Special article

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

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ABSTRACT

It has frequently been shown that patients with cancer are one of the largest hospital patient groups with a prevalence for malnutrition. Weight loss is a frequent manifestation of malnutrition in patients with cancer. Several large-scale studies over the past 35 y have reported that involuntary weight loss affects 50% to 80% of these patients with the degree of weight loss dependent on tumor site and type and stage of disease. The aim of this review was to determine the consequences of malnutrition, weight loss, and muscle wasting in relation to chemotherapy tolerance, postoperative complications, quality of life, and survival in patients with cancer. 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.

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Introduction

It has frequently been shown that patients with cancer are one of the largest hospital patient groups with a prevalence for malnutrition [1—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 past 35 y have reported that involuntary weight loss affects 50% to 80% of patients with cancer with the degree of weight loss dependent on tumor site, and type and stage of disease [4—6].

The prognostic effects of weight loss on overall survival (OS) has long been recognized, with recent data suggesting ongoing weight loss of >2.4% predicting survival, independent of disease site, stage, or performance score [6]. In addition to the adverse effects on survival, weight loss has been associated with severe chemotherapy-related toxicity [7—9] and leads to a significant deterioration in patients' performance status [PS], psychological well-being, and overall quality of life (QoL) [10].

Causes of nutritional deterioration in cancer

Nutritional deterioration unfortunately has 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 physiologic changes to the gut, side effects of treatment, or metabolic abnormalities caused by the tumor. Both the quantity and the quality of dietary intake can be significantly altered due to any one of a number of factors including dysphagia, nausea, changes in taste and smell, pain, early satiety, or fatigue. Additionally, 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 tumor and activated immune cells. Complex interactions between inflammation (proinflammatory cytokines), neurohormonal changes, and potential proteolytic and lipolytic factors produced by the host and the tumor, fuel weight loss and loss of lean mass [13].

Weight loss and changes in body composition after a cancer diagnosis

Involuntary weight loss is a hallmark feature of cancer-associated malnutrition and can lead to cancer cachexia; a multifactorial syndrome characterized 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]. Cachexia is characterized 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 y have reported that moderate to severe weight loss is present in 30% to 70% of cancer patients [2,4–6,11]. In the largest study to date of 8160 patients with locally advanced or metastatic disease, 73% experienced involuntary weight loss [6]. Table 1 summarizes the prevalence of >5% weight loss in 6 mo (a key component of the diagnostic criteria of cancer cachexia [14]), according to tumor site in the scientific literature, and weight loss has consistently been shown to be most frequent in patients with cancers in the upper gut and lung [15–19].

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% and 60% of patients with cancer are overweight or obese (body mass index [BMI] >25 kg/m^2) even in the setting of metastatic disease [6,28–31]. In a recent pooled analysis of 22 randomized 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 BMI or percentage of 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 become 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 etiology of muscle loss in these patients can be twofold. First resulting from 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 that has increased the 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 unfavorable outcomes in patients with cancer [6,33–35]. 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 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]. Although healthy adults >40 y of age have been shown to lose muscle at a rate of 1% to 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 healthy aging adults [20,38]. In studies examining the rate of muscle loss per 100 d, 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 mo weight loss >5% as per latest consensus definition [14]) can vary between 24% and 75%, depending on tumor site (Table 1), and between 38% and 70% of patients are considered to have sarcopenia (based on three of the most commonly used diagnostic criteria). The prevalence of low muscle mass is highest in lung (median 70%, range 47–79%) [42–45] and pancreatic cancer (median 56%, range 44–89%) [16,41,46–52]; however, it is noteworthy that the majority of studies report a prevalence >40% at most other sites in the body (Table 2).

The prevalence of sarcopenia as defined using three of the most common definitions for low muscle mass is displayed in Table 2. These definitions are as follow:

- Skeletal muscle index (SMI) <52.4 cm^2/m^2 in men and <38.5 cm^2/m^2 in women [121];
- SMI <43 cm^2/m^2 in men with a BMI <25 kg/m^2 and <53 cm^2/m^2 in men with a BMI >25 kg/m^2 and SMI <41 cm^2/m^2 in women [29]; and
- Baumgartner et al. [123] converted dual-energy x-ray absorptiometry cut points by Mourtzakis et al. [124] 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 this patient population, including poorer tolerance to anticancer treatment, poorer overall QoL, increased risk for postoperative complications, and poorer OS [6,10,36,37].

Table 1
Prevalence of patients with >5% weight loss in <6 mo according to primary tumor location in the scientific literature

Primary cancer [reference]	>5% weight loss in 6 mo, %
Pancreatic [15,16]	41–53
Colorectal [20–22]	32–48
Gastric [23,24]	42–75
Esophageal [25]	33
Lung [22,26]	44–49
Breast [22]	24

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

Primary cancer	Stage [reference]	% With sarcopenia, median (range, %)
Colorectal	Stage I−IV [20,34,53−69]	49 (20−80)
Esophagus	Stage I−IV [54,70−80]	53 (16−75)
Gastric	Stage I−IV [81−86]	47 (23−70)
Lung	Stage I−IV [42−45]	70 (47−79)
Kidney	Stage I−IV [87−94]	53 (29−90)
Pancreatic	Stage I−IV [16,41,46−52]	56 (44−89)
Liver	Stage I−IV [95−99]	54 (28−76)
Breast	Stage I−IV [100−106]	38 (14−67)
Ovarian	Stage I−IV [39,107,108]	47 (45−50)
Melanoma	Stage I−IV [35,109]	44 (24−63)
Bladder	Stage I−IV [110−114]	48 (33−69)
Prostate	Stage I−IV [115,116]	52 (47−56)
Head & neck	Stage I−IV [117]	64
Lymphoma	Stage I−IV [118−120]	51 (47−55)
Mixed	Stage I−IV [29,31,38,121−122]	4 (15−4)

Effects of malnutrition on tolerance to systemic chemotherapy

Chemotherapy often can be associated with severe toxicity that can result in dose delays, dose reductions, and treatment termination, referred to as dose-limiting toxicities (DLTs). Severe toxic events can result in hospitalizations and can 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 [61−63].

To date, >40 studies have examined the relationship between sarcopenia and the prevalence of DLT in patients with cancer. The relationship between low lean mass and increased toxicity to chemotherapy has been shown to be true in both early- and late-stage disease regardless of cancer site and type of systemic chemotherapy (cytotoxic single agents, regimens, targeted agents, and immunotherapies) [74,81, 105,121]. 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 (Table 3) [20,50,71,94,122,125−127].

Increased toxicity in patients with low lean mass may be attributed to alterations in the distribution, metabolism, and clearance of systemic chemotherapy drugs [101]. Chemotherapy is traditionally dosed according to body surface area (BSA) but its use has been criticized in the dosage of medications with a narrow therapeutic index, such as chemotherapy. A 4- to 10-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 [128,129]. Its continued use relies on the lack of other more precise methods for dose individualization [130].

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 [131,132]. Therefore, variability in individual lean 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 affect the tolerance of hydrophilic drugs by resulting in a disproportionally small volume of drug distribution in relation to their body weight or BSA [101,131]. Variations in lean and fat mass, therefore, can 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 [131,133,134]. Pharmacokinetic data have supported this hypothesis,

with patients with low lean mass experiencing higher plasma concentrations of antineoplastic drugs and experiencing more toxicity [95,135]. For lipophilic drugs such as doxorubicin or trabectedin, individuals with a low fat mass also may present with toxicity due to a reduced volume of distribution [132].

In addition to the argument that pharmacokinetic parameters can explain the higher risk for toxicity in patients with low lean mass, it also is important to note that these patients are excessively fragile and highly susceptible to acute medical events that exacerbate chemotherapy-related toxicity [90]. 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) also may affect the distribution of highly protein-bound drugs such as vandetanib, sorafenib, and epirubicin [95,132,135]. Future clinical trials investigating dosing chemotherapy drugs according to individual body composition are warranted and the outcome of these studies could inform future practice.

Effefcts of malnutrition on performance status and QoL

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 effects of weight loss on QoL in patients with cancer reported a negative correlation between weight loss and QoL in 23 of 27 studies [10]. The negative effects on QoL are not surprising as cancer-related malnutrition is a major cause of fatigue [147,148], reduced functional ability [149], and a source of emotional distress [147,150].

Inconsistent reports on the relationship between muscle parameters and QoL have been published [125,151−153]. Parsons et al. reported no significant associations between low muscle mass, and symptom burden or functional life domains assessed by the M.D. Anderson Symptom Inventory, in a cohort of 104 patients with advanced cancer [125]. However, in a study of 734 patients with advanced lung cancer, low muscle mass was nonlinearly associated with lower global QoL, physical function, and role function, and associated with more symptoms (fatigue and pain), whereas low MA was associated with poor physical function and more dyspnea [153]. Low muscle mass also has been associated with more depression symptoms and more fatigue in patients with advanced cancer [151,152].

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 proinflammatory cytokines (i.e., interleukin [IL]-6, IL-8 and tumor necrosis factor-α) in cancer cachexia often leads to physical, biochemical, and nutritional deterioration, which subsequently lead to poor QoL [154]. Systemic inflammation and loss of muscle is also thought to drive cancer-related fatigue, which is thought to affect ≤80% of patients [155] both during and after treatment cessation [155−158]. 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 [155]. 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 [159]. Systemic inflammation has been shown to be associated with poorer QoL even in those with a good performance score [160].

Table 3

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

Studies [reference]	Stage/n	Treatment	Summary of findings
Breast cancer			
Prado et al., 2009 [101]	Metastatic/55	Capecitabine	DLT ↑ in sarcopenic pts (50 vs 20%, $P = 0.03$)
Prado et al., 2011 [136]	Stage II–III/24	5-FU, Epirubicin, cyclophosphamide	LM was lower in pts with toxicity (41.6 vs 56.2 kg, $P = 0.002$)
Shachar et al., 2016 [105]	Metastatic/40	Taxane based (paclitaxel, docetaxel, nab-paclitaxel)	Grade 3 to 4 toxicity ↑ in sarcopenic pts (57 vs 18%, $P = 0.02$) and ↑ in treatment related hospitalizations (39 vs 0%, $P = 0.005$)
Shachar et al., 2016 [137]	Stage I–III/151	Anthracycline and taxanes	Every 5-unit decrease in SMI was associated with increased risk for grade 3 to 4 toxicity (RR, 1.29; 95% CI, 1.10−1.53; $P = 0.002$)
Mazzuca et al., 2018 [103]	Stage I–III/21	Anthracyclines	Lower baseline SMI was associated with grade 3 to 4 vs grade 0 to 2 toxicities (33.4 cm^2/m^2 [31.1−39.9] vs 40.5 cm^2/m^2 [33.4−52]; $P = 0.028$).
Colorectal cancer			
Prado et al., 2007 [131]	Stage II–III/62	5-FU	Drug dose >20 mg/kg LM associated with increased toxicity (93 vs 52%, $P = 0.005$)
Barret et al., 2013 [68]	Metastatic/51	FP+Oxaliplatin; FP+ irinotecan; FP alone; irinotecan without FP	Sarcopenia independently associated with ↑ risk for grade 3 to 4 toxicity (OR, 13.55; $P = 0.043$)
Ali et al., 2015 [138]	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 [139]	Non-metastatic/533	FOLFOX	Lowest tertile of LM 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 <25 kg/m^2 developed more DLTs than patients with higher LM and BMI >25 kg/m^2 (71.4 vs 18.8%; $P = 0.0017$)
Sjoblom et al., 201 [134]	Stage IIIb−IV/153	Gemcitabine and vinorelbine or Carboplatin and vinorelbine	Higher doses of gemcitabine per kg LM were independently associated with grade 3 to 4 hematologic toxicity in multivariate analyses (OR, 1.15; 95% CI, 1.01−1.29; $P = 0.018$), as were higher doses of vinorelbine per kg LBM.
Srdic et al., 2016 [126]	Advanced/100	Platinum-doublet therapy	Cachexia and sarcopenia were not found to be predictors of chemotoxicity
Sjoblom et al., 2016 [133]	Stage IIIb−IV/424	Carboplatin-Doublet (pemetrexed, gemcitabine or vinorelbine)	Drug dose per kg LM was associated with hematologic toxicity. For doses >20% above or below the mean, the risk for grade 3 to 4 hematologic 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 [71]	Stage I–III/35	5 FU; Platinum/5-FU; ECX/ECF	Sarcopenia was not associated with ↑ toxicity or treatment dose reduction
Tan et al., 2015 [74]	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 [72]	Resectable/72	Cisplatin, 5-FU	Patients with a DLT had lower SMM than those without DLT (47 vs 51 kg; $P = 0.04$). Sarcopenic obesity associated with increased risk for DLT (OR, 5.54; 95% CI, 1.12−27.44; $P = 0.04$)
Palmela et al., 2017 [81]	Stage II–III/48	Neoadjuvant chemotherapy	DLT ↑ in sarcopenic pts (65 vs 39%; $P = 0.181$)
Dijksterhuis et al., 2019 [140]	Advanced/88	Capecitabine, oxaliplatin	Grade 2 to 4 neuropathy ↑ in pts with sarcopenic obesity (OR, 3.82; 95% CI, 1.20−12.18; $P = 0.024$)
Pancreatic cancer			
Rollins et al., 2016 [50]	Advanced/228	Gemcitabine	Sarcopenia was not associated with rates of completion of palliative chemotherapy
Kurita et al., 2019 [141]	Advanced/82	FOLFIRINOX	Grade 3 to 4 hematologic toxicity was ↑ in sarcopenic obese pts ($P = 0.008$)
Renal cell carcinoma			
Antoun et al., 2010 [142]	Metastatic/55	Sorafenib	DLT was most common (41%) in sarcopenic pts whose BMI was <25 kg/m^2 and least common (13%) in those who were not sarcopenic and/or overweight or obese ($P = 0.03$)
Huillard et al., 2013 [91]	Metastatic/61	Sunitunib	Sarcopenic pts with BMI <25 kg/m^2 experienced ↑ DLTs (OR, 4.1; 95% CI, 1.3−13.3), ↑ cumulative grade 2 or 3 toxicities ($P = 0.008$), ↑ grade 3 toxicities ($P = 0.04$), and ↑ acute vascular toxicities ($P = 0.009$)
Cushen et al., 2017 [88]	Metastatic/55	Sunitunib	Pts with the lowest compared with the highest measurements of LM experienced more DLTs (92 vs 57%, $P = 0.05$)
Auclin et al., 2017 [94]	Metastatic/124	Everolimus	SMI was not associated with ↑ toxicity
Melanoma			
Heidelberger et al., 2017 [109]	Metastatic/68	Nivolumab/Prembrolizumab	Sarcopenia and overweight (BMI >25 kg/m^2) women had a 6.5-fold ↑ risk for toxicity

Table 3 (Continued)

Studies [reference]	Stage/n	Treatment	Summary of findings
Hepatocellular carcinoma			
Daly et al., 2017 [35]	Metastatic/84	Ipilimumab	Sarcopenia was associated with ↑ high-grade adverse events (OR, 5.34; P = 0.033)
Mir et al., 2012 [95]	Advanced/40	Sorafenib	DLT ↑ in sarcopenic pts (82 vs 31%; P=0.005)
Nault et al. 2015 [99]	Advanced/52	Sorafenib, brivanib	Sarcopenia was associated with a greater rate of hand−foot syndrome (P = 0.049)
Other cancer sites			
Parsons et al., 2012 [125]	Mixed cancer sites/Advanced/48	Hepatic arterial infusion	Sarcopenia was not associated with ↑ toxicity
Moryoussef et al., 2015 [143]	GI stromal tumors/Advanced /31	Imatinib	Grade 1 to 2 toxicity ↑ in sarcopenic pts (100 vs 73.7%)
Massicotte et al., 2013 [135]	Medullary thyroid/Advanced/33	Vantetanib	SMI was lower in pts with DLT (37.2 vs 44.3 cm²/m²; P=0.003)
Veasy-Rodrigues et al., 2013 [144]	Mixed solid tumors/Advanced/16	Temsirolimus	Sarcopenia was not associated with ↑ toxicity
Cousin et al., 2014 [145]	Mixed cancer sites/Stage I−IV/93	Phase 1 drugs	Severe toxic events were observed in 25.5% of pts when the SMI was below the median value compared with 6.5% of pts with a high SMI (P=0.02)
Prado et al. 2014 [132]	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 [115]	Prostate/Metastatic/63	Docetaxel	Sarcopenia and low MA associated with ↑ DLT toxicity
Xiao et al., 2016 [120]	Lymphoma/stage I−IV/522	CHOP-based chemotherapy	Sarcopenia was independently associated with ↑ risk for 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 [146]	Head & neck/Locally advanced/132	Platinum−based chemotherapy	Pts with low SMM experienced more DLTs more frequently than those with normal SMM (44.3 vs 13.7%; P < 0.001)
Versteeg et al. 2018 [128]	Mixed sites/Advanced/103	Not specified	Muscle parameters were not associated with ↑ toxicity

5-FU, 5-flurouracil; BMI, body mass index; CAPOX, capecitabine + oxaliplatin; CHOP, cyclophosphamide + doxorubicin hydrochloride + vincristine sulfate + prednisone; DLT, dose-limiting toxicity; FM, fat mass; FOLFIRINOX, 5-flurouracil + leucovorin + irinotecan + oxaliplatin; FOLFOX, folinic acid + 5-flurouracil + oxaliplatin; FP, fluoropyrimidine; GI, gastrointestinal; HCC, hepatocellular carcinoma; LBM, lean body mass; LM, lean mass; MA, muscle attenuation; pts, patients; SMI, skeletal muscle index; SMM, skeletal muscle mass.

Importantly, interventions aimed at targeting nutritional status and attenuating weight loss have proven successful in improving aspects QoL in patients with cancer [161]. Additionally, novel cachexia treatments, such as anamorelin, an oral ghrelin-receptor agonist with appetite-enhancing and anabolic activity have shown a favorable 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.

Effects on survival

Over the past decade, an array of studies have examined the relationship between the presence of sarcopenia and its effects on survival in patients with cancer. Most studies report a significant decrease in OS in patients with low muscle mass compared with their counterparts, regardless of the primary cancer site and stage (Fig. 1). Figure 1 displays the risk for mortality (adjusted hazard ratio [HR]; 95% confidence interval [CI]) in sarcopenic patients compared with non-sarcopenic patients according to primary tumor location.

The relationship between low muscle mass and poor survival has been the topic of various systematic reviews and meta-analysis [162−165]. In a recent systematic review and meta−analysis of 38 studies that included 7843 patients with solid tumors, low muscle cross−sectional area was observed in 27.7% of patients with cancer and associated with poorer OS (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 (PFS; HR, 1.54; 95% CI, 0.90−2.64) [163]. This meta-analysis demonstrated that the adverse effects of low muscle mass on OS 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 tumor sites. Recently, in two of the largest observational cohort studies to date, Caan et al. [166,167] demonstrated the prognostic value of low muscle mass in non-metastatic breast (n = 3241) and colorectal cancer (CRC; n = 3262). Low lean mass was present in 34% and 42% of patients, respectively, and was independently associated with a 27% to 41% higher risk for overall mortality (colon: HR, 1.24; 95% CI, 1.09−1.48; breast: HR, 1.41; 95% CI, 1.18−1.69) [166,167].

In addition to sarcopenia, low MA (indicative of fatty infiltration of muscle tissue) is also associated with poorer survival in a variety of tumors including non-small cell lung cancer, CRC, endometrial, renal, and ovarian cancers [108,168−174]. Importantly, in some cases, low MA appears to superior in predicting mortality than low lean mass alone [86,106,168,175,176]. In a cohort of 1681 patients with early-stage CRC, low MA was associated with higher all-cause mortality (HR 1.91; 95% CI, 1.53−2.38) [171]. Ataseven et al. [108] 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 OS compared with patients with a higher MA (median survival 28 versus 56 mo; 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 = 3262), low MA also has 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 for overall and cancer-specific mortality (HR, 2.02; 95% CI, 1.65−2.47 and HR, 2.54; 95% CI, 1.91−3.37, respectively) [169]. It also has been demonstrated that the risk for mortality associated with low muscle mass and low MA can be independent of each other [177−181].
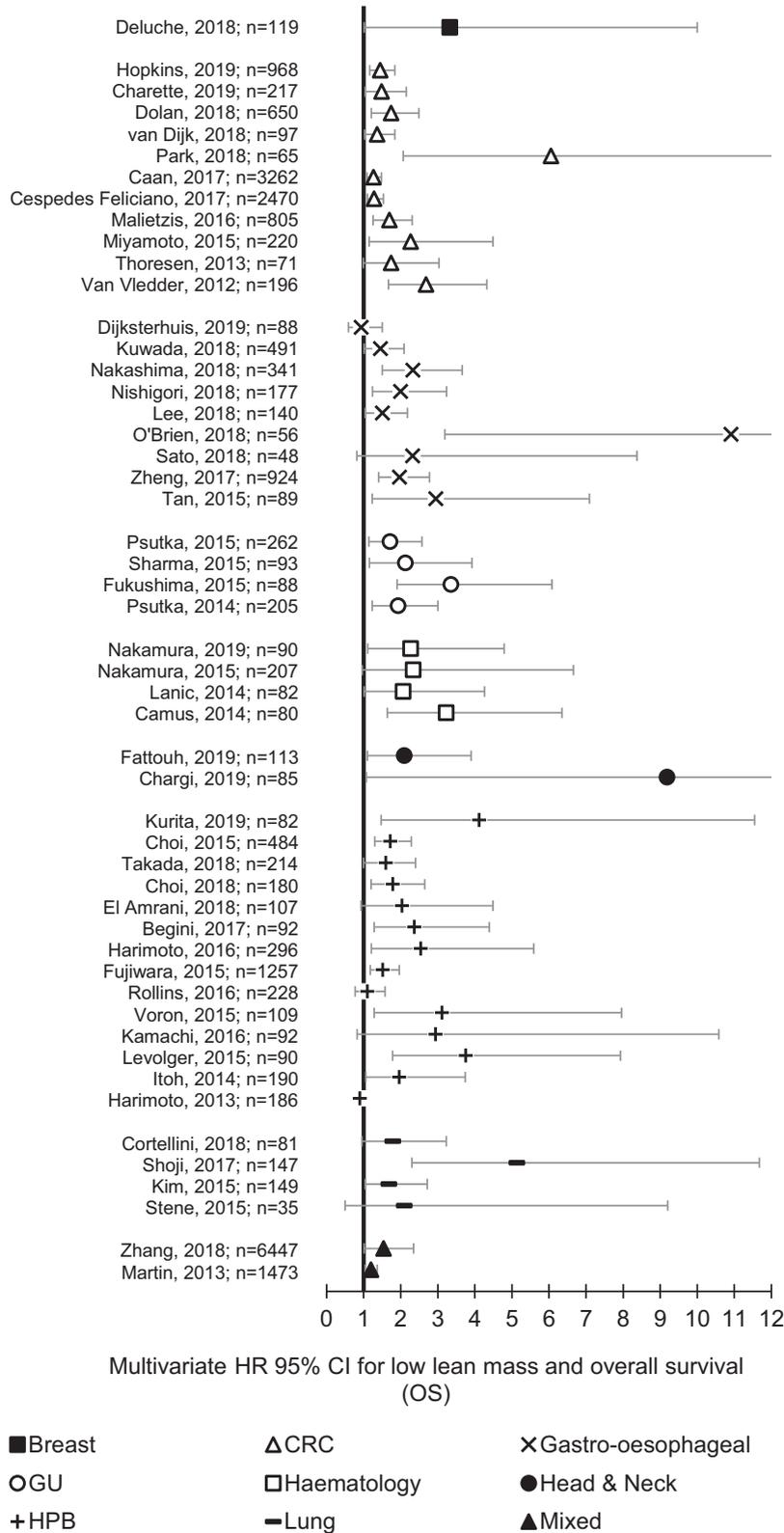
Fig. 1. Forest plot of hazard ratio of death according to low muscle mass status. CRC, colorectal cancer; GU, genitourinary; HPB, hepato-pancreato-biliary [182−207].

Loss of muscle during treatment and survival

Notwithstanding the effects of low muscle mass on survival, several studies have emphasized that patients continually lose

muscle while on treatment and that this is associated with an increased risk for mortality in a number of cancers. Patients with advanced pancreatic cancer (n = 97) who experienced early loss of skeletal muscle (>10% within 3 mo of diagnosis) were at increased

risk for poorer OS and PFS than 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) [208]. In patients with surgically resected stage I−III CRC (n = 1924), those who experienced the largest decrease in muscle mass (≥2 SD 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 for 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 [170]. To date, losses in muscle have been shown to be prognostic of reduced survival in pancreatic [51,208], esophageal, gastric [209], lung [210], CRC [20,211,212], ovarian [39], melanoma [35], and foregut cancers [38].

Conclusions

Although weight loss and malnutrition have been frequently reported in patients with cancer over the past 40 y, research over the past 15 y 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 MA, which are associated with poorer tolerance to chemotherapy; significant deterioration in a patient PS and QoL, 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 randomized controlled trials [213]. 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 effects 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 and offers tremendous promise to help patients with cancer live longer and healthier lives [214].

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