Original Article

Sarcopenia is poor risk for unfavorable short- and long-term outcomes in stage I non-small cell lung cancer

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Background: Sarcopenia characterized by skeletal muscle loss may influence postoperative outcomes through physical decline and weakened immunity. We aimed to investigate clinical significance of sarcopenia in resected early-stage non-small cell lung cancer (NSCLC).

Methods: We retrospectively reviewed 315 consecutive patients with pathologic stage I NSCLC who had undergone lobectomy with systematic nodal dissection. Sarcopenia was defined as the lowest quartile of psoas muscle area on the 3rd vertebra on the high-resolution computed tomography (HRCT) image. Clinicopathological variables were used to investigate the correlation to postoperative complications as well as overall and recurrence-free survival.

Results: Upon multivariable analysis, male sex [odds ratio (OR) =5.780, 95% confidence interval (CI): 2.681–12.500, P<0.001], and sarcopenia (OR =21.00, 95% CI: 10.30–42.80, P<0.001) were independently associated with postoperative complications. The sarcopenia group showed significantly lower 5-over all survival (84.4% *vs.* 69.1%, P<0.001) and recurrence-free survival (77.2% *vs.* 62.0%, P<0.001) comparing with the non-sarcopenia group. In a multivariable analysis, sarcopenia was an independent prognostic factor [hazard ratio (HR) =1.978, 95% CI: 1.177–3.326, P=0.010] together with age ≥70 years (HR =1.956, 95% CI: 1.141–3.351, P=0.015) and non-adenocarcinoma histology (HR =1.958, 95% CI: 1.159–3.301, P=0.016).

Conclusions: This is the first study which demonstrates that preoperative sarcopenia is significantly associated with unfavorable postoperative complications as well as long-term survival in pathologic stage I NSCLC. This readily available factor on HRCT may provide valuable information to consider possible choice of surgical procedure and perioperative management.

Keywords: Skeletal muscle mass; psoas muscle; anti-cancer immunity; node-negative; surgery

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Introduction

Non-small cell lung cancer (NSCLC) is one of the most common cause of cancer-deaths worldwide (1). Lobectomy with systematic lymph node dissection has been a standard therapeutic option for early-stage NSCLC (2,3). A major lung resection including lobectomy often causes impaired immune system as well as cardiopulmonary function, resulting in increased risk of postoperative complications (4,5). Despite recent advances of diagnostics and

therapeutics in NSCLC, approximately 20–30% of patients with completely resected early-stage NSCLC develop recurrence which may arise from occult micrometastasis facilitated by tumor-promoting microenvironment during perioperative period (6), while post-recurrence survival is still poor (7).

Preoperative clinical status including age, tumor stage, and smoking history is generally assessed in patients with early-stage NSCLC. A better prediction of prognosis with using pretreatment clinical factors in early-stage NSCLC may lead appropriate decision-making on therapeutic strategy.

Recently, frailty is most often defined as a state of physiological decline associated with ageing (8,9). It was characterized by unintentional weight loss, weakness, exhaustion, slow walking speed, and low physical and mental activity so that frailty can be evaluated with using various subjective methods, for instance, self-evaluation questionnaires and the assessment of certain physical activities of daily life (10). Since sarcopenia does more specifically focus on decline of physical activity characterized by loss of skeletal muscle (11), sarcopenia is more quantitative and suitable for preoperative evaluation (12).

Lots of publications demonstrated its association to postoperative survival outcome in various pathologies including cardiovascular (13,14), chronic renal failure (15), and sepsis (16). In addition, its clinical significance in predicting survival outcomes of solid malignancies has been well documented (17-20). However, the clinical significance of sarcopenia in patients undergoing lung resection has not been well understood to date. Especially, prognostic significance of sarcopenia in thoracic surgery for NSCLC is controversial. On the background, we hypothesized that sarcopenia is associated with higher risk of either short- and long-term outcomes in patients with NSCLC resected. The aim of this study was to clarify whether sarcopenia is significant in predicting postoperative complications and long-term survival in patients with pathologic stage I NSCLC. We present the following article in accordance with the REMARK reporting checklist (available at http://dx.doi.org/10.21037/atm-20-4380).

Methods

Study design and patient's selection

This retrospective study was approved by the institutional review board at Sagamihara Kyodo Hospital (2018-004) and performed in adherence with the Declaration of Helsinki (as revised in 2013). During the period from April 2007 to July 2015, a total of 490 consecutive patients underwent surgery for primary lung cancer at our institution. Medical records of the patients were reviewed and the patients with pathologic stage I NSCLC who underwent complete resection were included as previously described (21,22). The following exclusion criteria were applied: (I) patients with history of lung cancer within past two years; (II) those with clinical stage II–IV disease; (III) those had undergone sublobar resection; (IV) those had undergone induction therapy prior to surgery, and (V) those with carcinoid or large cell neuroendocrine carcinoma.

Preoperative examination and surgical treatment

Preoperatively, a physical examination, blood chemistry analysis, pulmonary function test, bronchoscopy, chest radiography, and computed tomography (CT), brain magnetic resonance imaging (MRI), and integrated positron emission tomography scan and CT scan (PET/CT) were routinely performed. All patients underwent a lobectomy with systematic lymph node dissection. Our operative indication of lobectomy is predicted postoperative forced expiratory volume in 1 second (FEV1) larger than 0.8 L.

Preoperative CT scan and evaluation of sarcopenia

CT scan was routinely performed using 64-detector-row CT scanner (Light Speed VCT; General Electric, CT, USA). Whole chest and abdomen were scanned during a breath-hold at deep inspiration phase in supine position, and 1.25-mm thick high-resolution images were reconstructed using standard spatial-frequency reconstruction algorithm. Digital imaging and communications in medicine data was transferred to the commercially available workstation as previously described (Synapse Vincent; Fujifilm Medical Co., Tokyo, Japan) (23). On the workstation, psoas muscle area, a validated marker of sarcopenia, at the level of the top of the iliac crest was semi-automatically measured in all patients as shown in *Figure 1*. Sarcopenia was defined as the lowest sex-specific quartile in the average of both psoas muscle areas at preoperative CT scan as previously described (13,24).

Definition of postoperative complications

Postoperative complications were evaluated in accordance

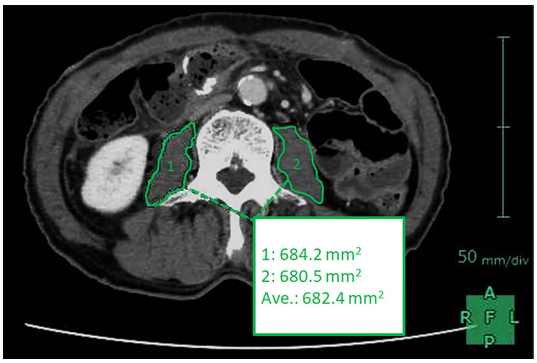

Figure 1 Representative high-resolution computed tomography image used in measuring psoas muscle area.

with Common Terminology Criteria for Adverse Events (version 4.03) (4,25). Severe morbidities were defined as grade 3 and higher of the classification, occurring within 30 days after surgery (3,5,25).

Based on our postoperative follow-up policy, we examined patients at 3-month intervals for the first 3 years and typically at 6-month intervals thereafter on an outpatient basis in accordance with the National Comprehensive Cancer Network guidelines (21,26). The routine follow-up evaluation included physical examination, chest radiography, chest CT, and blood analysis including serum tumor markers. Whenever any symptoms or signs of recurrence were detected, further evaluation was performed, including CT of the chest and abdomen, brain MRI, and bone scintigraphy, or PET/CT. Biopsy was performed for histological confirmation for diagnosis of recurrent disease if necessary. If unfeasible, radiological evidence of recurrent lesion was accepted by the institutional multidisciplinary board of lung cancer.

Statistical analysis

Overall survival (OS) was measured by comparing the date of surgery to the date of death from any cause or the date on which the patient was last known to be alive. The data cut-off was December 2019. Survival curves were plotted according to the Kaplan-Meier method and comparisons were drawn using the log-rank test in a univariable analysis. The recurrence-free survival (RFS) time was measured as the interval between the date of surgery and the date of recurrence, the date of death from any cause, or the most recent date on which the patient was last known to be alive. To determine the independent prognostic factors, a multivariable analysis was conducted using the Cox proportional hazard model as previously described (22,27). Two-category comparisons were performed using the Pearson χ^2 test and the Fisher exact test for quantitative data. We used the following variables into the statistical models: age at surgery (years), smoking index (pack-years), body mass index (kg/m^2), sex, diabetes mellitus, sarcopenia, forced vital capacity (FVC; L), %FVC, FEV1 (L), FEV1/FVC (%), and tumor diameter on high-resolution computed tomography (HRCT) (cm). All the tests were two-sided, and P values less than 0.05 were considered statistically significant. R software (version 3.2.2; R Foundation for Statistical Computing, Vienna, Austria) was used for the statistical analysis.

Results

Baseline demographic data

We included 489 patients with resected and pathologically diagnosed NSCLC patients. Then, 115 patients who had undergone sublobar resections, 3 with prior history of lung cancer, 2 who had undergone induction therapy before lung resection, 54 with clinically diagnosed stage II–IV disease, and 3 patients with carcinoid as well as 4 patients with large cell neuroendocrine carcinoma were excluded from the primary cohort in accordance with the exclusion criteria above (*Figure 2*). Our final study cohort was 315 patients with NSCLC who had undergone lobectomy with systematic lymph node dissection. The study cohort included 192 (61.0%) men and 123 (39.0%) women, with a median age of 70.0 years [quartile deviation (QD): 6.0 years]. Of the 315 patients, 201 (63.8%) had smoking history (*Table 1*). The median follow-up time was 58.8 months (range, 0.7–137.0 months). Histologically, 229 (72.7%) had adenocarcinoma, 73 (23.2%) had squamous cell carcinoma, and 13 (4.1%) had other histology. EGFR mutation status was wild type in 160 (50.8%), mutated in 95 (30.2%), and unknown in 60 (19.0%). For each patient, psoas muscle area was semi-automatically measured on preoperative HRCT as above (*Figure 1*). A median psoas muscle area was 673.53 (QD: 166.12) mm^2 for men and 525.52 (QD: 75.771) mm^2 for women (P<0.001) and the distribution was shown in Figure S1. In the current study, sarcopenia was defined as the lowest sex-specific quartile in the average of both psoas muscle areas at preoperative HRCT scan as previously described (13).

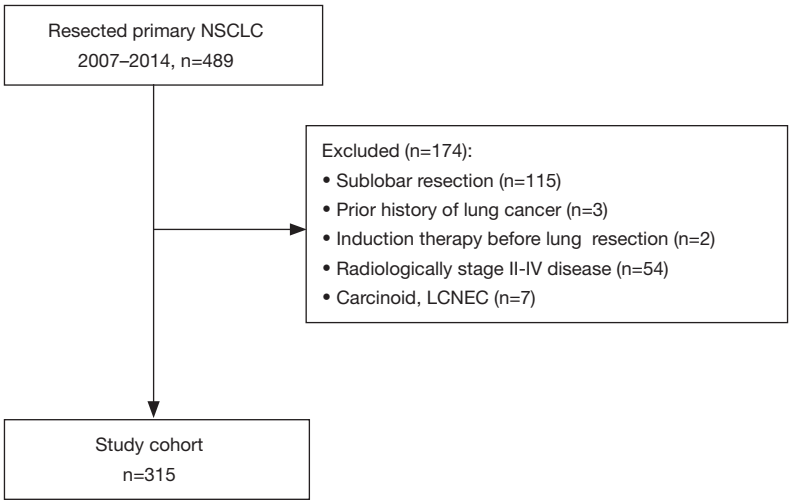

Figure 2 CONSORT diagram which demonstrates patient number included and excluded (the numbers include overlapping).

We thus performed following analysis with the cut-off value of 491.53 mm^2 for men and 460.55 mm^2 for women. Consequently, we have observed 38 cancer-related and 29 non-cancer-related deaths during the follow-up period in this study. Also, 54 patients have experienced recurrence.

Comparison of clinical data and sarcopenia as well as postoperative complications

Table 2 demonstrates correlation between sarcopenia and preoperative variables. The variables other than FEV1 (P<0.001) did not significantly differ according to presence or absence of sarcopenia.

Next, we investigated correlation between postoperative complications and clinical factors. As shown in *Table 3*, larger smoking index (P<0.001), lower body mass index (P=0.027), male sex (P<0.001), and sarcopenia (P<0.001) were significantly associated with postoperative severe complications. Among the postoperative severe complications observed in 82 cases (26.0%), pulmonary fistula (41/315, 13.0%) was the most frequent, followed by atrial fibrillation (18/315, 5.7%), atelectasis (15/315, 4.8%), and pneumonia (14/315, 4.4%) as shown in Table S1. To investigate independent risk factors, a multivariable logistic regression analysis was performed (*Table 4*). As a result, male sex [odds ratio (OR) =5.780; 95% confidence interval (CI), 2.681–12.500; P<0.001] and sarcopenia (OR =21.00; 95% CI, 10.30–42.80; P<0.001) were independently associated with postoperative severe complications.

Survival analyses

We then performed univariable and multivariable prognostic analysis of OS using Cox hazard model (*Table 5*). In the univariable analysis, age at surgery ≥70 years [hazard ratio (HR) =2.027; 95% CI, 1.217–3.376; P<0.001], male sex (HR =2.387; 95% CI, 1.359–4.184, P<0.001), smoking index ≥400 pack-years (HR =2.496; 95% CI, 1.467–4.247, P<0.001), serum carcinoembryonic antigen (CEA) ≥5.0 ng/mL (HR =1.991; 95% CI, 1.183–3.350, P<0.001), sarcopenia (HR =2.237; 95% CI, 1.374–3.625, P<0.001), and non-adenocarcinoma histology (HR =2.771; 95% CI, 1.708–4.464, P<0.001) were significant unfavorable prognostic factors in OS. Then, multivariable analysis using these factors revealed that age at surgery ≥70 years (HR =1.956; 95% CI, 1.141–3.351, P=0.015), serum CEA ≥5.0 ng/mL (HR =1.040; 95% CI, 1.024–1.056, P<0.001), sarcopenia (HR =1.978; 95% CI, 1.177–3.326, P=0.010), and non-adenocarcinoma (HR =1.958; 95% CI, 1.159–3.301, P=0.016) were independently associated with unfavorable OS. Additionally, prognosticators of RFS were investigated using Cox regression models. Univariable analysis demonstrated that age at surgery ≥70 years (HR =1.593; 95% CI, 1.051–2.415, P=0.022), male sex (HR =1.542; 95% CI, 1.009–2.325, P=0.043), smoking index ≥400 pack-years (HR =1.567; 95% CI, 1.034–2.376, P=0.034), serum CEA ≥5.0 ng/mL (HR =1.034; 95% CI, 1.021–1.049, P<0.001), and sarcopenia (HR =2.316; 95% CI, 1.592–3.324, P<0.001) were significant prognostic factors in RFS. In the multivariable analysis, age

Table 1 Baseline characteristics of the patient cohort (n=315)

Characteristics	Value
Age, median [range]	70 [35–88]
Gender	
Male	192
Female	123
Smoking history	
Never-smoker	114
Ex or current smoker	201
Body mass index (kg/m^2), median (range)	22.5 (14.9–33.3)
FVC (L), median (range)	3.04 (1.44–5.99)
%FVC (%), median (range)	109.2 (53.1–174.7)
FEV1 (L), median (range)	2.19 (1.14–4.76)
FEV1/FVC (%), median (range)	74.1 (35.7–98.9)
Comorbidities	
Hypertension	100
Chronic obstructive pulmonary disease	55
Diabetes mellitus	47
Interstitial lung disease	12
Infectious lung disease	8
Tuberculosis	6
Acute coronary disease	8
Chronic kidney disease	3
Histology	
Adenocarcinoma	229
Squamous cell carcinoma	73
Adenosquamous carcinoma	5
Large cell carcinoma	8

FVC, forced vital capacity, FEV1, forced expiratory volume in 1 second.

at surgery ≥70 years (HR =1.594; 95% CI, 1.065–2.319, P=0.034), serum CEA ≥5.0 ng/mL (HR =1.037; 95% CI, 1.021–1.056, P<0.001), and sarcopenia (HR =1.914; 95% CI, 1.237–2.894, P=0.005) were independent prognostic factors of RFS (Table S2).

To illustrate survival differences according to presence or absence of sarcopenia, Kaplan-Meier curves were generated. As shown in *Figure 3A*, non-sarcopenia group had a 5-year OS probability of 84.4% which was significantly better compared with 69.1% of sarcopenia group (P<0.001). Sarcopenia was also associated with unfavorable RFS (5-year RFS, 62.0% of sarcopenia group *vs.* 77.2% of non-sarcopenia group; P<0.001; *Figure 3B*).

Discussion

The current data demonstrated that sarcopenia was an independent risk factor for postoperative severe complications as well as RFS in patients with resected stage I NSCLC. Our hypothesis was shown to be correct as above.

Our findings may be reliable as our study cohort which was consisted of homogeneous patients in terms of disease stage and race. Several previous reports have demonstrated that sarcopenia is a prognostic factor after surgery in resected NSCLC (28,29). To our knowledge, only 3 publications documented significant correlation between sarcopenia and postoperative complication after surgery NSCLC (30-32). On the other hand, it has been well documented regarding significant correlation between sarcopenia and postoperative complications following surgical resection in other solid malignancy (33-38). In NSCLC patients, however, there are some reports which demonstrated sarcopenia as an unfavorable prognostic impact on OS (29,32,39-43), among them 3 employed only stage I NSCLC patients (40,41,43). Altogether, this is the first publication which demonstrates clinical significance of sarcopenia on both long- and short-term outcomes after surgery in patients with stage I NSCLC. The findings are mostly consistent with previous literature as above (29-32,39-43), even our data is limited to stage I NSCLC which may emphasize clinical significance of sarcopenia in surgically resected NSCLC. Previous studies used various measurement methods and cut-off values in evaluating sarcopenia. Although our "sarcopenia group" may reflect slightly weakened physical properties because we employed the lowest quartile of psoas muscle area as the cut-off value, it should include some of just relatively sarcopenic patients in the current study. Although there are some controversies respect to evaluation methods of sarcopenia, our findings may suggest clinical relevance in short- and long-term outcomes with evaluating "pre-sarcopenia" even in early-stage NSCLC.

Skeletal muscle loss is emerging issue in the context of sarcopenia and frailty which was reported to be decreasing as a patient becomes older with the decreases at an annual rate of 1% to 2% in average (44). Whereas the current data

Table 2 Baseline patient characteristics according to presence or absence of sarcopenia

Factors	Non-sarcopenia (n=236)	Sarcopenia (n=79)	P value*
Age at surgery (years)	70.2±7.5	70.4±5.0	0.197
Smoking habit (pack-years)	410±480	720±520	0.468
Body mass index (kg/m^2)	22.60±1.75	22.20±2.07	0.144
Male (%)	142 (60.2)	46 (58.2)	1.000
Diabetes mellitus (%)	24 (10.2)	12 (15.2)	0.352
FVC (L)	3.10±0.59	2.93±0.52	0.064
%FVC	110.0±11.8	107.0±12.7	0.069
FEV1 (L)	2.32±0.50	1.97±0.28	<0.001
FEV1/FVC (%)	74.60±6.43	72.90±6.50	0.160
Tumor diameter on HRCT (cm)	2.50±0.84	2.50±0.68	0.822

*, Mann-Whitney U-test for non-categorical factors and Fischer's exact test for categorical factors. FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; HRCT, high resolution computed tomography.

Table 3 Baseline patient characteristics according to presence or absence of postoperative complications

Factors	Complication (n=82)	No complication (n=233)	P value*
Age at surgery (years)	71.2±5.3	70.3±6.5	0.242
Smoking index (pack-years)	920±475	300±450	<0.001
Body mass index (kg/m^2)	21.90±1.95	22.70±1.76	0.027
Male (%)	65 (79.3)	127 (54.3)	<0.001
Diabetes mellitus (%)	12 (14.6)	26 (11.1)	0.453
Sarcopenia	53 (64.6)	26 (11.1)	<0.001
FVC (L)	3.23±0.58	2.99±0.53	0.057
%FVC	106.0±13.4	110.0±11.8	0.189
FEV1 (L)	2.07±0.55	2.21±0.49	0.899
FEV1/FVC (%)	72.10±9.88	74.60±5.78	0.059
Tumor diameter on HRCT (cm)	2.51±0.60	2.46±0.72	0.117

*, Mann-Whitney U-test for non-categorical factors and Fischer's exact test for categorical factors. FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; HRCT, high resolution computed tomography.

suggests that age at surgery is not necessarily related to the presence or absence of sarcopenia, which may be supported by the previous publications (13,30,43). It is thus indicated that sarcopenia may be caused by genetic factors, exercise habit, and nutrition status in addition to ageing.

Possible explanations for unfavorable long-term prognostic impact of sarcopenia are the following. First, sarcopenia is associated with impaired antitumor immunity via increased transforming growth factor β (TGF-β) and interleukin (IL)-6 in previously reported data (45,46). It may lead higher risk of recurrence and cancer-related death, resulting in shorter RFS and OS of sarcopenic patients. Second, it is reported that sarcopenic state could lead higher risk of short- and long-term complications following

Table 4 Multivariable logistic regression analysis of risk factors for postoperative complications

Variables	Odds ratio	95% CI	P value*
Smoking index ≥400 pack-years (*vs.* <400)	1.020	0.450–2.300	0.968
Body mass index <18.5 (*vs.* ≥18.5)	1.536	0.654–3.597	0.324
Male sex (*vs.* female)	5.780	2.681–12.500	<0.001
Sarcopenia (*vs.* non-sarcopenia)	21.00	10.30–42.80	<0.001
FEV1/FVC <70.0 (*vs.* ≥70.0)	1.610	0.817–3.170	0.169

*, logistic regression analysis was used. CI, confidence interval; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second.

Table 5 Univariable and multivariable Cox-regression analysis of overall survival

Variables	Univariable analysis			Multivariable analysis		
	Hazard ratio	95% CI	P value*	Hazard ratio	95% CI	P value*
Body mass index <18.5 (*vs.* ≥18.5)	1.716	0.782–3.765	0.178	N/A	–	–
Age ≥70 y/o (*vs.* <70 y/o)	2.027	1.217–3.376	<0.001	1.956	1.141–3.351	0.015
Male (*vs.* female)	2.387	1.359–4.184	<0.001	1.865	0.531–3.429	0.057
Smoking index ≥400 pack-years (*vs.* <400)	2.496	1.467–4.247	<0.001	1.272	0.575–2.813	0.552
Diabetes (*vs.* non-diabetes)	1.847	0.993–3.775	0.059	N/A	–	–
Serum CEA ≥5.0 ng/mL (*vs.* <5.0 ng/mL)	1.991	1.183–3.350	<0.001	1.040	1.024–1.056	<0.001
%FVC <80.0 (*vs.* ≥80.0)	1.116	0.404–3.083	0.832	N/A	–	–
FEV1/FVC% <70.0 (*vs.* ≥70.0)	1.156	0.704–1.897	0.567	N/A	–	–
Sarcopenia (*vs.* non-sarcopenia)	2.237	1.374–3.625	<0.001	1.978	1.177–3.326	0.010
Non-adenocarcinoma (*vs.* adenocarcinoma)	2.771	1.708–4.464	<0.001	1.958	1.159–3.301	0.016
Pathologic stage IB (*vs.* IA)	1.095	0.672–1.783	0.715	N/A	–	–

*, Cox-regression analysis was used. CI, confidence interval; CEA, carcinoembryonic antigen; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second.

surgical resection, including pneumonia which may result in higher risk of non-cancer related death (47,48). Muscle loss and dysfunction cause impaired respiratory function with increased TGF-β, IL-6, and tumor necrosis factor-α (TNF-α) (49-52). Third, sarcopenic patients are likely to be more sensitive to chemotherapy toxicity and have a lower response to chemotherapy (53,54).

Particularly, it is notable that there is certain correlation between sarcopenia and inflammation as well as anticancer immunity. However, the actual detailed pathophysiology of sarcopenia is complex and still unclear to date (55). Underlying cellular mechanisms of both sarcopenia and frailty are not well understood. Sarcopenic patients are reportedly on the systemic low-grade proinflammatory state in which increased pro-inflammatory cytokines including IL-1β, IL-6, TNF-α (56,57) and decreased IL-10 secreted by regulatory T lymphocyte was demonstrated in some publications (58). On the flip side, adiposity leads increased secretion of pro-inflammatory adipokines including lectin and decreased anti-inflammatory adipokines including adiponectin (59). In addition, reduced physical activity with ageing reportedly increases proinflammatory cytokines (60) and increased serum IL-6 is also significantly associated with development of sarcopenia (61). Inflammatory cytokines,

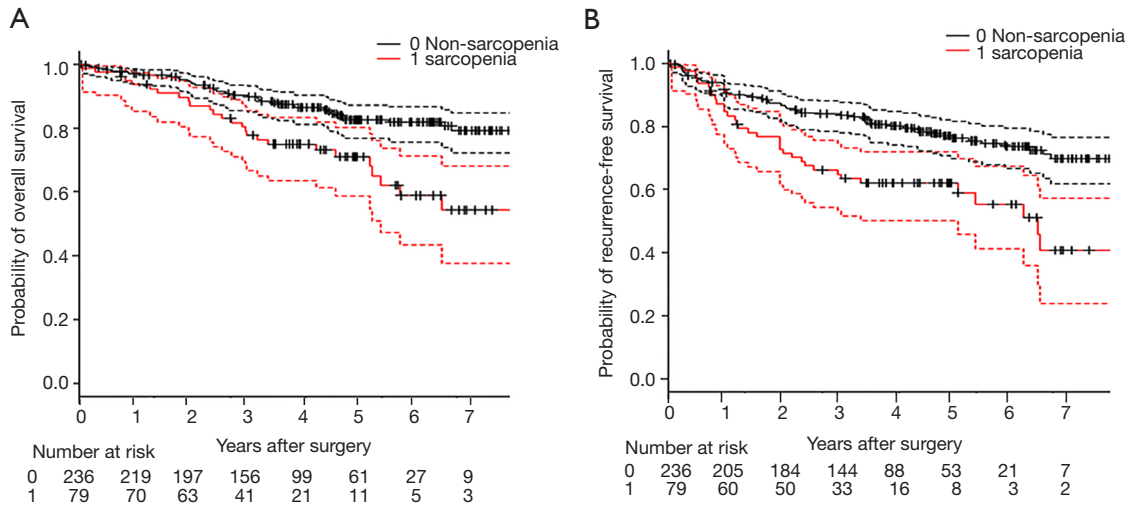

Figure 3 Overall and recurrence-free survival curves are well stratified according to sarcopenia. (A) Kaplan-Meier overall survival curves for patients with stage I NSCLC of sarcopenia (sarcopenia 1) and non-sarcopenia (sarcopenia 0) groups. The dotted curves represent 95% CI curves of the groups. (B) Kaplan-Meier recurrence-free survival curves for patients with stage I NSCLC of sarcopenia (sarcopenia 1) and non-sarcopenia (sarcopenia 0) groups. The dotted curves represent 95% CI curves of the groups. NSCLC, non-small cell lung cancer; CI, confidence interval.

which was produced by skeletal muscle after exercise, play a crucial role in complexed immune system (62). Then, inflammation with increased neutrophil migration causes muscle damage and impaired anti-tumor immune response (63).

Possible clinical application is another point. An important application of sarcopenia is potential to stratify patients at risk for recurrence as well as death. Also, there are some considerable choices in modifying perioperative management and treatment in sarcopenic patients. First, sarcopenic patients were at higher risk for short- and long-term postoperative outcomes compared with non-sarcopenic patients. It is thus one consideration to select sublobar resection or stereotactic body radio therapy instead of lobectomy with systematic lymph node dissection, even though it is still unclear whether sublobar resection or stereotactic radiotherapy can improve outcomes of the sarcopenic patients in actual. Second, sarcopenia could be reversible by the combination of nutrition support and exercise therapies in some range (64,65). Therefore, there is a possibility that perioperative nutrition support and intensive rehabilitation therapies lead improved outcomes of sarcopenic patients after pulmonary resection for NSCLC (66,67). Third, it is considerable choice to provide closer follow-up to the poor risk population, but it should be considered case-by-case basis together with other factors including pathologic lymphovascular invasion. Adjuvant chemotherapy for poor risk patients is another choice, even though careful patient selection is further required.

The definition of sarcopenia, especially evaluation method and cut-off value, is not well established to date. Measurement of psoas muscle area is simple and widely used method in evaluating sarcopenia. Some recent studies described that psoas muscle volume (53,68,69) or total skeletal muscle area (70) are more reliable and sensitive despite of the difficulty in measuring. We would also note that lowest quartile of muscle area has been widely used as the cut-off by previous investigators (13,71-73).

There are several limitations in the current study. First, the data were collected and analyzed retrospectively that can cause selection bias. Second, this is single-center study with relatively small sample size. Third, the current measurement method and cut-off value of psoas muscle area are possibly arbitrary even though there is no consensus regarding the cut-off value, measuring methods, and normalization in evaluating sarcopenia (13,71-73). In addition, it should be also noted that some publications demonstrated that contrast media and CT slice thickness can strongly affect the evaluation of skeletal muscle mass (74-76). It may cause methodological errors in evaluating sarcopenia. Although skeletal muscle area on CT imaging is the gold standard of evaluating sarcopenia, it is only an aspect of sarcopenia in

which includes multiple dimensions such as muscle mass, muscle strength, muscle quality, and physical performance. Recent studies have highlighted decline in the quality and strength of skeletal muscle mass in addition to the quantity (77-79). There are some possibilities that combination of the assessment of skeletal muscle area in addition to physiological and oncological factors could improve capacity to predict outcomes following pulmonary resection for NSCLC. Since skeletal muscle area may differ according to race, sex, and age, it may be difficult to generalize the current findings. We performed analysis with using sex-specific cut-off value, but our cohort consists of single race. That may cause one of the significant limitations.

Conclusions

In conclusion, it is clinically significant that the sarcopenia group demonstrated unfavorable outcomes in short- and long-term outcomes after surgical resection in only patients with stage I NSCLC. Psoas muscle area measurement is easily applicable as CT imaging is preoperative routine examination in general practice. Similarly, evaluation of sarcopenia may also enable modification of perioperative management, for example, indication of sublobar resection, nutrition support, intensive rehabilitation, follow-up examination, and adjuvant therapy. Further studies on modified management should shed a light on further clinical significance of sarcopenia in patients with early-stage NSCLC.

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Footnote

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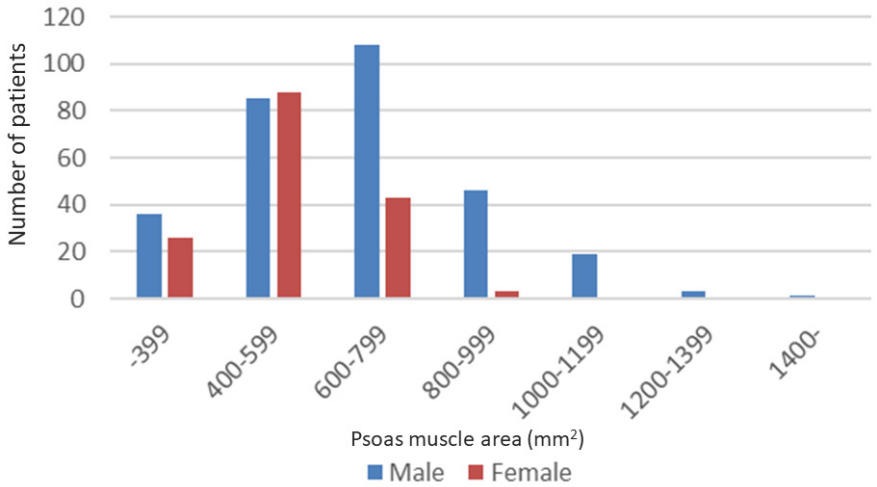

Figure S1 A bar graph that demonstrates distribution of psoas muscle area according to sex.

Table S1 Frequency of postoperative severe complications

Complications	N
Acute respiratory distress syndrome	3
Pneumonia	14
Pulmonary fistula	41
Bronchopleural fistula	3
Pleural effusion	3
Atelectasis	15
Atrial fibrillation	18
Cerebral infarction	4
Myocardial infarction	2
Pleural infection	4
Chylothorax	8
Delirium	2
Heart failure	1
Acute exacerbation of interstitial pneumonitis	2
Wound infection	4

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Table S2 Multivariable logistic regression analysis of recurrence-free survival

Variables	Univariable analysis			Multivariable analysis		
	Hazard ratio	95% CI	P value*	Hazard ratio	95% CI	P value*
Body mass index <18.5 (*vs.* ≥18.5)	1.542	0.654–2.674	0.194	N/A	–	–
Age ≥70 y/o (*vs.* <70 y/o)	1.593	1.051–2.415	0.022	1.594	1.065–2.319	0.034
Male (*vs.* female)	1.542	1.009–2.325	0.043	1.361	0.897–2.212	0.119
Smoking index ≥400 pack-years (*vs.* <400)	1.567	1.034–2.376	0.034	1.272	0.691–2.238	0.574
Diabetes (*vs.* non-diabetes)	1.368	0.694–2.168	0.282	N/A	–	–
Serum CEA ≥5.0 ng/mL (*vs.* <5.0 ng/mL)	1.034	1.021–1.049	<0.001	1.037	1.021–1.056	<0.001
%FVC <80.0 (*vs.* ≥80.0)	1.043	0.467–2.428	0.814	N/A	–	–
FEV1/FVC% <70.0 (*vs.* ≥70.0)	0.938	0.609–1.437	0.762	N/A	–	–
Sarcopenia (*vs.* non-sarcopenia)	2.316	1.592–3.324	<0.001	1.914	1.237–2.894	0.005
Non-adenocarcinoma (*vs.* adenocarcinoma)	1.512	0.897–1.983	0.112	N/A	–	–
Pathologic stage IB (*vs.* IA)	1.386	0.906–2.092	0.124	N/A	–	–

*, Cox-regression analysis was used. CI, confidence interval; CEA, carcinoembryonic antigen; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity.

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