

Evaluation of body Computed Tomography-determined sarcopenia in breast cancer patients and clinical outcomes: A systematic review

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ARTICLE INFO

Keywords:

Sarcopenia
Breast cancer
Computed tomography
Body composition
Clinical outcome

ABSTRACT

Purpose: Sarcopenia has been considered a poor prognostic factor in various malignant diseases. However, the studies that evaluated the association between CT-determined sarcopenia and outcome in breast cancer patients reported different results. Therefore, the aim of the present study is to perform a systematic review of the current literature on the evaluation of body CT-determined sarcopenia in breast cancer patients, focusing on the correlation with outcome values.

Methods: Two reviewers evaluated independently all studies dealing with CT-determined sarcopenia in breast cancer women from major medical libraries up to 24 April 2019. The keywords used for database searching were: “sarcopenia” or “muscles” or “muscle weight” or “body composition” and “breast neoplasms” or “breast cancer” and “computed tomography”. Studies reporting clinical outcome values were finally compared.

Results: Of the $n = 191$ studies identified, a total of $n = 15$ articles were included in the systematic review. In all studies, sarcopenia was assessed at the level of the third lumbar vertebra (L3) on CT; $n = 14/15$ studies were retrospective. $N = 13/15$ studies evaluated the impact of sarcopenia on clinical outcomes. Among these studies, $n = 8/13$ studies concluded that sarcopenia is an important risk factor for poor prognosis in breast cancer and $n = 5/13$ studies concluded that body composition changes are not associated with poor prognosis.

Conclusions: Most studies concluded that sarcopenia assessed on CT is an important prognostic risk factor in breast cancer patients. High-quality prospective studies to strongly confirm and assess the impact of sarcopenia evaluated on CT and breast cancer outcome are needed.

Introduction

Sarcopenia, historically defined as the age-related loss of skeletal muscle mass, is recognized as an important independent prognostic risk factor in cancer patients [1,2]. Indeed, cancer can lead to a loss of muscle mass, to an increased protein catabolism and consequently to adverse clinical outcomes [3]. In breast cancer patients, sarcopenia has been considered a predictor of poor survival associated with increased incidence of toxicity and shorter time to tumor progression [4–8]. Some studies evaluating body composition, concluded that sarcopenia increased risk of death in breast cancer patients [9–11]. Prado et al. found that sarcopenia is an important predictor of toxicity and tumor progression in metastatic breast cancer patients treated with capecitabine [12]. To assess muscle mass, different imaging techniques can be used, such as magnetic resonance imaging (MRI), dual energy X-ray absorptiometry (DXA) and computed tomography (CT). Compared with DXA, CT and MRI are more precise and usually preferred

for research and clinical purposes. [13] CT is considered the gold standard imaging technique to assess muscle mass and muscle attenuation. Indeed, it is assumed that muscular cross-sectional area is strongly correlated to total body muscle mass [14,15]. In most studies, muscle areas are calculated on a single-slice of the abdominal CT at the third lumbar vertebra (L3). Consequently, the skeletal muscle index (SMI) is calculated dividing the muscle area at L3 calculated in cm^2 by patient height calculated in meters squared (m^2). Many studies evaluated also the skeletal muscle radiodensity (SMD) using the average radiation attenuation of tissue in Hounsfield Units (HU) [4,10,11]. Evaluation of CT-determined sarcopenia provide relevant prognostic data that could be easily used and integrated into the daily clinical work-up and could improve survival results. The importance of body composition on breast cancer patients is of considerable interest. Even if, many studies correlated CT-determined sarcopenia with clinical outcome in breast cancer women, a wide variability of results are reported. Therefore, the aim of the present study is to perform a systematic literature review of

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CT-determined sarcopenia in breast cancer women to examine the impact of sarcopenia on clinical outcomes.

Materials and methods

This systematic review was performed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [16].

Information sources and search

All relevant studies that assessed the evaluation of CT-determined sarcopenia in breast cancer women were identified. Two reviewers (AT and LT) performed independently and blindly a literature search using PubMed (<https://www.ncbi.nlm.nih.gov/pubmed>), ScienceDirect, MEDLINE, Google Scholar, Ovid (www.ovid.com) and Cochrane library (<https://www.cochranelibrary.com>) up to 24 April 2019. Indeed, no restriction were placed on the year of study. In addition, we also performed a manual revision of the reference lists to eventually integrate the initial research with further studies. It was not considered necessary to contact the authors for supplementary information. The search terms used for database searching were: “sarcopenia” or “muscles” or “muscle weight” or “body composition” and “breast neoplasms” or “breast cancer” and “computed tomography”, in the MeSH headings, title or abstract, or author-supplied keywords.

Eligibility criteria

We included studies that evaluated the CT-determined sarcopenia in breast cancer patients in tumor-staging setting or in post-therapy follow-up; included at least 10 women with any stage of breast cancer, metastatic or not. After the initial search, we also selected the studies that reported outcomes parameters, including the overall survival, the treatment-related toxicity, the recurrence, the tumor progression and the quality of life. Only publication in English were considered.

Exclusion criteria were as followed:

- Male gender
- Studies which did not report original data,
- Case reports or case series or reviews or letters to the editor or editorials.
- Duplicate publication or simulation articles
- Studies that assessed sarcopenia using different techniques, such as dual energy X-ray absorptiometry (DXA) were excluded.
- Studies which did not clearly state diagnostic criteria and outcomes values in material and methods section.

Study selection

According to eligibility criteria for study selection, all article titles and abstracts, followed by full text, were manually and independently reviewed by two independent reviewers (AT and LT) to determine appropriateness for inclusion. There was no discordance among reviewers regarding inclusion criteria. Duplicate studies were removed.

Data collection process

We created a predefined form to extract information from included articles: first author, publication year and journal, country of the study,

study designation (retrospective or prospective), study population, anatomical level used to measure cross-sectional area on CT (for example the third lumbar vertebra), overall prevalence of sarcopenia and sarcopenia cut-off value, breast cancer stage (I-IV) and clinical outcomes for sarcopenia in breast cancer patients. Among all the included studies, the reviewers also selected the articles where intra-reader and inter-reader agreement were calculated. We finally compared studies that reported clinical outcome values (overall survival, the treatment-related toxicity, the recurrence, the tumor progression and the quality of life) of sarcopenia on body CT images in breast cancer patients.

Risk of bias

The quality of the eligible studies was assessed using a modified Quality Assessment of Studies of Diagnostic Accuracy Studies (QUADAS-2) checklist based on two key domains (patient selection, index test). This quality assessment was performed by two authors independently and disagreement was based on consensus considering risk of bias concerning homogeneity of patients selection (age, breast cancer stage, case-control study avoided, random or consecutive sample and inappropriate exclusion avoided) and index test (CT parameters, including technical parameters, skeletal muscle index cut-off value, muscle mass attenuation value).

Results

Study selection

A total of 191 studies were identified through initial database reaching. A total of 17 full-text articles were selected after removal of duplicates and reading abstracts that did not meet the eligibility criteria. From the 17 full-text studies, 2 studies were removed because they did not respect the screening criteria; finally, $n = 15$ articles met the predefined inclusion criteria and were included in the systematic review. Fig. 1 shows a flowchart with details about study selection and exclusion criteria.

Overview of included studies

In Table 1 characteristics of the 15 selected studies are showed. Among these articles, $n = 6/15$ (40%) were published in 2018, $n = 5/15$ (33,3%) in 2017, $n = 1/15$ (6,7%) in 2019, in 2016, in 2009 and in 2012. Most of the studies were conducted in the USA ($n = 5/15$) and the Netherlands ($n = 5/15$). Most studies were retrospective ($n = 14/15$). In all the studies, skeletal muscle mass was calculated on a single-slice abdominal transverse image at the third lumbar vertebra (L3), $n = 2/15$ evaluated muscle area also at the fourth thoracic vertebra (T4) level [18–21], but no additional values were found assessing sarcopenia not only at L3 level but also at T4 level. Only one study compared mass muscle estimation on CT and on MRI [20]. In most studies, sarcopenia cut-off point was defined as Skeletal Muscle Index (SMI) with different values (generally $< 41 \text{ cm}^2/\text{m}^2$ or $< 38,5 \text{ cm}^2/\text{m}^2$). Only one study evaluated sarcopenia assessed as muscle volume. [19] Among studies population, the prevalence of sarcopenia was at least 43,2%. The patient population of the 15 studies ranged from 21 to 3283 women and all breast cancer stages (I-IV) metastatic or not were at least included. Among all the selected studies, $n = 2/15$ included studies, the inter-reader agreement was assessed according to Cohen's kappa test with a k value respectively of 0,66 and 0,99 [4,10]. Only one study

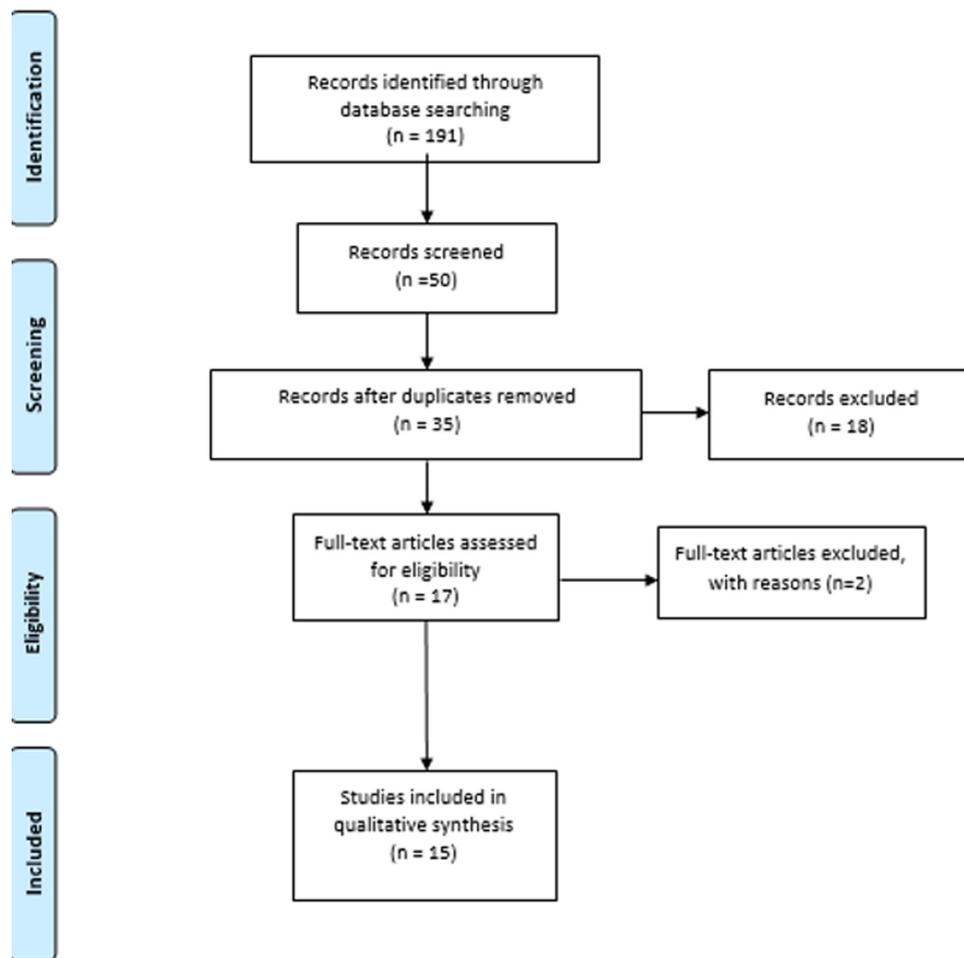


Fig. 1. Flowchart of the studies inclusion. CT-determined sarcopenia.

reported both intra- and inter-reader agreement, respectively of $k = 0,81$ and $k = 0,96$ [20].

A total of 13/15 studies reported clinical outcome correlated to sarcopenia. Among these studies, $n = 8/13$ studies concluded that sarcopenia is an important risk factor for poor prognosis in breast cancer and $n = 5/13$ studies concluded that body composition changes are not associated with poor prognosis (Table 2).

Risk of bias

The quality assessments overview of the selected studies recorded in a QUADAS-2 form is shown in Table 3. The domain “Index Test” was the only that potentially contribute a high risk of bias in the eligible papers. Therefore, only two papers reported details about CT parameters, including slice thickness and the type of scanner used [10,20]. A total of 4/15 studies did not report a cut-off value (reported as SMI or Volume) for sarcopenia [11,17,20,22]. The QUADAS-2 domain “Patient selection” was felt to be at low risk of bias for all studies.

Discussion

There is increasing interest in evaluating relationships between

sarcopenia and breast cancer outcomes. Indeed, sarcopenia has been considered an important independent prognostic risk factor and a key predictor of poor survival with increased risk of death in breast cancer women. Therefore, the purpose of the present study was to perform a literature review of sarcopenia assessed on body CT images in breast cancer patients and to examine the different impact of sarcopenia on clinical outcomes. Even if, many studies correlated CT-determined sarcopenia with clinical outcome in breast cancer women, a wide variability of results were reported. Indeed, while most studies supported the fact that sarcopenia in breast cancer is associated with higher overall mortality and higher grade of toxicity, some articles reported different results and contradictory results. Versteeg et al. found that muscle mass and radiodensity were not significantly associated with overall survival in older patients with advanced breast cancer. [24] However, in this study patients with multiple treatment lines and heterogeneous treatment regimens were included. In this study, the small number of patients ($n = 15$) and the retrospective study design could have reduced the possibility to find a relationship between sarcopenia and clinical outcomes. Rier et al. reported that in metastatic breast cancer patients treated with first line palliative chemotherapy, low muscle mass was not associated with overall survival (OS) and time to next treatment (TNT), whereas low muscle attenuation was

Table 1
Characteristics of the 15 studies included in the final analysis.

Author	Year of Publication	Country	Study Design	Number of Patients	Psoas Level on CT	Prevalence of Sarcopenia	Cut-off value for Sarcopenia	Cancer Stage	Outcome	Inter- intra-reader agreement	Muscle attenuation (HU)
Rier et al. [22]	2018	The Netherlands	Retrospective	98	L3	NA	NA	IV	OS	NA	A (31HU)
Caan et al. [4]	2018	USA	Retrospective	3241	L3	34%	< 40 cm ² /m ²	II-III	OS	Inter-reader	A
Weinberg et al. [17]	2016	USA	Retrospective	241	L3	34%	NA	I-II	OS	NA	A (35,6HU)
Versteeg et al. [24]	2018	The Netherlands	Prospective	15	L3	66%	< 38 cm ² /m ²	NA	Toxicity	NA	A (27,4HU)
Deluche et al. [6]	2018	France	Retrospective	119	L3	48,8%	< 41 cm ² /m ²	I-II	OS	NA	NA
Blauwhoff-Buskermolen et al. [18]	2017	The Netherlands	Retrospective	36	L3	NA	< 39 cm ² /m ²	IV	DFS	NA	A
Mazzuca et al. [3]	2018	Italy	Retrospective	21	L3	38,1% (before treatment); 47,6% (after treatment)	< 38,5 cm ² /m ²	I-III	Quality of life toxicity	NA	NA
Rier et al. [10]	2017	The Netherlands	Retrospective	166	L3	66,9%	< 41,0 cm ² /m ²	IV	OS	Inter-reader	A (41HU and 33HU)
Neefjes et al. [21]	2017	The Netherlands	Retrospective	32	L3	NA	< 41 cm ² /m ²	IV	Time to Next Treatment	NA	A
Rossi et al. [20]	2019	Italy	Retrospective	26	L3	NA	NA	I-III	Cancer-related fatigue	Inter-reader	A
Song et al. [19]	2018	Korea	Retrospective	1460	L3	NA	93,3 cc	I-III	OS	Intra-reader	A
Prado et al. [12]	2009	Canada	Retrospective	55	L3	25%	< 38,5 cm ² /m ²	IV	RFS	NA	A
Shachar et al. [11]	2017	USA	Retrospective	151	L3	NA	NA	I-III	Toxicity	NA	A
Shachar et al. [23]	2017	USA	Retrospective	50	L3	58%	< 41 cm ² /m ²	IV	TTP	NA	A
Del Fabbro et al. [5]	2012	USA	Retrospective	67	L3	27%	< 38,5 cm ² /m ²	I-III	Treatment Related Toxicity	NA	A
									OS	NA	A (29,8HU)
									TTP	NA	A
									OS	NA	A
									Pathological Complete Response	NA	A
									Progression Free Survival	NA	A

OS: overall survival. NA: not available. A: available. DFS: disease free survival. RFS: recurrence free survival. TTP: Time to tumor progression. TTF: Time to treatment failure.

Table 2
Association between sarcopenia and clinical outcomes: results.

Author	Association between sarcopenia and poor clinical outcome	Clinical outcome evaluated and reported results
Rier et al. [22]	Negative	During taxane-based chemotherapy, lumbar skeletal muscle index remained stable ($p = 0,40$)
Caan et al. [4]	Positive	In non-metastatic breast cancer patients, sarcopenia is correlated with higher overall mortality (HR 1,41. 95%CI:1,18–1,69)
Weinberg et al. [17]	Not available	Not available
Versteeg et al. [24]	Negative	Muscle mass and radiodensity were not significantly associated with overall survival in older patients with advanced cancer (p value $> 0,05$)
Deluche et al. [6]	Positive	Sarcopenia and inter-muscular adipose tissue areas are independent prognostic risk factor in early breast cancer for disease free survival ($p = 0,02$ and $p = 0,04$) and overall survival ($p = 0,05$ and $p = 0,02$)
Blauwhoff-Buskermolen et al. [18]	Positive	Patients with cachexia had worse overall survival (HR 1,64)
Mazucca et al. [3]	Positive	Skeletal muscle index $< 38,5 \text{ cm}^2/\text{m}^2$ is associated with G3-G4 toxicities in early breast cancer patients receiving adjuvant chemotherapy
Rier et al. [10]	Negative	Low muscle mass showed no association with overall survival (HR:0,98, p value = 0,923) and with time to next treatment (HR: 0,84, p value = 0,486)
Neefjes et al. [21]	Negative	In advanced cancer, higher skeletal muscle index seemed to be associated with more cancer-related fatigue, but this was not statistically significant (p value = 0,090)
Rossi et al. [20]	Not available	Not available
Song et al. [19]	Positive	Higher muscle volume had better prognosis (overall survival: HR = 0,56. 95%CI = 0,34–0,92. $P = 0,022$. Recurrence free survival: HR = 0,72. 95%CI = 0,52–0,99. $P = 0,046$)
Prado et al. [12]	Positive	In metastatic breast cancer, toxicity was present in 50% of sarcopenic patients (vs 20% of non-sarcopenic) ($p = 0,03$) and time to tumor progression was shorter in sarcopenic women (101,4 days. 95%CI = 59,8–142,9 vs 173,3 days).
Shachar et al. [11]	Positive	In early stage patients receiving anthracycline and taxane, poor body composition is associated with G3-G4 toxicities ($p = 0,002$).
Shachar et al. [23]	Positive	Metastatic breast cancer sarcopenic women receiving taxane developed G3-G4 toxicities (57% vs 18% in non-sarcopenic) ($p = 0,02$). Dose reduction or dose delay were higher in sarcopenic patients (74% vs 35%, $p = 0,02$)
Del Fabbro et al. [5]	Negative	Pathological complete response in sarcopenic patients was lower ($p = 0,0386$)

HR: Hazard Ratio. CI: Confidence Interval.

correlated with both OS and shorter TNT. They also found that patients with low muscle mass had a median OS and TNT of 15 and 8 months respectively compared to 23 and 10 months in patients with normal muscle mass [10]. These results are in contrast with the study performed on metastatic breast cancer patients by Prado et al. reporting a shorter time to disease progression in patients with low muscle mass [12]. Explanations for this discrepancy could be found in various factors such as differences in cancer type, disease stage at the time of muscle assessment and different radiological cut-offs to diagnose sarcopenia.

In additions, our systematic review showed that most studies had a retrospective design (most studies were performed in a single-centre) and only one study was prospective. A known limitation of the majority of the studies is the relatively small number of patients that could lead to a type II statistical error. Moreover, according to international guidelines and recommendations, CT scans are not used to assess extension in early breast cancer. Indeed, in early breast cancer, routine staging evaluations directed at loco-regional disease are done with different techniques (mammography, ultrasound, tomosynthesis and MRI).

Regarding the quality assessment, we used a modified QUADAS-2 checklist considering two domains, the patient selection and the index test. In addition to the standard questions of the domain “patients’ selection” we also considered the patients’ age and the breast cancer staging, because these data could be important for the body composition assessment. The domain “index test”, especially CT parameters,

was the only to potentially contribute a high risk of bias in the eligible papers. However, we were not able to find consistent studies addressing this technical issue. In large multicentric trials it would be mandatory to have a highly reproducible protocol to perform psoas muscle evaluation at L3 to assess skeletal muscle mass in every single patient. Therefore, this systematic review underlined that implementation of muscle mass assessment in clinical oncological practice is partially due to the lack of a standardized method of measurement. In addition, we found that only few studies reported data on reproducibility of CT-based measurements of psoas area and density at the level of L3. Only $n = 2/15$ studies reported the inter-reader agreement and only one study reported both intra- and inter-reader agreement. The lowest value of reported inter-reader agreement was 0,66, therefore we believe that it is still possible to study strategies to improve the agreement among different readers.

In conclusion, we performed a comprehensive evaluation of the current medical literature where muscle mass in breast cancer patients was measured with CT and correlated with clinical outcomes. Although different methods are used to evaluate muscle mass, sarcopenia could be easily assessed using already available body CT images. In most studies, sarcopenia has been recognized as a prognostic risk factor for clinical outcome in breast cancer patients. Our systematic review suggests that high-quality prospective studies are needed to strongly confirm and fully understand the clinical impact of CT-determined sarcopenia in breast cancer women.

Table 3
Quality appraisal of included studies.

Study	Patient Selection					Index Test		
	Age	Random or consecutive sample	Case-control study avoided	inappropriate exclusion avoided	Breast Cancer Stage	CT parameters	Skeletal muscle index cut-off	Muscle mass attenuation
Rier et al. [22]	☺	☺	☺	☺	☺	☹	☹	☺
Caan et al. [4]	☺	☺	☺	☺	☺	☹	☺	☺
Weinberg et al. [17]	☺	☺	☺	☺	☺	☹	☹	☺
Versteeg et al. [24]	☺	☺	☺	☺	☹	☹	☺	☺
Deluche et al. [6]	☺	☺	☺	☺	☺	☹	☺	☹
Blauwhoff-Buskermolen et al. [18]	☺	☺	☺	☺	☺	☹	☺	☺
Mazzuca et al. [3]	☺	☺	☺	☺	☺	☹	☺	☺
Rier et al. [10]	☺	☺	☺	☺	☺	☺	☺	☺
Neefjes et al. [21]	☺	☺	☺	☺	☺	☹	☺	☺
Rossi et al. [20]	☺	☺	☺	☺	☺	☺	☹	☺
Song et al. [19]	☺	☺	☺	☺	☺	☹	☺	☺
Prado et al. [12]	☺	☺	☺	☺	☺	☹	☺	☺
Shachar et al. [11]	☺	☺	☺	☺	☺	☹	☹	☺
Shachar et al. [23]	☺	☺	☺	☺	☺	☹	☺	☺
Del Fabbro et al. [5]	☺	☺	☹	☺	☺	☹	☺	☺

Acknowledgement

The authors of this manuscript certify that they comply with the ethical guidelines for authorship. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

None.

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