

Review Article

The Influence of Muscle Morphology on Oncological Outcomes: A Review

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Abstract

Cancer is a common disease with significant impact on patients and society. Cancer and oncological treatment can negatively affect muscle, and muscle health impacts oncologic outcomes. This review studied the effect of different muscle parameters on oncologic outcomes. A systematic search was performed until April 2023. Parameters included were muscle thickness, cross-sectional area, skeletal muscle index, skeletal muscle mass, pennation angle, fascicle length, muscle density, echo intensity and elastography. Imaging methods included were computerized tomography, magnetic resonance imaging, ultrasound and dual-energy X-ray absorptiometry. Outcome parameters assessed were survival, chemotoxicity, surgical outcome, treatment response, duration of hospitalization, and quality of life. This review included 117 articles. Individuals with reduced skeletal muscle index or muscle density had lower survival rates, higher chemotoxicity and surgical complications, more hospitalizations, less treatment response and lower quality of life. Reduced muscle quantity and quality can impact oncological outcomes, either through primary or secondary sarcopenia. These findings warrant the need for holistic assessment by using comprehensive geriatric assessment to establish a correct treatment dosage. These results also suggest a beneficial effect of exercise and nutritional support. Further research can be useful to better understand the underlying mechanisms and optimize specific treatments for muscle in oncological patients.

Keywords: Oncology, Sarcopenia, Muscle, Body composition, Outcome

The authors have no conflict of interest.

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Edited by: Yannis Dionyssiotis

Accepted 24 July 2025

Introduction

Cancer is a prevalent disease with significant impact on a persons' quality of life, perceived health, and life expectancy¹⁻³. It is one of the main causes of death worldwide, with more than 10 million deaths in 2020¹. The most prevalent cancer types are breast, lung, colorectal, prostate, skin and stomach. One of the consequences of cancer and cancer treatment is muscle wasting, a condition with reduced muscle mass that negatively impacts prognosis and quality of life⁴.

Muscle health is gaining increasing interest not only in an oncological setting but also in other medical fields. While awaiting the currently ongoing global definition of sarcopenia, which is a work in progress by the Global Leadership Initiative on Sarcopenia (GLIS)⁵, the most updated definition states that sarcopenia is a muscular disease with low strength as key feature, combined with low muscle quantity or quality⁶. This occurs mainly in older persons but can also appear earlier in life or even in children⁶. Sarcopenia can be primary and thus age-related, however certain disease states, such as cancer but also declines in nutritional intake and physical activity, can induce secondary sarcopenia^{6,7}. Sarcopenia is closely linked with cachexia, which is defined as a multifactorial syndrome with severe loss of weight due to an underlying disease and is cytokine-mediated. Cachexia mainly involves loss of fat and muscle^{7,8}. Both sarcopenia and cachexia are common in cancer patients: 15-50% has sarcopenia, and 25-80% suffers from cachexia⁷. These two entities often co-exist and can exacerbate each other⁷.

Different imaging methods are available to evaluate muscle status. Dual-energy X-ray absorptiometry (DXA) and bioelectrical impedance analysis (BIA) measure muscle quantity. For these techniques cut-off values have been established. For computed tomography (CT) measurements cut-off values for sarcopenia have been more recently proposed⁹. However, multiple studies use different values. Magnetic resonance imaging (MRI) is often used in research and in oncological or surgical settings. Ultrasound (US) is a technique that is gaining more attention for the evaluation of muscle status since it is easily accessible, inexpensive, and non-invasive. The advantages of CT, MRI and US are that they can assess both muscle quantity and quality^{6,10,11}.

Muscle quantity can be assessed through muscle thickness (MT), cross-sectional area (CSA), skeletal muscle mass (SMM) and skeletal muscle index (SMI): skeletal muscle area divided by height. Muscle quality is possibly equally important, and covers assessments of histology, radiology, functionality or metabolism⁵. It is determined by a combination of metabolic features, number of type II fibres, insulin resistance, fat infiltration, fibrosis, disrupted aerobic capacity and neurological derangements¹². The evaluation of muscle quality is more challenging however. Suggestions have been made to measure the pennation

Search Strategy: Medline via Ovid, last search April 11th 2023

1	Ultrasonography/(199091)
2	echotomograph*.ti,ab,kf. (761)
3	ultrasound*.ti,ab,kf. (309414)
4	ultrasonograph*.ti,ab,kf. (127003)
5	(ultrasonic adj2 (diagnos* or imaging or tomograph*)).ti,ab,kf. (4291)
6	echograph*.ti,ab,kf. (10275)
7	echotomograph*.ti,ab,kf. (761)
8	sonograph.ti,ab,kf. (76)
9	Tomography, X-Ray Computed/(416021)
10	((xray or x-ray) adj3 (tomograph* or ct or scan*)).ti,ab,kf. (31561)
11	tomodensitometr*.ti,ab,kf. (1230)
12	Magnetic Resonance Imaging/(469570)
13	mri* adj2 (functional or scan*).ti,ab,kf. (43199)
14	"chemical shift imaging*".ti,ab,kf. (1105)
15	"magnetic resonance imaging*".ti,ab,kf. (292219)
16	((imaging* or tomography) adj2 (echo or chemical or nmr)).ti,ab,kf. (10793)
17	or/1-16 (1392522)
18	(pennation adj2 (muscle* or angle*)).ti,ab,kf. (854)
19	(muscle adj2 (fiber or fibre) adj2 (angle or length)).ti,ab,kf. (309)
20	(muscle adj2 (brightness or thickness or density)).ti,ab,kf. (5140)
21	(muscle adj4 (echo-intensity or echointensity or echo intensity)).ti,ab,kf. (311)
22	(muscle adj2 (cross-sectional or surface or cross sectional) adj2 area).ti,ab,kf. (2514)
23	(fascicle adj2 (angle or rotation or length)).ti,ab,kf. (915)
24	or/18-23 (8753)
25	17 and 24 (4091)
26	exp animals/ not humans.sh. (5110748)
27	(exp infant/ or exp child/ or adolescent/) not exp adult/ (2121700)
28	25 not 26 not 27 (3669)
29	limit 28 to English language (3620) 30 limit 29 to dt=20210901-20230411 (605)

Table 1. Search strategy.

angle (PA), fascicle length (FL), echo intensity (EI), muscle elastography (ME), phase angle (PhA) and muscle density (MD)⁶. The latter is defined as the mean attenuation coefficient, expressed in Hounsfield Units (HU), measuring muscular fat infiltration¹³. Skeletal muscle gauge (SMG)

is a less frequently computed muscle parameter that is calculated by multiplying the SMI and the MD¹⁴.

Sarcopenia is prevalent, especially in older individuals, with prevalence varying from 10 to 27% in older persons, depending on the definition and cut-off values used. However, muscles of younger individuals aged <60 years can also be affected, with prevalence ranging from 8 to 36%¹⁵. Muscle status is an important parameter for general health. It is already known that sarcopenia confers higher mortality rates, more functional decline, higher risk of falling and an increased risk of hospitalization¹⁶. Sarcopenia and oncological problems often co-exist, and the combination is associated with higher prevalence of adverse outcomes. In oncological treatment, decisions are often made considering chronological age. However, sarcopenia is associated with poorer prognosis and more postoperative complications in oncology patients. This is due to a combination of primary and secondary sarcopenia. Sarcopenic patients with cancer suffer from more pulmonary complications, infections, higher readmission rates and increased length of hospitalization¹⁷. A higher treatment toxicity and a reduced quality of life are also seen¹⁸.

The aim of this study was twofolded. First, to review which muscle parameters were associated to certain clinical outcomes in oncology, such as: overall survival, progression-free survival, cancer-specific survival, chemotoxicity, surgical outcomes, response to oncologic treatment, length of stay and rehospitalisation, and quality of life. Second, we wanted to give an insight in the current literature about muscle status and oncological outcomes, so that an impetus can be given for a more routine geriatric assessment and follow-up when considering oncologic treatments.

Methods

This systematic review is part of a series of systematic reviews considering clinical health outcomes and muscle parameters which will be published separately, and are part of Sarcopenia through Ultrasound (SARCUS), a larger European non-funded academic project initiated in 2016, which involves researchers in different institutions in different countries, and has been gathered under the auspices of the European Union Geriatric Medicine Society (EuGMS) and the University of Antwerp, Belgium. This manuscript presents the efforts of the SARCUS project in gathering knowledge about the different outcomes in Oncology.

The combined systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (19). The protocol was registered in the Prospective Register of Systematic Reviews Database (PROSPERO) under the registration number CRD42020179671. In this protocol, numerous clinical outcomes were investigated

Study Characteristic	N (TOTAL = 117)
Type of Study	
Original Article	117
Retrospective	98
Prospective	19
Subject of Study	
Survival	96
Chemotoxicity	20
Outcomes After Surgery	33
Response To Treatment	12
Duration of Hospitalization and Rate of Readmission	20
Quality of Life	3
Radiographic Method	
CT	102
MRI	14
US	3
BIA	3
DXA	1
More Than 1	4
Muscle Parameter Investigated	
SMI	74
MD	54
CSA	23
MT	14
SMG	6
SMM	1
PMI	8
EI	1

BIA = bioelectrical impedance analysis; CSA = cross-sectional area; CT = computed tomography; DXA = dual-energy X-ray absorptiometry; EI = echo intensity; MD = muscle density; MRI = magnetic resonance imaging; MT = muscle thickness; PMI = psoas muscle index; SMG = skeletal muscle gauge; SMI = skeletal muscle index; SMM = skeletal muscle mass; US = ultrasound.

Table 2. General study characteristics.

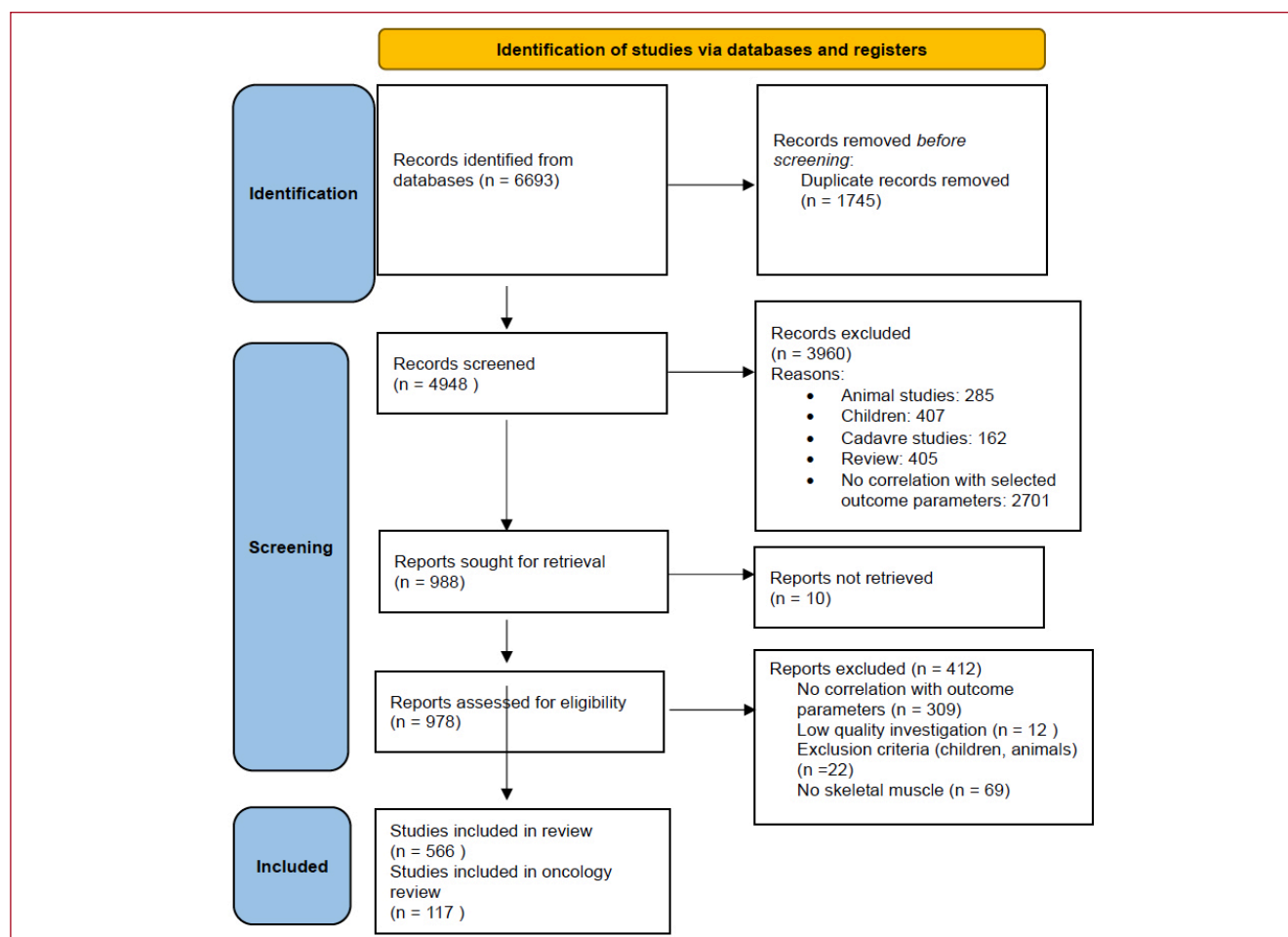


Figure 1. PRISMA flow diagram.

in association with macroscopic muscle parameters (such as oncological, surgical, medical, survival, length of stay, mobility, frailty, nutritional, bone health, respiratory, masticatory, functionality, dysphagia, ...). Later, these results were divided into different articles with focus on one specific outcome parameter.

Inclusion and exclusion criteria

The following keywords and their related MESH terms were used for the search (see Table 1 for the complete search terms): Ultrasound, Computed Tomography, Magnetic Resonance Imaging, Pennation angle, Muscle thickness, Echo-intensity, Muscle density, Cross-sectional area, Fascicle length. In the first article selection, all possible clinical outcomes were included. Exclusion criteria were studies involving children, animals or cadaver studies, review studies and case reports. Only articles in English were included in the study according to existing literature^{20,21}.

Search strategy and article selection

An initial search was performed on April 14th 2020. Because numerous new articles were published in the time of data extraction and analysis, follow-up searches were conducted on September 29th 2021 and April 11th 2023 to check for the latest published research to improve the quality of the paper. Systematic searches were performed using SCOPUS, AMED and EBM Reviews - ACP Journal Club. Duplicates were removed and titles and abstracts were selected for eligibility by two investigators (SB and SP) using Rayyan software. In case of disagreement about in- or exclusion, the article was included. Then, the full text articles were sought through different libraries or through contacting the authors via Researchgate. Subsequently, the articles were subdivided among the authors for further selection and data extraction. Each full text article was checked on suitability for the study by SB and one other reviewer out of 18 different researchers, and data extraction was performed by both reviewers.

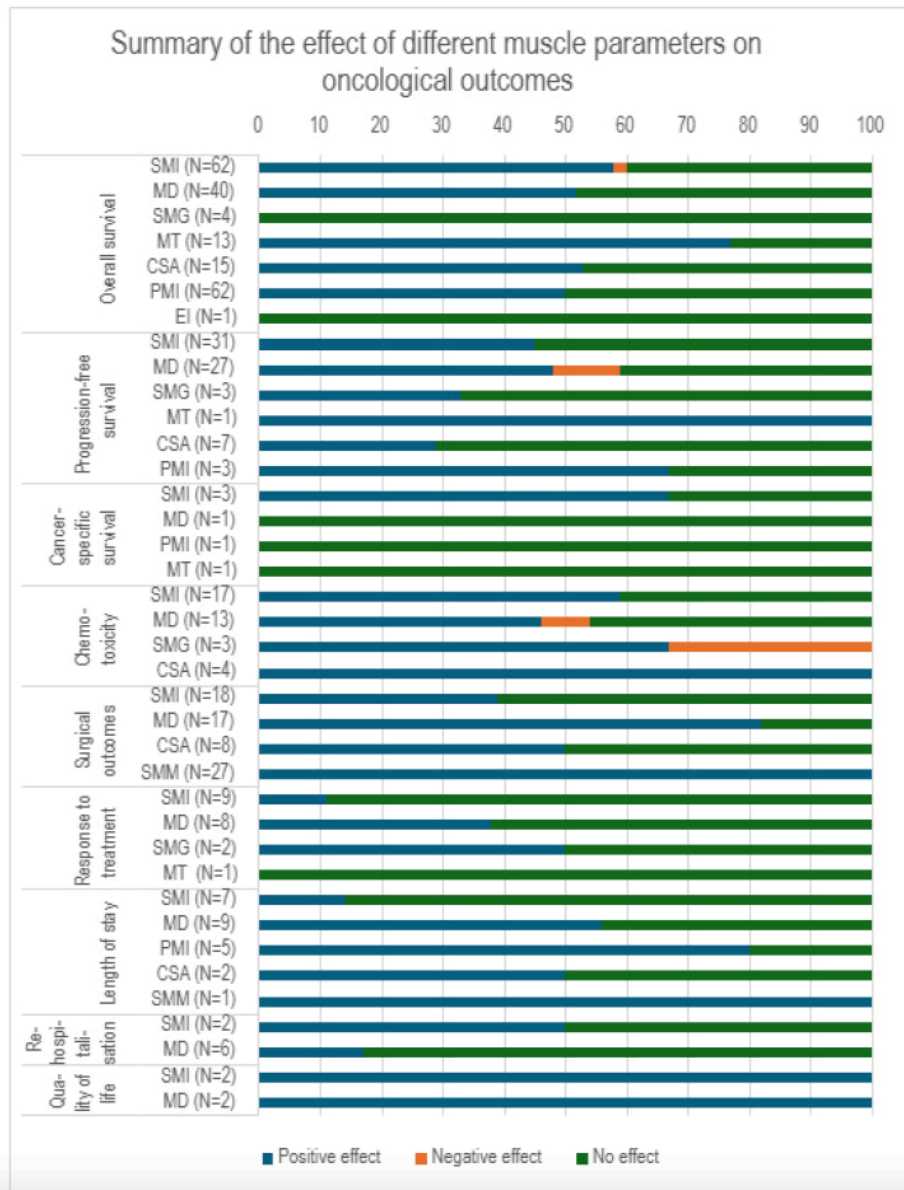


Figure 2. Summary of the effect of different muscle parameters on oncological outcomes. (Abbreviations: CSA = cross-sectional area; EI = echo intensity; MD = muscle density; MT = muscle thickness; PMI = psoas muscle index; SMG = skeletal muscle gauge; SMI = skeletal muscle index).

Data extraction and analysis

Data were extracted by 18 different researchers, and checked personally by SB. Disagreement was solved through intensive discussion. The extracted data included author, year of publication and country of investigation, population of interest (with gender and mean age), examined muscle or muscle group, imaging technique, muscle parameter, the investigated outcome measure, and the findings.

Results of the analysis on oncological outcomes were subdivided into six categories: survival, chemotoxicity, postoperative outcomes, response to treatment, duration of hospitalization and quality of life. Since survival can be defined in different ways, the differentiation was made between overall survival, progression-free survival, and cancer-specific survival.

Results

Study selection

A total of 6693 articles were identified after the last search for the combined health outcomes. After eliminating duplicates, the study yielded 4948 unique articles. After title and abstract selection, 988 studies remained. Full text articles were found in 978 cases for the total health study for article selection and quality assessment. 10 articles could not be found, either because no full text was available in the English language, or because they could not be retrieved on the different libraries or through Researchgate. Of these, 566 articles were eventually considered suitable for data extraction of all outcome parameters. For the review focused on oncological outcomes, 117 of 566 articles were included. The overview of study selection can be found in Figure 1. Table 2 shows the general study characteristics of the included articles. Table 3 indicates the different investigated primary tumor locations. An overview of the included articles is shown in Tables 4-9.

General study characteristics

All of the included articles were original studies. Ninety-eight had a retrospective set-up and 19 were prospective. Ninety-six had data on survival. Twenty articles contained information on chemotoxicity and 33 on outcomes after oncological surgery. Twelve articles involved the response to the oncologic treatment. The duration of hospitalization and the rate of readmission was described in 20 articles. Finally, three articles highlighted the association of muscle parameters with the quality of life in patients suffering from cancer.

Most included studies measured muscle parameters by CT (102 articles). The remainder of the studies used MRI (14 studies), US (3 studies), BIA (3 studies) or DXA (1 study). Four articles included more than one measurement method. Most studies described the effect of skeletal muscle index (SMI, a quantitative measure) and muscle density (MD, a qualitative measure) on oncologic outcomes. In the great majority of these studies, SMI was calculated by CT as the CSA or all muscle tissue at the level of L3, divided by the square of height (cm^2/m^2). However, few studies used the CSA of all muscles at L4 or T12 divided by the square of height, or used DEXA or BIA to define SMI (by appendicular skeletal muscle mass divided by the square of height). Most, but not all studies used the cut-off values for SMI as stated by Martin et al. CSA, MT, and SMG are other muscle parameters used in the included studies. All results with positive, negative or no effect are summarized in Figure 2.

Oncology and survival

Ninety-six articles studied the effect of radiographic muscle parameters on survival. An overview of all the included articles can be found in Table 4²²⁻¹¹⁵.

Tumor Location	Number of Included Studies
Pulmonary	16
Lower Gastro-Intestinal	14
Hematological	12
Urogenital	12
Head/Neck	9
Neurological	8
Liver/Bile	8
Upper Gastro-Intestinal	7
Breast	7
Pancreas	3
Ovarium	3
Melanoma	3
Endometrial	2
Sarcoma	2
Different/Not Stated	9

Table 3. Overview of the tumor locations in the included studies.

Overall survival

Overall survival (OS) was the most commonly used parameter used in survival analysis. It is defined as the time from randomization in the study until death. Ninety studies investigated the effect of muscle parameters on OS.

Sixty-two studies investigated the impact of skeletal muscle index (SMI) as measured by CT. An association between higher SMI and improved overall survival was seen in 36/62 (58%), with hazard ratios (HR) reported in 31 of these ranging from 1.22 to 4.9 (median 2.1). In 25/62 (40%) no significant association of SMI on overall survival was seen. One article revealed conflicting results favouring low SMI, with HR of 0.19. The authors attributed this to the high number of women in their population.

Forty articles described the association of muscle density by CT with OS. Higher MD was associated with better survival in 21/40 (52%), with HR for low MD ranging from 1.11 to 4.02 (median 2.01). In 19/40 (48%), no significant impact of MD could be found.

Although SMG is calculated from SMI and MD, the four articles that investigated SMG did not significantly show an effect on OS. MT showed a beneficial association between greater MT and OS in 10/13 (77%) studies, with HR ranging from 1.23 to 10.79 (median 2.13). The studies on MT mostly used MRI, but one article described the use of US. CSA was measured by CT in 13 articles, and by MRI in two. In 8/15 (53%) of the studies higher CSAs were

Table 4. Characteristics and results of included studies on survival in oncology.

First author, year, country	Design	Population (%men, mean age (year))	Mean follow-up	Investigated muscle(s)	Muscle parameters + imaging method	Outcome	Statistical results
Abbass, 2020, UK ²²	R	643 advanced lung cancer patients (51.3%, 70y)	10 months	L3	SMI (CT) MD (CT)	OS	<ul style="list-style-type: none"> • Low SMI: <ul style="list-style-type: none"> o Univariate: HR 1.22* o Multivariate: HR 1.17 • Low MD: <ul style="list-style-type: none"> o Univariate: HR 1.11
Abe, 2018, Japan ²³	R	87 metastatic urothelial cell carcinoma patients treated with systemic chemotherapy (74.7%, 73)	15.4 months	L3	SMI (CT)	OS	<ul style="list-style-type: none"> • Low SMI: <ul style="list-style-type: none"> o Multivariate (stratified for BMI): HR 3.1**
Akce, 2021, USA ²⁴	R	57 advanced HCC patients treated with immunotherapy (77.2%, 66)	6 months	L3	SMI (CT)	OS	<ul style="list-style-type: none"> • Low SMI: <ul style="list-style-type: none"> o OS 5 vs. 14.3 months o Multivariate: HR 1.71
						PFS	<ul style="list-style-type: none"> • Low SMI: <ul style="list-style-type: none"> o Multivariate: 0.99
Al Khaldi, 2022, Canada ²⁵	R	312 patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for peritoneal metastases (34.3%, 57.6)	28 months	L3	SMI (CT)	OS	<ul style="list-style-type: none"> • Low SMI: <ul style="list-style-type: none"> o Multivariate: HR 1.17
Antoun, 2013, France ²⁶	P	149 renal cell carcinoma patients treated with Sunitinib, Sorafenib or Everolimus (76%, 58)	Not stated	L3	CSA (CT) MD (CT)	OS	<ul style="list-style-type: none"> • Low MD below median: <ul style="list-style-type: none"> o Univariate: HR 2** o Multivariate: HR 1.9** • CSA: No significant association
						PFS	<ul style="list-style-type: none"> • MD < median: o Univariate: HR 1.9** o Multivariate: HR 2** • CSA: No significant association
Arayne, 2023, Australia ²⁷	R	80 patients with stage I – III rectal cancer undergoing curative resection (74%, 63)	Not stated	T4, T12, L3	SMI (CT)	OS	<ul style="list-style-type: none"> • Low SMI = higher mortality: <ul style="list-style-type: none"> o T4: 45 vs. 5%** o For T12: 45 vs. 10%* o For L3: 45 vs. 10%*
Arien, 2020, Belgium ²⁸	R	180 older adults with cancer (48%, 80)	Not stated	Left psoas mid-L3	CSA (CT) MD (CT)	OS	<ul style="list-style-type: none"> • Low MD: <ul style="list-style-type: none"> o Univariate: HR 1.04 • Low CSA: <ul style="list-style-type: none"> o Univariate: HR 1.52*
Asai, 2023, Japan ²⁹	R	456 patients undergoing major hepatectomy for perihilar cholangiocarcinoma (68%, 69)	Not stated	Psoas at L3	MD (CT) PMI (CT)	OS	<ul style="list-style-type: none"> • Lowest tertile PMI: <ul style="list-style-type: none"> o OS 37.8 versus 54.2 months. • Lowest tertile MD: NS
Bardoscia, 2022, Italy ³⁰	R	225 head and neck cancer patients undergoing radiation or chemoradiation (75.6%, 64.5)	5.6 year	L3	SMI (CT) MD (CT)	OS	<ul style="list-style-type: none"> • Low SMI: <ul style="list-style-type: none"> o Univariate: HR 1.19 o Multivariate: HR 0.86 • Low MD: <ul style="list-style-type: none"> o Univariate: HR 2.12** o Multivariate: HR 1.88* (age, sex, stage, DM, BMI and weight loss)
						PFS	<ul style="list-style-type: none"> • Low SMI: o Univariate: HR 1.18 o Multivariate: HR 0.84 • Low MD: o Univariate: HR 2.37** o Multivariate: HR 2.26 (age, sex, stage, DM, BMI and weight loss)

Table 4. (Cont. from previous page).

First author, year, country	Design	Population (%men, mean age (year))	Mean follow-up	Investigated muscle(s)	Muscle parameters + imaging method	Outcome	Statistical results
						CSS	<ul style="list-style-type: none"> • Low SMI: o Univariate: HR 1.25 o Multivariate: HR 0.94 • Low MD: <ul style="list-style-type: none"> o Univariate: HR 2.46* o Multivariate: HR 2.40* (age, sex, stage, DM, BMI, weight loss)
Begini, 2017, Italy ³¹	R	92 cirrhosis patients with HCC (70.6%, 71.6)	Not stated	L3	SMI (CT)	OS	<ul style="list-style-type: none"> • Sarcopenia (low SMI): <ul style="list-style-type: none"> o Univariate: HR 2.20** o Multivariate: HR 2.37 (BCLC, TNM, Child-Pugh, bilirubin, performance status)
Besutti, 2021, Italy ³²	R	116 diffuse large B-cell lymphoma patients (51.7%, 63.7)	30 months	L3 Proximal thigh (PT)	SMI (CT) MD (CT)	OS	<ul style="list-style-type: none"> • Low L3 SMI (continuous) <ul style="list-style-type: none"> o Univariate: HR 0.81 o Multivariate: HR 0.48* (IPI, sex, BMI, and therapy) • Low PT SMI (continuous): <ul style="list-style-type: none"> o Univariate: HR 1.18 o Multivariate: HR 0.98 • Low L3 MD (continuous): <ul style="list-style-type: none"> o Univariate: HR 2.17 o Multivariate: HR 1.69 • Low PT MD (continuous): <ul style="list-style-type: none"> o Univariate: HR 2.57** o Multivariate: HR 2.17** (IPI, sex, BMI, and therapy)
						PFS	<ul style="list-style-type: none"> • Low L3 SMI (continuous) o Univariate: HR 1.04 o Multivariate: HR 0.86 • Low PT SMI (continuous): o Univariate: HR 1.16* o Multivariate: HR 1 • Low L3 MD (continuous): o Univariate: HR 1.56* o Multivariate: HR 2.27 • Low PT MD (continuous): o Univariate: HR 2.44** o Multivariate: HR 1.61
Bronger, 2017, Germany ³³	R	128 patients with advanced serous ovarian cancer (65)	117 weeks	L3	SMI (CT)	OS	<ul style="list-style-type: none"> • Low SMI (sarcopenia): <ul style="list-style-type: none"> o Lower OS: 23 vs. 48 months o Univariate: HR 3.17* o Multivariate: HR 2.89* (age, residual tumor)
						PFS	<ul style="list-style-type: none"> • Low SMI (sarcopenia): <ul style="list-style-type: none"> o Lower PFS: 15 vs. 22 months o Univariate: HR 2.64* o Multivariate: HR 2.52* (age, residual tumor, FIGO)
Chakedis, 2018, USA ³⁴	R	177 patients with biliary tract cancer (44%, 66)	12.2 months	L3 Psoas	PMI (CT) MD (CT)	OS	<ul style="list-style-type: none"> • Low PMI (sarcopenia): <ul style="list-style-type: none"> o Lower OS: 12.6 vs. 38.7 months** o Higher 1-year mortality: 40 vs. 21% o Univariate: HR 2.33** o Multivariate: HR 3.52** (age, sex, ethnicity, mFI category, pathology diagnosis, NLR) • Low MD: <ul style="list-style-type: none"> o Univariate: HR 2.10* o Multivariate: HR 2.96*
						PFS	<ul style="list-style-type: none"> • Low PMI (sarcopenia): <ul style="list-style-type: none"> o Higher mortality: 71 vs. 40%**

Table 4. (Cont. from previous page).

First author, year, country	Design	Population (%men, mean age (year))	Mean follow-up	Investigated muscle(s)	Muscle parameters + imaging method	Outcome	Statistical results
Charette, 2019, Belgium ³⁵	P	217 chemorefractory advanced colorectal cancer patients (57%, 63)	Not stated	L3	MD (CT) SMI (CT)	OS	<ul style="list-style-type: none"> • Low SMI: <ul style="list-style-type: none"> o Univariate: HR 2.06* o Multivariate: HR 1.49** (age, BMI, sex, performance status, time since diagnosis, low SMI, low MD, low SC fat index, high SC fat density, low visceral fat index, high visceral fat density) • Low MD: <ul style="list-style-type: none"> o Univariate: HR 1.54* o Multivariate: HR 1.80** (age, BMI, sex, performance status, time since diagnosis, low SMI, low MD, low SC fat index, high SC fat density, low visceral fat index, high visceral fat density) • Best cut-offs for association with survival: SMI 47.5 cm²/m², MD 22.5HU
Cho, 2022, Austria ³⁶	R	566 patients with brain metastases from NSCLC (48%, 63)	Not stated	Temporal muscle at level of orbital roof	MT (MRI)	OS	<ul style="list-style-type: none"> • Low MT (≤ 6.3mm in men and ≤ 5.2 mm in women): <ul style="list-style-type: none"> o Univariate: HR 1.90** o Multivariate: HR 1.68** (age groups, sex, number of brain metastases, presence of ECMs, NSCLC subtype, KPS groups, RPA classes, and concomitant IT or TT) o Shorter survival: 7.5 vs. 18.6 months
Chu, 2017, Canada ¹⁶⁰	R	224 DLBCL patients treated with Rituximab-containing therapy (56%, 62)	Not stated	L3	MD (CT) SMI (CT)	OS	<ul style="list-style-type: none"> • Low SMI: o Univariate: HR 0.77 • Low MD: <ul style="list-style-type: none"> o Univariate: HR 3.45** o Multivariate: HR 2.52** (R-IPi scores and gender)
						PFS	<ul style="list-style-type: none"> • Low SMI: o Univariate: HR 0.65 • Low MD: o Univariate: HR 2.28** o Multivariate: HR 3.76 (R-IPi and gender)
Chu, 2015, Canada ³⁷	R	145 follicular lymphoma patients who received chemoimmunotherapy (55%, 59)	Not stated	L3	MD (CT) SMI (CT)	OS	<ul style="list-style-type: none"> • Low SMI: o Univariate: HR 1.06 • Low MD: o Univariate: HR 4.02** o Multivariate: HR 3.40 (FLIPI-1 scores and gender)
						PFS	<ul style="list-style-type: none"> • Low SMI: o Univariate: HR 0.65 • Low MD: o Univariate: HR 1.85* o Multivariate: HR 1.65 (FLIPI-1 scores and gender)
Chu, 2020, Canada ³⁸	R	97 metastatic melanoma patients treated with Ipilimumab (60%, 56)	Not stated	L3	MD (CT) SMI (CT)	OS	<ul style="list-style-type: none"> • Low SMI (sarcopenia) <ul style="list-style-type: none"> o Multivariate: HR 2.46** (gender, LDH, line of therapy, BRAF) • Low MD: <ul style="list-style-type: none"> • Univariate: HR 2.47** Multivariate: HR 2.12* (gender, LDH, line of therapy, BRAF)
						PFS	<ul style="list-style-type: none"> • Low SMI (sarcopenia) <ul style="list-style-type: none"> o Multivariate: HR 1.85* (gender, LDH, line of therapy, BRAF) • Low MD: <ul style="list-style-type: none"> • Univariate: HR 1.77** • Multivariate: HR 1.55 (gender, LDH, line of therapy, BRAF)
Cinar, 2022, Turkey ³⁹	R	180 patients undergoing resection for NSCLC (80%, 65)	26.3 months	T12 para-vertebral muscles	PVMI (CT) MD (CT)	OS	<ul style="list-style-type: none"> • Low PVMI: <ul style="list-style-type: none"> o Lower survival: 52.5 vs. 57.5 months** o Univariate: HR 2.10** o Multivariate: HR 1.77** • Low MD: <ul style="list-style-type: none"> o Lower survival: 50.8 vs. 59.4 months** o Univariate: HR 2.71** o Multivariate: HR 1.84

Table 4. (Cont. from previous page).

First author, year, country	Design	Population (%men, mean age (year))	Mean follow-up	Investigated muscle(s)	Muscle parameters + imaging method	Outcome	Statistical results
Cortellini, 2020, Italy ¹⁶¹	R	100 patients with advanced cancer receiving anti-PD-1/PD-L1 checkpoint inhibitors (67%, 66)	20.3 months	L3	SMI (CT) MD (CT)	OS	<ul style="list-style-type: none"> • Low SMI: <ul style="list-style-type: none"> o Univariate: HR 2.19** o Multivariate: HR 2.19** o Melanoma subgroup: HR 3.11* • Low MD: <ul style="list-style-type: none"> o Univariate: HR 1.15
						PFS	<ul style="list-style-type: none"> • Low SMI: <ul style="list-style-type: none"> o Univariate: HR 1.66* o Multivariate: HR 1.48 • Low MD: <ul style="list-style-type: none"> o Univariate: HR 1.09
Cushen, 2014, Ireland ⁴¹	R	55 metastatic renal cell carcinoma treated with Sunitinib (78%, 66)	6 months + until drug was stopped	L3 (all muscles)	SMI (CT)	PFS	• No difference in low vs. high SMI group
DeFilipp, 2018, USA ⁴²	R	218 lymphoma patients who received high-dose chemotherapy and auto-HCT (59%, 56) and 97 who received allo-HCT (60%, 53)	Not stated	L3 (all muscles)	SMI (CT)	OS	<ul style="list-style-type: none"> • Low SMI-based sarcopenia: <ul style="list-style-type: none"> o Univariate: HR 1.63*
Dijksterhuis, 2019, the Netherlands ⁴³	R	88 advanced esophagogastric cancer patients treated with 1 st line CapOx (75%, 63)	Not stated	L3 (all muscles)	SMI (CT) MD (CT)	OS	<ul style="list-style-type: none"> • Low SMI pre-treatment: <ul style="list-style-type: none"> o Univariate: HR 0.70 o Multivariate: HR 0.94 • Low MD pre-treatment: <ul style="list-style-type: none"> o Univariate: HR 0.94 o Multivariate: HR 1.40
						PFS	<ul style="list-style-type: none"> • Low SMI pre-treatment: <ul style="list-style-type: none"> o Univariate: HR 0.72 o Multivariate: HR 0.78 o After 3 cycles: HR 0.56* • Low MD pre-treatment: <ul style="list-style-type: none"> o Univariate: HR 1.04 o Multivariate: HR 1.05
Ferraro, 2022, Germany ⁴⁴	R	72 patients with primary central nervous system lymphoma (51%, 68)	At least 2 years or until death	L3 (all muscles)	SMI (CT) MD (CT) SMG (CT)	OS	<ul style="list-style-type: none"> • Low SMI (sarcopenia): <ul style="list-style-type: none"> o Univariate: HR 0.61 • Low MD pre-treatment: <ul style="list-style-type: none"> o Univariate: HR 0.97* o Multivariate: HR 0.98 (age and gender)
						PFS	<ul style="list-style-type: none"> • Low SMI (sarcopenia): <ul style="list-style-type: none"> o Univariate: HR 0.65
Furtner, 2021, Austria ⁴⁵	R	128 patients with CNS lymphoma (52%, 62.7)	Not stated	Temporal muscle at level of orbital roof	MT (MRI)	OS	<ul style="list-style-type: none"> • Low MT (sarcopenia): <ul style="list-style-type: none"> o Univariate: HR 3.19* o Multivariate: HR 2.50** (gender, age, deep brain involvement, ECOG, and MTX-based therapy)
Ganju, 2019, USA ¹⁶²	R	46 stage Ib-IVa patients with endometrial cancer treated with hysterectomy and pelvic radiation (0%, 51)	27 months	L3	SMI (CT) MD (CT)	OS	<ul style="list-style-type: none"> • Low SMI (sarcopenia): <ul style="list-style-type: none"> o Univariate: 2.42 • Low MD: <ul style="list-style-type: none"> o Univariate: 3.52 • Low SMI + low MD: <ul style="list-style-type: none"> o Univariate: HR 4.25**

Table 4. (Cont. from previous page).

First author, year, country	Design	Population (%men, mean age (year))	Mean follow-up	Investigated muscle(s)	Muscle parameters + imaging method	Outcome	Statistical results
Golder, 2022, UK ⁴⁷	R	1 146 patients with colon cancer (51%, age not stated)	Minimum 4 years	L3 (all muscles)	SMI (CT) MD (CT)	OS	<ul style="list-style-type: none"> • Stage III: <ul style="list-style-type: none"> o SMI and 3-year OS: NS o Low MD = worse 3-year OS: 76 vs. 75%* • Stage IV: <ul style="list-style-type: none"> o Low SMI = worse 3-year OS: 43 vs. 16%** o Low MD: NS
Haehl, 2022, Germany ⁴⁸	R	280 head and neck squamous cell carcinoma patients receiving curative (chemo)radiation (gender not stated, age >65)	127 days	C3 (perivertebral + SCM) L3 (calculated from C3)	SMI (CT) CSA (CT)	OS	<ul style="list-style-type: none"> • Low SMI: o OS 26 vs. 47 months* o 2-year survival 51.0 vs. 68.0%* o Univariate: HR 1.55* o Continuous: HR 1.33* o Low CSA (sarcopenia): <ul style="list-style-type: none"> o OS 23 vs. 91 months** o 2-year survival 49.6 vs. 71.1%** o Univariate: HR 1.79** o Multivariate: HR 1.64* (age, smoking status and Karnofsky Index) o Continuous: HR 1.56**
Hirai, 2020, Japan ⁴⁹	R	163 soft tissue sarcoma patients (59.5%, 64.2)	27 months	L3	SMI (CT) MD (CT) SMG (CT)	OS	<ul style="list-style-type: none"> • No impact of SMI, MD, or SMG on 5-year survival
Huang, 2021, China ⁵¹	P	587 patients with BMI >23 kg/m ² who underwent radical gastrectomy for gastric cancer (74%, 65)	43.8 months	L3	MD (CT)	OS	<ul style="list-style-type: none"> • Low MD + GLIM-defined malnutrition: HR 2.15** • GLIM-defined malnutrition alone: HR 2.24*
						PFS	<ul style="list-style-type: none"> • Low MD + GLIM-defined malnutrition: HR 1.99** • GLIM-defined malnutrition alone: HR 1.97**
Huang, 2021, China ⁵⁰	P	597 older patients (aged 65 years) who underwent radical gastrectomy for gastric cancer (77%, 72)	33.5 months	L3	SMI (CT) MD (CT)	OS	<ul style="list-style-type: none"> • Low SMI: o Univariate: HR 1.525** o Multivariate: HR 0.933 • Low MD: <ul style="list-style-type: none"> o Univariate: HR 1.497* o Multivariate: HR 1.24
						PFS	<ul style="list-style-type: none"> • Low SMI: <ul style="list-style-type: none"> o Univariate: HR 1.459* o Multivariate: HR 0.937 • Low MD: <ul style="list-style-type: none"> o Univariate: HR 1.501* o Multivariate: 1.24
Huq, 2021, USA ⁵²	R	384 patients undergoing surgery for glioblastoma (41%, 57.8)	Not stated	Temporalis muscle	MT (MRI)	Post-operative survival	<ul style="list-style-type: none"> • High MT: <ul style="list-style-type: none"> o Multivariate in progressive glioblastoma: HR 2.13* o Multivariate in primary glioblastoma: HR 0.99
Jeon, 2021, South Korea ⁵³	R	479 breast cancer patients who underwent surgery and adjuvant chemotherapy (0%, 51)	79 months	L3	SMI (CT) MD (CT)	OS	<ul style="list-style-type: none"> • Low SMI (sarcopenia): o Univariate: HR 1.22 • Low MD: o Univariate: HR 0.65
						CSS	<ul style="list-style-type: none"> • Low SMI (sarcopenia): <ul style="list-style-type: none"> o Univariate: HR 1.35 • Low MD: <ul style="list-style-type: none"> o Univariate: HR 1.07
Kim, 2015, South Korea ⁵⁴	R	149 newly diagnosed, pathologically proven SCLC patients (85.2%, 68.6)	29 months	L3	SMI (CT)	OS	<ul style="list-style-type: none"> • Low SMI (sarcopenia): <ul style="list-style-type: none"> o Univariate: HR 1.66* o Multivariate: HR 1.68* (age, extensive stage, ECOG-PS>2, supportive care only, sarcopenia, and LDH)

Table 4. (Cont. from previous page).

First author, year, country	Design	Population (%men, mean age (year))	Mean follow-up	Investigated muscle(s)	Muscle parameters + imaging method	Outcome	Statistical results
Kim, 2021, South Korea ⁵⁵	R	330 pancreatic cancer patients undergoing chemotherapy (49%, 63.4)	Not stated	L3	MD (CT) SMI (CT)	OS	<ul style="list-style-type: none"> • Low SMI: o Univariate: HR 1.52* o Multivariate: HR 1.53* • Low MD: o Multivariate: HR 1.45* • Low MD + low SMI: HR 1.58*
Kim, 2022, Korea ⁵⁶	R	221 NSCLC patients with brain metastasis (60%, 65)	5 months	Temporal muscle at level of orbital roof	MT (MRI)	OS	<ul style="list-style-type: none"> • Lower MT: o Multivariate: HR 1.37* (gender, age, ECOG) o Lower survival: 4.0 vs. 7.0 months*
Kuroki, 2015, USA ⁵⁷	R	122 endometrial cancer patients (0%, 65.9)	Not stated	Psoas L3	CSA (CT)	OS	<ul style="list-style-type: none"> • Low CSA (sarcopenia): o Univariate: HR 1.57 o Multivariate: HR 1.98
						PFS	<ul style="list-style-type: none"> • Low CSA (sarcopenia): o Shorter PFS: 23.5 vs. 32.1 months* o Multivariate: HR 3.99* (race, BMI, lymphocyte count, and tumor histology)
Lanza, 2020, Italy ⁵⁸	R	142 HCC who received bland transarterial embolization (77%, 73)	27 months	L3	SMI (CT)	OS	<ul style="list-style-type: none"> • Low SMI (sarcopenia): o Multivariate: HR 2.22*
Lee, 2018, South Korea ⁵⁹	R	140 advanced gastric cancer patients (76%, 67)	31.9 months	L3	SMI (CT)	OS	<ul style="list-style-type: none"> • Low SMI: o Univariate: HR 1.47* o Multivariate: HR 1.51* (no response on chemotherapy, no second line, >3 metastatic sites, albumin <3.5)
Leone, 2021, Italy ⁶⁰	R	43 patients with primary central nervous system lymphoma (35%, 61)	23 months	L3 Temporal muscle	SMI (DXA) MT (MRI)	OS	<ul style="list-style-type: none"> • L3-SMI < sex-specific cut-off: HR 3.27* • Low L3-SMI: o Univariate: HR 3.27* o Multivariate: HR 3.16* • Low TMT < sex-specific cut-off: o Univariate: HR 4.61 o Multivariate: HR 4.94**
						PFS	<ul style="list-style-type: none"> • L3-SMI < sex-specific cut-off: HR 4.42** • Low L3-SMI: o Univariate: HR 4.42* o Multivariate: HR 4.40** • Low TMT < sex-specific cut-off: o Univariate: HR 4.57** o Multivariate: HR 4.39**
Li, 2021, China ⁶¹	R	192 treatment-naïve intermediate-stage HCC patients undergoing TACE (82%, 60)	21.3 months	L3	SMI (CT) MD (CT)	OS	<ul style="list-style-type: none"> • Low SMI: o Univariate: HR 1.02 • Low MD: o Multivariate: HR 1.01
						PFS	<ul style="list-style-type: none"> • Low SMI: o Univariate: HR 1.01 • Low MD: o Multivariate: HR 1.02
Liu, 2020, China ⁶²	R	130 patients with primary glioblastoma (62.3%, 61.5)	Not stated	Temporal muscle	MT (MRI)	OS	<ul style="list-style-type: none"> • MT < median: o Univariate: HR 1.25** o Multivariate: HR 0.86* (age, concurrent chemoradiotherapy)
Looijaard, 2019, the Netherlands ⁶³	R	378 colorectal cancer patients (60.3, 73.4)	5.3 years	L3	SMI (CT) MD (CT)	OS	<ul style="list-style-type: none"> • Low SMI: o Univariate: HR 1.05 • Low MD: o Univariate: 1.23*

Table 4. (Cont. from previous page).

First author, year, country	Design	Population (%men, mean age (year))	Mean follow-up	Investigated muscle(s)	Muscle parameters + imaging method	Outcome	Statistical results
Loumaye, 2017, Belgium ⁶⁴	P	149 patients treated for colorectal or lung cancer (57%, 67)	24 months	L3	SMI (CT) MD (CT)	OS	<ul style="list-style-type: none"> • Low SMI: <ul style="list-style-type: none"> o Univariate: HR 1.96* o Multivariate: HR 3.63** (lung cancer, ECOG, activin A, albumin) • Low MD <30 HU: <ul style="list-style-type: none"> o Univariate: HR 2.01*
Martin, 2020, Germany ⁶⁵	R	114 anal carcinoma patients treated with 5-FU or MMC (51%, 58.5)	30 months	L4	SMI (CT)	OS	<ul style="list-style-type: none"> • Low SMI: <ul style="list-style-type: none"> o Univariate: HR 1.94 o Multivariate: HR 0.78
						PFS	<ul style="list-style-type: none"> • Low SMI: <ul style="list-style-type: none"> o Univariate: HR 1.01 o Multivariate: HR 0.97
Maurits, 2022, the Netherlands ⁶⁶	R	719 stage I-III renal cell cancer patients (61%, 64) 320 stage IV renal cell cancer patients (64%, 66.5)	6.35 years	L3	SMI (CT) MD (CT)	OS	<ul style="list-style-type: none"> • Stage I-III: <ul style="list-style-type: none"> o SMI per 10 cm²/m² decrease: NS o MD per 10 HU decrease: HR 1.45* in women • Stage IV: <ul style="list-style-type: none"> o SMI per 10 cm²/m² decrease: NS o MD per 10 HU decrease: HR 1.35* in men • Low SMI: <ul style="list-style-type: none"> o Univariate: HR 1.45* o Multivariate: HR 1.20 • Low SMI: <ul style="list-style-type: none"> o Univariate: HR 1.89* o Multivariate: HR 1.19
						PFS	<ul style="list-style-type: none"> • Stage I-III: <ul style="list-style-type: none"> o SMI per 10 cm²/m² decrease: HR 2.01* o MD per 10 cm²/m² decrease: NS
McGoldrick, 2022, UK ⁶⁷	R	111 older adults with squamous cell carcinoma of the head and neck (69%, 74)	26-60 months	Masseter 2cm below the zygomatic arch	CSA (CT)	OS	<ul style="list-style-type: none"> • Low CSA (sarcopenia) <ul style="list-style-type: none"> o Univariate: HR 1.74* o Multivariate: HR 1.65
Mi, 2022, UK ⁶⁸	R	96 glioblastoma patients (70%, 57)	19.2 months	Temporal muscle between mid-orbital and orbital roof	CSA (MRI)	OS	<ul style="list-style-type: none"> • Low CSA: <ul style="list-style-type: none"> o Univariate: HR 2.27* o Multivariate: HR 2.16* (age and gender)
						PFS	<ul style="list-style-type: none"> • Low CSA: <ul style="list-style-type: none"> o Univariate: HR 2.27* o Multivariate: HR 2.32* (age and gender)
Miller, 2012, USA ⁶⁹	R	125 adrenocortical carcinoma patients (40.8%, 45.7)	2.0 years	L4 psoas	MD (CT) PMA (CT)	OS	<ul style="list-style-type: none"> • PMA per 100 mm² decrease: HR 1.09* • Predictors of survival: MD**, PMA**
Miyamoto, 2018, Japan ⁷⁰	R	52 metastatic colorectal cancer patients (62%, 67)	4 months	L3	SMI (CT)	OS	<ul style="list-style-type: none"> • Low SMI: <ul style="list-style-type: none"> o Shorter OS: 3.7 vs. 7.3 months** o Univariate: HR 2.872** Multivariate: HR 2.381* (EOCG 2 and obesity)
						PFS	<ul style="list-style-type: none"> • Low SMI: <ul style="list-style-type: none"> o Shorter PFS: 1.9 vs. 2.8 months**
Muglia, 2020, Italy ⁷¹	R	51 glioblastoma patients (72.6%, 57)	Not stated	Temporalis muscle	MT (MRI)	OS	<ul style="list-style-type: none"> • Low MT: <ul style="list-style-type: none"> o Univariate: HR 1.34
Munoz-Rodríguez, 2021, Spain ⁷²	R	59 metastatic prostate cancer patients who received androgen deprivation therapy (100%, 72.5)	30.5 months	Psoas	MD (CT)	OS	<ul style="list-style-type: none"> • Low MD: <ul style="list-style-type: none"> o Univariate: HR 1.11** o Multivariate: HR 1.10** (bone metastases, visceral metastases, no testosterone escape)

Table 4. (Cont. from previous page).

First author, year, country	Design	Population (%men, mean age (year))	Mean follow-up	Investigated muscle(s)	Muscle parameters + imaging method	Outcome	Statistical results
Nishikawa, 2018, Japan ⁷³	R	85 head and neck squamous cell carcinoma patients (78%, 66)	888 days	L3	SMI (CT)	OS	<ul style="list-style-type: none"> • Low SMI: <ul style="list-style-type: none"> o Univariate: HR 3.4** o Multivariate: HR 3.5* (pre-treatment weight loss, albumin, and CRP)
Nishioka, 2020, Japan ⁷⁴	R	156 NSCLC patients receiving immunotherapy (65%, 67)	Not stated	L3	MD (CT) SMI (CT)	OS	<ul style="list-style-type: none"> • Low SMI: o Univariate: NS • Low MD: o Univariate: NS
						PFS	<ul style="list-style-type: none"> • Low SMI: o No difference in PFS • Low MD: o Lower PFS: 2 vs. 4.5 months*
Nozawa, 2020, Japan ⁷⁵	R	98 stage IV unresectable colorectal cancer patients who received systemic therapy (59%, 64)	44.3 months	L3	SMI (CT)	OS	<ul style="list-style-type: none"> • Low SMI (sarcopenia): <ul style="list-style-type: none"> o Univariate: HR 3.22* • Multivariate: HR 4.0* (age, CCI, lung metastasis, postoperative chemotherapy)
						PFS	<ul style="list-style-type: none"> • Change in SMI: NS
Omarini, 2019, Italy ⁷⁶	R	137 breast cancer patients (stage I–III) treated with primary chemotherapy (0%, 50)	Not stated	L3	CSA (CT) SMI (CT)	OS	<ul style="list-style-type: none"> • No significant correlation with CSA or SMI
						PFS	<ul style="list-style-type: none"> • No significant correlation with CSA or SMI
Ozeki, 2020, Japan ⁷⁷	R	165 squamous cell type lung carcinoma patients (88%, 69.6) + 556 adeno-type lung carcinoma patients (57%, 38.1)	61 months	Psoas bilateral	PMI (CT)	OS	<ul style="list-style-type: none"> • Low PMI: o Multivariate for SCC: HR 2.0** o Multivariate for ADC: HR 1.03
						PFS	<ul style="list-style-type: none"> • Low PMI: o Multivariate for SCC HR 1.78** o Multivariate for ADC: HR 1.02
Özer, 2022, Turkey ⁷⁸	R	66 glioblastoma patients (58%, 57)	14.0 months	Temporal muscle at level of orbital roof	MT (MRI)	OS	<ul style="list-style-type: none"> • Low TMT: <ul style="list-style-type: none"> o Multivariate: HR 10.786*
Peng, 2020, Taiwan ⁷⁹	R	116 pancreatic adenocarcinoma with pancreaticoduodenectomy patients (58.6%, 66.2)	Not stated	L3	SMI (CT) MD (CT)	OS	<ul style="list-style-type: none"> • Low SMI (Sarcopenia): <ul style="list-style-type: none"> o Univariate: HR 2.34* o Multivariate: HR 2.51* (age, gender, preoperative sarcopenia, sarcopenic obesity, diabetes, tumor size, stage, grade, lymphogenic invasion, resection margin) o Sarcopenic obesity: HR 3.19* o SMI continuous: NS • Low MD: <ul style="list-style-type: none"> o Univariate HR 1.28 o Continuous: NS
						PFS	<ul style="list-style-type: none"> • Low SMI (Sarcopenia): o Univariate: HR 1.0 • Low MD: o Univariate: HR 1.11
Pereira, 2021, Brazil ⁸⁰	P	50 hematologic cancer patients admitted for autologous and allogeneic HSCT (58%, 49)	Not stated	QF	MT (US) EI (US)	OS	<ul style="list-style-type: none"> • 100-day mortality not correlated with MT or EI
Phan, 2020, USA ⁸¹	R	89 soft tissue sarcoma patients (60%, 58.5)	Not stated	T12	MD (CT) SMI (CT)	OS	<ul style="list-style-type: none"> • Low SMI: <ul style="list-style-type: none"> o Univariate: HR 0.92 o Multivariate: HR 0.79 • Low MD: <ul style="list-style-type: none"> o Univariate: HR 1.64** o Multivariate: 0.65*
						PFS	<ul style="list-style-type: none"> • Low SMI: <ul style="list-style-type: none"> o Univariate: HR 1.28 o Multivariate: HR 1.35 • Low MD: <ul style="list-style-type: none"> o Univariate: HR 1.47* o Multivariate: HR 1.47

Table 4. (Cont. from previous page).

First author, year, country	Design	Population (%men, mean age (year))	Mean follow-up	Investigated muscle(s)	Muscle parameters + imaging method	Outcome	Statistical results
Rier, 2020, the Netherlands ⁸²	R	164 diffuse large B-cell lymphoma patients (49%, 64.5)	57 months	L3	SMI (CT) MD (CT)	OS PFS	<ul style="list-style-type: none"> • Low SMI: <ul style="list-style-type: none"> o Univariate: HR 1.24 o Multivariate: HR 1.16 • Low MD: <ul style="list-style-type: none"> o Univariate: HR 2.05* o Multivariate: HR 1.68 • Low MD + Low SMI: <ul style="list-style-type: none"> o Univariate: HR 2.74** o Multivariate: HR 2.42* (age, gender, BMI, IPI) <ul style="list-style-type: none"> • Low SMI: <ul style="list-style-type: none"> o Univariate: HR 1.26 o Multivariate: HR 1.19 • Low MD: <ul style="list-style-type: none"> o Univariate: HR 1.74 o Multivariate: HR 1.43 • Low MD + Low SMI: <ul style="list-style-type: none"> o Univariate: HR 2.48** o Multivariate: HR 2.16* (age, gender, BMI, IPI)
Rutten, 2017, the Netherlands ⁸³	R	216 ovarian cancer patients undergoing primary debulking surgery (0%, 63.1)	At least 6 months	L3	SMI (CT) MD (CT)	OS	<ul style="list-style-type: none"> • SMI <38.73 cm²/m² is the best cut-point for predicting OS • Low SMI (sarcopenia): <ul style="list-style-type: none"> o Univariate: HR 1.54* o Multivariate: HR 1.36 • Low MD: <ul style="list-style-type: none"> o Univariate: HR 1.42*
Sabel, 2011, USA ⁸⁴	P	101 stage III melanoma patients (62%, 52.8)	21 months	L4 psoas	MD (CT)	PFS	<ul style="list-style-type: none"> • Low MD: <ul style="list-style-type: none"> o Univariate: HR 1.82**
Sánchez-Torralvo, 2021, Spain ⁸⁵	P	208 patients with active cancer (55%, 60.5)	Not stated	L3	CSA (CT) SMI (CT) MD (CT)	OS	<ul style="list-style-type: none"> • In survivors vs. deceased after 6 months: <ul style="list-style-type: none"> o Higher CSA: 126 vs. 113 cm²** o Higher MD: 41 vs. 32 HU** o Higher SMI: 45.7 vs. 41.3 cm²/m²** • Higher 6-month mortality in GLIM-malnourished using SMI: <ul style="list-style-type: none"> o Multivariate: HR 2.47*
Shachar, 2017, USA ⁸⁶	P	40 metastatic breast cancer patients receiving Taxane-based chemotherapy (55)	1.9 years	L3	SMI (CT) MD (CT) SMG (CT)	OS	<ul style="list-style-type: none"> • Low SMI (sarcopenia): <ul style="list-style-type: none"> o Univariate: HR 2.21 • Low MD: <ul style="list-style-type: none"> o Univariate: HR 1.02 • Low SMG: <ul style="list-style-type: none"> o Univariate: HR 1.07
Shaver, 2022, USA ⁸⁷	R	403 head and neck cancer patients (82%, 60.9)	64.5 months	L3	SMI (CT) MD (CT)	OS	<ul style="list-style-type: none"> • Low SMI after propensity-score matching for 5-year OS: <ul style="list-style-type: none"> o 52.9 vs. 67.3% o Univariate: HR 1.58* • Low MD: <ul style="list-style-type: none"> o 55.8 vs. 63.4% 5-year survival o Univariate: HR 1.55*
Sheikhabahei, 2020, USA ⁸⁸	R	22 prostate cancer patients (100%, 58)	34.5 months	Psoas at L3-4	CSA (CT) MD (CT)	PFS	<ul style="list-style-type: none"> • No correlation between survival and CSA or MD
Sjoberg, 2016, Norway ⁸⁹	R	734 NSCLC patients (57.2%, 65.4)	Not stated	L3 (all muscles)	SMI (CT) MD (CT)	OS	<ul style="list-style-type: none"> • Low SMI in men: <ul style="list-style-type: none"> o Univariate: HR 1.02* o Multivariate: HR 1.02 (gender, age, disease stage, PS1, PS2, BMI, loss of appetite)
Song, 2018, South Korea ⁹⁰	R	1460 breast cancer patients (0%, 46)	8.07 years	L3 (all muscles)	Muscle volume (CT)	OS	<ul style="list-style-type: none"> • Lower volume: <ul style="list-style-type: none"> o Worse 5-year OS: 94.9% vs. 98%** o Univariate: HR 1.78*

Table 4. (Cont. from previous page).

First author, year, country	Design	Population (%men, mean age (year))	Mean follow-up	Investigated muscle(s)	Muscle parameters + imaging method	Outcome	Statistical results
						PFS	<ul style="list-style-type: none"> • Lower volume: o Worse 5-year OS: 89.6% vs. 94.6%* o Univariate: HR 1.39*
Sütcüoğlu, 2023, Turkey ⁹¹	R	74 glioblastoma multiforme patients (62%, 57)	Not stated	Temporal muscle at level of orbital roof	MT (MRI) CSA (MRI)	OS	<ul style="list-style-type: none"> • Low MT: o Univariate: HR 1.37 • Low CSA: o Univariate: HR 1.69
Souwer, 2019, the Netherlands ⁹²	P	174 (70 years or older) colorectal cancer patients (51%, 78)	956 days	Psoas, paraspinal, TA, EO, IO, RA at L3	SMI (CT) MD (CT)	OS	<ul style="list-style-type: none"> • Low SMI (1-year OS): o Univariate: HR 1.08 o Multivariate: HR 1.05 • Low MD (1-year OS) o Univariate: HR 1.49 o Multivariate: HR 1.43
Souza, 2019, Brazil ⁹³	P	188 colorectal cancer patients (57%, 61)	17 months	L3	SMI (CT) SMI (BIA)	OS	<ul style="list-style-type: none"> • Severe muscle loss by lower SMI on CT: o Multivariate: HR 2.14* (age, gender, and prior cancer treatment) • Severe muscle loss by lower SMI on BIA: o Multivariate: HR 2.46* (age, gender, and prior cancer treatment) • Moderate muscle loss: NS
Suzuki, 2016, Japan ⁹⁴	R	90 stage 1 NSCLC patients undergoing complete resection (57.8%, 68.7)	Not stated	L3	SMI (CT)	OS	<ul style="list-style-type: none"> • Low SMI (sarcopenia): o Lower 5-year survival: 72.8 vs. 85.8%* o Univariate: HR 2.71* o Multivariate: HR 7.09** (gender, stage, differentiation)
Taguchi, 2015, Japan ⁹⁵	R	64 metastatic urothelial carcinoma patients (80%, 68)	Not stated	L3 Psoas at umbilicus Psoas at L3	SMI (CT) TPA (CT) MT psoas (CT)	CSS	<ul style="list-style-type: none"> • Low SMI: o Multivariate: HR 2.07* • Other predictors of CSS: o Psoas CSA* o Umbilical psoas MT*
Takeoka, 2016, Japan ⁹⁶	R	56 newly diagnosed multiple myeloma patients (34%, 71)	2.3 years	L3 (Psoas, abdominal RA, paraspinal)	SMI (CT)	OS	<ul style="list-style-type: none"> • Low SMI (sarcopenia): o Univariate: HR 1.96 o Multivariate: HR 2.32
Thormann, 2021, Germany ⁹⁷	R	60 breast cancer patients (0%, 57)	Not stated	Psoas at L3	MD (CT) CSA (CT) PMI (CT) SMG (CT)	OS	<ul style="list-style-type: none"> • Low MD: o Univariate: HR 1.03 • Low CSA: o Univariate: HR 0.96 • Low PMI: o Univariate: HR 0.95 • Low SGM: o Univariate: HR 1.00
Troschel, 2019, Germany ⁹⁸	R	128 lung cancer patients undergoing pneumectomy (55.5%, 61)	23.6 months	T8	CSA (CT)	OS	<ul style="list-style-type: none"> • CSA per 10 cm² decrease: o Multivariate: HR 1.25*
Troschel, 2021, Germany ⁹⁹	R	367 patients undergoing pneumonectomy for lung cancer (stage IIIA NSCLC (45.5%) and squamous cell histology (58%)) (67%, 62.2)	20.5 months	T8, T10, T12 (all muscles)	CSA (CT)	OS	<ul style="list-style-type: none"> • Low CSA <2SD (sarcopenia): o Lower OS: 17.7 vs. 46.5 months** o Multivariate: HR 1.68**
						CSS	<ul style="list-style-type: none"> • Low CSA <2SD (sarcopenia): o Lower CSS: 29.4 vs. 78.9 months** o Multivariate: HR 1.74**
Ueki, 2022, Japan ¹⁰⁰	R	96 patients with renal cell carcinoma who received Nivolumab (74%, >75y)	9.7 months	L3 (all muscles)	SMI (CT) PMI (CT)	OS	<ul style="list-style-type: none"> • Low SMI (sarcopenia): o Univariate: HR 1.15 • Low PMI (sarcopenia): o Shorter OS: 10.1 vs. 48.4 months** o Univariate: HR 4.53** o Multivariate: HR 3.85**

Table 4. (Cont. from previous page).

First author, year, country	Design	Population (%men, mean age (year))	Mean follow-up	Investigated muscle(s)	Muscle parameters + imaging method	Outcome	Statistical results
						PFS	<ul style="list-style-type: none"> • Low SMI (sarcopenia): <ul style="list-style-type: none"> o Univariate: HR 1.07 • Low PMI (sarcopenia): <ul style="list-style-type: none"> o Univariate: HR 2.45* o Multivariate: HR 1.80*
Van Baar, 2018, the Netherlands ¹⁰¹	R	1681 early stage colorectal cancer patients (59%, 67.7)	48 months	Ps, ES, QL, TA, EO, IO, RA	MD (CT)	OS	<ul style="list-style-type: none"> • Low MD: <ul style="list-style-type: none"> o Univariate HR 1.91* • Low MD (COLON-study): <ul style="list-style-type: none"> o Univariate HR 2.15* • MD (continuous): HR 0.98*
						PFS	<ul style="list-style-type: none"> • Low MD: o Univariate: HR 1.68*
Van der Zanden, 2021, the Netherlands ¹⁰²	R	213 women ≥ 70 years old receiving surgery for primary, advanced stage ovarian cancer (0%, 75.9)	Not stated	L3	MD (CT) SMI (CT)	OS	<ul style="list-style-type: none"> • No association MD or SMI with 30 days, 6 months, or 1-year mortality
Van Rijssen, 2017, the Netherlands ¹⁰³	P	166 patients undergoing pancreatoduodenectomy for periampullary non-pancreas cancer (62.6%, 63)	71 months	L3	SMI (CT) MD (CT)	OS	<ul style="list-style-type: none"> • Low SMI: <ul style="list-style-type: none"> o Univariate: HR 1.33 • Low MD: <ul style="list-style-type: none"> o Univariate: HR 2.44** o Multivariate: HR 1.95* (age, women, ASA, tumor category, lymph node metastasis, tumor differentiation)
Van Vugt, 2018, the Netherlands ¹⁰⁴	P	816 stage I-III colorectal cancer patients (54%, 70)	76.5 months	L3	SMI (CT) MD (CT)	OS	<ul style="list-style-type: none"> • Low SMI: <ul style="list-style-type: none"> o Univariate: HR 1.35* o Multivariate: HR 1.06 • Low MD: <ul style="list-style-type: none"> o Univariate: HR 1.75** o Multivariate: HR 0.91
						PFS	<ul style="list-style-type: none"> • No difference in low vs. high SMI or MD
Van Vugt, 2019, the Netherlands ¹⁰⁵	R	233 perihilar cholangiocarcinoma patients (60.1%, 66)	25.3 months	L3	SMI (CT) MD (CT)	OS	<ul style="list-style-type: none"> • Low SMI: <ul style="list-style-type: none"> o Univariate: HR 1.99 • Low MD: <ul style="list-style-type: none"> o Univariate: HR 3.38** for 3-month survival; HR 1.92* after 1 year. o Multivariate: HR 1.78* after 6 months (age, tumor size and suspected metastases)
Von Geldern, Chili, 2020 ¹⁰⁶	P	103 adult cancer patients (45%, 54.9)	38 months	Psoas at L3	SMI (CT)	OS	<ul style="list-style-type: none"> • Low SMI (sarcopenia): <ul style="list-style-type: none"> o Multivariate: HR 2.38*
Williams, 2021, USA ¹⁰⁷	R	142 multiple myeloma patients undergoing autologous stem cell transplantation (65%, 61.6)	27-33 months	Psoas at L3	MD (CT)	OS	<ul style="list-style-type: none"> • Sarcopenia as defined by 80% high density muscle: o Multivariate: HR 1.28
Xiao, 2022, China ¹⁰⁸	R	172 patients with primary liver cancer (87%, 51.4)	9 months	L3 (all muscles)	SMI (CT) MD (CT)	OS	<ul style="list-style-type: none"> • Low SMI (sarcopenia): <ul style="list-style-type: none"> o Univariate HR 4.90 ** o Multivariate: HR 5.39** (gender, BMI, ECOG PS score, Child-Pugh score, baseline metastasis, CRP, and NLR) • Low MD: <ul style="list-style-type: none"> o Univariate: HR 1.64 o Multivariate: HR 1.06
						PFS	<ul style="list-style-type: none"> • Low SMI (sarcopenia): <ul style="list-style-type: none"> o Univariate: HR 1.62 ** • Low MD: o Univariate: HR 0.83 o Multivariate: HR 0.56* (gender, BMI, ECOG PS score, Child-Pugh score, baseline metastasis, CRP, and NLR)

Table 4. (Cont. from previous page).

First author, year, country	Design	Population (%men, mean age (year))	Mean follow-up	Investigated muscle(s)	Muscle parameters + imaging method	Outcome	Statistical results
Yamashita, 2020, Japan ¹⁰⁹	R	230 bladder cancer patients undergoing radical cystectomy (80%, 73)	25.5 months	Psoas at L3	MD (CT)	OS	<ul style="list-style-type: none"> • Low MD: <ul style="list-style-type: none"> o Univariate: HR 1.04* o Multivariate: HR 1.02
						CSS	<ul style="list-style-type: none"> • Low MD: <ul style="list-style-type: none"> o Univariate: HR 1.04** o Multivariate: HR 1.07 • Low MD: <ul style="list-style-type: none"> o Univariate: HR 1.04** o Multivariate: HR 1.04* (ECOG PS≥1, low ATPD, non-UC, pT≥3, and pN positivity)
Yan, 2021, China ¹¹⁰	R	261 glioma patients (53%, 47)	Not stated	Temporal muscle at level of orbital roof	MT (MRI)	OS	<ul style="list-style-type: none"> • Low MT < 7.5 mm: <ul style="list-style-type: none"> o Univariate: HR 4.61** o Multivariate: HR 3.50** o Survival: 11 vs. 22 months* o 1-, 2- and 3-year survival in thinner vs. thicker groups: 46.5%, 28.8%, 13.6% vs. 93.6%, 78.4%, 58.3% *
Yesil, 2020, Turkey ¹¹¹	R	47 glioblastoma multiforme patients (62%, 56)	Not stated	Temporal muscle at level of orbital roof	MT (MRI)	OS	<ul style="list-style-type: none"> • Low MT < 4.9: <ul style="list-style-type: none"> o Univariate: HR 2.40* o Multivariate: HR 2.07* (age)
Yesil, 2020, Turkey ¹¹²	R	94 lung cancer patients with brain metastasis (SCLC and NSCLC) (87%, 60)	Not stated	Temporal muscle at level of orbital roof	MT (MRI)	OS	<ul style="list-style-type: none"> • Low MT < 4.32: <ul style="list-style-type: none"> o Univariate: HR 1.23* o Per 1 mm reduction of MT: increased risk of death of 18.8%*
Yokoi, 2022, Japan ¹¹³	R	341 stage III colorectal cancer patients (59%, 70)	44 months	L3	SMI (CT) MD (CT)	PFS	<ul style="list-style-type: none"> • Lower SMI (men): <ul style="list-style-type: none"> o Univariate: HR 2.38** o Multivariate: HR 1.87** o Lower MD (men): o Univariate: HR 2.37** o Multivariate: 1.47
Youn, 2021, Canada ¹⁶³	R	44 metastatic myeloma patients treated with Nivolumab (57%, 57)	Not stated	L3	MD (CT)	OS	<ul style="list-style-type: none"> • Low MD < 25.65 HU: <ul style="list-style-type: none"> o Univariate: HR 3.81** o Multivariate: HR 4.40** (age, gender, performance status, and number of prior lines of therapy)
Young, 2020, USA ¹⁶⁴	R	287 melanoma patients treated with immune checkpoint inhibitors (64%, 63)	519 days	L3	SMI (CT) MD (CT) SMG (CT)	OS	<ul style="list-style-type: none"> • Low SMI: o Univariate: HR 1.15 • Low MD: o Univariate: HR 1.03 • Low SMG: o Univariate: HR 1.11
						PFS	<ul style="list-style-type: none"> • Low SMI: o Univariate: HR 1.28 • Low MD: o Univariate: HR 1.32 • Low SMG: o Univariate: HR 1.28

* = $P < 0.05$; ** = $P < 0.01$. ADC = adeno-type cell carcinoma; Allo-HCT = allogeneic hematopoietic cell transplantation; ASA = American Society of Anesthesiologists; ATPD = average total psoas muscle density; auto-HCT = autologous hematopoietic cell transplantation; BCLC = Barcelona Clinic Liver Cancer; BIA = bioelectrical impedance analysis; BMI = body mass index; BRAF = v-Raf murine sarcoma viral oncogene homolog B; C3 = cervical vertebra 3; CCI = Charlson comorbidity index; CNS = central nervous system; CRP = C-reactive protein; CSA = cross-sectional area; CSS = cancer-specific survival; CT = computed tomography; DM = diabetes mellitus; DXA = dual-energy X-ray absorptiometry; ECM = extracranial metastasis; ECOG = Eastern Cooperative Oncology Group; ECOG-PS = Eastern Cooperative Oncology Group performance status; EO = external oblique; ES = erector spinae; 5-FU = 5-fluorouracil; FLIPI = Follicular Lymphoma International Prognostic Index; GLIM = Global Leadership Initiative on Malnutrition; HCC = hepatocellular carcinoma; HR = hazard ratio; HU = Hounsfield units; IO = internal oblique; IPI = International Prognostic Index; IT = immunotherapy; KPS = Karnofsky Performance Status; L3 = lumbar vertebra 3; L4 = lumbar vertebra 4; LD = latissimus dorsi; LDH = lactate dehydrogenase; MD = muscle density; mFI = modified frailty index; MMC = mitomycin C; MRI = magnetic resonance imaging; MT = muscle thickness; MTX = methotrexate; NLR = neutrophil-to-lymphocyte ratio; non-UC = non-urothelial carcinoma; NS = not significant; NSCLC = non small cell lung cancer; OR = odds ratio; OS = overall survival, P = prospective; PD-1 = Programmed Cell Death Protein 1; PD-L1 = Programmed Cell Death Ligand 1; PFS = progression-free survival; Pm = psoas minor; PM = psoas major; PMA = psoas muscle area; PMI = psoas muscle index; Ps = paraspinal; PS = performance status; PT = proximal thigh; PVMI = paravertebral muscle index; RPA = recursive partitioning analysis, QF = quadriceps femoris; QL = quadratus lumborum; R = retrospective; RA = rectus abdominus; RF = rectus femoris; R-IPI = revised International Prognostic Index; SC = subcutaneous; SCC = squamous cell carcinoma; SCM = sternocleidomastoid muscle; SMLC = small cell lung cancer; SMG = skeletal muscle gauge; SMI = skeletal muscle index (=CSA/height²); T4 = thoracic vertebra 4; T8 = thoracic vertebra 8; T10 = thoracic vertebra 10; T12 = thoracic vertebra 12; TA = transverse abdominis; TACE = Transarterial chemoembolization; TMT = temporal muscle thickness; TNM = tumor, nodes and metastasis classification; TT = targeted therapy; US = ultrasound; vs. = versus

Table 5. Characteristics and results of included studies on chemotoxicity.

First author, year, country	Design	Population (%men, mean age (years))	Mean follow-up	Investigated muscle(s) or region	Muscle parameters + imaging method	Statistical results
Aleixo, 2021, USA ¹⁶⁵	R	338 stage I-III breast cancer patients receiving (neo)adjuvant chemotherapy (51)	Not stated	L3 (all muscles) Psoas ES	MD (CT)	<p>For L3 MD:</p> <ul style="list-style-type: none"> • RR for any AE (cont): 0.74** For myosteatosis: 1.81 • RR for dose reduction (cont): 0.78* <p>For myosteatosis:</p> <ul style="list-style-type: none"> 1.54 • RR for treatment discontinuation (cont): 0.66** <p>For myosteatosis:</p> <ul style="list-style-type: none"> 2.44 • RR for hospitalisation due to AE (cont): 0.73** <p>For myosteatosis: 1.69</p> <p>For psoas MD:</p> <ul style="list-style-type: none"> • RR for any AE (cont): 0.73** For myosteatosis: 1.8 • RR for dose reduction (cont): 0.77* For myosteatosis: 1.8 • RR for treatment discontinuation (cont): 0.68** For myosteatosis: 2.82 • RR for hospitalization due to AE (cont): 0.75* For myosteatosis: 1.58 <p>For ES MD:</p> <ul style="list-style-type: none"> • RR for any AE (cont): 0.81** For myosteatosis: 1.66 • RR for dose reduction (cont): 0.82** For myosteatosis: 1.72 • RR for treatment discontinuation (cont): 0.72** • For myosteatosis: 2.61
Al Khalidi, 2022, Canada ²⁵	R	312 patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for peritoneal metastases (34.3%, 57.6)	28 months	L3 (all muscles)	SMI (CT)	<ul style="list-style-type: none"> • SMI-based sarcopenia did not have a significant effect on HIPEC toxicity
Bardoscia, 2022, Italy ³⁰	R	225 head and neck cancer patients undergoing (chemo)radiation (75.6%, 64.5)	5.6 year	L3 (all muscles)	SMI (CT) MD (CT)	<ul style="list-style-type: none"> • Both low SMI and low MD did not significantly alter rates of chemotherapy suspension or acute toxicity
Chu, 2020, Canada ³⁸	R	97 metastatic melanoma patients treated with Ipilimumab (60%, 56)	Not stated	L3 (all muscles)	MD (CT)	<ul style="list-style-type: none"> • High MD causes more immune-related adverse events (21.7 vs. 11.3%, P=0.051) • High MD is related to lower NLR values (21 vs. 39%*)
Cortellini, 2020, Italy ¹⁶¹	R	100 patients with advanced cancer receiving anti-PD-1/PD-L1 checkpoint inhibitors (67%, 66)	20.3 months	L3 (all muscles)	SMI (CT) MD (CT)	<ul style="list-style-type: none"> • No significant difference in irAEs in low vs. non-low SMI (P=0.49) • No significant difference in irAEs in low vs. non-low MD (P=0.21)

Table 5. (Cont. from previous page).

First author, year, country	Design	Population (%men, mean age (years))	Mean follow-up	Investigated muscle(s) or region	Muscle parameters + imaging method	Statistical results
Cushen, 2014, Ireland ⁴¹	R	55 metastatic renal cell carcinoma patients treated with Sunitinib (78%, 66)	6 months	L3 (all muscles)	CSA (CT) SMM (CT)	<ul style="list-style-type: none"> • Lower CSA (151.5 vs. 173.7 cm²) causes earlier DLT < 6 months** • Lower SMI (51.7 vs. 59.4 cm²/m²) causes earlier DLT < 6 months * • In < 25th SMM centile (44.8 cm²/m²) compared to >75th centile (63.2 cm²/m²): <ul style="list-style-type: none"> o More DLT (92% vs. 57%*) o More early DLT <6 months (77 vs. 28%*) o Higher number of toxicities (2.7 vs. 1.8%**)
Dijksterhuis, 2019, the Netherlands ⁴³	R	88 advanced esophagogastric cancer patients treated with 1 st line CapOx (75%, 63)	Not stated	L3 (all muscles)	SMI (CT) MD (CT)	<ul style="list-style-type: none"> • Lower pre-treatment MD is associated with more CTCAE grade 3/4: OR 0.94* • SMI-based sarcopenic obesity is associated with peripheral sensory neuropathy CTCAE ≥2: OR 3.82*
Ganju, 2019, USA ¹⁶²	R	46 stage IB-IVA endometrial cancer patients treated with hysterectomy and pelvic radiation (0%, 61)	27 months	L3 (all muscles)	SMI (CT) MD (CT)	<ul style="list-style-type: none"> • Neither SMI alone (P = 0.51), MD alone (P = 0.10) nor both adverse features (P = 0.07) were correlated with delays during radiation due to toxicity • Neither low SMI (P = 0.08) nor low MD (P = 0.25) were associated with inability to complete or delays in chemotherapy • Patients with both low SMI and low MD were less likely to complete chemotherapy: 94% vs. 58%** • Predictors of failure of chemotherapy completion: <ul style="list-style-type: none"> o Low SMI: OR 4.47 (P0.08) o Low MD: OR 0.16 (P0.25) o Low SMI + low MD: OR 9.55**
Haehl, 2022, Germany ⁴⁸	R	280 head and neck squamous cell carcinoma patients receiving curative (chemo) radiation (gender not stated, age >65)	127 days	C3 (paravertebral + SCM) L3 (calculated from C3)	CSA (CT) SMI (CT)	<ul style="list-style-type: none"> • Acute toxicity related to CSA: p -0.111 (P0.06) • Acute toxicity related to SMI: p -0.147* • Chronic toxicity not related to CSA or SMI • Higher acute toxicity in SMI-defined sarcopenia: 20.8, 69.4 and 9.7% for maximum CTCAE grade 2, 3 and 4 toxicities, compared to 30.9, 66.2 and 3.0%* • Higher chronic grade III/IV toxicity in low L3 CSA: 24.8 vs. 11.8%* • No significant effect of SMI on chronic toxicity
Huang, 2020, China ¹¹⁷	P	82 nasopharyngeal carcinoma patients treated with (chemo) radiotherapy (67%, 45.7)	Until the end of the RT	L3 (all muscles)	CSA (CT) SMI (CT) MD (CT)	<ul style="list-style-type: none"> • Predictors of CTCAE grade 3-4 chemotoxicity: <ul style="list-style-type: none"> o CSA: OR 0.98* o SMI: OR 0.95 (P0.06, women) o MD: NS o Sarcopenia (defined by SMI): NS • Higher DLT in sarcopenic men: OR 4.00* • Higher DLT in lower CSA: OR 0.97* • Higher DLT in lower SMI: OR 0.91* • No correlation between severe RT toxicity and muscle loss
Kim, 2021, South Korea ⁵⁵	R	330 pancreatic cancer patients undergoing chemotherapy (49%, 63.4)	Not stated	L3 (all muscles)	MD (CT) SMI (CT)	<ul style="list-style-type: none"> • Higher grade ≥3 toxicity in low SMI: 59 vs. 43%* • Higher grade ≥3 toxicity in low MD: 60 vs. 44%* • No differences in neutropenia, anaemia, thrombocytopenia, fatigue or diarrhea in high or low SMI or MD
Looijaard, 2019, the Netherlands ⁶³	R	378 colorectal cancer patients (60.3, 73.4)	5.3 years	L3 (all muscles)	MD (CT) SMI (CT)	<ul style="list-style-type: none"> • SMI and MD could not predict DLT

Table 5. (Cont. from previous page).

First author, year, country	Design	Population (%men, mean age (years))	Mean follow-up	Investigated muscle(s) or region	Muscle parameters + imaging method	Statistical results
Martin, 2020, Germany ⁶⁵	R	114 anal carcinoma patients treated with 5-FU or MMC (51%, 58.5)	30 months	L4 (all muscles)	SMI (CT)	<ul style="list-style-type: none"> • Patients with SMI-determined sarcopenia suffer more leukopenia: 56 vs. 27%** • Sarcopenia gives higher rates of thrombocytopenia: 22 vs. 6%* • No difference regarding diarrhea or dermatitis
Mazzuca, 2018, Italy ¹¹⁸	R	21 stage I-III breast cancer patients undergoing anthracycline-based adjuvant therapy (0%, 54)	Not stated	L3 (all muscles)	CSA (CT) SMI (CT)	<ul style="list-style-type: none"> • Lower SMI in G3-4 toxicity: 40.5 vs. 33.4 cm²/m²* • Lower CSA in G3-4 toxicity: 109 vs. 86.8 cm² * • L3 SMI = independent predictor of G3-4 toxicity in multivariate analysis*
Miyamoto, 2018, Japan ⁷⁰	R	52 metastatic colorectal cancer patients (62%, 67)	4 months	L3 (all muscles)	SMI (CT)	<ul style="list-style-type: none"> • Low SMI (<50.9 (M) or <39.1 (F)) cm²/m²: more CTCEA grade 3-4 adverse events than high SMI group (>52.8 (M) or >39.2 (F): 46 vs. 12%*
Phuong, 2022, USA ¹¹⁹	R	141 testicular germ cell carcinoma patients (100%, 30)	Not stated	L3 (all muscles)	SMI (CT) MD (CT) SMG (CT)	<ul style="list-style-type: none"> • Higher incidence of adverse events if: <ul style="list-style-type: none"> ◦ Post-chemo decrease in SMI: OR 0.89* ◦ Post-chemo decrease in SMG: OR 0.88* ◦ Post-chemo decrease in SMG: OR 0.94* • Pre-chemotherapy muscle status and post-chemotherapy SMI and MD were not associated with adverse events.
Shachar, 2017, USA ⁸⁶	P	40 metastatic breast cancer patients receiving taxane-based chemotherapy (100%, 55)	1.9 years	L3 (all muscles)	SMI (CT) SMG (CT)	<ul style="list-style-type: none"> • Higher toxicity in sarcopenia patients (SMI < 41 cm²/m²): 57% vs. 18%* • Higher toxicity-related hospitalizations in sarcopenia: 39 vs. 0%** • Higher rate of adverse events of any kind (hospitalization, grade 3-4 toxicity, dose reductions, dose delay) in sarcopenic patients: 74 vs. 35%* • Low SMG: more toxicity*, more hospitalizations*, more adverse events (PO.06)
Smit, 2022, the Netherlands ¹²⁰	R	202 colorectal cancer survivors (54%, 66)	Not stated	L3 (all muscles)	SMI (CT) MD (CT)	<ul style="list-style-type: none"> • No significant associations were found between MD or SMI and total chemotherapy-induced peripheral neuropathy. • No significant associations were found for MD or SMI with motor, sensory, or autonomic chemotherapy-induced peripheral neuropathy.
Youn, 2021, Canada ¹⁶³	R	44 metastatic myeloma patients treated with Nivolumab (57%, 57)	Not stated	L3 (all muscles)	MD (CT)	<ul style="list-style-type: none"> • MD did not alter toxicity (gastro-intestinal, transaminitis, dermatitis, endocrinopathy)
Young, 2020, USA ¹⁶⁴	R	287 melanoma patients treated with immune checkpoint inhibitors (64%, 63)	519 days	L3 (all muscles)	MD (CT) SMI (CT) SMG (CT)	<ul style="list-style-type: none"> • SMI, MD and SMG did not have a significant effect on chemotoxicity

* = P<0.05; ** = P<0.01. AE = adverse events; C3 = cervical vertebra 3; CSA = cross-sectional area; cont. = continuous; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; DLT = dose-limiting toxicity; ES = erector spinae; 5-FU = 5-fluorouracil; HIPEC = hyperthermic intraperitoneal chemotherapy; ir-AE = Immune-Related Adverse Events; L3 = lumbar vertebra 3; MD = muscle density; MMC = mitomycin C; NLR = neutrophil-to-lymphocyte ratio; NS = not significant; OR = odds ratio; P = prospective; PD-1 = Programmed Cell Death Protein 1; PD-L1 = Programmed Cell Death Ligand 1; R = retrospective; RR = relative risk; RT = radiotherapy; SCM = sternocleidomastoid muscle; SMG = skeletal muscle gauge; SMI = skeletal muscle index; vs. = versus

Table 6. Characteristics and results of included studies on surgical outcomes in oncology patients.

First author, year, country	Design	Population (%men, mean age (years))	Mean follow-up	Investigated muscle(s) or region	Muscle parameters + imaging method	Statistical results
Al Khaldi, 2022, Canada ²⁵	R	312 patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for peritoneal metastases (34.3%, 57.6)	28 months	L3 (all muscles)	SMI (CT)	<ul style="list-style-type: none"> No effect of SMI-defined sarcopenia on CD \geq 3 complications
Arayne, 2023, Australia ²⁷	R	80 stage I – III rectal cancer patients undergoing curative resection (74%, 63)	Not stated	T4, T12, L3 (all muscles)	SMI (CT)	<ul style="list-style-type: none"> No effect of SMI on medical or surgical complications.
Asai, 2023, Japan ²⁹	R	456 patients undergoing major hepatectomy for perihilar cholangiocarcinoma (68%, 69)	Not stated	Psoas at L3	MD (CT) TPI (CT)	<ul style="list-style-type: none"> Lowest tertile of TPI: <ul style="list-style-type: none"> No difference on operation time, CD > 3, bile leakage, liver failure, infectious complications, wound infections, abscesses Higher intra-operative blood loss: 21.3 ml/kg vs. 17.2 ml/kg** More bacteraemia: 8 vs. 3%* More ascites: 16 vs. 7%** Lowest tertile of MD: <ul style="list-style-type: none"> No difference in operation time, intra-operative blood loss, bile leakage, liver failure, wound infections, bacteraemia, ascites More CD > 3 complications: 55 vs. 44%* More infectious complications: 41 vs. 26%** More abscesses: 33 vs. 22%*
Baker, 2018, USA ¹²¹	P	298 patients undergoing abdominal surgery for cancer treatment (46%, 60)	Not stated	Psoas at L3	MD (CT) CSA (CT)	<ul style="list-style-type: none"> Patients who had complications had lower MD: 22.4 vs. 24.4 HU* MD: OR 0.937* No difference in total psoas area in complications vs. non-complication group
Bozkurt, 2018, Turkey ¹²²	R	60 advanced laryngeal cancer patients (100%, 59.4)	Not stated	Paravertebral muscles at C3	PvMI (CT)	<ul style="list-style-type: none"> Patients who had complications had a lower neck muscle index: 770 vs. 875 mm²/m²*
Chakedis, 2018, USA ³⁴	R	177 biliary tract cancer patients (44%, 66)	12.2 months	L3 (all muscles) Psoas	PMI (CT)	<ul style="list-style-type: none"> PMI-defined sarcopenia did not have a significant effect on postoperative complication rates
Cinar, 2022, Turkey ³⁹	R	180 patients undergoing resection for NSCLC (80%, 65)	26.3 months	T12 para-vertebral muscles	PvMI (CT) MD (CT)	<ul style="list-style-type: none"> More complications in low PvMI: 18 vs. 3.3%* More complications in low MD: 19 vs. 4.3%**
Fintelmann, 2018, USA ¹²³	R	135 patients who underwent lobectomy or bilobectomy for primary lung cancer (42%, 69)	Not stated	T5 (all muscles)	CSA (CT)	<ul style="list-style-type: none"> Higher risk of any postoperative complications with lower CSA: OR 0.86* Higher risk of postoperative respiratory complications with lower CSA: OR 0.80* Higher risk of postoperative ICU admission with lower CSA: OR 0.73*
Galli, 2022, Italy ¹²⁴	R	65 stage III-IV head and neck cancer patients (82%, 65.9)	Not stated	RF C3 (paravertebral and SCM)	CSA (US) CSA (CT/MRI) SMI (CT/MRI)	<ul style="list-style-type: none"> Higher 30-days major complications: <ul style="list-style-type: none"> RF CSA <1.32cm²: OR 7.72** C3 CSA <34.91 cm²: OR 4.11** CT SMI <11.25 cm²/m²: OR 2.9*
Hirai, 2020, Japan ⁴⁹	R	163 soft tissue sarcoma patients (59.5%, 64.2)	27 months	L3 (all muscles)	CSA (CT) MD (CT) SMI (CT) SMG (CT)	<ul style="list-style-type: none"> CSA, and SMI were not risk factors for wound complications More wound complications in low MD: 18 vs. 3%** More wound complications in low SMG: 17 vs. 4%**; OR 3.27**

Table 6. (Cont. from previous page).

First author, year, country	Design	Population (%men, mean age (years))	Mean follow-up	Investigated muscle(s) or region	Muscle parameters + imaging method	Statistical results
Huang, 2021, China ⁵¹	P	587 patients (with BMI >23 kg/m ²) who underwent radical gastrectomy for the treatment of gastric cancer (74%, 65)	43.8 months	L3 (all muscles)	MD (CT)	<ul style="list-style-type: none"> Higher postoperative complications in GLIM-defined malnutrition + low MD-based muscle quality: 38.1 vs. 28.6% in GLIM alone*; OR 2.03* (GLIM alone: NS)
Huang, 2021, China ⁵⁰	P	597 patients (gender not stated, aged 65+ years) who underwent radical gastrectomy for gastric cancer (77%, 72)	33.5 months	L3 (all muscles)	SMI (CT) MD (CT)	<ul style="list-style-type: none"> Low SMI had higher postoperative complications: OR 1.54* Low MD: no effect on complication risk
Joglekar, 2015, USA ¹²⁵	R	118 patients who underwent pancreaticoduodenectomy or distal pancreatectomy (64%)	Not stated	Psoas at L3	PMI (CT) MD (CT)	<ul style="list-style-type: none"> Risk of ICU admission per 5 units HUAC decrease: OR 2.33* Risk of any complication per 5 units HUAC decrease: OR 2.78* <ul style="list-style-type: none"> Risk of major grade III complications per 5 units HUAC decrease: OR 3.45* Risk of infectious complications per 5 units HUAC decrease: OR 1.69* Risk of gastro-intestinal complications per 5 units HUAC decrease: OR 1.75* Risk of pulmonary complications per 5 units HUAC decrease: OR 2.56* Risk of cardiac complications per 5 units HUAC decrease: OR 2.70* Risk of delayed gastric emptying per 5 units HUAC decrease: OR 2.33*
Kim, 2019, South Korea ¹²⁶	P	50 colorectal cancer patients (56%, 63.4)	Not stated	Back muscles at L3	SMM (BIA)	<ul style="list-style-type: none"> SMM had no effect on postoperative ileus or surgical site infection
Kim, 2018, South Korea ¹²⁷	R	272 newly diagnosed, pathologically proven NSCLC patients that underwent curative-intent surgery (60%, 62.9)	Not stated	L3 (all muscles)	SMI (CT)	<ul style="list-style-type: none"> SMI-defined sarcopenia did not affect postoperative complications
Kuroki, 2015, USA ⁵⁷	R	122 endometrial cancer patients (0%, 65.9)	Not stated	Psoas L3	CSA (CT)	<ul style="list-style-type: none"> CSA-based sarcopenia was not associated with postoperative complications
Lanza, 2020, Italy ⁵⁸	R	142 HCC patients who received bland transarterial embolization (77%, 73)	27 months	L3 (all muscles)	SMI (CT)	<ul style="list-style-type: none"> No significant difference between sarcopenic and non-sarcopenic patients concerning early complication rates
Looijaard, 2019, the Netherlands ⁶³	R	378 colorectal cancer patients (60.3, 73.4)	5.3 years	L3 (all muscles)	MD (CT) SMI (CT)	<ul style="list-style-type: none"> No significant correlation between MD or SMI and severe surgery-related complications
Lin, 2019, China ¹²⁸	R	594 patients undergoing radical surgery for primary gastric cancer treatment (75%, 64.3)	Not stated	L3 (all muscles)	MD (CT) SMG (CT) SMI (CT)	<ul style="list-style-type: none"> Factors associated with postoperative complications: <ul style="list-style-type: none"> MD (low/high): HR 1.61* SMI (low/high): 1.91** SMG (low/high): 2.45**

Table 6. (Cont. from previous page).

First author, year, country	Design	Population (%men, mean age (years))	Mean follow-up	Investigated muscle(s) or region	Muscle parameters + imaging method	Statistical results
Martini, 2020, France ¹²⁹	R	234 lung cancer patients undergoing pneumonectomy (71%, 64)	Not stated	L3 (all muscles)	CSA (CT) SMI (CT)	<ul style="list-style-type: none"> • CSA-based sarcopenia: <ul style="list-style-type: none"> o Increased ARDS risk: 58.3 vs. 31.9%* o Increased risk of acute respiratory failure: 52.5 vs. 30.9%** • SMI-based sarcopenia: <ul style="list-style-type: none"> o Increased ARDS risk: 58.3 vs. 31%** o Increased risk of acute respiratory failure: 50 vs. 30.4%*
Namm, 2017, USA ¹³⁰	P	116 undergoing pancreaticoduodenectomy for pancreatic malignancy (53%, 65.5)	33 months	Psoas at L3	MD (CT) PMI (CT)	<ul style="list-style-type: none"> • No effect of TPI or MD on major complications, wound infection, return to ICU • Higher risk of organ infection/pancreas fistula with low TPA: OR 2.41* (MD NS).
Nishigori, 2016, Japan ¹³¹	R	199 thoracic esophageal cancer patients who underwent esophagectomy (82%, 65)	Not stated	L3 (all muscles)	SMI (CT)	<ul style="list-style-type: none"> • No difference in complication rates between SMI-defined sarcopenia and non-sarcopenia • Sarcopenia group: more pulmonary complications: 32 vs. 12%**; OR 3.38* • No difference concerning cardiac, gastro-intestinal, infectious, neurologic, thrombo-embolic, or other complications
Rutten, 2017, the Netherlands ⁸³	R	216 ovarian cancer patients undergoing primary debulking surgery (0%, 63.1)	At least 6 months	L3 (all muscles)	SMI (CT) PMI (CT) MD (CT)	<ul style="list-style-type: none"> • Low MD associated to a higher risk of major complications: OR 2.32* • No significant risk in SMI-based sarcopenia or PMI
Sabel, 2011, USA ⁸⁴	P	101 stage III melanoma patients (62%, 52.8)	21 months	L4 psoas	CSA (CT) MD (CT)	<ul style="list-style-type: none"> • Risk for complications: <ul style="list-style-type: none"> o CSA: OR 1.001* o MD per 10 HU: OR 1.08*
Şengül Ayçiçek, 2021, Turkey ¹³²	P	49 gastrointestinal cancer patients (51%, 70)	Not stated	RA, IO, EO, TA, RF, GM	CSA (US) SMI (BIA)	<ul style="list-style-type: none"> • Wound infection, non-infectious complications, anastomotic leakage: not correlated to sarcopenia as measured by SMI
Souwer, 2019, the Netherlands ⁹²	P	174 70y+ colorectal cancer patients (51%, 78)	956 days	Psoas, paraspinal, TA, EO, IO, RA at L3	SMM (CT) MD (CT)	<ul style="list-style-type: none"> • SMM: <ul style="list-style-type: none"> o Cardiac complications: OR 0.44* o No difference in pulmonary complications or severe complications • MD: <ul style="list-style-type: none"> o Higher risk of any complication in Q1 vs. Q4: 49 vs. 28%*; OR 0.78 (PO.08) o More pulmonary complications in Q1 vs. Q4: 14 vs. 2%*, OR 0.53* o More cardiac complications in Q1 vs. Q4: 16 vs. 2%*, OR 0.42* o More severe complications in Q1 vs. Q4: 28 vs. 7%*, OR 0.72 (PO.06)
Sun, 2022, Japan ¹³³	R	341 NSCLC patients undergoing lobectomy (59%, 70)	65 months	Pectoralis at T4	PeMI (CT) MD (CT)	<ul style="list-style-type: none"> • More major complications in lower MD: 27.1, 13.8, 15.5 and 8.2%* • More major complications in lower PeMI: 22.4, 18.4, 16.7, and 7.1%*
Suzuki, 2016, Japan ⁹⁴	R	90 stage I NSCLC patients undergoing complete resection (57.8%, 68.7)	Not stated	L3 (all muscles)	SMI (CT)	<ul style="list-style-type: none"> • SMI-based sarcopenia did not have a significant effect on postoperative complications
Van der Zanden, 2021, the Netherlands ¹⁰²	R	213 women ≥ 70 years old receiving surgery for primary, advanced stage ovarian cancer (0%, 75.9)	Not stated	L3 (all muscles)	MD (CT) SMI (CT)	<ul style="list-style-type: none"> • Higher complications in low MD: 53.7 vs. 29.1%**; OR 2.83* • Higher infectious complications in low MD: 34.1 vs. 25.7%*; OR 2.79* • Higher severe complications in low MD: 17.1 vs. 6.4%*; OR 3.01* • No differences in MD in severe delirium • Low SMI and infectious complications: OR 2.32* • No association between SMI and other outcomes

Table 6. (Cont. from previous page).

First author, year, country	Design	Population (%men, mean age (years))	Mean follow-up	Investigated muscle(s) or region	Muscle parameters + imaging method	Statistical results
Van Rijssen, 2017, the Netherlands ¹⁰³	P	166 patients undergoing pancreatoduodenectomy for periampullary non-pancreas cancer (62.6%, 63)	71 months	L3 (Psoas, ES, QL, EO, IO, RA, TA)	SMI (CT) MD (CT)	<ul style="list-style-type: none"> • SMI did not show significant effect on overall morbidity, major complications, postoperative fistulas, postpancreatectomy hemorrhages or delayed gastric emptying • Low MD: o Higher overall morbidity: 75.3 vs. 57.6%* o Higher incidence of major complications: 58 vs. 36.5%** o More postpancreatectomy hemorrhages: 11.1 vs. 2.4%* o More delayed gastric emptying: 46.9 vs. 29.4%*
Van Vugt, 2018, the Netherlands ¹⁰⁴	P	816 stage I-III colorectal cancer patients (54%, 70)	76.5 months	L3 (all muscles)	SMI (CT) MD (CT)	<ul style="list-style-type: none"> • Low SMI: o No effect on overall complications o More CD ≥ 3 complications: 20.9 vs. 13.6%** • Low MD: o More overall complications: 51.7 vs. 38.5%** o More CD ≥ 3 complications: 20 vs. 11.8%**
Williams, 2021, USA ¹⁰⁷	R	142 multiple myeloma patients undergoing autologous stem cell transplantation (65%, 61.6)	27-33 months	Psoas at L3	MD (CT)	<ul style="list-style-type: none"> • Sarcopenia (defined by 80% high density muscle) had a higher rate of cardiovascular complications: 12.5 vs. 2.9%* • No significant effect on other complications

* = $P < 0.05$; ** = $P < 0.01$. ARDS = Acute respiratory distress syndrome; BIA = bioelectrical impedance analysis; BMI = body mass index; C3 = cervical vertebra 3; CD = Clavien-Dindo; CSA = cross-sectional area; CT = computed tomography; EO = external oblique; GLIM = Global Leadership Initiative on Malnutrition; GM = Gastrocnemius medialis; HCC = hepatocellular carcinoma; HR = hazard ratio; HU = Hounsfield units; HUAC = Hounsfield unit average calculation; ICU = intensive care unit; IO = internal oblique; L3 = lumbar vertebra 3; MD = muscle density; MRI = magnetic resonance imaging; NS = not significant; NSCLC = non small cell lung cancer; OR = odds ratio; P = prospective; PMI = psoas muscle index; PeMI = pectoralis muscle index; PvMI = paravertebral muscle index; QL = quadratus lumborum; R = retrospective; RA = rectus abdominus; RF = rectus femoris; SCM = sternocleidomastoid muscle; SMG = skeletal muscle gauge; SMI = skeletal muscle index; SMM = skeletal muscle mass; T4 = thoracic vertebra 4; T5 = thoracic vertebra 5; T12 = thoracic vertebra 12; TA = transverse abdominis; TPA = total psoas area; TPI = total psoas index; US = ultrasound; vs. = versus

Table 7. Characteristics and results of included studies on response to treatment in oncology patients.

First author, year, country	Design	Population (%men, mean age (years))	Mean follow-up	Investigated muscle(s) or region	Muscle parameters + imaging method	Statistical results
Al Khaldi, 2022, Canada ²⁵	R	312 patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for peritoneal metastases (34.3%, 57.6)	28 months	L3 (all muscles)	SMI (CT)	<ul style="list-style-type: none"> • No effect of SMI-defined sarcopenia on completeness of cytoreduction
Arayne, 2023, Australia ²⁷	R	80 stage I – III rectal cancer patients undergoing curative resection (74%, 63)	Not stated	T4, T12, L3 (all muscles)	SMI (CT)	<ul style="list-style-type: none"> • No effect of SMI on recurrence
Bardoscia, 2022, Italy ³⁰	R	225 head and neck cancer patients undergoing (chemo) radiotherapy (75.6%, 64.5)	5.6 years	L3 (all muscles)	SMI (CT) MD (CT)	<ul style="list-style-type: none"> • No effect of SMI or MD on local disease control
Chiu, 2020, Taiwan ¹³⁴	R	183 esophageal cancer patients who received neoadjuvant chemoradiotherapy + esophagectomy (95%, 53)	4 years	Dorsal muscles at L3	CSA (CT) MD (CT)	<ul style="list-style-type: none"> • Larger CSA was associated with pathological complete response: OR 1.59* • MD: NS
Cho, 2022, Austria ³⁶	R	566 patients with brain metastases from NSCLC (48%, 63)	Not stated	Temporal muscle at level of orbital roof	MT (MRI)	<ul style="list-style-type: none"> • No difference on local brain metastasis progression
Haehl, 2022, Germany ⁴⁸	R	280 head and neck squamous cell carcinoma patients receiving curative (chemo) radiation (gender not stated, age >65)	127 days	C3 (paravertebral + SCM) L3 (calculated from C3)	CSA (CT) SMI (CT)	<ul style="list-style-type: none"> • L3 CSA and L3 SMI were no significant predictors of locoregional control

Table 7. (Cont. from previous page).

First author, year, country	Design	Population (%men, mean age (years))	Mean follow-up	Investigated muscle(s) or region	Muscle parameters + imaging method	Statistical results
Otemuyiwa, 2017, USA ¹³⁵	R	75 metastatic renal cell carcinoma patients initiating IL-2 therapy (67%, 55)	Not stated	Dorsal muscles at T11	MD (CT)	<ul style="list-style-type: none"> • MD of low-density muscles was a significant predictor of IL-2 response* • OR for responding is 5.8x higher for high-attenuation-low MD muscles* • Optimal cut-off: 18.1 HU*
Shachar, 2017, USA ⁸⁶	P	40 metastatic breast cancer patients receiving taxane-based chemotherapy (55)	1.9 years	L3 (all muscles)	SMI (CT) MD (CT) SMG (CT)	<ul style="list-style-type: none"> • Time to treatment failure is dependent of: <ul style="list-style-type: none"> o SMI and MD: NS o SMG: OR 0.91*
Kim, 2021, South Korea ⁵⁵	R	330 pancreatic cancer patients undergoing chemotherapy (49%, 63.4)	Not stated	L3 (all muscles)	MD (CT) SMI (CT)	<ul style="list-style-type: none"> • MD and SMI were no significant predictors of treatment response.
Nishioka, 2020, Japan ⁷⁴	R	156 NSCLC patients receiving immunotherapy (65%, 67)	Not stated	L3 (all muscles)	MD (CT) SMI (CT)	<ul style="list-style-type: none"> • Predictors for efficacy of PD-1/PD-L1 inhibitors: <ul style="list-style-type: none"> o Quality (high MD): HR 0.64* o Quantity (high SMI): NS • Overall response rate higher in high quality: 35 vs. 15.8%*. • No effect of quantity
Pan, 2021, China ¹³⁶	R	273 urinary tract urothelial carcinoma patients treated by radical nephroureterectomy (54.2%, 68)	Not stated	L3 (RA, EO, IO, TA, PS, Ps)	MD (CT) SMI (CT) MT (CT)	<ul style="list-style-type: none"> • Effect on local progression: <ul style="list-style-type: none"> o MD: NS (multivariate: HR 0.97*) o SMI: NS (multivariate: HR 0.89*)
Young, 2020, USA ¹⁶⁴	R	287 melanoma patients treated with immune-checkpoint inhibitors (64%, 63)	519 days	L3 (all muscles)	MD (CT) SMI (CT) SMG (CT)	<ul style="list-style-type: none"> • No significant effect of MD, SMI, or SMG on response to treatment

* = $P < 0.05$; ** = $P < 0.01$. C3 = cervical vertebra 3; CSA = cross-sectional area; CT = computed tomography; EO = external oblique; HR = hazard ratio; HU = Hounsfield units; IL-2 = interleukin 2; IO = internal oblique; L3 = lumbar vertebra 3; MD = muscle density; MRI = magnetic resonance imaging; MT = muscle thickness; NS = not significant; NSCLC = non small cell lung cancer; OR = odds ratio; OS = overall survival; PD-1 = Programmed Cell Death Protein 1; PD-L1 = Programmed Cell Death Ligand 1; P = prospective; Ps = paraspinal; PS = psoas muscles; R = retrospective; RA = rectus abdominis; SCM = sternocleidomastoid muscle; SMG = skeletal muscle gauge; SMI = skeletal muscle index; T4 = thoracic vertebra 4; T11 = thoracic vertebra 11; T12 = thoracic vertebra 12; TA = transverse abdominis; vs. = versus

Table 8. Characteristics and results of included studies on duration of hospitalization and rehospitalization in oncology patients.

First author, year, country	Design	Population (%men, mean age (years))	Mean follow-up	Investigated muscle(s) or region	Muscle parameters + imaging method	Statistical results
Al Khaldi, 2022, Canada ²⁵	R	312 patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for peritoneal metastases (34.3%, 57.6)	28 months	L3 (all muscles)	SMI (CT)	<ul style="list-style-type: none"> • SMI-defined sarcopenia did not have a significant effect on LOS or duration of TPN.
Arayne, 2023, Australia ²⁷	R	80 stage I – III rectal cancer patients undergoing curative resection (74%, 63)	Not stated	T4, T12, L3 (all muscles)	SMI (CT)	<ul style="list-style-type: none"> • SMI-defined sarcopenia did not have a significant effect on LOS
Asai, 2023, Japan ²⁹	R	456 patients undergoing major hepatectomy for perihilar cholangiocarcinoma (68%, 69)	Not stated	Psoas at L3	MD (CT) TPI (CT)	<ul style="list-style-type: none"> • Lowest tertile of TPI had longer hospital stay: 26 vs. 24 days* • Lowest tertile of MD had longer hospital stay: 28 vs. 23 days**
Cinar, 2022, Turkey ³⁹	R	180 patients undergoing resection for NSCLC (80%, 65)	26.3 months	T12 para-vertebral muscles	PvMI (CT) MD (CT)	<ul style="list-style-type: none"> • Longer LOS in low PvMI: 8 vs. 6 days** • Longer LOS in low MD: 7 vs. 6 days*
Fintelmann, 2018, USA ¹²³	R	135 patients who underwent lobectomy or bilobectomy for primary lung cancer (42%, 69)	Not stated	T5 (all muscles)	CSA (CT)	<ul style="list-style-type: none"> • Hospital LOS (in quartiles) was associated with CSA: OR 0.87* • Readmission within 30 days was associated with CSA: OR 0.58*

Table 8. (Cont. from previous page).

First author, year, country	Design	Population (%men, mean age (years))	Mean follow-up	Investigated muscle(s) or region	Muscle parameters + imaging method	Statistical results
Joglekar, 2015, USA ¹²⁵	R	118 patients who underwent pancreaticoduodenectomy or distal pancreatectomy (64%)	Not stated	Psoas at L3	TPI (CT) MD (CT)	<ul style="list-style-type: none"> • LOS was associated with: <ul style="list-style-type: none"> o MD: OR 2.00* o TPI: OR 1.75*
Kim, 2019, South Korea ¹²⁶	P	50 colorectal cancer patients (56%, 63.4)	Not stated	Back muscles at L3	SMM (BIA)	<ul style="list-style-type: none"> • Longer LOS in low muscle mass group: 11.5 vs. 8.3 vs. 6.5 days**
Kim, 2018, South Korea ¹²⁷	R	272 newly diagnosed, pathologically proven NSCLC patients that underwent curative-intent surgery (60%, 62.9)	Not stated	L3 (all muscles)	SMI (CT)	<ul style="list-style-type: none"> • SMI-defined sarcopenia did not affect LOS
Kuroki, 2015, USA ⁵⁷	R	122 endometrial cancer patients (0%, 65.9)	Not stated	Psoas L3	CSA (CT)	<ul style="list-style-type: none"> • CSA-based sarcopenia was not associated with LOS or 90-day readmission rate
Lanza, 2020, Italy ⁵⁸	R	142 HCC patients who received bland transarterial embolization (77%, 73)	27 months	L3 (all muscles)	SMI (CT)	<ul style="list-style-type: none"> • No significant difference in LOS between SMI-based sarcopenic or non-sarcopenic patients
Looijaard, 2019, the Netherlands ⁶³	R	378 colorectal cancer patients (60.3, 73.4)	5.3 years	L3 (all muscles)	MD (CT) SMI (CT)	<ul style="list-style-type: none"> • LOS: no significant effect of MD or SMI. • Readmission: no significant effect of MD or SMI
Namm, 2017, USA ¹³⁰	P	116 undergoing pancreaticoduodenectomy for pancreatic malignancy (53%, 65.5)	33 months	Psoas at L3	MD (CT) TPI (CT)	<ul style="list-style-type: none"> • No effect of TPI or MD on LOS or 90-day readmission • Higher risk of discharge to nursing facility in low TPI: OR 0.30** and in low MD: OR 0.9*
Shachar, 2017, USA ⁸⁶	P	40 metastatic breast cancer patients receiving taxane-based chemotherapy (55)	1.9 years	L3 (all muscles)	MD (CT) SMG (CT)	<ul style="list-style-type: none"> • Lower MD in hospitalized patients: 23 vs. 32 HU* • Lower SMG in hospitalized patients: 862 vs. 1362*
Souwer, 2019, the Netherlands ⁹²	P	174 70+year old patients with colorectal cancer (51%, 78)	956 days	Psoas, paraspinal, TA, EO, IO, RA at L3	SMI (CT) MD (CT)	<ul style="list-style-type: none"> • SMI: o No difference in discharge destination o More readmissions in Q4 vs. Q1: 19 vs. 5%*; OR 1.61* • MD: o No difference in discharge destination or readmission
Sun, 2022, Japan ¹³³	R	341 NSCLC patients undergoing lobectomy (59%, 70)	65 months	Pectoralis at T4	PeMI (CT) MD (CT)	<ul style="list-style-type: none"> • Longer hospital stay in lower CSA/BMI: 8, 8, 7, 6 days** • Longer hospital stay in lower MD: 8, 8, 7, 7 days* • Longer hospital stay in lower PeMI: 8, 8, 7, 6 days**
Suzuki, 2016, Japan ⁹⁴	R	90 stage I NSCLC patients undergoing complete resection (57.8%, 68.7)	Not stated	L3 (all muscles)	SMI (CT)	<ul style="list-style-type: none"> • SMI-defined sarcopenia had no significant effect on hospital stay
Van der Zanden, 2021, the Netherlands ¹⁰²	R	213 women ≥ 70 years old receiving surgery for primary, advanced stage ovarian cancer (0%, 75.9)	Not stated	L3 (all muscles)	MD (CT)	<ul style="list-style-type: none"> • MD had no significant effect on extended LOS (> 14 days) or rehospitalization • Higher risk of discharge to care facility in low MD group: 20 vs. 7.6%*
Van Vugt, 2018, the Netherlands ¹⁰⁴	P	816 stage I-III colorectal cancer patients (54%, 70)	76.5 months	L3 (all muscles)	SMI (CT) MD (CT)	<ul style="list-style-type: none"> • Longer LOS in patients with low SMI* • Longer LOS in patients with low MD**
Williams, 2021, USA ¹⁰⁷	R	142 multiple myeloma patients undergoing autologous stem cell transplantation (65%, 61.6)	27-33 months	Psoas at L3	MD (CT)	<ul style="list-style-type: none"> • No difference in ICU transfer, total days in hospital, discharge to rehabilitation facility, or unplanned hospitalization
Youn, 2021, Canada ¹⁶³	R	44 metastatic myeloma patients treated with Nivolumab (57%, 57)	Not stated	L3 (all muscles)	MD (CT)	<ul style="list-style-type: none"> • MD did not have a significant effect on hospitalization rates

* = $P < 0.05$; ** = $P < 0.01$. AUC = area under the curve; BIA = bioelectrical impedance analysis; BMI = body mass index; CSA = cross-sectional area; CT = computed tomography; EO = external oblique; HCC = hepatocellular carcinoma; ICU = intensive care unit; IO = internal oblique; L3 = lumbar vertebra 3; LOS = length of stay; MD = muscle density; NS = not significant; NSCLC = non small cell lung cancer; OR = odds ratio; P = prospective; PeMI = pectoralis muscle index; PS = psoas muscles; PvMI = paravertebral muscle index; R = retrospective; Q = quartile; RA = rectus abdominis; SMG = skeletal muscle gauge; SMI = skeletal muscle index; SMM = skeletal muscle mass; T4 = thoracic vertebra 4; T5 = thoracic vertebra 5; T12 = thoracic vertebra 12; TA = transverse abdominis; TPI = total psoas index; TPN = total parenteral nutrition; vs. = versus

Table 9. Characteristics and results of included studies on quality of life in oncology patients.

First author, year, country	Design	Population (%men, mean age (years))	Mean follow-up	Investigated muscle(s) or region	Muscle parameters + imaging method	Statistical results
Cortellini, 2020, Italy ¹⁶¹	R	100 patients with advanced cancer receiving anti-PD-1/PD-L1 checkpoint inhibitors (67%, 66)	20.3 months	L3 (all muscles)	SMI (CT)	• Lower SMI was associated with lower ECOG-PS*
Dolan, 2020, UK ¹³⁷	P	523 patients with advanced cancer (51%, >65)	10.5 months	L3 (all muscles)	MD (CT) SMI (CT)	• ECOG-PS was associated with low SMI: OR 1.53* • ECOG-PS was associated with low MD: OR 2.01**
Shaver, 2021, USA ¹³⁸	R	163 head and neck cancer patients (82%, 61.8)	Not stated	L3 (all muscles)	MD (CT)	• Men with myosteosis had lower physical QOL score after 1 year: 48.84 points lower* • Men with myosteosis had lower total QOL score after 1 year: 57.57 points lower*

* = $P < 0.05$; ** = $P < 0.01$. CT = computed tomography; ECOG-PS = Eastern Cooperative Oncology Group Performance Status; L3 = lumbar vertebra 3; MD = muscle density; OR = odds ratio; P = prospective; PD-1 = Programmed Cell Death Protein 1; PD-L1 = Programmed Cell Death Ligand 1; QOL = quality of life; R = retrospective; SMI = skeletal muscle index

significantly associated with better OS, with HR ranging from 1.09 to 2.16 (median 2.36) in the six articles that mentioned HR. Concerning the CT-based psoas muscle index (PMI), 3/6 (50%) showed a significant beneficial association of higher PMI on OS (median HR 2.33). Only one study used EI, but no significant effect on survival was shown.

Progression-free survival

Progression-free survival (PFS) is measured as the time from randomisation until either disease progression or death and was discussed in 39 original studies. Of the 31 studies on CT-based SMI and SMI-defined sarcopenia, 45% showed a significant impact, with HR ranging from 1.16 to 4.40 (median 1.82). Twenty-seven articles measured the effect of MD on PFS. In 16 studies (59%), significant results were seen. Of these, 13 favoured high MD with HR for low density ranging from 1.50 to 2.42 (median 1.99). Three however found higher PFS in low MD, with HR ranging from 0.49 to 0.68. Seven studies used CSA, but only two had significant results (28%), with a mean HR of 3.38. PMI was described in three articles, with significant benefit of higher PMI in two. One out of three articles showed a positive effect of SMG with HR of 1.10, but no significant correlations were found in two out of three articles. Only one article described effect of MT, with a HR of 4.57.

Cancer-specific survival

Cancer-specific survival (CSS) is the time from randomization until death caused by the index cancer. Only

three articles searched for the effect on CSS. All three investigated SMI, with significant results in two of them (HR 1.74 and 2.07). One article did not find a significant correlation with MD, PMI nor MT.

Chemotoxicity

Twenty articles were included in the chemotoxicity search, 18 of them were retrospective. Seventeen investigated SMI, 13 MD, three SMG and four CSA. Of the 17 articles investigating SMI, 10 showed a significant relation with chemotoxicity (59%), with lower SMI appearing to be associated with dose-limiting toxicity or showing less chance of chemotherapy completion. Other studies showed more grade three or higher chemotoxicity, more leukopenia or more neuropathy. One study found only an effect on acute toxicities and not on chronic toxicity. Of those reporting MD, 7 out of 13 (54%) reported an association with chemotoxicity rates: 6/7 demonstrated a higher rate of adverse events, grade 3 or higher chemotoxicity and less chemotherapy completion in the presence of low MD or myosteosis. Conversely, one article showed higher immune-related adverse events in high MD, probably because of better immune response. Lower SMG showed more adverse events and toxicity in 2/3 articles. All four articles showed that lower CSA gave rise to earlier drug-lowering toxicity, more grade three or higher toxicity and more acute and chronic toxicity. All results are shown in Table 5^{25,30,38,40,41,43,46,48,55,63,65,70,86,114-120}.

Surgical outcomes in oncology

Results of surgical outcomes can be found in Table 6 ^{25,27,29,34,39,49-51,57,58,63,83,84,92,94,102-104,107,121-133}. Thirty-two articles on surgical outcomes were included, of which 10 are prospective (31%). Eighteen described SMI. Seven (39%) saw a beneficial effect of a higher SMI, with lower risk of overall complications, respiratory failure, and infectious complications. Fourteen out of 17 MD studies (82%) noted that low MD gave rise to more postoperative complications, and more infectious, haemorrhagic, and cardiovascular problems. Half of the 8 articles on CSA showed that a lower CSA was related to more complications and respiratory failure. Low SMM showed more ileus and infectious and cardiac problems in 2 studies.

Response to oncologic treatment

Results generally favoured improved response with higher muscle parameters. Twelve articles described muscle parameters in relation to the chance of response to oncologic treatment (11 retrospective). Nine described the effect of SMI, of which only 1 found a significant effect on local progression (HR 0.89). Out of 8 studies, 3 found relevant correlations between MD and treatment response, with higher MD rendering a higher chance of IL2- response, higher treatment response and higher pathological response. SMG could predict time to treatment failure in 1 out of 2 articles. For CSA, 1 out of 2 articles found a higher pathological response in patients with greater CSA (OR 1.50). The one article on MT could not show a significant effect. These results are summarized in Table 7 ^{25,27,30,36,48,55,74,86,115,134-136}.

Length of stay and rehospitalization.

On this topic, 20 articles were retained (15 retrospective), which can be found in Table 8 ^{25,27,29,39,57,58,63,86,92,94,102,104,107,114,123,125-127,130,133}. For SMI, 7 investigated the effect on length of stay, of which only 1 found longer hospitalization duration in lower SMI. In 1 out of 2 articles, a higher rate of rehospitalization was found in those with low SMI. Half of the articles (56%) which looked at MD in relation to length of stay found that those with lower MD had a longer length of stay. One in 6 saw more rehospitalization in low MD patients. People with more hospitalizations had lower SMG. Patients with lower psoas or pectoralis muscle index had an increased risk of longer hospital stay in 4 out of 5 articles. Similar results were found for CSA in 1 out of 2 articles. One article described that patients with lower SMM had to stay longer in the hospital. Two studies looked at discharge destination in relation to muscle parameters in oncological patients, one of which found higher discharge rates to a care facility seen in those with lower MD or total psoas index.

Quality of life in oncology

Finally, quality of life was assessed in 3 articles (Table 9) ^{40,137,138}. Lower SMI was associated with lower ECOG-PS in 2 articles. MD was associated with lower ECOG-PS and lower total and physical quality of life scores.

Discussion

This study aimed to provide a high-quality, updated overview on the current knowledge on association of muscle parameters and certain clinical outcomes in oncology. Second, we wanted to give insight in the current literature regarding muscle parameters assessable in radiology and oncological outcomes.

In this systematic review, 117 articles were included and divided into six outcome categories: survival, chemotoxicity, surgical outcomes, treatment response, length of stay, and health-associated quality of life. Although the search included CT, MRI, US, BIA and DXA, most studies used CT to measure muscle parameters. This is because most patients with cancer have already undergone CT scans for staging. US and MRI are sometimes used in head and neck oncology because often MRI is superior to CT to distinguish different structures. Quantitative measurements included were mostly SMI, but also MT or CSA. MD was used as a qualitative parameter.

Six different cancer outcomes were described, of which survival is the most frequently investigated. In older studies, OS was mainly used. However, since this endpoint is more expensive and time-consuming, a shift towards PFS and CSS was seen in studies concerning pharmacologic treatment in oncology research. Quantitative muscle parameters were clearly associated with survival, as were qualitative parameters in a substantial number of studies. Although SMG can be seen as a good combination of quantitative and qualitative characteristics, it could not show a significant impact in most survival studies. These findings are in concordance with previous systematic reviews and meta-analyses on oncology survival. Ge et al. found significant associations between low SMI and low MD and lower long-term OS in ovarian cancer patients. However, they could not find an association with PFS ¹³⁹. In solid tumors, low SMI was associated with worse survival according to a study by Shachar ¹⁴⁰. Aleixo et al. found shorter OS in patients with myosteatorsis in different cancer types ¹⁴¹. A study by Yang et al. measured lower OS and PFS with lower temporal MT in patients with brain tumor ¹⁴². To our knowledge, this is the first systematic review including multiple muscle parameters in different types of cancer.

Chemotoxicity could be predicted by muscle parameters. Low MD, but also low SMI increased the risk of chemotoxicity, with concomitant morbidity and early treatment discontinuation. Until now, dosage of chemotherapy is most frequently guided by body surface area (BSA) since

this has been shown to correlate with blood volume, cardiac output, and renal function. However, patients with similar BSA can have very different distributions of muscle and adipose tissue. This often leads to over- or underdosing of chemotherapy, with reduced survival and increased complications¹⁴³. Therefore, the American Society of Clinical Oncology (ASCO) guidelines suggest using muscle parameters and measures of body composition in drug dosage determination¹⁴⁴. Using a combination of SMI and MD can therefore be helpful to guide clinicians in their treatment regimen decisions.

Sarcopenia and unfavourable muscle parameters negatively impact outcomes and increase adverse effects in cardiac and abdominal surgery^{145,146}. This review found a clear impact of SMI, CSA, and MD in most of the included studies, with lower muscle quantity or quality related to higher postoperative complications. In oncology, a negative influence of sarcopenia on surgical complications and survival is also described¹⁴⁷⁻¹⁵⁰. Assessing the patients' muscle status could help determining who is suitable for surgical treatment or deciding whether a patient needs more rigorous follow-up for complications after surgery. It can even be helpful to optimize muscle health through preoperative rehabilitation and nutritional interventions to potentially enhance the chances of positive postoperative outcomes and reduce complications.

Objective response rate (ORR), disease control rate (DCR) and local progression (LP) are less well described in current literature. Muscle quality seems to have a better prognostic impact on response than quantitative measurements. However, in a previous study, sarcopenia was associated with lower ORR and DCR in patients treated with Immune Checkpoint Inhibitors¹⁵¹. It is probable that body composition often predicts treatment response, since treatment dosages are generally determined by BSA, which does not always reflect differences in body composition. Therefore, people with similar BSA but distinct muscle parameters can suffer from over-or undertreatment, and, thus, a worse therapeutic response¹⁴³.

Length of stay and rehospitalization rate can be predicted by lower qualitative or quantitative muscle parameters in half of the investigated articles. Patients with lower muscle quality or quantity often suffer from more surgical complications and toxicity of treatment, which can reduce quality of life and cause an increase in healthcare expenses. Selecting the most suitable therapy for the individual can therefore be a cost-reducing tool for public healthcare systems that can simultaneously – and, more importantly – improve the patients' wellbeing.

Adding to this, prolonging survival should not be the only goal in cancer treatment. Adding quantity of life years is important, but even more so is expanding qualitative time. Unfortunately, very few articles discuss the effect of muscle parameters on the patient's perspective of treatment and life quality. A tendency towards lower quality of life (QOL)

in oncological patients with lower muscle quantity and quality is seen, as is previously ascertained in sarcopenia in a general population¹⁵². Since the patients' perspective and say in their treatment are very important, future studies should be not only focusing on hard end points, but also on the perception of a certain therapy.

The use of muscle parameters in determining the proper treatment dosage and maximising outcomes of oncologic therapy seems promising. Currently, SMI and MD as measured by CT at the level of L3 are the most studied parameters and can be utilized in a large proportion of oncology patients since the majority undergo abdominal CT in oncological staging. In other cancer types that don't include abdominal CT in routine work-up, other muscle parameters can be used. Ultrasound is a promising technique since it is cheap, easy to use and can evaluate both quantitative and qualitative muscle characteristics. More research on this assessment technique is needed to confirm its usability.

Considering that muscle parameters influence survival and other outcomes in cancer patients, it could be helpful to improve the muscle status as early as possible after diagnosis. A systematic review by Rostoft et al. demonstrated that a geriatric assessment can be very helpful in oncological patients, can improve patient-centred outcomes and treatment completion, and can decrease toxicity and other complications¹⁵³. Survival could potentially be improved with relatively simple interventions such as a protein-rich diet and resistance training, in accordance with their effect on mobility, as is proven in the SPRINTT trial¹⁵⁴. If muscle status can be improved by treating sarcopenia in advance of starting chemotherapy, immune therapy, or surgery, the complications could be reduced, with less treatment dropouts and thus more success of the oncological treatment.

Another point of consideration and for further research can be follow-up of muscle parameters throughout the oncologic treatment trajectory. Oncology treatments have an unfavourable impact on muscle status through both sarcopenia and cachexia. Chemotherapy often leads to anaemia due to its myelotoxic trait, which impairs oxygen transport to the muscles. In addition, therapies such as anthracyclines can lead to myocardial damage and decrease cardiac output or lung damage. Immunosuppressants can cause loss of muscle mass. Chemotherapy-induced nausea and anorexia diminish protein intake. Cancer treatment is often accompanied by inactivity which can lead to secondary sarcopenia^{155,156}. Treatment-independent cancer cachexia occurs as well in 80% of patients undergoing cancer treatment and is responsible for 22-30% of cancer-related deaths¹⁵⁷. This is due to a systemic inflammatory response mediated by cytokines, chemokines and inflammatory mediators released by cancer cells¹⁵⁷. This decline in muscle quantity and quality can further impair prognosis and necessitate adaptation of treatment. Additional

research is desirable to study the pattern of muscle decline in oncology and in the different treatment options, and to determine how this should influence treatment dosages during therapy. Frequent follow-up of muscle status can then be performed regularly using easily accessible tools such as US.

Cut-off values or ranges for the different muscle parameters still need to be established. The EWGSOP2 did not suggest specific values for sarcopenia by measurement via CT, MRI, or US. For SMI, multiple cut-off values have been proposed, but without standard values it remains difficult to assess studies and guide practitioners to adapt therapy. The next policy-changing step in oncology would be to detect which (combination of) muscle parameters can be used to determine the individualized dose of chemotherapy or immune therapy instead of BSA. With gender- and age-specific cut-offs, an algorithm for treatment could be made. Frail patients often suffer more from the proposed therapy than from the cancer itself. The ideal range of the muscle parameters could then be an additional parameter to be considered in treatment decision, in order to prevent a potentially harmful therapeutic persistence.

Several strengths of this systematic review should be highlighted. First, this is the first systematic review investigating all muscle parameters measurable by CT, MRI, DXA, and US. It is not limited to a specific cancer type. The review did not only search for evidence about survival, but also other clinically meaningful outcome measures in an oncological setting, showing the advantages of measuring muscle mass and its parameters. This review can certainly help the field of oncology stepping away from the outdated BSA-based regimens and going towards more personalized, patient-tailored treatment plans, and can endorse the use of geriatric assessment and pretreatment interventions to improve muscle. Certain limitations can be mentioned. The extent of the study, including a heterogeneous group of cancer types, treatment options and macroscopic muscle measurements could influence outcomes. As there is a clear tendency towards worse outcomes with lower muscle status, all patients should be screened for this underlying condition, regardless of the cancer type. Another point of consideration is that different studies use different cut-off values for SMI to establish the presence of low muscle mass. Finally, the review aimed to be as inclusive and comprehensive as possible and included several definitions of sarcopenia in the studies retrieved. Some of these studies were not recent and did not follow the most updated standard definitions (EWGSOP2, AWGSOP, NIH, etc.), but previous or unstandardized definitions, which considered the use of muscle mass alone for the term sarcopenia¹⁵⁸. Due to this, it is possible that some of the studies included were not actually measuring sarcopenia, but low quality or quantity of muscle mass instead. Therefore, they were actually measuring alternative muscle diseases or nutrition-related disorders which are also characterized

and involve muscle issues, such as malnutrition, frailty, or importantly within this population, cachexia¹⁵⁹. Although this could have repercussions on the comparability of the studies, this was not the set-up of this review.

Conclusion

Both qualitative and quantitative muscle parameters can be predictive for cancer survival, surgery outcomes, chemotoxicity, treatment response, length of stay and quality of life. It is strongly advised to start including muscle measurements in oncological treatment plans. This can help to determine who is suitable for a certain treatment and help identify patients who need more rigorous follow-up during their treatment. Furthermore, people could receive personalized pre-treatment plans including rehabilitation and nutritional support in order to enhance their outcomes and minimize the risk of complications. Further research is needed to clarify at which cut-off points better outcomes could be reached.

Authors' contributions

Sophie Bastijns wrote the manuscript. Charlotte Beaudart performed the article search and provided statistical support. Sophie Bastijns, Blanca Alabadi, Thiago Gonzalez Barbosa-Silva, Kristoffer Brockhattingen, Scott Lamers, Karolina Piotrowicz, Carly Welch, and Stany Perikis participated in the article selection and assessment. Blanca Alabadi, Thiago Gonzalez Barbosa-Silva, Kristoffer Brockhattingen, Scott Lamers, Karolina Piotrowicz, Carly Welch, Anne-Marie De Cock, and Stany Perikis reviewed the manuscript. All authors read and approved the final version of the manuscript.

Acknowledgements

We wish to thank the following individuals for their contribution in data collection and article review: Femke Ariën, David Beckwée, Florence Benoit, Justin Chew, Olgun Deniz, Katleen Jegers, Meltem Halil, Suzy Hope, Nina Lefebber, Magdalena Malek, Dolores Sanchez-Rodriguez, Aldo Scafoglieri, Kate Taylor, Jona Van den Broeck, Daisy Wilson, Tilo Wunsch

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