

Muscle mass and association to quality of life in non-small cell lung cancer patients

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Abstract

Background Cancer wasting is characterized by muscle loss and may contribute to fatigue and poor quality of life (QoL). Our aim was to investigate associations between skeletal muscle index (SMI) and skeletal muscle radiodensity (SMD) and selected QoL outcomes in advanced non-small cell lung cancer (NSCLC) at diagnosis.

Methods Baseline data from patients with stage IIIB/IV NSCLC and performance status 0–2 enrolled in three randomized trials of first-line chemotherapy ($n = 1305$) were analysed. Associations between SMI (cm^2/m^2) and SMD (Hounsfield units) based on computed tomography-images at the third lumbar level and self-reported physical function (PF), role function (RF), global QoL, fatigue, and dyspnoea were investigated by linear regression using flexible non-linear modelling.

Results Complete data were available for 734 patients, mean age 65 years. Mean SMI was $47.7 \text{ cm}^2/\text{m}^2$ in men ($n = 420$) and $39.6 \text{ cm}^2/\text{m}^2$ in women ($n = 314$). Low SMI values were non-linearly associated with low PF and RF (men $P = 0.016/0.020$, women $P = 0.004/0.012$) and with low global QoL ($P = 0.001$) in men. Low SMI was significantly associated with high fatigue ($P = 0.002$) and more pain ($P = 0.015$), in both genders, but not with dyspnoea. All regression analyses showed poorer physical outcomes below an SMI breakpoint of about $42\text{--}45 \text{ cm}^2/\text{m}^2$ for men and $37\text{--}40 \text{ cm}^2/\text{m}^2$ for women. In both genders, poor PF and more dyspnoea were significantly associated with low SMD.

Conclusions Low muscle mass in NSCLC negatively affects the patients' PF, RF, and global QoL, possibly more so in men than in women. However, muscle mass must be below a threshold value before this effect can be detected.

Keywords Non-small cell lung cancer; Quality of life; Body composition; Muscle mass

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Introduction

Lung cancer is the leading cause of cancer death worldwide,¹ most patients (85%) present with non-small cell lung cancer (NSCLC), and the majority is diagnosed with advanced disease.² Despite modern chemotherapy and/or novel agents targeting genetic mutations and rearrangements,^{3,4} the

majority of advanced disease patients does not attain disease control, with 5-year survival rates not exceeding 1–2%.^{3–5} Major treatment goals are therefore to minimize the patients' symptom burden and maintain functioning and quality of life (QoL).^{6,7} Weight loss and malnutrition are identified as contributors to poor QoL in NSCLC,^{8,9} and weight-losing patients with inoperable NSCLC report more

fatigue, pain, and poorer global QoL than their weight-stable counterparts.¹⁰ Because weight loss leads to loss of lean body mass, these findings might be directly linked to muscle waste. Less muscle mass may influence muscle function and lead to loss of strength, reduced pulmonary function, increased disability, and thereby poorer QoL.^{11,12}

Recent studies utilizing computed tomography (CT) images to assess skeletal muscle mass have detected that muscle wasting is a prominent feature in NSCLC even with normal or high body mass index (BMI).^{13,14} Furthermore, muscle wasting and low muscle mass have been linked to poorer survival and increased risk of treatment toxicity in various cancer diagnoses, including NSCLC.^{15–19} In advanced NSCLC, a recent study from our group showed that low muscle mass was a significant predictor for chemotherapy-induced haematological toxicity.²⁰

Increased fat content within the skeletal muscle may affect the muscle quality and influence both muscle strength and function.^{21,22} The fat content in muscle is reflected by the skeletal muscle radiation attenuation also known as skeletal muscle radiodensity (SMD).²³ The SMD of human muscle can be obtained by CT scans and is measured as mean Hounsfield units (HU) of the cross-sectional muscle area.^{21,23}

Recent studies on cancer patients have indicated that reduced SMD is associated with poorer survival,^{14,24} and former results from the present population suggested that SMD may be a more important prognostic factor than skeletal muscle index (SMI) in advanced NSCLC.²⁵ Despite the emerging evidence on the negative impact of low muscle mass, less attention has been paid to the importance of muscle wasting for muscle function in cancer. To our knowledge, the direct associations between CT-based measures of muscle mass and patient-reported outcomes reflecting functional status have not formerly been reported in NSCLC. This paper aims to investigate these associations at the time of diagnosis, and we hypothesize that pronounced low muscle mass and low SMD affect patient-reported functional status, global QoL, dyspnoea, and fatigue negatively and are associated with loss of appetite.

Material and methods

Patients and assessments

The study is based on three subsequent randomized controlled trials (RCTs), conducted between 2003 and 2009, comparing different first-line chemotherapy regimens in advanced NSCLC.^{26–28} Overall survival, QoL, and toxicity were the main endpoints, and the main inclusion criteria were similar: chemo-naïve patients, age ≥ 18 years, stage IIIB/IV, and performance status 0–2. Median survival was not significantly different between trial arms, in any of the RCTs and ranged between 6.3 and 7.3 months in all trials. For

the present study, only baseline data acquired before start of treatment were used. Complete data on relevant muscle measures and appetite loss were required for inclusion in the present study.

Baseline data comprised demographics, disease stage, histology, performance status, height, weight, and QoL. QoL was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (QLQ)-Core 30²⁹ and the lung cancer-specific module QLQ-Lung Cancer 13.³⁰ The QoL baseline assessments were performed at inclusion, before start of chemotherapy. For the purpose of the present study, we used the two functional scales: physical function (PF) with five items and role function (RF) with two items, the global QoL scale (two items), the fatigue scale (three items), and one single item on appetite loss. From QLQ-Lung Cancer 13, the three-item dyspnoea scale was used as it gives a wider picture of respiratory problems than the single dyspnoea item of the QLQ-Core 30. All items are scored on a 4-point ordinal scale, except the two items of the global QoL scale that are scored on a 7-point scale. Before statistical analyses, the scale scores were linearly transformed to a 0–100 scale as recommended in the European Organization for Research and Treatment of Cancer scoring manual.³¹ Higher scores on the functional and global QoL scales represent better functioning/QoL, whereas higher scores on fatigue, dyspnoea, and appetite loss indicate more symptoms. Differences of 10 points or more are usually regarded as clinically significant³² and as such perceptible to patients.

A CT scan of the thorax/upper abdomen was performed within 4 weeks before the baseline QoL registrations and start of chemotherapy. The CT scans were analysed using Slice-O-Matic software (v.4.3 Tomovision, Montreal Canada) by three observers blinded for patient data. The total cross-sectional areas of skeletal muscle and adipose tissue (cm²) were quantified from images at the third lumbar (L3) level, which is strongly correlated to the corresponding whole body tissue masses.³³ For tissue demarcation, pre-established thresholds of HU in the range of –29 to +150 HU for muscle tissue, –150 to –50 HU for visceral adipose tissue, and –190 to –30 HU for subcutaneous and intramuscular adipose tissue were used.³⁴ As a measure of skeletal muscle mass, the total cross-sectional skeletal muscle area (cm²) was normalized for stature by dividing by squared height (m²) and expressed as SMI (cm²/m²). SMD was measured as the mean HU of the entire cross-sectional muscle area at L3. BMI was calculated from the weight and height (kg/m²).

Statistics

Data from all RCTs were analysed jointly. Because of the descriptive context, we report mean values and range.

Independent sample *t*-tests were used to investigate differences between groups on continuous variables. For categorical variables, Pearson's chi-squared tests were applied.

Because of gender differences in muscle mass, the association to baseline QoL parameters were analysed separately for men and women. SMI was defined as the explanatory variable for muscle mass. The association between SMI and the defined outcomes was investigated by linear regression using flexible non-linear modelling with restricted cubic splines^{35,36} and likewise the association between SMD and the defined outcomes.

Using restricted cubic splines, no assumption of the specific form of the relationship is needed. It means that the independent variable is transformed into segments, defined by knots allowing for smoothly fitted curves for each segment. The procedure includes formal tests of linearity in the relationships and allows for flexible descriptions of non-linearity. The increase of degrees of freedom is moderate. Modelling using restricted cubic splines is available in commonly used regression models including linear, logistic, and Cox regression. The main analyses were unadjusted, and in addition, sensitivity to adjustment for age and stage was investigated as these variables were judged to be the most relevant, possible confounding factors.

Being assessed by a single item, the scores for appetite loss had only four possible response categories. Thus, the linear regression method applied for the other QoL parameters was not suitable to investigate the association between the muscle measures and this symptom. Hence, to explore a possible relationship, mean SMI and mean SMD were compared between patients reporting no appetite loss and those who indicated having either 'a little', 'quite a bit', or 'very much'.

All *P*-values were two-sided, and values <0.05 defined statistical significance. Analyses were performed using R (The R foundation for statistical computing, Vienna, Austria) with the R package rms for flexible non-linear modelling and with IBM SPSS v.18 (Armonk, NY, USA).

Ethics

The study was performed according to the Helsinki declaration and approved by the Regional Committee for Medical Research Ethics South-East.

Results

Study population and general characteristics

A total of 1305 patients were included in the RCTs. Baseline CT scans were collected from 1119 patients (86%). Because

of lack of images at the L3-level or poor image quality, only 771 patients were available for quantification of muscle mass. Another 37 patients were excluded because of missing data on height, appetite loss, or SMD, leaving 734 patients for the present analyses. Most missing CT scans were from the earliest study (RCT 1, *n* = 174) as they were stored on film and not analysable. The final sample of the present study included 420 men (57%) and 314 women (43%) with a mean age of 66.5 and 63.7 years, respectively. The included patients comprised a lower proportion of stage IIIB and a higher proportion of performance status one than the excluded. Otherwise, the two cohorts were comparable. The distribution of chemotherapy regimens and baseline characteristics were also comparable between genders. A full description of the selection of patients, the study population, and the excluded patients has been presented earlier.²⁵

Body composition

The mean BMI of both genders was within the normal range (Table 1). Overall, a BMI below 20 (underweight) was found in 18% of our patients, while 5% presented with a BMI \geq 30 (obesity). The muscle measures varied largely, but the variables did not deviate substantially from normal distributions. The mean skeletal muscle area was 148.8 cm² (SD 23.8) in men and 107.3 cm² (SD 16.3) in women (*P* < 0.001), and the SMI was 47.7 cm²/m² (SD 7.6, range 27.9–74.5) and 39.6 cm²/m² (SD 5.7, range 26.1–54.6) (*P* < 0.001) in men and women, respectively. The mean SMD was 37.4 HU (SD 8.1, range 15.8–60.4) in men and 37.0 HU (SD 9.0, range 14.8–62.3) in women (ns). A detailed description of how SMI and SMD differed according to stage of disease, age, and performance status for each gender separately is to be found in a supplementary table (Supplementary Information, Table S1).

Quality of life and association to muscle measurements

The patients' baseline QoL data are presented in Table 2. There were statistically significant differences between men and women for global QoL and fatigue. None of these differences exceeded 10 points, and they were all in favour of better scores among men. Appetite loss was reported by 224 (53.3%) men and 178 (56.7%) women.

Diagrams illustrating the associations between SMI and PF, RF and global QoL including 95% confidence intervals are displayed in Figure 1. For both genders, the regression analyses showed significant non-linear associations between SMI and PF (men: *P* = 0.016, women: *P* = 0.004), and between SMI and RF (men: *P* = 0.020, women: *P* = 0.012).

Table 1 Baseline patient characteristics

	Patients					
	All <i>n</i> = 734 (100%)		Men <i>n</i> = 420 (57.2%)		Women <i>n</i> = 314 (42.8%)	
Age, years, mean (SD)	65.4 (9.4)		66.5 (8.8)		63.7 (9.8)	
Follow-up, months, median (SD)	7.2 (7.5)		6.4 (7.1)		8.0 (8.0)	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Age ≥ 75	132	18.0	80	19.0	52	16.6
Histology						
Squamous	171	23.3	122	29.0	49	15.6
Adenocarcinoma	388	52.9	197	46.9	191	60.8
Large cell	46	6.3	23	5.5	23	7.3
Other	129	17.6	78	18.6	51	16.2
Disease stage						
Stage IIIB	152	20.7	83	19.8	69	22.0
Stage IV	582	79.3	337	80.2	245	78.0
Performance status (PS)						
PS 0	165	22.5	98	23.3	67	21.3
PS 1	404	55.0	226	53.8	178	56.7
PS 2	165	22.5	96	22.9	69	22.0
Study						
RCT 1	153	20.8	93	22.1	60	19.1
RCT 2	266	36.2	153	36.4	113	36.0
RCT 3	315	42.9	174	41.4	141	44.9
BMI, kg/m ² , mean (SD)	23.4 (3.9)		23.5 (3.6)		23.4 (4.3)	

BMI, body mass index; RCT, randomized controlled trial; SD, standard deviation.

Table 2 Baseline scores on the quality of life scales hypothesized to be affected by muscle wasting and low muscle radiation attenuation, all patients and according to gender

	Quality of life scores				
	All patients		Men	Women	<i>P</i>
	Mean	SD	Mean	Mean	
QLQ-C30					
Physical function	64.3	+/-24.0	65.6	62.4	0.080
Role function	51.5	+/-35.0	51.5	51.4	0.950
Global QoL	52.7	+/-24.6	55.0	49.7	0.004
Fatigue	47.7	+/-27.3	46.0	50.0	0.047
Appetite loss	33.4	+/-36.3	32.1	35.2	0.240
LC-13					
Dyspnoea	38.7	+/-26.3	38.7	38.6	0.979

QoL, quality of life; SD, standard deviation; QLQ-C30, Quality of Life Questionnaire-Core 30; LC-13, Lung Cancer-13.

For global QoL, there was a significant association to SMI only for men ($P = 0.001$). Below a breakpoint at about 42–45 cm²/m² for men and 37–40 cm²/m² for women, the patients' scores deteriorated with decreasing SMI. SMI values above this breakpoint were associated with relatively stable PF and RF scores. Fatigue (Figure 2) varied significantly with SMI but only in the male population ($P = 0.002$). The associations between SMI and dyspnoea were insignificant for both genders ($P \geq 0.493$). All regression curves had breakpoints corresponding to those observed for PF and RF, below which the reported symptom level rapidly increased with decreasing SMI. Adjustment for age and stage of disease did not substantially change the

slopes of any of the regression curves, and the breakpoints generally corresponded to those found in the unadjusted analyses. Furthermore, the associations that were significant in the unadjusted analyses were also significant in adjusted analyses.

Men who reported appetite loss had a significantly lower SMI (46.6 cm²/m²) compared with those who did not (48.8 cm²/m²) ($P = 0.003$). For women, there was a trend in the same direction. SMI was 39.1 cm²/m² and 40.3 cm²/m² among women with and without appetite loss, respectively ($P = 0.058$).

For both genders, the regression analyses showed significant associations between SMD and PF (men: $P = 0.015$, women: $P < 0.001$) and between SMD and dyspnoea (men: $P = 0.002$, women: $P = 0.01$). These associations were not significantly non-linear, but a trend of patterns with a breakpoint as for the associations between SMI and the QoL variables was seen. This breakpoint was similar for men and women, around 32–34 HU. Adjusted for age and stage of disease, the slopes and the corresponding breakpoints remained visually similar. SMD and dyspnoea were also still significantly associated (men: $P = 0.005$, women $P = 0.029$), whereas the association between SMD and PF was significant for women only (men: $P = 0.053$, women: $P = 0.002$). In the unadjusted analysis, SMD was also significantly associated to fatigue among men ($P = 0.041$), and the association was significantly non-linear ($P = 0.028$). With adjustment for age and stage of disease, the association was no longer significant ($P = 0.066$), but the association was significantly non-linear ($P = 0.035$).

Figure 1 The relation between the third lumbar (L3) skeletal muscle index (cm^2/m^2) and physical function, role function, and global quality of life (QoL).

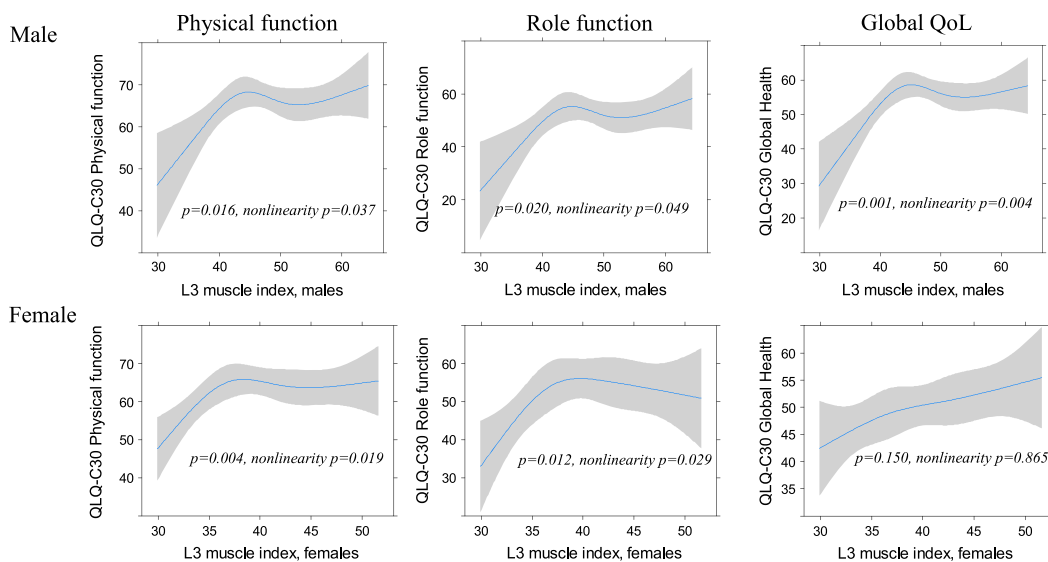
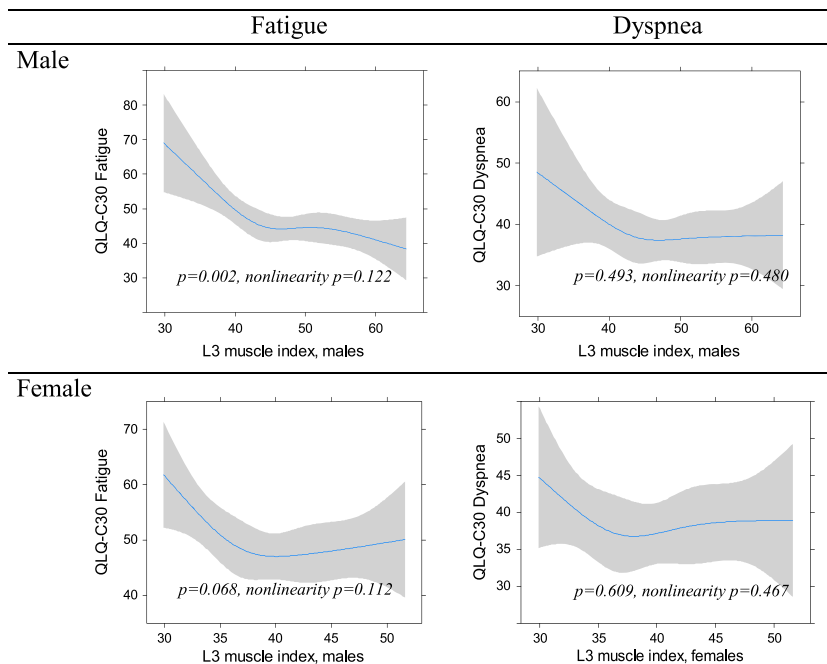


Figure 2 The relation between the third lumbar (L3) skeletal muscle index (cm^2/m^2) and fatigue and dyspnoea.



Discussion

This study provides new findings regarding the relationship between low muscle mass in cancer and QoL. We found that low muscle mass (expressed as SMI) was significantly non-linearly associated with self-reported functional

deterioration in advanced NSCLC patients of both genders also when adjusted for age and stage of disease. In our male cohort, low SMI was also significantly associated with poor global QoL and high intensity of fatigue but did not show significant non-linearity. SMD, which gives an indication of fat infiltration in muscle that may affect both muscle strength

and function,^{23,21} was significantly associated with PF and dyspnoea for both genders. However, adjusted analyses demonstrated no significant association with PF in the male cohort but a significant association to fatigue.

In the present study, muscle assessments were performed with a well-established radiological method,¹⁴ and we used widely accepted attenuation ranges for the demarcation of muscle area (−29 to +150 HU).²³ To assess QoL, validated and widely used questionnaires were applied, and the results are based on data from a large, disease-specific, relatively homogeneous cohort with advanced NSCLC. All patients were enrolled in nationwide RCTs according to similar criteria, and all assessments were obtained before start of treatment. A primary study limitation was that muscle measures could not be obtained for a substantial proportion of the targeted population. The exclusion of patients from the original cohorts was, however, mainly due to technicalities, and we therefore believe that our findings are representative for NSCLC patients eligible for first-line palliative chemotherapy. Because the RCTs were not designed for the present purpose and the cross-sectional design, data on weight loss and comorbidity were not available for all patients, and we do not know if the muscle loss was recent or not. Thus, we cannot rule out that the influence of low muscle mass on QoL may differ according to aetiology and rate of development.

To the best of our knowledge, only one study has performed analyses that are somewhat similar to ours in a cancer population. In this study of a variety of advanced cancers, there were no statistically significant associations between SMI and dyspnoea, fatigue, or appetite loss.³⁷ However, the results from our cohort visually indicated that muscular mass had to fall below a certain value before a negative impact on physical function and the other QoL scores could be detected. A corresponding trend was found for SMD. Declining physical function and performance has traditionally been attributed to decreased muscle mass, but our results indicate that modest reductions in skeletal muscle mass, as measured by SMI, may not affect function. This is in line with emerging evidence from non-cancer populations showing similar non-linear relationships between muscle mass and functional status. In elderly patients, it is demonstrated that muscle waste has to progress to a point below 30% of the mean of young adults before decrease in functional abilities are observed.^{38,21} It has also been shown that physical performance is not solely dependent on muscle mass but also muscle strength.^{22,39} Muscle strength, in turn, is reported to be independently associated with muscle radiodensity,⁴⁰ and in accordance with our findings, greater muscular fat infiltration is found to increase the risk of immobility in older men and women.⁴¹

Former studies in cancer patients have mainly linked low muscle mass to increased morbidity and mortality.^{15,16,19,34,38}

Our study indicates that skeletal muscle mass below formerly reported threshold values (male, SMI < 43 cm²/m² when BMI < 25 and female, SMI < 41 cm²/m² for all BMI groups)¹⁴ is also associated with low physical function and probably affects global QoL. Similar findings have been found in connection with chronic heart failure.³⁹ As low SMI appears to be a benchmark for higher morbidity and mortality, low physical functioning and QoL, maintaining patients above these threshold values could potentially be associated with important clinical benefit. Treatments that will enhance muscle mass or at least slow its depletion, improve strength, and enhance the capacity for independent functioning are therefore needed. Nutritional supplements that are able to generate an anabolic response⁴⁰ and drugs, for example Anamorelin,⁴¹ have demonstrated effects in the prevention and treatment of muscle loss in NSCLC. In future studies, it would be of interest to further investigate these effects as well as combine them with physical activity. It has already been demonstrated that physical activity may enhance muscle mass or at least slow its depletion, improve strength, and enhance the capacity for independent functioning in advanced stages of cancer.⁴²

Our findings indicate a difference between men and women regarding the impact of muscular depletion on global QoL and fatigue. An explanation may be that both global QoL and fatigue are measures that are likely to be influenced by several factors other than muscular depletion and functional ability.

In contrast to our hypothesis, we did not detect a significant association between SMI and dyspnoea. Accordingly, no beneficial effects of muscle mass on lung function have been demonstrated in studies of chronic pulmonary disease,^{43,44} indicating that in lung diseases, the disease itself may be more important for the respiratory function than skeletal muscle waste. Still, the regression curves for SMI and dyspnoea showed a similar pattern as the curves for physical and RF, possibly indicating a point below which muscle waste affects dyspnoea. The significant association between SMD and dyspnoea may support this assumption. As documented in geriatric patients, elevated fat content in the skeletal muscle may affect muscle strength more than plain muscle waste.^{22,21}

Loss of appetite is one of the most prevalent symptoms in advanced cancer and considered an important component of cancer cachexia.⁴⁵ Both the female and male patients in this study reported average scores above 30 on appetite loss, which is significantly higher than scores seen in the general population.⁴⁶ We found significant associations between SMI and poor appetite, which may indicate that reduced food intake may have affected the ability to preserve muscle mass.⁴⁵ Normally, loss of weight includes muscle loss and evolves from decreased food intake. However, many patients with NSCLC lose more weight than expected from an estimated energy deficit.^{47–49} This may indicate the presence

of cancer cachexia where loss of skeletal muscle mass is considered to be driven by metabolic alterations.⁴⁹ Whether low muscle mass in this study was related to undernutrition, cancer cachexia, comorbid conditions, or a combination of these cannot be determined from the available data. Thus, the impact of these factors should be further investigated in larger prospective studies.

In conclusion, pronounced low skeletal muscle mass in patients with NSCLC seemed to affect functional status and global health negatively. Our data indicate that these effects occur when muscle mass falls below a breakpoint quite similar to the threshold values formerly found to be associated with increased mortality.^{34,38} Our findings show the importance of connecting CT derived body composition to meaningful patient-centred outcomes. Further studies are warranted both to confirm these findings and to determine the importance of weight loss and cachexia for QoL in cancer patients.

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The authors certify that they comply with the ethical guidelines for authorship and publishing of the *Journal of Cachexia, Sarcopenia and Muscle*.⁵⁰

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Online supplementary material

Additional Supporting Information may be found online in the supporting information tab for this article.

Table S1. Body composition according to stage, age and physical performance in relation to gender.

Conflict of interest

There are no conflicts of interests connected to the manuscript.

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