



Sarcopenia predicts poor postoperative outcome in elderly patients with lung cancer

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Abstract

Purpose Sarcopenia gradually progress with age; hence, it is necessary to define sarcopenia to predict postoperative outcomes in elderly patients with lung cancer. The purpose of this study is to propose a definition of sarcopenia in elderly patients with lung cancer, and to demonstrate the post operative outcomes.

Methods Using computed tomography scans, the cross-sectional area (cm²) of the psoas muscle at the third lumbar vertebral level was measured. The psoas area was normalized for height. The psoas muscle mass index was calculated as total psoas muscle area at L3 level/height² (cm²/m²).

Results A total of 173 patients aged > 75 years of age received lobectomy for non-small cell lung cancer in our hospital. We defined sarcopenia as the psoas muscle mass index under 3.70 cm²/m² in males and 2.50 cm²/m² in females, based on the morbidity rate. The postoperative complication rate was significantly higher in patients with sarcopenia (62.5%) than in those without sarcopenia (22.7%). The 5-year survival rate was 26.5% in patients with sarcopenia, and 66.3% in patients without sarcopenia.

Conclusions In elderly lung cancer patients, sarcopenia was observed to be a high risk for morbidity and predicted poor prognosis.

Keywords Sarcopenia · Lung cancer · Elderly patients · Surgery

Introduction

Sarcopenia is defined as a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength, resulting in physical disability, poor quality of life, and death [1].

Patients with cancer frequently suffer from sarcopenia [2]. As prognosis depends not only on disease aggressiveness, but also on the patient's physical condition, sarcopenia can predict survival in patients with various types of malignancies [3–5]. For patients with lung cancer, several studies have shown that sarcopenia is an independent predictor of

poor postoperative survival [6–8], and only one study has shown that sarcopenia predicts major postoperative complications [8]. Postoperative morbidity is higher in elderly patients with lung cancer than in younger patients [9]. Furthermore, the incidence of postoperative complications may strongly predict poor prognosis [10]. In addition, skeletal muscle mass gradually declines with age [11].

On the basis of these reports, elderly patients with cancer are easy to become sarcopenic. Therefore, it is necessary to define sarcopenia which can predict postoperative complications and prognosis in these patients. Measuring the psoas muscle mass index (PMI) at the third lumbar level on computed tomography (CT) was proposed because it reflects the skeletal muscle mass of the whole body [11] so this can be used to define sarcopenia. The purpose of this study was to propose a definition of sarcopenia in elderly patients with lung cancer using PMI, and to demonstrate the association between postoperative outcomes and sarcopenia.

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Methods

Patients

Approval from the institutional review board was obtained for this study (Approval Number: 29–011). The requirement for patient consent was waived because of the retrospective nature of this study.

The data of 173 patients over 75 years of age who underwent lobectomy for non-small cell lung cancer (NSCLC) at our hospital between December 2005 and December 2017 were included. The routine preoperative assessments included a medical history, performance status evaluation, physical examination, basic blood tests, electrocardiogram, and pulmonary function testing. Clinical staging was based on CT scans of the chest and abdomen, brain CT or magnetic resonance imaging, radionuclide bone scan, and/or positron emission tomography with fluorine-18 fluorodeoxyglucose. Mediastinal and hilar lymph node status was defined as positive if the chest CT showed that the short axis of any node was greater than 1 cm. Mediastinoscopy and endobronchial ultrasound guided-biopsy were not routinely performed. The eighth edition of the TNM classification for lung cancer was used for preoperative staging. All intraoperative and postoperative events were recorded. Operative mortality included deaths that occurred within 30 days after the operation and deaths that occurred later during the same hospitalization period. Morbidity was defined as the occurrence of at least one postoperative event. Postoperative complications were assessed using Clavien–Dindo classification system. In this study, complications were included if they were classified into grade 2 or higher.

Measurements

Preoperative CT scans were performed within 3 months prior to surgery. The cross-sectional area (cm^2) of the right and left psoas muscle at third lumbar vertebral (L3) level on CT scans was measured by manual tracing (Fig. 1). Subsequently, the total psoas area was normalized for height. The PMI was calculated as follows; $\text{PMI} = \text{total psoas muscle area at L3 level}/\text{height}^2$ (cm^2/m^2).

Statistical analysis

Statistical analysis was performed using SPSS statistical software (version 22, SPSS, Inc, Chicago, IL, USA). We divided the patients into two groups: with and without sarcopenia. To compare the differences in patient characteristics between the two groups, we performed a multivariate

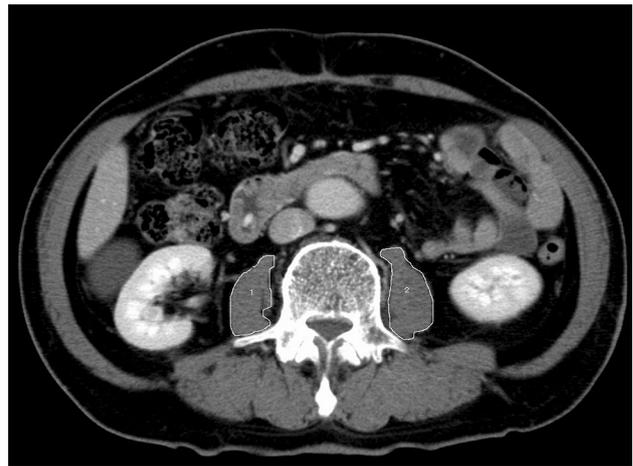


Fig. 1 Cross-sectional area (cm^2) of the psoas muscle at the level of the third lumbar vertebra (L3) measured by manual tracing on computed tomography scans

analysis using a logistic regression model. The postoperative complication rate was compared using the χ^2 test. Survival curves were constructed using the Kaplan–Meier method and overall survival rates were compared using log-rank test. Independent clinical factors associated with survival were calculated using Cox proportional hazard model. Results were considered statistically significant for $p \leq 0.05$.

Results

During the study period, 173 patients over 75 years received lobectomy for NSCLC in our hospital. Median follow-up for overall survival was 33.3 months (range 1–104 months). The mean age was 78.8 years. There were 121 male and 52 female patients. The median PMI was $4.80 \text{ cm}^2/\text{m}^2$ (range 2.08–8.10) in male patients and $3.64 \text{ cm}^2/\text{m}^2$ (range 1.61–6.32) in female patients. The rate of postoperative complications was less than 30% in male patients with PMI over $3.71 \text{ cm}^2/\text{m}^2$, but 58% with PMI under $3.70 \text{ cm}^2/\text{m}^2$. The rate of postoperative complications was less than 20% in female patients with PMI over $2.51 \text{ cm}^2/\text{m}^2$, but 83% with PMI under $2.50 \text{ cm}^2/\text{m}^2$ (Fig. 2). PMI under $3.70 \text{ cm}^2/\text{m}^2$ in male patients and $2.50 \text{ cm}^2/\text{m}^2$ in female patients was defined as sarcopenia. In predicting of postoperative complications, this definition of sarcopenia had a sensitivity of 86.4%, specificity of 65.0%, area under the ROC curve was 0.628 in male, and a sensitivity of 97.5%, specificity of 58.3%, area under the ROC curve was 0.594 in female (Fig. 3).

Characteristics of patients with and without sarcopenia are summarized in Table 1. We compared groups with and without sarcopenia with respect to preoperative risk factors

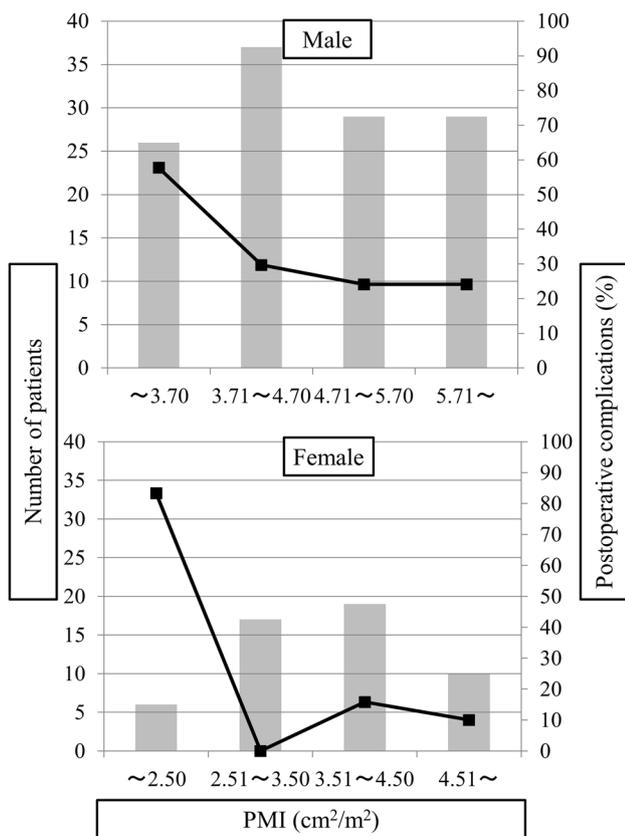
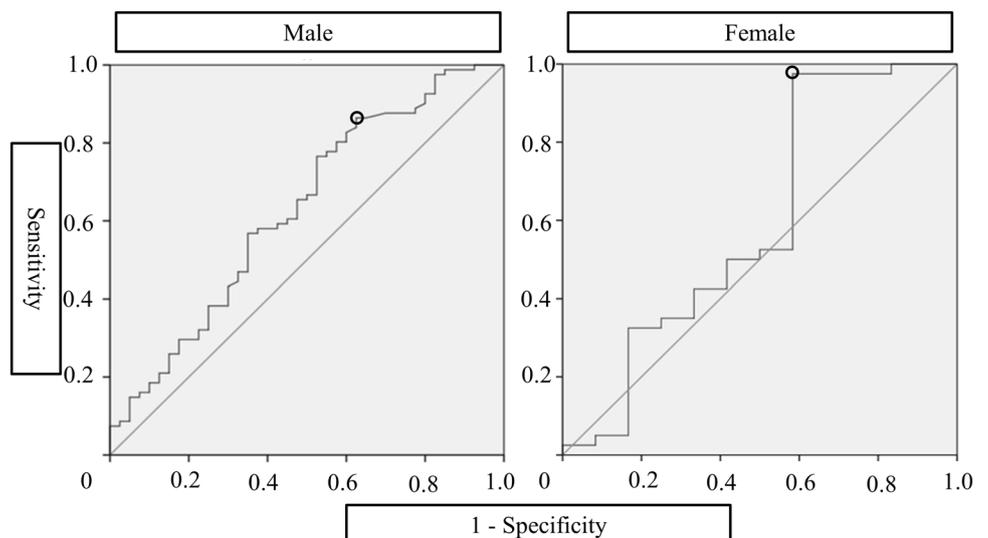


Fig. 2 Numbers of patients and postoperative complication rates in male and female patients. The bars represent the number of the patients and the curve represents the postoperative complication rate (%). *PMI* psoas muscle mass index

for morbidity such as age, sex, performance states, vital capacity, forced expiratory volume in 1 s, interstitial pneumonia, coronary artery disease, and history of cerebrovascular accidents. There were no significant differences in these

Fig. 3 ROC curve in predicting of postoperative complications with PMI. *ROC* receiver operating characteristic, *PMI* psoas muscle mass index



factors but performance states. In addition, we compared both groups with and without sarcopenia with respect to factors associated with prognosis such as histology and stage. There were no significant differences between these factors for the two groups.

Postoperative mortality occurred in 4 (2.3%) patients, and postoperative morbidity occurred in 52 (30.1%) patients. The postoperative complication rate was significantly higher in patients with sarcopenia (62.5%) than in those without sarcopenia (22.7%) (Fig. 4). The 5-year survival rate after surgery was 56.8% and median survival time was 46.9 months. In patients with sarcopenia, the 5-year survival rate was 26.5% and the median survival time was 33.2 months. In patients without sarcopenia, the 5-year survival rate was 66.3% and median survival time was 50.7 months. Log-rank test showed significantly worse overall survival in patients with sarcopenia (Fig. 5).

In multivariate analysis, coronary artery disease, clinical stage 2 or 3, and sarcopenia were significant predictors of poor prognosis. In these factors, sarcopenia had the strongest association with poor prognosis (Table 2).

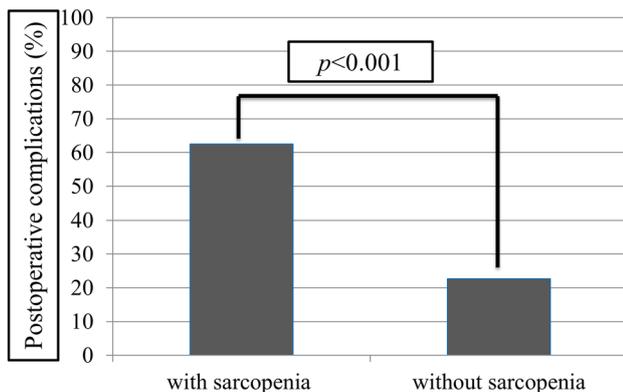
Discussion

The purpose of this study was to propose a definition of sarcopenia in elderly patients with lung cancer using PMI, and to show their postoperative outcomes such as complications and prognosis. In the past, five studies on postoperative outcome of NSCLC with sarcopenia in whole generations have been reported [6–8, 12, 13]. Three reports demonstrated that sarcopenia was a predictor of poor prognosis after surgery [6–8], 2 reports demonstrated that sarcopenia was significantly associated with mortality [12, 13], and only 1 report demonstrated that sarcopenia predicted postoperative major

Table 1 Multivariate associations of clinical factors and sarcopenia

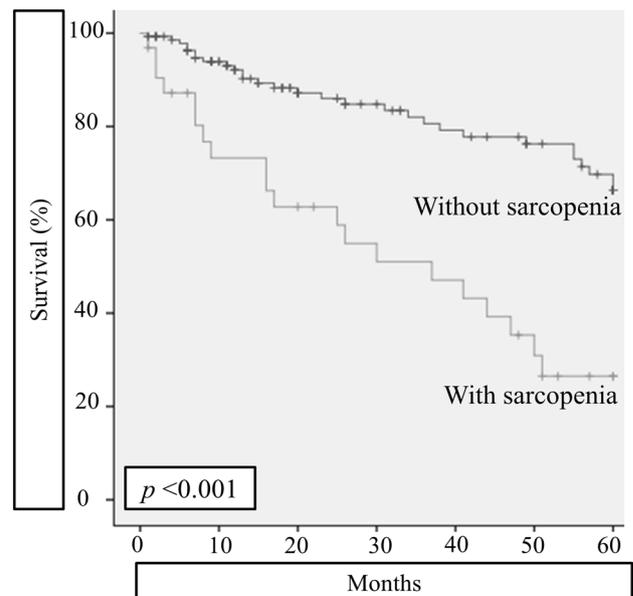
Characteristics	With sarcopenia, <i>N</i> =32 (18.5%)	Without sarcopenia, <i>N</i> =141 (81.5%)	<i>p</i> value
Age	79.0 (75–88)	78.8 (75–88)	–
Sex			
Male	26 (81.2%)	95 (67.4%)	0.122
Female	6 (18.8%)	46 (32.6%)	
Performance status			
0	9 (28.1%)	81 (57.4%)	0.003
1 or 2	23 (71.9%)	60 (42.6%)	
%VC			
≥80	28 (87.5%)	133 (94.3%)	0.170
<80	4 (12.5%)	8 (5.7%)	
FEV1.0%			
≥70	14 (43.8%)	80 (56.7%)	0.183
<70	18 (56.2%)	61 (43.3%)	
Interstitial pneumonia	0 (0%)	7 (5.0%)	0.198
Coronary artery disease	7 (21.9%)	18 (12.8%)	0.186
History of cerebrovascular accident	3 (9.4%)	9 (6.4%)	0.548
Histologic type			
Sq	12 (37.5%)	51 (36.2%)	0.888
Non-Sq	20 (62.5%)	90 (63.8%)	
Clinical stage			
0 or 1	19 (59.4%)	82 (58.2%)	0.900
2 or 3	13 (40.6%)	59 (41.8%)	

%VC percent of vital capacity, FEV1.0 forced expiratory volume in 1 s, Sq squamous cell carcinoma

**Fig. 4** Postoperative complication rate

complications [8]. With respect to elderly patients with lung cancer, surgical decision-making would become easier if the complications and prognosis of patients with sarcopenia were predictable.

Sarcopenia has been defined using various imaging techniques to assess skeletal muscle mass, such as dual-energy x-ray absorptiometry, CT, magnetic resonance imaging, and bioimpedance analysis. CT being performed as routine examination, can evaluate muscle mass appropriately.

**Fig. 5** Kaplan–Meier curves for overall survival after surgery

Measuring PMI and bilateral psoas muscle area at the third lumbar level on CT, was proposed to define sarcopenia because it reflects the skeletal muscle mass of the whole

Table 2 Univariate and multivariate analyses of overall survival

Characteristics	Univariate analysis	Multivariate analysis	
	<i>P</i> value	<i>P</i> value	OR (95% CI)
Age: over 80 years old	0.741	0.828	1.075 (0.562–2.056)
Sex: male	0.003	0.237	0.555 (0.209–1.472)
Performance status: 1 or 2	0.279	0.883	1.050 (0.551–1.999)
%VC < 80	0.066	0.291	0.615 (0.250–1.515)
FEV1.0% < 70	0.055	0.314	0.706 (0.359–1.389)
Interstitial pneumonia	0.746	0.405	0.528 (0.117–2.377)
Coronary artery disease	0.003	0.010	0.355 (0.161–0.781)
History of cerebrovascular accident	0.536	0.852	1.124 (0.328–3.852)
Histologic type: Sq	0.042	0.210	0.656 (0.340–3.852)
Clinical stage: 2 or 3	0.017	0.029	0.487 (0.255–0.929)
Sarcopenia	<0.001	<0.001	0.263 (0.138–0.499)

OR odds ratio, %VC percent of vital capacity, FEV1.0 forced expiratory volume in 1 s, Sq squamous cell carcinoma

body [11]. In addition to many measurement modalities, there were many complicated forms of analysis, and proposed cutoff values because of diverse patient groups such as type of disease, progression of disease, sex, or age. Hence, it is necessary to formulate an original definition of sarcopenia which can predict postoperative complications and prognosis in elderly patients with lung cancer. Hamaguchi et al. defined low skeletal muscle mass as <2SD below the mean PMI of healthy individuals; under 6.36 cm²/m² in men and 3.92 cm²/m² in women [11]. Nakamura et al. demonstrated that using this cutoff value as sarcopenia, patients with sarcopenia tended to have increase in major complications (Clavien–Dindo grade ≥ 3) and had poor prognosis after surgery for NSCLC [8].

We demonstrated that there were cutoff values in sarcopenia which showed rapid rise in postoperative complications rate (Fig. 2). It was thought that sarcopenia in patients with surgically resected cancer was associated with an increased postoperative inflammatory response, and this response might play a role of high incidence of postoperative complications with sarcopenia [14]. In patients who underwent surgery for gastrointestinal and hepatopancreatobiliary cancer, sarcopenia was also independently associated with postoperative complications [5, 14]. In addition, in elderly patients with lung cancer, the incidence of postoperative complications may strongly predict poor prognosis [10]. Hence, clinicians need to find a cutoff value which could predict postoperative complications in these patients. The reasons for sarcopenia being a strong predictor of postoperative complications in present study might be as follows: first, we defined sarcopenia based on postoperative complication rate. Second, it was reported that postoperative morbidity was generally higher in elderly patients than in younger patients [9], so they

were easily affected by sarcopenia. In addition, performance status highly correlated with sarcopenia (Table 1), so it might suggest that sarcopenia could be alternative marker of performance status.

Sarcopenia defined in our study could predict not only postoperative complications but also poor prognosis. Many studies have showed an association with sarcopenia and poor prognosis [6–8, 13], similar to our study. Patients with sarcopenia might change from pre-cachexic to cachexic, and in whom sarcopenia could have been the initial symptom. These patients were more likely to suffer from poor response to therapies and worse prognosis [7]. These data suggest interventions such as enrolling patients with sarcopenia in physical therapy or nutritional rehabilitation programs. It is well known that muscle mass can recover through nutrition management by administration of nutrients and rehabilitation before surgery [15, 16]. In the future, if assessment of sarcopenia becomes a standard preoperative testing, our definition may be useful to predict postoperative complications and prognosis.

The main limitation of this study is its retrospective nature. The final decisions to select patients for surgery and the choice of surgical procedure may vary among surgeons. Therefore, our study does not reflect the entire population of patients. A second limitation is that our definition of sarcopenia contained only one of the components of original definition of sarcopenia [1], which requires evaluation of muscle mass, muscle strength, and physical performance. The final limitation is the low number of cases in our study. The sarcopenia group contained only 32 patients, and hence, the power of statistical analysis was not sufficient. To achieve more precise results, a prospectively designed, large clinical trial is required.

Conclusion

We defined sarcopenia when the PMI was under $3.70 \text{ cm}^2/\text{m}^2$ in male patients and $2.50 \text{ cm}^2/\text{m}^2$ in female patients. In elderly NSCLC patients, the sarcopenia was found to be a high risk for postoperative complications and poor prognosis. Our definition may be useful to select the patients who require the preoperative nutrition management and rehabilitation.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest that exist with any companies/organizations whose products or services may be discussed in this article.

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