Support Care Cancer (2016) 24:2075–2084
DOI 10.1007/s00520-015-2997-x

ORIGINAL ARTICLE

Sarcopenia and inflammation are independent predictors of survival in male patients newly diagnosed with small cell lung cancer

Se-Il Go[1] · Mi Jung Park[2] · Haa-Na Song[1] · Myoung Hee Kang[1] · Hee Jung Park[3] · Kyung Nyeo Jeon[2] · Seok-Hyun Kim[3] · Moon Jin Kim[4] · Jung-Hun Kang[5] · Gyeong-Won Lee[5]

Received: 8 June 2015 / Accepted: 26 October 2015 / Published online: 7 November 2015

Abstract
Purpose Sarcopenia is suggested to be associated with cancer-related inflammation. We assessed the clinical outcome of small cell lung cancer (SCLC) patients according to sarcopenia and the neutrophil-to-lymphocyte ratio (NLR).
Methods A total of 117 male SCLC patients treated with first-line chemo- or chemoradiotherapy were assessed based on a retrospective chart review. The mass of the pectoralis muscle was measured by computed tomography and normalized to height. Patients with the lowest quartile of muscle mass were considered to have sarcopenia. Patients were classified into four groups according to their sarcopenia and NLR statuses: sarcopenia/high NLR, sarcopenia/low NLR, non-sarcopenia/high NLR, and non-sarcopenia/low NLR.
Results Sarcopenic patients had lower progression-free survival (PFS) than did non-sarcopenic patients (median 6.0 vs. 7.5 months, $p=0.009$), but the difference in overall survival (OS) was not statistically significant (median 10.5 vs. 13.5 months, $p=0.052$). However, the OS of sarcopenic patients with high NLR was significantly lower than that in all other groups (median 3.2 vs. 16.0 vs. 12.5 vs. 13.7 months, respectively, $p<0.001$), as was PFS (median 3.2 vs. 7.7 vs. 7.6 vs. 7.1 months, respectively, $p<0.001$). On multivariate analysis, sarcopenia with high NLR was an independent prognostic factor for shorter PFS and OS. Early discontinuation of treatment (20.0 vs. 10.3 %) and treatment-related mortality (50.0 vs. 8.4 %) occurred more frequently in these patients than in the other groups ($p<0.001$).
Conclusions In SCLC, sarcopenic male patients with high NLR have a poor prognosis and do not tolerate standard treatment. Intensive supportive care is needed in these patients.

Keywords Sarcopenia · Cachexia · Neutrophil-to-lymphocyte ratio · Small cell lung carcinoma · Toxicity · Prognosis

Se-Il Go and Mi Jung Park contributed equally to this work.

✉ Gyeong-Won Lee
brightree24@gmail.com

[1] Division of Hematology-Oncology, Department of Internal Medicine, Gyeongsang National University Hospital, Gyeongsang National University School of Medicine, Jinju, Republic of Korea

[2] Department of Radiology, Gyeongsang National University Hospital, Gyeongsang National University School of Medicine, Jinju, Republic of Korea

[3] Division of Hematology and Medical Oncology, Department of Internal Medicine, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, Republic of Korea

[4] Myongji Hospital, Goyang, Republic of Korea

[5] Division of Hematology-Oncology, Department of Internal Medicine, Gyeongsang Institute of Health Science, Gyeongsang National University Hospital, Gyeongsang National University School of Medicine, Gangnam-ro 79, Jinju 660-702, Republic of Korea

Introduction

Sarcopenia, the loss of skeletal muscle mass and strength [1], is a key criterion for cancer cachexia [2]. Using dual-energy X-ray absorptiometry (DEXA), sarcopenia has been defined as appendicular skeletal muscle mass (kg)/height^2 (m^2) less than two standard deviations below the mean values for a young reference group [3]. Recently, computed tomography (CT) has also been recommended to identify patients with sarcopenia, because CT allows precise differentiation between fat and other soft tissues, including muscle, and is routinely

performed as a diagnostic assessment in those with cancer [4]. Previous studies based on CT imaging have demonstrated that sarcopenia is associated with poorer functional status [5], increased risk of chemotherapy toxicity [6, 7], and shorter survival [8, 9] in cancer patients. Even though cancer cachexia is characterized by "ongoing" loss of skeletal muscle mass [2], the prognostic value of muscle mass measured by CT imaging alone at a specific time point is limited. In one pilot study, the change in muscle mass during chemotherapy, but not sarcopenia at baseline, was a significant prognostic factor in patients with advanced non-small cell lung cancer [10]. Poor performance status (PS) and a history of involuntary weight loss may help identify patients with progressive loss of muscle mass [5, 11]. However, these factors are highly subjective, and their interpretation is variable among investigators.

Numerous studies have suggested that inflammation plays an important role in sarcopenia. First, several markers of immune activation, such as C-reactive protein, interleukin (IL)-6, and tumor necrosis factor (TNF)-α, are inversely related to mixed-muscle and myosin heavy chain protein synthesis rates [12]. More directly, TNF-α induces skeletal muscle protein loss [13] by activating nuclear factor-κB [14]. An interaction between the tumor and high levels of circulating IL-6 creates an environment favoring catabolism of skeletal muscle [15]. Furthermore, the anorectic effects of proinflammatory cytokines may negatively influence skeletal muscle through indirect mechanisms [16]. The neutrophil-to-lymphocyte ratio (NLR) is a useful and inexpensive marker of systemic inflammation, and its prognostic value has been validated in various solid tumors [17–20]. Colorectal cancer patients with a high NLR have a significantly lower skeletal muscle index (SMI) [18], and NLR is higher in underweight than in obese patients after chemotherapy for advanced-stage ovarian cancer [19].

Small cell lung cancer (SCLC) is an aggressive and rapidly growing malignancy. Despite a high response rate to systemic chemotherapy, this cancer is rarely cured due to a high relapse rate [21]. Although weight loss is one of the factors associated with poor prognosis [22], the relationship between sarcopenia and SCLC outcomes has not been examined. Therefore, in this study, we investigated the prognostic value of sarcopenia through baseline CT imaging in newly diagnosed SCLC patients treated with chemotherapy or chemoradiotherapy. Additionally, to elucidate the relationship between sarcopenia and systemic inflammation, clinical outcomes were analyzed according to both sarcopenia and NLR statuses.

Methods

Patients

Based on a retrospective chart review, we identified all consecutive male patients diagnosed with SCLC and treated with first-line chemotherapy or chemoradiotherapy between July 2006 and December 2013 at the Gyeongsang National University Hospital (GNUH). Those patients who had available baseline CT scans of the chest were included in this study. Female patients were excluded because of the small case number and physiologically lower muscle mass, which would require statistical adjustment. Other exclusion criteria were as follows: decision to refuse chemotherapy, lack of baseline complete blood count with differential, and active infection at diagnosis. This study was approved by the institutional review board of GNUH.

Muscle mass measurement

Contrast-enhanced CT examinations were performed using a 64-detector CT (Brilliance-64; Philips Medical Systems, the Netherlands), with a detector configuration of 64×0.625 mm, a tube voltage of 120 kVp, a fixed tube current of 200 mAs, a pitch of 0.923, a gantry rotation time of 0.5 s, and a smooth reconstruction filter (Philips "B" filter). Following administration of 80 mL iohexol (Omnipaque 350, GE Healthcare, Waukesha, WI, USA) delivered at a rate of 2.5 mL/s, the patient, in the arm-raised position, was asked to hold his breath at full inspiration. The whole lung parenchyma, from the lung apex to the diaphragm, was scanned in the craniocaudal direction with a minimal scan delay of 7 s. Bolus tracking was performed in the aortic arch with an attenuation threshold of 150 HU.

The mass of the pectoralis muscle, including pectoralis major and minor, was approximated by measuring the cross-sectional area on CT by two independent radiologists. Reconstructed axial images with a 3-mm slice thickness and 3-mm interval were analyzed at the level of the fourth thoracic vertebra. The region of interest (ROI) was drawn freehand at the outermost border of the pectoralis muscles, and its area, ranging from −29 to 100 HU, was calculated using CT histogram analysis ("X section" analysis tool, Advantage Window 4.4; GE Healthcare, Milwaukee, WI, USA). The areas of the left and right pectoralis muscles were measured separately and averaged. Muscle area was normalized to height in meters squared (m^2) and reported as T4 SMI (mm^2/m^2).

Data collection and definitions

Clinical data including demographics, Eastern Cooperative Oncology Group (ECOG) PS, tumor stage, initial serum lactate dehydrogenase (LDH) level, and treatment information were collected from electronic medical records. Using the National Health Insurance Service Program run by the Ministry of Health and Welfare, Republic of Korea, we confirmed the survival status and the date of death of patients with follow-up loss. Poor PS was defined as an ECOG score ≥2. Tumor response to first-line treatment was assessed by the

Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [23]. Treatment-related mortality (TRM) was defined as death due to any cause other than disease progression during or within 30 days of the last cycle of first-line treatment. Early discontinuation and dose reduction of the first-line treatment due to toxicity were also recorded. Patients who experienced TRM or early discontinuation of the first-line treatment before the first evaluation of treatment response were excluded from the analysis for response to treatment.

Body mass index (BMI) was calculated from the weight and height measured at diagnosis (weight in kilograms divided by height in meters squared). BMI categories were defined according to the World Health Organization recommendation for Asian populations: underweight, <18.5 kg/m^2, and normal to obese, ≥18.5 kg/m^2 [24].

Patients with T4 SMI in the lowest quartile among this sample were considered to have sarcopenia. The NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count measured at diagnosis. The cutoff values of NLR reported in previous studies are highly variable with a range from 2.5 to 5 in lung cancer [25, 26]. Furthermore, in SCLC, the cutoff value of NLR has not been determined due to the paucity of data. In this study, based on the cutoff value reported in our previous study on SCLC [20], a NLR≥4 was considered high. Additionally, patients were grouped according to their sarcopenia and NLR statuses: sarcopenia with high NLR, sarcopenia with low NLR, non-sarcopenia with high NLR, and non-sarcopenia with low NLR.

Statistical analysis

Chi-square and Fisher's exact tests were used to compare categorical variables. Progression-free survival (PFS) was defined as the time from diagnosis to first progression, death from any cause, or last follow-up. Overall survival (OS) was defined as the time from diagnosis to death from any cause or last follow-up. The Kaplan-Meier method was used to estimate survival, and differences were compared by log-rank test. All variables with a p value <0.10 were included in multivariate analysis using a Cox proportional hazards model with the enter selection method. A p value <0.05 was considered statistically significant. All statistical analysis was performed using SPSS version 21.0 software (SPSS, Chicago, IL, USA).

Results

Patient characteristics

A total of 117 consecutive male patients met the eligibility criteria during the study period. The cutoff value for the lowest quartile of T4 SMI was 437 mm^2/m^2; 29 patients had a SMI lower than this value and were thus classified as sarcopenic. Comparison of characteristics between sarcopenic and non-sarcopenic groups is described in Table 1. As expected, the proportion of patients who were underweight tended to be higher among sarcopenic (20.7 %) than non-sarcopenic patients (6.8 %, p=0.070). Old age, poor PS, and extensive disease (ED) were more frequent in sarcopenic than in non-sarcopenic patients, but these differences were not statistically significant. TRT, applied mainly to patients with limited disease (LD), was less commonly performed in sarcopenic patients (p=0.008), while treatments with irinotecan and cisplatin were more common (p=0.017). Other variables including smoking status, LDH, prophylactic cranial irradiation (PCI), NLR, and response to first-line treatment were not different between the two groups (Table 1).

Survival analysis according to sarcopenia status

Over a median follow-up duration of 41.9 (range 2.6–92.5) months, 94 patients died. For all 117 patients, the median PFS and OS were 6.9 (95 % CI 6.2–7.6) and 12.5 (95 % CI 9.2–15.8) months, respectively. Sarcopenic patients had a shorter PFS than non-sarcopenic patients (median 6.0 vs. 7.5 months, p=0.009; Fig. 1a), but the difference in OS between the two groups was of borderline significance (median 10.5 vs. 13.5 months, p=0.052; Fig. 1b).

Subgroup analysis was performed with stratification by age and stage (Table 2). In patients ≥65 years of age, sarcopenia was associated with shorter PFS (p=0.007) and OS (p=0.026), whereas in patients <65 years of age, there was no significant difference in PFS (p=0.526) or OS (p=0.989) between the sarcopenia and non-sarcopenia groups. When stratified by stage, sarcopenic patients had shorter PFS (p=0.013) and OS (p=0.005) than non-sarcopenic patients with limited, but not extensive, disease (PFS, p=0.734; OS, p=0.695).

Survival analysis according to sarcopenia and NLR statuses

As mentioned in the "Methods" section, patients were classified into four groups according to their sarcopenia and NLR statuses, and survival was compared among these groups (Fig. 2). Whereas all patients with sarcopenia and a high NLR died or had disease progression within 7 months after diagnosis, sarcopenic patients with a low NLR did not show any difference in PFS when compared with non-sarcopenic patients (median PFS, 3.2 vs. 7.7 vs. 7.6 vs. 7.1 months, respectively, p<0.001; sarcopenic/high NLR vs. all others, p<0.001; sarcopenic/low NLR vs. non-sarcopenic/high NLR and vs. non-sarcopenic/low NLR, p=0.905 and p=0.249, respectively; Fig. 2a). A similar result was observed in the analysis for OS (median OS, 3.2 vs. 16.0 vs. 12.5 vs. 13.7 months, respectively, p<0.001; sarcopenic/high NLR vs. sarcopenic/

Table 1 Patient characteristics

Factor	Total $n=117$	Sarcopenia $n=29$	Non-sarcopenia $n=88$	p value
Age (years)				0.165
<65	45 (38.5)	8 (27.6)	37 (42.0)	
≥65	72 (61.5)	21 (72.4)	51 (58.0)	
Smoking				0.436
Non-smoker	2 (1.7)	1 (3.4)	1 (1.1)	
Smoker	115 (98.3)	28 (96.6)	87 (98.9)	
ECOG PS				0.119
0–1	96 (82.1)	21 (72.4)	75 (85.2)	
2–3	21 (17.9)	8 (27.6)	13 (14.8)	
Stage				0.075
LD	53 (45.3)	9 (31.0)	44 (50.0)	
ED	64 (54.7)	20 (69.0)	44 (50.0)	
LDH				0.300
Normal	50 (42.7)	10 (34.5)	40 (45.5)	
Elevated	67 (57.3)	19 (65.5)	48 (54.5)	
First-line CTx regimen				0.017
Etoposide and platinum	104 (88.9)	22 (75.9)	82 (93.2)	
Irinotecan and cisplatin	13 (11.1)	7 (24.1)	6 (6.8)	
Thoracic RT				0.008
Yes	53 (45.3)	7 (24.1)	46 (52.3)	
No	64 (54.7)	22 (75.9)	42 (47.7)	
PCI				0.410
Yes	41 (35.0)	12 (41.4)	29 (33.0)	
No	76 (65.0)	17 (58.6)	59 (67.0)	
Response to first-line treatment[a]				0.615
CR or PR	105 (95.5)	23 (95.8)	82 (95.3)	
SD or PD	6 (4.5)	2 (8.0)	4 (4.7)	
Body mass index (kg/m^2)				0.070
<18.5 (underweight)	12 (10.3)	6 (20.7)	6 (6.8)	
≥18.5 (normal to obese)	105 (89.7)	23 (79.3)	82 (93.2)	
NLR				0.617
<4	81 (69.2)	19 (65.5)	62 (70.5)	
≥4	36 (30.8)	10 (34.5)	26 (29.5)	

ECOG PS Eastern Cooperative Oncology Group performance status, *LD* limited disease, *ED* extensive disease, *LDH* lactate dehydrogenase, *CTx* chemotherapy, *RT* radiotherapy, *PCI* prophylactic cranial irradiation, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NLR* neutrophil-to-lymphocyte ratio. Values are presented as numbers of patients (percentages)

[a] Six patients who experienced treatment-related mortality before the first evaluation for treatment response were excluded from the analysis for response to treatment

low NLR, non-sarcopenic/high NLR, and non-sarcopenic/low NLR, $p=0.003$ and $p=0.008$, $p<0.001$, respectively; sarcopenic/low NLR vs. non-sarcopenic/high NLR and vs. non-sarcopenic/low NLR, $p=0.813$ and $p=0.395$, respectively; Fig. 2b). There were no significant differences in PFS or OS between non-sarcopenic patients with a high versus low NLR. Given the poor prognosis and small sample size of the sarcopenic, high NLR patients, this group was compared with all other patients as one group.

Survival between patients with sarcopenia and high NLR versus all other patients was compared after stratification by age and stage. In patients ≥65 years of age, the sarcopenic, high NLR patients survived for shorter periods without progression (median 3.2 vs. 6.9 months, $p<0.001$) and overall (median 3.2 vs. 13.0 months, $p=0.001$) than did the other patients. In contrast to the subgroup analysis (Table 2), PFS (median 3.2 vs. 6.5 months, $p<0.001$) and OS (median 3.2 vs. 10.9 months, $p=0.035$) were also significantly shorter in the

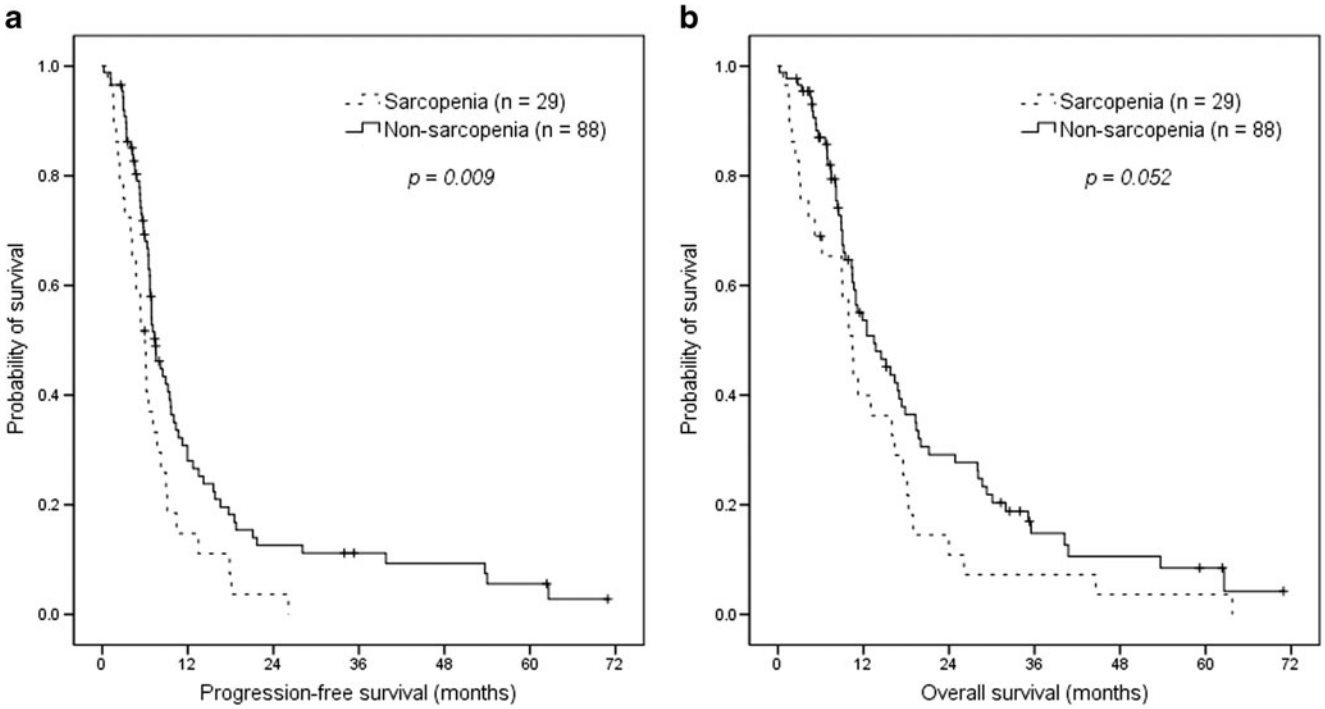

Fig. 1 Kaplan-Meier curves for **a** progression-free survival (PFS) and **b** overall survival (OS) by sarcopenia status

sarcopenic, high NLR patients than in other patients with ED. Subgroup analyses in patients <65 years of age and those with LD were not informative due to their small numbers (n=2 in each subgroup).

On univariate analysis for PFS, poor PS, ED, elevated LDH, irinotecan and cisplatin regimen, no PCI, underweight BMI, and sarcopenia with high NLR were poor prognostic factors. On multivariate analysis, ED (HR, 1.849; 95 % CI, 1.139–3.000, p=0.013), no PCI (HR, 1.730; 95 % CI, 1.086–2.754, p=0.021), and sarcopenia with high NLR (HR, 3.805; 95 % CI, 1.774–8.158, p=0.001) were independent poor prognostic factors. On univariate analysis for OS, poor PS, ED, no PCI, and sarcopenia with high NLR were associated with poor prognosis; ED (HR, 1.763; 95 % CI, 1.128–2.757, p=0.013) and sarcopenia with high NLR (HR, 2.230; 95 % CI, 1.048–4.743, p=0.037) were confirmed by multivariate analysis as independent poor prognostic factors (Table 3).

Treatment course and toxicity

Of 117 patients, the chemotherapeutic dose was reduced after the first cycle due to toxicity in 41 (35.0 %). Early

Table 2 Subgroup analysis for survival according to sarcopenia status

Sarcopenia status		Number	PFS (months)			OS (months)		
			Median	95 % CI	p	Median	95 % CI	p
Age (years)								
<65	Sarcopenic	8	7.7	3.6–11.8	0.526	10.5	9.2–11.8	0.989
	Non-sarcopenic	37	7.5	6.7–8.4		13.5	8.7–18.3	
≥65	Sarcopenic	21	4.8	3.0–6.5	0.007	9.9	3.4–16.5	0.026
	Non-sarcopenic	51	7.4	5.1–9.6		13.7	8.0–19.5	
Stage								
LD	Sarcopenic	9	4.2	3.6–4.8	0.013	5.2	2.5–7.9	0.005
	Non-sarcopenic	44	10.3	7.3–13.4		19.7	11.2–28.2	
ED	Sarcopenic	20	6.0	4.6–7.4	0.734	10.6	8.7–12.4	0.695
	Non-sarcopenic	44	6.5	5.1–7.8		10.4	8.8–12.1	

PFS progression-free survival, *OS* overall survival, *CI* confidence interval, *LD* limited disease, *ED* extensive disease

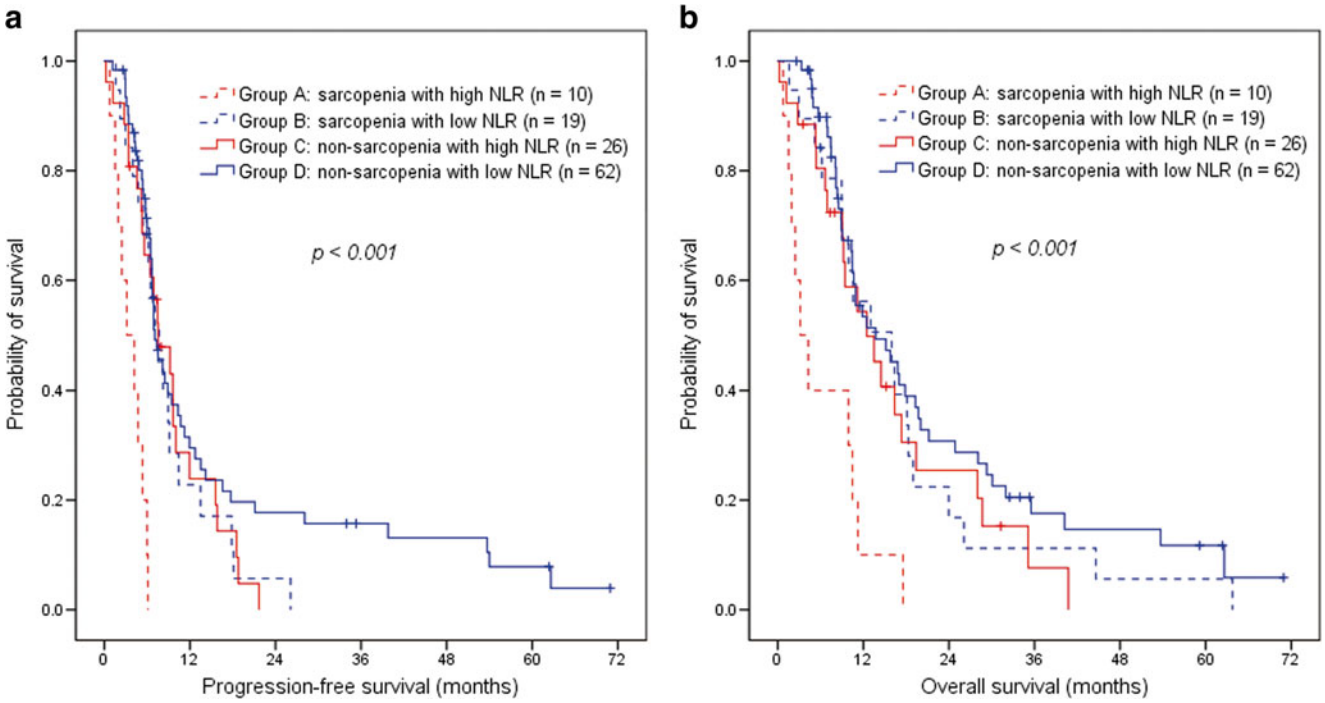

Fig. 2 Kaplan-Meier curves for **a** PFS and **b** OS by sarcopenia and neutrophil-to-lymphocyte ratio (NLR) statuses

discontinuation of first-line treatment due to toxicity and TRM occurred in 13 (11.1 %) and 14 (12.0 %) patients, respectively. Dose reduction was more frequent among sarcopenic than among non-sarcopenic patients (51.7 vs. 29.5 %, p=0.030); there was no significant difference in the incidence between sarcopenic/high NLR patients and all others (50.0 vs. 33.6 %, p=0.317). The incidence of early discontinuation due to toxicity did not differ between sarcopenic and non-sarcopenic patients (10.3 vs. 11.4 %), while TRM tended to occur more frequently in sarcopenic patients (24.1 vs. 8.0 %) (p=0.066; Fig. 3, left). In contrast, early discontinuation due to toxicity was observed more frequently in the sarcopenic/high NLR patients than in the others (20.0 vs. 10.3 %) and the difference in the incidence of TRM was much greater (50.0 vs. 8.4 %) (p<0.001, Fig. 3, right). A poor PS at baseline was more commonly observed in patients with sarcopenia and high NLR than in the others (50.0 vs. 15.0 %, p=0.016).

Discussion

This study demonstrates the impact of sarcopenia on prognosis in male patients with SCLC. Despite the lack of a difference in the response rate, sarcopenia was a significant predictor of a shorter PFS; OS also tended to be shorter in sarcopenic than in non-sarcopenic patients. Currently, there is little evidence that sarcopenia itself is related to a poor response to chemotherapy. In contrast, Fabbro et al. reported that the rate of a complete response to neoadjuvant chemotherapy in patients with operable breast cancer was significantly higher in sarcopenic patients [27], which may result from greater drug exposure caused by sarcopenia-associated alterations in the distribution, metabolism, and clearance of anticancer drugs [28]. Higher drug exposure in sarcopenic patients, however, would correlate with increased chemotherapy toxicity, leading to early cessation of therapy and early relapse [29–31]. In our study, dose reduction due to toxicity and TRM were observed more frequently in sarcopenic than in non-sarcopenic patients, which could explain the difference in PFS. Our finding of greater differences in survival according to sarcopenia status in subgroups expected to have greater treatment toxicity, such as those ≥65 years of age and those with LD, supports this conclusion.

Another important finding in this study is that among the patients with sarcopenia, only those with a high NLR had a grave prognosis; PFS and OS in sarcopenic patients with a low NLR were similar to those in non-sarcopenic patients. In contrast, in the analysis of sarcopenia status alone, a poor prognosis in sarcopenic patients with a high NLR was confirmed in those with ED as well as those ≥65 years of age, although the small number of patients with both sarcopenia and a high NLR prevented comparison of those <65 years of age and those with LD. Notably, although there was no difference in the incidence of dose reduction between sarcopenic patients with a high versus low NLR, the incidence of early discontinuation of first-line treatment due to toxicity was higher, and TRM occurred fivefold more frequently in sarcopenic/high NLR patients than in all others. Moreover, all sarcopenic/high NLR patients who did not die from TRM had rapid disease progression. These findings indicate that

Table 3 Univariate and multivariate analyses for survival

Factor	PFS						OS					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95 % CI	*p*	HR	95 % CI	*p*	HR	95 % CI	*p*	HR	95 % CI	*p*
Age (years)												
<65	Ref.						Ref.					
≥65	1.046	0.694–1.578	0.830				1.117	0.734–1.700	0.605			
ECOG PS												
0–1	Ref.			Ref.			Ref.			Ref.		
2–3	1.785	1.087–2.933	0.022	1.275	0.719–2.260	0.406	1.836	1.112–3.029	0.017	1.323	0.758–2.311	0.325
Stage												
LD	Ref.			Ref.			Ref.			Ref.		
ED	2.360	1.540–3.617	<0.001	1.849	1.139–3.000	0.013	2.037	1.328–3.123	0.001	1.763	1.128–2.757	0.013
LDH												
Normal	Ref.			Ref.			Ref.					
Elevated	1.511	1.016–2.248	0.042	1.157	0.739–1.813	0.524	1.300	0.861–1.963	0.211			
First-line CTx regimen												
Etoposide and platinum	Ref.			Ref.			Ref.					
Irinotecan and cisplatin	1.754	0.973–3.163	0.062	1.570	0.794–3.107	0.195	1.201	0.664–2.173	0.544			
PCI												
Yes	Ref.			Ref.			Ref.			Ref.		
No	1.821	1.194–2.777	0.005	1.730	1.086–2.754	0.021	1.832	1.184–2.835	0.007	1.555	0.988–2.447	0.057
Body mass index (kg/m^2)												
≥18.5 (normal to obese)	Ref.			Ref.			Ref.					
<18.5 (underweight)	1.749	0.930–3.291	0.083	1.001	0.500–2.006	0.998	1.077	0.554–2.096	0.827			
Sarcopenia and NLR status												
Sarcopenic with low NLR and non-sarcopenic	Ref.			Ref.			Ref.			Ref.		
Sarcopenic with high NLR	5.991	2.925–12.268	<0.001	3.805	1.774–8.158	0.001	3.654	1.857–7.190	<0.001	2.230	1.048–4.743	0.037

PFS progression-free survival, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval, *ECOG PS* Eastern Cooperative Oncology Group performance status, *LD* limited disease, *ED* extensive disease, *LDH* lactate dehydrogenase, *CTx* chemotherapy, *PCI* prophylactic cranial irradiation, *NLR* neutrophil-to-lymphocyte ratio

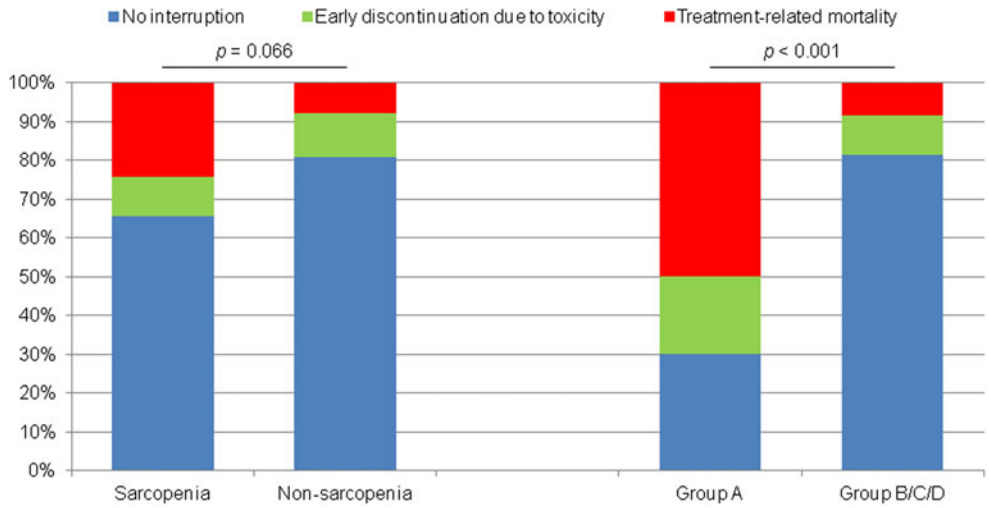

Fig. 3 Comparison of the rate of early discontinuation of treatment and treatment-related mortality according to sarcopenia and NLR statuses. *Group A* sarcopenia with high NLR, *Group B* sarcopenia with low NLR, *Group C* non-sarcopenia with high NLR, and *Group D* non-sarcopenia with low NLR

sarcopenic patients with a high NLR have very aggressive disease refractory to the current standard first-line treatment, which these patients cannot tolerate.

As mentioned in the "Introduction" section, inflammation is closely associated with the progression of sarcopenia [12–16]. Thus, we hypothesized that a high NLR, a marker of progressive inflammation, is related to the ongoing loss of muscle mass rather than pre-existing sarcopenia in cancer patients. A recent international consensus concluded that a diagnosis of cancer cachexia requires both ongoing weight loss of more than 2 % and sarcopenia [2]. Based on this information, we suggest that sarcopenia alone is insufficient to diagnose cancer cachexia, and a high NLR in cancer patients with sarcopenia may be an "objective alternative" to the subjective evaluation of weight loss. Further, rapid disease progression observed in sarcopenic patients with a high NLR in our study may be explained by the relationship between cancer cachexia, rather than sarcopenia itself, and aggressive tumor characteristics. For example, the activin signal is related to promotion of cachexia and enhanced cellular growth in some pancreatic cancers via a non-SMAD pathway [32]. Similarly, time to tumor progression was shorter in sarcopenic patients compared with non-sarcopenic patients in a prospective study for metastatic breast cancer [6]. Proinflammatory cytokines, including TNF-α, IL-1β, IL-6, and IFN-γ, produced by tumor cells or by host immune cells in response to the tumor, have been identified as key mediators of cancer cachexia [33]. These results are consistent with our findings that cancer cachexia may be related directly to tumor progression as well as intolerance to chemotherapy. In addition, in our study, half of the sarcopenic patients with a high NLR had poor PS. Rapid tumor progression may lead to a deteriorated PS in these cachectic patients, and poor PS together with higher drug exposure caused by sarcopenia-altered metabolism may result in severe intolerance to chemotherapy. Such an interaction would account for the greater frequency of early discontinuation due to toxicity and TRM in sarcopenic patients with a high versus low NLR.

The major limitation of this study was its retrospective study design and small sample size, limiting generalization of the results. The small sample size also prevented analysis of adverse events. In particular, the number of sarcopenic patients with a high NLR who had the worst prognosis was only 10. Despite the small sample size, the differences in survival and toxicity between these patients and other groups were striking. Therefore, further prospective studies with larger sample sizes are warranted to validate our findings. Another limitation was that the pectoralis muscle (T4 SMI in this study) has not yet been validated for predicting the prognosis of cancer patients. While lumbar SMI at the level of the third lumbar vertebra is a more common indicator of prognosis [4, 9, 29], lumbar vertebrae are not routinely scanned in CT examinations of lung cancer patients. As the pectoralis muscle is easy to identify, and its area can be standardized across cohorts [34] and has been reported to be associated with chronic obstructive pulmonary disease morbidity [34], our study suggests this measure may be a good surrogate marker of sarcopenia. Additionally, we defined the cutoff value for sarcopenia as the lowest quartile of T4 SMI. Several previous studies also used the lowest quartile of other muscle index as the cutoff value for sarcopenia [7, 35, 36]. The cutoff value of T4 SMI for sarcopenia used in this study needs to be more validated in future study. Another potential limitation is that the mass of the pectoralis muscle was measured in two-dimensional contrast-enhanced CT images and, thus, may not accurately reflect the entire muscle volume.

In conclusion, this study is the first to show that baseline sarcopenia is associated with poor prognosis and a high incidence of dose-limiting toxicity of the standard first-line treatment in male SCLC patients. This association is stronger in patients with a high NLR among those with sarcopenia. Given that the standard first-line treatment, etoposide or irinotecan

combined with platinum, has not changed in over 20 years [21, 37], intensive supportive care should be provided to cachectic patients with both sarcopenia and a high NLR. Additionally, we expect that the results of this study may help to identify patients who are most likely to benefit from clinical trials for cancer cachexia. A large-scale, prospective study is needed to confirm our results.

Acknowledgments No funding was received for the present study.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board and with the 1964 Helsinki declaration and its later amendments.

Informed consent This study is a retrospective analysis without any intervention and thus did not require informed consent.

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