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Characterising the impact of body composition change during neoadjuvant chemotherapy for pancreatic cancer

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ABSTRACT

Background: Pancreatic Cancer remains a lethal disease for the majority of patients. New chemotherapy agents such as Folfirinox offer therapeutic potential for patients who present with Borderline Resectable disease (BRPC). However, results to date are inconsistent, with factors such as malnutrition limiting successful drug delivery. We sought to determine the prevalence of sarcopenia in BRPC patients at diagnosis, and to quantify body composition change during chemotherapy.
Methods: The diagnostic/restaging CT scans of BRPC patients were analysed. Body composition was measured at L3 using Tomovision Slice-O-Matic™. Total muscle and adipose tissue mass were estimated using validated regression equations. Sarcopenia was defined as per gender- and body mass index (BMI)-specific lumbar skeletal muscle index (LSMI) and muscle attenuation reference values.
Results: Seventy-eight patients received neo-adjuvant chemotherapy, and 67 patients underwent restaging CT, at which point a third were deemed resectable. Half were sarcopenic at diagnosis, and sarcopenia was equally prevalent across all BMI categories.. Skeletal muscle and adipose tissue (intramuscular, visceral and sub-cutaneous) area decreased during chemotherapy ($p < 0.0001$). Low muscle attenuation was observed in half of patients at diagnosis, and was associated with increased mortality risk. Loss of lean tissue parameters during chemotherapy was associated with an increased mortality risk; specifically fat-free mass, HR 1.1 (95% CI 1.03–1.17, $p = 0.003$) and skeletal muscle mass, HR 1.21 (95%CI 1.08–1.35, $p = 0.001$).
Conclusions: Sarcopenia was prevalent in half of patients at the time of diagnosis with BRPC. Low muscle attenuation at diagnosis, coupled with lean tissue loss during chemotherapy, independently increased mortality risk.

Introduction

Pancreatic cancer is currently the fourth leading cause of cancer related mortality in Europe [1], with median 5-year survival rates largely remaining static over the last 40 years [2]. Patients frequently present with advanced disease at the time of diagnosis, limiting their potential for curative resection. Recent developments include international consensus regarding disease staging and classification, and the advent of neo-adjuvant therapy for patients with borderline resectable disease [3].

Malnutrition and cachexia affect up to 80% of patients at diagnosis [4], and remain limiting factors to successful treatment delivery and tolerance [5,6]. Increasing pre-morbid obesity levels increase the risk of developing pancreatic cancer, as well as delaying diagnosis. Initial unintentional weight loss experienced by overweight and obese patients 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 [6].

The prevalence and prognostic significance of cachexia,

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sarcopenia and sarcopenic obesity in cancer have gained recognition in recent years [7,8]. 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 [9]. This precludes adequate comparison of studies and presents a degree of uncertainty around the true prevalence of sarcopenia and its impact on clinical outcomes in pancreatic cancer [10]. Recent attempts to evaluate the impact of sarcopenia on survival in pancreatic cancer concluded that future studies evaluating body composition in pancreatic cancer utilise the international consensus definition for cachexia [9,11] and include a direct measurement of muscle mass (dual-energy X-ray absorptiometry, Computed Tomography (CT) or Magnetic Resonance Imaging (MRI)).

Given the uncertainty to date, we designed a study to evaluate the impact of body composition in pancreatic cancer patients undergoing neoadjuvant chemotherapy. Specifically, we had three aims. Firstly, we sought to determine the prevalence and degree of cachexia, sarcopenia and low muscle attenuation at baseline for patients with BRPC. Secondly, we sought to investigate changes in body composition between baseline (diagnosis) and post-chemotherapy. Finally, we evaluated the impact of both baseline body composition characteristics, and changes endured during treatment, on survival.

Methods

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 National Surgical Centre for Pancreatic Cancer (NSCPC), at diagnosis for specialist multidisciplinary discussion. The NSCPC was established at St Vincent's University Hospital (SVUH) in Dublin, following the centralisation of pancreatic cancer surgery in Ireland. Following discussion and team consensus 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 [3]. Chemotherapy agent selection was decided by the local treating oncologist, and individual patient private health insurance policy cover. 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 potentially proceeding to radiotherapy.

Body composition assessment

Existing CT scans, acquired for cancer diagnosis and restaging, were analysed for body composition by a single, trained investigator (OMG) 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. 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 [7]. Lumbar Skeletal Muscle Index (LSMI) was calculated by normalising skeletal muscle area for height, and subsequently compared values to gender- and body mass index (BMI)-specific references [8]. Muscle attenuation (MA) was quantified by measuring average skeletal muscle radio-density, and defined as per BMI−specific values (<33 Hounsfield Units in patients with BMI≥25 Kg/M^2, and <41 Hounsfield Units in patients whose BMI < 25 Kg/M^2) [8]. Validated regression equations [12] 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 fat-free mass(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 [13]. A density of 1.04 g/ml was subsequently applied to estimate skeletal muscle mass from volume [14]. 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 [11]:

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/m^{2}or sarcopenia was present.

BMI was categorised as per World Health Organisation (WHO) classification (REF).

Statistical analysis

Statistical analysis was conducted using SPSS (IBM SPSS Statistics version 24, Chicago, Illinois, USA). Data were expressed using mean ± standard deviation (SD) or median ± interquartile range (IQR) as appropriate following assessment of distribution. Differences between groups were assessed using Mann-Whitney or independent t tests for continuous variables, while chi-square tests were used to compare categorical variables. 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 hazard ratios (HR) with 95% Confidence Intervals.

Ethical approval was obtained from St Vincent's Healthcare Group Ethics and Medical Research Committee prior to undertaking this study.

Results

Of 100 patients diagnosed with BRPC between 2012 and 2015, 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 1. Following neo-adjuvant therapy 67patients were re-staged. 50 (64%) went on to receive radiotherapy, after which 25 (32%) were considered to have a either a clinical response or stable disease and underwent resection.

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

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

[a] Mean (SD).
[b] Median (IQR).

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 (Fig. 1). Over half (55%) 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/m^2 vs 27.8 kg/m^2, p = 0.015) and lower total mean fat mass (23.8 kg vs 27.3 kg, 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 43.7 kg p = 0.862, skeletal muscle 24.1 kg vs 24.2 kg p = 0.93, muscle attenuation 35.8HU vs 33.6HU P = 0.234). Fewer than half (43%) of the study group had been prescribed pancreatic enzyme replacement therapy (PERT) to treat pancreatic exocrine insufficiency (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.

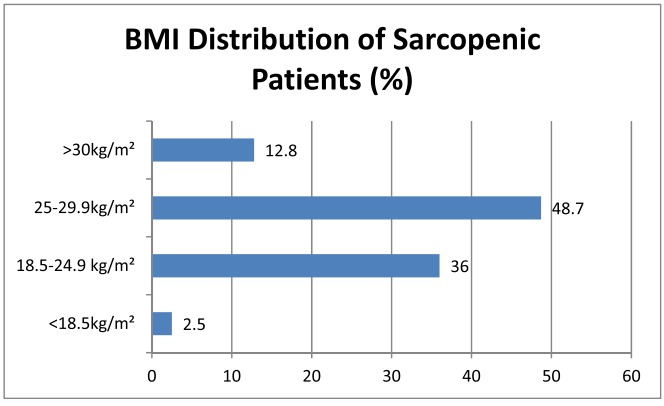

Fig. 1. BMI distribution of Sarcopenic Patients.

The change in body composition from baseline to post-chemotherapy treatment in the 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 1.3 kg (−8.3 − +4.0). All body composition parameters, except muscle attenuation, deteriorated during treatment (Table 2). The majority of patients (73%) experienced loss of lean tissue (SMI, fat-free mass, skeletal muscle mass) during treatment.

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, 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) (Fig. 2). Loss of lean tissue during neoadjuvant chemotherapy was also associated with an higher mortality risk (mean fat-free mass loss 2.6 kg, HR 1.1, 95% CI 1.03–1.17, p = 0.003, mean skeletal muscle mass loss 1.5 kg, HR 1.21, 95% CI 1.08–1.35, p = 0.001) (Fig. 3a and b). Loss of fat mass during neoadjuvant chemotherapy was also associated with a higher mortality risk (mean loss 2.8 kg HR 1.09, 95% CI 1.03–1.16,

Table 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

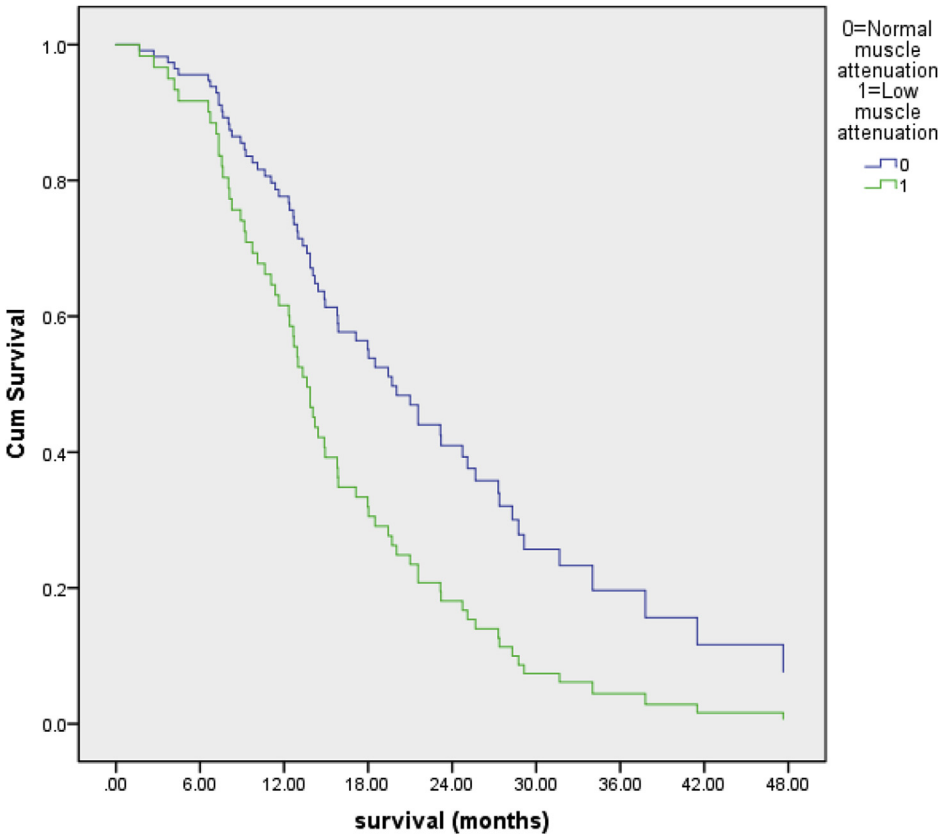

Fig. 2. Impact of low muscle attenuation at diagnosis on mortality risk (cox regression).

p = 0.004) (Fig. 4). In a multivariable model, the following indices remained predictive of better survival; administration of radiotherapy as part of neoadjuvant therapy, normal muscle attenuation at baseline, amd preservation of muscle during therapy. No other factors remained significant (Table 3).

Discussion

We 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, we highlighted the extent of cancer cachexia and sarcopenia at diagnosis for patients with BRPC.

While previous studies showed that cancer cachexia affects between 40 and 80% of patients with pancreatic cancer, we believe that this is the first study to evaluate the incidence using the Fearon classification [11] in a BRPC cohort.. We have shown that cancer cachexia is an early feature of the disease. Despite this, we did not find an association between cachexia at diagnosis and resectability, treatment tolerance, treatment delivery or overall survival. This is consistent with the findings of a recent study which evaluated the impact of baseline body composition on survival in nearly 800 patients with untreated pancreatic cancer [15]. They also reported that sarcopenia and depletion of 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, low muscle attenuation at the time of diagnosis was found to double mortality risk. 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 [16]. In fact, muscle attenuation may be superior to mass measure in predicting functional and strength assessment [17]. 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

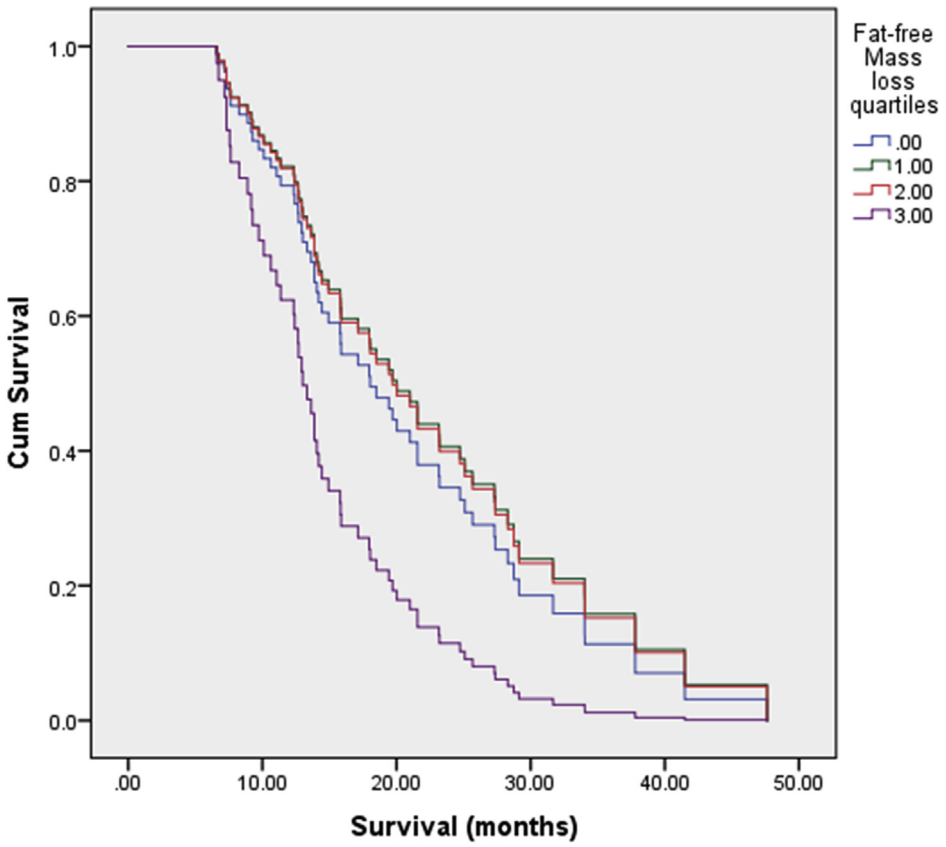

Fig. 3a. Impact of Fat-free Mass Loss (kg) during chemotherapy (Cox regression analysis).

demonstrated in patients with increased inflammation associated with cachexia [18]. 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 sarcopenia while disruption of oxidative phosphorylation and lipid accumulation were seen in patients with low muscle radiodensity [19]. Unlike most studies evaluating muscle radiodensity in pancreatic cancer patients to date, we measured muscle attenuation in muscle only 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 [20].

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 [21]. The majority (64%) achieved resectability following treatment. A significant loss of skeletal muscle, visceral and subcutaneous adipose tissue were observed, and degree of muscle loss correlated with disease-free survival, while visceral adipose loss was associated with overall and progression-free survival. Another study from that institution longitudinally evaluated 127 patients who achieved resectability following neoadjuvant therapy [22]. Similar to our work, a combination 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 4 institutions over 3 year period were evaluated [23]. 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 [24]. A common finding among all four studies is that sarcopenia is 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 previous advanced disease cohort [14], 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 [25].

Despite malnutrition being an established feature of pancreatic cancer, fewer than half of patients in our study were referred for specialist nutritional assessment/intervention at any point during their treatment. Timing of referral varied across centres due to

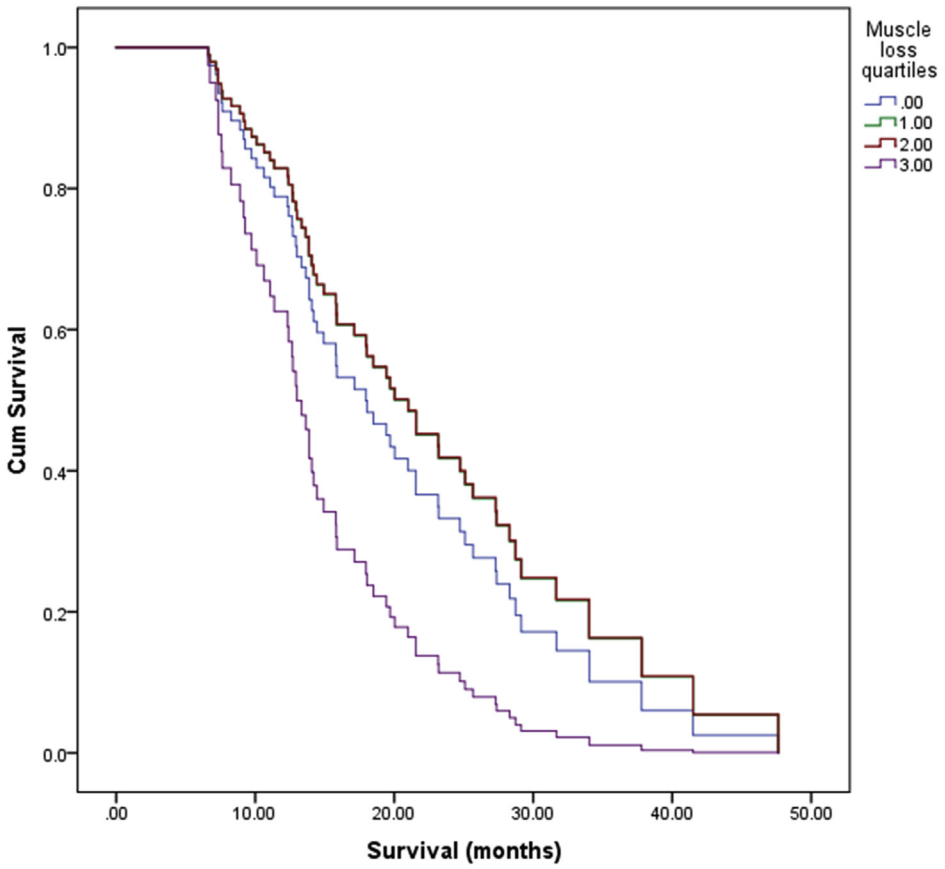

Fig. 3b. Impact of Skeletal Muscle Mass Loss during chemotherapy (Cox regression analysis).

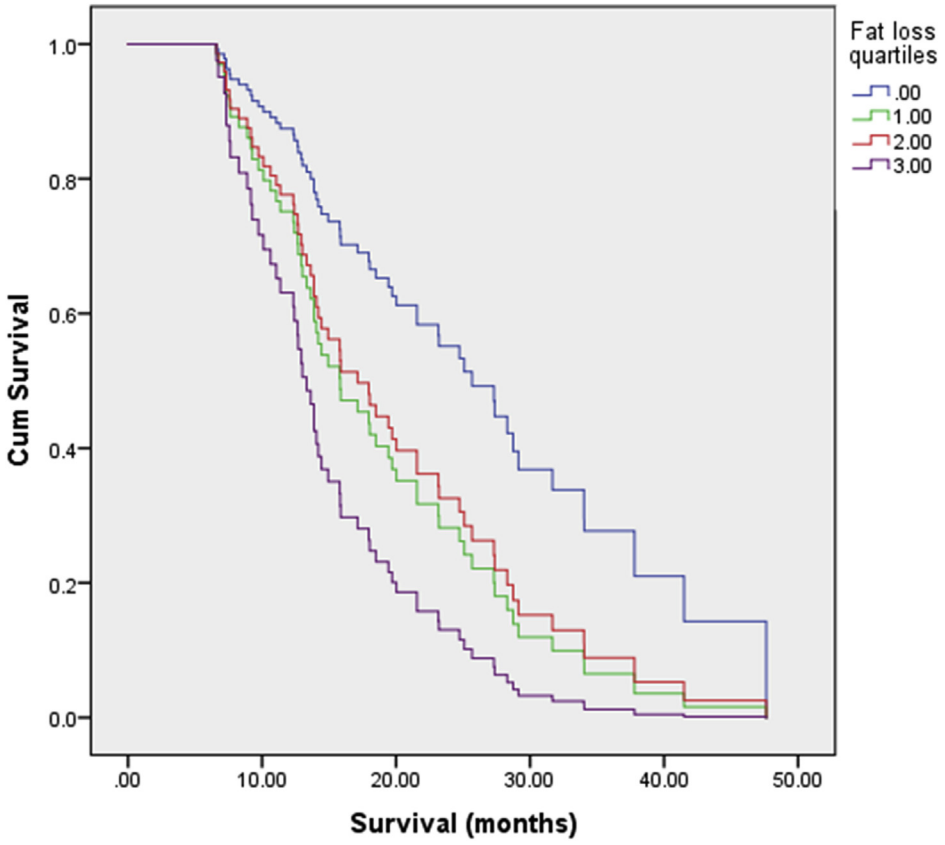

Fig. 4. Impact of fat loss during chemotherapy (Cox Regression Analysis).

Table 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	3.49 (1.82-6.71)	<0.0001
Full chemotherapy dose delivered.	0.5 (0.28-0.88)	0.016		
Radiotherapy delivery	2.82 (1.57-5.1)	0.001		
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	0.36 (0.19-0.69)	0.002
Sarcopenia	0.84 (0.51-1.39)	0.47		
Muscle attenuation	0.53 (0.31-0.88)	0.011		
Loss of fat-free mass during chemotherapy	1.1 (1.03-1.17)	0.003	1.21 (1.02-1.42)	0.025
Loss of muscle during chemotherapy	1.19 (1.07-1.33)	0.002		
Loss of fat mass during chemotherapy	1.09 (1.03 -1.16)	0.004		

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.

Most patients with sarcopenia were overweight or obese, potentiating the risk of excess adiposity masking underlying muscle depletion [8]. Sarcopenic obesity has previously been shown to significantly increase the mortality risk and dose-limiting toxicity in patients receiving palliative chemotherapy [6].

This study has several limitations. 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.

Nevertheless, these findings highlight the need for routine body composition in line with cancer staging to accurately identify patients with muscle depletion and monitor body composition change throughout treatment. Where agent choice is still largely determined by patient fitness and perceived ability to tolerate, muscle mass or attenuation measure may offer an objective parameter to aid clinician decision-making. They add strength to the argument for multimodal interventions to address malnutrition and cachexia during treatment [27,28]. The recent progress with characterising pancreatic cancer [29], and developments with chemotherapeutics for patients with BRPC provide hope for future treatment of the disease [24]. 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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2019.07.039.

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