients on the basis of faecal elastase testing. All patients were prescribed PERT and reported adherence to their prescription. The majority of patient required 25,000 IU with snacks, 50,000 IU with light meals, and 75,000IU with their main meal (median 250,000 IU lipase per day). One patient with a known prior history of chronic pancreatitis required doses in excess of this.

One patient stopped taking PERT during week 10 of the study as they felt it was exacerbating symptoms of constipation. They later restarted it of their own volition following completion of the study, when their analgesia requirements reduced on initiating radiotherapy.

Two patients with a prior history of diarrhoea post cholecystectomy and/or pelvic radiotherapy for prostate cancer were prescribed bile acid sequestrant therapy to control symptoms of persistent post prandial faecal urgency despite escalation of PERT dosage. All patients were established on a proton pump inhibitor prior to enrolment in the study.

8.6.4.3 Omega -3 PUFA Supplement

- Nearly two-thirds (11/18) of patients drank the full dose of 440ml Prosure daily throughout the intervention, reporting they had established this dose by week four of the intervention.
- Another 4 patients could take one bottle (220mls) daily but were unable to manage any volume beyond this.

- Three patients refused to take the supplement due to taste aversion and anticipatory nausea experienced on trialling. These three patients all reported recurrent biliary sepsis throughout treatment, requiring recurrent hospital admission and biliary stent changes.

None of the patients reported diarrhoea or gastrointestinal upset following ingestion of the supplements, as described in previous studies evaluating the use of Prosure in patients with pancreatic cancer (104, 252). One patient who opted to continue the intervention beyond the 12- week study period was advised to reduce the dose to 220mls daily because of thrombocytopenia with associated epistaxis on week 14 of treatment. Another patient was advised to reduce and then stop the supplement due to persistent weight gain, above their premorbid weight. No patient reported financial pressures limited their adherence to the oral nutritional supplement, and all who reported adhering to the prescription collected a supply on a monthly basis from their community pharmacist.

8.6.4.4 Exercise Target.

All participants agreed to wear the accelerometer for a period of seven days, and measurement was successful in 17 (one failed due to equipment failure following accidental submerging in water). The median daily steps taken by participants was 4500 (range 995-12105, IQR 3475 -6900), and the remaining findings of the physical activity assessment are summarised in table 8.4.

One-third of participants reported high levels of physical activity in the weeks preceding their initial assessment, and overall the percentage of patients reporting moderate or high levels of physical activity increased following the intervention (67%, increasing to 78%), and those reporting low levels of activity reduced (33% vs 22%), figure 8.4. Individual changes in weekly MET equivalent and daily step count are shown in figures 8.5 and 8.7 respectively.

Overall 11/18 participants achieved their daily step target. Maintenance of physical activity during chemotherapy was described as the most difficult component of the intervention. Reasons cited included;

- Fear of infection
- Rural isolation
- Hospital admission
- Lack of interest in exercise prior to diagnosis
- Fatigue
- Chemotherapy- induced neuropathies

Some patients who reported high levels of activity at diagnosis were unable to continue their preferred activity (swimming, aqua aerobics, horse riding) during treatment. Patients who were able to maintain activity stressed the importance of social support in this regard.

Table 8. 4 Physical activity assessment

Parameter	N (%)/ Median (IQR)/Mean +/- SD
IPAQ – baseline	
Low	6 (33%)
Moderate	9 (50%)
High	3 (17)
Weekly Met	1037 (654 -2691)
IPAQ – post intervention	
Low	4 (22%)
Moderate	9 (50%)
High	5 (28%)
Weekly Met	1935 (808-3281)
Accelerometry	
Daily step count at baseline	4500 (3475-6900)
Daily sit to stand transitions	41 (12-82)
Daily Sitting time (hours)	20.51 (1.5)
Daily Standing time (hours)	2.33(1.35)
Daily Stepping time (hours)	1.16 (0.6)
Pedometer	
Steps final week	4400 (1846-6900)

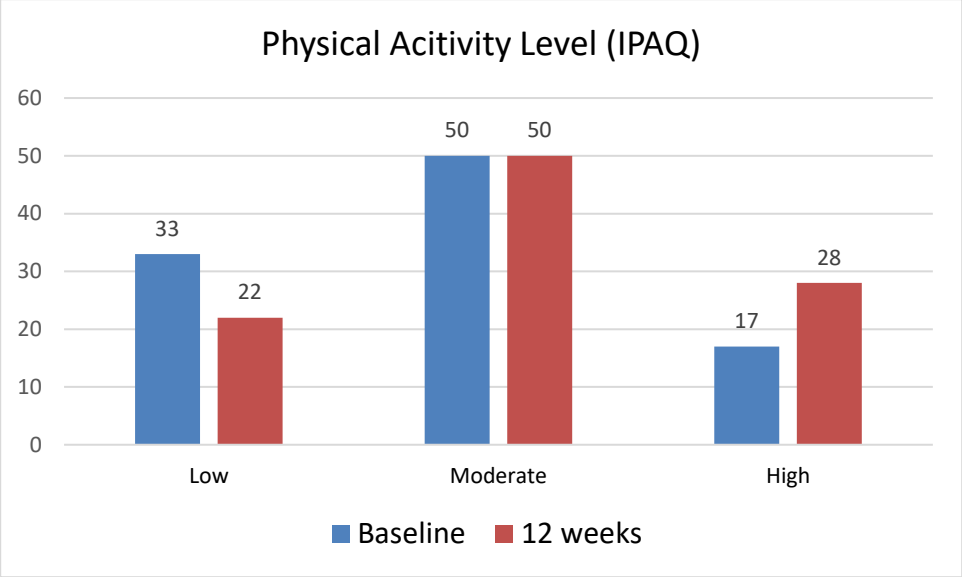

Figure 8. 4 IPAQ- assessed MET change from baseline to week 12.

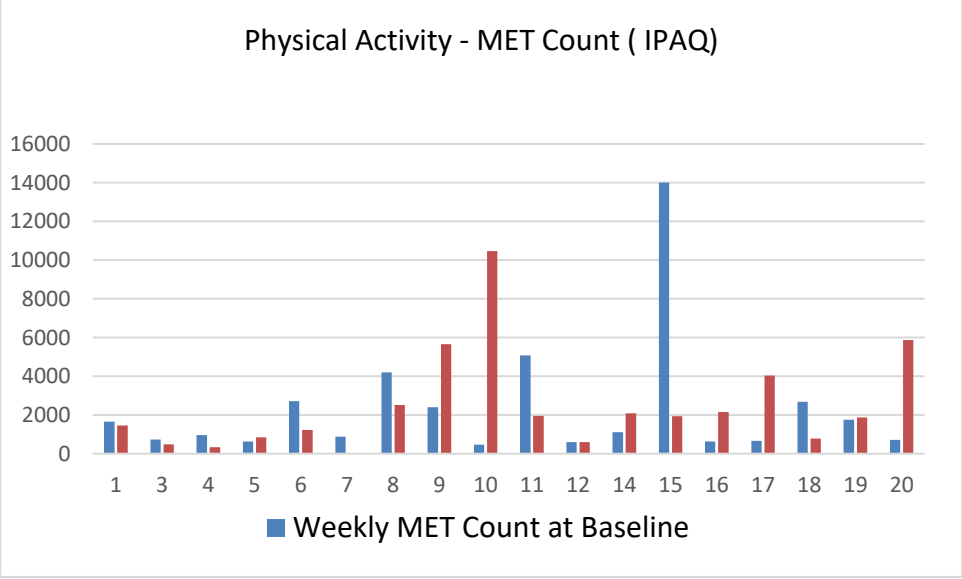

Figure 8. 5 Individual patient MET count change during intervention

Table 8. 5 Summary of feasibility of the FEED intervention (n=18)

		N (%)	
	Component	**Week 6**	**Week 12**
F	Fish Oil (Prosure) supplement intake equivalent to 2g N-3 PUFA /day	11 (61%)	11 (61%)
E	PERT	18 (100%)	17 (94%)
E	Exercise (step target)	13 (72%)	11 (61%)
D	Dietary Counselling:		
	Energy target	13 (72%)	14 (78%)
	Protein target	10 (50%)	11 (61%)
	Complete intervention	10 (50%)	11 (61%)

8.6.4 Resources required to manage the study

- Dietetic resourcing;

The median time required to deliver this 12-week intervention was 14 hours. Two-thirds of patients contacted me by telephone during their first month of treatment, with most seeking reassurance about nutrition impact symptoms, further clarification of nutritional advice, and/or referral to psycho-oncology services

- PERT and N-3 PUFA ONS;

Financial barriers did not contribute to the feasibility of this intervention. Only five patients had a medical card (and free GMS prescriptions) at the outset of the study. All other patients reported already meeting or exceeding the monthly threshold amounts.

- Physical activity

Measurement of physical activity using accelerometry was feasible for most patients (17/18). An alternative dressing was provided for attachment following patient feedback (Mepore rather Tegaderm). Only two patients preferred to use their own device rather than the Medicare pedometer provided to track to their daily steps (Fitbit alta).

- Monitoring

Half of the patients used the self-monitoring form routinely throughout the study. The remainder opted to only use it for recording daily activity. Three patients stipulated that they did not find the IPAQ questionnaire user-friendly, suggesting a second week of accelerometry assessment as an alternative. Interestingly all of the participants requested additional HGS testing, with two-thirds requesting it at every appointment.

- Information preferences

One quarter of patients declined to take any diet sheet or patient information leaflet labelled pancreatic cancer, universally saying that the inclusion of “pancreatic cancer” on the front page or cover meant they would not read it. All of these patients were happy to take generic cancer resources, or the original information re-labelled. Interestingly, in three of these five patients, their spouse or offspring contacted me sought out pancreatic cancer specific information, highlighting potential different information seeking needs and preferences among patients and their families.

8.6.5 Secondary objectives and participants response to the intervention.

8.6.5.1 Body composition parameters

8.6.5.1.1Weight change.

The majority of patients (14/18) had achieved weight maintenance by the end of the 12-week intervention, with more than half returning to, or exceeding their baseline, pre-illness weight (Figure 8.6).

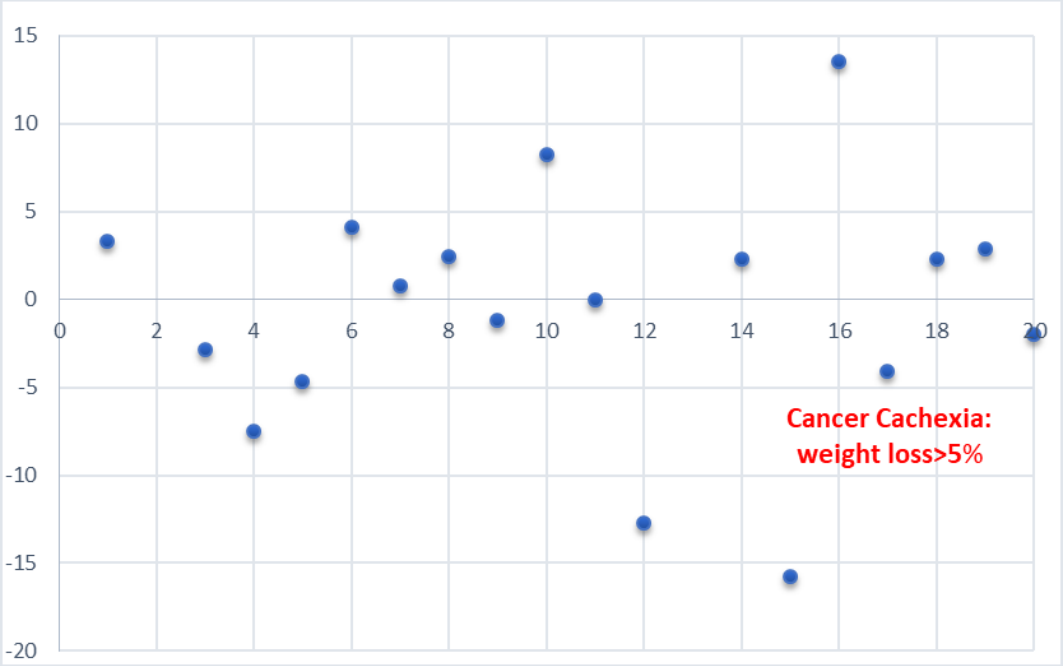

Figure 8. 6 Graph showing weight change for individual patients from week 0 to week 12 of the intervention period. Values >0 on the Y-axis show those who gained weight, and values <0 on the Y-axis show those who lost weight.

Data were analysed according to percentage weight loss at diagnosis and/or during the 12-week study intervention period. Figure 8.7 illustrates the percentage weight change at diagnosis for those without diabetes (n=10), those who had known DM (n=4), and those who had a new DM diagnosis during the intervention (n=6)

Figure 8.8 illustrates the percentage weight change during the 12 week intervention period for those without DM (n=10), those who had known DM (n=4), and those who had a new DM diagnosis duing the intervention (n=6). Figure 8.9 illustrates percentage weight change during the intervention by modified Glasgow Prognostic Score.

Figure 8.10 illustrates the percentage weight change during the intervention for patients according to their compliance with the n-3 PUFA enriched supplement prescription.

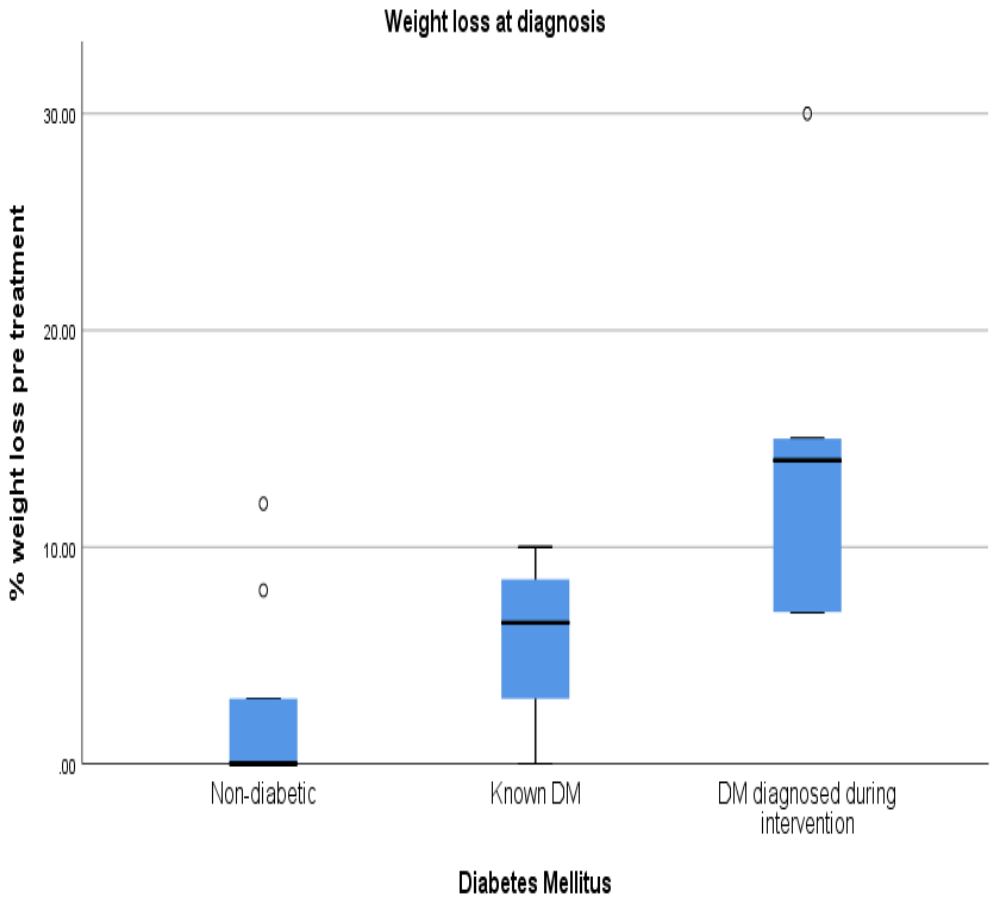

Figure 8. 7 Weight loss at diagnosis (%), classified by DM status

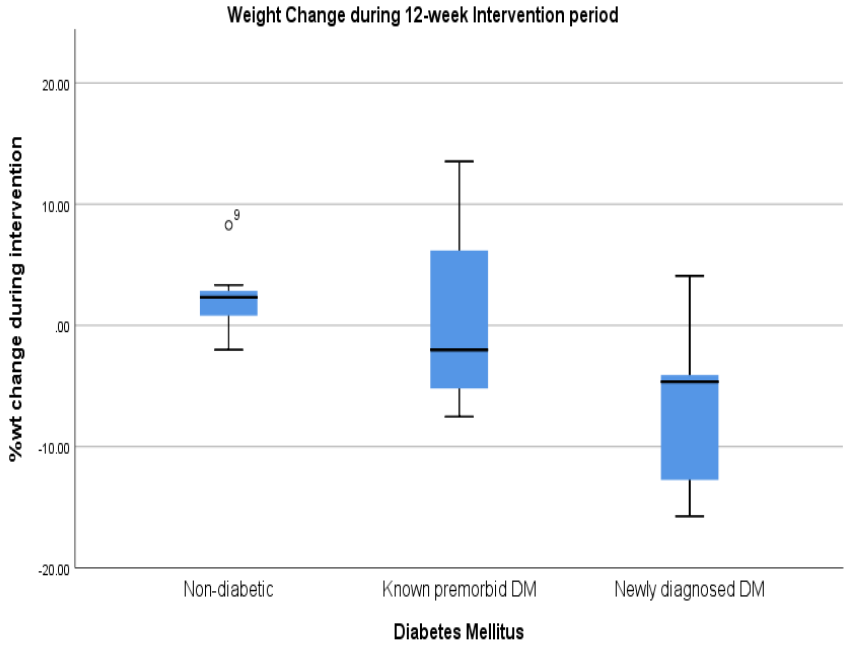

Figure 8. 8 Weight change during intervention (%), classified by DM status

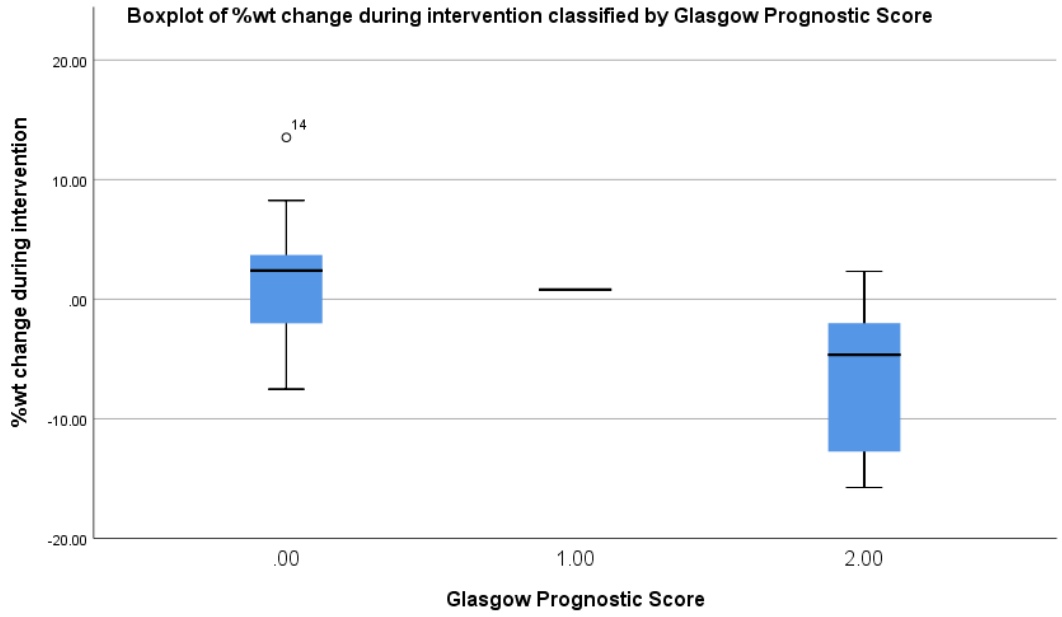

Figure 8. 9 Weight loss during intervention (%), classified by baseline modified Glasgow prognostic score

Patients who were ultimately resectable had a median weight gain of 2.3% while those who did not achieve resectability lost a median of 1.2 %. Similarly, patients who could consume the n-3 PUFA enriched ONS appeared to maintain or improve their weight, while those who could not lost weight (figure 8.10).

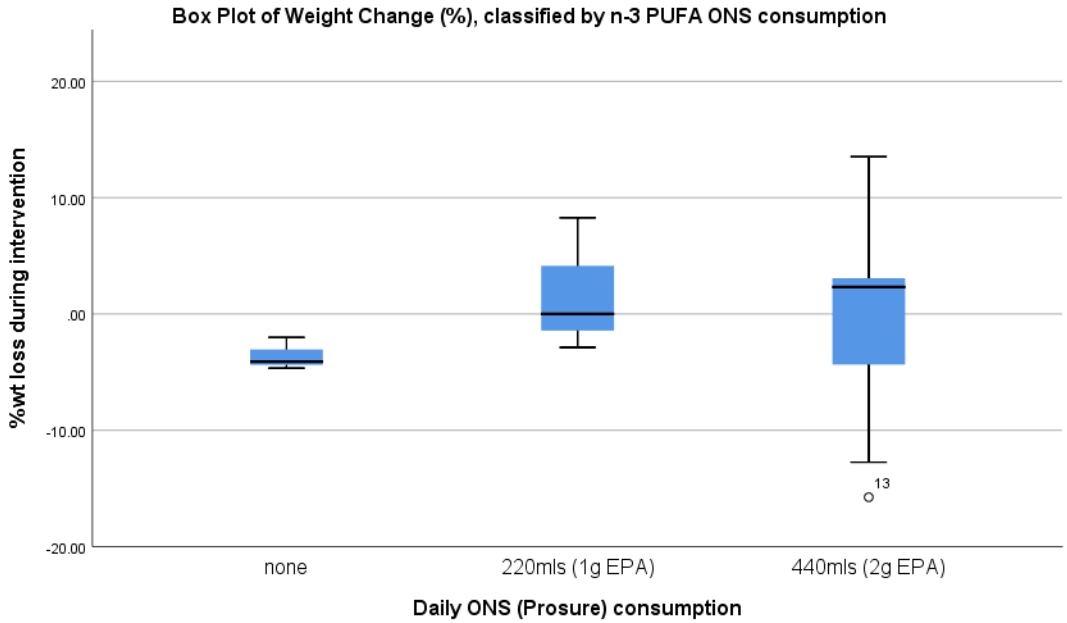

Figure 8. 10 Weight change during intervention (%), classified by ONS consumption

8.6.5.1.2 Body composition change.

Applying the gender and BMI-specific criteria for muscle indices(151), two-thirds of patients were sarcopenic at the outset, while the entire cohort had low muscle attenuation. Applying the international consensus definition for cancer cachexia (either 5% weight loss in the absence of starvation, or 2% in those with sarcopenia), 68% had cancer cachexia (81). Overall, participants in this study maintained or improved their body composition indices (Figure 8.11). There was a small but signficant increase in lean tissue indices (FFM and muscle). Change in body composition did not differ among participants who found the study feasible compared to those who did not.

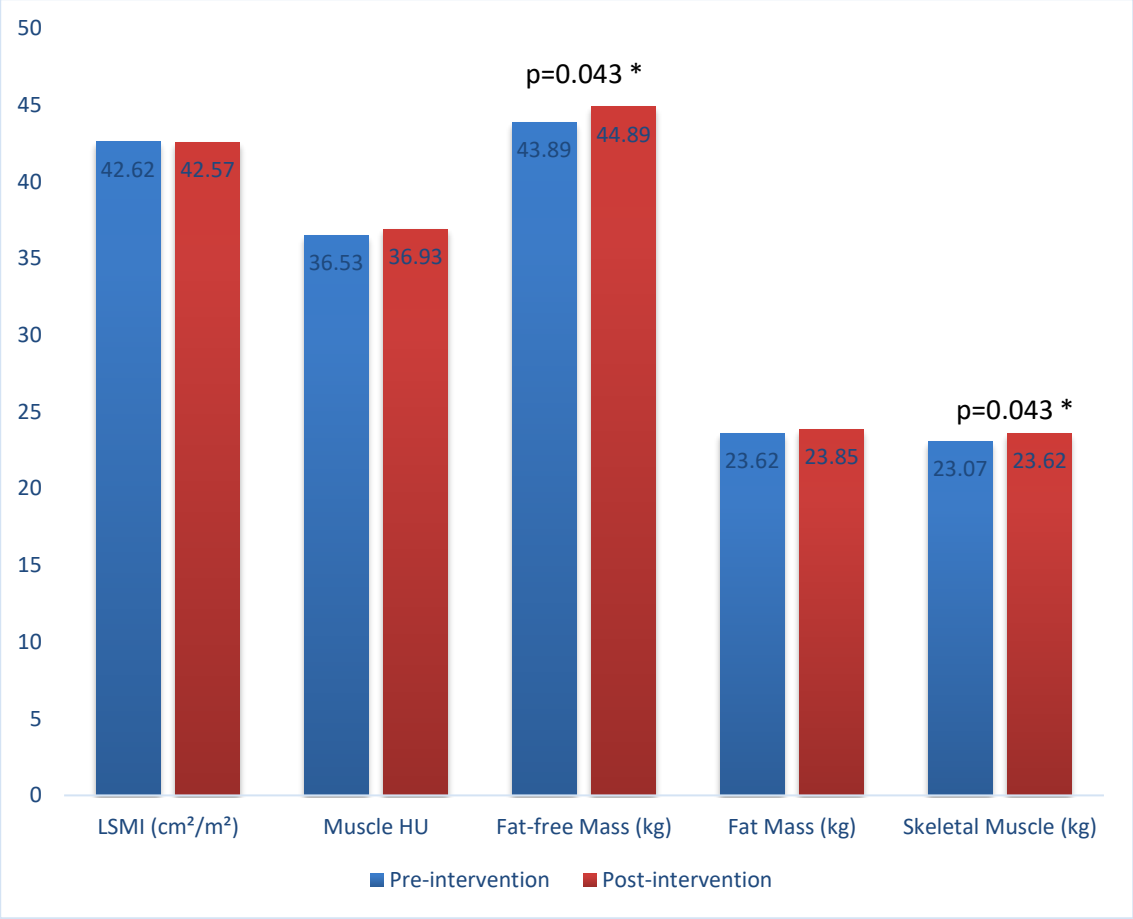

Figure 8. 11 Changes in body composition indices

LSMI Lumbar Skeletal Muscle Index; HU Hounsfield units.

(* statistically significance $p<0.05$ assessed by Wilcoxon Rank Test)

8.6.5.2 Functional parameters and physical activity

The majority of patients (14/18) preserved or improved their HGS during the intervention (Figure 8.12), median 24.5 vs 28kg, P=0.026.

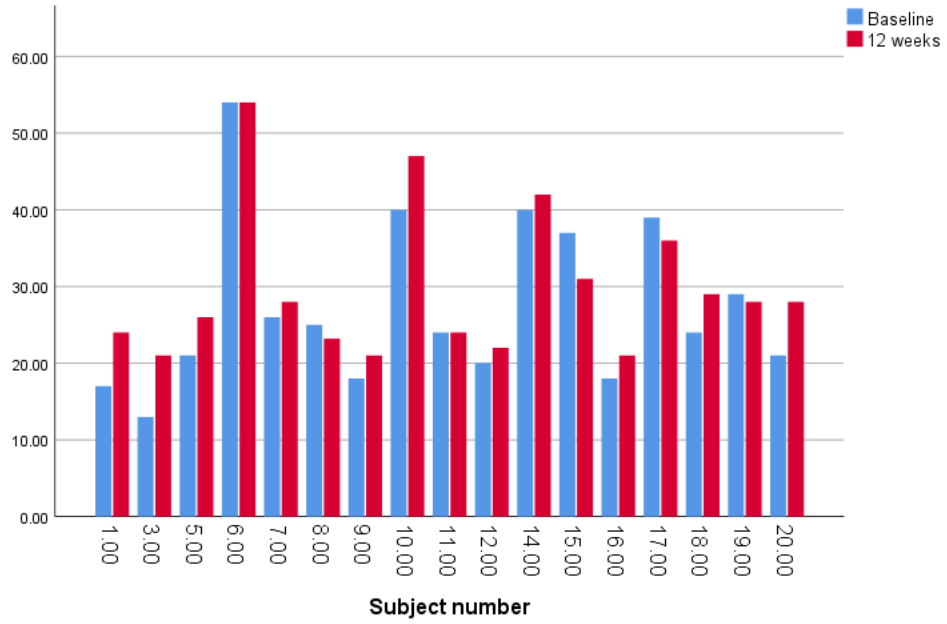

Figure 8. 12 Individual changes in hand grip strength (kg) pre and post intervention

The majority of participants had significantly faster TUG measures at 12 weeks compared to baseline (overall baseline median 11 seconds vs 10 seconds at 12 weeks, P=0.048). Four patients were unable to maintain or

improve their TUG score (Figure 8.13). Two of these patients had endured grade 3-4 neuropathy as a side- effect of their treatment and needed walking aids by the 12-week point. One patient had endured a fall as a consequence of this neuropathy, and subsequently had a soft tissue injury requiring splinting and immobilisation during week 15 of his treatment.

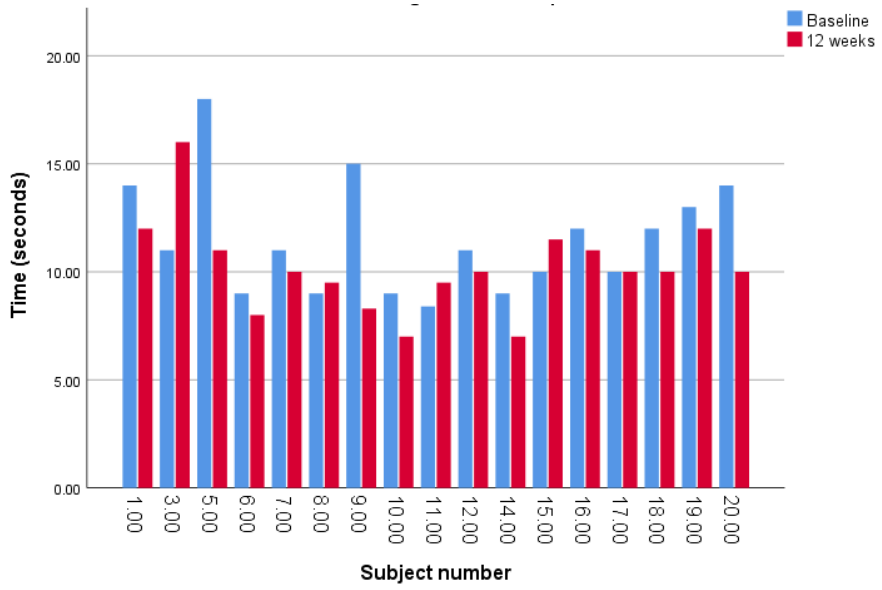

Figure 8. 13 Individual changes in Timed-Up-and Go time (seconds)

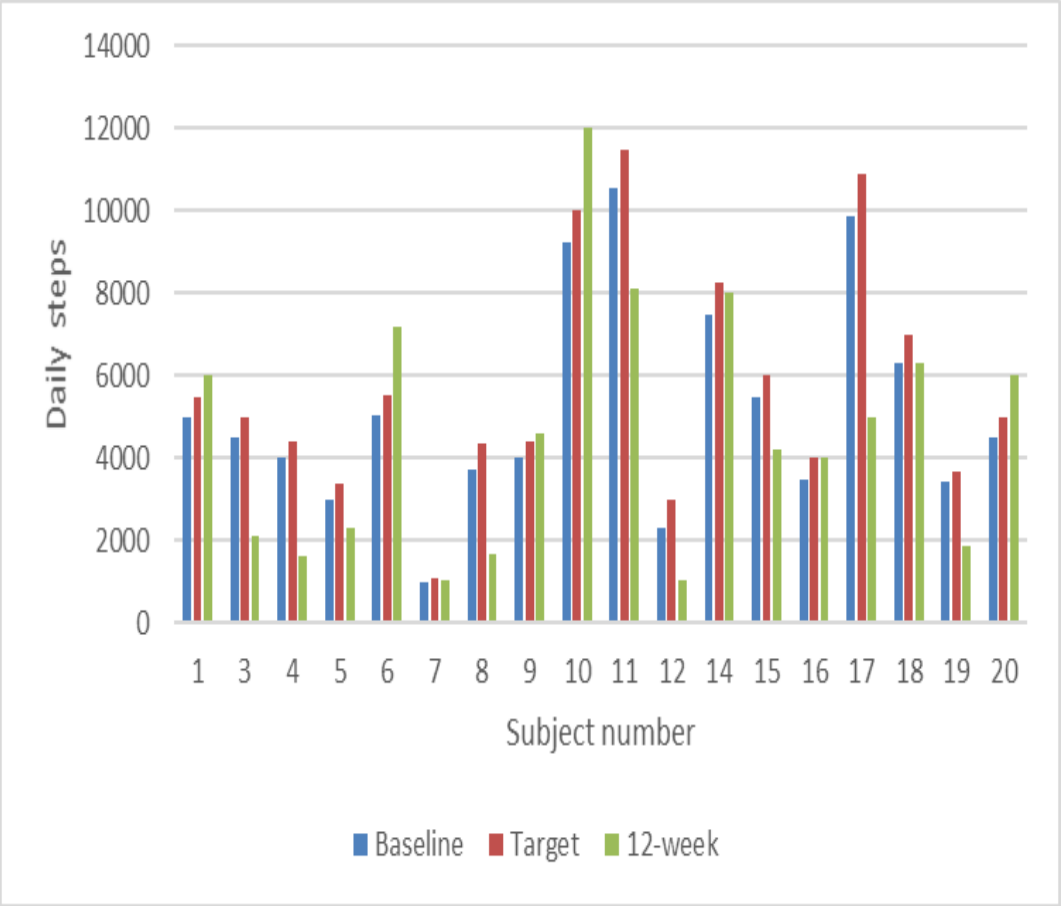

Figure 8. 14 Daily step count at baseline and by week 12, compared to individually-prescribed values

8.6.5.3 Health-related quality of life

There was an improvement or maintenance of quality of life and function comparing pre and post intervention (Figure 8.15). The majority (14/18) of patients reported some impairment in cognitive function at baseline, and while only mild for most, limited their ability to take on information, necessitating repitition and staggered delivery of advice and goal setting. In addition emotional distress was prevalent at baseline (15/18), but had improved on re-assessment at 12 weeks. The most visible improvement was seen in social functioning with 13/18 reporting an increased score at 12-weeks.

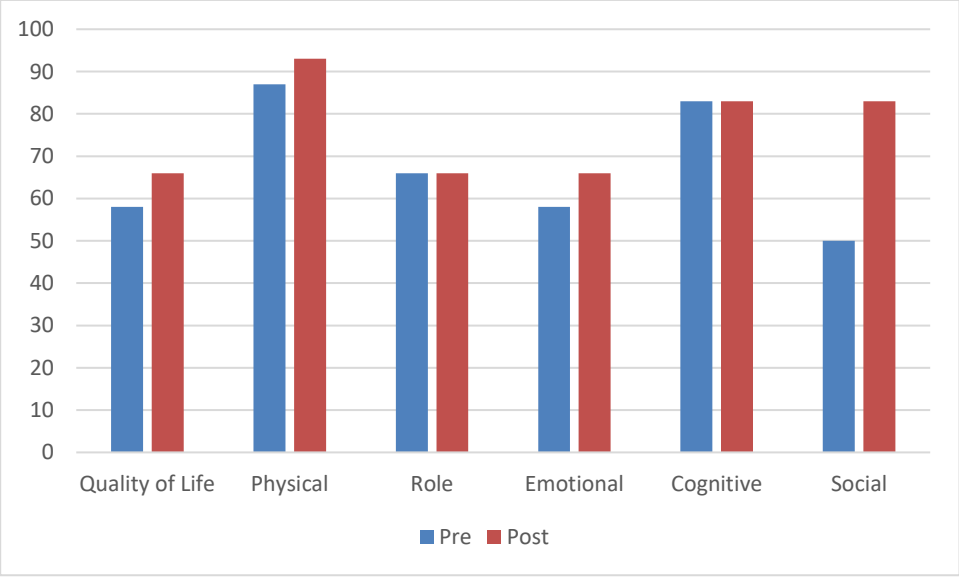

Figure 8. 15 Changes in quality of life and functional domains pre and post intervention.

Fatigue was the most prevalent symptom at baseline with every patient reporting some levels of fatigue, and half reporting increased levels at the end of the intervention. While pain levels and nausea/ vomiting improved for the majority of patients, n=4 patients reported persistent and increasing insomnia at 12 weeks. Appetite loss was present in half the patients at baseline and persisted in one – third on re-evaluation at 12 weeks, albeit at a reduced level. Changes in symptom scale are summarised in Figure 8.16

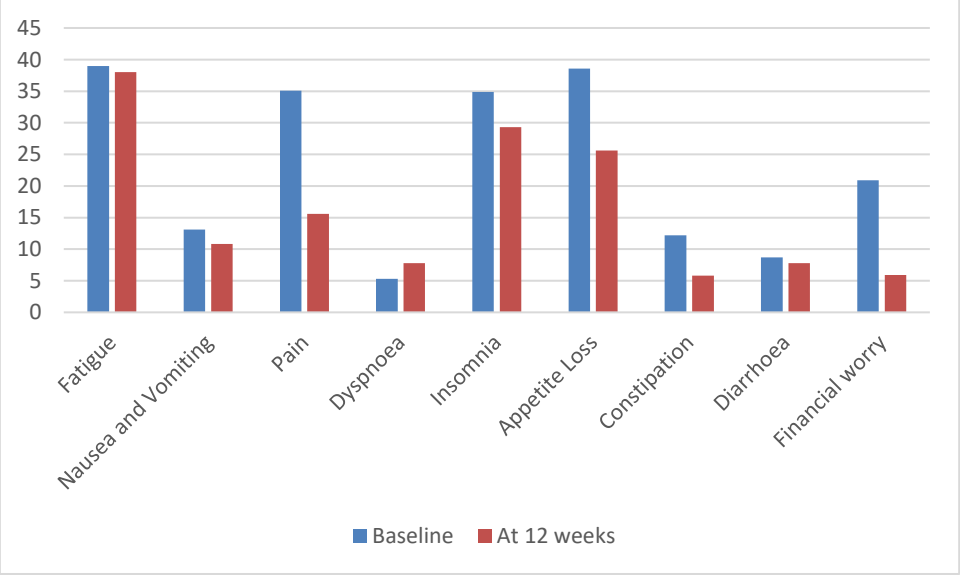

Figure 8. 16 Changes in symptom scale assessment pre and post intervention.

8.6.5.4 Cytokines and insulin

Changes in serum IGF- 1 and IL- 6 are shown in figures 8.17 and 8.18 respectively. Baseline levels of IGF-1 positively correlated with LSMI (R=0.604, P=0.008) and muscle attenuation or radiodensity (R=0.502, P=0031), but were negatively associated with percentage weight loss (R=0.519, P=0.027). Similarly, IGF was positively associated with HGS (R=0.582, P=0.011) and negatively associated with TUG (R=-0.646, P=0.001). No association were seen with body composition or weight change at 12 weeks.

Unfortunately, only 4 patients in this study had detectable levels of TNF-α in their serum, precluding the potential for evaluation.

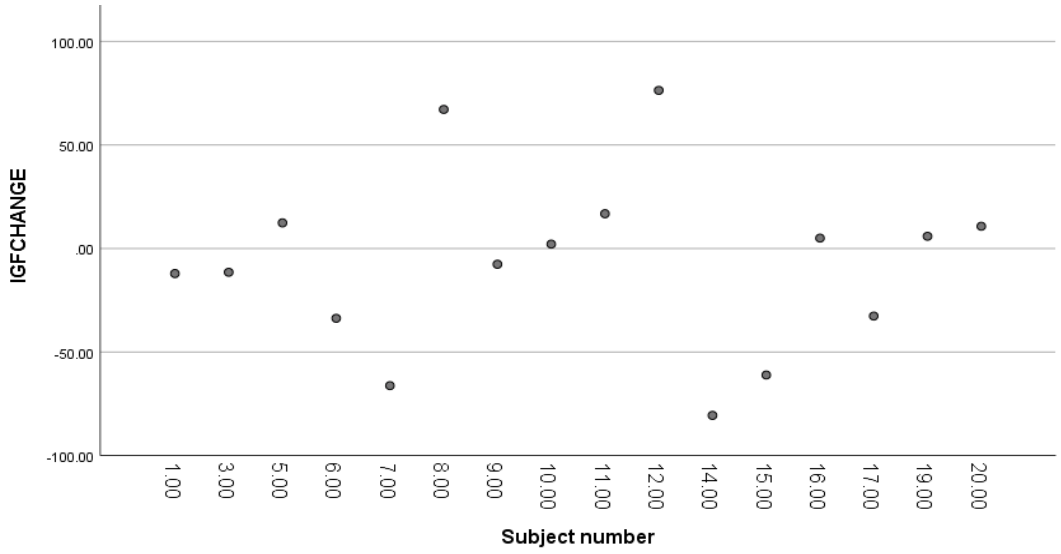

Figure 8. 17 Individual patient changes in serum IGF-1 concentration (ng/ml) at 12 weeks.

Serum IL-6 was not associated with any body composition indices or weight loss, but did correlate, as anticipated, with CRP (R=0.548, P=0.019) and Albumin (R=-0.518, P=0.028). Minimal changes in serum IL- 6 following the intervention

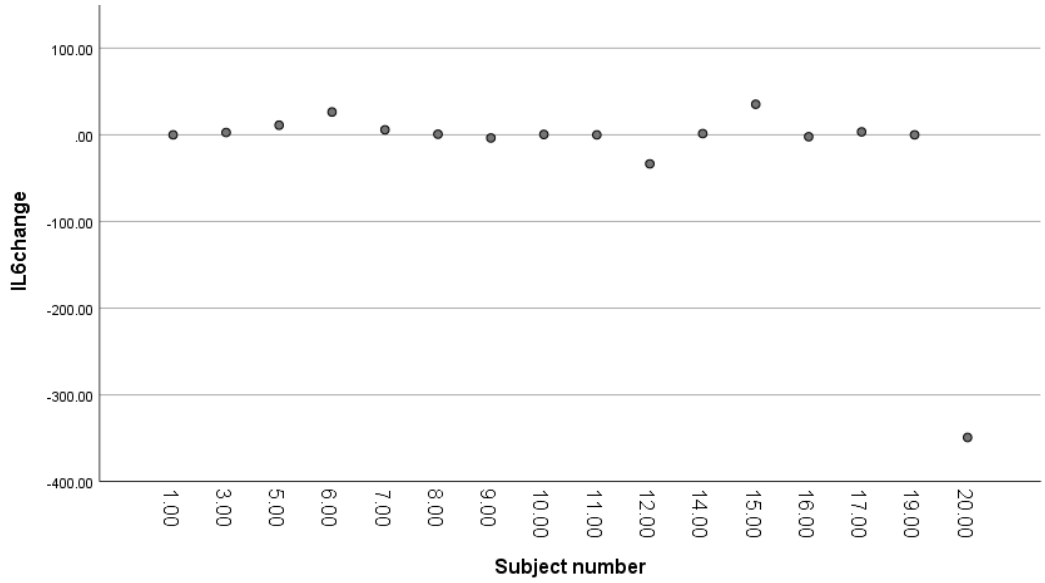

Figure 8. 18 Individual patient changes in serum IL-6 (pg/ml) from baseline.

The high prevalence of DM prompted evaluation of serum insulin levels. Only four patients have hyperinsulinaemia at diagnosis (>25 IU/L), with three of these patients subsequently being newly diagnosed with DM during the course of the study. The other patient developed biliary sepsis within 24 hours of assessment. Serum insulin levels at baseline correlated with baseline LSMI (R=0.479, P=0.044).

8.7 Discussion

This study demonstrates that a multi-modal nutrition-led intervention was both appealing (opt-in rate of 71%) and feasible for most patients undergoing neoadjuvant chemotherapy for pancreatic cancer. Twelve weeks was deliberately selected as the time period for this study as it matched the median duration of neoadjuvant chemotherapy for patients treated in our unit, and patients routinely undergo CT restaging at this point, allowing opportunistic assessment of body composition. The majority of patients required additional chemotherapy following this restaging CT, and all opted to continue with the interventional study beyond the 12 weeks.

To the best of my knowledge, it is the first study to evaluate pancreatic function (both endocrine and exocrine) in patients undergoing neoadjuvant therapy. The prevalence of both PEI and DM were much higher than anticipated, both were double what was observed in the previous retrospective cohort study (Chapter 7).

PEI is underestimated outside specialist centres (66), and has previously been reported as a key unmet supportive care need among patients and carers(68). These findings support the need for routine evaluation of exocrine function for patients with BRPC and LAPC, along with the recommendations put forward by the NCCN that patients undergoing neoadjuvant chemotherapy for pancreatic cancer should receive PERT to avoid any unecessary symptom burden, and preventable weight loss(218). The majority of patients in this study adhered to their PERT prescription,

with most reporting they had noticeable symptoms if they accidentally missed a dose. The provision of extra pill boxes was highlighted as a helpful strategy to aid adherence by patients.

Half of this cohort had DM, with more than half being diagnosed during the first 6 weeks of the study period, a key finding of this study. The majority of these patients were hyper-insulinaemic at diagnosis. Whether this was a consequence of premorbid insulin resistance present prior to their diagnosis or associated with or implicated in the development of their pancreatic tumour is not known. The higher than anticipated prevalence highlights both limitations of one-off HbA1c monitoring in this patient group, alongside the need to re-evaluate and monitor glycaemic control throughout treatment, particularly when weight loss persists despite treatment of PEI. Jaundice, and associated maldigestion, is coupled with an underappreciation of the predominance of PEI and resultant malabsorption in the weeks preceeding diagnosis/starting treatment. While pancreatogenic DM is characterised by decrease in hepatic insulin sensitivity leading to unsuppressed hepatic glucose production and severe hyperglycaemia, reduced secretion of glucagon and pancreatic polypeptide hormones due to islet cell destruction may result in hypoglycaemia(253). This precludes the reliability of using HbA1c as an isolated diagnostic tool in this patient group; patients may endure both severe hyperglycaemia and common episodes of hypoglycaemia, potentially leading to a near-normal average level.

While weight loss as a feature of pancreatic cancer is well recognised in the literature (42, 46, 254), few studies have characterised ongoing weight loss during treatment. Dalal and colleagues reported that 81% of patients had persistent weight loss (>5%) during chemoradiation for LAPC (255), with obese patients experiencing higher rates of loss. More recently, Naumann and colleagues also evaluated patients with LAPC undergoing chemoradiation of neoadjuvant intent, and reported similar levels of weight loss during treatment (mean 5% weight loss during treatment, affecting half their cohort) (44). Another international study highlighted the prognostic significance of weight maintenance following diagnosis in a randomised, double- blind study evaluating the impact of a N-3 PUFA enriched oral nutritional supplement in weight losing unresectable pancreatic cancer patients. Here only 41% of patients continued to lose weight at eight weeks. In contrast, the findings of the present study demonstrated that only 23% of patients continued to lose weight after 12 weeks of treatment, while 61% had managed to return to, or exceed their pre-morbid weight. This finding supports the main hypothesis for this study; that weight loss in pancreatic cancer has a multi-factorial aetiology,and may be preventable for some patients by addressing modifiable factors and the implementation of a multi-modal intervention.

A recent study by Purcell and colleagues in Alberta evaluated the accuracy of 23 REE predictive equations in cancer patients, and concluded that none of these equations currently used in clinical practice could accurately predict REE, even with the addition of body composition measurement by

DEXA (60). I adopted the ESPEN guidelines for total energy provision, which are based on international expert consensus opinion (119). All of the patients who returned to their premorbid weight reported an estimated daily intake of at least 25kcal/kg with some gaining in excess of their baseline weight at this caloric intake. Where patients could not achieve this minimum energy target, the main causative factor were cumulative calorie deficits associated with chemotherapy toxicity, suggesting the need for escalated supportive care for these patients. Addressing symptom burden, chemotherapy dose modification and individualised patient assessment for articifial nutritional support may be warranted. While previous studies have shown increased levels of resting energy expenditure in patients with pancreatic cancer, others have demonstrated that overall total energy expenditure is reduced due to declining physical activity levels (58, 91). These results suggest, that when pancreatic insufficiency is identified and corrected, achieving adequate energy intake is possible for most patients with BRPC and LAPC.

Achieving an adequate protein was more difficult for patients, with many relying on the nutritional supplement to meet the minimum target of 1g/kg/day. Most reported uneven protein distribution throughout the day, habitually consuming a carbohydrate- rich breakfast and reporting an over reliance on their main meal to meet protein needs. Often this meal was taken in the evening where symptoms of early satiety and anorexia were noted to be most severe, limiting their portion size. In addition, many had negative connotations with meat products, either due to ingestion

amplifying dysgeusia associated with chemotherapy, or reporting impaired ability to tolerate higher fat following biliary stent placement.

The need for even protein distribution with at least 20g per meal to stimulate muscle protein synthesis in older adults with anabolic resistance as a consequence of aging is well recognised in the literature (99, 256, 257). The optimal protein dosing strategy for cancer patients is not known however. One study evaluating the impact of nutrition on protein kinetics in pancreatic cancer(56) observed muscle breakdown and synthesis following the ingestion of ONS containing 10g protein in cachectic patients compared to controls. Baseline levels of basal protein metabolism were higher in patients compared to controls, and while feeding reduced the rate of muscle breakdown in both, muscle synthesis was only stimulated in the control group. Other researchers have questioned whether protein dosing should be based on body composition rather than overall weight, while the PRIMe study is currently underway in Canada, comparing the effect of varying protein dosage regimens in patients with colorectal cancer (NCT027889955).

Tolerance of N-3 PUFA enriched ONS was higher than reported in previous studies using the same product in pancreatic cancer patients (117). Unlike previous studies which reported gastrointestinal dose-limiting toxicity as the main barrier to patient compliance(252), only palatability and anticipatory nausea were identified as barriers in this study. Initiation of the supplement was delayed until PERT had been established, and a

dose escalation strategy with measuring cups provided to each patient. Recipes were also provided to each patient to encourage compliance. One-third of patients reported adding the supplement to coffee or serving over ice. Only one patient required a dose reduction due to thrombocytopenia when they continued to the ONS beyond the study period.

While one-third of patients reported low levels of physical activity at baseline, the majority of patients reported an increase in their levels at week 12, assessed using the IPAQ. Only one other study evalauated physical activity levels among pancreatic cancer patients undergoing neoadjuvant treatment. Parker and colleagues utilised the IPAQ to evaluate physical activity levels among a cohort of pancreatic cancer patients recruited to a randomised controlled trial evaluating the efficacy of exercise prescription concurrent to neoadjuvant treatment (NCT03187951). They compared MET count assessed by IPAQ (using the shorter form of the questionnaire) before and after their 16-week intervention. They also observed an increase in physical activity (average 1503 MET-minutes at baseline, compared to 2219- MET minutes at 16 weeks), but both measures were higher than observed in this study (1037 at baseline, 1935 at the end of the intervention). Parker et al also reported minimal differences between self-assessment of MET count with the objective accelerometry measurement. While the present study focused on increased physical activity using a step target alone, their RCT includes both endurance and resistance exercise. The authors concluded that there

was wide variability in activity levels, and while most could achieve their endurance target, additional support was needed for patients to adhere to their resistance training prescription (258). Participants in the present study reported that consistently meeting their individual step target was the most difficult component of the intervention, with many suggesting additional support was needed. Some suggested having a variety of activities to choose from e.g drop- in supervised gym sessions or using a stationary bike.

The observed prevalence of cancer cachexia, sarcopenia and low muscle attenuation at baseline were higher in this patient group than had been observed in the previous study (Chapter 7). Nevertheless, the majority of patients maintained or improved both their weight and functional indices. While the overall cohort maintained or improved their lean tissue indices, there was no difference in patients who found the intervention feasible or not. The ability of patients, thought to be cachectic at the outset of their treatment, to maintain and regain weight, along with improved function, demonstrates a key limitation of the international consensus definition for cancer cachexia (81) in pancreatic cancer. The defined cut-offs of weight loss >5% in the absence of simple starvation, or weight loss >2% in those with sarcopenia or low BMI, may be induced by malabsorption or maldigestion caused by biliary obstruction or pancreatic insufficiency, and are therefore not specific enough to diagnose cancer cachexia in this patient group. While they may offer value as phenotypic criteria for the diagnosis of assessment, the relevant aetiological factors e.g. reduced

dietary intake, malabsorption and in particular systemic inflammation, a key component of cancer cachexia should also be included in future cancer cachexia assessment. Failure to correctly identify cancer cachexia is limiting necessary advances in the treatment of the disease, despite increased awareness and study over the last ten years, there is still no pharmacological agent for the condition.

The number of patients achieving resectability following completion of neoadjuvant chemotherapy is higher than the previous study, but the incidence of dose-limiting toxicity and need for crisis admission were similar. This was despite most patients receiving more chemotherapy than initially planned. Recurrent biliary sepsis and/or stent occlusion were the most common reasons for admission and treatment interruption. The occurrence of biliary obstruction and sepsis also limited the feasibility of the intervention for patients; reducing their tolerance of the N-3 PUFA ONS, necessitating fasting for stent replacement, and impacting the patient's ability to achieve their daily step target.

8.7.1 Study limitations

This study has a number of limitations which should be acknowledged. While the study design allowed an assessment of the feasiblity of this multimodal intervention, the sample size and exploratory nature do not allow evaluation of efficacy. Measurement of patient adherance to most components of the intervention relied on patient reporting, and the

shortcomings of dietary assessment methodologies are well documented in the literature (259-261). The inclusion of patients with different staging and chemotherapy regimens may be a confounding factor, however given that studies have shown the limitation of radiological assessment of resectability, targeting interventions at any patient undergoing treatment of neoadjuvant intent seems both relevant and important.

The lack of success with TNF-α detection due to assay failure was unfortunate and limited the ability to evaluate the impact of the N-3 PUFA ONS on proteolysis. A further limitation was the exercise/physical acitvity component; while patients adopted the step target, and reported an overall increase in activity levels, there was no formal resistance training element. This should be incorporated in future studies, and additional support provided to patients, as most reported achieving the step target as the most difficult component of the intervention.

8.7.2 Study strengths

The findings of this study clearly demonstrate the need for individualised, systematic nutritional assessment for patients with pancreatic cancer undergoing neoadjuvant therapy. They reveal for the first time, that pancreatic insufficiency (both endocrine and exocrine), is prevalent in patients undergoing neoadjuvant therapy. Most assessment methods are routinely used in clinical practice. With the exception of body composition and cytokine assessment, all can be routinely applied by dietitians working in oncology with little or no additional training.

Unlike many cancer trials where access is limited to older patients with cancer, there were no upper restrictions on age; if the patient was deemed eligible for chemotherapy, they were eligible for enrolment. Another key strength is the lack of industry sponsorship, involvement or potential conflict of interest, unlike previous studies evaluating the N-3 PUFA ONS in cancer patients.

8.8 Conclusion

The results from this study confirm that the aetiology of malnutrition in pancreatic cancer is multi factorial, and some of the causes are modifiable. They demonstrate that weight loss and decline in physical performance are not inevitable consequences of pancreatic cancer disease and treatment, and that neoadjuvant treatment offers time and impetus to improve and maximise nutritional status and physical function prior to potential curative resection.

Chapter 9 Discussion

9.1 Introduction

Pancreatic cancer continues to pose a significant oncological challenge. Unlike other cancers which have seen improving outcomes in recent years, this cancer has seen minimal meaningful change in five- year survival rates over the last 30 years. The latent profile of the disease necessitates a number of key priorities for improving outcomes:

1. Earlier detection through a combination of increased public awareness, further identification of high-risk individuals/groups who would benefit from regular screening, and the development of biomarkers for the detection and characterisation of tumours.
2. The discovery and availability of meaningful oncological treatment options for patients with pancreatic cancer, irrespective of their initial disease stage at presentation.

While these priorities are well recognised and accepted, the need to address supportive care needs of patients living with pancreatic cancer is less well established. The consequential physical decline and weight loss associated with pancreatic cancer is debilitating for patients, and often assumed to be an inevitable component of the disease and associated cachexia. The application of CT as a tool for body composition assessment allows opportunistic in-depth evaluation of body composition parameters

without subjecting patients to additional investigations. The emergence of neoadjuvant therapy for BRPC provides a discrete window of opportunity to evaluate a nutritional intervention, delivered concurrently, without necessitating treatment delay or modification.

9.2 Summary of objectives and findings

The dual aims of this thesis were to investigate the impact of body composition and nutritional intervention strategies in pancreatic cancer. To achieve these objectives, 4 inter-related studies were designed and conducted, the findings of which are summarised as follows:

1. A systematic review and meta-analysis examined the prevalence of sarcopenia in patients with resectable and borderline resectable cancer. The findings of this meta-analysis demonstrated that 40%of patients with R/ BRPC have low muscle indices at diagnosis.

2. A retrospective cohort study evaluated the impact of sarcopenia in patients in patients with resectable pancreatic cancer. Both sarcopenia and low muscle attenuation or radio-density are prevalent in patients undergoing surgery for suspected pancreatic malignancy in our centre, affecting half of patients. Low muscle indices were associated with increased mortality risk, and reduced

overall survival. Low muscle attenuation increased the risk of major post-operative morbidity.

3. The next cohort study sought to characterise the impact of body composition change during neoadjuvant therapy. Low muscle attenuation at diagnosis was an independent risk factor for mortality in patients with BRPC. Further loss of lean tissue indices (either FFM or SM) during chemotherapy also independently increased mortality risk. The worst affected patients experienced muscle loss equivalent to that encountered during two decades of normal physiological aging in a five-month period.

4. Lastly, a multi-modal nutritional interventional study was designed for patients undergoing neoadjuvant chemotherapy for pancreatic cancer. Systematic nutritional evaluation of these patients highlighted a high prevalence of cancer cachexia. Pancreatic insufficiency was common; with exocrine insufficiency diagnosed in 90% of participants and endocrine insufficiency affecting 50%. The primary outcome found that the study was feasible as designed for most patients, with many opting to continue the intervention beyond the 12-week study period. Weight maintenance, preservation of body composition indices and improvement of functional parameters were achieved by most participants

9.3 Novel and original contribution to knowledge

9.3.1 Impact of body composition in pancreatic cancer

While previous systematic reviews have evaluated the prevalence of sarcopenia in all disease stages, and/or in combination with other gastrointestinal cancers, the systematic review described in Chapter 5 study was the first to focus specifically on earlier stages of pancreatic cancer (R/BRPC). This meta-analysis established that sarcopenia was present in nearly half of patients at diagnosis. The high level of heterogeneity observed highlights ongoing limitations in the CT-based assessment of body composition in pancreatic cancer. The results of this study led to the development of recommendations for the design of future studies investigating body composition (Table 5.4).

Both cohort studies evaluating body composition in pancreatic cancer patients are among the first to utilise validated body composition technique and gender- and BMI- specific cut-offs for the assessment of sarcopenia. To the best of my knowledge, the study described in Chapter 5 is the first study to evaluate this is the first study evaluating the impact of sarcopenia on long-term survival following pancreatic cancer surgery that specified a minimum five-year follow-up period for all participants. For the first time, the negative prognostic effects of muscle indices on five-year survival following surgery for resectable PDAC were demonstrated.

While previous studies have examined body composition change during neoadjuvant chemotherapy in relation to resectability, this was the first study to fully characterise these changes and demonstrate the independent predictive prognostic effects of muscle indices.

9.3.2 Nutritional intervention for patients with BRPC

The findings of multi-modal interventional study were perhaps the most novel discoveries of this thesis. The high level of opt-in among eligible subjectsts suggested that the patients themselves were quite aware of the nutritional and functional deficit which resulted from living with pancreatic cancer. The systematic nutritional evaluation of patients on enrolment confirms that malnutrition and weight loss have a multi-factorial aetiology in pancreatic cancer.

This was the first time that exocrine function was measured in patients undergoing neoadjuvant therapy and demonstrated near-universal prevalence of PEI. Perhaps more striking was the observation that 50% of patients had DM, with the majority of patients being diagnosed after the initiation of chemotherapy and PERT. Latent endocrine insufficiency may only be unmasked when exocrine insufficiency is corrected. These patients only achieved weight maintenance when glycaemic control was optimised with medication, highlighting that regular assessment and monitoring of endocrine function is warranted in patients with persistent weight loss during chemotherapy.

Over half of the patients had returned to their pre-illness weight on 12-week assessment. The majority demonstrated improvements in functional assessment parameters, and only those with chemotherapy-induced neuropathy were unable to maintain their baseline levels. The near-universal anabolic potential of patients observed, regardless of their individual treatment outcome, is a novel finding which questions the relevance of the international consensus definition for cachexia in patients with pancreatic cancer. Some of these patients would have been initially staged as having refractory cachexia, where aggressive nutritional support is deemed to be of limited benefit. This study showed, for the first time, that intensive multi-modal intervention may improve indices of muscle mass and potentially improve functional capacity.

9.4 Implications for clinical practice

The findings of these studies provide additional evidence that disparities in body composition exist among patients with early stage pancreatic cancer and occur independently of BMI. This disparity should be considered for the nutritional and pre-operative assessment of patients with R/BRPC and functional assessment incorporated into routine clinical dietetic practice. Where possible, and where user operator skill and equipment availability allow, formal body composition assessment should be used to confirm the diagnosis of sarcopenia, and/or low muscle attenuation.

Routine enteral feeding tube placement at the time of PD has reduced in recent years, largely related to the success of enhanced recovery programmes. A negative result of this practice change is PN dependence in patients who develop major post-operative morbidities, with the associated need for central venous catheter placement and prolonged hospital admission. Pre-operative identification of patients with depleted physiological reserves by CT-based body composition analysis could objectively identify patients where pre-operative optimisation and intra-operative enteral tube placement is warranted.

Systematic evaluation of pancreatic function is arguably essential for all patients undergoing neoadjuvant therapy as both exocrine and endocrine insufficiency are prevalent and are limiting factors to preservation of nutritional status. The observed ability of patients to improve their nutritional status during their chemotherapy highlights the need for routine

specialist dietetic assessment and monitoring as a necessary component of patient care. When assessing patients with pancreatic cancer for cachexia severity, clinicians should consider the aetiological criteria for any weight loss experienced. Extreme weight loss caused by pancreatic insufficiency may be misattributed to cancer cachexia. Where weight loss persists despite optimising oral intake and initiating PERT, endocrine function should be re-evaluated and monitored. The use of n-3 PUFA ONS should be considered for patients who have persistent weight loss and persistently elevated inflammatory markers.

9.5 Suggestions for future research

The improvement of opportunistic CT-derived body composition analysis technique along with the potential for the automated measurement should be future research priorities. The emergence of muscle attenuation as a prognostic factor in pancreatic cancer also warrants further study, both to fully define the mechanisms involved, and identify the potential for treatment strategies. Muscle and/or functional indices should be included as parameters for future predictive nomogram development, particularly those relying on data available prior to surgery. Alternative chemotherapy dosing strategies should also be explored, utilising body composition parameters rather than rely on body surface area.

Future studies evaluating the impact of prehabilitation programmes in pancreatic cancer should incorporate objective assessment of muscle mass and function and include long-term recurrence-free and overall survival rates as outcome measures.

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Appendices

Appendix A Body composition training certificate

UNIVERSITY OF ALBERTA

FACULTY OF AGRICULTURAL, LIFE & ENVIRONMENTAL SCIENCES

Department of Agricultural, Food & Nutritional Science

This is to certify that **Oonagh Griffin** received training on computerized tomography body composition analysis using the slice-O-matic™ (Tomovision, Montreal, Canada) from Nov 16th to Nov 20th, 2015 at the Department of Agricultural, Food & Nutritional Science, University of Alberta, in Edmonton, Alberta, Canada.

Dr. Carla Prado
AFNS Assistant Professor and CAIP Chair
in Nutrition, Food and Health

Nov 2015

Appendix B Letters of ethical approval

St. Vincent's Healthcare GROUP LIMITED

UCD DUBLIN

Ethics and Medical Research Committee
ELM PARK, DUBLIN 4
Tel. (01) 2214117 Fax (01) 2214428
email: joan.mcdonnell@ucd.ie or jacinta.mcmanus@ucd.ie

4th January, 2016

Ms Oonagh Griffin,
Research Dietician,
Department of Dietetics,
SVUH

Re: Investigating the Incidence of Sarcopenia and Sarcopenic Obesity in Irish Pancreatic Cancer Patients.
Correspondence dated 31st December, 2015. Study Protocol.

Dear Ms Griffin,

Thank you for your correspondence and proposal requesting chairman's approval for your project.

Following review of your proposal I have granted chairman's approval for your project.

Yours sincerely,

Dr. E. Molloy,
Chairman,
Ethics and Medical Research Committee

cc. Professor Kevin Conlon, Professor of Surgery, SVUH.

St. Vincent's Healthcare GROUP LIMITED

UCD DUBLIN

Ethics and Medical Research Committee
ELM PARK, DUBLIN 4
Tel. (01) 2214117 Fax (01) 2214428
email: joan.mcdonnell@ucd.ie or jacinta.mcmanus@ucd.ie

5th July, 2017.

Professor Kevin Conlon,
Consultant HPB Surgeon/Professor of Surgery,
St. Vincent's University Hospital,
Elm Park,
Dublin 4.

Re: Exploring the feasibility of a multi-modal intervention: the FEED Trial (Comprising a Fish oil supplement, pancreatic Enzyme supplement, Exercise advice and individualised dietary counselling) for patients undergoing neoadjuvant chemotherapy for pancreatic cancer. **Response correspondence dated 27th June, 2017**. Checklist and Signatory page. **Revised Standard Application Form Version on 2 27th June, 2017 (clean & track change). Revised Protocol vs 2 27 June 2017 (clean & track change).** Letter for Participation. PIL/Consent Version 1. Letter to GP. Quality of Life Questionnaire. IPAQ.

Dear Professor Conlon,

Thank you for the clarifications and revised documents that were requested at the Ethics and Medical Research Committee meeting held on Wednesday 3rd May 2017, at which the above study was reviewed.

Following review of the revised documents and clarifications, this study is now granted full ethical approval.

Yours sincerely,

Dr. R. Crowley,
Deputy Chair,
Ethics & Medical Research Committee

cc. Ms Oonagh Griffin, Research Dietitian and PhD Candidate, SVUH.

Appendix C Data collection sheets

Data Collection: Surgical Cohort			
Subject ID	Age at surgery		Gender
Date of Referral	Date of MDT		Date of Decision for Surgery
Date of CT analysis	Site of CT procedure		Contrast Y/N
Histo pre-op	Y/N		Details:
Date of Surgery			
Procedure delayed/cancelled	Y/N		Details
CA19-9			
Pre-operative Symptom			
Biliary Obstruction Y/N	Max Serum Bilirubin		Stenting Y/N
Pancreatitis	Y/N		Acute/Chronic
Diabetes Y/N	Duration	HbA1c	Treatment
CRP	Albumin		Haemoglobin
Surgery			
Surgeon	Procedure Type		
EBL	Intra-op events		
Feeding device insertion	Y/N		Type
Histopathology	T N R M		Type
Post surgery			
LOS	Alive at 30 days		Alive at 90 days
Delayed Gastric Emptying	Y/N		Grade
Post-Operative Pancreatic Fistula	Y/N		Grade
Collection requiring intervention	Y/N		
Ischaemia	Y/N		
Haemorrhage	Y/N		Site
Chyle leak	Y/N		No of nodes harvested
Return to theatre	Y/N		Findings
ICU readmission	Indication		LOS

Subject ID		
Nutritional and Body Composition Assessment		
Baseline Weight	BMI	% weight loss
Pre –operative intervention by dietitian	Y/N Date of assessment	Type Diet ONS ETF PN PERT
CT scan	Complete field Y/N	Comments
Skeletal Muscle		
Intramuscular Adipose Tissue		
Visceral Adiposity		
Subcutaneous Adipose Tissue		
Muscle GLU		

Data Collection Form: Neo-adjuvant Treatment Group			
Subject ID	Age at diagnosis		Gender
Date of Referral	Date of MDT		Date of Decision for Treatment
Date of initial CT analysis	Site of CT procedure		Contrast Y/N
Histology	Details:		
Date of initial treatment			
CA19-9			Creatinine
Pre-Treatment Symptom			
Biliary Stent Y/N Type of stent Repeat Procedure Required			Max Bilirubin
Pancreatitis	Y/N		Acute/Chronic/ AIP
Diabetes Y/N	Duration	HbA1c	Treatment
CRP	Albumin		Haemoglobin
Treatment			
Oncologist	Regimen		
Planned dose			
Actual delivered dose			
Dose reduction required	Y/N		Details
ECOG at	Initial dose		Last dose
Need for crisis admission	No of occasions		Total LOS Seen by physio during admission Y/N
Treatment outcome	Proceed to surgery		
	Disease Progression		
30 day mortality 90 day mortality	Radiotherapy		Dosage

Subject ID		
Nutritional and Body Composition Assessment		
Baseline Weight	BMI	% weight loss pre treatment
Intervention by dietitian	Y/N Date of assessment	Type Diet ONS ETF PN PERT
Pre- Treatment Scan		
CT scan date	Complete field Y/N	Comments
Skeletal Muscle		
Intramuscular Adipose Tissue		
Visceral Adiposity		
Subcutaneous Adipose Tissue		
Muscle GLU		
Post Treatment Scan		
CT scan	Complete field Y/N	Comments
Skeletal Muscle		
Intramuscular Adipose Tissue		
Visceral Adiposity		
Subcutaneous Adipose Tissue		
Muscle GLU		

Study Selection & Data Extraction Form

First author	Journal/Conference etc	Year
CONTACT DETAILS FOR AUTHOR:		

Study eligibility

Relevant participants: Resectable or Borderline Reseactable Pancreatic Cancer	**Relevant outcomes:** Sarcopenia
Yes / No / Unclear	Yes / No* / Unclear

Do not proceed if any of the above answers are 'No'. If study to be included in 'Excluded studies' section of the review, record below the information to be inserted into 'Table of excluded studies'.
Further exclusions: Children, Cystic Fibrosis, Locally Advanced or Metastatic Pancreatic Cancer, Pancreatic Neuroendocrine Tumours, Acute Pancreatitis, Chronic Pancreatitis

Study included? (Circle) YES NO

Aim of the study

Participant characteristics – give as much detail as is available. Describe patients and controls	
Study (PC) group	**Control group:**
Number of subjects	
Age (mean, median, range, etc)	
Sex (numbers / %, etc)	
Previous GI or HPB surgery (details etc)	
Diabetes (type/duration/treatment)	
Patient exocrine status	
Ethnicity, SE group etc	
Obstructive jaundice (duration, max bilirubin, need for stent)	
Relevant co-existing chronic illness (e.g IBD, autoimmune disease, previous cancer and how treated)	
Patient BMI	
Inflammatory markers measured (type/details)	
Tumour marker (e.g CA 19-9)	
Percentage weight loss experienced at diagnosis	
Physical activity levels (how measured etc)	

Outcomes	CP group *Or specify study group*		Control group *Or specify control group*		Additional info
Units	N	**%**	**N**	**%**	
Number of patients with sarcopenia					
Units					
OR for Sarcopenia (and 95% CI)					
Units					
HR for Sarcopenia (and 95% CI)					
Units					
Outcome 4					

Other information on outcomes

How is sarcopenia defined	
Method of muscle measurement	
Reference value used to specify sarcopenia/low muscle mass/ function e.g. LSMI level,	
Reference supporting value/ definition used	
Details of measurement technique: Equipment/ Programme used	
Training/Accuracy of technician (e.g. ISAK trained, co-efficient of variance if multiple staff involved)	
Criteria used to diagnose stage pancreatic cancer e.g NCCN/ MD Anderson, and year	
Any other relevant clinical data	

Other information which you feel is relevant to the results Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by you using a formula (this should be stated and the formula given). In general if results not reported in paper(s) are obtained this should be made clear here to be cited in review.

State here any associations, conclusions or observations made by the study authors *e.g impact on treatment toxicity, surgical complications, survival.*

Study characteristics
Single centre / multicentre
Country / Countries
Trial design (e.g. case=controlled, cross-sectional, cohort)
Other

References to other trials

Did this report include any references to **published reports** of potentially eligible trials not already identified for this review?		
First author	Journal / Conference	Year of publication
Did this report include any references to **unpublished data** from potentially eligible trials not already identified for this review? If yes, give list contact name and details		

Appendix D Patient information leaflet and consent form

St. Vincent's Healthcare GROUP LIMITED

ELM PARK, DUBLIN 4

DEPT OF SURGERY, NATIONAL SURGICAL CENTRE FOR PANCREATIC CANCER, ST VINCENT'S UNIVERSITY HOSPITAL

PARTICIPANT INFORMATION AND CONSENT FORM

STUDY TITLE:

'The FEED Trial'

Exploring the feasibility of a combined package of care for patients undergoing neo-adjuvant chemotherapy for pancreatic cancer: The FEED Trial (a Fish oil supplement, pancreatic Enzyme supplement, Exercise advice and individualised Dietary counselling)

NAME OF PRINCIPAL INVESTIGATOR

Professor Kevin Conlon

You are being invited to participate in a research study. Thank you for taking time to read this information leaflet.

WHAT IS THE PURPOSE OF THIS STUDY?

We aim to find out if a new nutritional care package is acceptable and realistic for patients with pancreatic cancer. This care package is designed to keep your weight and strength steady while you are on chemotherapy.

WHY HAVE I BEEN CHOSEN?

You have been chosen because you have pancreatic cancer, and are undergoing a course of chemotherapy before possibly having surgery.

WHAT WILL HAPPEN IF I VOLUNTEER?

Your participation is entirely voluntary. If you initially decide to take part you can change your mind afterwards without difficulty. This will not affect your future treatment in any way. Furthermore, your doctor may decide to withdraw you from this study if he feels it is in your best interest.
If you agree to participate, you will be requested to:

1. Donate blood samples (equivalent to 1 teaspoon – at beginning and end of the 12-week study)
2. Donate a stool (faeces) sample (this is a once off, there is no fasting or preparation required)
3. Complete two surveys (at the beginning and end of your chemotherapy treatment)
4. Undergo fitness testing at the beginning and end of the 12 week study. We measure how quickly you can get up from a chair, walk a short

distance, and sit back down again. We would also record your hand grip strength, your weight, height and weight history.

5. Allow us to access to your CT scans for nutritional and body composition analysis (we will look at your scans and use a special software to work out how much muscle and fat you have)
6. Allow us to access your medical notes and clinical record to record any relevant medical history, and how you tolerate your treatment
7. Undergo regular review follow up appointments with a dietitian throughout your chemotherapy.

As part of this assessment (which will last 2 hours approx.) you will meet with a dietitian who will provide dietary advice and recommend a fish oil enriched nutritional supplement (Prosure), pancreatic enzyme replacement tablets (Creon), and a daily step (walking) target. You will be asked to record how many supplements you manage, how many enzyme tablets you take, and your daily steps throughout the 12-week study.

The initial (first) assessment will take place before you start treatment and you will need to come to St Vincent's University Hospital for this extra appointment.
All other follow-up appointments will happen at the same time as your normal hospital appointments.

ARE THERE ANY BENEFITS FROM MY PARTICIPATION?

You will not benefit directly from taking part in this study, but the information we get may help us to understand more about weight loss and muscle loss in patients with pancreatic cancer.

ARE THERE ANY RISKS INVOLVED IN PARTICIPATING?

There are some risks associated with this study

- As with all blood samples, there are minor risks when taking the bloods, such as bruising at the needle site, swelling, dizziness, fainting, and infection at the needle site
- The fish oil supplement (Prosure) may have side effects, include a higher risk of bleeding when more than 3g per day is taken (this is because fish oils thin the blood). Other possible side-effects of fish oils are indigestion, rash, nausea and loose stools
- The pancreatic enzyme supplements (Creon) may have side-effects such as nausea and vomiting, diarrhoea, constipation, abdominal pain, cramps, bloating, and flatulence (note that these symptoms may also happen due to pancreatic cancer), and rectal irritation, and skin rashes
- Increasing your exercise levels may also have extra risks, such as a higher risk of falls, soft tissue injury, hypoglycaemia if you have diabetes, worsening of high blood pressure if you have high blood pressure

WHAT HAPPENS IF I DO NOT AGREE TO PARTICIPATE?

If you decide not to take part in this study your treatment will not be affected in any way.

CONFIDENTIALITY

Your identity will remain confidential at all times. A study number will be used identify you. Your name will not be published or disclosed to anyone.

COMPENSATION

Your doctors are adequately insured by virtue of their participation in the clinical indemnity scheme. Your dietitian is insured via the Irish Nutrition & Dietetics Institute.

WHO IS ORGANISING AND FUNDING THIS RESEARCH?

This study is funded by the Health Research Board (HPF-2015-977) by means of a Health Professional's Fellowship Grant. The study is being done along with the Departments of Surgery in St Vincent's University Hospital, and Trinity College Dublin.

Will I be paid for taking part in this study? No, there is no payment

Will my expenses be covered for taking part in this study? No, there is no reimbursement of expenses

HAS THIS STUDY BEEN REVIEWED BY AN ETHICS COMMITTEE?

The St. Vincent's Healthcare Group, Ethics and Medical Research Committee have reviewed and approved this study.

CONTACT DETAILS

Oonagh Griffin – Research Dietitian (PhD Candidate),
National Surgical Centre for Pancreatic Cancer,
St Vincent's University Hospital, Dublin 4
Tel 01-2215270
Email o.griffin@st-vincents.ie

RESEARCH PARTICIPANT'S RIGHTS
If you have any questions about your rights as a research participant, then you may contact the Hospital's Quality & Patient Safety Department 01 2214013

PLEASE TICK YOUR RESPONSE IN THE APPROPRIATE BOX

- I have read and understood the Participant Information YES ☐ NO ☐
- I have had the opportunity to ask questions and discuss the study YES ☐ NO ☐
- I have received satisfactory answers to all my questions YES ☐ NO ☐
- I have received enough information about this study YES ☐ NO ☐
- I understand that I am free to withdraw from the study at any time without giving a reason and without this affecting my future medical care YES ☐ NO ☐
- I agree to take part in the study YES ☐ NO ☐

Participant's Signature: _____ Date: _____

Participant's Name in print: _____

Investigator's Signature: _____ Date: _____

Investigator's Name in print: _____

Appendix E Questionnaires

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE (October 2002)

LONG LAST 7 DAYS SELF-ADMINISTERED FORMAT

FOR USE WITH YOUNG AND MIDDLE-AGED ADULTS (15-69 years)

The International Physical Activity Questionnaires (IPAQ) comprises a set of 4 questionnaires. Long (5 activity domains asked independently) and short (4 generic items) versions for use by either telephone or self-administered methods are available. The purpose of the questionnaires is to provide common instruments that can be used to obtain internationally comparable data on health–related physical activity.

Background on IPAQ

The development of an international measure for physical activity commenced in Geneva in 1998 and was followed by extensive reliability and validity testing undertaken across 12 countries (14 sites) during 2000. The final results suggest that these measures have acceptable measurement properties for use in many settings and in different languages, and are suitable for national population-based prevalence studies of participation in physical activity.

Using IPAQ

Use of the IPAQ instruments for monitoring and research purposes is encouraged. It is recommended that no changes be made to the order or wording of the questions as this will affect the psychometric properties of the instruments.

Translation from English and Cultural Adaptation

Translation from English is encouraged to facilitate worldwide use of IPAQ. Information on the availability of IPAQ in different languages can be obtained at www.ipaq.ki.se. If a new translation is undertaken we highly recommend using the prescribed back translation methods available on the IPAQ website. If possible please consider making your translated version of IPAQ available to others by contributing it to the IPAQ website. Further details on translation and cultural adaptation can be downloaded from the website.

Further Developments of IPAQ

International collaboration on IPAQ is on-going and an ***International Physical Activity Prevalence Study*** is in progress. For further information see the IPAQ website.

More Information

More detailed information on the IPAQ process and the research methods used in the development of IPAQ instruments is available at www.ipaq.ki.se and Booth, M.L. (2000). *Assessment of Physical Activity: An International Perspective*. Research Quarterly for Exercise and Sport, 71 (2): s114-20. Other scientific publications and presentations on the use of IPAQ are summarized on the website.

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** and **moderate** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

PART 1: JOB-RELATED PHYSICAL ACTIVITY

The first section is about your work. This includes paid jobs, farming, volunteer work, course work, and any other unpaid work that you did outside your home. Do not include unpaid work you might do around your home, like housework, yard work, general maintenance, and caring for your family. These are asked in Part 3.

1. Do you currently have a job or do any unpaid work outside your home?

   ☐ Yes

   ☐ No → ***Skip to PART 2: TRANSPORTATION***

The next questions are about all the physical activity you did in the **last 7 days** as part of your paid or unpaid work. This does not include traveling to and from work.

2. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, heavy construction, or climbing up stairs **as part of your work**? Think about only those physical activities that you did for at least 10 minutes at a time.

   _____ **days per week**

   ☐ No vigorous job-related physical activity → ***Skip to question 4***

3. How much time did you usually spend on one of those days doing **vigorous** physical activities as part of your work?

   _____ **hours per day**
   _____ **minutes per day**

4. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads **as part of your work**? Please do not include walking.

   _____ **days per week**

   ☐ No moderate job-related physical activity → ***Skip to question 6***

5. How much time did you usually spend on one of those days doing **moderate** physical activities as part of your work?

_____ **hours per day**
_____ **minutes per day**

6. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **as part of your work**? Please do not count any walking you did to travel to or from work.

_____ **days per week**

☐ No job-related walking → ***Skip to PART 2: TRANSPORTATION***

7. How much time did you usually spend on one of those days **walking** as part of your work?

_____ **hours per day**
_____ **minutes per day**

PART 2: TRANSPORTATION PHYSICAL ACTIVITY

These questions are about how you traveled from place to place, including to places like work, stores, movies, and so on.

8. During the **last 7 days**, on how many days did you **travel in a motor vehicle** like a train, bus, car, or tram?

_____ **days per week**

☐ No traveling in a motor vehicle → ***Skip to question 10***

9. How much time did you usually spend on one of those days **traveling** in a train, bus, car, tram, or other kind of motor vehicle?

_____ **hours per day**
_____ **minutes per day**

Now think only about the **bicycling** and **walking** you might have done to travel to and from work, to do errands, or to go from place to place.

10. During the **last 7 days**, on how many days did you **bicycle** for at least 10 minutes at a time to go **from place to place**?

_____ **days per week**

☐ No bicycling from place to place → ***Skip to question 12***

11. How much time did you usually spend on one of those days to **bicycle** from place to place?

_____ **hours per day**
_____ **minutes per day**

12. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time to go **from place to place**?

_____ **days per week**

☐ No walking from place to place → ***Skip to PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY***

13. How much time did you usually spend on one of those days **walking** from place to place?

_____ **hours per day**
_____ **minutes per day**

PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY

This section is about some of the physical activities you might have done in the **last 7 days** in and around your home, like housework, gardening, yard work, general maintenance work, and caring for your family.

14. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, chopping wood, shoveling snow, or digging **in the garden or yard**?

_____ **days per week**

☐ No vigorous activity in garden or yard → ***Skip to question 16***

15. How much time did you usually spend on one of those days doing **vigorous** physical activities in the garden or yard?

_____ **hours per day**
_____ **minutes per day**

16. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, sweeping, washing windows, and raking **in the garden or yard**?

_____ **days per week**

☐ No moderate activity in garden or yard → ***Skip to question 18***

17. How much time did you usually spend on one of those days doing **moderate** physical activities in the garden or yard?

_____ **hours per day**
_____ **minutes per day**

18. Once again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, washing windows, scrubbing floors and sweeping **inside your home**?

_____ **days per week**

☐ No moderate activity inside home → ***Skip to PART 4: RECREATION, SPORT AND LEISURE-TIME PHYSICAL ACTIVITY***

19. How much time did you usually spend on one of those days doing **moderate** physical activities inside your home?

_____ **hours per day**
_____ **minutes per day**

PART 4: RECREATION, SPORT, AND LEISURE-TIME PHYSICAL ACTIVITY

This section is about all the physical activities that you did in the **last 7 days** solely for recreation, sport, exercise or leisure. Please do not include any activities you have already mentioned.

20. Not counting any walking you have already mentioned, during the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **in your leisure time**?

_____ **days per week**

☐ No walking in leisure time → ***Skip to question 22***

21. How much time did you usually spend on one of those days **walking** in your leisure time?

_____ **hours per day**
_____ **minutes per day**

22. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like aerobics, running, fast bicycling, or fast swimming **in your leisure time**?

_____ **days per week**

☐ No vigorous activity in leisure time → ***Skip to question 24***

23. How much time did you usually spend on one of those days doing **vigorous** physical activities in your leisure time?

_____ **hours per day**
_____ **minutes per day**

24. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like bicycling at a regular pace, swimming at a regular pace, and doubles tennis **in your leisure time**?

_____ **days per week**

☐ No moderate activity in leisure time → ***Skip to PART 5: TIME SPENT SITTING***

25. How much time did you usually spend on one of those days doing **moderate** physical activities in your leisure time?
_____ **hours per day**
_____ **minutes per day**

PART 5: TIME SPENT SITTING

The last questions are about the time you spend sitting while at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television. Do not include any time spent sitting in a motor vehicle that you have already told me about.

26. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekday**?

_____ **hours per day**
_____ **minutes per day**

27. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekend day**?

_____ **hours per day**
_____ **minutes per day**

This is the end of the questionnaire, thank you for participating.

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix F Prosure

ProSure

1 FLAVOUR — GMS APPROVED

1.3kcal/ml nutritional drink, enriched with omega-3 fatty acids, antioxidants and FOS^ for patients with cancer cachexia.

NUTRITIONAL INFORMATION	UNIT	PER 100ml	PER BOTTLE (220ml)
Energy	kJ	536	1179
	kcal	127	280
Protein (nitrogen)	g	6.65 (1.06)	14.6 (2.34)
Carbohydrate	g	18.3	40.3
of which sugars	g	6.5	14
Fat	g	2.56	5.63
of which saturates	g	0.69	1.5
of which EPA+*	g	0.45	0.99
Fibre	g	3.07	6.55
of which FOS^	g	1.1	2.42

VITAMINS	UNIT	PER 100ml	PER BOTTLE (220ml)
Vitamin A	µg	205	451
of which ß-carotene	µg	70	154
Vitamin D_3	µg	1.7	3.7
Vitamin E	mg	20	44
Vitamin K_1	µg	10	22
Vitamin C	mg	43	95
Folacin (folic acid)	µg	32	70
Thiamin (vitamin B_1)	mg	0.25	0.55
Riboflavin (vitamin B_2)	mg	0.29	0.64
Vitamin B_6	mg	0.34	0.75
Vitamin B_{12}	µg	0.35	0.77
Niacin	mg	2.4	5.3
Pantothenic acid	mg	1.1	2.4
Biotin	µg	5	11

MINERALS	UNIT	PER 100ml	PER BOTTLE (220ml)
Sodium	mg (mmol)	115 (5)	253 (11)
Potassium	mg (mmol)	175 (4.48)	385 (9.8)
Magnesium	mg (mmol)	42 (1.75)	92 (3.8)
Phosphate	mg (mmol)	80 (2.58)	176 (5.7)
Calcium	mg (mmol)	100 (2.5)	220 (5.5)
Chloride	mg (mmol)	152 (4.29)	334 (9.4)
Iron	mg	0.65	1.43
Zinc	mg	2.5	5.5
Manganese	mg	0.42	0.93
Copper	mg	0.08	0.17
Iodine	µg	16	35
Selenium	µg	7.9	17
Chromium	µg	9	20
Molybdenum	µg	14	31
Choline	mg	51	112
Taurine	mg	20	44
L-carnitine	mg	10	22

Osmolality	mOsm/kg H_2O	753
Osmolarity	mOsm/litre	597
Water	ml/100ml (ml/bottle)	79.6 (175)
Renal solute load	mOsm/litre	517

Order code: Vanilla: S712

^Fructooligosaccharides.
+The recommended intake is 2 bottles per day.
*Eicosapentaenoic acid.
ProSure is Gluten Free and Clinically Lactose Free.

ProSure

1.3 kcal/ml liquid enriched with omega 3 fatty acids, antioxidants and fructo-oligosaccharides (FOS)

PRESENTATION

- Presented in a 220 ml (280 kcal) bottles.
- ProSure is available in vanilla flavour.

USES

Food for Special Medical Purposes, for use under medical supervision. Not suitable as a sole source of nutrition.

ProSure is to be used as a nutritional supplement, specifically designed for the dietary management of oncology patients with weight loss. The recommended intake is 2 bottles per day to obtain approximately 2 g of eicosapentaenoic acid (EPA) a day. Do not exceed this intake.

COMMUNITY USE—PRESCRIPTIONS

ProSure is available on the DPS (Drug Payment Scheme) and the GMS (General Medical Services) Scheme in Ireland for the following indication:

- Patients with cancer cachexia

STORAGE & DIRECTIONS FOR SIP FEEDING

- Store unopened at room temperature.
- Ready for use. Open immediately prior to use.
- Shake well before use.
- Best served chilled.
- Once opened, unused product should be resealed and stored in a refrigerator. Unused contents should be discarded after 24 hours.
- Date and time of opening can be recorded on the lid sticker.

DIRECTIONS FOR TUBE FEEDING

- Ready for use.
- Two bottles daily can be incorporated as part of the feeding regimen.
- Administer at room temperature for tube feeding.
- The volume/flow rate should be adjusted to meet the patient's nutritional needs and tolerance. This product has a low viscosity and will pass down a fine nasogastric tube.
- A Flexitainer enteral nutrition container may be used if decanting is necessary.
- An Abbott enteral feeding pump may be used in conjunction with the Abbott enteral feeding system where a more accurately controlled delivery of feed is indicated. An ambulatory system is available.
- Bottles will attach to Abbott giving sets.

PRECAUTIONS

- In patients receiving some medications there may be a risk of drug nutrient interactions (e.g. warfarin and vitamin K). Careful prescribing and monitoring practices will serve to reduce the risk (please refer to pharmacist).
- Patients should not make any additions to the feed without consulting their pharmacist or dietitian.
- Many nutritional products contain sucrose and other sugars. It is important for patients who are taking supplements as sip feeds to observe good oral hygiene.
- Unless recommended by a qualified healthcare professional, not intended for use in children.
- When feeding to patients with dysphagia, please thicken the product as appropriate.

CONTRA-INDICATIONS

- FOR ENTERAL USE ONLY.
- Not for use in galactosaemia.
- Do not use in children under 1 year of age.
- Suitable for people with diabetes provided that routine glucose checks are performed.

INGREDIENTS

Water, hydrolysed corn starch, ***milk*** proteins, sucrose, FOS, ***fish*** oil, gum arabic, minerals (magnesium chloride, potassium citrate, sodium citrate, potassium chloride, zinc sulphate, ferrous sulphate, manganese sulphate, cupric sulphate, sodium molybdate, chromium chloride, sodium selenate, potassium iodide), vegetable oils (MCT from palm kernel oil, canola, soy), flavouring, soy polysaccharide, vitamins (C, E, calcium pantothenate, niacinamide, beta carotene, B_6, B_1, B_2, vitamin A palmitate, folic acid, K_1, biotin, D_3, B_{12}), emulsifier: soy lecithin, choline chloride, acidity regulator: E525, taurine, L-carnitine, stabiliser: E418, antioxidants (E304, E306).

GENERAL INFORMATION

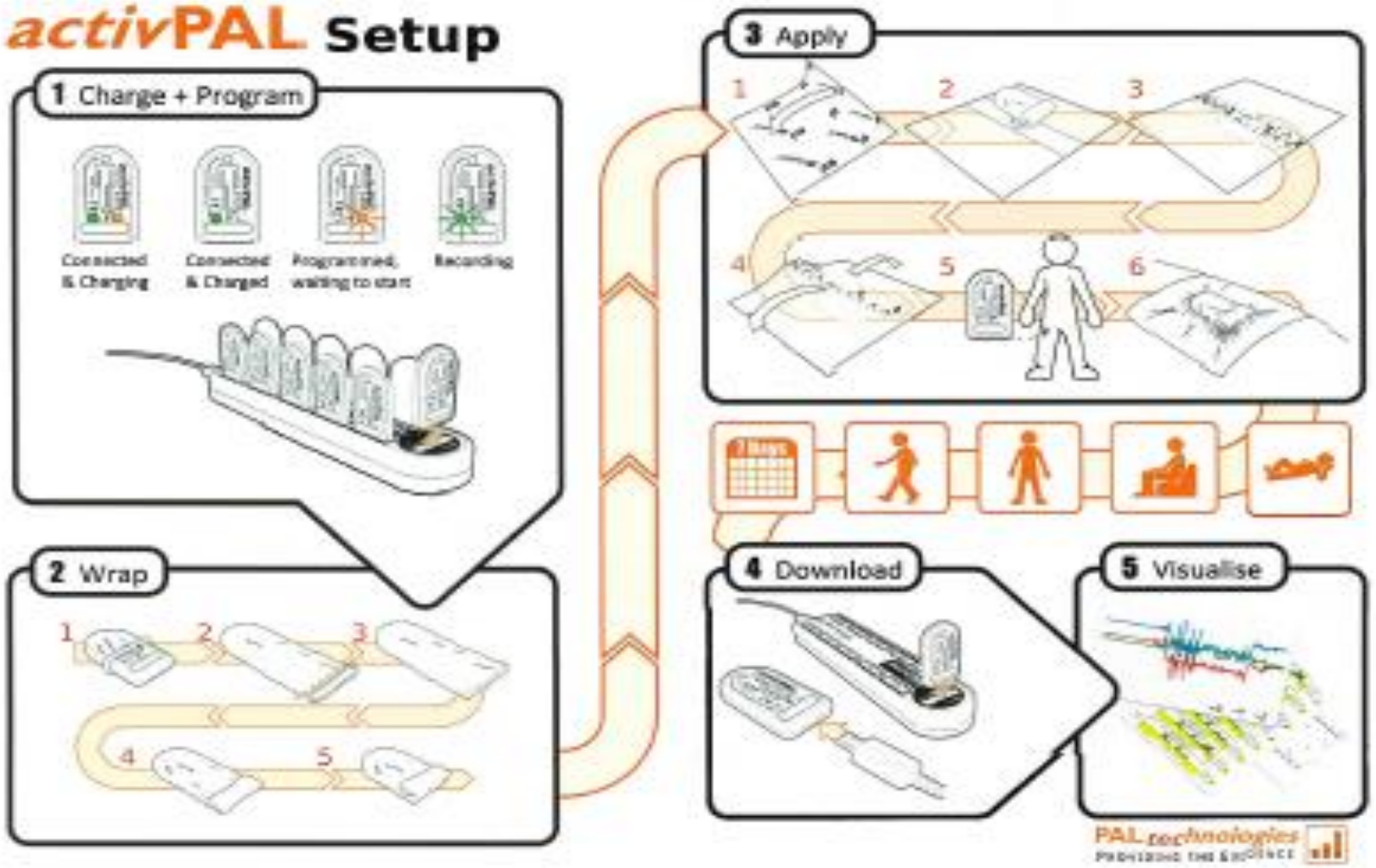
Energy density	1.3 kcal/ml
Energy distribution:	
Protein	20.9%
Carbohydrate	57.7%
Fat	18.1%
Fibre	3.26%
Renal solute load	517 mOsm/L
Osmolarity	597 mOsm/L
Osmolality	753 mOsm/kg H_2O
Gluten free?	✓
Clinically lactose free?	✓
Milk free?	✗
Suitable for vegetarians?	✗[1,2]

For suitability for other diets and free-from information, please contact Abbott Nutrition.

1. Vitamin D is synthesised from cholesterol, extracted from the grease in wool cleaned from live sheep.
2. Contains fish oil—not suitable for vegetarians or vegans.

Version 2: June 2017 (Ireland)

Appendix G Acclerometer patient information


activPAL Setup
1 Charge + Program
Connected & Charging
Connected & Charged
Programmed, waiting to start
Recording
2 Wrap
3 Apply
4 Download
5 Visualise
PAL technologies

Appendix H Patient self-monitoring diary

FEED Study Monitoring Diary

Patient Name:

_____

Week beginning: _____ daily step target: _____

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Prosure e.g. none, half a bottle, 2 bottles							
Steps							
Creon (number of capsules)							
Events e.g. chemo day, family party, hospital for CT,							
Symptoms e.g. nil new, pain, nausea etc.							

Useful Contact Details

St Vincent's University Hospital	
St Vincent's Private Hospital	
Oonagh Griffin	01-2215270
Oncology ward	
Chemotherapy day unit	
Consultant Oncologist	
Oncology liaison nurse	
Secretary	
Clinic	
Consultant Surgeon	
Surgical Clinical Nurse Specialist	
Secretary	
Clinic	
GP	
Chemist	

Appendix I Publications arising from this thesis

Journal articles/peer reviewed publications

1. Griffin OM, Duggan SN, Ryan R, McDermott R, Geoghegan J, Conlon KC. Characterising the impact of body composition change during neoadjuvant chemotherapy for pancreatic cancer. Pancreatology. 2019 Sep;19(6):850-857. doi:10.1016/j.pan.2019.07.039. Epub 2019 Jul 24. PubMed PMID: 31362865.

2. Gianotti L, Besselink MG, Sandini M, Hackert T, Conlon K, Gerritsen A, Griffin O, Fingerhut A, Probst P, Abu Hilal M, Marchegiani G, Nappo G, Zerbi A, Amodio A, Perinel J, Adham M, Raimondo M, Asbun HJ, Sato A, Takaori K, Shrikhande SV, Del Chiaro M, Bockhorn M, Izbicki JR, Dervenis C, Charnley RM, Martignoni ME, Friess H, de Pretis N, Radenkovic D, Montorsi M, Sarr MG, Vollmer CM, Frulloni L, Büchler MW, Bassi C. Nutritional support and therapy in pancreatic surgery: A position paper of the International Study Group on Pancreatic Surgery (ISGPS). Surgery. 2018 Nov;164(5):1035-1048. doi: 10.1016/j.surg.2018.05.040. Epub 2018 Jul 17. PubMed PMID: 30029989.

3. Griffin O, Conlon KC. Sarcopenia-A New Frontier in the Management Care of Patients With Borderline Resectable Pancreatic Cancer. JAMA Surg. 2018 Sep 1;153(9):816. doi: 10.1001/jamasurg.2018.1006. PubMed PMID: 29801035.

4. Lorton CM, Griffin O, Higgins K, Roulston F, Stewart G, Gough N, Barnes E, Aktas A, Walsh TD. Late referral of cancer patients with malnutrition to dietitians: a prospective study of clinical practice. Support Care Cancer. 2019 Sep 4. doi: 10.1007/s00520-019-05042-2. [Epub ahead of print] PubMed PMID:31485981

5. Memba R, Duggan SN, Ni Chonchubhair HM, Griffin OM, Bashir Y, O'Connor DB,Murphy A, McMahon J, Volcov Y, Ryan BM, Conlon KC. The potential role of gut microbiota in pancreatic disease: A systematic review. Pancreatology. 2017 Nov - Dec;17(6):867-874. doi: 10.1016/j.pan.2017.09.002. Epub 2017 Sep 6. Review.PubMed PMID: 28935288.

6. Duggan SN, Ewald N, Kelleher L, Griffin O, Gibney J, Conlon KC. The nutritional management of type 3c (pancreatogenic) diabetes in chronic pancreatitis. Eur J Clin Nutr. 2017 Jan;71(1):3-8. doi: 10.1038/ejcn.2016.127. Epub 2016 Jul 13. Review. PubMed PMID: 27406162.

Appendix J Presentations arising from this thesis

Work arising from this thesis has been presented at national and international conferences

(*invited presentations)

Oral Presentation

International

1. **Griffin OM,** Duggan SN, Fennelly D, McDermott R, Geoghegan J, Conlon KC. Exploring the feasibility of a supportive care intervention for patients undergoing neo-adjuvant chemotherapy for pancreatic cancer: The FEED Study. *European-African Hepato-Pancreatico-Biliary Association Conference, Amsterdam 2019*
2. *__Griffin OM.__ Nutritional assessment in oncology – What should we be measuring? *British Dietetic Association Oncology Group study day, Birmingham 2018*
3. **Griffin OM**, Duggan SN, Fennelly D, McDermott R, Geoghegan J, Conlon KC. Exploring the feasibility of a supportive care intervention for patients undergoing neo-adjuvant chemotherapy for pancreatic cancer: The FEED Study. *International Hepato-Pancreatico-Biliary Association Conference, Geneva 2018*
4. ***Griffin OM.** Malnutrition in Hepatobiliary Surgery: Assessment of Nutritional Risk in the Era of Obesity, Compagnons Hépato-Biliaires 2017
5. **Griffin OM**, Duggan SN, Ryan R, McDermott T, Geoghegan J, Conlon KC. Body composition change during neoadjuvant therapy for pancreatic cancer *European-African Hepato-Pancreatico-Biliary Association Conference, Mainz 2017*
6. * **Griffin OM.** Sarcopenia and pancreatic cancer. *Pancreatic Society of Great Britain and Ireland, Newcastle 2017*
7. ***Griffin OM**. Treatment strategies for cancer cachexia. *Nutrition Interest Group Symposium at PSGBI 2017*

8. **Griffin OM**, Duggan SN, Ryan R, McDermott T, Geoghegan J, Conlon KC. Skeletal muscle depletion is associated with disease progression during neo-adjuvant therapy for Borderline Resectable Pancreatic Adenocarcinoma *Pancreatic Society of Great Britain and Ireland, Manchester 2016 (plenary session)*

National

1. *__Griffin O__M Nutrition in cancer: can it make a difference? Irish Society of Clinical Nutrition and Metabolism, March 2019
2. **Griffin OM**, Duggan SN, Ryan R, McDermott T, Geoghegan J, Conlon KC. Characterising the impact of body composition change during neoadjuvant therapy for pancreatic cancer Joint *UCD SVHG Translational Research Seminar 2018* (Best oral presentation prize winner)
3. **Griffin OM**, Duggan SN, Ryan R, McDermott T, Geoghegan J, Conlon KC. Skeletal muscle depletion is associated with disease progression during neo-adjuvant therapy for Borderline Resectable Pancreatic Adenocarcinoma *Sylvester O' Halloran conference 2017*
4. **Griffin OM**, Duggan SN, Ryan R, McDermott T, Geoghegan J, Conlon KC. Body composition change during neoadjuvant therapy for pancreatic cancer *Irish Society of Clinical Nutrition and Metabolism 2017* (Oral presentation prize winner)
5. **Griffin OM**, Duggan SN, Ryan R, McDermott T, Geoghegan J, Conlon KC. Body Composition Analysis of Pancreatic Cancer Patients; A Feasibility Study. *Sir Peter Freyer Meeting 2016*
6. *__Griffin OM__ Nutritional management of pancreatic cancer. *Gastroenterology specialist interest group of the Irish Nutrition and Dietetic Institute 2015*

Poster presentations

1. **Griffin OM**, Duggan SN, Fennelly D, McDermott R, Geoghegan J, Conlon KC. Exploring the feasibility of a supportive care intervention for patients undergoing neo-adjuvant chemotherapy for pancreatic cancer: The FEED Study *Society of Cachexia, Sarcopenia and Muscle Wasting, Maastricht 2018*
2. **Griffin OM**, O'Donohoe R, Ryan R, McDermott T, Geoghegan J, Conlon KC. CT-based Body Composition Analysis in Pancreatic Cancer; a Feasibility Study. Irish Nutrition and Dietetic Institute Research Seminar 2016 (Third prize winner)

CT-based Body Composition Analysis in Pancreatic Cancer; a Feasibility Study

Oonagh Griffin[1 3], Rory O' Donohue[2], Ronan Ryan[2], Justin Geoghegan[1], Kevin C.Conlon[1 3]

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St Vincent's University Hospital is JCI Accredited 2013 - 2016

Introduction

Malnutrition affects up to 80% of patients with pancreatic cancer, and has been shown to reduce survival, increase chemotherapy toxicity and prolong post-operative length of stay.[1]
Increased level of pre-diagnosis obesity among Irish patients in recent years has led to difficulties in accurate nutritional assessment, increasing the extent of pre-operative weight loss.
Recent international consensus advocates the inclusion of sarcopenia in assessment of cancer cachexia, particularly in overweight/obese patients, and studies have validated CT based muscle measurement at the 3rd lumbar vertebrae as the gold standard technique.[3]

We sought to assess the feasibility of applying Tomovision Slice-O-Matic™ to diagnostic CT scans to measure and compare body composition in patients with short (<14 days) and prolonged (>28 days) post-operative stay.

Methods

1. Using Tomovision Slice-O-Matic™ and diagnostic abdominal CT scans, measure body composition at level of L3
2. Retrospective chart review, recording baseline nutritional info, age, gender and length of stay
3. Calculate Lumbar Skeletal Muscle Index(SMI), quantify total muscle and fat using validated regression equations[2]
4. Collate and record data using Microsoft Excel, Statistical Analysis using SPSS

Results

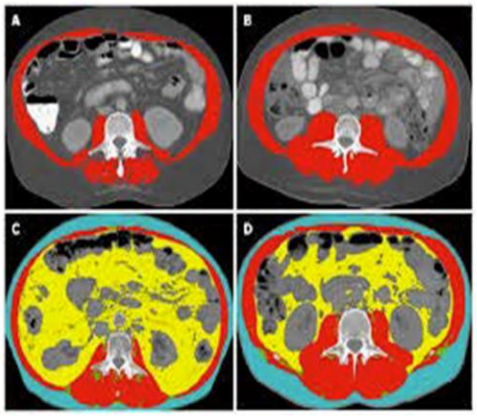
80 patients were identified for inclusion, 41 had suitable CT scans and complete data for analysis

Body Composition Analysis took an average of 45 mins per patient, inclusive of landmarking, measurement and data analysis

64% patients were male, average BMI 25.6kg/m²

66% of patients were sarcopenic, while 41% of patients were overweight/obese and sarcopenic

Patients with longer LOS had significantly higher levels of adiposity (27.2 vs 24kg, p=0.036), but no statistical difference in skeletal muscle index



Conclusion

CT based body composition analysis using Slice-O-Matic™ is feasible, but requires significant time input by clinician

High prevalence of sarcopenia exists among Irish patients with resectable pancreatic cancer, despite increased BMI, warranting further study and evaluation.

[1] Martin L et al , J Clin Onc 2013 April; 31(12)
[2] Mourtzakis et al App J Physiol Metab 2008 Oct; 33(5):997-1006
[3] Fearon KCH et al,Lancet Oncol 2011 May; Vol 12

Exploring the feasibility of a combined package of care for patients undergoing neo-adjuvant chemotherapy for pancreatic cancer: The FEED Study (Fish oil and Pancreatic Enzyme Supplementation, Exercise advice and Individualised Dietary counseling)

Oonagh Griffin[1,2], Sinead Duggan[1], David Fennelly[3], Ray Mc Dermott[3], Justin Geoghegan[2] & Kevin Conlon[1,2].
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[3] Department of Medical Oncology, St Vincent's University Hospital, Elm Park, Dublin 4, Ireland

Introduction

- Cancer cachexia and sarcopenia/ sarcopenic obesity are prevalent in pancreatic cancer, and are established adverse prognostic factors in advanced pancreatic cancer
- Multifactorial aetiology for weight and muscle loss in pancreatic disease
- Emerging evidence suggests neoadjuvant chemotherapy may allow patients with locally advanced and/ or borderline resectable pancreatic cancer undergo curative resection
- Accelerated muscle loss occurs during neoadjuvant therapy, significantly increasing mortality
- Preservation of lean tissue indices during neoadjuvant treatment is associated with conversion to resectable disease

Objective and Methods

- Primary Objective: To assess the feasibility of a 12 week, multi-modal supportive care intervention for patients with pancreatic cancer undergoing neoadjuvant chemotherapy (Folfirinox or Gemcitabine with Nab-Paclitaxel,) specifically:

1. *Individualised dietary counselling and review fortnightly throughout chemotherapy, feeding to ESPEN guidelines for energy and protein (25-30kcal/kg ; 1-1.5g protein/ kg per day), even protein distribution (minimum 20g per meal).*
2. *Pancreatic Enzyme Replacement Therapy (PERT)(50,000 IU with meals, 25,000 IU with snacks)*
3. *Eicosapentaenoic Acid (EPA)–enriched nutritional supplement (ProSure™) – target 2g EPA/ day*
4. *Individualised daily step target (10% above own baseline, quantified by 7-day accelerometry)*

- Secondary Objectives: To investigate changes in body composition measurements (CT-based), functional capacity (grip-strength, Timed-Up and Go), inflammatory cytokines (Il-6, IGF-1, TNF-α) and quality of life (EORTC) (upon study completion)
- Comprehensive nutritional assessment at enrolment, including evaluation of exocrine and endocrine function.




Results

- N=20 (100% accrual, 71% opt in) enrolled Sept '17 – Nov '18.
- 60% male, median age 68 years (41-80)
- At presentation: median BMI 24.9 kg/m² (20.4-35.5), median weight loss 6% (0-30%)
- Diabetes prior to diagnosis in 20% of patients, while 30% newly diagnosed on study enrolment, all requiring insulin therapy
- 95% moderately or severely exocrine insufficient
- Median daily step count 3,100 (995-12,105)

N=12 completed intervention to date, 6 are ongoing.
1 patient excluded (Parenteral Nutrition-dependent), 1 patient withdrew consent after 1st treatment

- 12/12 attended fortnightly assessment
- 10/12 achieving both protein and energy targets
- 11/12 PERT-adherent
- 9/12 tolerating ProSure™ (2x 220 ml/d), 10/12 (1 x 220ml/d)
- 8/12 achieving daily step target
- 9/12 maintained or improved weight and grip strength

Conclusions

- Exocrine and endocrine insufficiency are prevalent in this patient cohort, highlighting the need for routine assessment and monitoring to address preventable deterioration in nutritional status.
- Preliminary data highlight high patient opt-in and acceptance of this intensive multi-modal intervention
- Majority of patients maintained weight and grip strength, in a group known to be cachectic and nutritionally-at-risk

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