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The use of alternate vertebral levels to L3 in computed tomography scans for skeletal muscle mass evaluation and sarcopenia assessment in patients with cancer: a systematic review

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Abstract

Body composition measurement using diagnostic computed tomography (CT) scans has emerged as a method to assess sarcopenia (low muscle mass) in oncology patients. Assessment of skeletal muscle mass (SMM) using the cross-sectional area of a single vertebral slice (at lumbar L3) in a CT scan is correlated with whole-body skeletal muscle volume. This method is used to assess CT-defined sarcopenia in patients with cancer, with low SMM effecting outcomes. However, as diagnostic scans are based on tumour location, not all include L3. We evaluated the evidence for the use of alternate vertebral CT slices for SMM evaluation when L3 is not available. Five electronic databases were searched from January 1996 to April 2020 for studies using CT scan vertebral slices above L3 for SM measurement in adults with cancer (solid tumours). Validation with whole-body SMM, rationale for the chosen slice and sarcopenia cut-off values were investigated. Thirty-two studies were included, all retrospective and cross-sectional in design. Cervical, thoracic and lumbar slices were used (from C3 to L1), with no validation of whole-body SMM using CT scans. Alternate slices were used in lung, and head and neck cancer patients. Sarcopenia cut-off values were reported in 75 % of studies, with differing methods, with or without sex-specific values, and a lack of consensus. Current evidence is inadequate to provide definitive recommendations for alternate vertebral slice use for SMM evaluation in cancer patients. Variation in sarcopenia cut-offs warrants more robust investigation, in order for risk stratification to be applied to all patients with cancer.

Key words: **Sarcopenia: Skeletal muscle mass: Cancer: Computed tomography: Body composition**

Malnutrition and involuntary weight loss are common in cancer patients and can often be attributed to the metabolic burden of the tumour itself with associated cachexia, and/or the toxicities of the treatment modalities used[1–3]. Recently, skeletal muscle mass (SMM) depletion has gained particular interest, with the use of various body composition methods to determine actual loss of lean tissue rather than total body weight alone[4]. This is particularly relevant, as depletion of muscle mass can occur independently of adipose tissue, and overweight or obese patients may have low skeletal muscle reserves[5]. In patients with cancer, skeletal muscle and fat are not necessarily gained or lost in equal proportions and although patients may gain fat, muscle mass can be lost simultaneously[2,6], and as a result, these patients can be overlooked for potential nutritional risk[7].

The progressive and general depletion of SMM and related functional decline are key components of sarcopenia[8]. Full consensus on the definition of sarcopenia in terms of included variables and cut-off values has yet to be reached; however, diagnosis requires a combination of muscle mass measurement, muscle strength and physical performance indicators[9]. Sarcopenia has been associated with subsequent adverse outcomes, and although originally mostly investigated in the ageing population, with an increased risk of falls, frailty, functional decline and mortality[9], in patients with cancer, low SMM and low muscle attenuation have been shown to be poor prognostic indicators[10,11]. Where sarcopenia has been assessed in cancer research, it is generally defined as low muscle mass, with physical function assessment rarely included[8]. The term ‘skeletal

Abbreviations: CSA, cross-sectional area; CT, computed tomography; HNC, head and neck cancer; SMI, skeletal muscle index; SMM, skeletal muscle mass.

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muscle index' (SMI) is also used to define sarcopenia as a normalised measure of muscle (cm^2/m^2).

The negative impact of sarcopenia on outcomes, particularly survival, in patients with cancer, has been investigated across various malignancies such as head and neck, colorectal, upper gastrointestinal and lung[5,10,12–18]. As a result, there is increasing evidence that sarcopenia should be included in risk stratification tools to identify patients at high risk of potential nutritional issues and complications of treatment.

Measurement of body composition using diagnostic computed tomography (CT) scans has emerged as an effective method to determine levels of muscle depletion, in oncology patients, as images are readily available for analysis and do not require additional cost, radiation exposure or burden to the patient. The accuracy and reliability of a CT scan at the tissue-organ level has led to this being accepted as the 'gold-standard' imaging method in body composition analysis[4,6,18]. In this context, low muscle mass, without functional assessment, that is associated with an increased risk of mortality, has been described as 'CT-defined sarcopenia'[19,20]. For the purposes of this review, the term sarcopenia will refer to CT-defined sarcopenia.

The cross-sectional area (CSA) of a single vertebral slice in CT imaging at the lumbar vertebral level of L3 has been shown to correlate well with total body skeletal muscle volume in healthy subjects[21]. The CSA of muscle at the level of L3 can be used to diagnose sarcopenia; however, cut-off values have been previously defined by numerous researchers based on mortality outcomes, often with varied values for sex, BMI, specific populations, and in varying tumour groups[5,6,10,22,23], making direct comparisons difficult in patients with cancer without standardisation.

One of the issues with the use of CT scans in muscle mass evaluation for many tumour types is that diagnostic, rather than whole-body scans, is frequently used to evaluate a specific anatomical area such as: the head and neck, chest or abdomen and pelvis. As a result, those who have not had an abdominal CT are unable to be assessed using validated measures. This has led researchers to use alternative landmarks.

The selection of an alternate slice to L3 should consider whole-body musculature, specifically whether muscle groups are more susceptible to wasting than others, and minimum mass required for actual function. Alternate CT scan slices have been investigated in non-cancer or healthy subjects, with vertebral levels ranging from T4 to L5, with varying results[21,24–32]. Dertstine *et al.*, in a study of 735 healthy subjects, compared vertebral levels from T10 to T5, and the authors concluded that the further away from L3 that SMM is measured, the less reflective it is of whole-body SMM[24]. Although validation of alternate slices has been conducted in healthy subjects, this may not be applicable to patients with solid tumours, due to potential alterations in body composition caused by altered metabolic and energy balance[33–35].

Single muscle groups at a particular vertebral level have also been used, such as the psoas or pectoralis muscle, rather than the CSA of the entire slice, again with varying definitions of sarcopenia cut-offs (if any), and subsequent varied results[36–47]. Baracos raises significant concerns with using one sentinel muscle for sarcopenia measurement, including that all muscles have specific functions, and wasting can occur differently in certain muscle groups, bringing into question whether one muscle can be representative of whole-body muscle status[48]. This approach has also yet to be validated by any expert group. Adiposity at a particular vertebral level should ideally also be considered to enable the impact of sarcopenia and obesity to be explored; however, for the purposes of this review, assessment of SMM is the focus.

With much being currently explored in this area, and the importance of identifying sarcopenia in cancer patients, the aim of this systematic review was to investigate the use of alternate vertebral levels above the lumbar L3 in the evaluation of skeletal muscle in this population. The objective of this narrative synthesis is to determine if there is a feasible alternative that can be used when L3 is not available.

Methodology

Search strategy

This systematic review followed criteria outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines[49] and has been registered with PROSPERO (the international prospective register of systematic reviews) with Registration number CRD42019137317 in October 2019.

All relevant studies were identified through extensive searches of electronic databases and reference lists of eligible papers. The search included the databases: Ovid MEDLINE, Embase, CINAHL (Cumulative Index to Nursing and Allied Health Literature), Web of Science and Scopus (papers published from January 1996 to 30 April 2020). The medical subject headings (MeSH) used in each database were: (sarcopenia, 'skeletal muscle', 'muscle wasting', 'muscle atrophy', 'body composition', 'muscle mass', cachexia and 'muscle weakness') combined (using Boolean operator AND) with (CT, 'computed tomography') and (cancer, carcinoma, neoplasms) and (lumbar, thoracic, cervical). The systematic selection process is illustrated in Preferred Reporting Items for Systematic Reviews and Meta-Analysis format in Fig. 1.

Eligibility criteria

Studies using adult human subjects (≥18 years) with a confirmed cancer diagnosis (solid tumours only) were included. All studies that used alternate vertebral landmark slices to the lumbar L3 in CT scans in the evaluation of SMM and all papers that investigated the CSA of skeletal muscle at any slice above the level of L3 were eligible. Those that included validation or comparison of the alternate slice with L3 were also included. Studies selected for review included only those that had measured skeletal muscle using the CSA of an entire vertebral slice and not isolated muscle groups. Other exclusions were conference abstracts, case studies, opinion papers, non-English papers and reviews.

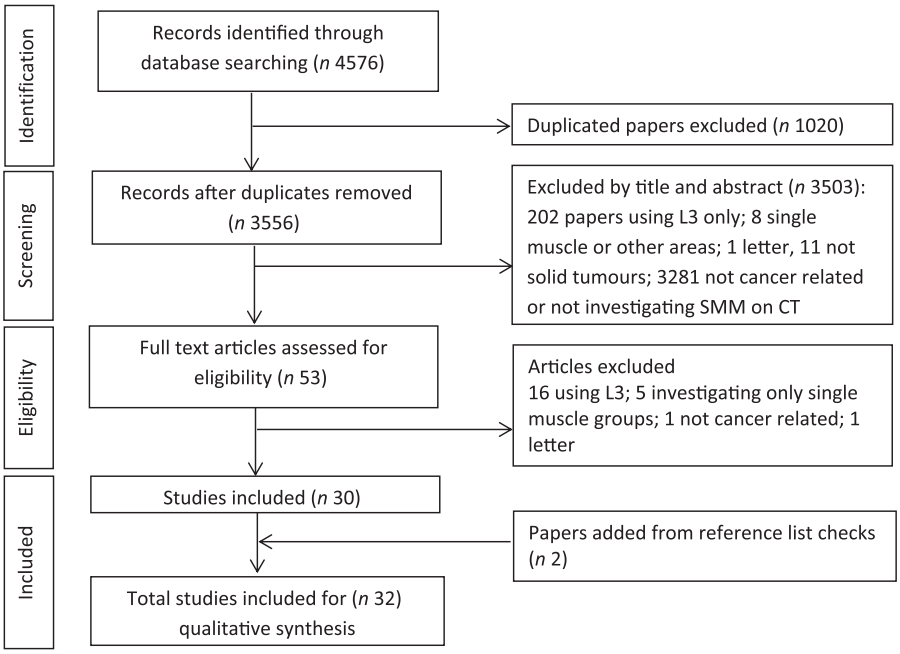

Fig. 1. PRISMA flow diagram of literature search and article selection.

Study appraisal and synthesis

Eligibility assessment was performed by the primary investigator, independently and unblinded. Electronic database search results were transferred into EndNote X9 (Thompson Reuters), where duplicates were then removed. The abstracts and titles of the remaining papers were assessed using the eligibility criteria, excluding those that did not obviously meet this. The full texts of publications that met the criteria were then reviewed once again to ensure compliance. The quality of the methodology used in each paper and validity of presented results were then assessed using the Academy of Nutrition and Dietetics Quality Criteria Checklist, where studies were given a positive (+), neutral (Ø) or negative (–) quality rating based on the appraisal tool[50]. Two independent reviewers completed the checklist individually and blinded, and findings were compiled and any discordance was discussed until consensus was reached.

Data extraction

Data relating to the type of cancer, specific vertebral slice and/or slices used, the rationale for selecting a particular slice, whether association with L3 was investigated and the sarcopenia cut-off points used (if included) are displayed in Table 1.

Results

There were 4576 studies identified through the database searching process. After screening titles and abstracts, fifty-three studies were scanned in full. Studies that did not meet the criteria for inclusion were then removed; reference lists of the remaining papers were checked, resulting in thirty-two included in the systematic review (Fig. 1).

Study characteristics

All thirty-two papers were retrospective, cross-sectional studies, with the largest proportion originating from The Netherlands (13/32, 41 %). The number of patient scans used in each study varied, with the majority 24/32 (75 %) having sample sizes <250, with only three studies having much larger cohorts of >800[51–53]. The majority (52 %) of papers focused on muscle mass assessment in patients with head and neck cancer (HNC) (seventeen studies[51,52,54–68]), with ten (32 %) investigating lung cancer[69–78] and the remaining papers focusing on a mixed tumour cohort of head and neck, lung, breast and colorectal[53,79–82]. More detailed characteristics of the studies are shown in Table 1.

Study quality and bias assessment found that there were no studies of negative quality and eighteen was rated as being neutral. As all studies were retrospective in nature and involved the use of CT scans from patients who had already had a scan for diagnostic purposes, patients were not 'recruited' into studies and received no intervention other than standard care. The risk of bias therefore was associated with the limiting of selected tumour groups, and as there was no randomisation and small populations, results may not be representative of larger sample cohorts. Due to the nature of CT scans, scans were excluded from all studies if they were not clear for analysis and this may have led to some bias in the assessment of the remaining scans. Potential biases were addressed in most papers; however, three failed to discuss risk of bias or limitations at all in the presented results[63,70,71].

Analysis of computed tomography scans

The Slice-O-Matic (Tomovision, Canada) medical imaging software was used in the majority of studies (15/32, 47 %), with the remainder using either in-house software or different

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Table 1. Characteristics of thirty-two selected studies using alternate vertebral computed tomography (CT) scan slices for skeletal muscle mass (SMM) estimation

Source & quality rating	Region of slice	Tumour site and sample size	Software used	Comparison with L3 and statistical methods	Sarcopenia outcomes measured (if any)	Sarcopenia cut-off values
Swartz *et al.* (2016)[56] *The Netherlands* Ø	C3	HNC *n* 103 51 trauma (control) 52 HNC	Volumetool Research software package (In-house tool)	Multivariate linear regression model compared CSA at C3 with L3 ($r = 0{\cdot}891$) when corrected for sex, age and weight Prediction rule for CSA at L3 from CSA at C3 established	None. Main aim was direct comparison of CSA at C3 with that at L3	Not investigated/used
Wendrich *et al.* (2017)[57] *The Netherlands*+	C3	HNC *n* 112	Volumetool v.1.6.5 (In-house tool)	Not compared Swartz *et al.*[56] prediction rule applied for "conversion" from C3 SMM to L3 SMM Low SMM based on lowest Log-Likelihood value for CDLT ($P < 0{\cdot}001$)	CDLT	Low SMM = lumbar SMI < 43·2 cm^2/m^2
Bril *et al.* (2019)[54] The Netherlands Ø	C3	HNC *n* 54	Volumetool v.1.6.5 (In-house tool)	Not compared	Evaluation of inter-observer agreement of SMM at C3	Not investigated/used
Chargi *et al.* (2019)[55] The Netherlands Ø	C3	HNC *n* 85 (elderly ≥ 70 years)	Slice-O-Matic (Tomovision, Canada)	Not compared Swartz *et al.*[56] prediction rule applied for "conversion" from C3 SMM to L3 SMM	OS Hand grip strength Gait speed	Low SMI < 43·2 cm^2/m^2 (previously published by Wendrich *et al.*[57])
Ganju *et al.* (2019)[60] *USA* +	C3	HNC *n* 246	ImageJ	Not compared Swartz *et al.*[56] prediction rule applied for "conversion" from C3 SMM to L3 SMM	Chemotherapy tolerance OS PFS	Males < 43 cm^2/m^2 if BMI < 25 and < 53 cm^2/m^2 if BMI > 25 Females < 41 cm^2/m^2 (Ranges referenced to Martin *et al.*[10])
Zwart *et al.* (2019)[61] *The Netherlands* +	C3	HNC *n* 112	iNtuition TeraRecon (Houston, TX, USA)	Not compared Swartz *et al.* [56] prediction rule applied	Frailty Mobility Nutritional status	Low SMM < 43·2 cm^2/m^2 (Wendrich *et al.*[57])
Karsten *et al.* (2019)[62] *Netherlands* Ø	C3	HNC *n* 128	Worldmatch (In-house tool)	Not compared Swartz *et al.* method used (for C3) but prediction equation not applied Neck SMI calculated using the Youden point of the ROC curve stratified with > 90 d tube dependency (AUC 0·64, sensitivity 72 %, specificity 57 %)	Prolonged feeding tube dependency	Neck SMI < 12·7 cm^2/m^2
Bril *et al.* (2019)[59] *The Netherlands* +	C3	Larynx *n* 235	Slice-O-Matic V5.0 (Tomovision, Canada)	Not compared Swartz *et al.*[56] prediction rule applied for "conversion" from C3 SMM to L3 SMM	Post-op complications OS	Low SMM = lumbar SMI < 43·2 cm^2/m^2 (previously published by Wendrich *et al.*[57])
Jung *et al.* (2019)[63] *Korea* Ø	C3 L3	HNC *n* 305	PetaVision (Seoul, Korea)	CSA at C3 and L3 measured and prediction models established for estimating L3 SMM from C3 SMM and applied to the cohort using CT planning scans Multivariate linear regression Adjusted $r^2 = 0{\cdot}721$, $P < 0{\cdot}001$ SMM calculated using the Youden point of the ROC curve predicting survival 0·809 (95 % CI 0·724, 0·833), $P < 0{\cdot}001$	OS	C3 SMM < 56·3 cm^2 L3 SMM < 174·5 cm^2
Muresan *et al.* (2019)[80] *Spain* Ø	C3 L3	23 Lung 1 Pancreas 1 Stomach 12 Oesophagus *n* 37	MIM 6·7 (Cleveland OH, USA)	Swartz *et al.*[56] prediction rule applied and C3 values compared with L3 using Pearson's correlation SMM ($r^2 = 0{\cdot}8769$) *P* value not reported	SMM at C3 *v* L3 SMI at C3 *v* L3 using planning scans	Males < 43 cm^2/m^2 if BMI < 25 and < 53 cm^2/m^2 if BMI > 25 Females < 41 cm^2/m^2 (Referenced to Martin *et al.*[10])
	C3	Nasopharynx *n* 56	MonacoTPS software V5.1 (MO, USA)			Males < 43 cm^2/m^2 if BMI < 25 and < 53 cm^2/m^2 if BMI > 25

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Table 1. (*Continued*)

Source & quality rating	Region of slice	Tumour site and sample size	Software used	Comparison with L3 and statistical methods	Sarcopenia outcomes measured (if any)	Sarcopenia cut-off values
Hua *et al.* (2020)[64] *China* +				Not compared Swartz *et al.*[56] prediction rule applied for "conversion" from C3 SMM to L3 SMM	QOL Patient characteristics Treatment response	Females < 41 cm^2/m^2 (Referenced to Martin *et al.*[10])
Chargi *et al.* (2020)[67] *The Netherlands* +	C3	HNC *n* 216	Slice-O-Matic (Tomovision, Canada)	Not compared Swartz *et al.*[56] prediction rule applied for "conversion" from C3 SMM to L3 SMM End point-specific cut-offs used using optimal stratification (methods not described referenced)	OS DFS	Low SMI < 43·2 $cm^2/m^2$for DFS and < 43 $cm^2/m^2$for OS
Lin *et al.* (2020)[65] *Taiwan* Ø	C3	Oral cavity *n* 276	Not specified	Not compared Swartz *et al.*[56] prediction rule applied for "conversion" from C3 SMM to L3 SMM Lean body muscle mass then calculated using equation by Mourtzakis *et al.*[6] Adjusted backward stepwise results for low SMI: (OS HR = 1·74, 95 % CI 1·14, 2·67) (DSS HR = 1·67, 95 % CI 1·04, 2·67)	OS DSS	Low SMI < 47·5 cm^2/m^2
Ansari *et al.* (2020)[66] *The Netherlands* Ø	C3	Oral cavity *n* 78	Slice-O-Matic (Tomovision, Canada)	Not compared Swartz *et al.*[56] prediction rule applied for "conversion" from C3 SMM to L3 SMM	Post-op complications OS	Low SMI < 43·2 cm^2/m^2 (previously published by Wendrich *et al.*[57])
Huiskamp *et al.* (2020)[68] *The Netherlands* +	C3	HNC *n* 91	Slice-O-Matic (Tomovision, Canada)	Not compared Swartz *et al.*[56] prediction rule applied for "conversion" from C3 SMM to L3 SMM prediction rule used Low SMI determined by calculating "log-likelihood" with the cut-off being the best associated with DLT. *P* value not reported	Dose-limiting toxicity OS DFS	Low SMI < 45·2 cm^2/m^2
Pai *et al.* (2018)[51] *Taiwan* Ø	T2	HNC *n* 881 398 used to compare T2 SAT and SM to L3	Eclipse V8.2, (Palo Alto, CA, USA)	Pearson's coefficients calculated for correlation between T2 and L3 SM in 173 pts with whole-body CT scans ($r = 0·63$, $P < 0·001$)	OS Local control Metastasis-free survival	SMI cut-offs were the median values in each sex at the level of T2 Males < 51·74 cm^2/m^2 Females < 34·3 cm^2/m^2
Wieland *et al.* (2007)[76] *Canada* Ø	T4	Lung *n* 65	Slice-O-Matic V4.2 (Tomovision, Canada)	Not compared	Proteolysis-inducing factor association with muscle loss OS	Not defined – not focus of the study Change in muscle area over time as a percentage
Popuri *et al.* (2016)[52] *Canada* Ø	T4 L3	HNC *n* 1659 images from 1004 pts (1069 abdominal)	Slice-O-Matic v4.3 (Tomovision, Canada) for the manual component	Not compared Both slices used for automatic segmentation model	Proposed method for auto-segmentation	Not investigated/used Sarcopenia not the focus of this paper
Blauwhoff-Buskermolen *et al.* (2017)[79] *The Netherlands* +	T4 L3	Prostate Breast Colorectal Lung (palliative) *n* 241 86 lung (for T4)	Slice-O-Matic V5.0 (Tomovision, Canada)	Not compared Previously published values used for L3 and T4 cut-offs from unpublished results	Cancer cachexia QOL OS	L3: <55 cm^2/m^2 males <39 cm^2/m^2 females (Fearon *et al.*[2]) T4: <66·0 cm^2/m^2 males <51·9 cm^2/m^2 females (data not published)

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Table 1. (*Continued*)

Source & quality rating	Region of slice	Tumour site and sample size	Software used	Comparison with L3 and statistical methods	Sarcopenia outcomes measured (if any)	Sarcopenia cut-off values
Dabiri *et al.* (2019)[53] *Canada* Ø	T4 L3	HNC Lung Colorectal Breast > 9000 L3 images Total pt number unclear	Slice-O-Matic V4.3 and V5.0 (Tomovision, Canada)	Not compared	Auto-segmentation algorithm using T4 and L3	None given or used
Sealy *et al.* (2019)[58] *The Netherlands* +	T4 L3	HNC *n* 213 93 T4, 120 L3	Slice-O-Matic V5.0 (Tomovision, Canada)	Not compared SMI results from L3 and T4 pooled using "corrected" measurement of deviations to the means of each sample group Mean difference males and female in both groups $P < 0{\cdot}001$	Early toxicity-related termination of chemotherapy related to low muscle mass	SMI L3: 51·62 cm^2/m^2 overall 53·4 cm^2/m^2 males 42·23 cm^2/m^2 females T4: 65·53 cm^2/m^2 overall 69·45 cm^2/m^2 males 52·88 cm^2/m^2 females
van de Kroft *et al.* (2019)[81] *Germany* Ø	T4 L3	Colorectal *n* 180	Slice-O-Matic V5.0 (Tomovision, Canada)	L3 SMA correlated with T4 SMA ($r = 0{\cdot}78$. $P < 0{\cdot}001$, $r^2 = 0{\cdot}60$) Authors developed their own cut-offs for L3 and T4	Post-op pneumonia Post-op pneumonia with low T4 SMI *v.* L3 SMI	Cut-offs for SMI based on tertiles in the cohort L3: <46·6 cm^2/m^2 males <36·8 cm^2/m^2 females T4: <65·2 cm^2/m^2 males <51·9 cm^2/m^2 females
Gronberg *et al.* (2019)[77] *Norway* Ø	T4 L3	Lung *n* 401	Slice-O-Matic V4.3 (Tomovision, Canada)	Agreement between T4 and L3 examined with Bland–Altman plots SMI: Males $r^2 = 0{\cdot}50$ Females $r^2 = 0{\cdot}28$ SMD: Males $r^2 = 0{\cdot}50$ Females $r^2 = 0{\cdot}58$	Comparison of SMI and SMD at T4 with L3	Cut-off values at T4 not given
Neefjes, *et al.* (2017)[82] *The Netherlands* Ø	T4 L3	82 lung 75 colorectal 44 prostate 32 breast *n* 233	Slice-O-Matic V5.0 (Tomovision, Canada)	Not compared T4 group analysed separately, with no sarcopenia cut-offs	CRF	L3: Males < 43 cm^2/m^2 if BMI < 25 and < 53 cm^2/m^2 if BMI > 25 Females < 41 cm^2/m^2 (Ranges referenced to Martin *et al.*[10]) T4: No reference values available
Fintelmann *et al.* (2018)[74] *USA* +	T5	Lung *n* 135	OsiriX Lite	Not compared Pts stratified by sex-specific muscle CSA Median used for high or low SM	Post-op complications LOS ICU admissions	Males < 181·2 cm^2 Females < 129·4 cm^2
Troschel *et al.* (2019)[75] *USA* +	T5 T8	Lung *n* 128	OsiriX Lite software V7·0.2 (Switzerland)	Not compared High and low SMA stratified by T8 CSA with	OS	T8: Males < 115·3 cm^2 Female < 74·0 cm^2

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Table 1. (*Continued*)

Source & quality rating	Region of slice	Tumour site and sample size	Software used	Comparison with L3 and statistical methods	Sarcopenia outcomes measured (if any)	Sarcopenia cut-off values
				sex-specific median (T5 values not used due to small numbers)		(method for sex-specific median referenced Fintelmann *et al.*[74] and Kinsey *et al.*[36])
Madariaga *et al.* (2020)[78] *USA* +	T8 T12	Lung *n* 130	OsiriX Lite software V7.0.2	Not compared Quartiles of TSMA used for sarcopenia grouping. (Combined T8 + T12 muscle areas used) The "low muscle group" was the lowest quartile	LOS Post-op complications Re-admission Discharge	Males < 211·1 cm^2 Females < 131 cm^2 (quartiles used as no reference values)
Goncalves *et al.* (2018)[69] *USA* Ø	T10 L1	Lung *n* 88	iNtuition TeraRecon	Not compared Muscle volume loss at T10 compared to L1 pre- and post-chemotherapy	OS Muscle volume change over time	Muscle volume measured in cm^3 No measure of high or low, change over time measured
Kim *et al.* (2016)[70] *Republic of Korea* Ø	L1	Lung *n* 90	Terarecon 3.4.2.11 (San Mateo, CA, USA)	Pearson's correlation, Bland–Altman plot used to assess relationship between L3 muscle index and L1 $r = 0{\cdot}851$	Relationship between SMI at L3 and L1 for sarcopenia criteria	Males < 46 cm^2/m^2 Females < 29 cm^2/m^2
Recio-Boiles *et al.* (2018)[71] *USA* Ø	L1	Lung *n* 37 73 scans	Slice-O-Matic (Tomovision, Canada)	Not compared Cut-offs for L3 applied to SMM at this slice	Sarcopenia correlation with BMI and weight	Males < 52·4 cm^2/m^2 Females < 38·5 cm^2/m^2 (reference Mourtzakis *et al.*[6] however quoted values differ from this ?error)
Sanders *et al.* (2019)[72] *The Netherlands* +	L1 L3 Pectoralis muscle	Lung *n* 115	Slice-O-Matic V5.0 (Tomovision, Canada)	CSA at L1 and pectoralis muscle compared with L3 Pearson's and Bland–Altman plots used Between L1 and L3 $r = 0{\cdot}90$, $P < 0{\cdot}001$ Bland–Altman difference between L1 and L3 = 14·9 % ± 9·0 % ($P < 0{\cdot}001$)	Comparison of skeletal muscle and adipose tissue at L1 and L3 OS	Not stated "loss of tissue" used over time (set at > −1·3 % loss)
Sun *et al.* (2019)[73] *Japan* +	L1	Lung *n* 314	SYNAPSE VINCENT (Fujifilm Medical, Tokyo, Japan)	Not compared	OS Recurrence-free survival	Lowest quartile of truncal muscle index used for "low muscle index" Males < 38 cm^2/m^2 Females < 29·6 cm^2/m^2

Quality rating: + positive, Ø neutral.
C, cervical; T, thoracic; L, lumbar; HNC, head and neck cancer; SMM, skeletal muscle mass; CSMA, cross-sectional muscle area; SMA, skeletal muscle area; SMI, skeletal muscle index; CSA, cross-sectional area; CDLT, chemotherapy dose-limiting toxicity; CT, computed tomography; SAT, subcutaneous adipose tissue; SM, skeletal muscle; pts, patients; Ca, cancer; N/A, not applicable; PNS, paranasal sinuses; SMD, skeletal muscle radiodensity; DFS, disease-free survival; PFS, progression-free survival; OS, overall survival; DSS, disease-specific survival; CRF, chronic renal failure; ROC, receiver operating characteristic.

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software packages. Fifteen papers used a cervical vertebral slice (C3)[54–57,59–66,68,80] with most using the study by Swartz *et al.* as the reference for the use of C3, and applying the prediction formula described to the CSA at C3 to predict CSA at L3[56]. Seven of these studies were conducted at the same institution in the Netherlands where the use of C3 in muscle mass estimation was first investigated[54–57,59,66–68]. The use of thoracic vertebral landmarks varied and included T2, T4, T5, T8, T10 and T12, and these levels were used in the studies investigating lung, head and neck and colorectal cancer[51–53,58,69,74–78,81,82]. The remaining studies used the higher lumbar vertebral slice of L1[69–73]. The most common reason given for using an alternative slice to L3 was that an abdominal scan was not available diagnostically for many tumour sites, and an alternative needed to be used for sarcopenia analysis. However, most gave no rationale as to why a specific slice level was chosen (either cervical or thoracic), or any previously published validation evidence to support its use.

Two Canadian studies investigated auto-segmentation modelling using a head and neck and lung cancer data set (1004 patients) of CT scans[52,53]. Both presented models for thoracic auto-segmentation at T4 and at L3 following comparison with manual segmentation of the same slices. Direct comparison of SMM at the thoracic level with that at L3 was not conducted. Both studies suggest 'good' performance from their models for auto-segmentation of muscle from CT images suitable for analysis of large-scale cancer databases. Although these two studies were quite clinically different to those measuring outcomes, they met the selection criteria for this review. Rationale for the use of the thoracic slice T4 as well as L3 was that both had been 'widely used for body composition analysis'[52].

Sarcopenia analysis and cut-off values

Sarcopenia was not the focus of all the studies in the review, and specific sarcopenia cut-off measurements were not provided in these instances. These studies investigated the association between L3 and another slice of choice as an alternative, however, did not determine actual sarcopenia incidence in the populations used[54,56,76]. Where sarcopenia cut-off values were used, there was inconsistency in the values provided. Five studies referenced the sarcopenia cut-off value determined by Wendrich *et al.*[57] of SMI < 43·2 cm^2/m^2 which was found to be predictive of chemotherapy dose-limiting toxicity, however provided no sex-specific values[55,59,61,66,67]. Others used the sex-specific cut-offs applied for CSA at L3 by Martin *et al.*[10] which also provides cut-off values for obese males[60,80,82]. Twelve studies provided their own cut-off values based on mortality or morbidity prediction, or using receiver operating characteristic curves in their population analysis, with or without sex-specific cut-offs, at the alternate vertebral slice levels[51,58,62,63,65,68,70,73–75,78,79]. Most papers provided cut-offs in comparable SMI format, others looked at volume or mass values only. All cut-off values are shown in Table 1, and those studies that provided sex-specific cut-off values are represented in Fig. 2 to graphically demonstrate the variation in cut-offs used.

Alternate vertebral slice results

All studies presented positive results for the use of the particular vertebral slice chosen as an alternative to L3. Few, however, performed direct comparative evaluation to CSA at L3[51,63,70,72,77,81], and none compared the alternate slice of choice with whole-body SMM. Swartz *et al.*[56] were the first to demonstrate a correlation between CSA at L3 and C3 in fifty-two patients with HNC ($r = 0{\cdot}891$, $P < 0{\cdot}001$) and developed a prediction equation for the estimation of skeletal muscle at L3 from C3 values (using the sum of the paravertebral and sternocleidomastoid muscles). This method has been applied in twelve of the studies in this review[55,57,59–62,64–68,80]. Jung *et al.* created differing models for survival prediction using CSA at C3 and provide low SMM cut-offs in mass measures, not SMI[63]. No studies were found that used other cervical vertebral levels.

In the studies that investigated thoracic SMM, Pai *et al.*[51] found a positive correlation between CSA at T2 and L3 ($r = 0{\cdot}63$, $P < 0{\cdot}001$) in 173 HNC patients with full-body scans (20 % of the total study cohort). Van de Kroft *et al.* compared CSA at T4 with L3 and showed significant correlations in patients with liver metastases from colorectal cancer and present their own sarcopenia cut-offs for L3 and T4 ($r^2 = 0{\cdot}60$, $P < 0{\cdot}001$)[81]. Gronberg *et al.* also compared CSA at L3 with T4 and only found a moderate agreement when 401 scans in patients with lung cancer were investigated at both levels, in males and females ($r^2 = 0{\cdot}51$ and $0{\cdot}28$)[77]. Another study used CSA at T4 in patients with lung cancer, and results were analysed separately with authors, suggesting that they be 'interpreted with caution' as validation of measurements at the T4 level was currently being undertaken[82]. Sealy *et al.* also looked at SMI at T4, however in HNC patients, and used a method of pooling the SMI values at L3 and T4 using standard deviations from the mean and presented their own set of sex-specific cut-off values[58].

The vertebral level L1 was used by two groups with L3 comparisons. Sanders *et al.* demonstrated a 'stronger' correlation with muscle CSA at L1 to L3 when compared with pectoralis muscle alone in patients with lung cancer ($r = 0{\cdot}90$, $P < 0{\cdot}001$)[72]. Kim *et al.* also compared muscle area at L1 and the pectoralis muscle to that of the area at L3, and they too demonstrated greater correlation between L1 and L3 than pectoralis muscle alone and L3 ($r = 0{\cdot}851$ *v.* $r = 0{\cdot}447$, $P < 0{\cdot}001$)[70]. This finding was then used to generate estimated sex-specific cut-offs for sarcopenia at the level of L1.

All but one study used baseline CT scans for analysis and did not investigate muscle changes over time in alternate slices. Wieland *et al.* compared scans at two time intervals to assess muscle changes at T4; however, sarcopenia was not a focus of this particular paper, and muscle loss or gain was for the purposes of unrelated investigation[76].

Discussion

This review demonstrates that there is limited work in the area of alternate CT slices for the diagnosis of sarcopenia in patients with cancer and, what does exist, varies widely not only in the choice of slice but also in the appropriate methods of comparison, and the sarcopenia cut-off values used. Overall, the evidence is not

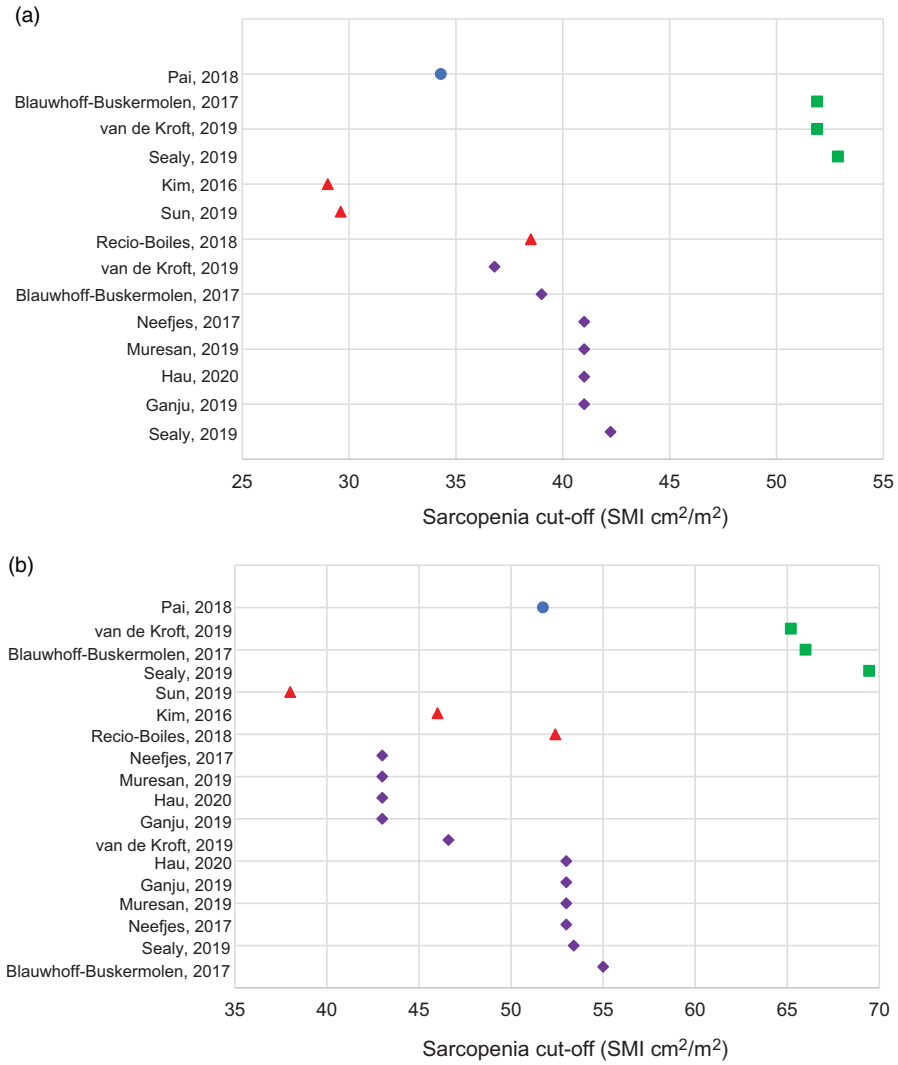

Fig. 2. Sarcopenia cut-offs using alternate vertebral slices in (a) females and (b) males. Legend: ● T2; ■ T4; ▲ L1; ◆ L3

sufficiently robust to offer a single suitable alternative to L3 for the assessment of CT-defined sarcopenia in this population.

The use of the CSA at the L3 level has been widely accepted as the site best associated with total body SMM. Since the pioneering work of Shen *et al.* in 2004, who compared the muscle CSA of lumbar slices in CT scans with whole-body MRI in healthy adults, total body SMM was best correlated with skeletal muscle area in a single abdominal slice about 5 cm above L4–L5 (around the L3 mark). Whole-body SMM was measured using the CSA of forty axial slices and the estimated volume measurements in between each slice[21]. Mourtzakis *et al.* also demonstrated whole-body correlation with L3 in patients with locally advanced or metastatic lung or colorectal cancer, when L3 CSA was compared with whole-body dual-energy X-ray absorptiometry measures[6]. No study in this review attempted to determine the association between CSA at an alternate vertebral slice, with actual total body SMM.

Full-body PET-CT scans are not routinely used in many centres, mainly due to access, costs involved or Oncologist preference for patient diagnostic requirements. A common issue in each study was a lack of rationale for the particular alternate slice chosen by the research team. Random selection of a vertebral level without consideration of the musculature in that area, and their functions, calls into question the validity and applicability of an alternate level for body composition analysis.

The highest alternate vertebral level in this review used was C3. Several papers investigating SMM in HNC have used the method introduced by Swartz *et al.* where muscle measurement at C3 is used to predict CSA at L3[56]. This initial study, however, only investigated a small population of HNC patients (n 52) and compared these with a control group of 'trauma' patients with no specific reason for the selection of C3 as the cervical level of choice. The agreement between muscle values at C3 and L3 was measured using both correlation ($r = 0{\cdot}785$, $P < 0{\cdot}001$) and Bland–Altman methodology[83]. 'Reasonable' agreement and a prediction rule were then established following multivariate analysis and involved the inclusion of a patient's age, sex and weight. Due to the very small cohort in this study, there is serious concern regarding imprecision, as well as results not validated against full-body SMM measurements. Muscles in the C3 area

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include the sternocleidomastoid and paravertebral muscles, and it is unclear if these muscles high in the neck region are susceptible to severe wasting, and even suitable to be associated with whole-body SMM. These muscles are very different to those found at the L3 level, and whether these can even be interconverted is questionable. A further limitation of the use of C3 in the HNC population is tumour invasion in this area, and although the authors addressed this with the suggestion of doubling one side of the sternocleidomastoid muscles, this is not feasible in patients with bilateral neck nodal involvement. Also missing at this level is adequate adipose tissue (specifically visceral), deeming adiposity analysis impossible. Twelve studies have subsequently used the Swartz equation method in patients with HNC with varying sample sizes and results[43,55,57,59–62,65,66,68,80,84].

Thoracic slices ranged from T2 to T10 with no clear indication of which particular slice is the most suitable, and cut-off values for sarcopenia varied with each vertebral level. The use of a thoracic slice makes clinical sense, especially in lung cancer patients, as most will have a chest CT scan at time of diagnosis. The muscles located in the thoracic region are responsible for respiration, which is itself important for function and recovery; therefore, analysis of muscle wasting in this area could be useful. Certain muscles in the L3 region extend to the thoracic level, such as the erector spinae; however, other muscles at the level of T4, for example, include the pectoralis muscle, and these have functions associated with arm and shoulder movements. This may impact on muscle volume in this area specifically in relation to manual activities, potentially more applicable to men, and these functional differences need to be considered when selecting a thoracic slice[77]. There was only one study that used T2. This study compared SMM at T2 with L3 in 173 HNC patients with $r = 0{\cdot}63$ ($P < 0{\cdot}001$)[51]. The r^2 value is low at 0·40, and no information is provided with regard to adjustments for co-variables. This slice was chosen 'along an alignment of both humeral heads and the secondary thoracic vertebra (T2)'; however, no mention is made of the potential issue of skewing of the shoulders and muscles in this area, and the difficulty of identifying a slice with identical muscle visible on both sides. Important also to note is that this study was conducted in a Taiwanese population, and ethnicity should also be taken into consideration. Due to the uncertainty of results presented in this study, the use of T2 may not be suitable, however, warrants further investigation. The Patient-Generated Subjective Global Assessment tool used in the nutritional assessment of cancer patients incorporates the physical examination of the clavicle and scapula regions for signs of muscle wasting[85]; therefore, the T2 area may have some validity for future use in sarcopenia analysis. Four studies investigated lower thoracic slices from T5 to 12, yet all provided skeletal muscle measurements in m^2 or as volume in m^3, not as SMI, making comparisons with other studies difficult[69,74,75,78].

The lumbar L1 slice was used by five studies[69–73] with two assessing the relationship between SMI at L3 and L1, both demonstrating reasonable correlation. The muscles found at L1 are similar to those at L3, so this is likely a suitable alternative which, however, may be too low down in a CT scan for many other cancer sites to be applicable for wider use.

Sarcopenia incidence or diagnosis was the focus of 24/32 (75 %) of the papers in this review, and there was heterogeneity in the SMI values used as the cut-off for diagnosis of sarcopenia. Sex-specific cut-offs associated with mortality have been published by Prado *et al.* and classify sarcopenia as <52·4 cm^2/m^2 for men and <38·5 cm^2/m^2 for women at L3, in obese patients with solid respiratory or gastrointestinal tumours[86]. Martin *et al.* have established sarcopenia cut-off values at L3 for mortality as: <53 cm^2/m^2 in obese males, <43 cm^2/m^2 in non-obese males and <41 cm^2/m^2 in females regardless of obesity status, in 1473 patients with lung or gastrointestinal cancers[10]. The studies in this review have used varied methods for low SMI assessment based on morbidity and mortality outcomes, and this makes comparability difficult, not only with specific vertebral levels but also on a tumour site level. Of concern is the lack of sex-specific threshold values for low SMM. Males generally have a higher proportion of SMM than females, and this is especially so in the upper body[87,88]. Therefore, alternate levels in the thoracic region need to account for this potential difference in muscularity. Van de Kroft *et al.*[81] provided sex-specific cut-off values for both L3 and T4 with quite varied results to those given by Sealy *et al.* at the same levels[58], especially at L3, in colorectal and HNC patients, respectively. In the papers that used C3, only three[43,60,80] gave sex-specific values based on previously defined cut-off values[10]. In the study by Wendrich *et al.*, sex was not shown to be a significant contributing variable when estimating risk of chemotherapy dose-limiting toxicities and low SMM in a HNC population[57]. The concern with this is that four other papers have used this outcome-specific sarcopenia cut-off value to apply to unrelated outcomes such as overall survival and post-operative complications[55,59,61,66]. Separate thresholds should be applied for males and females in any cohort when investigating sarcopenia.

Similarly, there is a difference in SMM with ethnicity. Patients of Asian origin have been shown to have reduced SMM when compared with Europeans[89], and sarcopenia seems to be less prevalent in not only the Asian population but also in African-Americans when compared with Caucasians[90]. This is an important factor to consider, as sarcopenia cut-off values may not be optimal across differing populations and should only be used where applicable. The majority of papers in this review were European in origin; however, all but one study that included an Asian population used their own established cut-off values. Hua *et al.* used cut-off values by Martin *et al.*[10], which includes BMI ranges that are not necessarily suitable for this Chinese population[43].

Cut-off values for sarcopenia diagnosis are yet to be established for all patients with cancer and have not been validated in vertebral landmarks other than L3, yet the papers in this review have established their own values without direct comparison with full-body SMM. Halpenny *et al.* compared six vertebral and regional measurements of SMM, including T10 and L3, in whole-body PET-CT images in 148 patients with advanced melanoma and found that skeletal muscle at T10 was strongly associated with whole body ($r^2 = 0{\cdot}78$); however, this paper was ineligible for inclusion in this review as it did not meet eligibility criteria for patient age (range 15–91 years)[91]. Including younger subjects under the age of 18 years is problematic as there may be changes in muscle mass with growth. T10 is also too low to be included in a head and neck scan, and this level

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may only have applicability to patients who have had a chest CT. Association of muscle mass to vertebral slices other than L3 has yet to be validated against full-body measurements using CT scans in adult cancer patients.

The lack of consensus and varying results not only for slices used but also tumour sites makes comparison challenging. In addition, the lack of validation methods investigating the relationship of muscle CSA at other vertebral slices to whole-body SMM, specifically in cancer, is a concern and brings into question their application in sarcopenia diagnosis. The muscle CSA at the level of L3 is a surrogate of whole-body SMM in healthy adults[21], and determining the association of muscle CSA at a different vertebral level by comparing with measures at L3 is a further surrogate of a surrogate value, increasing the possible degree of error. The myriad of results, many with poor correlations to L3, a lack of adequate consideration of musculature at alternate vertebral levels, and potentially unsuitable cut-offs for sarcopenia assessment, give cause for concern with the research that has been done in this area and should be interpreted with caution.

With emerging evidence of worse outcomes for patients with cancer who are sarcopenic, it is important that all patients are assessed where possible and that a consistent and clinically relevant evidence base be established. Having an accurate and validated alternative to the L3 slice will enable this crucial assessment in not only patients who have had an abdominal CT scan but also all patients with cancer. This review highlights the requisite need for more robust methods of validation in order for suitable alternate slices to be used for sarcopenia assessment and should ideally aim to include comparison of whole-body SMM measurements from the CT scans of patients with cancer.

Conclusion

This systematic review indicates that the current level of evidence is inadequate to provide definitive recommendations for the use of alternate vertebral slices to L3 in CT scans of cancer patients, for the evaluation of SMM and the diagnosis of CT-defined sarcopenia.

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