Sarcopenic obesity: What about in the cancer setting?

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ABSTRACT

Growing evidence suggests that changes in muscle mass and function may further contribute to health risk assessment in individuals who are obese. As numbers for both obese and aged population subgroups are increasing worldwide, sarcopenic obesity is emerging as a relevant factor associated with higher risk for adverse events and outcomes in several clinical settings, including cancer. Recent reports showing that prevalence of sarcopenic obesity may involve up to one-third of patients with cancer despite body mass index strongly support the need for its evaluation in oncological clinical practice. In fact, in several cancer types, sarcopenic obesity is associated with poorer outcomes that include metabolic and surgical complications, longer hospitalization, physical disability, and shorter survival. Importantly, sarcopenic obesity may also have an effect on chemotherapy, as it may induce a higher risk for dose-limiting-toxicity. The aim of this review was to present an updated overview on the definition, effects, mechanisms, and clinical relevance of sarcopenia in this setting.

Introduction

Sarcopenic obesity has been described as a "confluence of two epidemics" with individuals with increased fat mass but decreased muscle mass and function [1]. Although both these conditions are known to be associated with important metabolic derangements, it is still debated as to which extent their combination produces synergistic effects as well as whether sarcopenic obesity may be considered a syndrome in its own right [2]. Body composition assessment in individuals who are obese has shown that among individuals with comparable body mass index (BMI), those with sarcopenia are at higher risk for adverse events (AEs) and outcomes in several clinical settings including cancer [1,3–5].

In recent years, sarcopenic obesity has gained increasing clinical attention due to demographic and epidemiologic reasons [6,7]. Although the prevalence of obesity is increasing worldwide [8], its combination with sarcopenia is becoming an increasingly more relevant health concern. This is in part due to demographic changes that show increases, also among obese individuals, of adults ≥65 y of age [3], the population subgroup most affected by sarcopenia. In fact, individuals ≥65 y of age currently represent 13% of the global population and are the demographic subgroup with the fastest growing rate. Estimates show that this group is expected to reach 2.1 billion people in 2050 [9]. Within people ≥65 y of age, several studies identify a relevant subgroup that may be classified as having sarcopenic obesity, a high-risk geriatric syndrome predominantly observed in an aging population that is at risk for synergistic complications from both sarcopenia and obesity [3,6].

However, although sarcopenic obesity tends to be more common in older individuals, it has also been recognized as an increasingly frequent issue among younger patients who are obese and who have chronic diseases, such as cancer, and is associated with worse outcomes [10–14]. As in the case of individuals ≥65 y of age, growing figures may be related to the increasing prevalence of

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obesity worldwide, with more cancer patients presenting elevated body mass at diagnosis and to the increase of specific obesity-associated cancers [15]. In this context, specific mechanisms involving important muscle catabolism caused by the disease itself as well as by cancer treatment may also directly contribute to the onset of sarcopenic obesity, as well as to its metabolic effects and negative prognostic effect [4,5,16,17]. Moreover, risk for dose-limiting toxicity in chemotherapy also appears to be associated with body composition in these patients [18].

Although available literature globally acknowledges an increasing prevalence for sarcopenic obesity and its related effect in patients with cancer, it must be noted that epidemiologic and clinical research results on sarcopenic obesity from single studies may be at least in part difficult to compare or even controversial. Importantly, there currently is no unique accepted definition of sarcopenic obesity, and standard diagnostic criteria and cutoffs have not yet been established [19,20], potentially introducing bias in assessing the prevalence and the clinical implications of this condition also in the setting of cancer.

Recently, an international expert panel from the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO) has performed a systematic review as an initial step to analyze and summarize all available scientific literature on the definition and on the diagnostic criteria for human sarcopenic obesity [19], with the aim to spark discussion on the need for a unifying consensus on this topic [6,7]. Such achievement could indeed further contribute to characterize the role and relevance of sarcopenic obesity in patients with cancer.

Methods

This review was drawn after revision of the literature with the aim of producing an updated overview and comment on the topic. For original investigations, PubMed database was researched for the following keywords: sarcopenic obesity, cancer, neoplasia using the following string "sarcopenic obesity AND (cancer OR neoplasia)." All results were examined by authors to fulfill the following criteria:

- Original investigation regarding sarcopenic obesity in a cancer setting;
- Prevalence figures for sarcopenic obesity in the whole study cohort and/or obese subgroup;
- Statement of sarcopenic obesity diagnosis criteria (additional for sarcopenia and obesity or unified).

PubMed search was conducted on July 14, 2020, and produced 149 results. According to the above criteria, 40 were included for discussion and are reported in Table 1.

Assessment of sarcopenic obesity and related issues in patients with cancer

Diagnostic criteria and prevalence of sarcopenic obesity in cancer patients

Most authors agree that sarcopenic obesity may be defined as a condition characterized by the coexistence of excess fat mass and reduced muscle mass (sarcopenia) with low muscle strength (dynapenia) [19]. However, there is no specific consensus on whether sarcopenic obesity is the coexistence of two distinct diseases, each autonomously defined, or whether low skeletal muscle mass and higher fat mass interact synergistically to determine a clinical phenotype with its own specific identity. In the setting of cancer, definitions based on physiopathologic considerations might be even more complicated, given that interactions with cancer-induced adipose and muscle wasting still needs to be fully elucidated.

Several studies have investigated the potential relevance of sarcopenic obesity in different cohorts of patients with cancer, including oropharyngeal [21], lung [22,23], gastrointestinal tract [13,14,24–34], liver [35–37], pancreatic [38–45], urinary [46–48], and breast cancers [49,50], with reports also for patients with melanoma [51] and lymphoma [52] (Table 1).

Several diagnostic approaches for sarcopenic obesity in patients with. cancer have been proposed. Prado et al. have derived muscle mass cutoff from computed tomography (CT) images obtained at the level of the L3 lumbar vertebra. Due to the significant variation in body composition between men and women, sex-specific skeletal muscle index cutoffs (52.4 and 38.5 cm^2/m^2 for men and women, respectively) to define sarcopenia have been proposed in cancer patients and were shown to be associated with mortality [12]. Using these criteria, Prado et al. showed that 14% of obese (defined as BMI $\geq$30 kg/m^2) patients with cancer were sarcopenic [12]. In the following years, several authors have used the same criteria [34,38,40]. However, many others, while adopting the same diagnostic scheme, changed cutoffs by lowering BMI threshold to 25 kg/m^2 [14,23,25,39,49,51,53]. Dalal et al. clearly demonstrated, by applying both BMI cutoffs to the same cohort, that lowering the threshold allows for the detection of sarcopenic individuals also among overweight, thus potentially allowing the identification of more patients at risk [38]. However, it is questionable whether patients included by extending body mass cutoff values may be correctly defined as sarcopenic obese.

Other authors instead adopted a similar approach, but with different cutoffs for sarcopenia, mainly using those defined by Martin et al. to allow application also to patients who are nonobese (skeletal muscle index $\leq$43 or 53 if BMI $<$25 or $\geq$25 kg/m^2, respectively for men; $\leq$41 cm^2/m^2 for women) [5], with obesity defined as BMI $\geq$30 kg/m^2 in one case [22], but more often as BMI $\geq$25 kg/m^2 [24,29,41,48]. Moreover, some studies define their own cutoffs [21,26,27,30,35,47,50,54,55]. Among these, a retrospective analysis that included obese adult patients who underwent follow-up gastroduodenoscopy evaluated the association between gastric carcinogenesis and sarcopenia. Sarcopenic obesity was significantly associated with gastric cancer. Sarcopenic obesity also presented a strong relationship with metabolic syndrome and was associated with a higher risk for metabolic disorders and mortality than obesity or sarcopenia alone [26]. Despite interesting results, the use of different diagnostic criteria makes interpretation of these findings, as well as study comparison, even more difficult.

Although the Prado et al. and to some extent the Martin et al. unmodified or derived criteria are currently the most used in cancer settings, in the last few years several authors have questioned their value, reflecting the evolution of sarcopenia definition over time [56] and used modified or different criteria in their studies.

One important limitation to the above-described criteria is that they do not consider functional assessment, although the diagnosis of sarcopenia currently requires loss of function [19]. To address this issue, some authors have introduced functional assessment among criteria for sarcopenic obesity also in cancer patients [31,46].

The definition of obesity is also not irrelevant in this context either. Associations between BMI and long-term outcomes and prognosis are weak in comparison with visceral obesity in individuals with cancer [57,58]. Also, evidence suggests that waist circumference and waist-to-hip ratio are associated with inferior oncologic outcomes in colorectal cancer [59]. Despite single authors' choices on criteria, these findings clearly suggest the potential clinical relevance for the use of full body composition assessment rather than general population gross classification cutoffs. Accordingly, some authors have introduced assessment of fat mass [13,44,46] or visceral fat mass [28,35–37,43] instead of BMI in defining sarcopenic obesity in patients with cancer. Using fat mass $>$25% as a criterion for obesity, Kimura et al. observed a prevalence of 13.4% for sarcopenic obesity among patients with prostate cancer [46]. This finding was largely comparable to the results obtained by Cushen et al. using BMI in a similar cohort [48]. Finally, it must be noted that there is no current methodologic agreement on the use of fat mass measurements, as each author, or even the same author in different studies [43,44], applies different cutoffs or criteria.

Finally, a major emerging criticism to both Prado et al. and Martin et al.'s approach may be related to the fact that according to these authors, the diagnosis of sarcopenic obesity should be obtained by meeting separate criteria for sarcopenia and obesity, reflecting the idea of an overlap of two independent clinical conditions. Currently, only a small number of studies have opted for a single criterion considering contemporarily both fat and muscle measurements, as in the studies conducted by Siervo et al [45,60,61]. However, as growing evidence points toward sarcopenic obesity as a medical condition with specific features, some authors have taken advantage of the fact that the same CT scan analysis used to measure muscle mass could also easily provide other relevant information, including visceral and subcutaneous fat mass and myosteatosis. Most recent investigation is, in fact, progressively adopting unified criteria based on the ratio between visceral fat and skeletal muscle assessments, although still with different cutoffs among authors [32,33,42,52]. Using this approach, in a recent study Han et al. reported that among 1384 patients with non-metastatic rectal cancer, 22.2% had sarcopenic obesity, and that sarcopenic obesity associated with increased inflammatory status is an independent negative prognostic indicator for overall survival (OS) [33]. Although the use of unified criteria appears to be more in line with the emerging concept of sarcopenic obesity as a specific clinical condition in which muscle mass and function loss and increased fat mass interplay, the effective clinical advance obtained by unified diagnostic criteria still needs to be assessed.

Collectively, and despite variability in cancer types, time of treatment and definition criteria, the above studies suggest that sarcopenic obesity affects a non-negligible number of cancer patients, and thus represents a relevant clinical issue that needs to be addressed. This has been shown also by authors who attempted to merge or compare data available from different studies. Baracos et al. recently published that the prevalence of sarcopenic obesity in advanced solid tumor patient populations average 9% (range 2.3–14.6%) overall, and that one in four (24.7%, range 5.9–39.2%) patients with BMI $>$30 kg/m^2 are sarcopenic [2]. In a recent meta-analysis, Carneiro et al. included 14 studies linking sarcopenic obesity

Table 1
Prevalence of sarcopenic obesity in patients with cancer

First author, year	Site	Disease stage	Criteria for		Studied patients	Prevalence (%) among	
			Sarcopenia	Obesity	n	all	obese
Oropharyngeal cancer							
Chargi, 2020	Oropharyngeal SCC	Diagnosis	CT/MRI SMM: 43 or 43.2 cm^2/m^2	BMI ≥27 kg/m^2	216	6.00	n/a
Fattouh, 2018	Head and neck cancer	Invasive	CT L3 SMI: M ≤52.4, F ≤38.5 cm^2/m^2	BMI ≥30 kg/m^2	441	n/a	48.4
Lung cancer							
Recio Boiles, 2018	NSCLC	Diagnosis	CT L1 SMI: M ≤52.4, F ≤38.5 cm^2/m^2	BMI ≥25 kg/m^2	37	20.00	n/a
Kiss, 2018	NSCLC	Chemoradiation	CT L3 SMI: M ≤43 or 53 if BMI <25 or ≥25 kg/m^2 respectively, F ≤41 cm^2/m^2	BMI ≥30 kg/m^2	41	14.00	75.00
Gastrointestinal tract							
Anandavadivelan, 2016	Esophageal/Gastric cardia	Neoadjuvant chemotherapy	CT L3 SMI: M ≤52.4, F ≤38.5 cm^2/m^2	BMI ≥25 kg/m^2	72	14.00	34.10
Palmela, 2017	Esophageal/Gastric cardia	Neoadjuvant chemotherapy	CT L3 SMI: M ≤43 or 53 if BMI <25 or ≥25 kg/m^2 respectively, F ≤41 cm^2/m^2	BMI ≥25 kg/m^2	48	10.40	25.00
Grotenhuis, 2017	Esophageal/Gastric cardia	After esophagectomy	CT L3 SMI: M ≤52.4, F ≤38.5 cm^2/m^2	BMI ≥25 kg/m^2	120	25.00	54.00
Dijksterhuis, 2019	Esophageal/Gastric cardia	Palliative chemotherapy	CT L3 SMI: M ≤43 or 53 if BMI <25 or ≥25 kg/m^2 respectively, F ≤41 cm^2/m^2	BMI ≥25 kg/m^2	88	20.00	n/a
Sugawara, 2019	Esophageal/Gastric cardia	Before surgery	CT L3 SMI: M ≤47.24, F ≤36.92 cm^2/m^2	BMI ≥25 kg/m^2	75	40.60	n/a
Lou, 2016	Gastric	Resectable	CT L3 SMI: M ≤40.8, F ≤34.9 cm^2/m^2	BMI ≥23 kg/m^2	206	n/a	6.80
Nishigori, 2016	Gastric	Resectable	CT L3 SMI: M ≤52.4, F≤ 38.5 cm^2/m^2	Visceral fat ≥100 cm^2	157	24.20	n/a
Zhang, 2018,	Gastric	Resectable	Algorithm: CT L3 SMI: M ≤40.8, F ≤34.9 cm^2/m^2 + low strength or low performance	VFA: MI ≥132.6, F ≥91.,5 cm^2 or BMI: M >24.1, F >23.1	636	6.10	14.61
Kim, 2019	Gastric	Diagnosis or precancerous lesion	BIA ASM/BW: M <29.3, F = 27.6%	BMI ≥25 kg/m^2	8356	13.50	n/a
Lodewick, 2015	Colorectal	Metastatic (liver)	CT L3 SMI: M≤43 or 53 if BMI <25 or ≥ 25 kg/m^2 respectively, F ≤41 cm^2/m^2	% Body fat: M >35.7, F >44.4	80	28.70	71.00
Malietzis, 2016	Coloretal	Resectable	CT L3 SMI: M ≤52.4, F ≤38.5 cm^2/m^2	BMI ≥30 kg/m^2	805	9.90	39.20
Han, 2020	Rectal	Non-metastatic	VFA/TAMA >3.2	1384	22.20	n/a	
Giani, 2020	Rectal	Before surgery	VFA/SMI: M >1.82, F >1.89	173	24.86	32.30	
Liver cancer							
Itoh, 2016	HCC	Transplant	CT L3 SMI: M <43.75, F <41 cm^2/m^2	Q4 − muscle:visceral fat ratio	153	24.80	n/a
Kobayashi, 2017	HCC	Resectable	CT L3 SMI: M ≤40.31, F ≤30.88 cm^2/m^2	visceral fat ≥100 cm^2	465	7.00	n/a
Kroh, 2018	HCC	Resectable	CT L3 SMI: M ≤43 or 53 if BMI <25 or ≥ 25 kg/m^2 respectively, F ≤41 cm^2/m^2	Visceral fat > third quintile M or F	70	30.00	n/a
Pancreas cancer							
Tan, 2009	Pancreas	Locally advanced	CT L3 SMI: M ≤52.4, F ≤38.5 cm^2/m^2	BMI ≥25 kg/m^2	62	16.20	40.90
Dalal, 2012	Pancreas	Locally advanced	CT L3 SMI: M ≤52.4, F ≤38.5 cm^2/m^2	BMI ≥30 kg/m^2	41	14.60	26.10
Dalal, 2012	Pancreas	Locally advanced	CT L3 SMI: M ≤52.4, F ≤38.5 cm^2/m^2	BMI ≥25 kg/m^2	41	36.60	62.20
Rollins, 2016	Pancreas	Non-resectable	CT L3 SMI: M ≤43 or 53 if BMI <25 or ≥25 kg/m^2 respectively, F ≤41 cm^2/m^2	BMI ≥25 kg/m^2	228	25.40	59.80
Sandini, 2016	Pancreas	Resectable	CT L3 SMI: M ≤43 or 53 if BMI <25 or ≥25 kg/m^2 respectively, F ≤41 cm^2/m^2	Visceral fat: M >2.8, F >2.4	124	n/a	n/a
Gruber, 2019	Pancreas	Resectable	CT L3 SMI: M ≤52.4, F ≤38.5 cm^2/m^2	BMI≥25 kg/m^2	133	n/a	25.60
Kays, 2018	Pancreas	Advanced, chemotherapy	CT L3 SMI: M ≤52.4, F ≤38.5 cm^2/m^2	BMI ≥30 kg/m^2	53	11.00	25.00
Pecorelli, 2018	Pancreas	Before surgery	VFA/TAMA >3.2	120			
Ryu, 2020	Pancreas	Before surgery	VFA/SMI>2.5	548	36.90	n/a	
Sandini, 2018	Pancreas	Neoadjuvant chemotherapy	CT L3 SMI: M ≤43 or 53 if BMI <25 or ≥25 kg/m^2 respectively, F ≤41 cm^2/m^2	Fat mass >25%	193	13.47	n/a

(*continued*)

Table 1 (*Continued*)

First author, year	Site	Disease stage	Criteria for		Studied patients	Prevalence (%) among	
			Sarcopenia	Obesity	n	all	obese
Genitourinary cancers							
Kocher, 2017	Upper tract urothelial carcinoma UTUC	Resectable	CT L3 SMI: M ≤55, F ≤39 cm^2/m^2	BMI ≥30 kg/m^2	100	18.00	n/a
Cushen, 2016	Prostate	Metastatic	CT L3 SMI: M ≤43 or 53 if BMI <25 or ≥25 kg/m^2 respectively, F ≤41 cm^2/m^2	BMI ≥25 kg/m^2	63	12.60	34.80
Kimura, 2019	Prostate	Androgen deprivation therapy	Asia Working Group for Sarcopenia algorithm (SMI <7 kg/m^2 and low function)	Fat mass >25%	89	13.40	30.43
Breast cancer							
Rier, 2012	Breast	Metastatic	CT L3 SMI ≤41 cm^2/m^2	BMI ≥30 kg/m^2	166	7.20	n/a
Del Fabbro, 2012	Breast	Early stage	CT L3 SMI: M ≤52.4, F ≤38.5 cm^2/m^2	BMI ≥25 kg/m^2	129	2.30	5,90
Other sites							
Jabbour, 2019	Lymphoma	Before transplant	VFA/SMI: M >2.8, F >2.4	93	42.00	n/a	
Heidelberger, 2017	Melanoma	Treated with immunotherapy	CT L3 SMI: M ≤52.4, F ≤38.5 cm^2/m^2	BMI ≥25 kg/m^2	68	19.00	27.90
Multiple site studies							
Prado, 2008	Various sites (advanced respiratory, colorectal, other GI)	Any	CT L3 SMI: M ≤52.4, F ≤38.5 cm^2/m^2	BMI ≥30 kg/m^2	250	n/a	5.90
Prado, 2013	Lung, Colon	Advanced	DXA ASMI: M <7.26, F <5.45 kg/m^2	BMI ≥25 kg/m^2	28	n/a	34.20
Hopancı Bıçaklı, 2019	Various, geriatric (colorectal, gastric, pancreas, liver, biliary tract)	Before chemotherapy	BIA SMI: M <10.76, F <6.76 kg/m^2	BMI ≥25 kg/m^2	153	30.00	n/a

ASM, appendicular skeletal muscle mass; BIA, bioelectrical impedance analysis; BMI, body mass index; BW, body weight; CT, computer-aided tomography; DXA, dual-energy x-ray absorptiometry; HCC, hepatic cell carcinoma; MRI, magnetic resonance imaging; NSCLC, non-small-cell lung carcinoma; PMID, Pubmed ID; SCC, squamous cell carcinoma; SMI, skeletal muscle index; SMM, skeletal muscle mass; TAMA, total abdominal muscle area; TPA, total psoas area; VFA, visceral fat area

to clinical outcomes in cancer patients. The prevalence of sarcopenic obesity greatly varied among studies, being reported between 1% and 29% in studies including individuals from all BMI categories and between 15% and 36% for those including obese individuals only. In selected cohorts previously screened for surgical eligibility, sarcopenic obese individuals could account for >50% of the studied group [62]. Analysis showed that sarcopenic obesity was associated with higher risk for dose-limiting toxicity, surgical complications, physical disability, and shorter survival times [18]. Additionally, Mintziras et al. investigated the association between sarcopenic obesity and clinical outcomes in patients with pancreatic cancer by meta-analysis of 11 studies and found that sarcopenic obesity was reported in 0.6% to 25%, and was significantly associated with poorer OS (hazard ratio, 2.01; 95% confidence interval [CI], 1.55−2.61; $P < 0.001$). The risk for mortality was 1.4 times higher in sarcopenic patients and twice as high for those with sarcopenia who were obese [63].

On the one hand, it must again be recognized that the use of different cutoffs and diagnostic criteria among studies, in combination with the broad spectrum of differentiated metabolic effects among different cancers, is a strong limitation for fully consistent analyses, comparisons, and study result interpretation. Moreover, only part of available studies provides standardized information on outcomes, and often bases analyses on limited sample numerosity, thus being possibly affected by low statistical power. On the other hand, it is important to observe that despite these limitations, the majority of the authors agrees that sarcopenic obesity is a relevant problem in patients with cancer, where it represents a negative prognostic factor.

Body composition assessment: importance and limitations

As discussed, body composition analysis is of major importance in the assessment of sarcopenic obesity. Although various techniques have been developed, each presents specific advantages and disadvantages. These include bioelectrical impedance analysis (BIA), dual-energy x-ray absorptiometry (DXA), CT, and magnetic resonance imaging (MRI). CT and MRI are currently considered the gold standards for estimating muscle mass [64,65]. Both imaging modalities are obtained as part of the standard patient care pathway from tumor staging to response assessment and surveillance, thus providing an excellent opportunity to integrate body composition assessment into current patient care.

A general limitation of these imaging techniques is that they only provide anatomical information and not functional information such as muscle function. Thus, these imaging findings must be considered in conjunction with formal assessment of muscle function, particularly in the diagnosis of dynamo-sarcopenia [65]. However, there is a suggestion that skeletal muscle attenuation on CT (Hounsfield units [HU]) may potentially be considered a marker reflecting muscle function [66,67], with reduced HU within skeletal muscle representing increased intramuscular lipid deposition, which has been observed in several conditions including obesity and cancer [68−70]. Moreover, reduced skeletal muscle attenuation has been found to be a negative prognostic factor in patients with gastrointestinal and respiratory tract cancers [5,70]. Although validated assessments, including handgrip strength, 6-minute walk, chair stand, and balance tests are to be primarily recommended for muscle function assessment and sarcopenia diagnosis [65], muscle attenuation, available from cancer-staging CT scans, should be considered, especially when direct measurements are not possible.

Importantly, in addition to its potential prognostic effects, body composition may also affect individual tolerance to non-surgical treatment and could be predictive of treatment toxicity, as detailed in the “impact on non-surgical cancer treatments” section.

An objective assessment of body composition using cross-sectional imaging techniques such as CT and MRI has the potential to complement the current clinical and nutritional evaluation of patient fitness and treatment tolerability. This information can be obtained from standard diagnostic scans performed during the various stages of patient care. Nutritional support could then be initiated at an earlier and appropriate stage, which could improve treatment compliance and clinical outcome [71,72].

Molecular mechanisms potentially involved in the interaction between sarcopenic obesity and cancer

The decline in skeletal muscle mass and strength, which defines sarcopenia, is associated with several important specific changes at molecular level in skeletal muscle. However, sarcopenic obesity also features increased fat mass, which is in turn associated with other important molecular mechanisms at both tissue and systemic levels. Collectively, sarcopenic obesity is characterized by reduced baseline metabolic rate, decreased mitochondrial number and volume, and increased oxidative stress, which exacerbates metabolic derangements in a vicious cycle [3,73]. Importantly, both adipose tissue and skeletal muscle also interplay with several cancers at multiple metabolic levels [74−76], accounting for added complexity to the physiopathology of the interaction between sarcopenic obesity and cancer. Although sarcopenic obesity- and cancer-related molecular mechanisms are relatively well characterized, their interaction is largely unknown. To our knowledge, very few studies have specifically investigated molecular signaling pathways in the context of sarcopenic obesity in cancer. As mechanisms involved in the pathogenesis of metabolic derangements related to obesity are at least in part shared with pathways modulating cancer-related sarcopenia, further research could lead to identify in these common pathways specific regulators of cancer-associated sarcopenic obesity. To this purpose, some relevant information is

available from studies on sarcopenic obesity in the context of aging and other chronic diseases, and emerging evidence as well as pathway-sharing analysis may contribute to identify several mechanisms for further investigation.

In chronic diseases, as well as in cancer, changes in body composition are known to be strongly related to increased inflammation, low physical activity, inadequate nutrition, and neurodegenerative diseases [56,74,77]. Body composition imbalances importantly involve complex interactions among underlying mechanism, both within and between different cell types, including energetic inefficiency at mitochondrial level, oxidative stress, reduced protein anabolic pathways, and activation of proteolytic pathways [78].

Molecular mechanism of sarcopenic obesity also include a switch from type II muscle fiber to slow type I muscle fibers and increased lipid deposition and adipocytes infiltration [3,79]. Skeletal muscle fat infiltration, or myosteatosis, in its various forms, is an emerging factor associated with both systemic and muscular metabolic dysfunction and function loss [80,81]. Importantly, recent evidence shows that myosteatosis is generally associated with lower muscle mass and strength and is endemic in cancer-associated malnourished patients [17,80]. Fatty acid excess in relation to slow oxidative capacity of skeletal muscle causes the development of intramyocellular lipid (IMCL), which comprises triacylglycerol and other lipid intermediates, such as diacylglycerol, long-chain acetyl coenzyme A, sterol esters, and sphingolipids [82–84]. These lipids activate phosphoinositide 3-kinases and block glucose transporter type 4 (GLUT4) translocation through protein kinase C and insulin receptor substrate-1 phosphorylation [85]. GLUT4 is a membrane transporter of glucose from blood into myocytes and its dysfunction results in decreased glucose utilization and increased fatty acid oxidation in the mitochondria with an increase of adenosine triphosphate/adenosine diphosphate ratio resulting in the inhibition of mitochondrial respiration, increase in reactive oxygen species (ROS) formation, myocyte toxicity, and finally, development of sarcopenia [86]. In addition to IMCL, intermuscular adipose tissue contributes to secrete myostatin, mononuclear chemoattractant protein-1, tumor necrosis factor-α, interleukin (IL)-1 β, and IL-6, factors known to induce lipotoxicity and insulin resistance (IR) [87]. Similar effects are also associated with intramuscular adipose tissue (i.e., ectopic fat accumulation between muscle fibers) [80]. Globally taken, available data point at myosteatosis as a potentially relevant factor for sarcopenic obesity effects in the cancer setting. In agreement with metabolic disruptions associated with histological findings related to various forms of fat accumulation in skeletal muscle, reduced muscle radiodensity, the typical radiologic presentation of myosteatosis [5], has been associated with IR [88], mitochondrial dysfunction [89], and decreased muscle contractile force in humans [90]. Through these mechanisms, myosteatosis could therefore also contribute to further muscle dysfunction in sarcopenic obese cancer patients. Low insulin sensitivity and activity in skeletal muscle is, in fact, also an important down-regulator of muscle anabolism in chronic diseases [73,91,92]. Furthermore, ectopic fat deposition surrounding muscle, peri-muscular adipose tissue, enhances nuclear translocation of the forkhead box O (FoxO) transcription factors and upregulates Atrogin1 and MuRF1, leading to proteolysis in muscle tissues [93], contributing to further enhance muscle loss and worsen outcome. In addition to inducing metabolic dysfunction, missed detection of myosteatosis may also mask the loss of muscle mass in patients with cancer, potentially leading to worse outcomes. Importantly, myosteatosis is also an independent predictor of reduced survival in cancer [17,32,41]. In 322 patients with primary operable colorectal cancer [94], only myosteatosis and not visceral obesity or sarcopenia was associated with both OS and disease-specific survival at univariate analysis. However, this finding turned out not to be independent of inflammatory parameters [94], supporting the hypothesis that however strong the effects of myosteatosis on survival outcomes, the role of covariates in mediating its effects must always be considered and requires further investigation.

Moreover, cancer importantly affects skeletal muscle and adipose tissue metabolism also by interfering with pathways controlled by hormones [75]. Insulin, IR, and ghrelin are known to play a role in body composition in patients with cancer [95]. Skeletal muscle is known to be bidirectionally involved in the pathophysiology of obesity and related complications, with its metabolism and trophism being modulated by insulin levels and signaling activation [96]. More recently, unacylated ghrelin, another hormone that is modified in its levels by obesity [97], has been shown to modulate skeletal muscle metabolism, including the ability to recover muscle mass loss in a rodent model of muscle wasting [91,98]. Adipose tissue metabolism is also largely modulated by insulin as well as by several other hormones [99]. Interlinked metabolic hormone networks may thus deserve further investigation as far as their involvement in the interaction between sarcopenic obesity and cancer is concerned.

Both muscle and adipose tissue can be considered endocrine organs, as they are also known to release myokines and adipokines, respectively [99,100]. These hormones, which include myostatin, cytokines, leptin, and adiponectin, strongly contribute to modulate both skeletal muscle and adipose metabolism, in the context of a signaling network involving all tissues and mechanisms involved in energy balance [100] and are also known to be involved in several cancer-induced alterations of body composition [101]. Similarly, among most investigated interactions, low-grade adipose tissue inflammation with proinflammatory cytokine levels upregulation has emerged as a key feature of obesity and a driving for associated metabolic derangements, but also as a major player in cancer- and non-cancer–related muscle wasting [16,77,78]. Globally, these findings suggest that crosstalk between muscle and adipose tissue may be of potential primary importance in the context of cancer-associated sarcopenic obesity. Moreover, they also provide a strong rationale for considering sarcopenic obesity as well as the coexistence of two separate conditions.

Another emerging potential mechanism that requires further investigation is represented by endoplasmic reticulum (ER) stress and changes in tissue redox state. This mechanism is triggered by accumulation of unfolded or misfolded proteins within the ER in cancer [102] and causes an adaptive response involving ROS signaling via upregulation of NADPH oxidase 2 [102,103]. Interestingly, ER stress is associated with muscle mass loss as well as adiposity and dyslipidemia [102,104]. Potential importance of oxidative stress–related pathways is also shown by recent studies on natural antioxidants such as vitamins C, E, A, quercetin, curcumin, and resveratrol, which are involved in ROS moderation. Antioxidant supplementation is currently considered a potential intervention strategy in sarcopenia treatment, although no evidence is currently available in cancer setting.

Sarcopenic obesity in cancer treatment and outcome

As known, obesity per se entails many negative metabolic effects such as type 2 diabetes mellitus, hypertension, and dyslipidemia. Loss of muscle mass is also known to lead to poorer outcomes in several clinical settings. In sarcopenic obesity, as the burden of both sarcopenia and obesity is combined, evidence show a worse, at least cumulative effect on health outcomes [105]. In fact, patients with cancer and sarcopenic obesity present multiple specific negative clinical outcomes, including higher risk for dose-limiting toxicity, surgical complications, longer hospitalization, physical disability, and shorter survival [18] (Fig. 1).

Importantly, sarcopenic obesity does not only affect general outcome by modulating cancer-associated metabolic derangements, but it may also directly favor carcinogenesis and cancer progression. In fact, a recent study by Kim et al. showed that sarcopenia and sarcopenic obesity were significantly associated with gastric carcinogenesis [26]. However, this finding is likely related to factors such as diabetes mellitus, hypertension, and dyslipidemia, which are also per se significantly associated with gastric carcinogenesis [26], in line with current evidence indicating obesity and related metabolic complications as strong risk factors for cancer development [106].

Patients with sarcopenic obesity indeed show both lower survival and increased risk for severe complications in surgical and systemic cancer treatment, across multiple cancer sites [2] including hepatocellular [35] and urothelial carcinoma [47], and pancreatic [62], gastric [26], colorectal [107], head and neck, and bladder cancers [108] (Tables 2 and 3).

Effects on overall prognosis

In a study specifically addressing OS, Prado et al. found that sarcopenic obesity was a significant independent prognostic factor in patients with gastrointestinal and respiratory tract cancers [12]. Patients with coexisting sarcopenic obesity, along with lower OS, also had poorer functional status. These findings were also confirmed in patients with advanced pancreatic cancer [53]. Kobayashi et al. retrospectively analyzed 465 patients who underwent primary hepatectomy for hepatocellular carcinoma. Patients with sarcopenic obesity displayed worse median survival and worse median recurrence-free survival. Moreover, multivariate analysis identified sarcopenic obesity as a significant risk factor for death and hepatocellular carcinoma recurrence after hepatectomy for hepatocellular carcinoma [35]. Another retrospective analysis with 441 normal weight, overweight, and obese patients with head and neck squamous carcinoma, highlighted the effects of sarcopenic obesity: a poorer survival compared with non-sarcopenic patients,

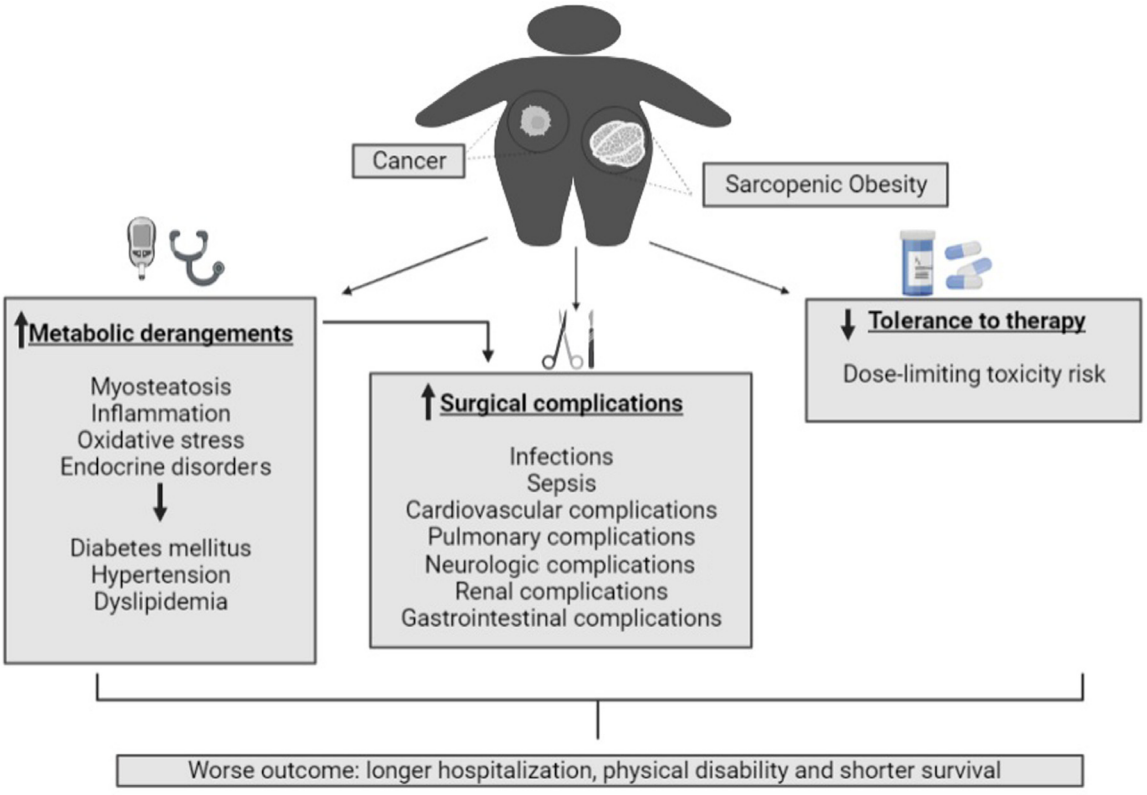

Fig. 1. Schematic representation of the broad clinical effects of sarcopenic obesity in cancer patients.

with the strongest association seen among overweight and obese patients [109]. Recent research by Chargi et al. on patients with oropharyngeal squamous cell carcinoma assessed sarcopenic obesity as a strong negative prognostic factor for OS and disease-free survival [21].

Effects on cancer surgery complications

Surgical complications in obesity can include infections, sepsis, and cardiovascular, pulmonary, neurologic, renal, or gastrointestinal complications. Moreover, sarcopenia is also related to higher prevalence of morbidity after surgery [110]. Some studies have investigated the effects of sarcopenic obesity on surgical complications and survival in different cancer settings.

Recently, Baracos and Arribas analyzed a possible relation between surgical complications and sarcopenic obesity, especially in colorectal, gastric, and pancreatic cancers [2]. Lou et al. demonstrated that patients with sarcopenic obesity independently had sixfold increased risk for developing severe complications after gastrectomy for gastric cancer [27]. Similar results were reported in patients with sarcopenic obesity who were at increased risk for developing surgical site infection after a laparoscopic gastrectomy for gastric cancer [28]. Additionally, patients with sarcopenic obesity had higher hospital costs and 30-d readmission rate after gastrectomy [27], higher prevalence of surgical complications such as abscess, cardiac, and pulmonary complications after pancreatoduodenectomy [43], compared with non-sarcopenic obese patients. Pecorelli et al. also found that sarcopenic obesity was associated with a significantly higher risk for failure to recovery from major complications after pancreaticoduodenectomy [62]. Malietzis et al [34]. reported a higher rate of major surgical complications in colorectal cancer in patients with sarcopenic obesity and increased mortality within 1 mo.

Effects on non-surgical cancer treatments

In addition to its potential prognostic effects, in recent years there has been increasing interest in the influence of body composition on patients with cancer as it may also affect the efficacy and toxicity of chemotherapy, with further effects on patient outcomes [12,111–114]. It has been demonstrated that chemotherapy can alter body composition reducing fat-free mass, thus favoring the development of sarcopenic obesity [115,116], with a significant effect on patient's tolerance to cancer therapy [117].

Body surface area (BSA) is currently the major parameter used to calculate cytotoxic chemotherapy dose. This index, derived from patient height and weight, is associated with several potential limitations and it is especially challenging in obese patients, at risk for under- or overdosing [118]. Prado et al. showed that lean body mass, instead of BSA, was a significant predictor of dose-limiting toxicity in patients treated with 5-fluorouracil and leucovorin for colon cancer. In particular, the risk for toxicity is increased in female patients caused by lower lean body mass compared with their BSA [112].

A better characterization of the specific effects of sarcopenic obesity in chemotherapy protocols and outcomes is therefore an emerging challenge. Among available data, sarcopenic and sarcopenic obese patients with esophageal cancer have been shown to be at a higher risk for developing dose-limiting toxicity during chemotherapy compared with non-sarcopenic patients with esophageal cancer [14]. Patients with dose-limiting toxicity had lower skeletal muscle mass than those without dose-limiting toxicity. Patients with sarcopenia showed a significant increase in dose-

Table 2
Impact of sarcopenic obesity on overall survival and disease-free survival

First author, year	Site	Disease stage	n (SO)	Impact of Sarcopenic Obesity on	
				Overall survival	Disease-free survival
Oropharingeal cancer					
Chargi, 2020	Oropharyngeal SCC	Diagnosis	13	Lower HR, 4.42; 95% CI, 1.52−12.90, $P <$ 0.01	Lower HR 3.90; 95% CI, 1.03−14.75, $P < 0.05$
Fattouh 2018	Head and neck cancer	Invasive	30	Lower HR, 2.08; 95% CI, 1.1−3.9, $P = 0.021$	n/a
Lung cancer					
Kiss, 2018	NSCLC	Chemoradiation	6	NS	n/a
Gastrointestinal tract					
Palmela, 2017	Esophageal/Gastric cardia	Neoadjuvant chemotherapy	5	Lower survival of 6 mo (95% CI, 3.9−8.5) vs 25 mo (95% CI, 20.2−38.2), log-rank test $P <0.001$	n/a
Dijksterhuis, 2019	Esophageal/Gastric cardia	Palliative chemotherapy	18	NS	NS
Malietzis, 2016	Colorectal	Resectable	73	Lower $P < 0.001$ vs non-SO	NS
Han, 2020	Rectal	Non metastatic	307	Lower (5 y) $P = 0.02$ vs non-SO	NS
Liver cancer					
Itoh, 2016	HCC	Transplant	12	Lower HR, 2.58; 95% CI, 1.17−5.52, $P = 0.019$	lower HR 5.26; 95% CI, 2.03−13.8, $P < 0.001$
Kobayashi, 2017	HCC	Resectable	31	lower HR, 2.504; 95% CI, 1.336−4.499, $P = 0.005$	lower HR, 2.031; 95% CI, 1.233−3.222, $P = 0.006$
Kroh, 2018	HCC	Resectable	21	NS	n/a
Pancreas cancer					
Tan, 2009	Pancreas	Locally advanced	18	Lower HR, 2.07; 95% CI, 1.23−3.50, $P = 0.006$	n/a
Dalal, 2012	Pancreas	Locally advanced	15	NS at multivariate	n/a
Rollins, 2016	Pancreas	Non-resectable	58	Lower $P = 0.049$ vs non-SO	n/a
Gruber, 2019	Pancreas	Resectable	34	Lower HR, 1.02; 95% CI, 1.00−1.03, $P <0.007$	n/a
Genitourinary cancers					
Kocher, 2017	Upper tract urothelial carcinoma	Resectable	18	n/a	Lower $P = 0.049$ vs non-SO
Cushen, 2016	Prostate	Metastatic	8	NS	n/a
Breast cancer					
Rier, 2012	Breast	Metastatic	12	NS	NS (Time to next treatment)
Other sites					
Jabbour, 2019	Lymphoma	Before transplant	39	Lower HR, 8.2; 95% CI, 1.9−36.2, $P = 0.06$	Lower $P = 0.047$ vs non-SO
Multiple-site studies					
Prado, 2008	Various sites (advanced respiratory, colorectal, other GI)	Any	38	Lower HR, 4.2; 95% CI, 2.4−7.2, $P < 0.0001$	n/a

HCC, hepatic cell carcinoma; HR, hazard ratio; SO, sarcopenic obese; n (SO), number of SO individuals assessed in the study*; NSCLC, non-small-cell lung carcinoma; NS, non-significant.
*For prevalence in the cohort refer to Table 1.

limiting toxicity risk. In patients with sarcopenic obesity, dose-limiting toxicity risk increased significantly.

Recently, Heidelberger et al. retrospectively investigated the early acute limiting toxicity of anti-PD1 in patients with melanoma treated with nivolumab or pembrolizumab. In this study, women with sarcopenia who were overweight had a 6.5-fold increased risk for acute limiting toxicity [51].

Sarcopenic obesity as a potential target in cancer therapy strategies

As described, sarcopenia in patients with cancer can coexist with obesity and is importantly defined by loss of muscle mass and strength. Although obesity is not univocally linked to worse outcome in all cancer types [119], low muscle mass is common in every stage of cancer and it is clearly recognized as an independent predictor factor of cancer progression, surgical complications, poorer survival, worse quality of life, and physical function [12,55,112,117], making it the prevalent target in sarcopenic obesity treatment approaches. Restoring an appropriate nutritional status with specific aim to revert low muscle mass and function could, in fact, be a potential strategy to ameliorate therapy outcomes, morbidity, and mortality in cancer patients with sarcopenic obesity [120]. Nevertheless, a nutritional approach is often not considered a priority in cancer therapy, mainly due to the low number of scientific evidences and experimental studies [71,72,121].

A recent review by Prado et al. addressed the role of nutrition in preventing and reversing sarcopenia in patients with cancer [120],

Table 3
Effects of SO on surgical and non-surgical cancer treatment.

First author, year	Site	Disease stage	n (SO)	Effect of SO on cancer treatment
Gastrointestinal tract				
Anandavadivelan, 2016	Esophageal/Gastric cardia	Neoadjuvant chemotherapy	10	Risk for dose-limiting toxicity increased OR, 5.54; 95% CI, 1.12−27.44, $P = 0.04$
Lou, 2016	Gastric	Resectable	14	Risk for major complications after gastrectomy increased OR, 6.071; 95% CI, 1.904−19.359, $P = 0.002$
Nishigori, 2016	Gastric	Resectable	45	Risk for surgical site infection after laparoscopic total gastrectomy increased OR, 4.59; 95% CI, 1.18−17.78, $P = 0.028$
Zhang, 2018,	Gastric	Resectable	39	Risk for severe postoperative complications increased vs normal OR, 6.575, $P = 0.001$ Risk for severe postoperative complications increased vs non-sarcopenic obese OR, 5.833, $P = 0.001$
Malietzis, 2016	Coloretal	Resectable	73	Associated with higher 30-d morbidity $P = 0.019$
Giani, 2020	Rectal	Before surgery	43	Overall and infectious morbidity, anastomotic failure and failure to rescue risk variation NS
Pancreas cancer				
Sandini, 2016	Pancreas	Resectable	n/a	Risk for complications after pancreatoduodenectomy increased OR, 3.20; 95% CI, 1.35−7.60, $P = 0.008$
Pecorelli, 2018	Pancreas	Before surgery	63	Probability of death after a complication increased OR, 5.7; 95% CI, 1.6−20.7, $P = 0.008$
Gruber, 2019	Pancreas	Resectable	34	Incidence of major postoperative complications increased $P < 0.001$ vs non-sarcopenic obese
Ryu, 2020	Pancreas	Before surgery	202	Risk for clinically relevant postoperative pancreatic fistula increased OR, 2.561; 95% CI, 1.18−5.56, $P = 0.018$ (Only independent risk factor at multivariate analysis)
Genitourinary cancers				
Kocher, 2017	Upper tract urothelial carcinoma UTUC	Resectable	18	Risk for perioperative complications variation NS
Other sites				
Heidelberger, 2017	Melanoma	Treated with immunotherapy	13	6.5-fold increased risk for acute-limiting toxicity in women OR, 12; 95% CI, 1.4−103, $P = 0.01$

BMI, body mass index; SO, sarcopenic obese; n (SO), number of SO individuals assessed in the study*; NS, non-significant.
*For prevalence in the cohort refer to Table 1.

also potentially applicable to sarcopenic obesity. Authors discussed the importance of the micro- and macronutrient quantity and quality: energy requirements (25−30 kcal·kg·d^{-1}), high-quality proteins (1−1.5 g/kg/d^{-1}), branched-chain amino acids and metabolites (in particular, leucine: 2−4 g/d; β-hydroxy-β-methylbutyrrate: 3 g/d), glutamine (0.3 g·kg·d^{-1}), creatine (5 g/d), carnitine (4−6 g/d), fish oil (2−2.2 g/d), eicosapentanoic acid (EPA; 2.0-2.2 g/d) docosahexaenoic acid (DHA; 1.5 g/d), and vitamins/minerals (vitamin D: 600−800 U.I./d). To this purpose it is also important to note that several studies have demonstrated the preservation of sufficient anabolic potential in patients with cancer, despite age, systemic inflammation, low physical activity, or IR [122−124]. Protein intake timing can also influence muscle protein synthesis: A study on young adults assessed that a constant protein intake throughout the day enhanced daily muscle protein synthesis compared with an unbalanced protein distribution [125]. Water intake appears also to be an important factor for improving protein anabolism in patients with cancer. Although one study suggested a water intake of 3.7 L/d in men and 2.7 L/d in women [126], further research is needed.

Regarding obese patients, it would be possible to speculate whether ketogenic diet could be taken into consideration due to its beneficial and rapid effect on weight loss with limited muscle mass loss [127], and this would also apply to patients with cancer. Although very little evidence is currently available, it is important to note that the last consensus statement from the Italian Society of Endocrinology recommends the use of a very-low-calorie ketogenic diet in the context of sarcopenic obesity and patients with cancer without relevant concerns for loss of lean body mass [128]. The rapid loss of adipose tissue, without lean mass decrease, could also potentially contribute to reduce inflammation and metabolic syndrome that often characterize these patients.

However, it must be stated that no intervention study has been done so far, and that although nutritional care may seem potentially relevant for sarcopenic obese patients, no specific evidence has been published yet.

In addition to nutritional intervention, physical exercise could also be a key point in reversing sarcopenia. Both resistance training and general exercise intervention (including aerobic, resistance, flexibility, and balance training) have been shown to improve muscle mass and/or physical performance. However, these findings come from training programs that were mainly conducted in community-dwelling elderly people. Although their recommendation could potentially be challenging or not possible for patients with cancer due to various reasons, including fatigue and cancer-related pain, it should be pointed out that growing evidence has specifically highlighted some benefits of exercise training in restoring strength and endurance in cachectic cancer settings [129−131]. Further research should therefore also investigate its potential clinical relevance, per se or in combination with nutritional treatment, in patients with cancer who have sarcopenic obesity.

Finally, further understanding of the molecular pathways specifically involved in the development of sarcopenia in the context

of obesity and cancer could lead to the identification of new markers to identify and treat selected individuals who could better benefit of selected therapeutical interventions. Moreover, basic research regarding signaling networks could also importantly provide new molecular targets for therapeutic strategies aiming to preserve muscle mass and function loss and therefore related metabolic complications and poorer outcome.

Conclusions

Although consensus on definitions is still lacking, increasing evidence globally suggests that sarcopenic obesity is an emerging factor of important clinical relevance in patients with cancer, both for its important prevalence in this setting as well as for its association with negative oncologic and general outcomes. Although further research is needed to fully elucidate all molecular mechanisms involved in the pathogenesis of sarcopenic obesity with the aim of potentially identifying new markers as well as potential therapeutic targets, current evidence strongly suggests that body composition and muscle function assessment in obese patients with cancer may help identify those with poorer outcome perspective.

To this purpose, body composition evaluation from cancer-staging cross-sectional imaging could be readily applied in the clinical setting and improve individual nutritional care and perhaps chemotherapy dose calculation. This personalized cancer management strategy may contribute to a reduction in treatment-related toxicities and ultimately improve patient outcomes.

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References

[1] Roubenoff R. Excess baggage: sarcopenia, obesity, and cancer outcomes. Lancet Oncol 2008;9:605–7.
[2] Baracos VE, Arribas L. Sarcopenic obesity: hidden muscle wasting and its impact for survival and complications of cancer therapy. Ann Oncol 2018;29:ii1–9.
[3] Batsis JA, Villareal DT. Sarcopenic obesity in older adults: aetiology, epidemiology and treatment strategies. Nat Rev endocrinol 2018;14:513–37.
[4] Prado CM, Antoun S, Sawyer MB, Baracos VE. Two faces of drug therapy in cancer: drug-related lean tissue loss and its adverse consequences to survival and toxicity. Curr Opin Clin Nutr Metab Care 2011;14:250–4.
[5] 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 2013;31:1539–47.
[6] Barazzoni R, Bischoff S, Boirie Y, Busetto L, Cederholm T, Dicker D, et al. Sarcopenic obesity: time to meet the challenge. Obes Facts 2018;11:294–305.
[7] Barazzoni R, Bischoff SC, Boirie Y, Busetto L, Cederholm T, Dicker D, et al. Sarcopenic obesity: time to meet the challenge. Clin Nutr 2018;37:1787–93.
[8] Malenfant J, Batsis J. Obesity in the geriatric population – a global health perspective. J Glob Health Rep 2019;3.
[9] Nations United. World population prospects: the 2017 Revision. New York, NY: United Nations; 2017.
[10] Stenholm S, Harris TB, Rantanen T, Visser M, Kritchevsky SB, Ferrucci L. Sarcopenic obesity: definition, cause and consequences. Curr Opin Clin Nutr Metab Care 2008;11:693–700.
[11] Rolland Y, Lauwers-Cances V, Cristini C, Abellan van Kan G, Janssen I, Morley JE, et al. Difficulties with physical function associated with obesity, sarcopenia, and sarcopenic-obesity in community-dwelling elderly women: the EPIDOS (EPIDemiologie de l'OSteoporose) study. Am J clin Nutr 2009;89:1895–900.
[12] Prado CM, 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;9:629–35.
[13] Lodewick TM, van Nijnatten TJ, van Dam RM, van Mierlo K, Dello SA, Neumann UP, et al. Are sarcopenia, obesity and sarcopenic obesity predictive of outcome in patients with colorectal liver metastases? HPB (Oxford) 2015;17:438–46.
[14] Anandavadivelan P, Brismar TB, Nilsson M, Johar AM, Martin L. Sarcopenic obesity: a probable risk factor for dose limiting toxicity during neo-adjuvant chemotherapy in oesophageal cancer patients. Clin Nutr 2016;35:724–30.
[15] Kyrgiou M, Kalliala I, Markozannes G, Gunter MJ, Paraskevaidis E, Gabra H, et al. Adiposity and cancer at major anatomical sites: umbrella review of the literature. Bmj 2017;356:j477.
[16] Baracos VE. Cancer-associated cachexia and underlying biological mechanisms. Ann Rev Nutr 2006;26:435–61.
[17] Martin L, Gioulbasanis I, Senesse P, Baracos VE. Cancer-associated malnutrition and CT-defined sarcopenia and myosteatosis are endemic in overweight and obese patients. JPEN J Parenter Enteral Nutr 2020;44:227–38.
[18] Carneiro IP, Mazurak VC, Prado CM. Clinical implications of sarcopenic obesity in cancer. Curr Oncol Rep 2016;18:62.
[19] Donini LM, Busetto L, Bauer JM, Bischoff S, Boirie Y, Cederholm T, et al. Critical appraisal of definitions and diagnostic criteria for sarcopenic obesity based on a systematic review. Clin Nutr 2020;39:2368–88.
[20] Waters DL, Baumgartner RN. Sarcopenia and obesity. Clin Geriatr Med 2011;27:401–21.
[21] Chargi N, Bril SI, Swartz JE, Wegner I, Willems SM, de Bree R. Skeletal muscle mass is an imaging biomarker for decreased survival in patients with oropharyngeal squamous cell carcinoma. Oral Oncol 2020;101:104519.
[22] Kiss N, Beraldo J, Everitt S. Early skeletal muscle loss in non-small cell lung cancer patients receiving chemoradiation and relationship to survival. Support Care Cancer 2019;27:2657–64.
[23] Recio-Boiles A, Galeas JN, Goldwasser B, Sanchez K, Man LMW, Gentzler RD, et al. Enhancing evaluation of sarcopenia in patients with non-small cell lung cancer (NSCLC) by assessing skeletal muscle index (SMI) at the first lumbar (L1) level on routine chest computed tomography (CT). Support Care Cancer 2018;26:2353–9.
[24] Dijksterhuis WPM, Pruijt MJ, van der Woude SO, Klaassen R, Kurk SA, van Oijen MGH, et al. Association between body composition, survival, and toxicity in advanced esophagogastric cancer patients receiving palliative chemotherapy. J Cachexia Sarcopenia Muscle 2019;10:199–206.
[25] Grotenhuis BA, Shapiro J, van Adrichem S, de Vries M, Koek M, Wijnhoven BP, et al. Sarcopenia/muscle mass is not a prognostic factor for short- and long-term outcome after esophagectomy for cancer. World J Surg 2016;40:2698–704.
[26] Kim YM, Kim JH, Baik SJ, Chun J, Youn YH, Park H. Sarcopenia and sarcopenic obesity as novel risk factors for gastric carcinogenesis: a health checkup cohort study. Front Oncol 2019;9:1249.
[27] Lou N, Chi CH, Chen XD, Zhou CJ, Wang SL, Zhuang CL, et al. Sarcopenia in overweight and obese patients is a predictive factor for postoperative complication in gastric cancer: a prospective study. Eur J Surg Oncol 2017;43:188–95.
[28] Nishigori T, Tsunoda S, Okabe H, Tanaka E, Hisamori S, Hosogi H, et al. Impact of sarcopenic obesity on surgical site infection after laparoscopic total gastrectomy. Ann Surg Oncol 2016;23:524–31.
[29] Palmela C, Velho S, Agostinho L, Branco F, Santos M, Santos MP, et al. Body composition as a prognostic factor of neoadjuvant chemotherapy toxicity and outcome in patients with locally advanced gastric cancer. J Gastric Cancer 2017;17:74–87.
[30] Sugawara K, Yamashita H, Okumura Y, Yagi K, Yoshimura S, Kawasaki K, et al. Relationships among body composition, muscle strength, and sarcopenia in esophageal squamous cell carcinoma patients. Support Care Cancer 2020;28:2797–803.
[31] Zhang WT, Lin J, Chen WS, Huang YS, Wu RS, Chen XD, et al. Sarcopenic obesity is associated with severe postoperative complications in gastric cancer

patients undergoing gastrectomy: a prospective study. J Gastrintest Cancer 2018;22:1861–9.
[32] Giani A, Famularo S, Riva L, Tamini N, Ippolito D, Nespoli L, et al. Association between specific presurgical anthropometric indexes and morbidity in patients undergoing rectal cancer resection. Nutrition 2020;75–76:110779.
[33] Han JS, Ryu H, Park IJ, Kim KW, Shin Y, Kim SO, et al. Association of body composition with long-term survival in non-metastatic rectal cancer patients. Cancer Res Treat 2020;52:563–72.
[34] Malietzis G, Currie AC, Athanasiou T, Johns N, Anyamene N, Glynne-Jones R, et al. Influence of body composition profile on outcomes following colorectal cancer surgery. Br J Surg 2016;103:572–80.
[35] Kobayashi A, Kaido T, Hamaguchi Y, Okumura S, Shirai H, Yao S, et al. Impact of sarcopenic obesity on outcomes in patients undergoing hepatectomy for hepatocellular carcinoma. Ann Surg 2019;269:924–31.
[36] Kroh A, Uschner D, Lodewick T, Eickhoff RM, Schoning W, Ulmer FT, et al. Impact of body composition on survival and morbidity after liver resection in hepatocellular carcinoma patients. Hepatobiliary Pancreatic Dis Int 2019;18:28–37.
[37] Itoh S, Yoshizumi T, Kimura K, Okabe H, Harimoto N, Ikegami T, et al. Effect of sarcopenic obesity on outcomes of living-donor liver transplantation for hepatocellular carcinoma. Anticancer Res 2016;36:3029–34.
[38] Dalal S, Hui D, Bidaut L, Lem K, Del Fabbro E, Crane C, et al. Relationships among body mass index, longitudinal body composition alterations, and survival in patients with locally advanced pancreatic cancer receiving chemoradiation: a pilot study. J Pain Symptom Manage 2012;44:181–91.
[39] Gruber ES, Jomrich G, Tamandl D, Gnant M, Schindl M, Sahora K. Sarcopenia and sarcopenic obesity are independent adverse prognostic factors in resectable pancreatic ductal adenocarcinoma. PLoS One 2019;14:e0215915.
[40] Kays JK, Shahda S, Stanley M, Bell TM, O'Neill BH, Kohli MD, et al. Three cachexia phenotypes and the impact of fat-only loss on survival in FOLFIRINOX therapy for pancreatic cancer. J Cachexia Sarcopenia Muscle 2018;9:673–84.
[41] Rollins KE, Tewari N, Ackner A, Awwad A, Madhusudan S, Macdonald IA, et al. The impact of sarcopenia and myosteatosis on outcomes of unresectable pancreatic cancer or distal cholangiocarcinoma. Clin Nutr 2016;35:1103–9.
[42] Ryu Y, Shin SH, Kim JH, Jeong WK, Park DJ, Kim N, et al. The effects of sarcopenia and sarcopenic obesity after pancreaticoduodenectomy in patients with pancreatic head cancer. HPB (Oxford) 2020;22:1782–92.
[43] Sandini M, Bernasconi DP, Fior D, Molinelli M, Ippolito D, Nespoli L, et al. A high visceral adipose tissue-to-skeletal muscle ratio as a determinant of major complications after pancreatoduodenectomy for cancer. Nutrition 2016;32:1231–7.
[44] Sandini M, Patino M, Ferrone CR, Alvarez-Perez CA, Honselmann KC, Paiella S, et al. Association between changes in body composition and neoadjuvant treatment for pancreatic cancer. JAMA Surg 2018;153:809–15.
[45] Van Aller C, Lara J, Stephan BCM, Donini LM, Heymsfield S, Katzmarzyk PT, et al. Sarcopenic obesity and overall mortality: results from the application of novel models of body composition phenotypes to the National Health and Nutrition Examination Survey 1999–2004. Clin Nutr 2019;38:264–70.
[46] Kimura Y, Yamada M, Ohji S, Ishiyama D, Nishio N, Otobe Y, et al. Presence of sarcopenic obesity and evaluation of the associated muscle quality in Japanese older men with prostate cancer undergoing androgen deprivation therapy. J Geriatr Oncol 2019;10:835–8.
[47] Kocher NJ, Jafri S, Balabhadra S, Lehman E, Gardner J, Vijay K, et al. Is sarcopenia and sarcopenic obesity associated with clinical and pathological outcomes in patients undergoing radical nephroureterectomy? Urol Oncol 2018;36:156. e17–22.
[48] Cushen SJ, Power DG, Murphy KP, McDermott R, Griffin BT, Lim M, et al. Impact of body composition parameters on clinical outcomes in patients with metastatic castrate-resistant prostate cancer treated with docetaxel. Clin Nutr ESPEN 2016;13:e39–45.
[49] Del Fabbro E, Parsons H, Warneke CL, Pulivarthi K, Litton JK, Dev R, et al. The relationship between body composition and response to neoadjuvant chemotherapy in women with operable breast cancer. Oncologist 2012;17:1240–5.
[50] Rier HN, Jager A, Sleijfer S, van Rosmalen J, Kock M, Levin MD. Low muscle attenuation is a prognostic factor for survival in metastatic breast cancer patients treated with first line palliative chemotherapy. Breast 2017;31:9–15.
[51] Heidelberger V, Goldwasser F, Kramkimel N, Jouinot A, Huillard O, Boudou-Rouquette P, et al. Sarcopenic overweight is associated with early acute limiting toxicity of anti-PD1 checkpoint inhibitors in melanoma patients. Invest New Drugs 2017;35:436–41.
[52] Jabbour J, Manana B, Zahreddine A, Saade C, Charafeddine M, Bazarbachi A, et al. Sarcopenic obesity derived from PET/CT predicts mortality in lymphoma patients undergoing hematopoietic stem cell transplantation. Curr Res Transl Med 2019;67:93–9.
[53] Tan BH, Birdsell LA, Martin L, Baracos VE, Fearon KC. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. Clin Cancer Res 2009;15:6973–9.
[54] Hopanci Bicakli D, Cehreli R, Ozveren A, Meseri R, Uslu R, Karabulut B, et al. Evaluation of sarcopenia, sarcopenic obesity, and phase angle in geriatric gastrointestinal cancer patients: before and after chemotherapy. Turk J Med Sci 2019;49:583–8.
[55] Prado CM. Body composition in chemotherapy: the promising role of CT scans. Curr Opin Clin Nutr Metab Care 2013;16:525–33.
[56] Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019;48:601.
[57] Clark W, Siegel EM, Chen YA, Zhao X, Parsons CM, Hernandez JM, et al. Quantitative measures of visceral adiposity and body mass index in predicting rectal cancer outcomes after neoadjuvant chemoradiation. J Am Coll Surg 2013;216:1070–81.
[58] Rickles AS, Iannuzzi JC, Mironov O, Deeb AP, Sharma A, Fleming FJ, et al. Visceral obesity and colorectal cancer: are we missing the boat with BMI? J Gastrointest Surg 2013;17:133–43.
[59] Fedirko V, Romieu I, Aleksandrova K, Pischon T, Trichopoulos D, Peeters PH, et al. Pre-diagnostic anthropometry and survival after colorectal cancer diagnosis in Western European populations. Int J Cancer 2014;135:1949–60.
[60] Poggiogalle E, Mendes I, Ong B, Prado CM, Mocciaro G, Mazidi M, et al. Sarcopenic obesity and insulin resistance: application of novel body composition models. Nutrition 2020;75–76:110765.
[61] Siervo M, Prado CM, Mire E, Broyles S, Wells JC, Heymsfield S, et al. Body composition indices of a load-capacity model: gender- and BMI-specific reference curves. Public Health Nutr 2015;18:1245–54.
[62] Pecorelli N, Capretti G, Sandini M, Damascelli A, Cristel G, De Cobelli F, et al. Impact of sarcopenic obesity on failure to rescue from major complications following pancreaticoduodenectomy for cancer: results from a multicenter study. Ann Surg Oncol 2018;25:308–17.
[63] Mintziras I, Miligkos M, Wachter S, Manoharan J, Maurer E, Bartsch DK. Sarcopenia and sarcopenic obesity are significantly associated with poorer overall survival in patients with pancreatic cancer: systematic review and meta-analysis. Int J Surg 2018;59:19–26.
[64] Mijnarends DM, Meijers JM, Halfens RJ, ter Borg S, Luiking YC, Verlaan S, et al. Validity and reliability of tools to measure muscle mass, strength, and physical performance in community-dwelling older people: a systematic review. J Am Med Dir Assoc 2013;14:170–8.
[65] Pahor M, Manini T, Cesari M. Sarcopenia: clinical evaluation, biological markers and other evaluation tools. J Nutr Health Aging 2009;13:724–8.
[66] Liu M, Chino N, Ishihara T. Muscle damage progression in Duchenne muscular dystrophy evaluated by a new quantitative computed tomography method. Arch Phys Med Rehabil 1993;74:507–14.
[67] Visser M, Kritchevsky SB, Goodpaster BH, Newman AB, Nevitt M, Stamm E, et al. Leg muscle mass and composition in relation to lower extremity performance in men and women aged 70 to 79: the health, aging and body composition study. J Am Geriatr Soc 2002;50:897–904.
[68] Hilton TN, Tuttle LJ, Bohnert KL, Mueller MJ, Sinacore DR. Excessive adipose tissue infiltration in skeletal muscle in individuals with obesity, diabetes mellitus, and peripheral neuropathy: association with performance and function. Phys Ther 2008;88:1336–44.
[69] Khan IM, Perrard XY, Brunner G, Lui H, Sparks LM, Smith SR, et al. Intermuscular and perimuscular fat expansion in obesity correlates with skeletal muscle T cell and macrophage infiltration and insulin resistance. Int J Obes 2015;39:1607–18.
[70] Bhullar AS, Anoveros-Barrera A, Dunichand-Hoedl A, Martins K, Bigam D, Khadaroo RG, et al. Lipid is heterogeneously distributed in muscle and associates with low radiodensity in cancer patients. J Cachexia Sarcopenia Muscle 2020;11:735–47.
[71] Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr 2017;36:11–48.
[72] Arends J, Bodoky G, Bozzetti F, Fearon K, Muscaritoli M, Selga G, et al. ESPEN Guidelines on Enteral Nutrition: non-surgical oncology. Clin Nutr 2006;25:245–59.
[73] Barazzoni R, Gortan Cappellari G, Ragni M, Nisoli E. Insulin resistance in obesity: an overview of fundamental alterations. Eat Weight Disord 2018;23:149–57.
[74] Abbass T, Dolan RD, Laird BJ, McMillan DC. The relationship between imaging-based body composition analysis and the systemic inflammatory response in patients with cancer: a systematic review. Cancers 2019:11.
[75] Fouladiun M, Korner U, Bosaeus I, Daneryd P, Hyltander A, Lundholm KG. Body composition and time course changes in regional distribution of fat and lean tissue in unselected cancer patients on palliative care–correlations with food intake, metabolism, exercise capacity, and hormones. Cancer 2005;103:2189–98.
[76] Baracos VE, Martin L, Korc M, Guttridge DC, Fearon KCH. Cancer-associated cachexia. Nat Rev Dis Primers 2018;4:17105.
[77] Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity and inflammation: the linking mechanism and the complications. Arch Med Sci 2017;13:851–63.
[78] Argiles JM, Busquets S, Stemmler B, Lopez-Soriano FJ. Cancer cachexia: understanding the molecular basis. Nat Rev Cancer 2014;14:754–62.
[79] Nilwik R, Snijders T, Leenders M, Groen BB, van Kranenburg J, Verdijk LB, et al. The decline in skeletal muscle mass with aging is mainly attributed to a reduction in type II muscle fiber size. Exp Gerontol 2013;48:492–8.

[80] Correa-de-Araujo R, Addison O, Miljkovic I, Goodpaster BH, Bergman BC, Clark RV, et al. Myosteatosis in the context of skeletal muscle function deficit: an interdisciplinary workshop at the National Institute on Aging. Front Physiol 2020;11:963.
[81] Poggiogalle E, Lubrano C, Gnessi L, Mariani S, Di Martino M, Catalano C, et al. The decline in muscle strength and muscle quality in relation to metabolic derangements in adult women with obesity. Clin Nutr 2019;38:2430–5.
[82] Brons C, Grunnet LG. Mechanisms in endocrinology: skeletal muscle lipotoxicity in insulin resistance and type 2 diabetes: a causal mechanism or an innocent bystander? Eur J Endocrinol 2017;176:R67–78.
[83] Gemmink A, Goodpaster BH, Schrauwen P, Hesselink MKC. Intramyocellular lipid droplets and insulin sensitivity, the human perspective. Biochim Biophys Acta Mol Cell Biol Lipids 2017;1862:1242–9.
[84] Pol A, Gross SP, Parton RG. Review: biogenesis of the multifunctional lipid droplet: lipids, proteins, and sites. J Cell Biol 2014;204:635–46.
[85] Shulman GI. Cellular mechanisms of insulin resistance. J Clin Invest 2000;106:171–6.
[86] Affourtit C. Mitochondrial involvement in skeletal muscle insulin resistance: a case of imbalanced bioenergetics. Biochim Biophysica Acta 2016;1857:1678–93.
[87] Rivas DA, McDonald DJ, Rice NP, Haran PH, Dolnikowski GG, Fielding RA. Diminished anabolic signaling response to insulin induced by intramuscular lipid accumulation is associated with inflammation in aging but not obesity. Am J Physiol Regul Integr Comp Physiol 2016;310:R561–9.
[88] Maltais A, Almeras N, Lemieux I, Tremblay A, Bergeron J, Poirier P, et al. Trunk muscle quality assessed by computed tomography: association with adiposity indices and glucose tolerance in men. Metabolism 2018;85:205–12.
[89] Simoneau JA, Colberg SR, Thaete FL, Kelley DE. Skeletal muscle glycolytic and oxidative enzyme capacities are determinants of insulin sensitivity and muscle composition in obese women. FASEB J 1995;9:273–8.
[90] Nordal HJ, Dietrichson P, Eldevik P, Gronseth K. Fat infiltration, atrophy and hypertrophy of skeletal muscles demonstrated by X-ray computed tomography in neurological patients. Acta Neurol Scand 1988;77:115–22.
[91] Gortan Cappellari G, Semolic A, Ruozi G, Vinci P, Guarnieri G, Bortolotti F, et al. Unacylated ghrelin normalizes skeletal muscle oxidative stress and prevents muscle catabolism by enhancing tissue mitophagy in experimental chronic kidney disease. FASEB J 2017;31:5159–71.
[92] Honors MA, Kinzig KP. The role of insulin resistance in the development of muscle wasting during cancer cachexia. J Cachexia Sarcopenia Muscle 2012;3:5–11.
[93] Zhu S, Tian Z, Torigoe D, Zhao J, Xie P, Sugizaki T, et al. Aging- and obesity-related peri-muscular adipose tissue accelerates muscle atrophy. PLoS One 2019;14:e0221366.
[94] McSorley ST, Black DH, Horgan PG, McMillan DC. The relationship between tumour stage, systemic inflammation, body composition and survival in patients with colorectal cancer. Clin Nutr 2018;37:1279–85.
[95] Dev R, Bruera E, Dalal S. Insulin resistance and body composition in cancer patients. Ann Oncol 2018;29:ii18–26.
[96] Richter-Stretton GL, Fenning AS, Vella RK. Skeletal muscle—a bystander or influencer of metabolic syndrome? Diabetes Metab Syndr 2020;14:867–75.
[97] Gortan Cappellari G, Barazzoni R. Ghrelin forms in the modulation of energy balance and metabolism. Eat Weight Disord 2019;24:997–1013.
[98] Gortan Cappellari G, Zanetti M, Semolic A, Vinci P, Ruozi G, Falcione A, et al. Unacylated ghrelin reduces skeletal muscle reactive oxygen species generation and inflammation and prevents high-fat diet-induced hyperglycemia and whole-body insulin resistance in rodents. Diabetes 2016;65:874–86.
[99] Luo L, Liu M. Adipose tissue in control of metabolism. J Endocrinol 2016;231:R77–99.
[100] Li F, Li Y, Duan Y, Hu CA, Tang Y, Yin Y. Myokines and adipokines: involvement in the crosstalk between skeletal muscle and adipose tissue. Cytokine Growth Factor Rev 2017;33:73–82.
[101] Johns N, Greig C, Fearon KC. Is tissue cross-talk important in cancer cachexia? Crit Rev Oncog 2012;17:263–76.
[102] Bohnert KR, McMillan JD, Kumar A. Emerging roles of ER stress and unfolded protein response pathways in skeletal muscle health and disease. J Cell Physiol 2018;233:67–78.
[103] Oudot A, Martin C, Busseuil D, Vergely C, Demaison L, Rochette L. NADPH oxidases are in part responsible for increased cardiovascular superoxide production during aging. Free Radic Biol Med 2006;40:2214–22.
[104] Ramos-Lopez O, Riezu-Boj JI, Milagro FI, Moreno-Aliaga MJ, Martinez JA. Endoplasmic reticulum stress epigenetics is related to adiposity, dyslipidemia, and insulin resistance. Adipocyte 2018;7:137–42.
[105] Prado CM, Wells JC, Smith SR, Stephan BC, Siervo M. Sarcopenic obesity: a critical appraisal of the current evidence. Clin Nutr 2012;31:583–601.
[106] Pothiwala P, Jain SK, Yaturu S. Metabolic syndrome and cancer. Metab Syndr Relat Disord 2009;7:279–88.
[107] Levolger S, van Vugt JL, de Bruin RW, IJ JN. Systematic review of sarcopenia in patients operated on for gastrointestinal and hepatopancreatobiliary malignancies. Br J Surg 2015;102:1448–58.
[108] Mayr R, Gierth M, Zeman F, Reiffen M, Seeger P, Wezel F, et al. Sarcopenia as a comorbidity-independent predictor of survival following radical cystectomy for bladder cancerJ. Cachexia Sarcopenia Muscle 2018;9:505–13.
[109] Fattouh M, Chang GY, Ow TJ, Shifteh K, Rosenblatt G, Patel VM, et al. Association between pretreatment obesity, sarcopenia, and survival in patients with head and neck cancer. Head Neck 2019;41:707–14.
[110] Joglekar S, Asghar A, Mott SL, Johnson BE, Button AM, Clark E, et al. Sarcopenia is an independent predictor of complications following pancreatectomy for adenocarcinoma. J Surg Oncol 2015;111:771–5.
[111] Antoun S, Baracos VE, Birdsell L, Escudier B, Sawyer MB. Low body mass index and sarcopenia associated with dose-limiting toxicity of sorafenib in patients with renal cell carcinoma. Annals of Oncol 2010;21:1594–8.
[112] Prado CM, Baracos VE, McCargar LJ, Mourtzakis M, Mulder KE, Reiman T, et al. Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. Clin Cancer Res 2007;13:3264–8.
[113] Thibault R, Genton L, Pichard C. Body composition: why, when and for who? Clin Nutr 2012;31:435–47.
[114] Yip C, Dinkel C, Mahajan A, Siddique M, Cook GJ, Goh V. Imaging body composition in cancer patients: visceral obesity, sarcopenia and sarcopenic obesity may impact on clinical outcome. Insights Imaging 2015;6:489–97.
[115] Awad S, Tan BH, Cui H, Bhalla A, Fearon KC, Parsons SL, et al. Marked changes in body composition following neoadjuvant chemotherapy for oesophagogastric cancer. Clin Nutr 2012;31:74–7.
[116] Yip C, Goh V, Davies A, Gossage J, Mitchell-Hay R, Hynes O, et al. Assessment of sarcopenia and changes in body composition after neoadjuvant chemotherapy and associations with clinical outcomes in oesophageal cancer. Eur Radiol 2014;24:998–1005.
[117] Prado CM, Baracos VE, McCargar LJ, Reiman T, Mourtzakis M, Tonkin K, et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. Clin Cancer Res 2009;15:2920–6.
[118] Griggs JJ, Mangu PB, Anderson H, Balaban EP, Dignam JJ, Hryniuk WM, et al. Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2012;30:1553–61.
[119] Petrelli F, Cortellini A, Indini A, Tomasello G, Ghidini M, Nigro O, et al. Association of obesity with survival outcomes in patients with cancer: a systematic review and meta-analysis. JAMA Netw Open 2021;4:e213520.
[120] Prado CM, Purcell SA, Laviano A. Nutrition interventions to treat low muscle mass in cancer. J Cachexia Sarcopenia Muscle 2020;11:366–80.
[121] Bossola M, Pacelli F, Rosa F, Tortorelli A, Doglietto GB. Does nutrition support stimulate tumor growth in humans? Nutr Clin Pract 2011;26:174–80.
[122] Deutz NE, Bauer JM, Barazzoni R, Biolo G, Boirie Y, Bosy-Westphal A, et al. Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN Expert Group. Clin Nutr 2014;33:929–36.
[123] Deutz NE, Safar A, Schutzler S, Memelink R, Ferrando A, Spencer H, et al. Muscle protein synthesis in cancer patients can be stimulated with a specially formulated medical food. Clin Nutr 2011;30:759–68.
[124] Engelen M, Safar AM, Bartter T, Koeman F, Deutz NEP. High anabolic potential of essential amino acid mixtures in advanced nonsmall cell lung cancer. Ann Oncol 2015;26:1960–6.
[125] Witard OC, Wardle SL, Macnaughton LS, Hodgson AB, Tipton KD. Protein considerations for optimising skeletal muscle mass in healthy young and older adults. Nutrients 2016;8:181.
[126] Institute of Medicine, Food and Nutrition Board. Panel on Dietary Reference Intakes for Electrolyte and Water, Standing Committee on the Scientific Evaluatuion of Dietary Reference Intakes. Dietary reference intakes for water, potassium, sodium, chloride, and sulfate. Washington DC: National Academies Press; 2005.
[127] Abbasi J. Interest in the ketogenic diet grows for weight loss and type 2 diabetes. JAMA 2018;319:215–7.
[128] Caprio M, Infante M, Moriconi E, Armani A, Fabbri A, Mantovani G, et al. Very-low-calorie ketogenic diet (VLCKD) in the management of metabolic diseases: systematic review and consensus statement from the Italian Society of Endocrinology (SIE). J Endocrinol Invest 2019;42:1365–86.
[129] Argiles JM, Busquets S, Lopez-Soriano FJ, Costelli P, Penna F. Are there any benefits of exercise training in cancer cachexia? J Cachexia Sarcopenia Muscle 2012;3:73–6.
[130] Adams SC, Segal RJ, McKenzie DC, Vallerand JR, Morielli AR, Mackey JR, et al. Impact of resistance and aerobic exercise on sarcopenia and dynapenia in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. Breast Cancer Res Treat 2016;158:497–507.
[131] Alves CRR, Neves WD, de Almeida NR, Eichelberger EJ, Jannig PR, Voltarelli VA, et al. Exercise training reverses cancer-induced oxidative stress and decrease in muscle COPS2/TRIP15/ALIEN. Mol Metab 2020;39:101012.