



# Association of Pre-treatment Sarcopenia with Side Effects and Prognosis in Non-small Cell Lung Cancer Patients Receiving Erlotinib

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## OBJECTIVE

We investigated the relationship of baseline sarcopenia with toxicities, treatment response, and survival in patients who had non-small cell lung cancer (NSCLC) harboring an epidermal growth factor receptor (EGFR) mutation and received erlotinib.

## METHODS

Computed tomography images from PET/CT scans before erlotinib treatment were retrospectively assessed. Skeletal muscle index, calculated as skeletal muscle area at third lumbar vertebra level/square of height, was used to define sarcopenia with  $<52.4 \text{ cm}^2/\text{m}^2$  for males and  $<38.5 \text{ cm}^2/\text{m}^2$  for females. Cox hazard models were conducted to determine predictors of survival.

## RESULTS

The study included 30 patients, and 11 (36.7%) were sarcopenic. All-grade and Grade 3 toxicities were more frequent in sarcopenic group, although it was statistically insignificant (81.8% vs. 63.2%,  $p=0.282$  for all-grade, and 18.2% vs. 10.5%,  $p=0.552$  for grade 3). Response rates were 63.6% in sarcopenic and 68.4% in non-sarcopenic patients ( $p=0.789$ ). Median progression-free survival was 7.9 and 9.2 months in sarcopenic and non-sarcopenic cases, respectively ( $p=0.561$ ). However, median overall survival (OS) of sarcopenic patients was significantly shorter than non-sarcopenic ones (11.8 vs. 30.2 months,  $p=0.023$ ), and sarcopenia predicted OS independently in multivariate analysis (Hazard ratio=2.63,  $p=0.029$ ).

## CONCLUSION

Early recognition, treatment, and prevention of sarcopenia may improve long-term survival in EGFR-mutant NSCLC patients treated with first-line erlotinib.

**Keywords:** Epidermal growth factor receptor; erlotinib; non-small cell lung cancer; prognosis; sarcopenia.

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## INTRODUCTION

Lung cancer currently leads new cancer diagnoses and causes of cancer deaths worldwide, according to GLOBOCAN 2018 statistics.[1] Its most frequent subtype is non-small cell lung cancer (NSCLC), which often presents at an advanced stage. Progression occurs frequently even in local disease that is initially amenable to local therapy. Activating mutations in epidermal growth factor receptor (EGFR) gene are found in 5-15% of Caucasian patients with NSCLC and sensitize the disease to EGFR tyrosine kinase inhibitors (TKIs).[2,3] Among these agents, erlotinib is a first-generation EGFR TKI which showed superior efficacy to cisplatin-based chemotherapy in frontline treatment of stage IIIB-IV NSCLC patients harboring activating EGFR mutations, as reported in Phase III trials.[4,5] Subsequently, it became one of the recommended first-line options for advanced NSCLC with activating EGFR mutations.[6]

Sarcopenia can be defined as progressive and generalized muscle loss accompanied by decline in muscle function and is recognized as an essential component of cancer cachexia syndrome.[7,8] As a consequence in oncology practice, sarcopenia increases drug toxicity, decreases response to therapy and is a prognostic indicator of survival in solid tumors.[9,10] Sarcopenia has a reported prevalence of more than 50% among NSCLC patients and was demonstrated to predict survival independently.[11,12] Targeted drugs are increasingly used during management of advanced NSCLC with actionable mutations and although they are prescribed at a fixed starting dose, toxicities are experienced at different levels between individuals. Given this observation, body composition might also be a potential factor affecting treatment tolerability in NSCLC patients receiving targeted agents. Nonetheless, a few studies have assessed whether sarcopenia had an impact on outcomes of EGFR-mutant NSCLC patients receiving TKIs so far. This study aimed to evaluate the association between pre-existing sarcopenia and adverse events (AEs), treatment response, and survival in NSCLC patients harboring an EGFR mutation who received first-line erlotinib.

## MATERIALS AND METHODS

### Study Design and Patient Selection

Medical records of patients with histologically proven NSCLC who were followed up in medical oncology

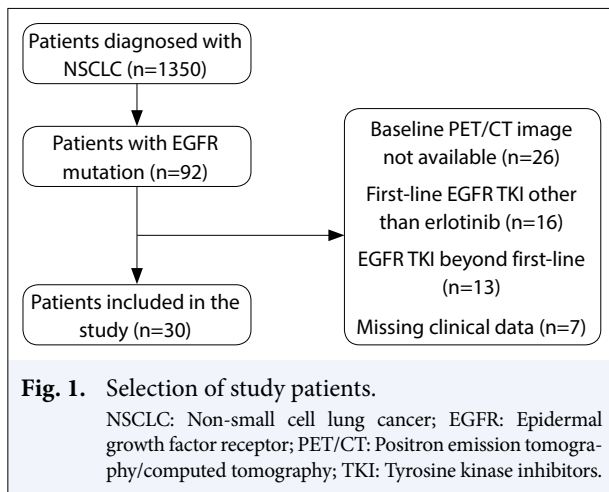
department of our institute between August 2012 and September 2019 were evaluated retrospectively. Inclusion criteria were as follows: (1) Confirmed EGFR mutation in the pathology department of our institute; (2) receiving erlotinib in first-line treatment for unresectable stage III or IV NSCLC; (3)  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography/computed tomography (CT) ( $^{18}\text{F}$ -FDG PET/CT) performed within 3 months before erlotinib treatment and images of which were available in nuclear medicine department of our institute (Fig. 1). Demographic data, height, weight, and performance status according to Eastern Cooperative Oncology Group (ECOG) criteria, comorbidities and smoking history were determined from patient records. Disease stage (according to AJCC TNM Staging System, 8<sup>th</sup> Edition), sites of distant metastasis and EGFR mutation type were also recorded. EGFR mutation was detected with real-time polymerase chain reaction in tissue specimens obtained before the treatment, using BIO-RAD CFX96<sup>®</sup> (Bio-Rad Laboratories, Inc., USA) and Amoy Dx<sup>®</sup> EGFR 29 Mutations Detection Kit (Amoy Diagnostics, China). Body mass index (BMI) was calculated as weight (kg)/square of height ( $\text{m}^2$ ). The Institutional Ethics Committee granted an approval for this study and waived the informed patient consent.

### Data Regarding Treatment

All patients had started erlotinib with a standard dose of 150 mg/day. Information regarding treatment efficacy and safety was acquired from patient files. Dates of treatment initiation and discontinuation were recorded. Toxicities were graded according to Common Terminology Criteria for Adverse Events Version 5.0. In addition, it was noted whether dose reduction (to 100 mg/day), dose interruption, or permanent discontinuation due to treatment-related AEs had occurred. Treatment response was assessed using Response Evaluation Criteria in Solid Tumors Version 1.1 and objective response rate (ORR) was defined as the percentage of patients who had either complete or partial response. It was also determined whether disease had progressed during or after erlotinib and dates of progression were noted. Dates of last visit and, if occurred, death were obtained.

### $^{18}\text{F}$ -FDG PET/CT Scan, Image Analysis and Assessment of Sarcopenia

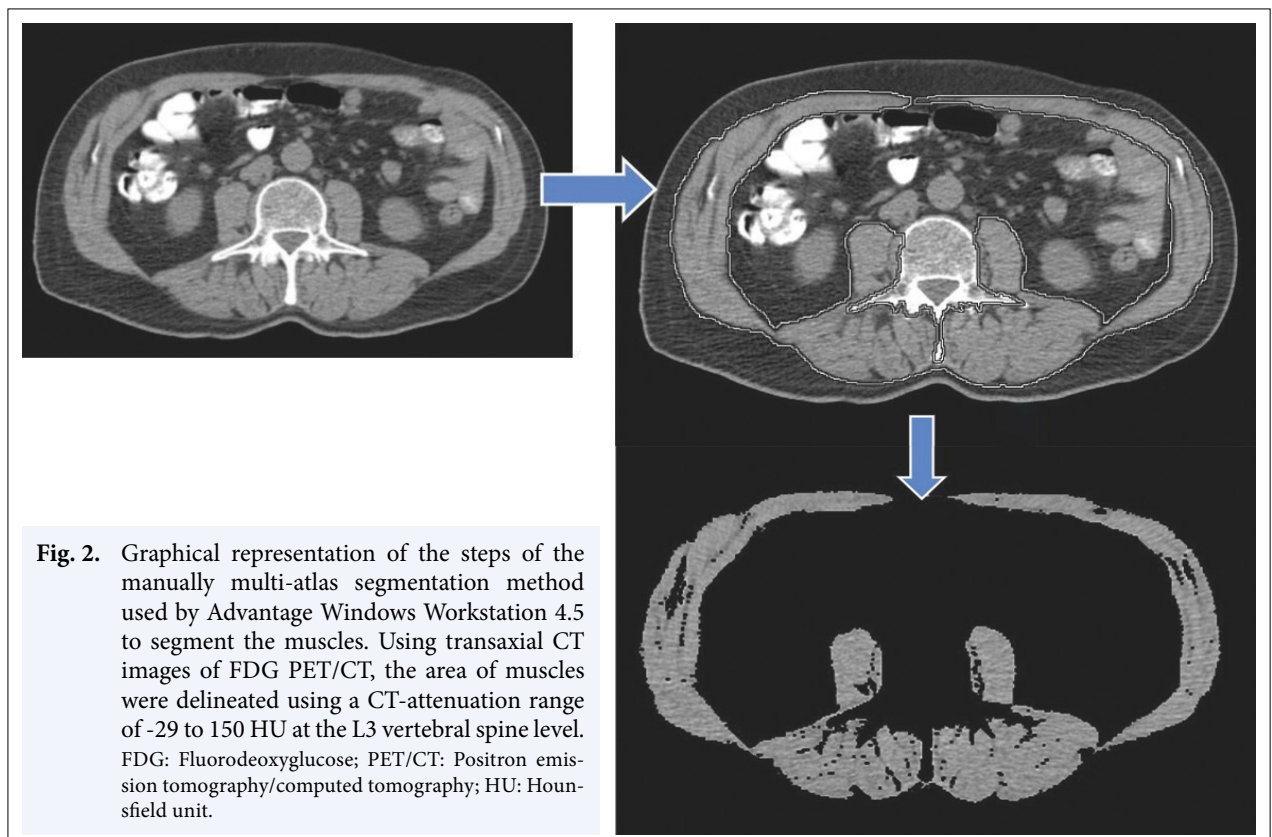
All patients had underwent whole-body  $^{18}\text{F}$ -FDG PET/CT (GE Discovery ST; GE Healthcare, Milwaukee, WI, USA) imaging and multislice CT was performed with a multidetector ST helical scanner using slip ring tech-



nology. All patients fasted for 6 h before PET/CT scan. After approximately 1 h, a multislice CT scan of areas from the upper thigh to skull base in shallow breathing patient was performed using a 16-slice multidetector scanner (Parameters: 80 mA, 140 kV, table speed 27 mm/rotation, and slice thickness 5.0 mm). A standard whole-body PET scan was performed in 3D mode with an acquisition time of 4 min per bed position (five to seven bed positions) covering the same field as the

CT scan. Acquired data were reconstructed using an iterative algorithm and CT images without contrast-enhancement were acquired for attenuation correction. Next, acquisition data were transferred to a workstation (Advantage Windows Server 3.2-Etx. 3.4; GE Healthcare, Milwaukee, WI, USA) for manual segmentation and interpretation. CT images were reviewed in transaxial, coronal and sagittal planes, and evaluated by two experienced nuclear medicine physicians.

Third lumbar vertebra (L3) was set as the anatomical landmark to measure cross-sectional total skeletal muscle area (TMA) because it was demonstrated to accurately reflect overall muscle mass.[13] TMA of each patient was computed with specific tissue demarcation of abdominal wall, paraspinal, and psoas muscles at L3 level (Fig. 2). To isolate tissue voxels, thresholding was applied with Hounsfield unit values between -29 and +150 for muscles. To assess sarcopenia, skeletal muscle index (SMI) of each subject was calculated as TMA (in cm<sup>2</sup>) divided by square of height (in m<sup>2</sup>).[13] Cutoff values of SMI for sarcopenia were accepted as per the definition of Prado et al., which was most commonly associated with prognosis in solid tumors: <52.4 cm<sup>2</sup>/m<sup>2</sup> for males and <38.5 cm<sup>2</sup>/m<sup>2</sup> for females.[10,14]



**Table 1** Baseline patient characteristics

Variable	Sarcopenic (n=11)		Non-sarcopenic (n=19)		p
	n	%	n	%	
Age					
<65 years	6	40	9	60	0.705
≥65 years	5	33.3	10	66.7	
Sex					
Female	5	27.8	13	72.2	0.216
Male	6	50	6	50	
ECOG-PS					
0-1	7	30.4	16	69.6	0.199
≥2	4	57.1	3	42.9	
Comorbidity					
Yes	6	40	9	60	0.705
No	5	33.3	10	66.7	
Smoking status					
Never-smoker	8	36.4	14	63.6	0.954
Current or former smoker	3	37.5	5	62.5	
No. of metastatic sites					
0-1	3	20	12	80	0.058
≥2	8	53.3	7	46.7	
Median TMA, cm <sup>2</sup> (IQR)	104.3 (99.4-129.7)		125.9 (103.8-157.2)		
Median SMI, cm <sup>2</sup> /m <sup>2</sup> (IQR)	38.2 (35.1-45.9)		46.6 (43.1-56.3)		

ECOG-PS: Eastern Cooperative Oncology Group performance status; TMA: Total skeletal muscle area; IQR: Interquartile range; SMI: Skeletal muscle index

## Statistical Analysis

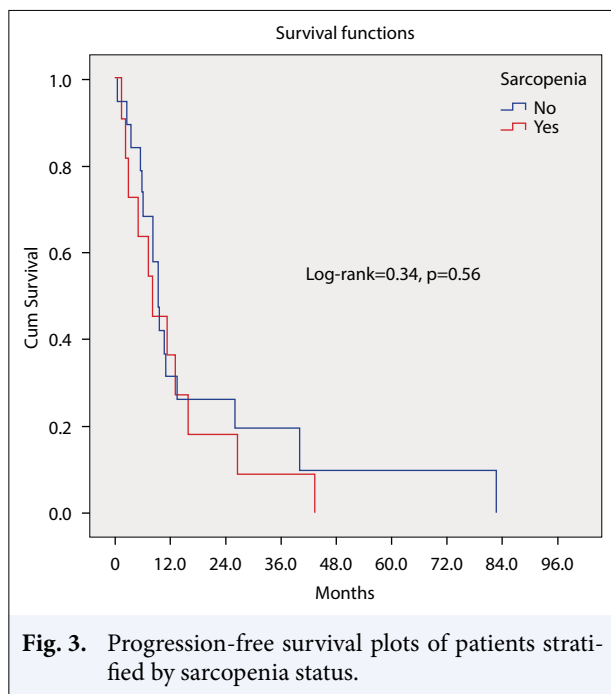
Descriptive data were recorded as frequencies and percentages. Continuous variables were presented as median values with interquartile ranges. Categorical variables were compared using Chi-square test. Progression-free survival (PFS) was defined as the time interval in months between start of erlotinib treatment and disease progression, death, or last visit if the patient was still alive. Overall survival (OS) was defined as the time interval in months between diagnosis of metastatic disease and death or last visit if the patient was still alive. Survival was estimated with Kaplan-Meier method and log-rank test. Cox proportional models were conducted to select factors affecting survival significantly or with a trend toward significance ( $p < 0.1$ ) in univariate analysis and to determine independent prognostic indicators in multivariate analysis using a backward step-wise method. Confidence interval (CI) was accepted as 95% and  $p < 0.05$  was set for statistical significance. All data were analyzed with the software “SPSS Version 22” (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.).

## RESULTS

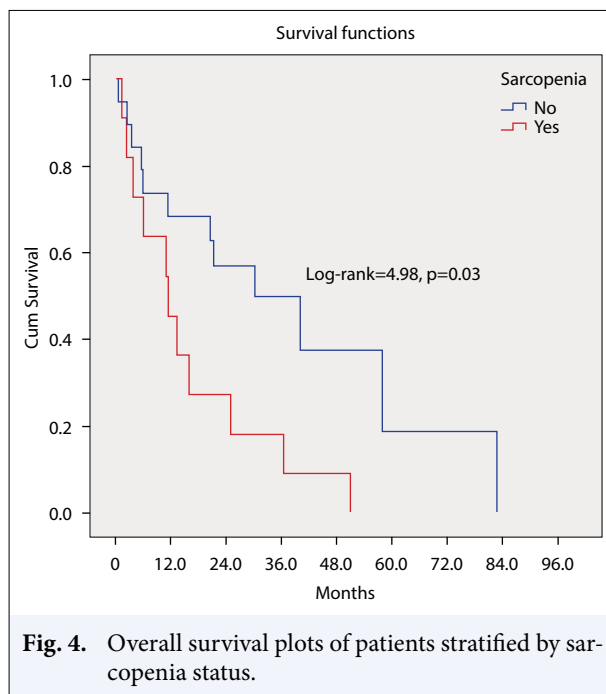
### Patient Characteristics

Thirty patients were found eligible for the study and their characteristics are shown in Table 1. Most patients were female (60%) and median age was 65 (54-71) years. ECOG performance status was 0 or 1 in 23 patients (76.7%), and 22 patients (73.3%) were nonsmoker. Half of the patients had at least one comorbid disease, with hypertension, diabetes mellitus, and chronic obstructive lung disease being most common. Except three patients with stage IIIB disease, all cases had stage IV disease at the beginning of erlotinib treatment. Most common sites of metastasis at baseline were pleura (43.3%), bone (40%), and distant lymph nodes (26.7%); and rate of brain metastasis was 20%. Half of patients had two or more metastatic sites. EGFR exon 19 deletion and exon 21 L858R mutation were each detected in 14 patients, one patient had an activating mutation in exon 18 and another one had an insertion in exon 20.

Sarcopenia was identified in 11 patients (36.7%). Among 16 overweight or obese patients (BMI 25-30 kg/



**Fig. 3.** Progression-free survival plots of patients stratified by sarcopenia status.



**Fig. 4.** Overall survival plots of patients stratified by sarcopenia status.

m<sup>2</sup> or >30 kg/m<sup>2</sup>), 3 (18.7%) were sarcopenic, whereas eight out of 14 patients who were underweight (only one patient) or had normal weight (BMI <18.5 kg/m<sup>2</sup> or 18.5-24.9 kg/m<sup>2</sup>) had sarcopenia (57.1%). One notable difference was that sarcopenia was more frequent among patients with two or more metastatic sites, which had a trend toward statistical significance (53.3% vs. 20%, p=0.058).

### Treatment Tolerability and Response

Median duration of erlotinib exposure was 9.3 (4.9-14.9) months. Treatment-related AEs of any grade had occurred in 21 patients (70%). Most frequent toxicities were rash (60%), fatigue (33.3%) and diarrhea (13.3%). Four patients (13.3%) had experienced Grade 3 AEs; two had rash, one had hand-foot syndrome, and one had conjunctivitis. Due to toxicity, erlotinib dose was reduced to 100 mg/day in 4 patients (13.3%), interrupted in one patient and discontinued in one.

Patients with sarcopenia experienced numerically more treatment-related AEs than non-sarcopenic patients but the difference was not statistically significant (81.8% vs. 63.2%, p=0.282). Of Grade 3 toxicities rash and hand-foot syndrome were seen in sarcopenic group, while rash and conjunctivitis in non-sarcopenic group (18.2% vs. 10.5%, p=0.552). Dose was reduced in three non-sarcopenic and one sarcopenic patient (15.3% vs. 9.1%, p=0.603).

There was a partial response in 20 (66.7%), progressive disease in 8 (26.7%), and stable disease in 2 patients

(6.7%). The patient with exon 18 deletion had a partial response, and the subject with exon 20 insertion had progressive disease. ORR was 66.7% in the whole study population and was similar in both groups (63.6% in sarcopenic and 68.4% in non-sarcopenic group, p=0.789).

The presence of any comorbidity was not associated with all-grade AEs (p=0.690), Grade 3 or 4 AEs (p=0.283), dose reduction (p=0.283), and ORR (p=0.439).

### Survival

At final analysis, 28 patients (93.3%) had progressed during erlotinib treatment. Median PFS of all patients was 9.2 months (95% CI, 7.6-10.7). Patients without sarcopenia had a median PFS of 9.3 months (95% CI, 7.7-10.8) whereas sarcopenic patients had a median PFS of 7.9 months (95% CI, 1.0-14.9). This PFS difference was not statistically significant (p=0.561) (Fig. 3). PFS of patients with and without comorbidity was also statistically similar (9.3 and 9.2 months, respectively; p=0.707).

Total of 23 patients (76.7%) had died at final analysis. Median OS of all patients was 21.5 months (95% CI, 6.8-36.2). Median OS was 30.2 months (95% CI, 9.7-50.8) and 11.8 months (95% CI, 3.6-19.9) in non-sarcopenic and sarcopenic groups, respectively. As demonstrated in Fig. 4, the difference in OS was statistically significant (p=0.023). Univariate Cox regression model showed that sarcopenia affected OS significantly, while ECOG performance status showed a trend toward statistical significance in predicting OS (p=0.029).



**Table 2** Univariate and multivariate analyses of prognostic factors for overall survival

Factor	Median OS (months)	Univariate analysis		Multivariate analysis	
		HR (95% CI)	p	HR (95% CI)	p
Age					
<65 years (n=15)	21.5	1.20 (0.51-2.85)	0.679		
≥65 years (n=15)	37	Reference			
Sex					
Female (n=18)	21.5	Reference	0.985		
Male (n=12)	16.7	1.01 (0.42-2.41)			
ECOG-PS					
0-1 (n=23)	30.2	Reference	0.054	Reference	0.169
≥2 (n=7)	11.8	2.71 (0.98-7.48)		2.11 (0.73-6.08)	
Comorbidity					
Yes (n=15)	16.7	1.37 (0.59-3.19)	0.468		
No (n=15)	30.2	Reference			
Smoking status					
Never-smoker (n=22)	21.5	Reference	0.478		
Current or former smoker (n=8)	8	1.49 (0.50-4.45)			
No. of metastatic sites					
0-1 (n=15)	30.2	Reference	0.243		
≥2 (n=15)	11.8	1.66 (0.71-3.86)			
Sarcopenia					
Yes (n=11)	11.8	2.63 (1.11-6.24)	0.029	2.63 (1.11-6.24)	0.029
No (n=19)	30.2	Reference		Reference	

OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; ECOG-PS: Eastern Cooperative Oncology Group performance status

and 0.054, respectively). In multivariate analysis, sarcopenia was found as an independent prognostic factor for OS (Hazard ratio=2.63, p=0.029) (Table 2).

## DISCUSSION

In oncological practice, muscle loss is an important and prevalent condition which has been generally associated with negative treatment outcomes. Our study revealed that baseline sarcopenia is an independent prognostic factor in patients with EGFR-mutant NSCLC receiving erlotinib. Although sarcopenia has been extensively studied in NSCLC patients so far, our study is the first report to demonstrate the prognostic value of pre-treatment sarcopenia in EGFR-mutant NSCLC treated with erlotinib in first-line setting.

Sarcopenia has been recognized as a significant prognostic factor in various malignancies, such as colon, breast, and gastric cancer.[15-17] As far as lung cancer is concerned, muscle loss was shown to predict mortality in both NSCLC and small-cell subtype.[18,19] (Table 3). Sarcopenia was also described as a negative

prognostic factor in NSCLC patients receiving immune checkpoint inhibitors.[20] However, patients with EGFR mutation compose a distinct subgroup of NSCLC and impact of sarcopenia on oncological outcomes has not been investigated sufficiently in this population. To date, two studies have addressed this issue. First, Arrieta et al.[21] found a non-significant trend toward shorter survival in sarcopenic patients with metastatic NSCLC to whom afatinib was administered after progression on chemotherapy. Second, Rossi et al.[22] showed that muscle loss was a significant prognostic factor in a retrospective analysis including 33 patients with metastatic, EGFR-mutant NSCLC who received gefitinib. In line with these studies, we demonstrated a remarkable difference in OS between sarcopenic and non-sarcopenic NSCLC cohorts who received erlotinib, and sarcopenia corresponded to an approximately 2.6-fold elevated risk of death. This outcome is especially interesting because there was no substantial difference between sarcopenic and non-sarcopenic groups in terms of response and PFS. Only two patients in the whole study cohort had to interrupt or discontinue treatment due to intolerance. Although sarcopenic patients tended to experi-

**Table 3** Studies of sarcopenia in lung cancer patients receiving systemic treatment. These studies were all retrospective and used CT images to assess sarcopenia

Study (Reference)	Patients	Anti-cancer treatment	Method of diagnosing sarcopenia	Prevalence of sarcopenia (%)	Outcome(s)
Kim et al.[18]	NSCLC (n=272)	Surgery (100%) Neoadjuvant chemotherapy (6.6%)	Men: L3MI <55 cm <sup>2</sup> /m <sup>2</sup> Women: L3MI <39 cm <sup>2</sup> /m <sup>2</sup>	Total: 22.4 Men: 32.9 Women: 6.5	OS, DFS, postoperative complications
Kim et al.[19]	SCLC (n=149)	CT (48.3%) CRT (29.5%) TRT (1.3%) SC (20.8%)	Men: L3MI <55 cm <sup>2</sup> /m <sup>2</sup> Women: L3MI <39 cm <sup>2</sup> /m <sup>2</sup>	Total: 79.2 Men: 87.4 Women: 36.4	OS
Roch et al.[20]	NSCLC (n=142)	1 <sup>st</sup> line pembrolizumab (13.4%) 2 <sup>nd</sup> line pembrolizumab or nivolumab (86.6%)	Men: L3MI <52.4 cm <sup>2</sup> /m <sup>2</sup> Women: L3MI <38.5 cm <sup>2</sup> /m <sup>2</sup>	Total: 65.7	OS, DCR
Arrieta et al.[21]	NSCLC (n=84)	Afatinib (100%), 2 <sup>nd</sup> line or beyond	LBM (cut-off values not specified)	Total: 68.8	OS, PFS, DLT
Rossi et al.[22]	NSCLC (n=33)	Gefitinib (100%)	Men: L3MI <55 cm <sup>2</sup> /m <sup>2</sup> Women: L3MI <39 cm <sup>2</sup> /m <sup>2</sup>	Total: 60.6 Men: 100 Women: 51.9	OS, skin toxicity

CT: Chemotherapy; NSCLC: Non-small cell lung cancer; L3MI: Skeletal muscle index at L3 vertebra level; OS: Overall survival; DFS: Disease-free survival; SCLC: Small-cell lung cancer; CRT: Chemoradiotherapy; TRT: Thoracic radiotherapy; SC: Supportive care; DCR: Disease control rate; LBM: Lean body mass; PFS: Progression-free survival; DLT: Dose-limiting toxicity

ence more treatment-related AEs, differences in toxicity rate and dose reduction were not statistically significant. As highlighted in baseline characteristics, patients with more metastatic sites were more likely to have sarcopenia. After, it can be hypothesized that this association develops naturally because tumor burden induces muscle wasting through increased catabolism.[23] In the face of these findings, shorter OS of sarcopenic patients in our study might be explained by impaired immunity and increased frailty due to protein degradation along with systemic inflammation, which have been addressed as possible mechanisms underlying the prognostic impact of muscle loss in cancer cachexia.[14,24,25]

For patients receiving anticancer therapy, pre-existing sarcopenia is also known to be associated with treatment-related toxicities. This observation may be linked to altered body composition, which causes changes in distribution, metabolism, and clearance of antineoplastic drugs.[26] Previously, sarcopenia was reported to predict severe toxicities in hepatocellular or renal cell cancer patients receiving anti-angiogenic

TKIs such as sorafenib or sunitinib.[26,27] One of the studies focusing on EGFR-mutant NSCLC revealed that malnourishment and sarcopenia were significant predictors of severe gastrointestinal and dose-limiting toxicity during afatinib treatment.[21] Sarcopenic patients also tended to develop more frequent and severe cutaneous rash related to gefitinib.[22] Our research demonstrated that there was a trend toward increased all-grade and Grade 3 AEs associated with erlotinib in sarcopenic patients, which, however, was not statistically significant. Taking the small sample size into account, we suggest that this finding might be clinically relevant and sarcopenic NSCLC patients should be carefully monitored for toxicity during erlotinib treatment.

Our study is mainly limited by its being done in single-center and retrospective design, which can cause selection bias. Furthermore, relatively small sample size might have precluded numerical differences translating into statistical significance and thus have complicated interpretation of the results. We analyzed CT images at L3 level because it has previously correlated

with whole-body muscle mass. However, a major concern when using SMI for assessment of sarcopenia was the selection of optimal cutoff values because these have varied across geographic regions and publications in the literature. We selected cutoff values that were most commonly used in the previous studies investigating sarcopenia in solid tumors.[10] Despite all limitations, we could demonstrate the prognostic value of sarcopenia in our study.

## CONCLUSION

Pre-treatment sarcopenia is obviously a significant prognostic marker also in NSCLC patients with EGFR mutation receiving erlotinib. Nutritional interventions and countermeasures to ameliorate muscle loss can therefore help improving long-term survival in this subpopulation. Our results need to be tested further in larger studies, which may clarify the prognostic importance of sarcopenia in NSCLC patients under erlotinib treatment.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** All authors declared no conflict of interest.

**Ethics Committee Approval:** The study was approved by the Marmara University Faculty of Medicine Clinical Research Ethics Committee (no: 09.2020.1107, date: 02/10/2020).

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**Authorship contributions:** Concept – N.C.D., T.Ö., P.F.Y.; Design – N.C.D., T.Ö., P.F.Y.; Supervision – N.C.D., Ö.E., F.D., T.Ö., P.F.Y.; Funding – None; Materials – C.Ö.E., S.Ö., T.Ö.; Data collection and/or processing – N.C.D., C.Ö.E., T.A.T, T.B., R.A., A.Y., A.Ç., Ö.A., S.I., H.K.; Data analysis and/or interpretation – N.C.D., Ö.E., F.D., T.Ö, P.F.Y.; Literature search – N.C.D., P.F.Y.; Writing – N.C.D., T.Ö., P.F.Y.; Critical review – N.C.D., T.Ö., P.F.Y.

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