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Aoife M Ryan PhD RD , Carla M. Prado PhD RD , Erin S. Sullivan BSc RD , Derek G. Power MD , Louise E. Daly PhD BSc

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Impact of weight loss and sarcopenia on response to chemotherapy, quality of life and survival.

Aoife M Ryan PhD RD[1,2], Carla M Prado PhD RD[3], Erin S Sullivan BSc RD[1,2], Derek G Power MD[4], Louise E Daly PhD BSc[1,2].

[1]School of Food and Nutritional Sciences, College of Science, Engineering and Food Science, University College Cork, Ireland;

[2]Cork Cancer Research Centre, University College Cork, Cork, Ireland;

[3]Department of Agricultural, Food and Nutritional Science, University of Alberta, 4-002 Li Ka Shing Centre, Edmonton, Alberta T6 G 2P5, Canada.

[4]Department of Medical Oncology, Mercy and Cork University Hospitals, Cork, Ireland.

Corresponding author:

Dr. Aoife Ryan PhD RD

Senior Lecturer,

School of Food & Nutritional Sciences

College of Science, Engineering & Food Science==

University College Cork

Cork

Ireland

Email: a.ryan@ucc.ie

Ph: +353 21 4902406

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Abstract: The prevalence of malnutrition in patients with cancer has frequently been shown to be one of the highest of all hospital patient groups. Weight loss is a frequent manifestation of malnutrition in patients with cancer. Several large-scale studies over the last 35 years have reported that involuntary weight loss affects 50-80% of these patients with the degree of weight loss dependent on tumour site, type and stage of disease. This review will focus on the consequences of malnutrition, weight loss and muscle wasting in relation to chemotherapy tolerance, post-operative complications, quality of life and survival in oncology patients.

The prognostic impact of weight loss on overall survival has long been recognised with recent data suggesting losses as little as 2.4% predicts survival independent of disease, site, stage or performance score. Recently the use of gold-standard methods of body composition assessment, including computed tomography, have led to an increased understanding of the importance of muscle abnormalities, such as low muscle mass (sarcopenia), and more recently low muscle attenuation, as important prognostic indicators of unfavourable outcomes in patients with cancer. Muscle abnormalities are highly prevalent (ranging from 10-90%, depending on cancer site and the diagnostic criteria used). Both low muscle mass and low muscle attenuation have been associated with poorer tolerance to chemotherapy; increased risk of postoperative complications; significant deterioration in a patients' performance status, and poorer psychological well-being, overall quality of life, and survival.

The prevalence of malnutrition in patients with cancer has frequently been shown to be one of the highest of all patient groups[1; 2; 3]. Weight loss is a frequent manifestation of malnutrition and is an important criterion included in several malnutrition screening tools commonly used in clinical settings. Several large scale studies over the last 35 years have reported that involuntary weight loss affects 50-80% of patients with cancer with the degree of weight loss dependent on tumour site, type and stage of disease[4; 5; 6].

The prognostic impact of weight loss on overall survival has long been recognised with recent data suggesting ongoing weight loss of more than 2.4% predicts survival, independent of disease site, stage or performance score[6]. In addition to the adverse impact on survival, weight loss has been associated with severe chemotherapy-related toxicity[7; 8; 9];and leads to a significant deterioration in a patients' performance status, psychological well-being and overall quality of life[10].

Causes of nutritional deterioration in cancer

Nutritional deterioration has unfortunately become an accepted part of the pathogenesis of cancer and its treatment[11]. Changes in nutrition status can occur at any point in the timeline of a cancer diagnosis, treatment, or support. The degree of malnutrition that occurs is affected by cancer type, stage and therapy modality; however, the etiology of cancer-induced weight loss and malnutrition is both multifactorial and complex. The form of malnutrition that occurs in malignancy is particularly challenging to address as it is not driven by simple starvation but occurs secondary to a negative energy balance caused by the detrimental combination of reduced oral intake and metabolic derangements unique to cancer[12; 13].

Cancer-associated malnutrition can occur as a result of poor oral intake, mechanical or physiological changes to the gut, side effects of treatment, or metabolic abnormalities caused by the tumour. Both the quantity and the quality of dietary intake can be significantly altered due any one of a number of factors including: dysphagia, nausea, changes in taste and smell, pain, early satiety or fatigue. In addition to this, the presence of cancer in the body causes a variety of metabolic and endocrine changes (such as inflammation, anabolic resistance, proteolysis, lipolysis and futile cycling) induced by the tumour and activated immune cells. Complex interactions between inflammation (pro-

inflammatory cytokines), neuro-hormonal changes, and potential proteolytic and lipolytic factors produced by the host and the tumour, fuel weight loss and loss of lean mass[13].

Weight loss and changes in body composition following a cancer diagnosis

Involuntary weight loss is a hallmark feature of cancer-associated malnutrition and can lead to cancer cachexia; a multifactorial syndrome characterised by the ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutrition support[14]. It is a condition characterised by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism[14]. Studies dating back over the past 35 years have reported that moderate-to-severe weight loss is present in 30-70% of cancer patients [2; 4; 5; 6; 11]. In the largest study to-date of 8,160 patients with locally advanced or metastatic disease, 73% experienced involuntary weight loss[6]. Table 1 summarises the prevalence of >5% weight loss in six months (a key component of the diagnostic criteria of cancer cachexia[14]) according to tumour site in the scientific literature. Weight loss has consistently been shown to be most frequent in patients with cancers in the upper gut and lung[15; 16; 17; 18; 19].

Table 1. Prevalence of patients with >5% weight loss in less than 6 months according to primary tumor location in the scientific literature.

Primary Cancer	Percentage with >5% weight loss in 6 months.
Pancreatic [15; 16]	41-53%
Colorectal [20; 21; 22]	32-48%
Gastric[23; 24]	42-75%
Oesophageal[25]	33%
Lung[22; 26]	44-49%
Breast[22]	24%

Despite the fact that the majority of patients present with involuntary weight loss at the time of diagnosis[6], in the era of obesity, patients may not appear malnourished and many in fact are well-nourished according to international standards[27]. Recent studies have reported that between 40-60% of patients with cancer are overweight or obese (BMI > 25kg/m^2) even in the setting of metastatic disease[6; 28; 29; 30; 31]. In a recent pooled analysis of 22 randomised therapeutic treatment trials including 11,724 patients with cancer, 67%

were shown to be overweight or obese at the time of enrolment (i.e. cancer diagnosis)[32]. However, the simple measure of body mass index (BMI) or percentage weight loss does not capture abnormal body composition, including muscle mass[27]. The most clinically relevant phenotypic feature of cancer cachexia is muscle loss and identifying those with low muscle mass can becomes a huge challenge in patients with overweight or obesity [11].

Although low muscle mass is a symptom commonly associated with cancer, it is important to note that cancer is a disease associated with aging, therefore the aetiology of muscle loss in these patients can be two-fold. First resulting from the age-related decline in muscle mass and second due to cytokine-mediated degradation of muscle and adipose depots, hypermetabolism and anorexia associated with cancer cachexia[13]. As such, distinguishing the exact cause of muscle loss can be difficult.

Muscle mass

Advancements in image-based technologies including computed tomography (CT) that allows the precise quantification of both muscle and adipose tissue has led to a large volume of research which has increased our understanding of the importance of abnormal body composition phenotypes, such as low muscle mass (sarcopenia), and more recently low muscle attenuation (MA) as important prognostic indicators of unfavourable outcomes in patients with cancer[6; 33; 34; 35]. Reduced skeletal muscle attenuation (radiodensity) is indicative of intramuscular adipose tissue infiltration and therefore poor 'quality' skeletal muscle[36].

Low muscle mass is now known to relate to asthenia, fatigue, impaired physical function, increased chemotherapy toxicity, impaired quality of life (QoL) and reduced survival[6; 10; 27; 37]. Recent studies have shown that cancer, and its treatment, exacerbate muscle loss and that patients continually lose muscle mass while on treatment[35; 38; 39]. While healthy adults over the age of forty have been shown to lose muscle at a rate of 1-1.4% per year,[40] patients with cancer have been shown to have a 24-fold higher rate of muscle loss than that observed in health aging adults[20; 38]. In studies examining the rate of muscle loss per 100 days, rates of 3.9% have been reported in foregut cancer[38], 3.1% in pancreatic cancer[41] 3.3% in metastatic melanoma[35] and 5.2% in ovarian cancer[39].

Prevalence of cancer cachexia and sarcopenia in oncology

The prevalence of cancer cachexia and low muscle mass can vary widely depending on the method of assessment and diagnostic criteria used[36]. From the literature, it can be estimated that the prevalence of cancer cachexia (based on past 6 months weight loss >5% as per latest consensus definition[14]) can vary between 24-75%% depending on tumor site (table 1), and between 38-70% of patients are considered to have low muscle mass (i.e. sarcopenia, based on 3 of the most commonly used diagnostic criteria). The prevalence of low muscle mass is highest in lung (median 70%, range 47-79%)[42; 43; 44; 45] and pancreatic cancer (median 56%, range 44-89%)[16; 41; 46; 47; 48; 49; 50; 51; 52] however it is noteworthy that the majority of studies report a prevalence of above 40% at most other sites in the body (see table 2).

Table 2. Prevalence of sarcopenia in patients with cancer according to the primary tumor location in the literature (all stages)

Primary Cancer	Stage	% with sarcopenia, median (range)
Colorectal	Stage I-IV [20; 34; 53; 54; 55; 56; 57; 58; 59; 60; 61; 62; 63; 64; 65; 66; 67; 68; 69]	49% (20-80%)
Esophagus	Stage I-IV [70; 71; 72; 73; 74; 75; 76; 77; 78; 79; 80; 81]	53% (16-75%)
Gastric	Stage I-IV [82; 83; 84; 85; 86; 87]	47% (23-70%)
Lung	Stage I-IV [42; 43; 44; 45]	70% (47-79%)
Kidney	Stage I-IV [88; 89; 90; 91; 92; 93; 94; 95]	53% (29-90%)
Pancreatic	Stage I-IV [16; 41; 46; 47; 48; 49; 50; 51; 52]	56% (44-89%)
Liver	Stage I-IV [96; 97; 98; 99; 100]	54% (28-76%)
Breast	Stage I-IV [101; 102; 103; 104; 105; 106; 107]	38% (14-67%)
Ovarian	Stage I-IV [39; 108; 109]	47% (45-50%)
Melanoma	Stage I-IV[35; 110]	44% (24-63%)
Bladder	Stage I-IV [111; 112; 113; 114; 115]	48% (33-69%)
Prostate	Stage I-IV [116; 117]	52% (47-56%)
Head & Neck	Stage I-IV[118]	64%
Lymphoma	Stage I-IV[119; 120; 121]	51% (47-55%)
Mixed	Stage I-IV [29; 38; 122; 123; 124]	41% (15-47%)

Prevalence of sarcopenia defined using three of the most common definitions for defining low muscle mass is displayed in table 2. These definitions are as follows;

- Prado *et al.* (2008)[122]: Skeletal muscle index (SMI)<52.4 cm^2/m^2 in men and <38.5 cm^2/m^2 in women
- Martin *et al.* (2013)[29]: SMI <43.0 cm^2/m^2 in men with a BMI <25 kg/m^2 and <53.0 cm^2/m^2 in men with a BMI >25 kg/m^2 and SMI <41.0 cm^2/m^2 in women.
- Baumgartner *et al.* (1998)[125] converted DXA cut points by Mourtzakis *et al*. (2008)[126] as SMI <55.4 cm^2/m^2 in men and <38.9 cm^2/m^2 in women

The rates of low muscle mass seen in cancer populations are of huge public health importance, given that cancer cachexia and sarcopenia have been reported to be unequivocally associated with negative clinical outcomes in patients with cancer including poorer tolerance to anti-cancer treatment, poorer overall quality of life, increased risk of post-operative complications and poorer overall survival[6; 10; 36; 37].

Impact of malnutrition on tolerance to systemic chemotherapy

Chemotherapy can often be associated with severe toxicity that can result in dose delays, dose reductions and treatment termination, referred to as dose limiting toxicities (DLT). Severe toxic events can result in hospitalisations and can even be life threatening. Recent evidence suggests that variability in body composition of patients with cancer may be a source of disparities in the metabolism of cytotoxic agents resulting in increased toxicity[61; 62; 63].

To date, in excess of 40 studies have examined the relationship between low lean mass (sarcopenia) and the prevalence of dose limiting toxicity in patients with cancer (see summary of studies in table 3). The relationship between low lean mass and increased toxicity to chemotherapy has been shown to be true even in both early and late stage disease irrespective of the cancer site and type of systemic chemotherapy (cytotoxic single agents, regimens, targeted agents and immunotherapies)[75; 82; 106; 122]. Although the relationship between low lean mass and poorer tolerance to treatment has been observed in the majority of studies, few smaller studies have reported no association[20; 50; 72; 95; 123; 127; 128; 129].

Increased toxicity in patients with low lean mass may be attributed to alterations in the distribution, metabolism and clearance of systemic chemotherapy drugs[102]. Chemotherapy is traditionally dosed according to body surface area (BSA) but its use has been criticised in the dosage of medications with a narrow therapeutic index, such as chemotherapy. A four to ten-fold variation in drug clearance has been shown in individuals with similar BSA and there is growing concern that this approach to dosing is invalid[130; 131]. Its continued use relies on the lack of other more precise methods for dose individualisation[132].

If body weight comprises two major components (lean and fat mass) then these are the two major sites of distribution of hydrophilic and lipophilic drugs[133; 134]. Therefore,

variability in individual lean mass or fat mass may lead to changes in the volume of distribution of drugs and therefore adversely affect the tolerance of cytotoxic drugs[36]. Tolerance is further compromised in individuals with sarcopenic obesity where the combination of excessive fat mass and diminished lean mass may significantly impact the tolerance of hydrophilic drugs by resulting in a disproportionally small volume of drug distribution in relation to their body weight or body surface area[102; 133]. Variations in lean and fat mass can therefore lead to considerable variation in the milligram of chemotherapy drug per kilogram lean mass with higher doses per kilogram lean mass shown to be associated with more frequent and severe toxic side effects[133; 135; 136]. Pharmacokinetic data have supported this hypothesis, with patients with low lean mass experiencing higher plasma concentrations of antineoplastic drugs and experiencing more toxicity[96; 137]. For lipophilic drugs such as doxorubicin or trabectedin, individuals with a low-fat mass may also present with toxicity due to a reduced volume of distribution[134].

In addition to the argument that pharmacokinetic parameters can explain the higher risk of toxicity in patients with low lean mass it is also important to note that these patients are excessively fragile and highly susceptible to acute medical events that exacerbate chemotherapy-related toxicity[91]. Systemic inflammation has been shown to decrease liver cytochrome activities and drug clearance and may modify drug exposure. Low concentrations of circulation plasma proteins (e.g. albumin) may also affect the distribution of highly protein -bound drugs such as Vantetanib, sorafenib and epirubicin[96; 134; 137]. Future clinical trials investigating dosing chemotherapy drugs according to individual body composition are warranted and the outcome of these studies could inform future practice.

Table 3. Summary of studies examining the impact of computed tomography assessed skeletal muscle (at the third lumbar vertebrae) and treatment related toxicity in patients with cancer.

	Stage/n	Treatment	Summary of findings
Breast Cancer			
Prado *et al*. 2009[102]	Metastatic/55	Capecitabine	DLT ↑ in sarcopenic pts (50% vs. 20%, *p*=0.03)
Prado *et al*. 2011[138]	Stage II-III/24	5-FU, Epirubicin, cyclophosphamide	LM was lower in pts with toxicity (41.6 kg vs. 56.2 kg, *p*=0.002)
Shachar *et al*. 2016[106]	Metastatic/40	Taxane based (paclitaxel, docetaxel, nab-paclitaxel)	Gr 3-4 toxicity ↑ in sarcopenic pts (57% vs. 18%, *p*=0.02) and ↑ in treatment related hospitalisations (39% vs. 0%, *p*=0.005)
Shachar *et al.* 2016[139]	Stage I-III/151	Anthracycline and taxanes	Every 5 unit decrease in SMI was associated with increased risk of gr 3-4 toxicity (RR 1.29 (95% CI 1.10-1.53), *p*=0.002)
Mazzuca *et al*. 2018[104]	Stage I-III/21	Anthracyclines	Lower baseline SMI was associated with Gr 3-4 vs. Gr 0-2 toxicities (33.4 cm^2/m^2 (31.1–39.9) vs 40.5 cm^2/m^2 (33.4–52.0), *p* = 0.028).
Colorectal Cancer			
Prado *et al.* 2007[133]	Stage II-III/62	5-FU	Drug dose >20mg/kg LM associated with increased toxicity (93% vs. 52%, *p*=0.005)
Barret *et al.* 2013[68]	Metastatic/51	Fluoropyrimidine (FP)+Oxaliplatin; FP+ Irinotecan; FP Alone; Irinotecan without FP	Sarcopenia independently associated with ↑ risk of gr 3-4 toxicity (OR: 13.55, *p*=0.043)
Ali *et al.* 2015[140]	Stage I-IV/138	FOLFOX	Pts with the highest tertile of drug dose per kg LM experienced more DLT compared with those in the lowest tertile of drug dose (39.9% vs. 8.3%, *p*<0.01)
Chemama *et al*. 2016[58]	Advanced (liver mets)/97	Hyperthermic intraperitoneal chemotherapy	Toxicity ↑ in sarcopenic pts (57% vs, 26%, *p*=0.004)
Blauwhoff-Buskermolen *et al.* 2016[20]	Metastatic/67	CAPOX (±bevacizumab)	Sarcopenia was not associated with ↑ toxicity
Cespedes *et al.* 2017[141]	Non-metastatic/533	FOLFOX	Lowest tertile of lean mass associated with early treatment discontinuation (OR 2.34, *p*=0.03), treatment delay (OR 2.24, *p*=0.002) and dose reduction (OR 2.28, *p*=0.01)
Lung Cancer			
Arrieta *et al.* 2015[43]	Metastatic/84	Afatinib	Patients with lower LM and BMI <25kg/m^2 developed more DLT than patients with higher LM and BMI >25 kg/m^2 (71.4% vs. 18.8%, *p*=0.0017)
Sjoblom *et al.* 2015[136]	Stage IIIb-IV/153	Gemcitabine and vinorelbine or Carboplatin and vinorelbine	Higher doses of gemcitabine per kg LM were independently associated with gr 3-4 haematological toxicity in multivariate analyses (OR 1.15, 95% CI: 1.01-1.29, *p*=0.018), as were also higher doses of vinorelbine per kg LBM.
Srdic *et al*. 2016[128]	Advanced/100	Platinum-doublet therapy	Cachexia and sarcopenia were not found to be predictors of chemotoxicity
Sjoblom *et al*.	Stage IIIb-IV/424	Carboplatin-	Drug dose per kg/LM was associated with

	Stage/n	Treatment	Summary of findings
2016[135]		Doublet (pemetrexed, gemcitabine or vinorelbine)	haematological toxicity. For doses >20% above or below the mean, the risk of gr 3-4 haematological toxicity was almost doubled (OR 1.93 (95% CI:1.21-3.10) and halved (OR 0.52 (95% CI: 0.32-0.83) respectively.
Esophagogastric cancer			
Yip *et al*. 2014[72]	Stage I-III/35	5FU; Platinum/5-FU; ECX/ECF	Sarcopenia was not associated with ↑ toxicity or treatment dose reduction.
Tan *et al.* 2015[75]	Stage I-III/89	Cisplatin, 5-FU, Epirubicin or Cisplatin, Capecitabine	Sarcopenia independently associated with DLT (OR 2.95, *p*=0.015)
Anandavadivelan *et al.* 2016[73]	Resectable/72	Cisplatin, 5-FU	Patients with a DLT had lower SMM than those without DLT (47 kg vs. 51 kg, *p*=0.04). Sarcopenic obesity associated with increased risk of DLT (OR 5.54, 95% CI: 1.12-27.44, *p*=0.04)
Palmela *et al.* 2017[82]	Stage II-III/48	Neoadjuvant chemotherapy	DLT ↑ in sarcopenic pts (65% vs. 39%, *p*=0.181)
Dijksterhuis *et al.* 2019[142]	Advanced/88	Capecitabine, Oxaliplatin	Gr 2-4 neuropathy ↑ in patients with sarcopenic obesity (OR 3.82, 95% CI: 1.20-12.18, *p*=0.024)
Pancreatic Cancer			
Rollins *et al.* 2015[50]	Advanced/228	Gemcitabine	Sarcopenia was not associated with rates of completion of palliative chemotherapy
Kurita *et al.* 2019[143]	Advanced/82	FOLFIRINOX	Gr 3-4 hematologic toxicity was ↑ in sarcopenic obese patients (*p*=0.008)
Renal Cell Carcinoma			
Antoun *et al.* 2010[144]	Metastatic/55	Sorafenib	DLT was most common (41%) in sarcopenic patients whose BMI was <25 kg/m^2 and least common (13%) in patients who were not sarcopenic and/or overweight or obese (*p* = 0.03).
Huillard *et al*. 2013[92]	Metastatic/61	Sunitunib	Sarcopenic pts with a BMI< 25 kg/m^2 experienced ↑ DLTs (OR 4.1, 95% CI: 1.3-13.3), ↑ cumulative gr 2 or 3 toxicities (*p*=0.008), ↑ grade 3 toxicities (*p*=0.04) and ↑ acute vascular toxicities (*p*=0.009).
Cushen *et al.* 2017[89]	Metastatic/55	Sunitunib	Pts with the lowest compared with the highest measurements of LM experienced more DLT (92% vs. 57%, *p*=0.05)
Auclin *et al.* 2017[95]	Metastatic/124	Everolimus	SMI was not associated with ↑ toxicity
Melanoma			
Heidelberger *et al.* 2017[110]	Metastatic/68	Nivolumab/ Prembrolizumab	Sarcopenia and overweight (BMI >25kg/m^2) women had a 6.5 fold ↑ risk of toxicity.
Daly *et al.* 2017[35]	Metastatic/84	Ipilimumab	Sarcopenic was associated with ↑ high grade adverse events (OR 5.34, *p*=0.033)
Hepatocellular carcinoma			
Mir *et al.* 2012[96]	Advanced/40	Sorafenib	DLT ↑ in sarcopenic pts (82% vs. 31%, *p*=0.005)
Nault *et al.* 2015[100]	Advanced/52	Sorafenib, Brivanib	Sarcopenia was associated with a greater rate of hand-foot syndrome (*p*=0.049)
Other Cancer Sites			
Parsons *et al*.	Mixed cancer	Hepatic arterial	Sarcopenia was not associated with ↑ toxicity

	Stage/n	Treatment	Summary of findings
2012[127]	sites/Advanced/48	infusion	
Moryoussef *et al.* 2015[145]	GI stromal tumours/advanced /31	Imatinib	Gr 1-2 toxicity ↑ in sarcopenic pts (100% vs. 73.7%)
Massicotte *et al.* 2013[137]	Medullary thyroid /Advanced/33/	Vantetanib	SMI was lower in pts with DLT (37.2 vs. 44.3 cm^2/m^2, p=0.003)
Veasy-Rodrigues *et al.* 2013[146]	Mixed solid tumours/ Advanced/16	Temsirolimus	Sarcopenia was not associated with ↑ toxicity
Cousin *et al.* 2014[147]	Mixed cancer sites/ Stage I-IV/93	Phase 1 drugs	Severe toxic events were observed in 25.5% of the pts when the SMI was below the median value compared to 6.5% of patients with a high SMI (p = 0.02)
Prado *et al.* 2014[134]	Ovarian/Advanced/74	Doxil, trabectedin	LM alone was not predictive of DLT. A lower FM/LBM ratio was the most powerful variable associated with toxicity (p=0.006)
Cushen *et al.* 2016[116]	Prostate/Metastatic/ 63	Docetaxel	Sarcopenia and low MA associated with ↑DLT toxicity
Xiao *et al.* 2016[121]	Lymphoma/stage I-IV/522	CHOP based chemotherapy	Sarcopenia was independently associated with ↑ risk of febrile neutropenia hospitalization (OR 1.64, 95% CI: 1.01-2.65) and ↓ completion of standard treatment cycles (OR 1.49, 95% CI: 1.02-2.16)
Wendrich *et al.* 2017[148]	Head&neck/locally advanced/132	Platinum-based chemotherapy	Patients with low skeletal muscle mass experienced more DLT more frequently than patients with normal skeletal muscle mass (44.3% vs. 13.7%, p<0.001)
Versteeg *et al.* 2018[129]	Mixed sites/Advanced/103	Not specified	Muscle parameters were not associated with ↑ toxicity

DLT, Dose limiting toxicity; Pts, patients; LM, lean mass; Gr, Grade; SMI, Skeletal muscle index; CI, confidence interval; OR, odds ratio; RR, relative risk; mg, milligrams; kg, kilograms; 5-FU, 5-Flurouracil; BMI, body mass index; HCC, hepatocellular carcinoma; GI, gastrointestinal.

Impact of malnutrition on performance status and quality of life

Quality of life (QoL) in patients with cancer is a subjective multidimensional construct that represents the patient's psychological well-being, functional status, health perceptions, and disease- and treatment- related symptoms. It is now universally accepted that QoL is the central tenet in cancer care, especially in those patients with incurable disease.

Weight loss and malnutrition has been shown to have profound negative effects on QOL in patients with cancer. A recent systematic review examining the impact of weight loss on QoL in patients with cancer reported a negative correlation between weight loss and QoL in 23 out of 27 studies[10]. The negative impact on QoL is unsurprising, considering cancer-related malnutrition is a

major cause of fatigue[149; 150], reduced functional ability[151] and a source of emotional distress[149; 152].

Inconsistent reports on the relationship between muscle parameters and QoL have been published in the literature[127; 153; 154; 155]. Parsons and colleagues reported no significant associations between low muscle mass, and symptom burden or functional life domains assessed by the MD Anderson Symptom Inventory, in a cohort of 104 patients with advanced cancer[127]. However, in a study of 734 patients with advanced lung cancer, low muscle mass was non-linearly associated with lower global QoL, physical function and role function, and associated with more symptoms (fatigue and pain), while low MA was associated with poor physical function and more dyspnoea[155]. Low muscle mass has also been associated with greater depression symptoms and more fatigue in patients with advanced cancer[153; 154].

The mode by which weight loss exerts its influence on QoL is not fully understood but may relate to muscle atrophy associated with cachexia and weight loss leading to fatigue or reduced functional capacity. Recent work has suggested that the complex interplay between metabolic disruption and pro-inflammatory cytokines (i.e. IL-6, IL-8 and TNF-α) in cancer cachexia often leads to physical, biochemical and nutritional deterioration which subsequently leads to poor QoL[156]. Systemic inflammation and loss of muscle is also thought to drive cancer related fatigue, which is thought to affect up to 80% of patients[157] both during and after treatment cessation[157; 158; 159; 160]. Severe and persistent fatigue, along with muscle wasting has been shown to inhibit QoL by considerably reducing functional capacity to fully participate in daily living tasks[157]. Also, evidence from a variety of preclinical and clinical studies suggest that systemic inflammation has a direct role in the development of cancer associated symptom clusters including pain, fatigue, mood, anorexia and physical function[161]. Systemic inflammation has been shown to be associated with poorer QoL even in those with a good performance score[162].

Importantly, interventions aimed at targeting nutritional status and attenuating weight loss have proven successful in improving aspects QoL in patients with cancer[163]. In addition, novel cachexia treatments, such as Anamorelin, an oral ghrelin-receptor agonist with appetite enhancing and anabolic activity have shown a favourable clinical response in alleviating anorexia-cachexia symptoms[26]. Research is warranted to determine if attenuating the systemic inflammatory response leads to clinically relevant improvements in symptoms, which may represent a new therapeutic approach to symptom management in patients with advanced cancer.

Impact on survival

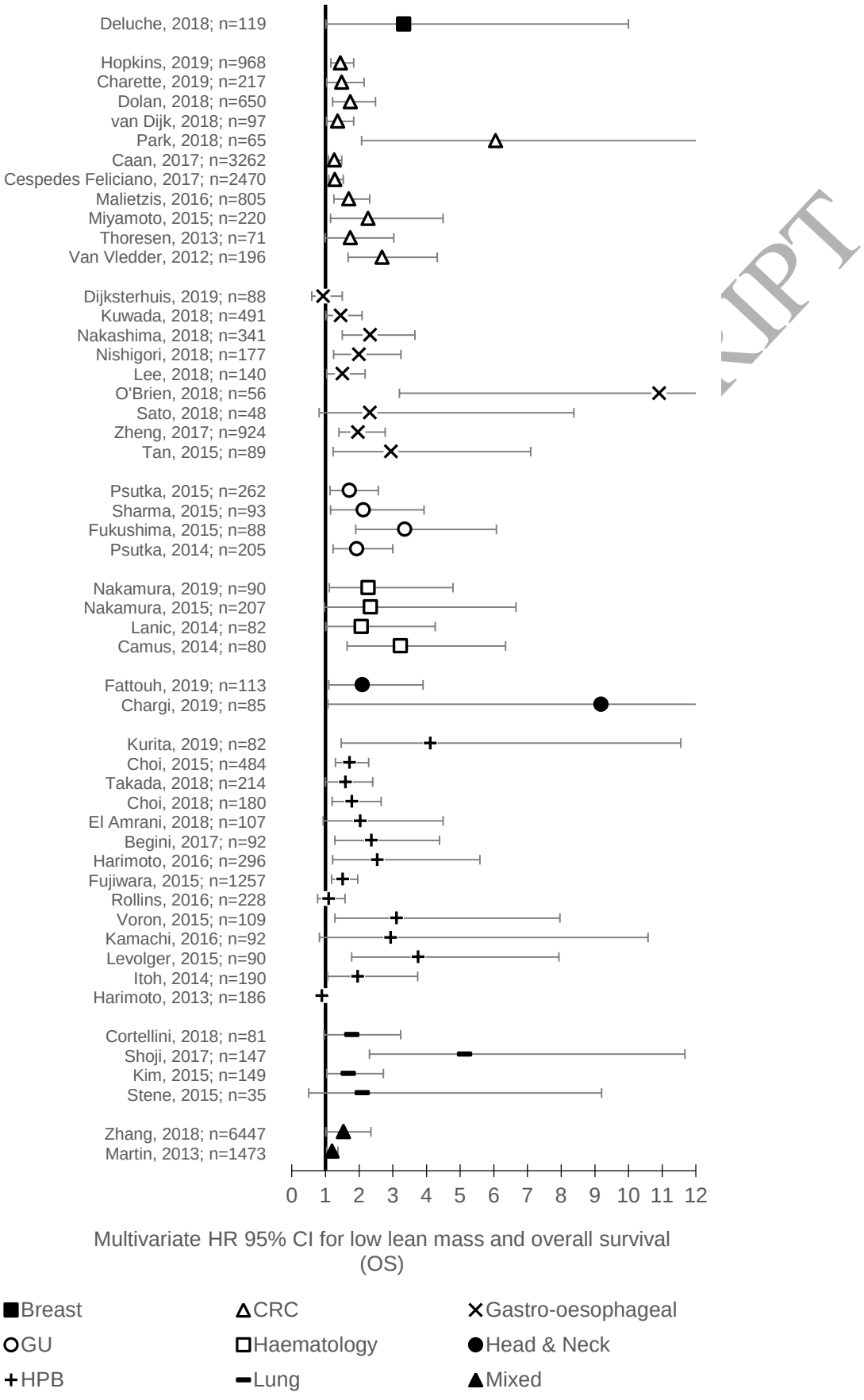
Over the past decade, an array of studies have examined the relationship between the presence of low muscle mass (sarcopenia) and its impact on survival in patients with cancer. Most studies report a significant decrease in overall survival in patients with low muscle mass compared with their counterparts, irrespective of the primary cancer site and stage (see Figure 1). Figure 1 displays the risk of mortality [adjusted HR (95% CI)] in sarcopenic patients compared with non-sarcopenic patients according to primary tumour location.

The relationship between low muscle mass and poor survival has been the topic of various systematic reviews and meta-analysis[164; 165; 166; 167]. In a recent systematic review and meta-analysis of 38 studies that included 7,843 patients with solid tumours, low muscle cross-sectional area was observed in 27.7% of patients with cancer and associated with poorer overall survival [HR: 1.44, 95% CI: 1.32–1.56], cancer-specific survival [HR: 1.93, 95% CI: 1.38–2.70,], as well as disease-free survival [HR: 1.16, 95% CI: 1.00–1.30] but not with progression free survival (HR: 1.54, 95% CI: 0.90-2.64)[165]. This meta-analysis demonstrated that the adverse effects of low muscle mass on overall survival were similar in both metastatic [HR: 1.37, 95% CI: 1.21–1.56] and non-metastatic disease [HR: 1.54, 95% CI: 1.31–1.79], and this relationship was observed across different primary tumour sites. Recently, in two of the largest observational cohort studies to date, Caan and colleagues[168; 169] demonstrated the prognostic value of low muscle mass in non-metastatic breast (*n*=3,241) and colorectal cancer (*n*=3,262). Low lean mass was present in 34 and 42% of patients, respectively, and was independently associated with a 27–41% higher risk of overall mortality [colon: HR 1.24, (95% CI: 1.09-1.48); breast: HR 1.41 (95% CI: 1.18-1.69)] [168; 169].

In addition to low muscle area (sarcopenia), low muscle attenuation (radiodensity) (indicative of fatty infiltration of muscle tissue) is also associated with poorer survival in a variety of tumours including non-small cell lung cancer, colorectal, endometrial, renal and ovarian cancer [170] [171; 172; 173] [174], [109; 175], [176]. Importantly, in some cases, low MA appears to superior in predicting mortality compared with low lean mass alone [87; 107; 170; 177; 178]. In a cohort of 1,681 early stage colorectal cancer (CRC) patients, low MA was associated with higher all-cause mortality [HR 1.91 (95% CI: 1.53-2.38)] [173]. Ataseven *et al.*[109] reported that in patients with advanced epithelial ovarian cancer receiving primary debulking surgery (*n*=323), low MA (<32 HU) was associated with a significantly reduced overall survival compared with patients with a higher MA (median survival 28 months vs. 56 months , $p<0.001$) and this relationship remained significant on multivariable

regression analysis (HR 1.79 (95% CI: 1.22-2.62). In another cohort of patients with early stage CRC (*n*=3,262), low MA has also been described as an important predictor of mortality [HR 1.61 (95% CI: 1.36-1.90)] and CRC-specific mortality [HR 1.74 (95% CI: 1.38-2.21)]. Of note, in this study, patients with both low muscle mass and low MA were at the highest risk of overall [HR: 2.02 (95% CI: 1.65-2.47)] and cancer-specific mortality [HR: 2.54 (95% CI: 1.91-3.37)][(171)]. It has also been demonstrated that the risk of mortality associated with low muscle mass and low MA can be independent of each other [(179; 180; 181)].

Figure 1: Forest plot of HR of death according to low muscle mass status



Deluche, 2018; n=119 [105] Hopkins, 2019; n=968 [182] Charette, 2019; n=217 [179] Dolan, 2018; n=650 [183] van Dijk, 2018; n=97 [184] Park, 2018; n=65 [185] Caan, 2017; n=3262 [168] Cespedes Feliciano, 2017; n=2470 [186] Malietzis, 2016; n=805 [187] Miyamoto, 2015; n=220 [188] Thoresen, 2013; n=71 [57] Van Vledder, 2012; n=196 [189]Dijksterhuis, 2019; n=88 [142] Kuwada, 2018; n=491 [190] Nakashima, 2018; n=341 [191] Nishigori, 2018; n=177 [192] Lee, 2018; n=140 [193] O'Brien, 2018; n=56 [194] Sato, 2018; n=48 [80] Zheng, 2017; n=924 [195] Tan, 2015; n=89 [75] Psutka, 2015; n=262 [196] Sharma, 2015; n=93 [88] Fukushima, 2015; n=88 [114] Psutka, 2014; n=205 [115] Nakamura, 2019; n=90 [197] Nakamura, 2015; n=207 [198] Lanic, 2014; n=82 [199] Camus, 2014; n=80 [200] Fattouh, 2019; n=113 [201] Chargi, 2019; n=85 [202] Kurita, 2019; n=82 [143] Choi, 2015; n=484 [203] Takada, 2018; n=214 [204] Choi, 2018; n=180 [205] El Amrani, 2018; n=107 [47] Begini, 2017; n=92 [206] Harimoto, 2016; n=296 [207] Fujiwara, 2015; n=1257 [208] Rollins, 2016; n=228 [209] Voron, 2015; n=109 [98] Kamachi, 2016; n=92 [99] Levolger, 2015; n=90 [210] Itoh, 2014; n=190 [211] Harimoto, 2013; n=186 [97] Cortellini, 2018; n=81 [212] Shoji, 2017; n=147 [213] Kim, 2015; n=149 [214] Stene, 2015; n=35 [215] Zhang, 2018; n=6447 [216] Martin, 2013; n=1473 [29]

Loss of muscle during treatment & survival

Notwithstanding the impact of low muscle mass on survival, several studies have emphasised that patients continually lose muscle while on treatment and that this is associated with an increased risk of mortality in a number of cancers. Patients with advanced pancreatic cancer (*n*=97) who experienced early loss of skeletal muscle (>10% within 3 months of diagnosis) were at increased risk of poorer overall survival and progression free survival compared to patients who did not experience muscle loss to the same degree [HR 2.16 (95% CI: 1.23-3.78), *p*=0.007 and HR 2.31 (95% CI: 1.30-4.09), *p*=0.004][217]. In patients with surgically resected stage I-III CRC (*n*=1924), those who experienced the largest decrease in muscle mass (≥2 standard deviations or the equivalent to ≥11.4% loss) and the largest decline in mean MA (≥2 SD; ≥20.2% loss) from baseline were at a significantly increased risk of mortality [HR 2.15 (95% CI: 1.59-2.92), *p*<0.001 and HR 1.61 (95% CI: 1.20-2.15), *p*=0.002, respectively], and these findings were independent of changes in body mass or other body composition parameters[172]. To date, losses in muscle have been shown to be prognostic of reduced survival in pancreatic[51; 217], oesophageal, gastric[218], lung[219], colorectal[20; 220; 221], ovarian[39], melanoma[35] and foregut cancers[38].

Conclusions

While weight loss and malnutrition have been frequently reported in cancer patients over the past 40 years, research over the past 15 years has unearthed the importance of low muscle mass as being the new face of malnutrition in oncology populations. The study of body composition in oncology has highlighted the importance of both low muscle mass and low muscle attenuation which are associated with poorer tolerance to chemotherapy; significant deterioration in a patients' performance status and quality of life, and poorer survival. Early screening to identify individuals with muscle loss and decreased muscle quality would allow for earlier multimodal interventions to attenuate adverse body composition changes. These include resistance exercise

training and optimal dietary intake and supplementation, combined with pharmacotherapy; these are currently the focus of randomised controlled trials[222]. It remains to be seen if multimodal therapies can provide a sufficient stimulus to prevent or slow the cascade of tissue wasting and if this then impacts on outcome in a positive manner. There also exists an equal need for routine, cost-efficient, and feasible methods to quantify muscle and adipose tissue in clinical practice. The study of body composition is one of the most provocative areas in oncology that offers tremendous promise to help patients with cancer live longer and healthier lives[223].

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