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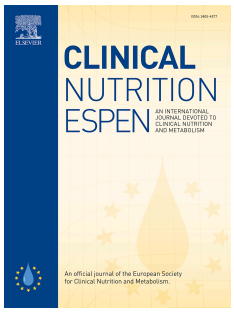

A Large, Multi-Centre Prospective Study Demonstrating High Prevalence of Malnutrition Associated with Reduced Survival in Ambulatory Systemic Anti-Cancer Therapy Patients

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TITLE: A Large, Multi-Centre Prospective Study Demonstrating High Prevalence of Malnutrition Associated with Reduced Survival in Ambulatory Systemic Anti-Cancer Therapy Patients.

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ABSTRACT

Background & Aims: The nutritional status of cancer patients is highly variable, and known to impact on clinical outcomes. To date, no large study evaluating the nutritional status of Irish cancer patients has been reported. The aim of this study was to describe the nutritional status, using gold standard methods, of a large cohort of ambulatory oncology patients receiving Systemic Anti-Cancer Therapy and to assess the impact of abnormal body composition phenotypes on survival.

Methods: A prospective study in adults undergoing Systemic Anti-Cancer Therapy for solid tumours enrolled patients between 2012-2016. Baseline details were collected incorporating demographics, cancer pathology, lifestyle, body composition (by computed tomography (CT), and inflammatory status. Skeletal muscle index (SMI) and mean muscle attenuation (MA) were obtained from CT images and categorised to low muscle mass and low MA using previously published sex specific cut points. Survival was monitored for a median of 25 months [IQR:10-46 months]. Survival analyses were conducted using multivariate Cox Proportional Hazards Models.

Results: Of 1015 patients recruited, 940 patients with an evaluable CT were included in this analysis. Median age was 64 years [IQR 55-71] and 56% were male. Colorectal cancer (28%) and gastro-oesophageal (16%) were the most common diagnoses and 58% of patients had stage IV disease. Despite 56% being overweight or obese (BMI >25kg/m^2), 52% were weight losing and 17% had lost >10% body weight. Cancer Cachexia (CC) was present in 42%, 39% had low muscle mass (MM) (sarcopenia) and 45% had low MA. Overall, 73% of patients exhibited an abnormal body composition (BC) phenotype (≥1 of CC, low MM/MA). Overall survival was significantly lower in those with abnormal BC phenotype, independent of site, stage, sex, ECOG and mGPS (HR: 1.416 [95% CI: 1.069 – 1.875], p=0.015).

Conclusions: Malnutrition and abnormal body composition phenotypes are common in cancer, but are often masked by adiposity. Appropriate screening and diagnostic tools should consider this co-presentation of overweight and obesity, alongside muscle depletion. Given that abnormal body composition phenotypes detectable only via CT are associated with reduced survival, these should be more widely employed to identify patients at risk of poor prognosis, and allow potentially more effective, early intervention.

INTRODUCTION

Poor nutritional status is an established predictor of poor outcomes in patients with cancer, from overall survival, to quality of life(1–3). The understanding of the link between nutrition and patient outcomes is ancient, with the term cachexia being coined by Hippocrates to describe the wasting and oedema seen in patients with heart failure(4). Our modern understanding of the impact of malnutrition in cancer is well-documented and spans almost a century, from a time when weight loss (WL) was the only available metric of nutritional status, to now, where computed tomography (CT), the de facto gold standard in body composition analysis allows us to precisely quantify muscle mass, fat mass and muscle radiodensity using routinely available images.

In 1932, Warren Shields, a pathologist at Harvard Medical School, identified cachexia as a leading cause of death in cancer(5), and despite extraordinary advances in the field of oncology, recent evidence from the past 2 decades using CT(6,7) and composite scores such as Martin's Weight Loss Grading Scale(8), overwhelmingly demonstrates that the presence of 'invisible' body composition abnormalities and even minor WL are linked to poor survival(8), quality of life(9), and dose limiting toxicities(10).

Despite this abundance of evidence, nutritional status is rarely incorporated into standard prognostic tools, and nutritional care remains outside of the scope of standard care in most cancer centres(11,12). This delay in incorporating nutrition into the standard of care is a complex issue, but is likely due in part to limited availability of specialist dietetic services, and a lack of widespread awareness of the risks associated with WL in the context of overweight and obesity.

While weight loss (WL) is closely monitored in oncology, due to its impact on dosing of systemic treatments, or radiotherapy planning(13), the WL itself often remains untreated until it has advanced to a severe form, which is identifiable by visual observation alone(14). Cancer cachexia (CC) is a multifactorial syndrome, characterised by weight loss, in particular muscle mass, but also fat wasting, on a background of systemic inflammation(15). CC is associated with reduced appetite and food intake, progressive loss of weight and declines in physical function(16), and can affect people at any body mass index (BMI)(17). Refractory Cachexia is the most severe form of CC, where simple nutritional interventions are no longer adequate to reserve the condition, and life expectancy is short (<3 months), with severe disability, impaired quality of life, and immunocompromise(18).

In order to identify early CC in a predominantly overweight and obese population, a more comprehensive assessment is required. However, the use of routine CT images in the evaluation of body composition has been slow to enter routine clinical practice(19). As such, CC often goes undetected until it is severe, or in the refractory stage, due to a reliance on practical screening tools based on BMI or severe WL(20).

Given the accepted role of nutrition in the quality and quantity of life for cancer patients, and the need to improve access to nutritional care, it is essential to characterise the nutritional status of the typical ambulatory oncology population, whose main contact with healthcare is in an outpatient setting. The aim of this study was to describe, for the first time, the prevalence of cancer-associated malnutrition (weight loss, cachexia, sarcopenia and low MA) in a large cohort of Irish cancer patients receiving outpatient Systemic Anti-Cancer Therapy (SACT) and to evaluate its impact on patient survival.

MATERIALS & METHODS

This paper reports on the cohort of patients with evaluable CT scans (n=940) of the SARCONC study cohort (n=1015) and characterizes in detail the nutritional status across disease presentations. A previous paper reported on the validity of MST, MUST and NRI screening tools in a preliminary analysis of this cohort (n=725)(20).

Study population

Consecutive adult (>18 years) ambulatory cancer patients undergoing SACT for a solid tumour were eligible to partake in a study that examined the impact of nutritional status on quality of life and survival. Subjects attending the day ward for SACT were recruited via convenience sampling over a five-year period (and followed for a median of 25 months [IQR:10-46 months]) at two university teaching hospitals in Cork (Cork University Hospital and Mercy University Hospital). Head & Neck cancers are not included in this study, as they are treated in another regional cancer centre. Eligible patients were given the choice to take part in this study, and willing participants provided written informed consent. Exclusion criteria included patients that were under the age of 18 years of age, those admitted for inpatient care, those with haematological malignancies and those that were unwilling or unable to participate due to cognitive impairment. Data was collected by a team of registered dietitians in conjunction with a medical oncologist and oncology nurses. This study was approved by the local ethics committee and conducted according to good clinical practice and applicable laws, in accordance with the Declaration of Helsinki.

Patient information recorded

On assessment, patient weight, height and body mass index (BMI) were recorded [weight (kg)/height (m^2)]. BMI was categorised as underweight (<20.0 kg/$m^{2)}$), normal (20.0-24.9 kg/m^2), overweight (25-29.9 kg/m^2) and obese (≥30 kg/m^2). The cut-point for underweight was

chosen to reflect a primarily Caucasian cohort, and the cut-points used in prevailing definitions of cachexia(15,16). Patients completed a researcher assisted questionnaire that that documented information on nutritional and lifestyle factors. History of unintentional weight loss (WL) in the preceding 3 and 6 months was reported by patients, and when possible, verified from medical records.

Clinical and pathological data was collected during medical chart review and included information on patient demographics (age, gender), primary tumour site, stage and extent of metastatic disease (if present), oncological treatment, type of SACT and routine laboratory blood biochemistry results [C-reactive protein (mg/L)(CRP) and albumin (g/L)]. Using both CRP and albumin, a modified Glasgow prognostic score (mGPS) was generated(21). Patients who had both evaluated CRP (<10 mg/L) and hypoalbuminemia (<35 g/L) were assigned a score of 2. Patients with only elevated CRP (>10 mg/L) were assigned a score of 1. Patients with neither of these abnormalities were assigned a score of 0.

Performance status was assessed by use of The Eastern Oncology Cooperative Group (ECOG) performance status scores(22). Cancer diagnoses were grouped and included: colorectal, gastric, oesophageal, hepatobiliary/pancreatic (HBP) cancers (pancreatic, gallbladder, liver and bile ducts), lung, gynaecological (ovarian, endometrial, cervical), breast, lymphoma, genitourinary (prostate, bladder, testicular) and other. Patient's date of death from any cause was recorded, with the latest update of survival statistics on 29th April 2019.

Body composition assessment

Abdominal CT images taken as part of routine patient care were used to assess body composition as previously described(20), using OsiriX software version 4.1.1 (Pixmeo,

Geneva, Switzerland). The third lumbar vertebrae (L3) was chosen as the standard landmark because it correlates best with whole body measures of muscle mass(23,24). Two consecutive transverse CT images where both transverse vertebral processes were clearly visible were analysed and the average result reported.

Skeletal muscle area (cm^2)(SMA) was manually outlined and segmentation of SMA was based on Hounsfield unit (HU) thresholds (-29 to +150 HU)(25). SMA was normalized for stature to compute the skeletal muscle index (SMI)(cm^2/m^2). Mean muscle attenuation (MA) in HU was assessed in all patients with a contrast enhanced CT image and was reported for the entire SMA at L3. Total adipose tissue area (cm^2)(TATA) was manually outlined and segmentation of TATA was based on Hounsfield unit (HU) thresholds (-190 to -30 HU)(25). TATA was normalized for stature to compute the total adipose tissue index (TATI)(cm^2/m^2). The equations used to determine whole body muscle and adipose tissue mass, proposed by Prado et al., 2013(26) are shown below:

$$\text{Skeletal Muscle Mass (SMM) (kg)} = [\text{L3 SMA } (cm^2)] \div 6.0$$

$$\text{Adipose Tissue Mass (ATM) (kg)} = [\text{L3 TATA } (cm^2)] \div 14.7$$

Cachexia was defined based on the international consensus definition published by Fearon et al. (2011)(15), using the Prado et al. cut-points for Sarcopenia on CT analysis(27). Elsewhere, Sarcopenia and Low Muscle Attenuation were defined based on the sex and BMI specific cut-points published by Martin et al. (2013)(17). WL was reported according to the 2%, 5% and 10% in 6 months cut-points, the first 2 of which are criteria in the Fearon CC definition(15) and all of which are widely accepted as clinically significant levels of unintentional WL(28).

Functional Assessment

In the final year of the study, hand-grip dynamometry was added to the protocol, after which point all patients had their hand-grip strength assessed. Muscle strength was evaluated by measuring handgrip strength (HGS) using a Jamar hand-held dynamometer (*Patterson Medical,* Warrenville, Illinois). Patients performed the test sitting in a chair with both feet touching the ground and the arm placed comfortably at 90 degrees, and forearm and wrist in a neutral position. The hand dynamometer was adjusted so that it fit comfortably in the patient's hand size to obtain their best performance. All measures were obtained from the patient's dominant hand. All participants underwent a familiarization period so that patients would get acquainted with the instrument and procedures. Patients were instructed to apply maximal strength for 3 times with the arm they were most comfortable using. The hand grip strength was expressed in kilograms (kg). After a total of three maximal isometric contractions, the mean HGS was calculated.

Statistical Analysis

Statistical analysis was completed using SPSS (version 21.0, SPSS Inc., Chicago, IL, USA). Data are expressed as median [IQR] or n(%), as appropriate. Comparisons between groups of patients were assessed using Chi-squared test for categorical variables and Mann-Whitney U tests to test for differences in continuous variables. Survival analyses were conducted using Kaplan-Meier Survival Curves and Univariate and Multivariate Cox Proportional Hazards (PH) Regression Models. Overall survival (OS) was calculated from the date of the evaluated CT, with vital status (dead/alive), and thus, censoring, last updated on 29th April 2019. Univariate survival analyses were conducted for all individual body composition abnormalities, but the final Cox PH model used the abnormal body composition phenotype (presence of any one of CC, sarcopenia or low MA), while weight loss, BMI, and

diagnoses of individual body composition abnormalities were excluded, as they are components of, or highly correlated with the abnormal body composition phenotype variable.

RESULTS

Patient characteristics

A total of 940 patients with an evaluable CT image were included in these analyses, of the 1015 total recruited. MA assessment was carried out on all patients with a contrast enhanced CT image (n=872) and TATA was measurable in those whose CT images were not truncated (n=870). All patients were receiving SACT, with 46.7% of patients receiving SACT only, while the remainder were receiving SACT in conjunction with surgery only (31.9%), surgery and chemoradiotherapy (13.3%) or definitive chemoradiotherapy (8.1%). In total 41.5% of the cohort were receiving SACT with a curative intent, with the remainder (56%) undergoing palliative SACT or 2% intent not recorded. Overall, 7% of patients received a regimen containing Rituximab, 6% Etoposide and 6% Irinotecan. All other treatments received by >5% of patients were traditional cytotoxic chemotherapies. Antimetabolites (fluorouracil, capecitabine and gemcitabine) (47%) and Platinum-based Agents (oxaliplatin and cisplatin) (34%) were the most prescribed treatments in this cohort. Baseline characteristics are presented, stratified by sex in Table 1A, by cancer site in Table 1B (Supplementary Material), and by the presence of abnormal body composition phenotype in Table 1C (Supplementary Material).

Table 1A. Baseline characteristics stratified by sex.

Colorectal (CRC), Oesophageal/Gastric (OG), Genitourinary (GU), Gynaecological (Gynae), Hepatobiliary/Pancreatic (HBP); Gastrointestinal (GI); ECOG, Eastern Cooperative Oncology Group; Systemic Anti-Cancer Therapy (SACT)

	Male (n=527)	Female (n=413)	Total (n=940)	*p*-value
Tumour Location, n(%) (n=940)				<0.001
Colorectal	172 (32.6)	92 (22.3)	264 (28.1)	<0.001
Oesophageal/Gastric (OG)	112 (21.3)	34 (8.2)	146 (15.5)	<0.001
Hepatobiliary/Pancreatic (HBP)	49 (9.3)	45 (10.9)	94 (10.0)	>0.05
Lung	75 (14.2)	44 (10.7)	119 (12.7)	>0.05
Gynaecological	0 (0.0)	54 (13.1)	54 (5.7)	-
Genitourinary	47 (8.9)	2 (0.5)	49 (5.2)	<0.001
Breast	0 (0.0)	80 (19.4)	80 (8.5)	-
Lymphoma	52 (9.9)	43 (10.4)	95 (10.1)	>0.05
Other	20 (3.8)	19 (4.6)	39 (4.1)	>0.05
Simplified Tumour Location, n(%) (n=940)				<0.001
Colorectal	172 (32.6)	92 (22.3)	264 (28.1)	<0.001
Upper GI & HBP	161 (30.6)	79 (19.1)	240 (25.5)	<0.001
Lung	75 (14.2)	44 (10.7)	119 (12.7)	>0.05
Other	119 (22.6)	198 (47.9)	317 (33.7)	<0.001
Treatment intent, n (%) (n=940)				0.134
Palliative	284 (53.9)	246 (59.6)	530 (56.4)	>0.05
Curative	229 (43.5)	161 (39.0)	390 (41.5)	>0.05
Not recorded	14 (2.7)	6 (1.5)	20 (2.1)	>0.05
Tumour stage, n (%) (n=882)				0.015
I	19 (3.8)	11 (2.9)	30 (3.4)	>0.05
II	58 (11.6)	54 (14.2)	112 (12.7)	>0.05
III	151 (30.1)	80 (21.1)	231 (26.2)	0.003
IV	274 (54.6)	235 (61.8)	509 (57.7)	0.031
Metastatic disease, n (%) (n=933)				0.156
Yes	261 (49.6)	221 (54.3)	482 (51.7)	>0.05
ECOG Performance Status, n (%) (n=876)				0.183
0	241 (48.4)	210 (55.6)	451 (51.5)	<0.036
1	165 (33.1)	104 (27.5)	269 (30.7)	>0.05
2	75 (15.1)	54 (14.3)	129 (14.7)	>0.05
3	17 (3.4)	10 (2.6)	27 (3.1)	>0.05
4	0 (0.0)	0 (0.0)	0 (0.0)	>0.05
Treatment Plan, n (%) (n=893)				0.039
SACT only	230 (45.8)	187 (47.8)	417 (46.7)	>0.05
SACT & surgery	157 (31.3)	128 (32.7)	285 (31.9)	>0.05
Chemo-radiotherapy & surgery	63 (12.5)	56 (14.3)	119 (13.3)	>0.05
Definitive chemo-radiotherapy	52 (10.4)	20 (5.1)	72 (8.1)	0.004

Anthropometry: Changes in Weight & Body Mass Index

Patients exhibited a wide variation in BMI (14.2-49.4 kg/m^2), the majority of patients (56%) were considered to be overweight (37%) or obese (19%), while only 9% of patients were considered to be underweight. Anthropometric details including weight loss history are presented, stratified by sex in Table 2A, by cancer site in Table 2B (Supplementary Material), by metastatic status in Table 2C (Supplementary Material), and by the presence of abnormal body composition phenotype in Table 2D (Supplementary Material).

Severe weight loss (>10%) was observed in 17% of this cohort, and was highest in gastro-oesophageal (29.8%), HBP (26.9%) and gynaecological (23.1%) cancers. As expected, severe WL (>10% in 6 months) was more common in patients with metastatic disease (20.6% vs. 13%, p=0.002). Weight gain was most commonly experienced by patients with breast (33%), gynae (28.8%) and lung (24.3%) cancers. Using BMI-adjusted Weight Loss Grading Score(8) to combine the prognostic factors of weight loss and resultant BMI, HBP cancers experienced the highest levels of grade 4 weight loss (24.7%), closely followed by gynae (19.2%) and gastro-oesophageal (16.1%).

Body Composition: Cachexia, Sarcopenia and Low Muscle Attenuation

Overall, 42% of patients had cancer cachexia, 39.4% had sarcopenia and 44.8% had low MA and in total, 73.4% of patients were found to have at least one of these abnormal body composition phenotypes. Sarcopenia was more common in women (46.5% vs. 33.8%, p<0.001). CC, sarcopenia and low MA were present in all cancer types, and were most prevalent in upper GI cancers. Patients treated for metastatic disease had marginally higher rates of sarcopenia, cachexia and low MA compared with patients with non-metastatic disease,

but the differences were not statistically significant. Body Composition, inflammatory and functional status parameters are presented, stratified by sex in Table 3A, by cancer site in Table 3B (Supplementary Material), by metastatic status in Table 3C (Supplementary Material), and by the presence of abnormal body composition phenotype in Table 3D (Supplementary Material).

Table 2A. Anthropometric details including weight loss history stratified by sex.

	Male (n=527)	Female (n=413)	Total (n=940)	*p*-value
Routine Anthropometry (Median (IQR))				
Height (m) (n=940)	1.75 (1.7 - 1.8)	1.62 (1.57 - 1.67)	1.7 (1.62 - 1.77)	<0.001
Weight (kg) (n=940)	80 (70.9 - 89.6)	65 (57.2 - 75.9)	74.4 (63.5 - 85.45)	<0.001
Body Mass Index (BMI) (kg/m^2) (n=940)	26.173 (23.665 - 28.898)	24.92 (21.837 - 28.506)	25.772 (22.84 - 28.724)	<0.001
Pre-Diagnosis Weight (kg) (n=929)	84.7 (75 - 95)	69.175 (60 - 78)	77.1 (67 - 89.6)	<0.001
Pre-Diagnosis BMI (kg/m^2) (n=929)	27.321 (24.772 - 30.557)	26.347 (22.907 - 29.617)	26.874 (24.112 - 30.263)	<0.001
Body Mass Index (BMI) Categories, n(%) (n=940)				<0.001
Underweight (<20 kg/m^2)	31 (5.9)	54 (13.1)	85 (9)	>0.05
Normal (≥20 kg/m^2 - <25 kg/m^2)	173 (32.8)	154 (37.3)	327 (34.8)	0.038
Overweight (≥25 kg/m^2 - <30 kg/m^2)	225 (42.7)	125 (30.3)	350 (37.2)	0.006
Obese (≥30 kg/m^2)	98 (18.6)	80 (19.4)	178 (18.9)	>0.05
Pre-Diagnosis BMI Categories, n(%) (n=929)				<0.001
Underweight (<20 kg/m^2)	18 (3.4)	22 (5.4)	40 (4.3)	>0.05
Normal (≥20 kg/m^2 - <25 kg/m^2)	125 (23.9)	140 (34.5)	265 (28.5)	<0.001
Overweight (≥25 kg/m^2 - <30 kg/m^2)	235 (44.9)	148 (36.5)	383 (41.2)	0.009
Obese (≥30 kg/m^2)	145 (27.7)	96 (23.6)	241 (25.9)	>0.05
6 Month Weight Change, n(%) (n=894)				0.134
Weight Gain >2%	91 (17.9)	86 (22.2)	177 (19.8)	>0.05
Weight Stable	147 (29)	109 (28.2)	256 (28.6)	>0.05
Weight Loss 2-4.9%	94 (18.5)	50 (12.9)	144 (16.1)	0.024
Weight Loss 5-9.9%	89 (17.6)	77 (19.9)	166 (18.6)	>0.05
Weight Loss >10%	86 (17)	65 (16.8)	151 (16.9)	>0.05
BMI adjusted Weight Loss Grading System (WLGS)(8), n(%) (n=896)				0.019
0	85 (16.8)	54 (13.9)	139 (15.5)	>0.05
1	56 (11)	50 (12.9)	106 (11.8)	>0.05
2	89 (17.6)	43 (11.1)	132 (14.7)	0.007
3	91 (17.9)	68 (17.5)	159 (17.7)	>0.05
4	49 (9.7)	57 (14.7)	106 (11.8)	0.022
Gain	137 (27)	117 (30.1)	254 (28.3)	>0.05

Table 3A. Body Composition, inflammatory and functional status parameters stratified by sex. Abbreviations: CRP: C-Reactive Protein; mGPS: Modified Glasgow Prognostic Score; HU: Hounsfield Units; FM: Fat Mass.

	Male (n=527)	Female (n=413)	Total (n=940)	*p*-value
Age at recruitment (Median (IQR))				
Age (years) (n=940)	65.243 (57.760 – 70.995)	60.977 (51.870 – 69.700)	63.792 (55.159 – 70.675)	<0.001
Functional Status (Median (IQR))				
Handgrip Strength (kg) (n=339)	29.5 (24.1 - 36.2)	18.85 (15 - 23.6)	24.3 (18.4 - 32.2)	<0.001
Inflammatory Markers (Median (IQR))				
CRP (mg/L) (n=633)	6 (3 - 25.3)	7 (3 - 27)	7 (3 - 26)	0.403
Albumin (g/L) (n=752)	35 (32 - 37)	36 (32 - 39)	35 (32 - 38)	<0.001
mGPS, n(%) (n=596)				0.315
0 (CRP <10 mg/L)	238 (62.5)	122 (56.7)	360 (60.4)	>0.05
1 (CRP ≥10 mg/L & Albumin ≥35 g/L)	44 (11.5)	25 (11.6)	69 (11.6)	>0.05
2 (CRP ≥10 mg/L & Albumin <35 g/L)	99 (26)	68 (31.6)	167 (28)	>0.05
Muscle Parameters (Median (IQR))				
Skeletal muscle area (cm^2) (n=940)	160.121 (141.527 - 178.233)	108.503 (99.293 - 119.033)	134.15 (109.625 - 164.767)	<0.001
Skeletal muscle index (cm^2/m^2) (n=940)	52.03 (45.904 - 57.652)	41.529 (37.667 - 45.75)	46.481 (40.917 - 54.208)	<0.001
Estimated SMM (kg) (n=940)	26.687 (23.588 - 29.706)	18.084 (16.549 - 19.839)	22.358 (18.271 - 27.461)	<0.001
Muscle attenuation (HU) (n=872)	38.081 (32.81 - 42.661)	37.188 (30.619 - 43.391)	37.715 (31.727 - 43.202)	0.390
Fat Parameters (Median (IQR))				
Adipose tissue area (cm^2) (n=870)	350.881 (241.365 - 479.19)	284.301 (174.395 - 414.678)	328.61 (203.603 - 456.069)	<0.001
Adipose tissue index (cm^2/m^2) (n=870)	115.652 (80.688 - 153.078)	107.472 (66.549 - 162.273)	112.826 (73.389 - 153.91)	0.352
Estimated FM (kg) (n=870)	23.869 (16.419 - 32.598)	19.34 (11.864 - 28.209)	22.354 (13.851 - 31.025)	<0.001
Body Composition Phenotypes, n(%)				
Sarcopenia (n=940)	178 (33.8)	192 (46.5)	370 (39.4)	<0.001
Sarcopenic Obesity (n=940)	23 (4.4)	18 (4.4)	41 (4.4)	0.996
Cachexia (n=940)	233 (44.2)	162 (39.2)	395 (42)	0.124
Low muscle attenuation (n=872)	199 (41.9)	192 (48.4)	391 (44.8)	0.056
Low muscle attenuation & Sarcopenia (n=918)	86 (16.8)	104 (25.6)	190 (20.7)	<0.001
Any of 3 (n=940)	383 (72.7)	307 (74.3)	690 (73.4)	0.568

Sarcopenia and low MA were present in all BMI categories. While rates of sarcopenia and cachexia were most prevalent in the underweight (70.6% and 71.8%, respectively), low muscle attenuation was most prevalent in people with a BMI in the 20-25 kg/m^2 range. Overall, 73.4% of the cohort experienced at least one of the 3 body composition abnormalities (hereafter termed the abnormal body composition phenotype). The abnormal body composition phenotype was present in 95.3% of the underweight patients, versus 82%, 66.3% and 61.2% in normal BMI, overweight and obese patients, respectively. Notably, of patients with a BMI in the normal range at recruitment, 38.2% had been overweight or obese according to their pre-diagnosis weight. Of those in the overweight range, 21.1% had been obese before diagnosis. Body composition, weight history, BMI, inflammatory and functional status parameters are presented, stratified by BMI category at recruitment in Table 4.

Systemic Inflammation

CRP and albumin were available and recorded in 633 and 752 patients, respectively (See tables 3A-D). For the entire cohort, the median CRP was 7 [IQR 3-26] mg/L and median albumin was 35 [32 – 38] g/L. Patients with cachexia, sarcopenia or low MA had a significantly lower level of albumin (34 [31 – 37] g/L vs. 37 [34 – 39] g/L, p<0.001). The difference in CRP between patients with abnormal and normal body composition phenotypes was not statistically significant (7 [3 – 27] mg/L vs. 5.55 [3 – 20] mg/L, p=0.161).

Functional Status

Hand grip strength was assessed in a subgroup of patients (n=339) (See tables 3A-D). As expected, male patients had a higher HGS compared with females (29.5 (24.1 - 36.2) kg vs. 18.85 (15 - 23.6) kg, p<0.001). HGS was lower in patients with abnormal body composition

compared to those without (p<0.001) (male 33.2 [26.4 – 37.8] kg vs. 27.9 [23.9 – 35.1] kg; female 22.9 [17.4 – 25.9] kg vs. 17.9 [14.5 – 21.0] kg).

Survival

Survival was monitored for a median of 25 months [IQR:10-46 months], at which point 560 deaths had occurred, and 380 cases were censored. Mortality rates at 3 months (n=940), 1 year (n=940) and 5 year (n=702) were 5.9% [95% CI: 4.4-7.5], 30.9% [95% CI: 27.9-33.9] and 78.6% [95% CI: 75.4-81.6], respectively. Follow-up was less than 5 years for 25.3% of censored cases.

Overall Survival (OS) was poorer in those with abnormal BC phenotypes (defined as the presence of one or more of CC, low MM, or low MA), (mean OS in non-metastatic 70.1 vs. 55.8 months (median not reached), Log rank p<0.001 (figure 1a) and median OS in metastatic 25.6 months (95% CI: 20.2 – 30.9) vs. 14.2 months (95% CI: 12.3 – 16.1), Log rank p<0.001 (figure 1b)). This relationship remained significant after adjustment for site, stage, age, sex, performance status (ECOG) and inflammatory status (mGPS) (HR: 1.416 [95% CI: 1.069 - 1.875], p=0.015 (See table 5).

Table 4. Body composition, weight history, BMI, inflammatory and functional status parameters stratified by BMI category at recruitment.

Body Mass Index Categories	Underweight (n=85)	Normal (n=327)	Overweight (n=350)	Obese (n=178)	Total (n=940)
Functional Status (Median (IQR))					
Handgrip Strength (kg) (n=339)	21.5 (15.9 - 27.3)	24.4 (18 - 31.2)	25.6 (19.5 - 32.7)	23.5 (17.4 - 34.4)	24.3 (18.4 - 32.2)
Inflammatory Markers (Median (IQR))					
CRP (mg/L) (n=633)	5.5 (2 - 14)	7 (2 - 30.5)	6 (3 - 21)	10 (3.2 - 31)	7 (3 - 26)
Albumin (g/L) (n=752)	35 (32 - 36)	35 (31 - 37)	35 (32 - 38)	35 (32 - 38)	35 (32 - 38)
mGPS, n(%) (n=596)					
0 (CRP <10 mg/L)	38 (69.1)	123 (58.6)	142 (63.7)	57 (52.8)	360 (60.4)
1 (CRP ≥10 mg/L & Albumin ≥35 g/L)	3 (5.5)	27 (12.9)	27 (12.1)	12 (11.1)	69 (11.6)
2 (CRP ≥10 mg/L & Albumin <35 g/L)	14 (25.5)	60 (28.6)	54 (24.2)	39 (36.1)	167 (28)
Body Composition Phenotypes, n(%)					
Sarcopenia (n=940)	60 (70.6)	122 (37.3)	147 (42)	41 (23)	370 (39.4)
Sarcopenic Obesity (n=940)	0 (0)	0 (0)	0 (0)	41 (23)	41 (4.4)
Cachexia (n=940)	61 (71.8)	172 (52.6)	115 (32.9)	47 (26.4)	395 (42)
Low muscle attenuation (n=872)	39 (48.1)	181 (59)	105 (31.9)	66 (42.6)	391 (44.8)
Low muscle attenuation & Sarcopenia (n=918)	27 (32.5)	80 (24.8)	62 (18.2)	21 (12.1)	190 (20.7)
Any of 3 (n=940)	81 (95.3)	268 (82)	232 (66.3)	109 (61.2)	690 (73.4)
Pre-Diagnosis BMI Categories, n(%) (n=929)					
Underweight	34 (40.5)	6 (1.9)	0 (0)	0 (0)	40 (4.3)
Normal	44 (52.4)	193 (59.9)	27 (7.8)	1 (0.6)	265 (28.5)
Overweight	3 (3.6)	110 (34.2)	246 (71.1)	24 (13.6)	383 (41.2)
Obese	3 (3.6)	13 (4)	73 (21.1)	152 (85.9)	241 (25.9)
6 Month Weight Change, n(%) (n=894)					
Weight Gain >2%	8 (10)	58 (18.3)	70 (21.3)	41 (24.4)	177 (19.8)
Weight Stable	12 (15)	73 (23)	110 (33.4)	61 (36.3)	256 (28.6)
Weight Loss 2-4.9%	9 (11.3)	46 (14.5)	63 (19.1)	26 (15.5)	144 (16.1)
Weight Loss 5-9.9%	23 (28.8)	64 (20.2)	55 (16.7)	24 (14.3)	166 (18.6)
Weight Loss >10%	28 (35)	76 (24)	31 (9.4)	16 (9.5)	151 (16.9)
Martin's Weight Loss Grading System (WLGS), n(%) (n=896)					
0	0 (0)	0 (0)	92 (27.9)	47 (28)	139 (15.5)
1	0 (0)	60 (18.9)	19 (5.8)	27 (16.1)	106 (11.8)
2	0 (0)	57 (18)	52 (15.8)	23 (13.7)	132 (14.7)
3	23 (28.4)	71 (22.4)	53 (16.1)	12 (7.1)	159 (17.7)
4	44 (54.3)	52 (16.4)	10 (3)	0 (0)	106 (11.8)
Gain	14 (17.3)	77 (24.3)	104 (31.5)	59 (35.1)	254 (28.3)

Figure 1. Kaplan Meier Curves Comparing Survival Trajectory in Patients According to Body Composition Phenotype (Normal (No Cachexia, Low Muscle Mass or Low MA); Abnormal (Cachexia, Low Muscle Mass or Low MA)) **Panel A) Non-Metastatic Disease,** Of n=451, 61.2% cases were censored. Mean (median not reached due to high censoring) Survival was 70.1 months in those with normal body composition phenotype vs. 55.8 months in those with abnormal body composition phenotype , Log rank $p<0.001$. **Panel B) Metastatic Disease,** Of n=482, 20.7% cases were censored. Median Survival was 25.6 months (95% CI: 20.2 – 30.9) in those with normal body composition phenotype vs. 14.2 months (95% CI: 12.3 – 16.1) in those with abnormal body composition phenotype , Log rank $p<0.001$.

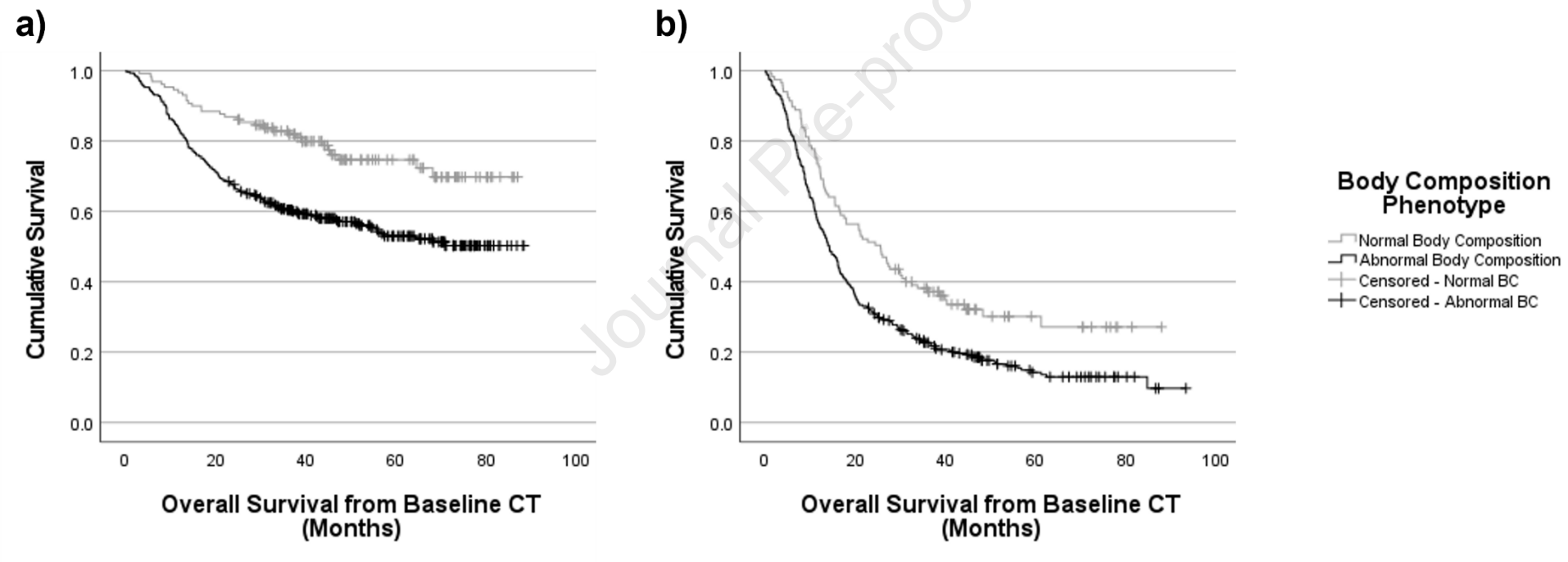

Table 5. Impact of Abnormal Body Composition Phenotypes on Overall Survival ***Multivariate Cox Proportional Hazards Model*** (n=940) Censoring in 227 (24.1%) cases.

Dropped cases due to missing data 348 (37.0%). Cases included in final analysis 592.

	Univariate Cox Proportional Hazards Model				Multivariate Cox Proportional Hazards Model				Kaplan-Meier Survival Analyses			
		Lower	Upper			Lower	Upper		Median OS	Lower	Upper	
	HR	95% CI		p-value	HR	95% CI		p-value		95% CI		p-value
Sex (ref. male) (n=379)									25.067	20.298	29.835	
Female (n=213)	.878	.742	1.039	0.129	0.945	0.760	1.173	0.606	35.167	26.703	43.631	0.129
Age (ref. younger than 65 years) (n=289)									31.267	20.745	41.788	
Older than 65 years (n=303)	1.160	.983	1.369	0.079	1.045	0.848	1.288	0.677	26.967	21.860	32.073	0.079
Metastasis (ref. no metastases) (n=294)									NR	NR	NR	
Metastatic Disease (n=298)	3.275	2.732	3.925	<0.001	3.203	2.552	4.021	<0.001	15.867	14.067	17.667	<0.001
ECOG (ref. 0/1) (n=463)									36.700	29.207	44.193	
2+ (n=129)	1.858	1.510	2.286	<0.001	1.310	1.033	1.663	0.026	13.667	10.122	17.211	<0.001
Cancer Location (ref. Other Locations) (n=129)				<0.001				<0.001	61.200	53.723	68.677	
CRC (n=181)	1.026	.809	1.301	.835	1.056	0.753	1.483	0.751	57.033	NR	NR	0.887
Upper GI incl. Hepatobiliary/Pancreatic (n=209)	2.476	1.989	3.081	<0.001	2.675	1.957	3.658	<0.001	15.133	13.130	17.137	<0.001
Lung (n=73)	3.272	2.530	4.231	<0.001	2.730	1.885	3.954	<0.001	13.333	11.661	15.005	<0.001
mGPS (ref. Score 0 [CRP <10 mg/L & Albumin ≥35 g/L]) (n=358)				<0.001				<0.001	44.867	29.018	60.716	
mGPS Score 1 [CRP ≥10 mg/L & Albumin ≥35 g/L] (n=69)	1.171	.836	1.641	.359	1.261	0.896	1.775	0.183	33.767	16.600	50.933	0.354
mGPS Score 2 [CRP ≥10 mg/L & Albumin <35 g/L] (n=165)	2.490	1.995	3.107	<0.001	1.949	1.546	2.457	<0.001	11.200	9.934	12.466	<0.001
Abnormal Body Composition Phenotype									55.444	50.938	59.950	
Any Body Composition Abnormality (n=458) (ref. none) (n=134)	1.796	1.459	2.212	<0.001	1.416	1.069	1.875	0.015	41.263	38.389	44.138	<0.001
Individual Body Composition Abnormalities												
Sarcopenia (ref. not present) (n=570)									33.633	26.215	41.052	
Sarcopenia, n (%) (n=370)	1.227	1.038	1.451	.017					24.100	18.413	29.787	0.017
Sarcopenic Obesity (ref. not present) (n=899)									29.900	24.741	35.059	
Sarcopenic Obesity (n=41)	1.489	1.030	2.151	0.034					23.767	7.540	39.993	0.033
Cachexia (ref. not present) (n=545)									39.067	28.985	49.148	
Cachexia, n (%) (n=395)	1.483	1.256	1.750	<0.001					20.133	16.175	24.092	<0.001
Low Muscle Attenuation (ref. not present) (n=481)									44.600	31.228	57.972	
Low muscle attenuation, n(%) (n=391)	1.616	1.360	1.919	<0.001					19.700	16.520	22.880	<0.001
Low Muscle Attenuation & Sarcopenia (ref. not present) (n=728)									33.633	26.397	40.870	
Low muscle attenuation & Sarcopenia (n=190)	1.388	1.139	1.690	0.001					19.700	14.368	25.032	0.001

DISCUSSION

This is the first study in Ireland and one of the largest conducted in Europe examining the prevalence of cancer-associated malnutrition, incorporating gold standard CT assessment of body composition, in ambulatory oncology patients receiving SACT. Our findings highlight the importance of body composition assessment in this patient group as very large proportion of patients were considered to be malnourished, despite the very low levels of malnutrition suggested by the use of BMI alone. The prevalence of malnutrition identified in this cohort is in line with recent international findings, which have used the same methodology and diagnostic criteria(1,6–8,17,29).

High Levels of Malnutrition Masked by High BMI

Within this study, alarmingly high levels of malnutrition were observed among patients, despite 57% considered to be overweight or obese (BMI ≥25 kg/m^2). Among patients, 42%, 39% and 45% were considered to have CC, sarcopenia and low MA, respectively. However, only 9% of patients had visible malnutrition with a BMI ≤20 kg/m^2, and even considering severe weight loss >10% in 6 months, only 17% of patients would be identified as malnourished. This highlights the limitation of using BMI, or even weight loss alone as sole measures of nutritional status in patients with cancer. A previous publication by our group showed that MUST screening in this cohort missed large numbers of patients with CT-diagnosable malnutrition.(20) These results are supported by large, international studies where sarcopenia and low muscle attenuation have been demonstrated in patients with BMIs in the obese range(17,27). Moreover, recent work in the C-SCANS cohort of early CRC showed that weight stability can disguise underlying sarcopenia(30). It has also been shown that subtle weight loss far lower the levels traditionally considered ‘significant’, is associated with poor survival(8), quality of life(9), and tolerance to planned anti-cancer treatments(10), and yet, patients with early weight loss are not identified for dietetic referral(14). The present study confirms these

findings, and demonstrates that when all body composition abnormalities are considered together as a phenotype, the majority of cancer patients experience invisible malnutrition.

Majority of Malnutrition Cases Occur in Normal-High BMI Range

Notably, although the prevalence of body composition abnormalities was higher in the underweight, this group accounts for only 9% of the cohort, and so, while the prevalence of the abnormal body composition was lower in those with normal to high BMIs, in absolute terms, more overweight and obese patients presented with sarcopenia, cachexia or low muscle attenuation. In addition to the inability of BMI to evaluate body composition, it was also noted in this study that a significant number of patients in the normal and overweight categories had experienced weight loss which resulted in a change in BMI classification. This is an additional source of concern as the use of BMI categories to classify nutrition risk does not take into account relatively recent, severe weight changes which have resulted in a significant BMI change. As such, simple anthropometric measures such as BMI and weight stability should be interpretated with caution at the individual patient level as these measures are not capable of accurately differentiating between subtle, but clinically significant changes in important body weight compartments. Importantly, while anthropometry is practical for identifying obviously severe cases of malnutrition, normal to high BMI and weight stability alone should not be used to rule out malnutrition. Additionally, these data highlight the importance of improving access to dietetic care for people who do not 'look malnourished', as they may be systematically excluded from referral for dietetic care due to the poor negative predictive power of the most commonly used screening tools(20).

CT Body Composition Analysis Provides Unique Insight Into Nutritional Status

Importantly, the presence of abnormal body composition phenotypes was found in this study to be significantly associated with poor survival, independent of known prognosticators. This suggests that in addition to the validated prognostic tools based on systemic inflammation

(mGPS) and performance status (ECOG), the routine assessment of these 3 body composition parameters using diagnostic CT scans can provide additional valuable information in terms of prognosis. Moreover, the results of this analysis indicate that while inflammation is associated with abnormal body composition, its inclusion in the prognostic model does not fully attenuate the impact of altered body composition on survival.

Functional Status Impaired In Those With The Abnormal Body Composition Phenotype

In this study, the term sarcopenia was used to describe low muscle mass, as this is the term commonly employed in oncology settings, however, it is worth noting that the consensus definition for sarcopenia includes a measure of strength and mass(31,32). Functional assessment was added to this study in the later stages and the median handgrip strength results (n=339) were only marginally above the UK population-based cut-point for low strength for both sexes (27 kg and 16 kg in males and females, respectively)(33) and there was a significantly lower handgrip strength when comparing patients with abnormal versus normal body composition phenotypes, so the low strength criterion appears to be relatively widespread in this cohort from the sub-group who were assessed.

Limitations of the Study

Despite the relatively large sample size, this study is associated with a number of limitations which need to be addressed. This study consisted of a heterogeneous group of patients in terms of cancers sites, stages, clinical conditions, and SACT regimens received. Importantly, head & neck cancers were systematically excluded, despite their obvious nutritional risk(34), as these patients are treated in a different cancer centre. Patients may have been receiving concomitant treatment for co-morbidities and clinical conditions and data on such was not collected (e.g. anti-inflammatory medication), in particular diabetes mellitus, which may impact upon body composition. However, inflammatory status, body composition, functional status and age were adjusted for in multivariate analyses, and patients with serious comorbidities such as heart

failure would have been unfit for SACT, and therefore, not included in this cohort. Measures of food intake and physical activity were not collected during this study, which are important measures when considering patients nutritional status and body composition(35). In addition, we did not document if patients received oral nutritional supplements, enteral or intravenous nutrition, whether they had been seen by a registered dietitian or if they were prescribed any medications that might influence appetite and weight gain. However, given that there was a persistent increase in risk in those with abnormal body composition phenotypes at baseline, without regard to their deterioration or improvement during follow-up, this may highlight the role for early intervention as an important opportunity to prevent the onset of malnutrition, as it is widely acknowledged that established cachexia is resistant to simple nutritional interventions.

Strengths of the Study

Finally, a strength of this study lies in the phenotypic approach to evaluating the prognostic impact of malnutrition in cancer. Typically, even in large cohorts such as this, assessing the survival impact of cachexia, sarcopenia, low muscle attenuation simultaneously is challenging due to high co-variance resulting from diagnostic overlap, but this study attempts to overcome this issue using the novel approach of combining each condition into a binary 'abnormal body composition phenotype'. This allows for all conditions to be assessed in a single model, although it does not assign greater value to any one condition, or to co-occurrence, so severity is not be reflected by the simple measure. Furthermore, despite attempts by the Global Leadership Initiative on Malnutrition (GLIM) to create a uniform set of criteria for diagnosing and staging malnutrition, choices of objective muscle mass cut-points remain unstandardised(36), due in part to the difficulty obtaining large datasets of 'healthy' CT scans for use as reference groups, although some reference datasets utilising machine learning

methods are now available(37). However, in this study, rather than focussing on the individual risk profiles of cachexia, sarcopenia and low muscle attenuation, by demonstrating the prognostic nature of the combined phenotype, this study may provide convincing justification for more widespread uptake of opportunistic CT body composition analysis in order to identify patients exhibiting this 'abnormal body composition phenotype', who may benefit from earlier access to nutritional assessment and intervention.

CONCLUSION

Cancer-associated malnutrition was highly prevalent in this large cohort of patients receiving SACT. Despite only 9% of patients exhibiting a BMI in the underweight range, 73% of patients were found to have at least one of cancer cachexia, sarcopenia or low MA when their CT scans were evaluated. These conditions were present at any given BMI, and overweight and obesity did not preclude their presence. In the face of a global obesity epidemic, a challenge for oncologists and healthcare professionals is evident as patients may not display overt wasting and hence may not necessarily appear malnourished. Moreover, this study shows that the presence of any one of the abnormal body composition phenotypes is independently associated with poor survival, and so, CT-body composition should be considered a value-adding assessment in terms of prognostication.

While the optimal management of cancer-related malnutrition remains unclear, and in the absence of licensed treatments for CC, once weight loss or, body composition abnormalities are identified, prompt referral should occur, and efforts should focus on multimodal interventions targeting the multifaceted nature of the syndrome. Such interventions should include individualised nutritional recommendations/support to promote energy balance and ensure optimal protein intake, decreasing inflammation and hyper metabolic stress with aid of

anti-inflammatory agents (NSAIDs and EPA) and increasing physical activity to stabilize/increase muscle quality and quantity(38).

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REFERENCES

1. Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino JR, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. Vol. 69, Am J Med. 1980. p. 491–7.

2. Bachmann J, Heiligensetzer M, Krakowski-Roosen H, Büchler MW, Friess H, Martignoni ME. Cachexia worsens prognosis in patients with resectable pancreatic cancer. Vol. 12, J Gastrointest Surg. 2008. p. 1193–201.

3. Martin L. Diagnostic criteria for cancer cachexia: data versus dogma. Vol. 19, Curr Opin Clin Nutr Metab Care. 2016. p. 188–98.

4. Galmarini CM. Lessons from Hippocrates: Time to Change the Cancer Paradigm. Int J Chronic Dis. 2020;2020:4715426.

5. Warren S. THE IMMEDIATE CAUSES OF DEATH IN CANCER. Am J Med Sci. 1932 Jan 1;184(5):610–5.

6. Shachar SS, Williams GR, Muss HB, Nishijima TF. Prognostic value of sarcopenia in adults with solid tumours: A meta-analysis and systematic review. Vol. 57, Eur J Cancer. 2016. p. 58–67.

7. Aleixo GFP, Shachar SS, Nyrop KA, Muss HB, Malpica L, Williams GR. Myosteatosis and prognosis in cancer: Systematic review and meta-analysis. Crit Rev Oncol Hematol. 2020;145.

8. Martin L, Senesse P, Gioulbasanis I, Antoun S, Bozzetti F, Deans C, et al. Diagnostic criteria for the classification of cancer-associated weight loss. J Clin Oncol Off J Am Soc Clin Oncol. 2015 Jan 1;33(1):90–9.

9. Daly L, Dolan R, Power D, Ní Bhuachalla É, Sim W, Fallon M, et al. The relationship between the BMI-adjusted weight loss grading system and quality of life in patients with incurable cancer. J Cachexia Sarcopenia Muscle. 2020;11(1):160–8.

10. Shaw C, Starling N, Reich A, Wilkes E, White R, Shepelev J, et al. Modification of systemic anti-cancer therapies and weight loss, a population-level real-world evidence study. Ther Adv Med Oncol. 2020;12:1758835920982805.

11. Sullivan ES, Daly LE, Power DG, Ryan AM. Epidemiology of cancer-related weight loss and sarcopenia in the UK and Ireland: incidence, prevalence, and clinical impact. JCSM Rapid Commun. 2020 Jul;3(2):91–102.

12. Trujillo EB, Claghorn K, Dixon SW, Hill EB, Braun A, Lipinski E, et al. Inadequate Nutrition Coverage in Outpatient Cancer Centers: Results of a National Survey. Vol. 2019, J Oncol. 2019. p. 7462940.

13. Sullivan ES, Rice N, Kingston E, Kelly A, Reynolds JV, Feighan J, et al. A national survey of oncology survivors examining nutrition attitudes, problems and behaviours, and access to dietetic care throughout the cancer journey. Clin Nutr ESPEN. 2021 Feb;41:331–9.

14. Lorton CM, Griffin O, Higgins K, Roulston F, Stewart G, Gough N, et al. Late referral of cancer patients with malnutrition to dietitians: a prospective study of clinical practice. Support Care Cancer. 2020 May 1;28(5):2351–60.

15. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 2011 May;12(5):489–95.

16. Evans WJ, Morley JE, Argilés J, Bales C, Baracos V, Guttridge D, et al. Cachexia: a new definition. Vol. 27, Clin Nutr. 2008. p. 793–9.

17. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor,

independent of body mass index. J Clin Oncol Off J Am Soc Clin Oncol. 2013 Apr 20;31(12):1539–47.

18. Millar C, Reid J, Porter S. Refractory cachexia and truth-telling about terminal prognosis; A qualitative study. Eur J Cancer Care (Engl). 2013 May;22(3):326–33.

19. Martin L, Tom M, Basualdo-Hammond C, Baracos V, Gramlich L. Piloting a training program in computed tomography (CT) skeletal muscle assessment for Registered Dietitians. J Parenter Enter Nutr. n/a(n/a).

20. Ní Bhuachalla ÉB, Daly LE, Power DG, Cushen SJ, MacEneaney P, Ryan AM. Computed tomography diagnosed cachexia and sarcopenia in 725 oncology patients: is nutritional screening capturing hidden malnutrition? J Cachexia Sarcopenia Muscle. 2018;9(2):295–305.

21. Proctor MJ, Morrison DS, Talwar D, Balmer SM, O'Reilly DS, Foulis AK, et al. An inflammation-based prognostic score (mGPS) predicts cancer survival independent of tumour site: a Glasgow Inflammation Outcome Study. Vol. 104, Br J Cancer. 2011. p. 726–34.

22. Azam F, Latif MF, Farooq A, Tirmazy SH, AlShahrani S, Bashir S, et al. Performance Status Assessment by Using ECOG (Eastern Cooperative Oncology Group) Score for Cancer Patients by Oncology Healthcare Professionals. Case Rep Oncol. 2019 Sep 25;12(3):728–36.

23. Mourtzakis M, Prado CMM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab Physiol Appl Nutr Metab. 2008 Oct;33(5):997–1006.

24. Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge MP, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. J Appl Physiol Bethesda Md 1985. 2004 Dec;97(6):2333–8.

25. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. J Appl Physiol. 1985;85(1):115–22.

26. Prado CM, Sawyer MB, Ghosh S, Lieffers JR, Esfandiari N, Antoun S, et al. Central tenet of cancer cachexia therapy: do patients with advanced cancer have exploitable anabolic potential? Vol. 98, Am J Clin Nutr. 2013. p. 1012–9.

27. Prado CMM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol. 2008 Jul;9(7):629–35.

28. Blackburn GL, Bistrian BR, Maini BS, Schlamm HT, Smith MF. Nutritional and metabolic assessment of the hospitalized patient. JPEN J Parenter Enteral Nutr. 1977;1(1):11–22.

29. Hebuterne X, Lemarie E, Michallet M, de Montreuil CB, Schneider SM, Goldwasser F. Prevalence of malnutrition and current use of nutrition support in patients with cancer. Vol. 38, JPEN J Parenter Enteral Nutr. 2014. p. 196–204.

30. Brown JC, Caan BJ, Cespedes Feliciano EM, Xiao J, Weltzien E, Prado CM, et al. Weight stability masks changes in body composition in colorectal cancer: A retrospective cohort study. Am J Clin Nutr. 2021;113(6):1482–9.

31. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019 Jan 1;48(1):16–31.

32. Donini LM, Busetto L, Bischoff SC, Cederholm T, Ballesteros-Pomar MD, Batsis JA, et al. Definition and diagnostic criteria for sarcopenic obesity: ESPEN and EASO consensus statement. Clin Nutr Edinb Scotl. 2022 Feb 22;S0261-5614(21)00523-9.

33. Dodds RM, Syddall HE, Cooper R, Benzeval M, Deary IJ, Dennison EM, et al. Grip Strength across the Life Course: Normative Data from Twelve British Studies. PLOS ONE. 2014 Dec 4;9(12):e113637.

34. Bye A, Sandmael JA, Stene GB, Thorsen L, Balstad TR, Solheim TS, et al. Exercise and Nutrition Interventions in Patients with Head and Neck Cancer during Curative Treatment: A Systematic Review and Meta-Analysis. Nutrients. 2020 Oct 22;12(11):E3233.

35. Martin L, Kubrak C. How much does reduced food intake contribute to cancer-associated weight loss? [Internet]. Curr Opin Support Palliat Care. 2018. Available from: https://www.ncbi.nlm.nih.gov/pubmed/30124527

36. Barazzoni R, Jensen GL, Correia MITD, Gonzalez MC, Higashiguchi T, Shi HP, et al. Guidance for assessment of the muscle mass phenotypic criterion for the Global Leadership Initiative on Malnutrition (GLIM) diagnosis of malnutrition. Clin Nutr. 2022 Jun 1;41(6):1425–33.

37. Magudia K, Bridge CP, Bay CP, Babic A, Fintelmann FJ, Troschel FM, et al. Population-Scale CT-based Body Composition Analysis of a Large Outpatient Population Using Deep Learning to Derive Age-, Sex-, and Race-specific Reference Curves. Radiology. 2021 Feb;298(2):319–29.

38. Prado CM, Purcell SA, Laviano A. Nutrition interventions to treat low muscle mass in cancer. J Cachexia Sarcopenia Muscle. 2020;11(2):366–80.

SUPPLEMENTARY MATERIALS

Table 1B. Baseline characteristics stratified by cancer site

Colorectal (CRC), Oesophageal/Gastric (OG), Genitourinary (GU), Gynaecological (Gynae), Hepatobiliary/Pancreatic (HBP); ECOG, Eastern Cooperative Oncology Group; Systemic Anti-Cancer Therapy (SACT)

	Breast (n=80)	CRC (n=264)	OG (n=146)	GU (n=49)	Gynae (n=54)	HBP (n=94)	Lung (n=119)	Lymphoma (n=95)	Other (n=39)	Total (n=940)
Sex, n(%) (n=940)										
Male	0 (0)	172 (65.2)	112 (76.7)	47 (95.9)	0 (0)	49 (52.1)	75 (63)	52 (54.7)	20 (51.3)	527 (56.1)
Female	80 (100)	92 (34.8)	34 (23.3)	2 (4.1)	54 (100)	45 (47.9)	44 (37)	43 (45.3)	19 (48.7)	413 (43.9)
Treatment intent, n (%)(n=940)										
Palliative	37 (46.3)	129 (48.9)	71 (48.6)	31 (63.3)	40 (74.1)	68 (72.3)	85 (71.4)	38 (40)	31 (79.5)	530 (56.4)
Curative	43 (53.8)	127 (48.1)	73 (50)	17 (34.7)	12 (22.2)	25 (26.6)	33 (27.7)	55 (57.9)	5 (12.8)	390 (41.5)
Not recorded	0 (0)	8 (3)	2 (1.4)	1 (2)	2 (3.7)	1 (1.1)	1 (0.8)	2 (2.1)	3 (7.7)	20 (2.1)
Tumour stage, n (%) (n=882)										
I	3 (4.1)	5 (1.9)	4 (2.7)	5 (10.6)	2 (4)	3 (3.2)	1 (0.9)	6 (10)	1 (3.2)	30 (3.4)
II	18 (24.3)	18 (6.8)	28 (19.2)	4 (8.5)	3 (6)	16 (17.2)	15 (12.8)	10 (16.7)	0 (0)	112 (12.7)
III	13 (17.6)	104 (39.4)	54 (37)	1 (2.1)	4 (8)	8 (8.6)	27 (23.1)	19 (31.7)	1 (3.2)	231 (26.2)
IV	40 (54.1)	137 (51.9)	60 (41.1)	37 (78.7)	41 (82)	66 (71)	74 (63.2)	25 (41.7)	29 (93.5)	509 (57.7)
Metastatic disease, n (%) (n=933)										
Yes	39 (50.6)	138 (52.3)	56 (38.4)	36 (73.5)	41 (78.8)	60 (63.8)	66 (55.5)	20 (21.3)	26 (68.4)	482 (51.7)
ECOG Performance Status, n (%) (n=876)										
0	57 (81.4)	133 (54.1)	68 (47.2)	25 (55.6)	30 (66.7)	39 (41.9)	44 (39.3)	45 (48.4)	10 (35.7)	451 (51.5)
1	9 (12.9)	77 (31.3)	47 (32.6)	13 (28.9)	10 (22.2)	30 (32.3)	41 (36.6)	32 (34.4)	10 (35.7)	269 (30.7)
2	4 (5.7)	31 (12.6)	22 (15.3)	5 (11.1)	5 (11.1)	20 (21.5)	24 (21.4)	11 (11.8)	7 (25)	129 (14.7)
3	0 (0)	5 (2)	7 (4.9)	2 (4.4)	0 (0)	4 (4.3)	3 (2.7)	5 (5.4)	1 (3.6)	27 (3.1)
4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Treatment Plan, n (%) (n=893)										
SACT only	28 (35.9)	74 (29.6)	50 (34.7)	22 (46.8)	24 (51.1)	56 (60.9)	65 (57)	81 (87.1)	17 (60.7)	417 (46.7)
SACT & surgery	28 (35.9)	144 (57.6)	24 (16.7)	19 (40.4)	13 (27.7)	29 (31.5)	22 (19.3)	2 (2.2)	4 (14.3)	285 (31.9)
Chemo-radiotherapy & surgery	22 (28.2)	26 (10.4)	43 (29.9)	2 (4.3)	7 (14.9)	4 (4.3)	6 (5.3)	4 (4.3)	5 (17.9)	119 (13.3)
Definitive chemo-radiotherapy	0 (0)	6 (2.4)	27 (18.8)	4 (8.5)	3 (6.4)	3 (3.3)	21 (18.4)	6 (6.5)	2 (7.1)	72 (8.1)

Table 1C. Baseline characteristics stratified by the presence of abnormal body composition phenotype.

Colorectal (CRC), Oesophageal/Gastric (OG), Genitourinary (GU), Gynaecological (Gynae), Hepatobiliary/Pancreatic (HBP); Gastrointestinal (GI); ECOG, Eastern Cooperative Oncology Group; Systemic Anti-Cancer Therapy (SACT)

	Normal BC (n=250)	Abnormal BC (n=690)	Total (n=940)	*p*-value
Tumour Location, n(%) (n=940)				<0.001
Breast	32 (12.8)	48 (7)	80 (8.5)	0.005
CRC	75 (30)	189 (27.4)	264 (28.1)	>0.05
GO	18 (7.2)	128 (18.6)	146 (15.5)	<0.001
GU	16 (6.4)	33 (4.8)	49 (5.2)	>0.05
Gynae	18 (7.2)	36 (5.2)	54 (5.7)	>0.05
HBP	12 (4.8)	82 (11.9)	94 (10)	0.001
Lung	33 (13.2)	86 (12.5)	119 (12.7)	>0.05
Lymphoma	34 (13.6)	61 (8.8)	95 (10.1)	0.032
Other	12 (4.8)	27 (3.9)	39 (4.1)	>0.05
Simplified Tumour Location, n(%)(n=940)				<0.001
Colorectal	112 (44.8)	205 (29.7)	317 (33.7)	<0.001
Upper GI & HBP	75 (30)	189 (27.4)	264 (28.1)	>0.05
Lung	30 (12)	210 (30.4)	240 (25.5)	<0.001
Other	33 (13.2)	86 (12.5)	119 (12.7)	>0.05
Treatment intent, n (%) (n=940)				0.012
Palliative	122 (48.8)	408 (59.1)	530 (56.4)	0.005
Curative	120 (48)	270 (39.1)	390 (41.5)	0.015
Not recorded	8 (3.2)	12 (1.7)	20 (2.1)	>0.05
Tumour stage, n (%) (n=882)				0.120
I	13 (5.8)	17 (2.6)	30 (3.4)	0.023
II	27 (12)	85 (12.9)	112 (12.7)	>0.05
III	62 (27.6)	169 (25.7)	231 (26.2)	>0.05
IV	123 (54.7)	386 (58.8)	509 (57.7)	>0.05
Metastatic disease, n (%) (n=933)				0.115
Yes	117 (47.4)	365 (53.2)	482 (51.7)	>0.05
ECOG Performance Status, n (%) (n=876)				0.001
0	136 (61.5)	315 (48.1)	451 (51.5)	0.001
1	58 (26.2)	211 (32.2)	269 (30.7)	>0.05
2	26 (11.8)	103 (15.7)	129 (14.7)	>0.05
3	1 (0.5)	26 (4)	27 (3.1)	0.009
4	0 (0)	0 (0)	0 (0)	-
Treatment Plan, n (%) (n=893)				0.364
SACT only	105 (45.7)	312 (47.1)	417 (46.7)	>0.05
SACT & surgery	83 (36.1)	202 (30.5)	285 (31.9)	>0.05
Chemo-radiotherapy & surgery	26 (11.3)	93 (14)	119 (13.3)	>0.05
Definitive chemo-radiotherapy	16 (7)	56 (8.4)	72 (8.1)	>0.05

Table 2B. Anthropometric details including weight loss history stratified by cancer site.

Colorectal (CRC), Oesophageal/Gastric (OG), Genitourinary (GU), Gynaecological (Gynae), Hepatobiliary/Pancreatic (HBP)

	Breast (n=80)	CRC (n=264)	OG (n=146)	GU (n=49)	Gynae (n=54)	HBP (n=94)	Lung (n=119)	Lymphoma (n=95)	Other (n=39)	Total (n=940)
Routine Anthropometry (Median (IQR))										
Height (m) (n=940)	1.65 (1.605 - 1.7)	1.7 (1.65 - 1.77)	1.72 (1.67 - 1.77)	1.77 (1.71 - 1.8)	1.606 (1.56 - 1.65)	1.68 (1.59 - 1.75)	1.7 (1.62 - 1.77)	1.7 (1.62 - 1.79)	1.69 (1.6 - 1.77)	1.7 (1.62 - 1.77)
Weight (kg) (n=940)	72.25 (61.2 - 82.4)	76.1 (66 - 87.41)	74.65 (64 - 85.7)	81.9 (73.7 - 85.9)	66 (57.2 - 74.4)	72.55 (57.2 - 80)	73 (61.3 - 86)	76.2 (62.5 - 86.6)	76.2 (60.3 - 84)	74.4 (63.5 - 85.45)
Body Mass Index (BMI) (kg/m^2) (n=940)	26.941 (23.726 - 29.926)	26.164 (23.438 - 29.193)	25.259 (23.14 - 27.901)	25.772 (24.555 - 29.029)	24.612 (22.377 - 28.453)	25.254 (21.667 - 28.504)	25.59 (21.865 - 28.35)	26.004 (21.914 - 29.035)	25.216 (23.307 - 27.465)	25.772 (22.84 - 28.724)
Pre-Diagnosis Weight (kg) (n=929)	73 (64.9 - 80)	80 (69.9 - 92)	80 (70 - 91.2)	82.6 (74.7 - 91.9)	69.45 (63 - 77)	78 (63.5 - 88.2)	73.5 (62 - 89.8)	79.7 (68 - 88.9)	77 (66 - 88.9)	77.1 (67 - 89.6)
Pre-Diagnosis BMI (kg/m^2) (n=929)	26.695 (24.509 - 30.76)	27.315 (24.382 - 30.255)	27.092 (24.977 - 30.387)	26.965 (24.605 - 30.442)	26.533 (23.795 - 30.273)	27.229 (23.543 - 31.245)	25.9 (22.322 - 29.733)	26.485 (23.519 - 29.743)	26.584 (24.474 - 28.71)	26.874 (24.112 - 30.263)
Body Mass Index Categories, n(%) (n=940)										
Underweight (<20 kg/m^2)	5 (6.3)	11 (4.2)	16 (11)	4 (8.2)	9 (16.7)	15 (16)	13 (10.9)	11 (11.6)	1 (2.6)	85 (9)
Normal (≥20 kg/m^2 - <25 kg/m^2)	22 (27.5)	101 (38.3)	52 (35.6)	15 (30.6)	20 (37)	30 (31.9)	42 (35.3)	29 (30.5)	16 (41)	327 (34.8)
Overweight (≥25 kg/m^2 - <30 kg/m^2)	33 (41.3)	97 (36.7)	60 (41.1)	21 (42.9)	14 (25.9)	34 (36.2)	40 (33.6)	36 (37.9)	15 (38.5)	350 (37.2)
Obese (≥30 kg/m^2)	20 (25)	55 (20.8)	18 (12.3)	9 (18.4)	11 (20.4)	15 (16)	24 (20.2)	19 (20)	7 (17.9)	178 (18.9)
Pre-Diagnosis BMI Categories, n(%) (n=929)										
Underweight (<20 kg/m^2)	1 (1.3)	5 (1.9)	9 (6.2)	2 (4.2)	5 (9.3)	4 (4.3)	7 (6)	6 (6.4)	1 (2.6)	40 (4.3)
Normal (≥20 kg/m^2 - <25 kg/m^2)	21 (27.3)	75 (28.7)	28 (19.2)	11 (22.9)	14 (25.9)	31 (33)	46 (39.7)	29 (30.9)	10 (25.6)	265 (28.5)
Overweight (≥25 kg/m^2 - <30 kg/m^2)	34 (44.2)	111 (42.5)	72 (49.3)	22 (45.8)	21 (38.9)	31 (33)	36 (31)	37 (39.4)	19 (48.7)	383 (41.2)
Obese (≥30 kg/m^2)	21 (27.3)	70 (26.8)	37 (25.3)	13 (27.1)	14 (25.9)	28 (29.8)	27 (23.3)	22 (23.4)	9 (23.1)	241 (25.9)
6 Month Weight Change, n(%) (n=894)										
Weight Gain >2%	24 (32.9)	52 (20.8)	16 (11.3)	10 (21.3)	15 (28.8)	13 (14)	27 (24.3)	16 (18)	4 (10.5)	177 (19.8)
Weight Stable	26 (35.6)	72 (28.8)	33 (23.4)	15 (31.9)	13 (25)	16 (17.2)	30 (27)	36 (40.4)	15 (39.5)	256 (28.6)
Weight Loss 2-4.9%	12 (16.4)	46 (18.4)	18 (12.8)	9 (19.1)	2 (3.8)	15 (16.1)	24 (21.6)	12 (13.5)	6 (15.8)	144 (16.1)
Weight Loss 5-9.9%	6 (8.2)	51 (20.4)	32 (22.7)	8 (17)	10 (19.2)	24 (25.8)	16 (14.4)	11 (12.4)	8 (21.1)	166 (18.6)
Weight Loss >10%	5 (6.8)	29 (11.6)	42 (29.8)	5 (10.6)	12 (23.1)	25 (26.9)	14 (12.6)	14 (15.7)	5 (13.2)	151 (16.9)
Martin's Weight Loss Grading System (WLGS), n(%) (n=896)										
0	13 (17.8)	39 (15.6)	22 (15.4)	9 (19.1)	6 (11.5)	10 (10.8)	14 (12.6)	18 (20.2)	8 (21.1)	139 (15.5)
1	10 (13.7)	39 (15.6)	9 (6.3)	5 (10.6)	2 (3.8)	8 (8.6)	18 (16.2)	11 (12.4)	4 (10.5)	106 (11.8)
2	5 (6.8)	40 (16)	25 (17.5)	8 (17)	6 (11.5)	18 (19.4)	18 (16.2)	6 (6.7)	6 (15.8)	132 (14.7)
3	6 (8.2)	47 (18.8)	41 (28.7)	3 (6.4)	9 (17.3)	18 (19.4)	13 (11.7)	14 (15.7)	8 (21.1)	159 (17.7)
4	5 (6.8)	15 (6)	23 (16.1)	6 (12.8)	10 (19.2)	23 (24.7)	12 (10.8)	10 (11.2)	2 (5.3)	106 (11.8)
Gain	34 (46.6)	70 (28)	23 (16.1)	16 (34)	19 (36.5)	16 (17.2)	36 (32.4)	30 (33.7)	10 (26.3)	254 (28.3)

Table 2C. Anthropometric details including weight loss history stratified by metastatic status.

	Non-Metastatic, (n=451)	Metastatic, (n=482)	Total, (n=933)	*p*-value
Routine Anthropometry (Median (IQR))				
Height (m) (n=933)	1.7 (1.62 - 1.77)	1.7 (1.62 - 1.77)	1.7 (1.62 - 1.77)	0.403
Weight (kg) (n=933)	75 (64.5 - 86.6)	73.75 (62.2 - 84.4)	74.4 (63.5 - 85.7)	0.032
Body Mass Index (BMI) (kg/m^2) (n=933)	26.101 (23.322 - 28.934)	25.225 (22.583 - 28.529)	25.772 (22.84 - 28.721)	0.024
Pre-Diagnosis Weight (kg) (n=922)	78 (69.9 - 90)	76.2 (65.8 - 89.6)	77 (66.8 - 89.8)	0.221
Pre-Diagnosis BMI (kg/m^2) (n=922)	26.971 (24.323 - 30.093)	26.775 (23.655 - 30.263)	26.883 (24.074 - 30.255)	0.297
Body Mass Index Categories, n(%) (n=933)				0.013
Underweight (<20 kg/m^2)	33 (7.3)	52 (10.8)	85 (9.1)	>0.05
Normal (≥20 kg/m^2 - <25 kg/m^2)	142 (31.5)	183 (38)	325 (34.8)	0.038
Overweight (≥25 kg/m^2 - <30 kg/m^2)	188 (41.7)	159 (33)	347 (37.2)	0.006
Obese (≥30 kg/m^2)	88 (19.5)	88 (18.3)	176 (18.9)	>0.05
Pre-Diagnosis BMI Categories, n(%) (n=922)				0.280
Underweight (<20 kg/m^2)	17 (3.8)	23 (4.8)	40 (4.3)	>0.05
Normal (≥20 kg/m^2 - <25 kg/m^2)	118 (26.4)	145 (30.5)	263 (28.5)	>0.05
Overweight (≥25 kg/m^2 - <30 kg/m^2)	198 (44.3)	183 (38.5)	381 (41.3)	>0.05
Obese (≥30 kg/m^2)	114 (25.5)	124 (26.1)	238 (25.8)	>0.05
6 Month Weight Change, n(%) (n=887)				0.014
Weight Gain >2%	88 (20.4)	86 (18.9)	174 (19.6)	>0.05
Weight Stable	135 (31.3)	119 (26.1)	254 (28.6)	>0.05
Weight Loss 2-4.9%	64 (14.8)	80 (17.5)	144 (16.2)	>0.05
Weight Loss 5-9.9%	88 (20.4)	77 (16.9)	165 (18.6)	>0.05
Weight Loss >10%	56 (13)	94 (20.6)	150 (16.9)	0.002
Martin's Weight Loss Grading System (WLGS), n(%) (n=889)				0.157
0	69 (16)	69 (15.1)	138 (15.5)	>0.05
1	51 (11.8)	55 (12)	106 (11.9)	>0.05
2	61 (14.1)	71 (15.5)	132 (14.8)	>0.05
3	76 (17.6)	82 (17.9)	158 (17.8)	>0.05
4	40 (9.3)	65 (14.2)	105 (11.8)	0.022
Gain	135 (31.3)	115 (25.2)	250 (28.1)	0.044

Table 2D. Anthropometric details including weight loss history stratified by the presence of abnormal body composition (BC) phenotype.

	Normal BC (n=250)	Abnormal BC (n=690)	Total (n=940)	*p*-value
Routine Anthropometry (Median (IQR))				
Height (m) (n=940)	1.7 (1.62 - 1.75)	1.7 (1.62 - 1.77)	1.7 (1.62 - 1.77)	0.289
Weight (kg) (n=940)	78 (70.2 - 88.9)	72.55 (61.8 - 84)	74.4 (63.5 - 85.45)	<0.001
Body Mass Index (BMI) (kg/m^2) (n=940)	27.231 (24.91 - 30.367)	24.934 (22.123 - 28.056)	25.772 (22.84 - 28.724)	<0.001
Pre-Diagnosis Weight (kg) (n=929)	78.15 (69.95 - 91.4)	77 (66.2 - 89)	77.1 (67 - 89.6)	0.112
Pre-Diagnosis BMI (kg/m^2) (n=929)	27.242 (24.843 - 30.761)	26.673 (23.723 - 29.762)	26.874 (24.112 - 30.263)	0.008
Body Mass Index Categories, n(%) (n=940)				<0.001
Underweight (<20 kg/m^2)	4 (1.6)	81 (11.7)	85 (9)	<0.001
Normal (≥20 kg/m^2 - <25 kg/m^2)	59 (23.6)	268 (38.8)	327 (34.8)	<0.001
Overweight (≥25 kg/m^2 - <30 kg/m^2)	118 (47.2)	232 (33.6)	350 (37.2)	<0.001
Obese (≥30 kg/m^2)	69 (27.6)	109 (15.8)	178 (18.9)	<0.001
Pre-Diagnosis BMI Categories, n(%) (n=929)				0.031
Underweight (<20 kg/m^2)	6 (2.5)	34 (5)	40 (4.3)	>0.05
Normal (≥20 kg/m^2 - <25 kg/m^2)	59 (24.2)	206 (30.1)	265 (28.5)	>0.05
Overweight (≥25 kg/m^2 - <30 kg/m^2)	102 (41.8)	281 (41)	383 (41.2)	>0.05
Obese (≥30 kg/m^2)	77 (31.6)	164 (23.9)	241 (25.9)	0.020
6 Month Weight Change, n(%) (n=894)				<0.001
Weight Gain >2%	80 (35.2)	97 (14.5)	177 (19.8)	<0.001
Weight Stable	103 (45.4)	153 (22.9)	256 (28.6)	<0.001
Weight Loss 2-4.9%	44 (19.4)	100 (15)	144 (16.1)	>0.05
Weight Loss 5-9.9%	0 (0)	166 (24.9)	166 (18.6)	-
Weight Loss >10%	0 (0)	151 (22.6)	151 (16.9)	-
Martin's Weight Loss Grading System (WLGS), n(%) (n=896)				<0.001
0	59 (26)	80 (12)	139 (15.5)	<0.001
1	36 (15.9)	70 (10.5)	106 (11.8)	0.030
2	15 (6.6)	117 (17.5)	132 (14.7)	<0.001
3	0 (0)	159 (23.8)	159 (17.7)	-
4	0 (0)	106 (15.8)	106 (11.8)	-
Gain	117 (51.5)	137 (20.5)	254 (28.3)	<0.001

Table 3B. Body Composition, inflammatory and functional status parameters stratified by cancer site.

Colorectal (CRC), Oesophageal/Gastric (OG), Genitourinary (GU), Gynaecological (Gynae), Hepatobiliary/Pancreatic (HBP)

	Breast (n=80)	CRC (n=264)	OG (n=146)	GU (n=49)	Gynae (n=54)	HBP (n=94)	Lung (n=119)	Lymphoma (n=95)	Other (n=39)	Total (n=940)
Age at recruitment (Median (IQR))										
Age (years) (n=940)	52.079 (42.527 - 60.293)	64.182 (56.624 - 70.96)	65.684 (59.567 - 73.152)	67.269 (51.677 - 73.186)	61.73 (50.295 - 66.146)	63.046 (53.51 - 70.422)	65.572 (59.094 - 70.582)	64.925 (53.344 - 72.356)	52.079 (42.527 - 60.293)	63.792 (55.159 – 70.675)
Functional Status (Median (IQR))										
Handgrip Strength (kg) (n=339)	19.7 (16.8 - 24)	26.4 (19.35 - 33.85)	27.1 (21.5 - 35.7)	23.4 (19.5 - 35.7)	20.4 (15.9 - 24.4)	21.7 (17.5 - 26.9)	25.2 (17.7 - 32.4)	25.35 (18 - 34.2)	24.8 (17.5 - 32.2)	24.3 (18.4 - 32.2)
Inflammatory Markers (Median (IQR))										
CRP (mg/L) (n=633)	5 (4.2 - 19)	6 (2 - 22)	5 (2 - 15)	4 (2 - 25)	31.45 (9.2 - 71.5)	9.5 (3 - 26)	12.05 (5 - 40.5)	6 (3 - 20)	8.5 (1 - 43)	7 (3 - 26)
Albumin (g/L) (n=752)	41 (38.5 - 44)	35 (32 - 37)	34 (31 - 36)	35 (33 - 38)	35.5 (32 - 40)	33 (29 - 35)	35 (31 - 38)	36 (33.5 - 39)	36 (31.5 - 39.5)	35 (32 - 38)
mGPS, n(%) (n=596)										
0 (CRP <10 mg/L)	6 (54.5)	121 (66.5)	89 (68.5)	24 (64.9)	4 (26.7)	40 (50.6)	34 (46.6)	33 (63.5)	9 (52.9)	360 (60.4)
1 (CRP ≥10 mg/L & Albumin ≥35 g/L)	3 (27.3)	21 (11.5)	8 (6.2)	4 (10.8)	3 (20)	8 (10.1)	13 (17.8)	7 (13.5)	2 (11.8)	69 (11.6)
2 (CRP ≥10 mg/L & Albumin <35 g/L)	2 (18.2)	40 (22)	33 (25.4)	9 (24.3)	8 (53.3)	31 (39.2)	26 (35.6)	12 (23.1)	6 (35.3)	167 (28)
Muscle Parameters (Median (IQR))										
Skeletal muscle area (cm^2) (n=940)	112.859 (105.505 - 121.56)	142.593 (113.754 - 167.869)	149.567 (124.049 - 171.597)	152.527 (139.051 - 167.872)	112.537 (97.804 - 120.448)	128.209 (104.779 - 161.651)	137.854 (110.654 - 169.366)	138.898 (110.447 - 169.214)	140.237 (108.137 - 167.331)	134.15 (109.625 - 164.767)
Skeletal muscle index (cm^2/m^2) (n=940)	42.169 (38.417 - 45.922)	48.18 (41.562 - 55.585)	49.225 (41.503 - 56.596)	48.924 (43.965 - 54.437)	42.574 (37.229 - 47.05)	46.546 (39.082 - 53.603)	46.058 (41.357 - 56.658)	46.912 (41.45 - 54.432)	48.893 (42.319 - 51.668)	46.481 (40.917 - 54.208)
Estimated SMM (kg) (n=940)	18.81 (17.584 - 20.26)	23.765 (18.959 - 27.978)	24.928 (20.675 - 28.6)	25.421 (23.175 - 27.979)	18.756 (16.301 - 20.075)	21.368 (17.463 - 26.942)	22.976 (18.442 - 28.228)	23.15 (18.408 - 28.202)	23.373 (18.023 - 27.889)	22.358 (18.271 - 27.461)
Muscle attenuation (HU) (n=872)	40.863 (34.071 - 48.571)	37.188 (32.127 - 42.535)	36.806 (31.017 - 41.096)	37.643 (32.175 - 42.71)	35.717 (27.158 - 42.149)	37.493 (31.196 - 43.216)	37.104 (30.781 - 41.226)	39.524 (33.456 - 46.087)	40.603 (35.073 - 46.33)	37.715 (31.727 - 43.202)
Fat Parameters (Median (IQR))										
Adipose tissue area (cm^2) (n=870)	279.89 (174.163 - 420.629)	347.856 (240.962 - 488.779)	314.307 (201.49 - 434.764)	387.448 (330.407 - 499.354)	297.761 (183.233 - 409.568)	289.262 (182.296 - 409.984)	326.638 (197.654 - 452.38)	323.813 (193.359 - 445.207)	338.488 (201.84 - 432.835)	328.61 (203.603 - 456.069)
Adipose tissue index (cm^2/m^2) (n=870)	105.857 (63.862 - 146.85)	121.778 (84.462 - 169.647)	108.381 (68.108 - 144.851)	138.691 (106.726 - 159.39)	120.977 (67.303 - 156.061)	103.423 (62.882 - 137.096)	111.654 (63.589 - 152.931)	102.522 (70.763 - 157.368)	111.582 (71.916 - 148.807)	112.826 (73.389 - 153.91)
Estimated FM (kg) (n=870)	19.04 (11.848 - 28.614)	23.664 (16.392 - 33.25)	21.381 (13.707 - 29.576)	26.357 (22.477 - 33.97)	20.256 (12.465 - 27.862)	19.678 (12.401 - 27.89)	22.22 (13.446 - 30.774)	22.028 (13.154 - 30.286)	23.026 (13.731 - 29.445)	22.354 (13.851 - 31.025)
Body Composition Phenotypes, n(%)										
Sarcopenia (n=940)	34 (42.5)	98 (37.1)	63 (43.2)	20 (40.8)	18 (33.3)	42 (44.7)	46 (38.7)	36 (37.9)	13 (33.3)	370 (39.4)
Sarcopenic Obesity (n=940)	6 (7.5)	12 (4.5)	5 (3.4)	5 (10.2)	0 (0)	6 (6.4)	3 (2.5)	3 (3.2)	1 (2.6)	41 (4.4)
Cachexia (n=940)	16 (20)	101 (38.3)	90 (61.6)	17 (34.7)	23 (42.6)	59 (62.8)	41 (34.5)	32 (33.7)	16 (41)	395 (42)
Low muscle attenuation (n=872)	21 (26.6)	116 (44.8)	66 (51.6)	21 (46.7)	26 (52)	44 (47.8)	57 (53.8)	28 (35.4)	12 (35.3)	391 (44.8)
Low muscle attenuation & Sarcopenia (n=918)	9 (11.4)	63 (24)	30 (21.3)	12 (26.1)	10 (18.9)	21 (22.3)	26 (22.8)	15 (16.7)	4 (10.5)	190 (20.7)
Any of 3 (n=940)	48 (60)	189 (71.6)	128 (87.7)	33 (67.3)	36 (66.7)	82 (87.2)	86 (72.3)	61 (64.2)	27 (69.2)	690 (73.4)

Table 3C. Body Composition, inflammatory and functional status parameters stratified by metastatic status.

	Non-Metastatic, (n=451)	Metastatic, (n=482)	Total, (n=933)	*p*-value
Age at recruitment (Median (IQR))				
Age (years) (n=933)	64.893 (56.033 – 70.941)	63.116 (54.372 – 70.415)	63.817 (55.220 – 70.664)	0.229
Functional Status (Median (IQR))				
Handgrip Strength (kg) (n=337)	24.6 (19.6 - 32)	24 (17.4 - 32.2)	24.4 (18.5 - 32.2)	0.297
Inflammatory Markers (Median (IQR))				
CRP (mg/L) (n=632)	5 (2 - 15.4)	10 (4 - 35)	7 (3 - 26)	<0.001
Albumin (g/L) (n=749)	35 (33 - 38)	34 (31 - 37)	35 (32 - 38)	<0.001
mGPS, n(%) (n=595)				<0.001
0 (CRP <10 mg/L)	155 (51.8)	205 (69.3)	360 (60.5)	<0.001
1 (CRP ≥10 mg/L & Albumin ≥35 g/L)	36 (12)	33 (11.1)	69 (11.6)	>0.05
2 (CRP ≥10 mg/L & Albumin <35 g/L)	108 (36.1)	58 (19.6)	166 (27.9)	<0.001
Muscle Parameters (Median (IQR))				
Skeletal muscle area (cm^2) (n=933)	139.044 (112.545 - 167.532)	130.202 (108.078 - 159.644)	134.09 (109.59 - 164.767)	0.002
Skeletal muscle index (cm^2/m^2) (n=933)	47.665 (41.863 - 54.713)	45.601 (39.849 - 53.238)	46.47 (40.924 - 54.224)	<0.001
Estimated SMM (kg) (n=933)	23.174 (18.758 - 27.922)	21.7 (18.013 - 26.607)	22.348 (18.265 - 27.461)	0.002
Muscle attenuation (HU) (n=865)	38.077 (31.35 - 43.579)	37.466 (32.029 - 42.768)	37.697 (31.734 - 43.211)	0.591
Fat Parameters (Median (IQR))				
Adipose tissue area (cm^2) (n=867)	339.406 (215.201 - 468.681)	317.462 (194.166 - 441.472)	328.832 (203.603 - 456.327)	0.144
Adipose tissue index (cm^2/m^2) (n=867)	114.896 (77.565 - 154.41)	111.517 (68.981 - 153.221)	112.83 (73.389 - 154.219)	0.223
Estimated FM (kg) (n=867)	23.089 (14.639 - 31.883)	21.596 (13.209 - 30.032)	22.369 (13.851 - 31.043)	0.144
Body Composition Phenotypes, n(%)				
Sarcopenia (n=933)	166 (36.8)	202 (41.9)	368 (39.4)	0.111
Sarcopenic Obesity (n=933)	16 (3.5)	25 (5.2)	41 (4.4)	0.222
Cachexia (n=933)	176 (39)	217 (45)	393 (42.1)	0.064
Low muscle attenuation (n=865)	178 (43.3)	209 (46)	387 (44.7)	0.421
Low muscle attenuation & Sarcopenia (n=911)	80 (18.3)	108 (22.8)	188 (20.6)	0.095
Any of 3 (n=933)	321 (71.2)	365 (75.7)	686 (73.5)	0.115

Table 3D. Body Composition, inflammatory and functional status parameters stratified by the presence of abnormal body composition (BC) phenotype.

	Normal BC (n=250)	Abnormal BC (n=690)	Total (n=940)	*p*-value
Age at recruitment (Median (IQR))				
Age (years) (n=940)	59.474 (50.716 – 67.277)	65.372 (56.860 – 71.342)	63.792 (55.159 – 70.675)	<0.001
Functional Status (Median (IQR))				
Handgrip Strength (kg) (n=339)	27.8 (21.8 - 35)	22.85 (17.6 - 29.25)	24.3 (18.4 - 32.2)	<0.001
Inflammatory Markers (Median (IQR))				
CRP (mg/L) (n=633)	5.55 (3 - 20)	7 (3 - 27)	7 (3 - 26)	0.161
Albumin (g/L) (n=752)	37 (34 - 39)	34 (31 - 37)	35 (32 - 38)	<0.001
mGPS, n(%) (n=596)				0.007
0 (CRP <10 mg/L)	90 (66.7)	270 (58.6)	360 (60.4)	>0.05
1 (CRP ≥10 mg/L & Albumin ≥35 g/L)	21 (15.6)	48 (10.4)	69 (11.6)	>0.05
2 (CRP ≥10 mg/L & Albumin <35 g/L)	24 (17.8)	143 (31)	167 (28)	0.003
Muscle Parameters (Median (IQR))				
Skeletal muscle area (cm^2) (n=940)	155.337 (123.131 - 179.404)	129.014 (106.902 - 157.557)	134.15 (109.625 - 164.767)	<0.001
Skeletal muscle index (cm^2/m^2) (n=940)	53.632 (45.008 - 59.299)	44.979 (39.082 - 51.417)	46.481 (40.917 - 54.208)	<0.001
Estimated SMM (kg) (n=940)	25.89 (20.522 - 29.901)	21.502 (17.817 - 26.26)	22.358 (18.271 - 27.461)	<0.001
Muscle attenuation (HU) (n=872)	42.837 (38.077 - 46.558)	35.434 (29.992 - 41.089)	37.715 (31.727 - 43.202)	<0.001
Fat Parameters (Median (IQR))				
Adipose tissue area (cm^2) (n=870)	361.804 (232.026 - 479.19)	316.852 (195.601 - 443.314)	328.61 (203.603 - 456.069)	0.003
Adipose tissue index (cm^2/m^2) (n=870)	124.492 (83.218 - 173.226)	108.263 (69.239 - 148.286)	112.826 (73.389 - 153.91)	<0.001
Estimated FM (kg) (n=870)	24.613 (15.784 - 32.598)	21.555 (13.306 - 30.157)	22.354 (13.851 - 31.025)	0.003
Body Composition Phenotypes, n(%)				
Sarcopenia (n=940)	0 (0)	370 (53.6)	370 (39.4)	<0.001
Sarcopenic Obesity (n=940)	0 (0)	41 (5.9)	41 (4.4)	<0.001
Cachexia (n=940)	0 (0)	395 (57.2)	395 (42)	<0.001
Low muscle attenuation (n=872)	0 (0)	391 (60.2)	391 (44.8)	<0.001
Low muscle attenuation & Sarcopenia (n=918)	0 (0)	190 (28.4)	190 (20.7)	<0.001
Any of 3 (n=940)	0 (0)	690 (100)	690 (73.4)	<0.001