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Authors	Daly, Louise E.;Ní Bhuachalla, Éadaoin B.;Power, Derek G.;Cushen, Samantha J.;James, Karl;Ryan, Aoife M.
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Loss of skeletal muscle during systemic chemotherapy is prognostic of poor survival in patients with foregut cancer

Louise E. Daly[1,2], Éadaoin B. Ní Bhuachalla[1,3], Derek G. Power[4], Samantha J. Cushen[1], Karl James[5] & Aoife M. Ryan[1,3*]

[1]*School of Food and Nutritional Sciences, College of Science, Engineering and Food Science, University College Cork, Cork, Ireland;* [2]*APC Microbiome Institute, University College Cork, Cork, Ireland;* [3]*Cork Cancer Research Centre, University College Cork, Cork, Ireland;* [4]*Department of Medical Oncology, Mercy and Cork University Hospitals, Cork, Ireland;* [5]*Department of Radiology, Cork University Hospital, Cork, Ireland*

Abstract

Background Malnutrition, weight loss, and muscle wasting are common in patients with foregut cancers (oesophagus, stomach, pancreas, liver, and bile ducts) and are associated with adverse clinical outcomes. However, little is known about the changes in body composition that occur in these patients during chemotherapy and its impacts clinical outcomes.

Patients and methods A prospective study of adult foregut cancer patients undergoing chemotherapy between 2012 and 2016 was conducted. Computed tomography images were evaluated for cross-sectional skeletal muscle area (SMA) and adipose tissue area (ATA) at two time points [interval 118 days (IQR 92–58 days)]. Longitudinal changes in SMA and ATA were examined using paired *t*-tests. Sarcopenia and low muscle attenuation (MA) were defined using published cut-points. Cox proportional hazards models were used to estimate mortality hazard ratios for key predictors.

Results A total of 225 foregut cancer patients were included (67% male, median age 66 years). At baseline, 40% were sarcopenic, 49% had low MA, and 62% had cancer cachexia. Longitudinal analysis (n = 163) revealed significant reductions in SMA [-6.1 cm^2 (3.9%)/100 days, $P < 0.001$]. Patients treated with neoadjuvant chemotherapy experienced greater losses in SMA and skeletal muscle mass compared with patients receiving palliative chemotherapy [-6.6 cm^2 (95%, confidence interval, CI: -10.2 to -3.1), $P < 0.001$ and -1.2 kg (95% CI: -1.8 to -0.5), $P < 0.001$, respectively]. Neither sarcopenia nor low MA at baseline was associated with reduced survival. A loss of SMA >6.0%/100 days (highest fourth) independently predicted overall survival in patients receiving palliative chemotherapy [hazard ratio: 2.66, (95% CI: 1.42 to 4.97), P = 0.002].

Conclusions Patients with foregut cancers, particularly those treated with neoadjuvant chemotherapy, experience significant losses of muscle during chemotherapy. A high level of SMA loss is prognostic of reduced survival in patients treated with palliative chemotherapy. Multimodal interventions to stabilize or increase muscle mass and influence outcome warrant further investigation.

Keywords Body composition; Sarcopenia; Cachexia; Muscle attenuation; Cancer; Foregut

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**Correspondence to: Dr Aoife Ryan, School of Food and Nutritional Sciences, College of Science, Engineering and Food Science, University College Cork, Cork, Ireland. Email: A.ryan@ucc.ie*

Introduction

Cancers of the foregut (oesophagus, stomach, pancreas, liver, and bile ducts), collectively account for over 350 000 cancer diagnoses in Europe annually. The 5 year survival remains low; 11% in oesophageal, 25% in stomach, and 6% in pancreatic cancer,[1] and they are historically associated with high rates of malnutrition that adversely effects clinical outcome.[2–4]

Cancer cachexia (CC) is a multifactorial syndrome that is characterized by the loss of muscle with or without the loss of fat mass leading to progressive functional impairment.[5] The syndrome encompasses involuntary weight loss,

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anorexia, a low body mass index (BMI), systemic inflammation, metabolic changes, and/or low skeletal muscle mass (sarcopenia).[5] Recent studies have shown that sarcopenia [assessed using computed tomography (CT) images] is common in foregut cancers with rates reported to be >40% in the setting of local[6,7] and advanced disease.[8,9] Sarcopenia is associated with physical disability,[10] increased length of hospital stay,[11–13] post-operative infections,[12] poorer tolerance to chemotherapy,[7,14] and reduced survival.[15] However, no consistent association between sarcopenia and reduced survival has been demonstrated in foregut cancers.[7,8,16] CT images provide not only a quantitative measure but also a qualitative measure of skeletal muscle. Muscle radiation attenuation is a radiological characteristic, and skeletal muscle with a low radiation attenuation is reflective of intramuscular adipose tissue infiltration and poor 'quality' skeletal muscle.[17] Importantly, low muscle attenuation (MA) is emerging as an important predictor of clinical outcome in patients with cancer and, in some instances, a stronger predictor of survival compared with muscle mass alone.[15,18–20]

The precision associated with CT analysis of body composition has allowed recent investigations to focus on the nature and magnitude of changes in body composition during the disease trajectory in patients with cancer. However, these studies are typically retrospective with small sample sizes ranging from 35 to 65 patients[6,9,16,21–25] and very few larger studies exist ($n > 100$).[26–28]

Loss of muscle during anticancer treatment has been shown to be prognostic of reduced survival in ovarian,[28] colorectal,[21,26] and pancreatic cancer patients;[22] however, this has not been consistently demonstrated, and no effect was observed in gastro-oesophageal and pancreatic cancer patients.[6,25] To our knowledge, larger studies evaluating the prevalence and significance of altered body composition that may occur in patients with foregut cancers undergoing standard chemotherapy are lacking.

The primary aim of this prospective study was to examine the longitudinal changes in body composition parameters using single slice CT images in foregut cancer patients undergoing chemotherapy and to determine if these changes had a prognostic impact on overall survival.

Methods

Study population

Adult patients (>18 years of age), with a solid malignancy of the foregut presenting for chemotherapy, were eligible to partake in this prospective observational study. All eligible patients were approached by a member of the research team (L. D., E. N. B., and S. C.), and data were collected from patients who provided informed written consent between June 2012 and September 2016. Subjects were admitted for chemotherapy to one of two university teaching hospitals in Cork City serving a catchment population of 870 000. Cork University Hospital is the regional cancer centre, and Mercy University Hospital is a satellite cancer centre as per the National Cancer Control Program. Both hospitals provide inpatient, day patient, and outpatient services along with a 24/7 emergency department. Mercy University Hospital is the specialist hospital for the surgical management of hepatopancreaticobiliary (HPB) and upper gastrointestinal cancers. Both hospitals have dedicated medical oncology wards, and Cork University Hospital is the regional centre for radiation oncology and is a level 1 trauma centre. The local ethics committee granted ethical approval for this study, and the study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Patient information recorded

On assessment, patient's weight, height, and BMI were recorded [weight (kg)/height (m^2)]. BMI was classified according to WHO classifications of BMI. CC was defined based on the international consensus definition.[5] Clinical and pathological data were collected during medical chart review and included information on patient demographics (age and gender), performance status (the Eastern Oncology Cooperative Group performance status), primary tumour site, stage and extent of metastatic disease (if present), oncological treatment, and type of chemotherapy. Cancer diagnoses were grouped and included gastro-oesophageal and HPB cancers (pancreatic, gallbladder, liver, and bile ducts). Response to chemotherapy was evaluated according to the response evaluation criteria in solid tumours criteria and obtained from patient's radiology reports. Patient's date of death from any cause (if present) or date of study completion (26/01/2017; censored date) was recorded.

Body composition assessment

Computed tomography images, taken as part of routine patient care, were used to assess body composition as previously described.[29] The third lumbar vertebrae were chosen as the standard landmark, and two consecutive transverse CT images where both transverse processes were clearly visible were analysed using OsiriX software version 4.1.1 (Pixmeo, Geneva, Switzerland), and the average result was reported. Different tissue compartments were manually outlined, and segmentation of the skeletal muscle and adipose tissue was based on Hounsfield unit (HU) thresholds (−29 to +150 HU and −30 to −190, respectively).[30] Skeletal muscle area (SMA) (cm^2) and adipose tissue area (ATA)

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(cm^2) were automatically calculated by summing tissue pixels and multiplying by pixel surface area after applying HU thresholds. SMA and ATA were normalized for stature to compute the skeletal muscle index (SMI) and adipose tissue index (ATI) in cm^2/m^2, respectively. Mean MA in HU was reported for the entire skeletal muscle area at the third lumbar vertebrae. Anonymized CT images were analysed by one trained study assessor who was blinded to the order of images. Pre-treatment images were taken prior to treatment administration (median 40 days; IQR 61 to 24 days). The median duration between scans was 118 days (IQR 92 to 158 days). To account for variation in the exact duration of scan intervals, changes in tissue are expressed as change/100 days.

Estimates of whole body fat mass (FM) and fat free mass (FFM) were calculated using published regression equations.[31] To estimate total body skeletal muscle mass, the regression equation of Shen *et al*. was used.[32] Changes are expressed as losses or gains of >1 kg of skeletal muscle mass (SMM) or FM on a whole body basis. It has previously been shown that 1 kg of skeletal muscle is associated with physical function (i.e. muscle strength)[33] and this cut point has been used to investigate significant changes in muscle mass throughout cancer disease trajectory previously.[23,27,34] Sarcopenia and low MA were defined according to pre-published cut points; sarcopenia was defined as a SMI <43 cm^2/m^2 in men with a BMI <25 kg/m^2, <53 cm^2/m^2 in men with a BMI ≥25 kg/m^2, and <41 cm^2/m^2 in women. Low MA was defined as a mean attenuation <41 HU in patients with a BMI <25 kg/m^2 and <33 HU in those with a BMI ≥25 kg/m^2.[15]

Statistical analysis

Statistical analysis was completed using SPSS (version 21.0, SPSS Inc., Chicago, IL, USA). Data are expressed as mean ± SD or median [IQR] where appropriate. Comparisons between groups of patients were assessed using chi-squared test for categorical variables and unpaired *t*-tests and Mann–Whitney U-tests to test for differences continuous variables. Paired *t*-tests were used to assess changes in body composition. The McNemar's test was to test for significances in paired categorical data. Variables that had significance of $P \leq 0.25$ on univariate analysis or had clinical relevance were eligible for inclusion in multivariable analysis. Survival curves were constructed using the Kaplan–Meier technique, and log-rank test was used to compare survival between groups of patients. Survival was measured from the date of the baseline (pre-treatment) CT image until the date of death or censored date (study completion). At the time of censoring, 88 of the 225 patients (39.1%) were still alive. Median follow-up time for these patients was 18.06 months [IQR 11.0 to 34.8 months]. Cox proportional hazard analyses were used to estimate adjusted hazard ratios (HR) with 95% confidence intervals (CI) calculated. All *P* values were two-sided, and the level of significance was $P < 0.05$.

Results

Participants

A total of 243 patients with a foregut tumour were enrolled in the study. Patients were excluded if they lacked an evaluable baseline CT image (*n* = 18). Therefore, 225 patients were included. MA analysis was carried out on all patients with a contrast enhanced CT image (*n* = 202).

Patient characteristics

Baseline characteristics are presented in *Table* 1. The majority of patients were male (67%), with a median age of 66 years (IQR 36 to 82 years). Oesophageal cancer was most prevalent (44%), and 51% of patients had stage IV disease. All patients were receiving standard systemic chemotherapy (*Table* S1).

Anthropometry and body composition

Baseline anthropometric and nutritional characteristics are presented in *Table* 2. In brief, the majority of the cohort was overweight/obese (52.4%); however, 62% met the criteria for CC, 40% were sarcopenic, and 49% had low MA. Cachexia and sarcopenia were most prevalent in patients with pancreatic cancer (71% and 47%, respectively) (*Figure* S1).

Table 1 Demographic and clinical characteristics of patients included in this study

	Total *n* = 225
Age and median (range)	65.6 (35.8–83.4)
Male	150 (66.7)
Current smoker, *n* (%)	38 (16.9)
Current drinker, *n* (%)	94 (41.8)
Tumour location, *n* (%)	
Gastro-oesophageal	138 (61.3)
Oesophaeal and GO junction	99 (44.0)
Gastric	39 (17.3)
Hepato pancreato-biliary	87 (38.7)
Pancreatic	55 (24.4)
Cholangiocarcinoma	18 (8.0)
Gallbladder	10 (4.4)
Liver	4 (1.8)
Tumour stage, *n* (%)	
I	7 (3.1)
II	40 (18.2)
III	62 (27.6)
IV	116 (51.1)
ECOG, *n* (%)	
0–1	176 (78.2)
>2	49 (22.7)
Chemotherapy (±radiotherapy) received, *n* (%)	
Palliative	126 (56.0)
Definitive chemorads	14 (6.2)
Neoadjuvant	54 (24.0)
Adjuvant	31 (13.8)

ECOG, Eastern Cooperative Oncology Group; GO, Gastro-oesophageal.

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Table 2 Anthropometric and nutritional status characteristics of patients according to gender, values expressed as mean (standard deviation), unless stated otherwise

Characteristic	Men, $n = 150$	Women, $n = 75$	Total, $n = 225$	P value
Weight (kg)	77.9 (12.9)	62.7 (13.6)	72.8 (14.9)	<0.001
Height (m)	1.75 (0.07)	1.61 (0.08)	1.7 (0.09)	<0.001
BMI (kg/m^2), *n* (%)	25.5 (3.9)	24.1 (4.9)	25.1 (4.3)	0.024
Underweight (≤18.5)	8 (5.3)	9 (12.0)	17 (7.6)	0.129
Normal (18.5–24.9)	56 (37.3)	34 (37.3)	90 (40.0)	0.312
Overweight (25–29.9)	66 (44.0)	22 (29.3)	88 (39.1)	0.048
Obese (≥30.0)	20 (13.3)	10 (13.3)	30 (13.3)	1.00
Cachexia, *n* (%)	91 (60.7)	48 (64.0)	139 (61.8)	0.734
Muscle parameters				
Skeletal muscle area (cm^2)	162.5 (25.2)	105.3 (15.2)	143.5 (35.0)	<0.001
Skeletal muscle index (cm^2/m^2)	53.5 (8.3)	40.6 (5.9)	49.2 (9.7)	<0.001
Sarcopenia, *n* (%)	42 (28.0)	48 (64.0)	90 (40.0)	<0.001
Estimated FFM (kg)[a]	54.8 (7.6)	37.6 (4.5)	49.1 (10.5)	<0.001
Estimated SMM (kg)[a]	30.3 (4.34)	20.41 (2.61)	26.99 (6.05)	<0.001
Muscle attenuation (HU)[b]	37.5 (7.3)	35.6 (7.6)	36.8 (7.5)	0.080
Low muscle attenuation, *n* (%)[b]	55 (42.0)	45 (63.4)	100 (49.5)	0.006
Fat parameters				
Adipose tissue area (cm^2)	346.1 (165.5)	293.6 (160.0)	328.7 (165.2)	0.028
Adipose tissue index (cm^2/m^2)	114.2 (54.6)	113.6 (63.0)	113.9 (57.4)	0.942
Estimated FM (kg)[a]	25.7 (6.9)	23.5 (6.7)	25.0 (6.9)	0.027

BMI, body mass index; FM, fat mass; FFM, fat free mass; HU, Hounsfield units; kg, kilogram; SD, standard deviation; SMM, skeletal muscle mass.
[a]Estimated kilograms of FFM and FM are calculated from regression equations reported by Mourtzakis *et al*.[31] and estimated kilograms of SMM are calculated from regression equations reported by Shen *et al*.[32]
[b]Muscle attenuation analysis based on 202 patients (131 men and 71 women).

More women were sarcopenic (64% vs. 28%, $P < 0.001$) and had low MA (63% vs. 42%, $P = 0.006$) compared with men. CC, sarcopenia, and low MA were present in all BMI categories, in fact, in those with a BMI >25 kg/m^2, 72% had CC, 41% had sarcopenia, and 56% had low MA.

Patients with sarcopenia had lower BMI (23.9 vs. 25.8 kg/m^2, $P = 0.001$) and, as expected, had lower SMA (men 169.4 vs. 144.8 cm^2, $P < 0.001$; women 97.8 vs. 118.7 cm^2, $P < 0.001$), SMI (men 46.9 vs. 56.0 cm^2/m^2, $P < 0.001$; women 36.9 vs. 47.2 cm^2/m^2, $P < 0.001$), and FFM (men 49.5 vs. 56.9 kg, $P < 0.001$; women 35.4 vs. 41.7 kg, $P < 0.001$). Female patients with sarcopenia had a lower ATA (366.2 vs. 254.1 cm^2, $P = 0.004$), ATI (146.3 vs. 95.7 cm^2/m^2, $P = 0.001$), and FM (26.6 vs. 21.9 kg, $P = 0.004$), and this was not observed in male patients. Patients with sarcopenia did not differ in age (64.8 vs. 63.9 years, $P = 0.510$) and had similar clinical features to non-sarcopenic patients.

Longitudinal changes in body composition

Longitudinal changes in body composition were assessed in a subset of patients who had a repeat CT image taken as part of their medical management ($n = 163$; 104 men and 59 women). The changes are presented in *Table* 3. Changes in overall body weight (kg) were not recorded.

On average, patients lost 6.1 cm^2 (95% CI: −7.7 to −4.5 cm^2, $P < 0.001$) of SMA per 100 days, corresponding to 1.0 kg of SMM and 2.0 kg of FFM on a whole body basis. Men lost more SMA than women [8.5 cm^2 (1.5 kg of SMM)/100 days vs. 1.8 cm^2 (0.3 kg SMM)/100 days, $P < 0.001$], amounting to a relative rate of loss of 5.0% vs. 1.8% per 100 days ($P = 0.002$). Patients without sarcopenia (at baseline) lost more SMA [8.9 cm^2 (1.5 kg SMM) vs. 2.0 cm^2 (0.3 kg SMM)/100 days, $P < 0.001$] and FFM (4.9 vs. 1.0 kg/100 days, $P < 0.001$), compared with sarcopenic patients. The prevalence of sarcopenia increased from 40.5% (66 out of 163) at baseline to 49.1% (80 out of 163) at the time of the second scan ($P = 0.016$). Changes in skeletal muscle did not significantly differ between cancer types (all P = NS). Patients experienced significant losses in ATA [−17.31 cm^2/100 days (95% CI: −28.07 to −6.54), $P = 0.002$], equivalent to 0.73 kg/100 days (95% CI: −1.18 to −0.27, $P = 0.002$) on a whole body basis. MA decreased by −0.84 HU (95% CI: −1.59 to −0.08 HU, $P = 0.031$) per 100 days. Changes in MA and measures of adiposity did not significantly differ between gender, cancer type, or the presence of sarcopenia (all P = NS).

Mean losses of muscle and adipose tissue obscure the fact that, in some instances, muscle and adipose tissue was gained or remained stable. The ranges of SMM change (−6.2 to 4.6 kg/100 days) and FM change (−7.7 to 5.6 kg/100 days) are displayed in *Figure* 1A and 1B, respectively. Overall, 45.4% of patients lost SMM, while 46% remained muscle stable (±1 kg). It is important to note that 23.9% of patients that lost >1 kg of SMM had a concurrent gain of >1 kg of FM.

Table 3 Change in skeletal muscle and adipose tissue area (cm^2) per 100 days according to cancer type

Tissue	Change per 100 days			Relative change per 100 days (%)		
	Mean	95% CI	*P*	Mean	95% CI	*P*
Skeletal muscle area (cm^2)						
All foregut cancers (*n* = 163)	−6.1	−7.7 to −4.4	<0.001	−3.9	−4.9 to −2.8	<0.001
Gastro-oesophageal, (*n* = 99)	−7.7	−9.9 to −5.5	<0.001	−4.8	−6.2 to −3.5	<0.001
Gastric, (*n* = 27)	−7.9	−12.2 to −3.7	0.001	−4.2	−7.1 to −1.3	0.006
Oesophageal, (*n* = 72)	−7.6	−10.3 to −4.9	<0.001	−5.1	−6.7 to −3.5	<0.001
Hepato pancreato-biliary, (*n* = 64)	−3.6	−5.8 to −1.4	0.002	−2.5	−4.1 to −0.8	0.004
Pancreatic, (*n* = 40)	−4.0	−7.0 to −1.1	0.009	−2.9	−5.2 to −0.8	0.010
Biliary (gallbladder, liver, and bile duct), (*n* = 24)	−2.8	−6.2 to 0.7	0.111	−1.6	−4.2 to 1.0	0.212
Total adipose tissue area (cm^2)						
All foregut cancers (*n* = 154)	−17.3	−28.1 to −6.5	0.002	−3.5	−7.7 to 0.7	0.105
Gastro-oesophageal, (*n* = 93)	−12.7	−26.6 to 1.2	0.074	−1.8	−7.6 to 4.0	0.533
Gastric, (*n* = 26)	−17.0	−44.1 to 10.0	0.207	0.1	−15.9 to 16.0	0.994
Oesophageal, (*n* = 67)	−11.0	−27.7 to 5.6	0.191	−2.6	−8.0 to 2.9	0.357
Hepato pancreato-biliary, (*n* = 61)	−24.3	−41.6 to −7.0	0.007	−6.0	−12.3 to 0.1	0.054
Pancreatic, (*n* = 39)	−33.5	−55.2 to −11.9	0.003	−8.8	−16.4 to −1.2	0.024
Biliary (gallbladder, liver, and bile duct), (*n* = 22)	−8.0	−38.0 to 21.9	0.583	−1.1	−12.0 to 9.8	0.837

CI, confidence interval.

Palliative vs. neoadjuvant chemotherapy

Changes in SMA, FFM, and SMM per 100 days varied significantly between chemotherapy types [palliative (*n* = 89), definitive chemo-radiotherapy (*n* = 3), neoadjuvant (*n* = 47), and adjuvant (*n* = 24)] ($P < 0.001$). The significant differences were observed among those treated with palliative and neoadjuvant chemotherapy (NACT) (*Table* 4). Patients treated with NACT experienced greater losses in SMA, FFM, and SMM compared with patients treated with palliative chemotherapy. No difference was observed in changes of ATA, FM, or MA between chemotherapy types. Patients treated with palliative and NACT did not significantly differ in terms of age, gender, or body composition at baseline.

Response to treatment and changes in body composition

Response to treatment was evaluated in 157 of the 163 patients. Of these, 56 patients (36%) responded to chemotherapy, while 62 (39%) progressed and 39 (25%) had stable disease. Overall, no difference was observed in changes in body composition parameters and response to treatment. However, within those treated with NACT, patients who responded (23/45 patients) to treatment lost less muscle (1.4 vs. 2.6 kg of SMM/100 days, $P = 0.090$; −4.0% vs. −8.7% of SMA/100 days, $P = 0.034$) and gained adipose tissue (+0.7 vs. −1.2 kg of FM/100 days, $P = 0.017$; +5.4% vs. −10.8% of ATA/100 days, $P = 0.019$) compared with those who did not respond.

Body composition and survival

Median overall survival (OS) for the entire cohort was 15.7 months (95% CI: 14.0 to 17.4 months). Patients with gastro-oesophageal cancer had a significantly longer survival than those with HPB cancer (19.7 vs. 13.5 months, log-rank $P < 0.001$). As expected, patients treated with palliative chemotherapy had a significantly shorter OS compared with those receiving treatment with a curative intent [11.7 months (95% CI: 9.9 to 13.5) vs. 36.9 months (95% CI: 18.7 to 55.2), log-rank $P < 0.001$].

To examine the effect of relative muscle loss on survival, quartiles of muscle change were devised. No effect on survival was observed when the whole cohort was examined together or in those treated with curative intent; however, within this group, a large proportion of cases was censored (60%). Conversely, in patients treated with palliative chemotherapy [*n* = 89; 23 (26%) censored], survival curves were significantly different across quartiles of %SMA change/100 days (log-rank $P = 0.031$). A median OS of 15.9, 15.7, 12.2, and 7.9 months was observed for group 1 [muscle gain (≥0.85%/100 days)], group 2 [stable/minor muscle loss (<0.85% to −2.35%/100 days)], group 3 [muscle loss (−2.35 to −6.0%/100 days)], and group 4 (highest muscle loss >6.0%/100 days), respectively. Patients with a muscle loss of >6.0%/100 days (group 4; highest muscle loss) had significantly lower OS compared with those with a muscle loss ≤6.0%/100 days [7.9 months (95% CI: 6.7 to 9.1) vs. 15.6 months (95% CI: 13.3 to 17.9), respectively, (log rank; $P = 0.006$)] (*Figure* 2). On multivariate analysis, muscle loss of ≥6.0% remained independently associated with shorter survival [HR: 2.66, (95% CI: 1.42 to 4.97), $P = 0.002$] (*Table* 5).

Neither sarcopenia nor low MA at baseline was associated with shorter OS. Foregut cancer patients with CC had a shorter median survival [15.1 months (95% CI: 13.1 to 17.1)] compared with patients without CC [17.5 months (95% CI: 12.5 to 22.6), log rank $P = 0.035$; univariate analysis HR: 1.46 (95% CI: 1.03 to 2.09), $P = 0.036$]. However, after accounting for known prognostic covariates in a multivariate model (age, gender, cancer type, cancer stage, and the

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Figure 1 (A) Change in skeletal muscle mass (SMM) (kg) per 100 days in patients with cancers of the foregut (n = 163) and (B) change in fat mass (FM) (kg) per 100 days in patients with cancers of the foregut (n = 154).

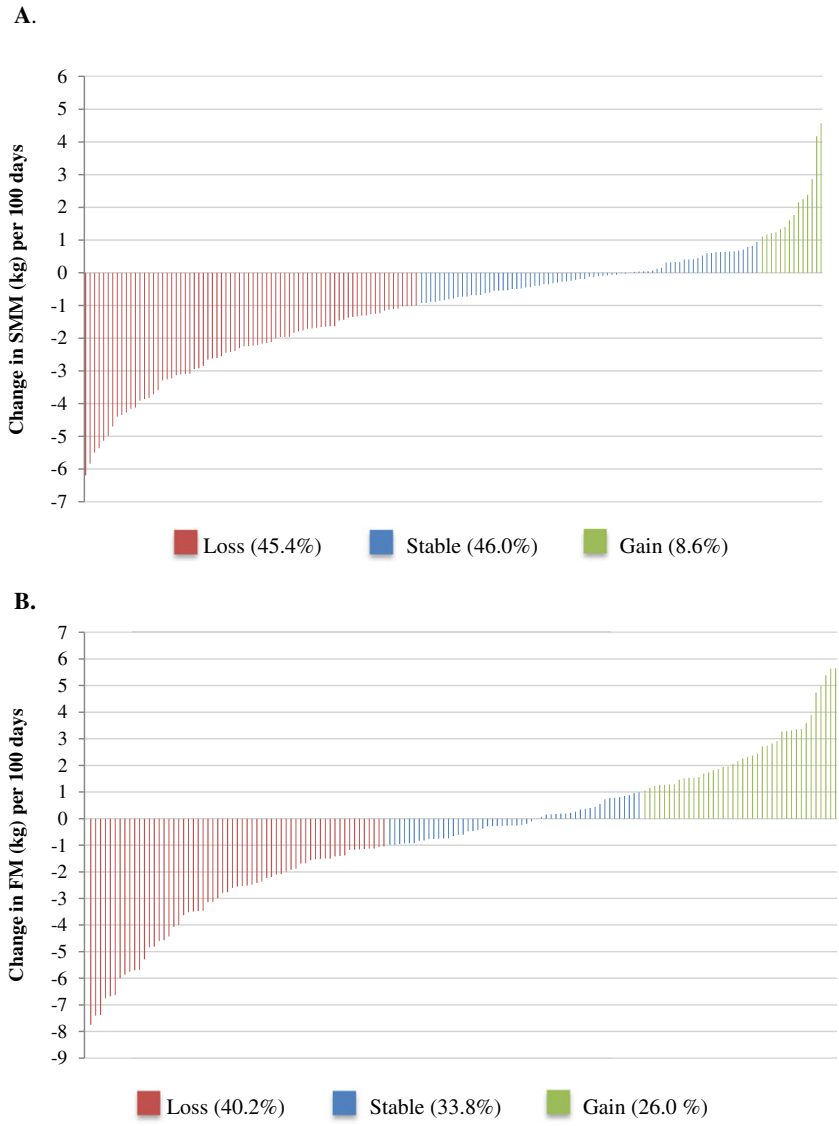


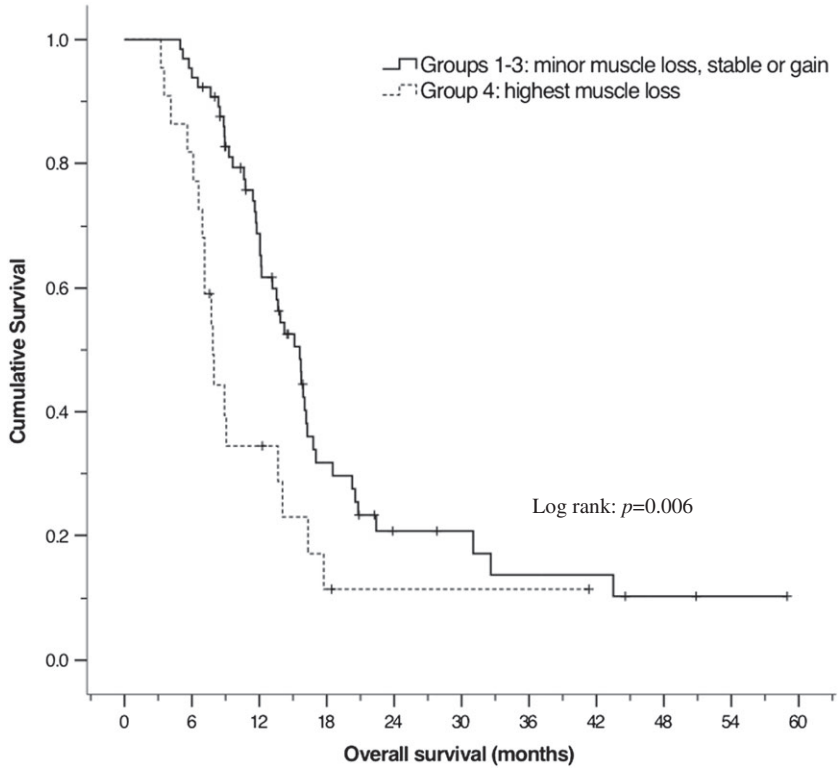
Table 4 Change in measures of muscle mass in patients treated with palliative vs. neoadjuvant chemotherapy. All values expressed as mean change (95% CI) per 100 days

	Palliative chemotherapy (n = 89)	Neoadjuvant chemotherapy (n = 47)	Mean difference	P value
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	
Δ SMA (cm^2)	−4.7 (−6.6 to −2.8)	−11.3 (−14.7 to −7.96)	−6.6 (−10.2 to −3.1)	<0.001
Δ SMA (%)	−2.8 (−4.2 to −1.4)	−7.3 (−9.1 to −5.4)	−4.5 (−6.8 to −2.1)	<0.001
Δ FFM (kg)	−1.4 (−3.7 to −1.3)	−3.4 (−4.4 to −2.4)	−2.0 (−3.1 to −0.9)	<0.001
Δ FFM (%)	−2.5 (−3.7 to −1.3)	−6.3 (−8.4 to −4.2)	−3.8 (−6.0 to −1.6)	0.001
Δ SMM (kg)	−0.8 (−1.1 to −0.5)	−1.9 (−2.4 to −1.4)	−1.2 (−1.8 to −0.5)	<0.001
Δ SMM (%)	−2.6 (−3.9 to −1.4)	−6.6 (−8.8 to −4.5)	−4.0 (−6.3 to −1.7)	0.001

All changes in measures of SMA (cm^2 and %), FFM (cm^2 and %), and SMM (cm^2 and %) listed within groups have a $P < 0.001$. CI, confidence interval; FFM, fat free mass; SMA, skeletal muscle area; SMM, skeletal muscle mass.

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Figure 2 Kaplan–Meier curves for groups of relative muscle change (% change skeletal muscle area/100 days). Patients with a muscle loss of ≥6.0%/100 days (group four, highest amount of muscle loss) had significantly lower overall survival compared with those with a muscle loss <6.0%/100 days (groups one to three; minor muscle loss/stable or gain). Censored cases are indicated by +.



Eastern Oncology Cooperative Group), CC did not remain significant (HR: 1.33 (95% CI: 0.93 to 1.90), P = 0.124).

Discussion

Our study details the changes in body composition in foregut cancer patients undergoing chemotherapy, highlighting the magnitude of muscle and adipose tissue wasting over time, particularly in patients treated with NACT. We describe the adverse prognostic impact of muscle loss on survival in patients treated with palliative chemotherapy.

Our data underscore the critical importance of muscle tissue assessment in patients with foregut cancer undergoing chemotherapy. High rates of cachexia (62%), sarcopenia (40%), and low MA (49%) were observed (despite a high BMI), and this is in line with previous research.[8,19,35] Compounding this is the ongoing loss of muscle patients experience undergoing chemotherapy, with a relative muscle loss of 3.9%/100 days (P < 0.001). This is considerably

Table 5 Estimated crude and adjusted HRs for factors thought to be associated with overall survival in patients receiving palliative chemotherapy (n = 89)

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Gender (ref male)	1.00 (0.61–1.64)	0.998	0.73 (0.39–1.38)	0.333
Age >65.6 years	0.76 (0.46–1.25)	0.281	0.77 (0.44–1.33)	0.342
Current smoker	1.29 (0.74–2.22)	0.374		
HPB cancer (ref GO cancer)	1.83 (1.11–3.01)	0.018	2.02 (1.09–3.76)	0.026
ECOG PS >2 (ref 0–1)	1.75 (0.95–3.24)	0.074	2.21 (1.12–4.26)	0.017
BMI <25 kg/m^2 (ref >25 kg/m^2)	1.47 (0.90–2.41)	0.128	1.64 (0.98–2.74)	0.062
Cachexia	0.81 (0.49–1.33)	0.397		
Sarcopenia	1.12 (0.69–1.83)	0.649		
Low MA	1.12 (0.67–1.85)	0.667		
Muscle loss >6% (ref <6%)	2.11 (1.22–3.67)	0.008	2.66 (1.42–4.97)	0.002

BMI, body mass index; CI, confidence interval; ECOG PS, the Eastern Oncology Cooperative Group performance score; GO, gastro-oesophageal; HPB, hepato-pancreato-biliary; HR, hazard ratio; MA, muscle attenuation; ref, reference.

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greater compared with ageing healthy adults, who typically lose muscle at a rate of 1–1.4% per year.[36,37] However, the mean rate of muscle loss is comparable with that observed in advanced pancreatic cancer patients (−3.1 ± 12%/100 days) receiving palliative care (n = 44)[25] and a recent report from our own group in metastatic melanoma patients (−3.3 ± 5.8%/100 days) receiving immunotherapy (n = 59).[38] Higher rates of muscle loss were observed in patients treated with NACT (−7.3%/100 days), similar to those observed in ovarian cancer patients (−5.2 ± 9.8%/100 days) undergoing NACT (n = 123).[28] Other studies have reported significant reductions in skeletal muscle in a variety of cancer types[8,24,26,39] but failed to report these as a change/100 days, which makes it difficult to compare with our cohort given the heterogeneity in the interval between scans.

We reported herein that foregut cancer patients receiving palliative chemotherapy with a muscle loss >6%/100 days were at a significantly increased risk of mortality. The increased mortality risk may be attributed to a more aggressive tumour profile in patients with muscle loss. Alternatively, patients with muscle loss may experience a higher degree of cachexia. Cachexia induces systemic inflammation and metabolic alterations, which in combination with a decrease in body protein stores may explain the poor prognosis in these patients. Loss of muscle mass may also affect the tolerability of systemic chemotherapy. Foregut cancer patients with low muscle mass are more prone to severe treatment-related toxicities, resulting in fewer completed cycles of chemotherapy.[7,14,39] This may result in inferior disease control and adversely impact on survival.

Our results corroborate the findings in metastatic colorectal cancer patients (n = 63) and metastatic melanoma patients (n = 59), whereby a loss of muscle >9% over 3 months of chemotherapy and >7.5%/100 days while undergoing immunotherapy, respectively, was independently associated with reduced survival.[21,38] Similarly, Miyamoto *et al*.[26] reported a muscle loss >5% during chemotherapy was significantly associated with poorer overall survival and progression free survival in unresectable colorectal cancer patients (n = 148). In contrast to our findings, Tan *et al*.[25] observed no significant difference in survival across tertiles of muscle loss in a small cohort of advanced pancreatic cancer patients (n = 44). Of note, patients in that study had a much poorer prognosis with a median survival of 4 months, compared with a median survival of 12 months in the present study. Moreover, the second CT scan was taken on average 95 days before death, indicating that patients may have been entering the refractory-cachexia phase. Therefore, the maintenance or gain of skeletal muscle in that setting may have only limited clinical benefit. In the neoadjuvant setting, Rutten *et al*.[28] reported that a loss of muscle >2%/100 days was independently associated with reduced survival in ovarian cancer patients [HR: 1.77 (95% CI 1.018 to 3.088, P = 0.043)]. Within our cohort, the relationship between the magnitude of muscle loss and mortality in patients treated with NACT was difficult to determine given the large proportion of censored cases (60%) at the time of analysis. However, it is possible that the impact of muscle loss may vary with cancer diagnosis, treatment, and overall prognosis. This has been observed in colorectal cancer patients; sarcopenia was predictive of survival in patients undergoing curative resection but not in patients with unresectable disease receiving chemotherapy.[26,40]

Sarcopenia and low MA at baseline were not associated with reduced survival. This is in contrast to some[10,15,25] but not all research findings.[8,16,21,24,41] This may be reflective of the fact that sarcopenia (at one time point) is not a measure of actual muscle loss and may be influenced by patients intrinsic level of muscularity**.** Alternatively, this may be reflective of the validity of commonly used cut points (for SMI) to diagnose sarcopenia. To date, no consensus exists on the optimal cut points to define sarcopenia in patients with cancer. Many cut points have been reported, which have been shown to vary widely in male (36 to 55.4 cm^2/m^2) and female (29 to 42.1 cm^2/m^2) patients.[42] Therefore, careful consideration should be given to the choice of cut point to define sarcopenia. Several factors influence patients muscularity (e.g. ethnicity, age, gender, obesity, socio-economic factors, and dietary habits), on which the cut point is dependant and should be taken into account. Ideally, cut points for sarcopenia and low MA would be ethnically specific; however, in the absence of well-defined and validated cut points derived from European populations, we chose to use the cut points for sarcopenia and low MA reported by Martin *et al*.[15] These cut points were devised from the largest available data set to date and are BMI specific. They were devised from a heterogenous group of patients in terms of cancer site, stage, and performance status, similar to our cohort. In addition, they have been validated to predict survival in a number of external cohorts.[43,44] However, large international (and European specific) data repositories are needed to further address this issue and define the most robust diagnostic criteria for sarcopenia in patients with cancer.

Loss of muscle in this cohort is likely multifactorial. It may be reflective of advancing disease, with the release of pro-inflammatory cytokines associated with the underlying malignancy promoting muscle protein catabolism.[45] In line with this, we noted that response to treatment and reduction in tumour burden was associated with less muscle loss in patients treated with NACT, and similar results have been reported in gastric[39] and lung cancer.[24] Reduced physical activity would undoubtedly contribute to muscle loss, and studies have shown that cancer patients are physically inactive.[46] Muscle loss may also be as a consequence of some cancer directed therapies.[47]

Our findings highlight the critical need for effective interventions to address muscle degradation and to negate the adverse outcomes associated with the phenomenon. To date, no pharmacotherapies have been approved for the treatment of the cancer cachexia syndrome, although phases II and III trials have yielded encouraging results.[48,49] It has been

proposed that multimodal interventions are required to address the multifactorial syndrome.[50,51] One such intervention that is currently under investigation is the multimodal exercise/nutrition/anti-inflammatory treatment for cachexia trial, whereby phase II studies have yielded encouraging results.[52] The phase III trial (NCT02330926) is currently being conducted across a number of international sites, the results of which are eagerly awaited. Furthermore, future studies examining cachexia interventions should consider recruiting patients beyond those with weight loss/cachexia at baseline (typical inclusion criteria of weight loss >5%). A study examining the inclusion criteria for cancer cachexia clinical trials identified that 41% of patients excluded from the trial due to insufficient weight loss (<5%) had a skeletal muscle loss >5% but had a concurrent gain of visceral adipose tissue.[53] Similarly, within our study, 24% of patients with a muscle loss (>1 kg) had a concurrent gain in fat mass (>1 kg), which can often lead to no net change in body weight.

Despite the relatively large sample size, this study has limitations. Patients were excluded if CT scans were not available, which may result in selection bias. Measures of food intake and physical activity were not collected in the present study, which represent a limitation as both may influence muscle mass and body composition, and particularly its change within this study. In addition, muscle depletion is only one aspect of functional depletion, and muscle function and strength were not measured in this study but should be investigated further. Future studies must focus on the aetiology of body composition change in patients with cancer and determine if these changes are preventable or reversible.

In conclusion, significant muscle loss occurred in patients with foregut cancers during chemotherapy, particularly in those treated with NACT. In patients receiving palliative chemotherapy, a muscle loss of 6% or more was independently associated with poorer survival. The routine availability of CT scans in oncology represents a unique and exploitable opportunity to assess body composition change, identifying those at nutritional risk and allowing earlier nutritional intervention. Prevention of cancer cachexia and its associated muscle loss have huge potential to improve patient focused clinical outcomes; however, better treatment options are sorely needed.

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Online supplementary material

Additional Supporting Information may be found online in the supporting information tab for this article.

Table S1: Prevalence of patients receiving different chemotherapy regimens according to cancer type.
Figure S1: Prevalence of cachexia, sarcopenia and low muscle attenuation by primary tumour location

Conflict of interest

None declared.

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