

## ORIGINAL ARTICLE

# Single-institution study of correlations between skeletal muscle mass, its density, and clinical outcomes in non-small cell lung cancer patients treated with first-line chemotherapy

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## Keywords

BMI; lung cancer; muscle density; NSCLC; sarcopenia.

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## Abstract

**Background:** Sarcopenia and muscle tissue degradation are hallmarks of the majority of chronic diseases, including non-small cell lung cancer (NSCLC). A computed tomography scan could be an easy modality to estimate the skeletal muscle mass through cross-sectional image analysis at the level of the third lumbar vertebra.

**Methods:** Baseline skeletal muscle mass (SMM) was evaluated through the skeletal muscle index (SMI), together with skeletal muscle radiodensity (SMD), in NSCLC patients undergoing first-line chemotherapy to evaluate correlations with safety and clinical outcomes. When SMIs at different time points were available, further comparison was made between patients with worse and improved SMIs.

**Results:** Among 81 stage IV NSCLC patients, 28 had low SMM and 23 had low SMD. There were no significant differences in univariate analysis of progression-free survival (PFS) between patients with baseline low and non-low SMM ( $P = 0.06388$ ) or between patients with low and non-low SMD ( $P = 0.9126$ ). Baseline low SMM, however, proved a significant predictor of shorter PFS in multivariate analysis (hazard ratio 0.54, 95% confidence interval 0.31–0.93;  $P = 0.0278$ ), but not low SMD. There were no differences in overall survival (OS) between patients with baseline low and non-low SMM or low and non-low SMD. No differences in PFS and OS between evaluable patients with worse or improved SMI were found. A significant difference in hematological toxicities between patients with baseline low and non-low SMM ( $P = 0.0358$ ) was observed.

**Conclusions:** Low SMM is predictive of shorter PFS, while consecutive changes in muscular mass do not seem to be a predictor of PFS or OS. The role of muscle radiodensity remains a matter of debate.

## Introduction

Nowadays it is becoming increasingly clear that nutritional status and a “healthy” body composition play a key role for cancer patients,<sup>1</sup> as these factors can affect quality of life, survival, and treatment tolerance.

Sarcopenia is a condition involving the loss of muscle mass, with decreased muscle power, and is one of the best-known nutritional parameters. In cancer patients, skeletal muscle mass (SMM) is often used as surrogate of sarcopenia, and together with the radiodensity of skeletal muscle tissue, has been investigated as a prognostic and predictive

parameter.<sup>2</sup> These can be assessed by computed tomography (CT) scan, which is essential for the proper staging of solid tumors and can be used to investigate the correlation of these parameters with other outcome variables on a retrospective basis. Skeletal muscle mass is usually quantified through cross-sectional analysis at the level of the third lumbar vertebra (L3) as a standard landmark, while skeletal muscle tissue quality is estimated using the mean radiodensity of that same muscle mass.<sup>2</sup>

Although there is growing interest regarding the deleterious effects of sarcopenia on tolerance to chemotherapy and prognosis, data specifically related to lung cancer patients is lacking. The prevalence of sarcopenia is reported to occur in lung cancer patients at a range of 46–79%<sup>3–10</sup> and is likely dependent on age, smoking habits,<sup>9</sup> duration of the disease, different body mass index (BMI)<sup>11</sup> and gender.<sup>4,8,10,12</sup> To our knowledge only a few papers have investigated the clinical consequences of sarcopenia in patients with lung cancer but the results are have not been homogeneous.<sup>5–8,13,14</sup>

Regarding the prognostic value of skeletal muscle radiodensity (SMD), only one study by Sjoblom *et al.* showed that SMD had a statistically significant negative prognostic value in non-small cell lung cancer (NSCLC) patients,<sup>15</sup> a finding also reported in other types of tumors.<sup>16–25</sup>

The purpose of this study was to analyze whether sarcopenia and SMD have an impact on clinical outcomes (overall and progression-free survival), and secondarily on toxicity, in NSCLC patients without actionable biomarkers treated with first-line chemotherapy.

## Methods

### Study design

This study is a retrospective observational analysis of 81 stage IV NSCLC patients without common actionable biomarkers (*EGFR* mutations, *ALK* translocations or PD-L1 expression  $\geq 50\%$ ), treated with first-line chemotherapy in clinical practice. Chemotherapy regimens (platinum-based doublets or single agent chemotherapy) were chosen in keeping with patient fitness, defined according to age, Eastern Cooperative Oncology Group performance status (ECOG PS), and comorbidities. It is now clear that sarcopenia is a condition characterized by a loss of muscle function as well as mass<sup>26</sup> as this is a retrospective study, we considered a definition of low skeletal muscle mass (SMM) as a surrogate of sarcopenia status more appropriate.

The procedures followed in this study were in accordance with the precepts of Good Clinical Practice and the Declaration of Helsinki. The study was conducted following the rules of the local bioethical committee competent

on human experimentation (*Comitato etico per le province di L'Aquila e Teramo*).

We evaluated the correlations between low baseline SMM, SMD, and median progression free survival (PFS) and overall survival (OS). Similarly, the correlation between baseline sarcopenia, SMD, and cumulative hematological and non-hematological toxicities was evaluated. Sarcopenia was evaluated through the skeletal muscle index (SMI), while the quality of the muscle mass was evaluated through the SMD,<sup>27</sup> expressed as the mean Hounsfield unit (HU) of the measured muscle area. We assessed the SMI in 58 patients at a second time point 4–6 months after the first measurement. In this group we also performed a comparison between patients with low and non-low SMIs. Comorbidities were evaluated using the Cumulative Index Rating Scale (CIRS).<sup>28</sup>

The correlation tests were performed between clinical outcomes and the following patient features: baseline SMM (low vs. non-low), baseline SMD (low vs. non-low), BMI (underweight vs. not underweight), age ( $< 70$  vs.  $\geq 70$  years old), gender (male vs. female), ECOG PS (0–1 vs.  $\geq 2$ ), CIRS stage (primary/intermediate vs. secondary), histological subtype (squamous cell carcinomas vs. non-squamous cell carcinomas), number of metastatic sites ( $\leq 2$  vs.  $> 2$ ), and regimen (platinum-based doublet vs. single agent chemotherapy).

To verify the relationships between SMI, SMD, and BMI, correlation analyses and linear regression were performed. The Pearson correlation coefficients ( $r$ ) were interpreted as follows:  $\leq 0.19$ , very weak correlation; 0.20–0.39, weak correlation; 0.40–0.69, moderate correlation; 0.70–0.89, strong correlation; and 0.90–1.00, very strong correlation.<sup>29</sup> The coefficients of determination  $R^2$  were interpreted as follows:  $> 0.67$  substantial,  $> 0.33$  moderate, and  $> 0.19$  weak.<sup>30</sup>

Responses were evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST, version 1.0 before 2010 and version 1.1 subsequently).<sup>31,32</sup> Chi-square and Fisher's exact tests were used to correlate cumulative toxicity with baseline sarcopenia and SMD, using the appropriate test according to the sample size in contingency tables for each comparison. Logistic regression was used in multivariate analysis to confirm factors that were significant in univariate toxicity analysis.<sup>33</sup> Median PFS and OS were evaluated using the Kaplan–Meier method. The median period of follow-up was calculated according to the reverse Kaplan–Meier method. A Cox proportional hazards model was used to evaluate predictor variables in univariate and multivariate analyses for median PFS and OS. Only factors significant in univariate analysis were used in multivariate analysis, with the exceptions of sarcopenia and SMD because of the possible influence of large within group variation and the possible interactions.<sup>34</sup>

The data cut-off was April 2018. All statistical analyses were performed using MedCalc Statistical Software version 18.2.1 (MedCalc Software bvba, Ostend, Belgium; <http://www.medcalc.org>; 2018).

### Patient eligibility

This study evaluated stage IV NSCLC patients without actionable biomarkers treated with first-line chemotherapy at our institute. Patients were eligible if they had a histologically confirmed diagnosis of measurable NSCLC (both squamous and non-squamous cell carcinomas) and available images (CT-scan or positron emission tomography-CT) for the baseline assessment (CT or positron emission tomography-CT). All patients provided written informed consent to the proposed treatment options.

### Anthropometric measurements and image analysis

Weight and height were obtained from patient records at diagnosis and during treatment. BMI was calculated using the formula of  $\text{weight/height}^2$  ( $\text{kg/m}^2$ ) and World Health Organization categories were used: underweight,  $\text{BMI} < 18.5$ ; normal,  $18.5 \leq \text{BMI} \leq 24.9$ ; overweight,  $25 \leq \text{BMI} \leq 29.9$ ; and obese,  $\text{BMI} \geq 30$ . Muscle mass was measured in the CT images. Axial images of the abdomen were analyzed by a single, trained observer blinded to patient outcomes, who reviewed all images in a workstation using OSIRIX-Lite software V5.0 (Pixmeo, Sarl, Switzerland). L3, with both transverse processes visible, was chosen as the standard landmark. Skeletal muscle was quantified based on HU thresholds ( $-29$  to  $+150$ ). SMM was evaluated using the SMI ( $\text{cm}^2/\text{m}^2$ ) for each patient. SMI was calculated dividing the total cross-sectional skeletal muscle area (TMA -  $\text{cm}^2$ ) at L3 level, by squared height, because TMA is linearly related to whole body muscle mass. TMA was computed for each patient with semi-automated specific tissue demarcation of the muscles in the L3 region (psoas, paraspinal, and abdominal wall muscles, excluding visceral organs). If other structures apart from those constituting TMA were automatically marked, they were eliminated by manual correction. To define low SMM, we used gender-specific, BMI-incorporated cutoff values of SMI ( $< 43 \text{ cm}^2/\text{m}^2$  for men with  $\text{BMI} \leq 25$ ,  $< 53 \text{ cm}^2/\text{m}^2$  for men with  $\text{BMI} \geq 25$ , and  $\leq 41 \text{ cm}^2/\text{m}^2$  for women).<sup>13</sup> SMD was assessed as the mean radiodensity (HU) of the entire cross sectional muscle area at L3. To define low SMD, we used gender-specific cutoffs previously reported for SMD in NSCLC patients ( $< 28.0$  HU for men and  $< 23.8$  HU for women).<sup>15</sup> In 58 out of 81 patients (71.6%), imaging was available at a second time point, and was evaluated to perform comparative analysis between patients with worse and improved SMIs.

## Results

### Patient features

The data of 81 stage IV NSCLC patients between November 2006 and October 2017 were analyzed: 64 (79.1%) were treated with platinum-based doublets and 17 (20.9%) with single agent chemotherapy. The combination agents used were: pemetrexed in 33 patients (51.6%), gemcitabine in 18 (28.2%), paclitaxel/bevacizumab in 7 (10.9%), single agent paclitaxel in 2 (3.1%), etoposide in 2 (3.1%), and vinorelbine in 2 patients (3.1%). Single agent chemotherapy regimens were: carboplatin in 8 patients (47.1%), docetaxel in 6 (35.3%), and vinorelbine in 3 (17.6%). Twenty-eight (34.6%) patients had low baseline SMM; interestingly, only 4 (4.9%) patients were underweight, while 36 (44.4%) were overweight or obese. Twenty-three (28.4%) patients had low baseline SMD. Among 58 evaluable patients, 34 (58.6%) had low SMM at the second time point evaluation. The SMM worsened in 40 (70%) patients and improved in 17 (30%). The clinical features of patients are summarized in Table 1.

There were very weak correlations between baseline SMI and SMD ( $r = 0.08$ ,  $P = 0.4740$ , 95% CI  $-0.14$ – $0.29$ ) and baseline BMI and SMD ( $r = -0.11$ ,  $P = 0.2935$ , 95% CI  $-0.33$ – $0.11$ ). There was a moderate correlation between baseline BMI and SMI ( $r = 0.57$ ,  $P < 0.0001$ , 95% CI  $0.41$ – $0.70$ ). A significant regression equation was found ( $F [1,79] = 38.977$ ;  $P < 0.0001$ ), with a “moderate” determination coefficient ( $R^2 = 0.3304$ ).

### Clinical outcome analysis

After a median follow-up of 34.8 months, median PFS was 5.7 months (95% CI 4.7–7.1) with 75 progression events, and median OS was 11.9 months (95% CI 9.6–13.4), with 66 death events resulting from progressive disease. Table 2 summarizes the univariate and multivariate analyses of PFS. There were no statistically significant differences in univariate analysis of PFS between patients with baseline low and non-low SMM or SMD. Similarly, there were no statistically significant differences in univariate analysis of PFS between underweight patients and those in all other weight categories, or between evaluable patients with a worse SMI compared to those with an improved SMI. Despite these results, low baseline SMM was confirmed as a significant predictive factor for shorter PFS in multivariate analysis (HR 0.54, 95% CI 0.31–0.93;  $P = 0.0278$ ) (Fig 1), but not low baseline SMD.

Table 3 summarizes the univariate and multivariate analyses of OS. There were no statistically significant differences in univariate analysis of OS between patients with baseline low and non-low SMM or SMD. Similarly, there

**Table 1** Patient features

	Overall 81 (100)
Patients, N (%)	81 (100)
Age (years)	
Range	39–90
Median	68
Gender	
Male	53 (65.4)
Female	28 (34.6)
Age (< 70 ≥)	
Non elderly	44 (54.3)
Elderly	37 (45.7)
ECOG PS	
0–1	56 (69.1)
≥ 2	25 (30.9)
CIRS	
Primary/intermediate	45 (55.6)
Secondary	36 (44.4)
Smoking history	
Yes	60 (74.1)
No	21 (25.9)
Histological subtype	
Squamous cell carcinoma	19 (23.5)
Non-squamous cell carcinoma	62 (76.5)
Sites of metastasis	
≤ 2	44 (54.3)
≥ 3	37 (45.7)
CNS metastasis	13 (16.1)
Regimen	
Platinum-based doublet	64 (79.1)
Single agent chemotherapy	17 (20.9)
Weight (kg)	
Median (range)	68 (40–120)
BMI (kg/m <sup>2</sup> )	
Median (range)	24.2 (17.3–45.2)
Underweight (BMI ≤ 18.5), N (%)	4 (4.9)
Normal weight (BMI 18.5 < BMI ≤ 24.9), N (%)	41 (50.6)
Overweight (25 < BMI ≤ 29.9), N (%)	23 (28.4)
Obese (BMI ≥ 30), N (%)	13 (16.1)
Lumbar skeletal muscle area (cm <sup>2</sup> )	
Median	126.1
(range)	(78.9–228.3)
Lumbar skeletal muscle index (cm <sup>2</sup> /m <sup>2</sup> )	
Median	45.7
(range)	(29–83.9)
Patients with SMM	
Time 0	28 (34.6)
Second time point (among evaluable patients)	34 (*58.6)
SMD (HU)	
Median	35.5
(range)	(7.4–60.1)
Patients with low SMD (Time 0)	23 (28.4)

BMI, body mass index; CIRS, Cumulative Index Rating Scale; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance score; SMD, skeletal muscle radiodensity; SMM, skeletal muscle mass.

were no statistically significant differences in univariate analysis of OS between underweight patients and those in all other weight categories, or between evaluable patients with a worse SMI compared to those with an improved SMI. Low baseline SMM and SMD were not confirmed in multivariate analysis of OS.

### Toxicity analysis

Overall, 67 patients (82.7%) were evaluable for toxicity analysis; 13 patients were treated with prophylactic colony stimulating factors. Table 4 summarizes the incidence of toxicities in the overall population; no patients died as a result of adverse events. There were no statistically significant differences between patients with baseline low and non-low SMD: hematological toxicities of any grade ( $P = 0.3543$ ), non-hematological toxicities of any grade ( $P = 1.0000$ ), G3/G4 hematological toxicities ( $P = 0.0532$ ), and G3/G4 non-hematological toxicities ( $P = 0.3136$ ). There were no statistically significant differences between patients with baseline low and non-low SMM regarding non-hematological toxicities of any grade ( $P = 0.1513$ ), G3/G4 hematological toxicities ( $P = 0.3903$ ), and G3/G4 non-hematological toxicities ( $P = 0.2618$ ). The only statistically significant difference was found in hematological toxicities of any grade between patients with baseline low and non-low SMM ( $P = 0.0358$ ). The correlations between the other factors and hematological toxicities of any grade were: CIRS ( $P = 0.5953$ ), regimen ( $P = 1.0000$ ), ECOG PS ( $P = 0.7597$ ), and age ( $P = 0.0409$ ). Both low baseline SMM ( $P = 0.0278$ ) and age ≥ 70 years ( $P = 0.0221$ ) were confirmed as significant predictors for a greater incidence of hematological toxicities of any grade.

### Discussion

Since 1980, weight loss, low lean body mass, and BMI have been well known factors associated with poor prognosis in lung cancer patients, affecting patient responsiveness, tolerance to oncologic therapy, survival, and quality of life.<sup>5,35–40</sup> However, our analysis showed no correlation between low SMM, the main component of weight loss, and OS, in contrast with the results of previous studies<sup>7,8,41</sup> that examined a population of lung cancer patients, despite different biological and histological characteristics between samples. Similarly, changes in SMI at different time points were not predictive of outcome. We were only able to confirm that PS remains the main prognostic factor of OS and the cornerstone to guide treatment decisions in daily clinical practice. However, interestingly, we found that low SMM adversely affected PFS, a measure that strongly correlates to chemotherapy treatment. To our knowledge this finding has not previously been reported in the literature. Our finding of shorter PFS in patients with low SMM, together

**Table 2** Univariate and multivariate analyses of progression-free survival

Variable (n)	PROGRESSION-FREE SURVIVAL					
	Univariate analysis		Multivariate analysis (low SMM)		Multivariate analysis (low SMD)	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Baseline non-low versus low SMM	0.89 (0.55–1.43)	0.6388	0.54 (0.31–0.93)	0.0278*	—	—
Baseline non-low versus low SMD	1.03 (0.61–1.72)	0.9126	—	—	0.67 (0.36–1.24)	0.2041
Underweight	0.94 (0.33–2.61)	0.9068	—	—	—	—
Change in SMI (58 evaluable patients)	1.47 (0.81–2.67)	0.1962	—	—	—	—
Age at diagnosis	1.59 (0.99–2.56)	0.0516	—	—	—	—
Gender	1.09 (0.67–1.77)	0.7119	—	—	—	—
ECOG PS	2.53 (1.51–4.23)	0.0004*	2.30 (1.26–4.21)	0.0067*	1.92 (1.08–3.42)	0.0260*
CIRS	1.61 (1.01–2.55)	0.0463*	1.26 (0.76–2.09)	0.3676	1.31 (0.78–2.18)	0.3006*
Histological subtype	1.51 (0.84–2.65)	0.1617	—	—	—	—
No. of metastatic sites	1.89 (1.19–2.99)	0.0069*	1.75 (1.07–2.87)	0.0255*	1.65 (1.01–2.71)	0.0471*
Regimen	2.73 (1.51–4.92)	0.0008*	2.51 (1.29–4.87)	0.0064*	2.54 (1.27–5.11)	0.0086*

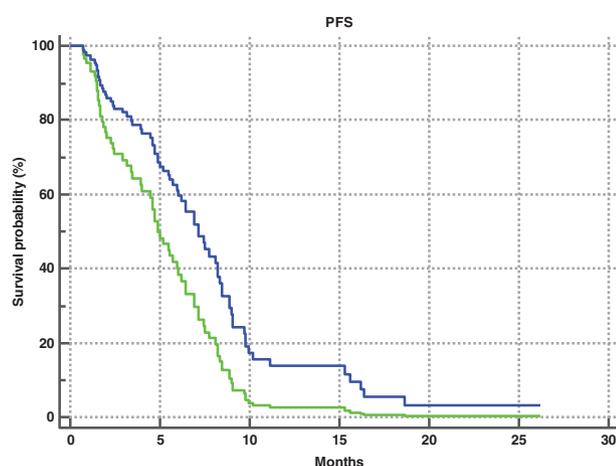
\*Indicates statistical significance. CI, confidence interval; CIRS, Cumulative Index Rating Scale; ECOG PS, Eastern Cooperative Oncology Group performance score; HR, hazard ratio; SMD, skeletal muscle radiodensity; SMI, skeletal muscle index; SMM, skeletal muscle mass.

with the greater incidence of hematological toxicities of any grade, leads us to speculate that good nutritional status assists chemotherapy delivery, without the need for discontinuation, and thus results in better effectiveness. Moreover, there was a trend of greater incidence of other toxicities (hematological G3/G4 and non-hematological) among patients with low baseline SMM, although this result was not statistically significant.

The literature on this topic is lacking and what is available is somewhat controversial. Martin *et al.* reported that low muscle index and low muscle attenuation were independent prognostic factors of survival, however these authors analyzed a very large mixed series of patients with both lung and gastrointestinal cancers.<sup>13</sup> In multivariate analysis of a small series of patients, Tsukioka *et al.*

reported that sarcopenia was not predictive of early recurrence after curative surgery.<sup>14</sup> Stene *et al.* found a mean reduction in muscle mass of 1.4 kg during nine weeks of first-line platinum-doublet chemotherapy, but baseline sarcopenia was not predictive of survival in multivariate analysis.<sup>5</sup> Finally, a large Norwegian study showed that muscle mass measured through the SMI was not a significant independent predictor of OS.<sup>15</sup> In contrast, Kimura *et al.* recently reported that baseline sarcopenic patients treated with chemotherapy had significantly shorter OS than non-sarcopenic patients.<sup>8</sup> Similarly Rossi *et al.* showed that baseline sarcopenia was associated with longer OS, even if it did not affect the response to gefitinib treatment, in *EGFR* mutated NSCLC patients.<sup>41</sup>

The discrepancies in these findings are difficult to explain, however, it is possible that in studies investigating the association between survival and muscle mass, SMI was dichotomized according to survival-related thresholds of the analysis samples, which were likely different among the studies, and this may to some extent have overestimated the effect.<sup>3,13</sup> In addition, the prognostic weight of sarcopenia seems to particularly affect obese patients, who accounted for only 16% of our cohort.<sup>42</sup> Age may also explain part of the discrepancy in the results between different studies, because sarcopenia is a continuum that starts at middle age and progressively worsens during aging.<sup>43</sup> Thus, the detection of a similar rate of sarcopenia in cancer patients might have a different meaning depending on age; in elderly patients, cancer overlaps a state of already consolidated sarcopenia and does not necessarily reflect an adverse metabolic impact of the tumor on the protein metabolism of the host. In younger patients, the occurrence of sarcopenia may more likely reflect the depletion of the protein component driven by cancer-related inflammation.<sup>44</sup>



**Figure 1** Cox proportional hazard regression curve of multivariate analysis for progression-free survival (PFS): hazard ratio 0.54, 95% confidence interval 0.31–0.93;  $P = 0.0278$ . Low skeletal muscle mass (SSM): (—) yes and (—) no.

**Table 3** Univariate and multivariate analyses of overall survival

Variable (n)	OVERALL SURVIVAL					
	Univariate analysis		Multivariate analysis (low SMM)		Multivariate analysis (low SMD)	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Baseline non-low versus low SMM	1.04 (0.61–1.77)	0.8662	0.56 (0.31–1.05)	0.0731	—	—
Baseline non-low versus low SMD	1.15 (0.67–1.97)	0.6142	—	—	0.69 (0.36–1.33)	0.2720
Underweight	0.92 (0.28–2.94)	0.8901	—	—	—	—
Change in SMI (58 evaluable patients)	1.37 (0.72–2.61)	0.3321	—	—	—	—
Age at diagnosis	1.48 (0.91–2.41)	0.1124	—	—	—	—
Gender	1.29 (0.76–2.18)	0.3306	—	—	—	—
ECOG PS	2.69 (1.61–4.51)	0.0002*	3.28 (1.81–5.96)	0.0001*	2.62 (1.55–4.42)	0.0003*
CIRS	1.69 (1.03–2.74)	0.0345*	1.46 (0.85–2.49)	0.1658	1.52 (0.89–2.59)	0.1297
Histological subtype	1.64 (0.92–2.92)	0.0917	—	—	—	—
No. of metastatic sites	1.45 (0.89–2.36)	0.1335	—	—	—	—
Regimen	2.15 (1.21–3.83)	0.0088*	1.85 (0.96–3.54)	0.0653	1.92 (0.95–3.90)	0.0700

\*Indicates statistical significance. CI, confidence interval; CIRS, Cumulative Index Rating Scale; ECOG PS, Eastern Cooperative Oncology Group performance score; HR, hazard ratio; SMD, skeletal muscle radiodensity; SMI, skeletal muscle index; SMM, skeletal muscle mass.

The small sample size and the complexity of the interactions between nutritional status and body composition do not allow us to make conclusive epidemiologic considerations about correlations between baseline BMI, SMI, and SMD. Our results confirm a certain inverse proportionality between BMI and sarcopenia, but certainly do not contrast with evidence that a good BMI does not imply good muscle mass.<sup>42,45</sup> Despite the limitations, our finding of a weak correlation between SMI and SMD suggests that the measurement of muscle mass may not be sufficient for a proper evaluation; even if the muscle area is sufficient, the same tissue could be of poor quality.

There were no differences in survival in our study when SMD was taken into account. Regarding the lack of a correlation between SMD and prognosis, it is noteworthy that only one previous study of a large patient sample by

Sjoblom *et al.* showed that SMD had a statistically significant negative prognostic value in NSCLC patients.<sup>15</sup> Similar findings have been reported in other types of tumors,<sup>16–19</sup> particularly in pancreatic cancer.<sup>24,25</sup>

Interestingly, the results of our study did not indicate the molecular substrate for low radiodensity, but low values are usually reflected in increased fat deposits, which are more common in elderly people and diabetics. A recent ad hoc investigation reported only a weak positive correlation between muscle protein content and SMD.<sup>46</sup> It is clear that we are now at the dawn of a new era. Further studies are warranted to understand the mechanisms behind loss of muscle density in cancer patients to clarify whether poorer prognosis reflects the aggressiveness of the disease or more simply a compromised general status, or both.

**Table 4** Cumulative toxicity analysis

	Overall	Low SMM	Non-low SMM	Low SMD	Non-low SMD
No. of evaluable patients	67	24	43	21	46
Hematological toxicities (%)	76.1	91.7	67.4	85.7	71.7
(any grade)	(95% CI 64.1–85.6)	(95% CI 73.0–98.9)†	(95% CI 51.4–80.9)	(95% CI 63.6–96.9)	(95% CI 56.5–84.1)
Events	52	22	29	18	33
Non-hematological toxicities (%)	92.5	100	88.4	95.2	91.3
(any grade)	(95% CI 83.4–97.5)	—	(95% CI 74.9–96.1)	(95% CI 76.2–99.8)	(95% CI 79.2–97.6)
Events	62	24	38	20	42
G3/G4 hematological toxicities (%)	19.4	25.0	16.3	33.3	13.0
(any grade)	(95% CI 10.7–30.8)	(95% CI 9.7–46.7)	(95% CI 6.8–30.7)	(95% CI 14.3–56.9)	(95% CI 4.9–26.2)
Events	13	6	7	7	6
G3/G4 non-hematological toxicities (%)	17.9	25.0	14.0	9.5	21.7
(any grade)	(95% CI 9.6–29.2)	(95% CI 9.7–46.7)	(95% CI 5.3–27.9)	(95% CI 1.2–30.4)	(95% CI 10.9–36.4)
Events	12	6	6	2	10

†Binomial confidence intervals were used. CI, confidence interval; SMD, skeletal muscle radiodensity; SMM, skeletal muscle mass.

This study has some limitations, mainly related to the small number of patients, which could expose the data to the risk of a type 1 error, and to some heterogeneity of chemotherapy regimens. On the contrary, points of strength include the centralized imaging analysis performed by a single trained observer blinded to patient outcomes, and the single institution, which assures strict homogeneity of the treatment characteristics (dose, interval, reduction), as well as of follow-up. In addition, we explored two areas not considered in previous studies: the impact of sarcopenia on PFS and the potential meaning of consecutive changes in SMI on clinical outcomes.

The results of our study indicate that in a homogeneous series of NSCLC patients on oncologic therapy, low SMM is predictive of shorter PFS, while consecutive changes in SMI do not affect PFS and OS. Regarding SMD, our results are not conclusive, thus ITS predictive/prognostic role remains a matter of debate.

## Disclosure

No authors report any conflict of interest.

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