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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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, 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. 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.

Although there is growing interest 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%, and is likely dependent on age, smoking habits, duration of the disease, different body mass index (BMI), and gender. 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.

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, a finding also reported in other types of tumors.

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 ≥ 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 now clear that sarcopenia is a condition characterized by a loss of muscle function as well as mass 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, 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 SMMs. Comorbidities were evaluated using the Cumulative Index Rating Scale (CIRS). 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. ≥ 70 years old), gender (male vs. female), ECOG PS (0–1 vs. ≥ 2), CIRS stage (primary/intermediate vs. secondary), histological subtype (squamous cell carcinomas vs. non-squamous cell carcinomas), number of metastatic sites (≤ 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: ≤ 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.

The coefficients of determination R² were interpreted as follows: > 0.67 substantial, > 0.33 moderate, and > 0.19 weak.

Responses were evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST, version 1.0 before 2010 and version 1.1 subsequently). 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. 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.
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 weight/height² (kg/m²) and World Health Organization categories were used: underweight, BMI < 18.5; normal, 18.5 ≤ BMI ≤ 24.9; overweight, 25 ≤ BMI ≤ 29.9; and obese, BMI ≥ 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 (cm²/m²) for each patient. SMI was calculated dividing the total cross-sectional skeletal muscle area (TMA - cm²) 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 cm²/m² for men with BMI ≤25, <53 cm²/m² for men with BMI ≥25, and ≤41 cm²/m² for women). 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). 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 (R² = 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     | Patients, N (%) |
|--------------------------------|-------------|-----------------|
| **Age (years)**                | 68          | 81 (100)        |
| **Gender**                     |             |                 |
| Male                           | 53 (65.4)   |                 |
| Female                         | 28 (34.6)   |                 |
| **BMI (kg/m²)**                |             |                 |
| Overweight (BMI ≤ 29.9)        | 41 (50.6)   |                 |
| Normal weight (BMI 18.5 < BMI ≤ 24.9) | 4 (4.9)       |                 |
| Underweight (BMI ≤ 18.5)       | 23 (28.4)   |                 |
| **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)   |                 |
| **CNS metastasis**             | 13 (16.1)   |                 |
| **Regimen**                    |             |                 |
| Platinum-based doublet         | 64 (79.1)   |                 |
| Single agent chemotherapy      | 17 (20.9)   |                 |
| **Weight (kg)**                | 68 (40–120) |                 |
| **BMI (kg/m²)**                | 24.2 (17.3–45.2) |     |
| Underweight (BMI ≤ 18.5)       | 4 (4.9)     |                 |
| Normal weight (BMI 18.5 < BMI ≤ 24.9) | 41 (50.6)   |                 |
| Overweight (BMI ≤ 29.9)        | 23 (28.4)   |                 |
| Obese (BMI ≥ 30)               | 13 (16.1)   |                 |
| **Lumbar skeletal muscle area (cm²)** |             |                 |
| Median                         | 126.1       |                 |
| (range)                        | (78.9–228.3) |                 |
| **Lumbar skeletal muscle index (cm²/m²)** | 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)**                   | 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.

There 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 = 0.1000), 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 = 0.1000), 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. 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 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
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. In multivariate analysis of a small series of patients, Tsukioka et al. reported that sarcopenia was not predictive of early recurrence after curative surgery.14 Steine 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. Finally, a large Norwegian study showed that muscle mass measured through the SMI was not a significant independent predictor of OS. In contrast, Kimura et al. recently reported that baseline sarcopenic patients treated with chemotherapy had significantly shorter OS than non-sarcopenic patients. 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.

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. In addition, the prognostic weight of sarcopenia seems to particularly affect obese patients, who accounted for only 16% of our cohort. 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. 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.

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

| Variable (n) | Univariate analysis | Multivariate analysis (low SMM) | Multivariate analysis (low SMD) |
|-------------|---------------------|---------------------------------|---------------------------------|
|             | 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                          | ——                            | ——                              |
| 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*                          |
| CIRS        | 1.61 (1.01–2.55)   | 0.0463*                         | 1.26 (0.76–2.09) | 0.3676                           |
| 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*                          |
| Regimen     | 2.73 (1.51–4.92)   | 0.0008*                         | 2.51 (1.29–4.87) | 0.0064*                          |

*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.
Muscle mass and radiodensity in NSCLC

Table 3 Univariate and multivariate analyses of overall survival

| Variable (n)                      | Univariate analysis | Multivariate analysis (low SMM) | Multivariate analysis (low SMD) |
|-----------------------------------|---------------------|---------------------------------|---------------------------------|
|                                   | 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                          | —                               | —                               |
| 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                          | —                               | —                               |
| ECOG PS                           | 1.29 (0.76–2.18)   | 0.3306                          | —                               | —                               |
| CIRS                              | 2.69 (1.61–4.51)   | 0.0002*                         | 3.28 (1.81–5.96)                | 0.0001*                         |
| Histological subtype              | 1.69 (1.03–2.74)   | 0.0345*                         | 1.46 (0.85–2.49)                | 0.1658                          |
| No. of metastatic sites           | 1.64 (0.92–2.92)   | 0.0917                          | 1.52 (0.89–2.59)                | 0.1297                          |
| Regimen                           | 1.45 (0.89–2.36)   | 0.1335                          | —                               | —                               |
|                                   | 2.15 (1.21–3.83)   | 0.0088*                         | 1.85 (0.96–3.54)                | 0.0653                          |

*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.42,45 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.15 Similar findings have been reported in other types of tumors,16–19 particularly in pancreatic cancer.24,25

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.46 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 (%) | (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 (%) | (95% CI 83.4–97.5) | —       | (95% CI 74.9–96.1) | (95% CI 76.2–99.8) | (95% CI 79.2–97.6) |
| G3/G4 hematological toxicities (%) | (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 (%) | (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) |

†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.

**References**

1. Arends J, Baracos V, Bertz H et al. ESPEN expert group recommendations for action against cancer-related malnutrition. *Clin Nutr* 2017; 36: 1187–96.
2. Bozzetti F. Forcing the vicious circle: Sarcopenia increases toxicity, decreases response to chemotherapy and worsens with chemotherapy. *Ann Oncol* 2017; 28: 2107–18.
3. Prado CM, Lieffers JR, McCargar LJ et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: A population-based study. *Lancet Oncol* 2008; 9: 629–35.
4. Baracos VE, Reiman T, Mourtzakis M, Gioulbasanis I, Antoun S. Body composition in patients with non-small cell lung cancer: A contemporary view of cancer cachexia with the use of computed tomography image analysis. *Am J Clin Nutr* 2010; 91: 1133S–7S.
5. Stene GB, Helbostad JL, Amundsen T et al. Changes in skeletal muscle mass during palliative chemotherapy in patients with advanced lung cancer. *Acta Oncol* 2015; 54: 340–8.
6. Kim CR, Kim EY, Kim YS et al. Histologic subtypes are not associated with the presence of sarcopenia in lung cancer. *PLoS One* 2018; 13: e0194626.
7. Kim EY, Kim YS, Park I, Ahn HK, Cho EK, Jeong YM. Prognostic significance of CT-determined sarcopenia in patients with small-cell lung cancer. *J Thorac Oncol* 2015; 10: 1795–9.
8. Kimura M, Naito T, Kenmotsu H et al. Prognostic impact of cancer cachexia in patients with advanced non-small cell lung cancer. *Support Care Cancer* 2015; 23: 1699–708.
9. Murphy RA, Mourtzakis M, Chu QS, Reiman T, Mazurak VC. Skeletal muscle depletion is associated with reduced plasma (n-3) fatty acids in non-small cell lung cancer patients. *J Nutr* 2010; 140: 1602–6.
10. Nakamura R, Inage Y, Tobita R et al. Sarcopenia in resected NSCLC: Effect on postoperative outcomes. *J Thorac Oncol* 2018; 13: 895–903.
11. Atlan P, Bayar MA, Lanoy E et al. Factors which modulate the rates of skeletal muscle mass loss in non-small cell lung cancer patients: A pilot study. *Support Care Cancer* 2017; 25: 3365–73.
12. Palomares MR, Sayre JW, Shekar KC, Lillington LM, Chlebowski RT. Gender influence on weight-loss pattern and survival of nonsmall cell lung carcinoma patients. *Cancer* 1996; 78: 2119–26.
13. Martin L, Birdsell L, Macdonald N et al. Cancer cachexia in the age of obesity: Skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol* 2013; 31: 1539–47.
14. Tsukioka T, Izumi N, Kuyukwang C et al. Loss of muscle mass is a novel predictor of postoperative early recurrence in N2-positive non-small-cell lung cancer. *Ann Thorac Cardiovasc Surg* 2018; 24: 121–6.
15. Sjoblom B, Grönbäck BH, Wentzel-Larsen T et al. Skeletal muscle radiodensity is prognostic for survival in patients with advanced non-small cell lung cancer. *Clin Nutr* 2016; 35: 1386–93.
16. Sabel MS, Lee J, Cai S et al. Sarcopenia as a prognostic factor among patients with stage III melanoma. *Ann Surg Oncol* 2011; 18: 3579–85.
17. Miller BS, Ignatoski KM, Daignault S et al. Worsening central sarcopenia and increasing intra-abdominal fat correlate with decreased survival in patients with adrenocortical carcinoma. *World J Surg* 2012; 36: 1509–16.
18. Antoun S, Lanoy E, Iacovelli R et al. Skeletal muscle density predicts prognosis in patients with metastatic renal cell carcinoma treated with targeted therapies. *Cancer* 2013; 119: 3377–84.
19. Rollins KE, Tewari N, Ackner A et al. The impact of sarcopenia and myosteatosis on outcomes of resectable pancreatic cancer or distal cholangiocarcinoma. *Clin Nutr* 2016; 35: 1103–9.
20. Chu MP, Lieffers J, Ghosh S et al. Skeletal muscle radiodensity is an independent predictor of response and outcomes in follicular lymphoma treated with chemoimmunotherapy. *PLoS One* 2015; 10: e0127589.
21. Brown JC, Caan BJ, Meyerhardt JA et al. The deterioration of muscle mass and radiodensity is prognostic of poor survival in stage I-III colorectal cancer: A population-based cohort study (C-SCANS). *J Cachexia Sarcopenia Muscle* 2018; 9: 664–72.
22. Caan BJ, Cespedes Feliciano EM, Prado CM et al. Association of muscle and adiposity measured by computed tomography with survival in patients with nonmetastatic breast cancer. *JAMA Oncol* 2018; 4: 798–804.
Kroenke CH, Prado CM, Meyerhardt JA et al. Muscle radiodensity and mortality in patients with colorectal cancer. Cancer 2018; 124: 3008–15.

Stretch C, Aubin JM, Mickiewicz B et al. Sarcopenia and myosteatosis are accompanied by distinct biological profiles in patients with pancreatic and periampullary adenocarcinomas. PLoS One 2018; 13: e0196235.

van Dijk DP, Bakens MJ, Coolsen MM et al. Low skeletal muscle radiation attenuation and visceral adiposity are associated with overall survival and surgical site infections in patients with pancreatic cancer. J Cachexia Sarcopenia Muscle 2017; 8: 317–26.

Santilli V, Bernetti A, Mangone M, Paoloni. M. Clinical definition of sarcopenia. Clin Cases Miner Bone Metab 2014; 11: 177–80.

Bulke JA, Crolla D, Termote JL et al. Computed tomography of muscle. Muscle Nerve 1981; 4: 67–72.

Extermann M, Overcash J, Lyman GH, Parr J, Balducci L. Comorbidity and functional status are independent in older cancer patients. J Clin Oncol 1998; 16: 1582–7.

Evans, J. D. 1996, Straightforward Statistics for the Behavioral Sciences. Pacific Grove, CA: Brooks/Cole Publishing.

Chin WW. The partial least squares approach for structural equation modeling. In: Marcoulides GA (ed.). Methodology for Business and Management. Modern Methods for Business Research. Lawrence Erlbaum Associates Publishers, Mahwah, NJ, US 1998; 295–336.

Therasse P, Arbuck SG, Eisenhauer EA et al. New guidelines to evaluate the response to treatment in solid tumors: European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 92: 205–16.

Eisenhauer EA, Therasse P, Bogaerts J et al. New Response Evaluation Criteria in Solid Tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228–47.

Hosmer DW Jr, Lemeshow S. Sturdivant RX Applied Logistic Regression, 3rd edn. John Wiley & Sons, Hoboken, NJ 2013.

Lo SK, Li IT, Tsou TS, See L. [Non-significant in univariate but significant in multivariate analysis: A discussion with examples]. Changgeng Yi Xue Za Zhi 1995; 18: 95–101. (In Chinese.)

Dewys WD, Begg C, Lavin PT et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Eastern Cooperative Oncology Group. Am J Med 1980; 69: 491–7.

Sjøblom B, Grønberg BH, Benth JS et al. Low muscle mass is associated with chemotherapy-induced haematological toxicity in advanced non-small cell lung cancer. Lung Cancer 2015; 90: 85–91.

Sjøblom B, Benth JS, Grønberg BH et al. Drug dose per kilogram lean body mass predicts hematologic toxicity from carboplatin-doublet chemotherapy in advanced non-small-cell lung cancer. Clin Lung Cancer 2017; 18: e129–36.

Arrieta O, De la Torre-Vallejo M, López-Macias D et al. Nutritional status, body surface, and low lean body mass/ body mass index are related to dose reduction and severe gastrointestinal toxicity induced by Afatinib in patients with non-small cell lung cancer. Oncologist 2015; 20: 967–74.

Scott HR, McMillan DC, Brown DJ et al. A prospective study of the impact of weight loss and the systemic inflammatory response on quality of life in patients with inoperable non-small cell lung cancer. Lung Cancer 2003; 40: 295–9.

Temel J. Can weight loss at presentation predict patient outcome in lung cancer? Nat Clin Pract Oncol 2004; 1 (2): 68–9.

Rossi S, Di Noia V, Tonetti I et al. Does sarcopenia affect outcome in patients with non-small-cell lung cancer harboring EGFR mutations? Future Oncol 2018; 14: 919–26.

Gonzalez MC, Pastore C, Orlandi SP et al. Obesity paradox in cancer: New insights provided by body composition. Am J Clin Nutr 2014; 99: 999–1005.

Wakabayashi H, Sakuma K. Comprehensive approach to sarcopenia treatment. Curr Clin Pharmacol 2014; 9: 171–80.

Baracos VE, Martin L, Korc M, Guttridge DC, Fearon KCH. Cancer-associated cachexia. Nat Rev Dis Primers 2018; 4: 17105.

Wannamethee SG, Atkins JL. Muscle loss and obesity: The health implications of sarcopenia and sarcopenic obesity. Proc Nutr Soc 2015; 74: 405–12.

Ramage MI, Johns N, Deans CDA et al. The relationship between muscle protein content and CT-derived muscle radio-density in patients with upper GI cancer. Clin Nutr 2018; 37: 752–4.