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Review

Association between low muscle mass and survival in incurable cancer patients: A systematic review

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ABSTRACT

Current data suggest that low skeletal muscle mass provides prognostic information in patients with cancer and may even be considered a biomarker in research and clinical evaluations. The aim of this systematic review was to explore whether low muscle mass is associated with overall survival (OS) in patients with incurable cancer. A systematic search was conducted for published literature using PubMed/MEDLINE, Scopus, LILACS, and the Cochrane Library, with no restrictions on language or publication date, to examine whether low muscle mass is associated with OS in patients with incurable cancer. Eligible studies included low muscle mass evaluated using gold standard techniques (dual energy x-ray absorptiometry or computed tomography). The studies quality assessment was performed using the Newcastle-Ottawa Scale. Thirteen studies were included. The studies reported on 1959 patients between 54.3 (median) and 72.9 (mean) y of age; pancreatic cancer was the most common type of tumor. According to the survival curves and most of the multivariate analyses, there was no statistically significant association between loss of muscle mass and reduced OS. Four studies reported that overweight or obese patients with muscle mass depletion had significantly shorter OS. These results indicate that there is insufficient evidence to associate low muscle mass with OS in patients with incurable cancer. Further studies deploying other muscle measurement methods suggest that use of low muscle mass cutoff alone is still necessary in the pursuit of OS prediction in this population.

Introduction

Cancer has been associated with severe muscle mass wasting owing to decreased calorie/protein intake, reduced endocrine signaling, and increased proinflammatory activity [1,2]. The resulting increased muscle protein breakdown leads to a loss of muscle function and depletion of protein reserves [1–3]. The impairment of nutritional status in patients with cancer is aggravated in the advanced stages of the disease, and its diagnosis may vary according to the assessment method adopted [4,5]. The importance of monitoring cancer cachexia, which has been defined as the "wasting of skeletal muscle, with or without loss of fat mass," is one reason for evaluating body composition during the course of the disease [5,6].

Current published recommendations provide multiple measurement techniques to assess muscle mass depletion [6–9]. In the clinical setting, mid upper-arm muscle area determined by anthropometric measurement, appendicular skeletal muscle index (ASMI) determined using dual energy x-ray absorptiometry (DXA), lumbar skeletal muscle index (SMI) identified by computed tomography (CT), and body fat-free mass index determined by bioelectrical impedance (BIA) can be used to identify loss of muscle mass [6,10]. Given the variety of techniques used to measure body components, the term *muscle mass* is used throughout this systematic review.

In recent years, muscle mass depletion has been widely investigated for its potential role in influencing clinical outcomes [11,12]. Some studies have highlighted the crucial role of skeletal muscle

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mass loss and muscle function deterioration in the reduction of physical and motor capacity and in increased fatigue, resulting in a poorer quality of life and a limited prognosis for patients with advanced cancer [13–15]. The negative prognostic effects of reduced SMI was demonstrated in a meta-analysis of adult patients with solid tumors, regardless of the type and stage of disease [16]. It has been suggested that muscle mass can be both a marker for cachexia syndrome and an important therapeutic target [3,5,10,17]. Furthermore, a better understanding of how body composition can be used in the prognosis of patients with metastatic cancer could contribute to a better standardization of diagnosis criteria for muscle mass assessments and consequently for improved the nutritional interventions of patients [17]. Thus, this systematic review of the literature explored the results of studies that analyzed the association between low muscle mass and overall survival (OS) in patients with incurable cancer.

Methods

Literature search and study selection

This systematic review was based on the following question: "Is low muscle mass associated with shorter survival in patients with incurable cancer?" Thus, the primary outcome was the association of low muscle mass (evaluated using gold standard techniques) with OS.

A comprehensive search of the literature was conducted (last search date, May 2019) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria [18] using well-known indexed databases, including MEDLINE/PubMed, Scopus, LILACS, and the Cochrane Library. The combination of search terms is described in Figure 1.

No restrictions were imposed on language or publication date. The selection of the studies was based on the following inclusion criteria:

- abstract available online;
- original articles;
- studies, case–control studies;
- performed on humans;
- participants ≥18 y of age;
- advanced (incurable) cancer;
- muscle mass measured by DXA or CT; and
- investigated relationship between low muscle mass and OS.

Advanced cancer was defined as metastatic cancer (histologic, cytologic, or radiologic evidence) or locally advanced cancer being treated with palliative intent. Studies involving patients undergoing active anticancer treatment were excluded.

No exclusion criteria were set regarding sample size or timing of study conduct (retrospective or prospective). The reference lists of related and cited papers were also screened to identify further studies.

Data extraction

Two authors performed the data extraction independently of one another. Disagreements in either the title/abstract or full-text paper review phases were resolved by consensus. When necessary, the opinion of a third reviewer was

Pubmed (https://www.ncbi.nlm.nih.gov/pubmed)
("advanced cancer") AND ("caquexia" OR "wasting syndrome" OR "weight loss" OR "sarcopenia" OR "malnutrition" OR "muscle" OR "skeletal muscle" OR "skeletal muscle loss" OR "skeletal muscle depletion" OR "skeletal muscle wasting" OR "muscle mass" OR "lean body mass" OR "body composition") AND ("survival" OR "prognosis" OR "mortality")
Scopus (https://www.scopus.com)
(cancer) AND (caquexia or wasting syndrome or weight loss or sarcopenia or malnutrition or muscle or skeletal muscle or skeletal muscle loss or skeletal muscle depletion or skeletal muscle wasting or muscle mass or lean body mass or body composition) AND (survival or mortality or prognosis)
Lilacs (http://lilacs.bvsalud.org/)
(cancer) AND (caquexia OR wasting syndrome OR weight loss OR sarcopenia OR malnutrition OR muscle OR skeletal muscle OR skeletal muscle loss OR skeletal muscle depletion OR skeletal muscle wasting OR muscle mass OR lean body mass OR body composition) AND (mortality OR survival OR prognosis)
Cochrane Library (http://onlinelibrary.wiley.com/cochranelibrary/search)
(("advanced cancer") AND ((“caquexia”) OR (“wasting syndrome”) OR (“weight loss”) OR (“sarcopenia”) OR (“malnutrition”) OR (“muscle”) OR (“skeletal muscle”) OR (“skeletal muscle loss”) OR (“skeletal muscle depletion”) OR (“skeletal muscle wasting”) OR (“muscle mass”) OR (“lean body mass”) OR (“body composition”)) AND ((“survival”) OR (“mortality”) OR (“prognosis”)))

Fig. 1. Search strategy in the electronic database.

requested. All excluded articles were reviewed by two authors to ensure they did not meet the eligibility criteria.

The following details were presented in this review: first author, year of publication, study design, sample size, study aims, statistical analysis, participant characteristics (age and cancer type), muscle mass evaluation method, definition of cutoff for low skeletal muscle mass, independent variables, outcome, and adjusted major confounders.

Quality assessment

The study's quality assessment was performed by two independent reviewers using the Newcastle-Ottawa Scale [19]. This scale consists of three criteria: selection, comparability, and outcome assessment. To ensure comparability, we evaluated whether the studies controlled for age and sex in their statistical confounding variables and other prognostic indicators, such as Eastern Cooperative Oncology Group performance status, Karnofsky performance status, palliative prognostic score, and so on. The score assigned for each paper is described in Supplementary Figure 1.

Results

Literature search and study characteristics

The flow diagram in Figure 2 shows the study selection process. The literature search retrieved 1450 records, of which only 37 fit the inclusion/exclusion criteria. After reading the texts in full, 11 studies were retained for review. A close examination of the articles' reference lists recovered a further 2 studies, bringing the total to 13 studies reporting on 1959 patients. All the papers were considered to be of high methodological quality (Supplementary Figure 1).

The characteristics of the papers included in this literature review are summarized in Table 1 [20–32]. All the publications were relatively recent, dating from the last decade between 2009 and 2018 [20,32]; all of the studies were cohort designs and most were prospective studies [21,22,24–26,30,34]. In terms of the patients' demographic characteristics, women accounted for ~52% of the investigated population and the median and mean ages ranged between 54.3 and 72.9 y, respectively [23,28]. Pancreatic cancer was the most prevalent tumor type [21,23,25,26,28] and the sample sizes in the studies were variable (Fig. 3).

Methods used for muscle mass evaluation

The analyses focused on the assessment of muscle mass, which was performed in the studies by two different methods: ASMI [25,32], determined using DXA, and SMI, determined by CT imaging [20–24,26–31] (Fig. 3). Eleven of the studies assessed muscle mass by a transverse CT image at the third lumbar vertebra level [20–24,26–31]. The most common cutoff values used to define low skeletal muscle mass ranged from 33.9 to 41.5 cm^2/m^2 in women and 42.2 to 55 cm^2/m^2 in men. Additionally, five studies defined sarcopenic obesity as low SMI simultaneous to body mass index (BMI) > 25 kg/m^2 [22] or ≥ 25 kg/m^2 [20,23,26,28] (Table 1).

Association of low muscle mass with OS

In most of the studies, Kaplan–Meier survival curves was performed using the log-rank test to compare differences between OS [20–24,26,28–32]. The hazard ratios (HRs) with 95% confidence interval (CI) derived from Cox regression analyses were used to verify the risk for death [20,21,23–32] (Table 1). There was some variability among the additional independent variables used in the statistical analyses, the main ones being age, sex, and BMI. Four studies evaluated performance status [23,25,26,32], and one assessed physical function and muscle strength [25].

The prevalence of low muscle mass varied from 21.3% to 67% (by different methods). The highest prevalence was found in Wallengren et al. [25]. Seven studies showed prevalence of low muscle mass >50% [20,21,23,25,28,29,31] (Fig. 3). The median of OS all evaluated patients ranged from 130 d [20] to 32.3 mo [31]. Among the patients with low muscle mass, a variation from 9.8 wk (2.5 mo) [32] to 30 mo [31] in the median OS was observed. Only two studies presented according to the survival curve that patients with low muscle mass had a significantly shorter median OS than those without. However, four studies (one of them only in women) [26] found that muscle mass depletion in overweight or obese patients was associated with poorer OS [20,21,26,28].

Not all of the studies reported the HRs of OS. The published results referring to low muscle mass in patients with incurable cancer are divergent, and most of the multivariate analyses did not demonstrate a statistically significant association between low muscle mass and mortality risk. Only two studies reported low muscle mass as an independent significant predictor of OS in multivariable analysis [23,26] (Table 1).

Discussion

The results of most of the studies included in this systematic literature review indicated that low muscle mass is not a significant predictor of OS in patients with incurable cancer. We believe that one of the possible hypotheses to explain these results is that low muscle mass (in quantitative terms) alone may not adequately reflect the components that represent qualitative muscularity. Therefore, it is necessary to evaluate other measures, such as muscle strength or physical function, especially in this type of cancer population [11,33].

It is important to emphasize that all the studies analyzed here referred to low muscle mass as sarcopenia, although the definition of sarcopenia remains controversial in the literature [3,5–10]. *Sarcopenia* has been used as an ample term for muscle depletion in advanced age and in a disparate variety of muscle-wasting conditions. The etiology behind muscle loss in each of these disease types is likely to be as different as the diseases themselves [34]. For example, the European Working Group on Sarcopenia in Older People has defined sarcopenia as primary (or age-related) when no other cause is evident but aging itself, and secondary when one or more other causes are evident, such as chronic diseases, bed rest, or sedentary lifestyles [6]. Because of this confusion, some authors understand that a better definition of low muscle mass in the context of cancer would be myopenia [34,35].

In some of the studies included in the present review, low muscle mass was associated with poorer OS in overweight or obese patients compared with normal and underweight patients, but no significant association was found with low muscle mass alone [20,21,28]. These findings are relevant because overweight or obese patients with cancer are often assumed to be normally nourished, when in fact they may have severe muscle depletion ("obesity paradox"), resulting in poor outcomes [12,13,17].

The prevalence of low muscle mass varied widely in the studies reviewed here. This could be explained by several factors, including different tumor locations, varying ages, cutoff used to classify low muscle mass, and the timing of CT scans. Furthermore, some studies focused on the change of muscle mass during treatment, whereas others on baseline muscle mass. These varying results, added to different diagnostic protocols, led to wide heterogeneity in the comparison of results.

For instance, if we compared just the studies that evaluated patients with pancreatic tumors using the same evaluation method (CT) but with different cutoff points, we get different results. A lower prevalence of low skeletal muscle mass (21.3%) [26] was found in studies that adopted a lower cutoff point (female SMI:

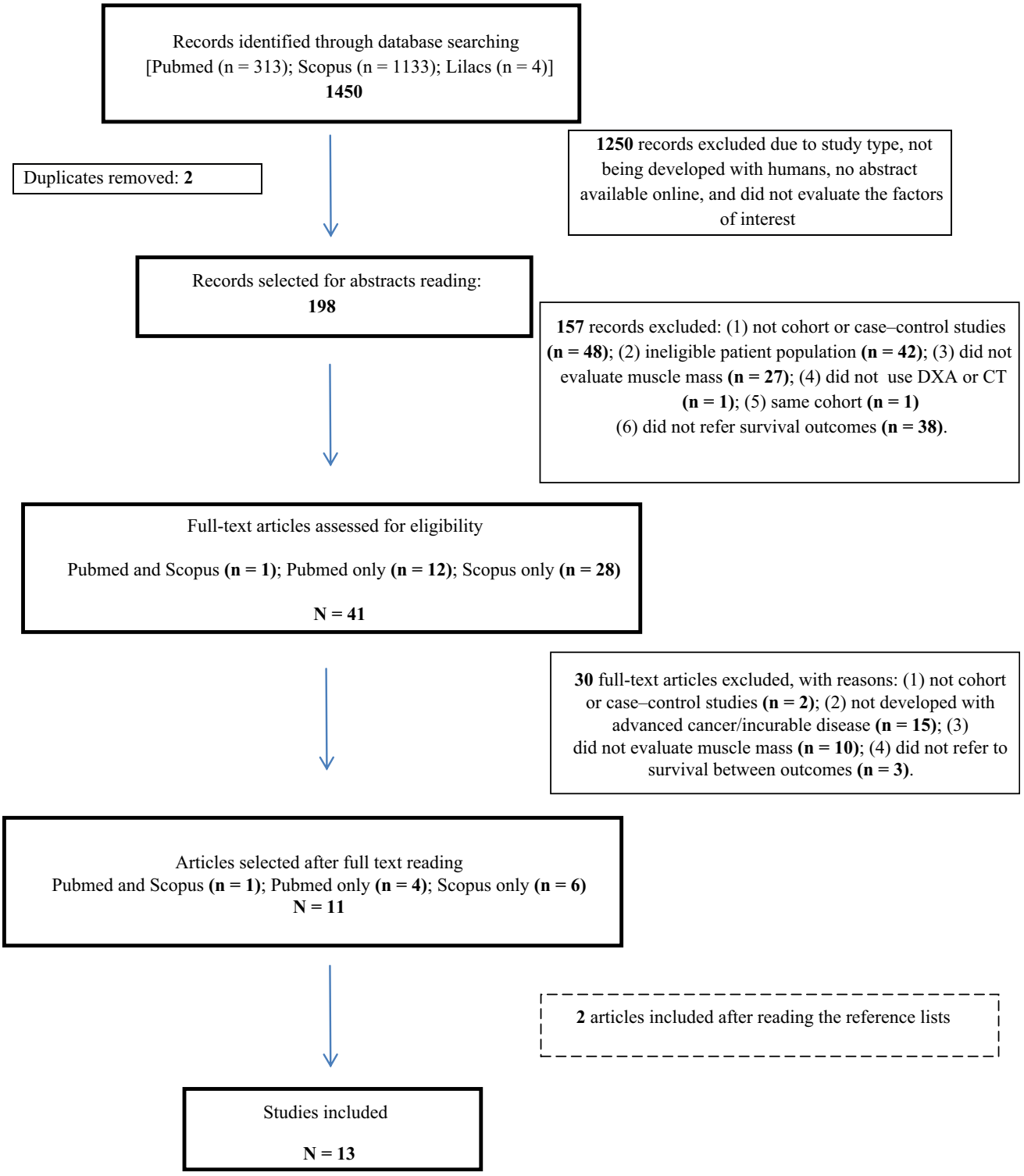

Fig. 2. Flow diagram of study selection process. CT, computed tomography; DXA, dual-energy x-ray absorptiometry.

<33.9 cm^2/m^2, and male SMI: <42.2 cm^2/m^2), whereas a higher prevalence (63%) [21] was found when the cutoff point was less restricted (female SMI: <38.5 cm^2/m^2, male SMI: <52.4 cm^2/m^2).

The standard SMI reported in the literature for the diagnosis of sarcopenia by CT considers the standard values for the radiodensity of each tissue, expressed in Hounsfield units (HU) [20–24,26–31]. Several of these publications investigated the association between survival and SMI dichotomized according to OS-related thresholds; however, the use of thresholds to diagnose low muscle mass has been questioned owing to the risk for classifying a high number of true or false positives. Usually, the definition of low muscle mass was based on sex-specific Canadian cutoff values for SMI [36], although it is possible that this cutoff may not be appropriate for the other populations owing to race-related differences in muscle mass.

Table 1
Description of included studies

First author, year [Reference]	Age, y (SD* IQR†)	Cutoff value low muscle mass	Aim	OS	Additional independent variables	Main findings	
						Kaplan–Meier	Cox analysis
Tan et al., 2009 [20]	64.4 (±9.3)*	F: SMI ≤38.5 cm^2/m^2 M: SMI ≤52.4 cm^2/m^2 Sarcopenic obesity: Low SMI + BMI ≥25 kg/m^2	Evaluate if weight and body composition, assessed from diagnostic CT scans, are of prognostic value	All 130 d (71–302)† LMM UN	Age, sex, tumor site, histology, stage of disease, WL, and body components (fat, lean tissue)	BMI ≥25 kg/m^2 + LMM had statistically significant differences in OS (log-rank, $P = 0.003$)	LMM not predict OS (HR, 1.25; 95% CI, 0.83–1.91). Overweight/obese + LMM (HR, 2.07; 95% CI, 1.23–3.50) were predictors of OS
Dalal et al., 2014 [21]	59 (42–81)†	F: SMI <38.5 cm^2/m^2 M: SMI <52.4 cm^2/m^2	To explore the relationships among BMI, longitudinal body composition alterations, and clinical outcomes	All 12 mo (9–18.7)† Lost muscle mass 10.7 mo Gain muscle mass 16.8 mo	Age, sex, WL, body components (fat, lean tissue)	Median OS for LMM was not significant (log-rank, $P = 0.246$); baseline obesity (log-rank, $P = 0.01$), and LMM in obese patients (log-rank $P = 0.004$) were associated with poorer OS	Higher VAT loss (HR, 2.06; 95% CI, 1.06–4.03) were significant predictors of OS.
Parsons et al., 2012 [22]	56 (32–73)†	F: SMI <38.5 cm^2/m^2 M: SMI <52.4 cm^2/m^2 Sarcopenic obesity: Low SMI + BMI >25 kg/m^2	Determine the association between body composition and toxicities; and association between clinical outcomes and body composition and pretreatment characteristics	All UN LMM 167 d (95% CI, 128–206) Normal muscle mass 280 d (95% CI, 214–346)	UN	Median OS for LMM was not significant (log-rank, $P = 0.271$); BMI ≥25 kg/m^2 + LMM had no statistically significant differences in OS (log-rank, $P = 0.541$)	Not performed
Parsons et al., 2012 [23]	From 54.3 (±2.9)* to 64 (±1.9)*	F: SMI <38.5 cm^2/m^2 M: SMI <52.4 cm^2/m^2 Sarcopenic obesity: Low SMI + BMI ≥25 kg/m^2	Examining the relationships among body composition, the incidence and severity of cancer-related symptoms, and OS	All 400 d (270–530)† LMM 304 d (201–406) Normal muscle mass 474 d (346–601)	Age, sex, PS, diagnosis, body components (fat, lean tissue)	Median OS for LMM was not significant (log-rank; $P = 0.151$); BMI <25 kg/m^2 + LMM had the shortest OS whereas BMI ≥25 kg/m^2 without LMM had best OS (log-rank; $P = 0.013$)	Patients with higher muscle indices (HR, 0.95; 95% CI, 0.92–0.98) predicted longer OS
Thoresen et al., 2013 [24]	63 (22–85)†	F: SMI ≤38.5 cm^2/m^2 M: SMI ≤52.5 cm^2/m^2	To investigate the associations between different nutritional assessments and OS	All median 15.8 mo (Norwegian) 20.6 mo (Canadian) LMM 15.3 mo Normal muscle mass 17.3 mo	BMI, WL, energy intake, CRP, NRS-2002, SGA, cachexia	There was no statistical significance for median days of OS in LMM group (log-rank, $P = 0.058$)	No statistical significance for prognostic among LMM patients (HR, 1.74; 95% CI, 0.99–3.03)
Wallengren et al., 2013 [25]	68 (±11)*	F: ASMI ≤5.45 kg/m^2; M: ≤7.26 kg/m^2 of appendicular (arm + leg) skeletal muscle mass/ $height^2$ Or AMC: <10th percentile of a Swedish reference population	Study the relation between different diagnostic criteria for cancer cachexia and adverse patient-centered outcomes and the prognostic significance of these criteria on OS	All 175 d (±235)*	BMI, WL, walking distance, HGS, fatigue, KPS, CRP, ESR, albumin, Hb, adverse QoL, cachexia	UN	Only LMM by AMC (HR, 1.3, $P = <0.05$) were significantly prognostic of OS
Choi et al., 2015 [26]	60.4 (20–85)†	F: SMI <33.9 cm^2/m^2 M: SMI <42.2 cm^2/m^2 Sarcopenic obesity: Low SMI + BMI ≥25 kg/m^2	Investigate whether sarcopenia at diagnosis and loss of skeletal muscle during palliative chemotherapy were associated with OS	All 8.4 mo (95% CI, 7.6–9.2) LMM 7.2 mo (95% CI, 6.2–8.1) Normal muscularity 9 mo (95% CI, 8.1–9.9)	Age, sex, extent of disease, PS, BMI, best response to chemotherapy	LMM in baseline had shorter OS ($P < 0.001$); LMM in men significantly shorter OS ($P < 0.001$) independent of BMI, but not for women ($P = 0.299$); median OS of BMI ≥25 kg/m^2 + LMM in women was reduced ($P = 0.003$)	LMM (HR, 1.72; 95% CI, 1.30–2.28), and decreased SMI during chemotherapy (HR, 1.39; 95% CI, 1.11–1.74) were significant prognostic factors

(*continued on next page*)

Table 1 (*Continued*)

First author, year [Reference]	Age, y (SD* IQR†)	Cutoff value low muscle mass	Aim	OS	Additional independent variables	Main findings	
						Kaplan–Meier	Cox analysis
Gu et al., 2015 [27]	58 (51–64)†	F: SMI <38.5 cm^2/m^2 M: SMI <52.4 cm^2/m^2	To evaluate the association between components of body composition and OS of patients treated with targeted therapies	All 24.7 mo (95% CI, 19.7–34.8) LMM UN	Heng risk, age, sex, BMI, body components (fat, lean tissue)	UN	VATI (HR, 0.981; 95% CI, 0.969–0.993) and SAT index (HR, 0.987; 95% CI, 0.974–1.000) were associated with decreased mortality.
Rollins et al., 2016 [28]	64.8 (±8.7)* (palliative chemotherapy) Others 72.9 (±11.1)*	F: SMI <41 cm^2/m^2 M: SMI <43 cm^2/m^2 (BMI <25 kg/m^2) and SMI <53 cm^2/m^2 (BMI ≥25 kg/m^2) Sarcopenic obesity: Low SMI + BMI ≥25 kg/m^2	Assess the association between body composition (sarcopenia and myosteatosis) and outcome.	All median 5.8 mo LMM + not myosteatotic 280.5 d Normal muscle mass + non-myosteatotic 229 d	Age, sex, Hb, NLR, extent of disease, CRP myosteatosis	LMM no difference in median OS (log-rank, $P = 0.779$); LMM after chemotherapy was associated with reduced OS (log-rank, $P = 0.03$) BMI >25 kg/m^2 + LMM had lower OS (log-rank, $P = 0.013$)	LMM was not prognostic factors for OS (HR, 1.1; 95% CI, 0.77–1.58)
Rutten et al., 2016 [29]	66.5 (±0.8)*	SMI <41.5 cm^2/m^2	Investigate OS related to changes in skeletal muscle for patients treated with neoadjuvant chemotherapy and interval debulking	All 986 d (±111)* Reduced muscle mass 916 d (±99) Gain muscle mass 1431d (±470)	Age, BMI, WL, extent of disease (FIGO), cycles of chemotherapy, complete, interval debulking, ascites at baseline body components	LMM at baseline was no different in OS (log-rank, $P = 0.613$); median OS for reduced muscle mass was significant from maintained or gained muscle mass during chemotherapy (log-rank, $P = 0.004$)	LMM in the baseline was not predictor of OS (HR, 0.88, $P = 0.613$). Loss of muscle mass during chemotherapy (HR, 1.77; 95% CI, 1.01–3.08) and loss of VATI (HR, 1.83; 95% CI, 1.13–2.95)
Srdic et al., 2016 [30]	64 (41–87)†	F: SMI ≤39 cm^2/m^2 M: SMI ≤55 cm^2/m^2	Evaluate prevalence of cachexia and sarcopenia and their relation to chemotherapy toxicity and survival prediction	All UN Low skeletal muscle 218 d Normal muscularity 209 d	Age, sex, cancer type, BMI, BSA, WL, CRP, fibrinogen, IL-6, albumin, Hb	There was no significant difference in OS in the LMM patients (log-rank not show)	LMM was not a predictor of outcomes (HR not shown)
Shachar et al., 2017 [31]	55 (34–80)†	SMI ≤41 cm^2/m^2	Investigates skeletal muscle measures in patients receiving first-line chemotherapy and evaluates associations with toxicity and other outcomes	All 32.3 (95% CI, 23.4–40.3) mo LMM 30 mo Normal muscle mass 40.3 mo	BMI, body composition measures	LMM had no significant difference in median OS (log-rank, $P = 0.07$)	LMM was not a significant predictor of OS (HR, 2.21; $P = 0.07$)
Chambard et al., 2018 [32]	65 (±11)*	ASMI F: ≤5.45 kg/m^2 M: ≤7.26 kg/m^2 of appendicular (arm + leg) skeletal muscle mass/ $height^2$	Identifying whether bone and metabolic biomarkers were associated with the prognosis of patienrs with lung adenocarcinoma and synchronous bone metastases	All 30.5 wk (9.1–67.4)† LMM 9.8 wk Normal MM 42.5 wk	Active smoking, DKK1, hypercalcemia, weight bearing bone metastasis HbA1c, PS, CRP	There was statistical significance for median OS in LMM patients (log-rank, $P = 0.005$)	Only in univariate analysis, the subgroup of patients with DXA, LMM was associated with poorer OS (HR, 2.96; 95% CI, 1.40–6.27)

ASMI, appendicular skeletal muscle mass index; AMC, midarm muscle circumference; BMI, body mass index; BSA, body surface area; CRP, C-reactive protein; DDK1, Dickkopf-related protein 1; ESR, erythrocyte sedimentation rate; FIGO, International Federation of Gynecology and Obstetrics; Hb, hemoglobin; HbA1c, glycated hemoglobin A1c; HGS, handgrip strength; IL, interleukin; IQR, interquartile range; IMAT, intramuscular adipose tissue; LMM, low muscle mass; NLR, neutrophil lymphocyte ratio; NRS, Nutritional Risk Screening; OS, overall survival; QoL, quality of life; PS, performance status; SGA, Subjective Global Assessment; SMI, skeletal muscle index; VAT, visceral adipose tissue; VATI, visceral adipose tissue index; UN, uninformed; KPS, Karnofsky performance status; SAT, subcutaneous adipose tissue; WL, weight loss.

*Mean (±SD).

†Median (IQR).

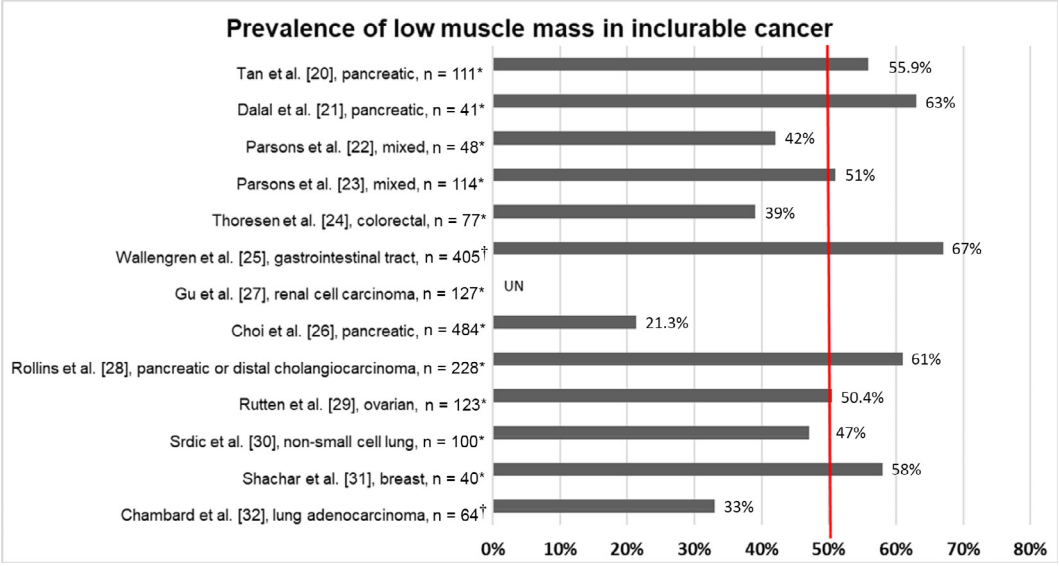

Fig. 3. Summary of studies reporting the prevalence of low muscle mass in incurable cancers. *Low muscle mass defined by computed tomography. †Low muscle mass defined by dual energy x-ray absorptiometry. UN, uninformed.

When Kumar et al. [37] evaluated body composition using mean skeletal muscle radiodensity (SMD; using the HU scale), they identified a significantly higher risk for mortality for those with low SMD (HR, 1.23; 95% CI, 1.05–1.43; $P = 0.009$). On the other hand, mortality did not differ significantly between patients with and those without low muscle mass measured by the SMI (HR, 0.99; 95% CI, 0.73–1.36; $P = 0.970$). Similarly, Sjøblom et al. [38], investigating the prognostic value of SMD in 734 patients with advanced non-small cell lung cancer in first-line chemotherapy regimens, found that SMD was independently prognostic for OS (HR, 0.98; 95% CI, 0.97–0.99; $P = 0.001$), whereas SMI was not (HR, 0.99; 95% CI, 0.98–1.01; $P = 0.329$). These studies highlighted the fact that lower SMD reflects to muscle lipid content that is closely related to fatty infiltration of skeletal muscle, known as myosteatosis, and thus indicates deteriorated skeletal muscle "quality" [39].

Interestingly, Rodrigues and Chaves [40] showed that skeletal muscle characteristics, related to either quantity or quality, may coexist. This study demonstrated that the "low SMI and low SMD" skeletal muscle phenotype showed the strongest association with 1-y mortality (HR, 5.36; 95% CI, 1.70–16.51) in patients with endometrial cancer. The authors suggested that making assessments according to skeletal muscle phenotype could be a promising tool for prognosis.

Another concern is related to the period that CT was performed. Some studies used CT scans 30 d before other assessment techniques [22-24,26,30], whereas in others there was a 60-d [20,28] or other interval [31,25], and in some, the time lag was not even mentioned [21,27,29,32]. The choice of when to perform CT scans varied according to the study purpose. In some, it was defined according to treatment or therapy initiation, whereas others established an interval of ≤30 d before or after the symptom questionnaire was filled out. These differences in the criteria for when to perform a CT scan could influence the results, especially when changes in muscle mass are concerned. These changes arise when cancer is highly metabolic, which is mainly observed in advanced stages [5,10].

Although the evaluation of low muscle mass (severe muscle depletion) is one of the most important domains for the definition of cancer cachexia, the present results demonstrated that the exclusive use of this measure was unable to predict OS in the studies reviewed. However, in Thoresen et al. [24], cachexia (assessed by two different criteria) and malnutrition were independent factors predicting OS. Similarly, Wallegren et al. [25] reported that cachexia assessed by several criteria was also a significant predictor of OS. In our opinion, measuring the skeletal muscle mass depletion over time improves the prognostic prediction, and ongoing loss of skeletal muscle mass is a hallmark of worsening cachexia [10], whereas the low muscle mass evaluated at a specific time, according to our results, is not.

Finally, and importantly, all these studies were combined and called "muscle mass," but they do not necessarily refer to same things. For example, BIA uses a two-compartment model of body composition—fat mass and fat-free mass (FFM; comprised of protein, intra- and extracellular water, and bone mineral)—and cannot differentiate between different components of fat mass or FFM. DXA uses a three-compartment model of body composition—fat mass, FFM, and bone mass—but cannot distinguish different compartments within fat (subcutaneous, visceral, or intramuscular) and cannot identify specific lean tissues like skeletal muscle and the internal organs within the thorax or abdomen. CT image analysis is able to evaluate the quantity and distribution of diverse skeletal muscles, the three adipose tissue depots (visceral, subcutaneous, and intramuscular), and different organ masses [41].

Furthermore, despite the appropriate statistical analysis, the studies presented some fragility regarding the statistical adjustment of potential confounding factors, which are considered important in advanced illness prognostics, including decreased performance status, weight loss, tumor site, metastasis, and laboratory abnormalities indicative of inflammation. We argue that the association between loss of skeletal muscle mass and OS in patients with metastatic and incurable cancer, and possible confounding factors, needs to be addressed and analyzed separately. Finally, statistical analyses using SMI and SMD or reduced muscle radiation attenuation as continuous variables or determine skeletal muscle phenotype could yield more consistent results in studies on prognostic factors once the use of cutoff as previously mentioned can limit this measure.

This systematic literature review had some limitations including the degree of inhomogeneity of the available data and lack of any further statistical analyses (e.g., meta-analysis) is because the included studies not reporting sufficient data for estimating HR besides that follow-up durations varied among studies or were not

defined in some of them. Additionally, only two studies evaluated muscle mass by DXA. All the studies included here evaluated muscle mass by CT and DXA, which are considered gold standard for evaluating muscle mass depletion.

Conclusion

The present study suggested that there is insufficient evidence to demonstrate that low muscle mass alone (in quantitative terms) can be considered an independent prognostic factor in patients with incurable cancer. The results suggested the importance of future studies incorporating other measures that include the quality of the respective measured muscle mass, such as muscle attenuation, muscle strength, and physical function compared with using only one cutoff to determine muscle mass to improve survival prediction in patients with incurable cancer.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.nut.2019.110695.

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