Risk factors for progressive sarcopenia 6 months after complete resection of lung cancer: what can thoracic surgeons do against sarcopenia?

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Background: Our previous report described how postoperative progression of sarcopenia predicted long-term prognosis after complete resection of non-small cell lung cancer (NSCLC) in heavy smokers. However, there are currently no effective means to treat progressive sarcopenia. In this study, we aimed to confirm our previous findings in a larger population and to identify factors associated with postoperative progression of sarcopenia to propose possible preventative measures.

Methods: This retrospective study analyzed the data of 1,095 patients who underwent curative lobar resection for NSCLC at Kanagawa Cancer Center. We divided patients into four groups according to sex and Brinkman index (BI) above or below 600. Six-month postoperative changes in the skeletal muscle index (SMI) were calculated and associations between clinicopathological factors including changes in SMI and mortality from postoperative 6 months were examined. Only in groups in which postoperative depletion of SMI was shown to be associated with the prognosis, we identified clinicopathological factors associated with depletive SMI.

Results: The overall survival rates of 1,095 patients were 89.8% and 82.5% at 3 and 5 years, respectively. The median 6-month change in SMI was −3.4% (range, −22.3% to +17.9%). Multivariate analysis revealed that poor prognosis was independently predicted by a large reduction in the SMI (cut-off value: −10%) in males with a BI ≥600. In 391 heavy-smoking males, factors associated with a postoperative change in SMI ≤−10% were history of other cancers (including gastric cancer) low forced expiratory volume in one second (FEV 1.0, cut-off value: 1,870 mL), and prolonged operation time (cut-off value: 200 minutes).

Conclusions: Perioperative measures to prevent postoperative sarcopenia are appropriate for heavy smokers. We obtained some clues regarding countermeasures, one of which may be avoiding long-time operation. Further studies including clinical trials to assess perioperative anti-sarcopenia treatments, are needed.

Keywords: Lung cancer; surgery; chronic obstructive pulmonary disease (COPD); gastric cancer; operation time

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Introduction

Sarcopenia is reportedly a poor prognostic factor following treatment for various diseases, including advanced cancer, chronic obstructive pulmonary disease (COPD), and cardiac disease (1-3). Low muscle mass is an essential element of sarcopenia and cachexia, defined as sarcopenia induced by affecting diseases. Recently, computed tomography (CT) has been more frequently used especially in cancer patients, and there have been attempts to assess muscle mass using CT images such as a skeletal muscle index (SMI), defined as skeletal muscle area (SMA) at the third lumbar vertebra (L3) on CT divided by the patient’s height in meters squared (4). A low SMI is associated with poor prognosis in various cancers, not only in advanced stages (5-7), but also after curative resection (8-12).

Preoperative sarcopenia can be estimated using particular cut-off values of the SMI or the psoas muscle index (calculated in the same way as the SMI but only referring to the psoas muscle) and it has represented a long-term prognostic factor in patients with resected non-small cell lung cancer (NSCLC) (10-13). Nevertheless, these studies have only demonstrated that sarcopenia is a risk factor for poor prognosis and may not suggest the actions to take based on the results. We reported that reduction in the SMI during the 6 months following complete resection of NSCLC is a significant prognostic factor after the postoperative 6-month follow-up, especially in heavy smokers (14). These results could justify acting to prevent postoperative progression of sarcopenia after curative resection of lung cancer for heavy smokers, although there is no current treatment for sarcopenia that has been demonstrated to improve long-term prognosis (6,15-17). In our previous study, we did not analyze risk factors associated with postoperative sarcopenia because of the limited number of patients for the analysis.

In this study, involving a larger population, we again confirmed the postoperative decline in the SMI could predict the poor prognosis after postoperative period, especially in heavy smokers. Moreover, we identified factors associated with postoperative reduction of the SMI so as to suggest possible measures for preventing perioperative sarcopenia. One study reported that postoperative 1-year decreases in SMI at the 12th thoracic vertebra level were significantly associated with poor prognosis in 100 patients after complete resection of stage 1 lung cancer (18) and that both performance status (PS) ≥1 and obstructive ventilatory impairment were associated with the postoperative 1-year decrease. There have been no other similar reports to date.

Methods

A total of 1,277 patients underwent lobectomy (excluding bilobectomy and pneumonectomy) with no evidence of pathological residual cancer for NSCLC at the Kanagawa Cancer Center between 2007 and 2014. We excluded 25 patients due to previous lung resection, 16 patients who died within the postoperative 6 months, and 34 patients who experienced recurrence within postoperative 6 months. Anonymized data for 1,102 patients were available for calculating the 6-month postoperative change of the SMI. We excluded five patients due to postoperative bronchopleural fistula and two patients due to postoperative acute respiratory distress syndrome, as these diseases could affect postoperative SMI considerably. This retrospective study therefore analyzed data from 1,095 patients. No other inclusion or exclusion criteria were applied. The study’s protocol complied with the Declaration of Helsinki and was approved by our institutional review board (ID 2018-103). The need for patient consent was waived because all data in this study were completely anonymized.

Medical records were analyzed to determine changes in SMI and survival outcomes. The associations of the changes in the SMI and survival outcomes with patients’ clinicopathological characteristics, obtained immediately before surgery, were evaluated using multivariate analyses.

Based on the previous study, we hypothesized that postoperative sarcopenia was associated with the prognosis only in heavy-smoking patients. In addition, analyses using variables related to the absolute value of muscle mass like SMI should be performed separately for males and females because the distribution of SMI differs for each sex. First, we divided 1,095 patients into four groups based on sex and Brinkman index (BI) values ≥600 or <600 and analyzed the association between the distribution of SMI changes across the six postoperative months and the long-term prognosis thereafter in each of the four groups. Next, for the group in which postoperative depletion of SMI was shown to be associated with long-term prognosis, we determined the cut-off value for the rate of change of SMI and investigated whether postoperative reduction in SMI correlated with any perioperative clinicopathological factors and operative factors.

Details of the operative procedure, postoperative follow-up, and definition of recurrence were reported previously (14). Most patients underwent video-assisted surgery with 10 to 15 cm posterolateral incision during the lobectomy. However, the incisions were changed according to any additional procedures to be performed, for example,
sleeve resection. No patient was treated using complete thoracoscopic surgery. We performed systematic hilar and mediastinal lymph node dissection according to the lymph node map presented by the International Association for the Study of Lung Cancer (19). In case of no clinical findings of lymph node metastasis (cN0), the upper mediastinal lymph nodes were systematically dissected for tumors located in the upper lobes; lymph nodes were dissected for tumors in the lower lobes. In the presence of clinical findings of lymph node metastasis (cN1 or 2) or of tumors in the middle lobe with cN0-2, both upper and lower mediastinal lymph nodes were systemically dissected. However, based on the clinical or surgical stage and the patient’s comorbidities, the range of lymph node dissection could be reduced to systematic hilar lymph node dissection or non-systematic lymph node sampling. Postoperative follow-up was conducted every 3 months for the first 2 years, every 6 months during the subsequent 2 years, and then annually thereafter. Recurrence was diagnosed pathologically via biopsy or clinically based on the presence of nodules that increased in size as assessed by CT or brain magnetic resonance imaging (MRI) with accumulation of 2-[18]-fluoro-2-deoxy-D-glucose during positron-emission tomography (FDG-PET). The lung cancer board at our institution officially diagnosed all cases.

**Calculating changes in SMI based on CT images**

SMI changes were calculated as described previously (14). We changed only the application used for calculation. SMIs before and 6 months postoperatively were determined using plain CT slices with 5-mm intervals. There was no standardized protocol or parameters for CT imaging. As indicated by previous reports, the abdominal and paraspinal muscles in an axial image at L3 can be identified using boundaries of −29 to +150 Hounsfield units (4-6,20). We routinely checked and manually corrected these boundaries on the CT images. The cross-sectional muscle areas were subsequently calculated using image analysis software (Slice-O-Matic® v5.0 rev-8; Tomovision, Montreal, Canada). The average of the cross-sectional areas from the two adjacent images was defined as the SMA (cm²), and the SMI was calculated as SMA/height² (cm²/m²). The 6-month postoperative change in SMI (%) was calculated as [(postoperative SMI – preoperative SMI)/preoperative SMI] ×100. A single investigator (Masashi Nagata) who was blinded to the patients’ outcomes performed these analyses. Preliminary measurements of intra- and inter-observer coefficients of variation were performed by two trained measurers (radiological technicians) using 100 patients chosen randomly from our cohort. Intra-observer and inter-observer variability was 1.49% and 1.76%, respectively, which were not inferior to those of previous reports (21,22) though statistical assessment was impossible.

**Statistical analysis**

Categorical and continuous variables that were significantly associated with survival on univariate analyses were included in the multivariate analysis, which was performed using a Cox proportional hazards model for survival or a logistic regression analysis for categorical variables constructed using the stepwise method. In the multivariate analyses, we confirmed there were no significant interactions between the variables. The cut-off value was determined using the maximum Youden’s index value on the receiver operating characteristic (ROC) curve. Survival curves were created using the Kaplan-Meier method. All tests were two-sided, and differences were considered statistically significant with P values of <0.05. All statistical analyses were performed using the JMP software package (version 12.1.0; SAS Institute, Cary, NC, USA).

**Results**

**Postoperative prognosis and 6-month changes in SMI in the four groups**

The median follow-up period from 6 months after the operation was 55.9 months (range, 1.5–121 months). Follow-up was discontinued for 31 patients (2.8%). The overall survival rates of all 1,095 patients were 89.8% and 82.5% at 3 and 5 years, respectively. Figure 1 shows the overall survival curves of the four groups. Among heavy smokers, there were substantially more males (n=391) than females (n=34). Therefore, we excluded heavy-smoking females from the study. The long-term prognosis of heavy smokers was significantly worse than that of non-heavy smokers. Table 1 presents the preoperative body mass index (BMI), preoperative SMI, postoperative SMI, the change of SMI in univariate analysis of the association with survival from postoperative 6 months in each of the four groups. In univariate and multivariate analyses, non-heavy-smoking males and females did not show any association between changes in SMI and long-term mortality (Tables S1–S3).
Figure 1 Overall survival of the four groups. N, number; M, male; F, female; BI, Brinkman index; 3OS, 3-year overall survival; 5OS, 5-year overall survival; P values, Log-rank test, *, statistically significant.

Table 1 Association of body mass index and skeletal muscle index with survival from postoperative six months in the four groups

| Variables                      | Males with BI ≥600 (N=391) | Males with BI <600 (N=225) | Females with BI ≥600 (N=34) | Females with BI <600 (N=445) |
|--------------------------------|-----------------------------|----------------------------|-----------------------------|----------------------------|
| Preoperative BMI (kg/m\(^2\))  | 22.8 (15.2–33.3)            | 22.8 (15.5–33.9)            | 20.9 (16.9–34.5)            | 21.8 (14.4–33.7)            |
| P\(^b\)                        | 0.025*                      |                            | 0.95                        |                            |
| HR\(^c\)                       | 0.93 (0.87–0.99)            | 0.97 (0.84–1.11)            | 1.00 (0.81–1.17)            | 1.00 (0.91–1.09)            |
| Preoperative SMI (cm\(^2\)/m\(^2\)) | 45.2 (28.3–64.3)            | 46.2 (27.7–71.4)            | 37.7 (29.4–49.6)            | 36.5 (22.6–52.8)            |
| P\(^b\)                        | 0.11                        |                            | 0.08                        |                            |
| HR\(^c\)                       | 0.98 (0.95–1.01)            | 0.95 (0.90–1.01)            | 0.91 (0.75–1.08)            | 0.99 (0.93–1.04)            |
| Postoperative SMI (cm\(^2\)/m\(^2\)) | 43.3 (27.2–63.5)            | 45 (23.7–69.0)              | 37.0 (29.0–46.9)            | 35.3 (21.8–50.9)            |
| P\(^b\)                        | 0.007*                      | 0.12                       | 0.79                        | 0.17                       |
| HR\(^c\)                       | 0.96 (0.93–0.99)            | 0.96 (0.90–1.01)            | 0.98 (0.83–1.14)            | 0.96 (0.91–1.02)            |
| Change of SMI (%)\(^a\)        | −3.68 (−22.4 to 12.0)       | −3.31 (−19.6 to 14.3)       | −5.00 (−12.6 to 17.9)       | −3.21 (−18.6 to 14.7)       |
| P\(^b\)                        | 0.003*                      | 0.66                       | 0.15                        | 0.031\(^d\)               |
| HR\(^c\)                       | 0.95 (0.92–0.98)            | 1.02 (0.94–1.09)            | 1.08 (0.97–1.17)            | 0.95 (0.90–0.99)            |

\(^a\), continuous variables are presented as median (range). \(^b\), Cox proportional hazard analyses were performed as univariate analysis. \(^c\), hazard ratios and 95% confidence intervals in parenthesis. Hazard ratios per one-unit increase were presented. \(^d\), the association of postoperative change of SMI and survival from postoperative 6 months was denied in multivariate analysis. See Table S1. *, statistically significant. BI, Brinkman index; N, number; HR, hazard ratio; BMI, body mass index; SMI, skeletal muscle index.
Changes in SMI associated with postoperative mortality in heavy-smoking males

Table S4 displays patient characteristics and the results of the univariate survival analyses in heavy-smoking males. Table 2 shows the results of the multivariate analyses, revealing that the 6-month depletion in SMI as a continuous variable was independently associated with poor prognosis.

### Table 2 Multivariate analysis of factors associated with poor survival from 6 months after surgery in 391 males with Brinkman index ≥600

| Variables                  | P value | HR (95% CI) |
|----------------------------|---------|-------------|
| SMI rate of change         | 0.0027* | 0.95 (0.93–0.98) |
| Preoperative BMI           | 0.0044* | 0.91 (0.85–0.97) |
| Brinkman index             | 0.0018* | 1.0006 (1.0002–1.0009) |
| Preoperative PaO₂          | 0.017*  | 0.97 (0.95–0.99) |
| Pathological stage ≥III    | 0.0074* | 2.03 (1.24–3.03) |
| Pleural invasion           | 0.037*  | 1.52 (1.03–2.27) |
| Lymphovascular invasion    | 0.005*  | 2.00 (1.24–3.23) |

a, Cox proportional hazards analysis. b, continuous variable. c, categorical variables. d, hazard ratio per one-unit increase. *, statistically significant. HR, hazard ratio; CI, confidence interval; SMI, skeletal muscle mass index; BMI, body mass index; PaO₂, partial pressure of oxygen in arterial blood.

### Identifying the optimal SMI change cut-off value

In our previous study (14), the optimal cut-off value of the 6-month SMI change in heavy smokers with BI ≥600 (N=196) was −10.2%. Similarly, in this study, the ROC analysis for mortality indicated the optimal cut-off value for the 6-month change in SMI was −10.0% [area under the curve (AUC): 0.56; Youden’s index: 0.13]. Figure 2 shows the curves for overall survival in patients with and without a change in the SMI of ≤−10%. A change in SMI ≤−10% was strongly associated with poor prognosis in the multivariate analysis (Table 3).

### Factors associated with postoperative changes in SMI ≤−10%

Table 4 illustrates the results of univariate analysis for the clinicopathological factors associated with postoperative changes of SMI ≤−10%. The results of multivariate analysis are shown in Tables 5 and 6. Operation time (cut-off value of 200 minutes), forced expiratory volume in one second (FEV 1.0, cut-off value of 1,870 mL) and past history of other cancers were significant risk factors for postoperative changes in the SMI.

### Discussion

In a larger population than our previous study, the present

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**Figure 2** Overall survival curve of patients with or without a change of ≤−10% in their postoperative skeletal muscle index. N, number; 3OS, 3-year overall survival; 5OS, 5-year overall survival; SMI, skeletal muscle index; ΔSMI, the SMI rate of change; P value, Log-rank test, *, statistically significant.
study confirmed that the 6-month postoperative changes in SMI as a continuous variable predicted the prognosis from 6 months after complete lung cancer resection in heavy-smoking males, independent of tumor factors such as pathological stage and lymphovascular invasion. Furthermore, we identified the risk factors associated with postoperative changes of SMI ≤−10%.

These results support the necessity of preventing perioperative progression of sarcopenia after curative resection of lung cancer, especially in heavy smokers. It is reasonable to investigate risk factors for postoperative sarcopenia only in heavy smokers (heavy-smoking males in our study) as postoperative sarcopenia was demonstrated to be associated with their prognosis. Sarcopenia is also seen in COPD patients, which is mainly caused by increased energy expenditure due to impaired respiration, which is also defined as pulmonary cachexia (23-25). The progression of sarcopenia after complete resection of lung cancer could be further facilitated as respiratory function is impaired by lung resection. The results in Table 1 showed there were no significant differences in the reduction of SMI values across the four groups stratified by sex and smoking history. It is possible that the decline in the SMI in the 6 months after surgery could be the trigger for progression of pulmonary- or cancer-related sarcopenia, or both, in patients with histories of heavy smoking. Many patients died because of cancer progression (lung cancer or other cancers) and respiratory diseases (e.g., pneumonia and interstitial pneumonitis) (Table S5), which could have been affected by sarcopenia. If recurrence of the primary cancer or another cancer occurs, the tendency toward sarcopenia may be accelerated. Several reports involving different chemotherapy regimens have described a decrease in SMA ranging between 5–8% (26,27) and sarcopenia were associated with treatment toxicity (28-30). These findings suggest that administering treatments for recurrent or other de novo cancers, the prevention of sarcopenia may be important.

It was expected that the low preoperative BMI would be a risk factor for poor prognosis from 6 months after lung cancer resection, independently of the change of SMI. As indicated by the currently proposed definitions and severity grading systems for both generic and cancer cachexia (1,2), an absolute value of a surrogate marker for cachexia should be considered alongside a decrease in value. In our former study (14), preoperative BMI was not identified as a risk factor. In the present study, the influence of the preoperative BMI was clarified mainly because we focused on large population of heavy-smoking males. Table 1 shows that the preoperative BMI value had a stronger association with prognosis than the preoperative SMI, although the preoperative BMI and SMI had a relatively strong linear association (correlation coefficient =0.64). Through progression of emaciation, adipose tissue is catabolized first and muscle tissue is consumed when adipose tissue is depleted. Therefore, the preoperative BMI value including the volume of adipose tissue may screen for patients at risk for postoperative sarcopenia and prognosis more comprehensively than preoperative SMI values. Postoperative SMI was supposed to be eliminated because of the change of SMI in our multivariate analysis. Unfortunately, we could not obtain postoperative BMI values. In western countries, where the proportion of overweight and obese patients is increasing, it has been reported that the SMI was superior to BMI as a prognostic factor (5). If we restrict our analysis to heavy smokers, both the absolute BMI value and the postoperative changes in the BMI, and not in the SMI, might be more strongly associated with postoperative prognosis. However, the preoperative BMI is a fixed value before surgery, which remains invariant perioperatively.

Tables 5 and 6 show preoperative history of other cancers, low preoperative FEV1.0 and prolonged operating
Table 4 Univariate analyses of SMI rate of change ≤−10% in 391 males with Brinkman index ≥600

| Variables                        | SMI rate of change | P value*  |
|----------------------------------|--------------------|-----------|
|                                 | ≤−10% (N=65)       | >−10% (N=326) |
| Preoperative SMI (cm²/m²)         | 47.6 (30.8–64.3)   | 44.9 (28.3–63.8) | 0.013<sup>d</sup> |
| Postoperative SMI (cm²/m²)        | 41.5 (27.2–56.6)   | 44.3 (30.4–63.5) | 0.0006<sup>d</sup> |
| Preoperative BMI (kg/m²)          | 23.5 (15.2–33.3)   | 22.6 (16.5–32.0) | 0.29 |
| Patient factors and comorbidities|                    |           |
| Age (years)                       | 71 [43–85]         | 68.5 [45–87] | 0.05* |
| Brinkman index                    | 980 [610–2,750]    | 940 [600–3,360] | 0.93 |
| Current smoker                    | 0                  | 8 [2] | 0.36 |
| Albumin (mg/dL)                   | 4.2 (3.2–4.8)      | 4.2 (2.8–5.0) | 0.98 |
| C-reactive protein (ng/mL)        | 0.11 (0.01–15.4)   | 0.13 (0.01–10.0) | 0.47 |
| Pulmonary disease                 | 21 [32]            | 100 [31] | 0.77 |
| Interstitial pneumonitis          | 5 [8]              | 20 [6] | 0.58 |
| Cardiac disease                   | 9 [14]             | 50 [15] | 0.85 |
| Arrhythmia                        | 5 [8]              | 21 [6] | 0.78 |
| Cerebrovascular disease           | 3 [5]              | 19 [6] | 1.00 |
| Diabetes mellitus                 | 12 [18]            | 62 [19] | 1.00 |
| Other cancers                     | 21 [32]            | 66 [20] | 0.049* |
| Respiratory functions             |                    |           |
| VC (L)                            | 3.43 (2.08–4.94)   | 3.45 (1.85–5.16) | 0.07 |
| % VC (%)                          | 102 (68.7–147)     | 103.5 (60.9–151) | 0.11 |
| FEV 1.0 (L)                       | 2.33 (0.75–3.45)   | 2.46 (1.14–4.64) | 0.056<sup>f</sup> |
| FEV 1.0% (%)                      | 72.7 (42.1–97.4)   | 73.2 (46.4–99.1) | 0.60 |
| PaO₂ (Torr)                       | 81.5 (60.7–105)    | 83.9 (59.2–164) | 0.13 |
| Tumor factors                     |                    |           |
| Pathological stage                | 0.29               |           |
| I                                | 37 [57]            | 217 [67] |
| II                               | 20 [31]            | 72 [22] |
| III, IV                          | 8 [12]             | 37 [11] |
| Histopathology                    | 0.50               |           |
| Ad                               | 42 [65]            | 195 [60] |
| AIS                              | 0                  | 6 [2] |
| MIA                              | 0                  | 2 [1] |
| Lepidic                          | 7 [11]             | 45 [14] |
| Acinar                           | 14 [22]            | 63 [19] |
| Papillary                        | 6 [9]              | 17 [5] |

Table 4 (Continued)
### Table 4 (Continued)

| Variables                        | SMI rate of change | P value<sup>a</sup> |
|----------------------------------|--------------------|---------------------|
|                                 | ≤–10% (N=65) | >–10% (N=326) |
|                                 |                  |                    |
| Micropapillary                   | 1 [2]            | 4 [1]              |
| Solid                            | 9 [14]           | 42 [13]            |
| Mucinous                         | 3 [4]            | 6 [2]              |
| Others                           | 2 [3]            | 10 [3]             |
| Sq                               | 17 [26]          | 84 [26]            |
| Others                           | 6 [9]            | 47 [14]            |
| Pleural invasion<sup>c</sup>     | 27 [42]          | 110 [34]           | 0.25 |
| Lymphovascular invasion<sup>c</sup> | 39 [60] | 170 [52] | 0.28 |
| CEA of >5.0 ng/mL<sup>c</sup>    | 21 [32]          | 103 [32]           | 0.88 |
| Recurrence                       | 21 [32]          | 72 [22]            | 0.08<sup>f</sup> |
| Operative factors                |                  |                    |
| Resected lobe<sup>e</sup>        |                  | 0.92               |
| RUL                              | 25 [38]          | 117 [36]           |
| RML                              | 3 [5]            | 16 [5]             |
| RLL                              | 12 [18]          | 52 [16]            |
| LUL                              | 18 [28]          | 93 [28]            |
| LLL                              | 7 [11]           | 48 [15]            |
| Lymph node dissection<sup>f</sup> |                  | 0.22               |
| Sampling<sup>a</sup>             | 2 [3]            | 9 [3]              |
| Hilar<sup>f</sup>                | 19 [29]          | 63 [20]            |
| Mediastinal<sup>f</sup>          | 44 [68]          | 253 [77]           |
| Complications<sup>c,i</sup>      | 22 [34]          | 71 [22]            | 0.054<sup>j</sup> |
| Operation time (min)<sup>b</sup>| 187 [72–467]     | 168 [68–380]       | 0.018* |
| Bleeding (mL)<sup>b</sup>        | 40 [little–2,105]| 30 [little–1,210]  | 0.001* |
| Preoperative therapy<sup>e</sup> | 5 [8]            | 14 [4]             | 0.33 |
| Postoperative therapy<sup>e</sup>| 23 [35]          | 103 [32]           | 0.05* |

<sup>a</sup>, Wilcoxon rank sum test for continuous variables and Fisher’s exact test or χ² test (for more than 2×2 test) for categorical variables. <sup>b</sup>, continuous variables are presented as median (range). <sup>c</sup>, categorical variables are presented as number [percentage]. <sup>d</sup>, preoperative and postoperative SMI were excluded from multivariate analysis because there were strong linear associations between SMI rate of change and pre- and postoperative SMI. <sup>e</sup>, history of other cancers that were cured or were under control at the time of operation for lung cancer. <sup>f</sup>, these variables were included in multivariate analysis though P value did not reach <0.05 in these variables. <sup>g</sup>, non-systemic sampling of lymph nodes. <sup>h</sup>, systemic dissection to the extent of hilar lymph nodes. <sup>i</sup>, systemic dissection to the extent of upper or/and lower mediastinal lymph nodes. <sup>j</sup>, short-term postoperative complications (all types and grades of short-term postoperative complications in the patients’ medical records). *, statistically significant. SMI, skeletal muscle index; N, number; BMI, body mass index; VC, vital capacity; %VC, vital capacity percentage; FEV 1.0, forced expiratory volume in one second; FEV 1.0%, forced expiratory volume in one second percentage; PaO<sub>2</sub>, partial pressure of oxygen in arterial blood; Ad, adenocarcinoma; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; Sq, squamous cell carcinoma; CEA, carcinoembryonic antigen; LUL, left upper lobe; LLL, left lower lobe; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe.
time were risk factors for postoperative progression of sarcopenia. There has been some speculation as to whether preoperative sarcopenia indicates the presence of micro-residual lesions or micro-metastases (31); however, our results suggest that cancer recurrence after postoperative 6 months and tumor factors such as pathological stage and lymphovascular invasion were not related to the decrease in the SMI during the 6-month post-operative follow-up.

Table S6 displays the cancers affected before the lung cancer resection. These include cancers of the upper gastro-intestinal tract and urinary system, the occurrences of which are more common in heavy smokers. All forms of cancer other than colorectal cancer tended to have a higher proportion of postoperative change in SMI of ≤−10%; however, the differences were not statistically significant. Gastric cancer was observed most commonly and tended to be associated with the postoperative change of SMI of ≤−10% (P=0.08, Fisher’s exact test). Patients with gastric cancer had a BMI ≤20.3 before the lung cancer surgery significantly more often. These patients likely had nutritional problems mainly due to gastric resection. Reports on the association of sarcopenia defined by SMI with mortality after curative resection of gastric cancer have recently been published (9). Heavy smokers with a history of gastric cancer should be regarded as high-risk for progressive sarcopenia both before and after the lung cancer surgery, which is associated with long-term prognosis. This may not be frequently encountered in Europe and America, as gastric cancers are more common in Eastern Asia, including in Japan.

Low preoperative FEV1.0 was a risk factor for postoperative sarcopenia, although we analyzed many other variables in the respiratory function tests, including predicted postoperative values for the resected lobe and the COPD grade based on the of Global Initiative for Obstructive Lung Disease (GOLD) criteria. Preoperative factors of respiratory test outcomes were not related to long-term mortality; Takamori et al. reported similar results (18). There have been reports regarding the association between COPD and low respiratory function with prognosis following a lung cancer diagnosis (25,32,33). However, patient backgrounds and the variables selected for analyses and outcomes differed across reports. In our analysis, we confined the study objectives to heavy-smoking males and excluded early death, recurrence, and severe complications. Moreover, we investigated the relationship between perioperative sarcopenia and the long-term prognosis from 6 months after complete resection of lung cancer. Our results suggest that patients with preoperative low FEV1.0 have a higher risk for postoperative sarcopenia leading to poor prognosis.

We found that longer operating time was a risk factor for postoperative sarcopenia. As thoracic surgeons, we would like to contribute to the prevention of postoperative progression of sarcopenia. Therefore, we should pay particular attention to the association of postoperative sarcopenia with factors associated with surgical procedures. There were no associations with other operative factors, including postoperative complications such as prolonged air leakage, associated with postoperative sarcopenia. Table S7 reveals the relationship between additional procedures leading to prolonged operating times and postoperative sarcopenia. Additional procedures tended to prolong the operating time; however, these did not result in an increased frequency of postoperative sarcopenia. To our knowledge, there have been no reports that prolonged operating or anesthetic time can lead to the depletion of respiratory function or muscle mass following lung cancer surgery. Our cut-off value of two hundred minutes for operative time in our study may not be clinically significant regarding postoperative sarcopenia. The operation time affecting postoperative respiratory function and sarcopenia may be longer. We have often experienced patients with adhesions between visceral and parietal pleura leading to prolonged operation time due to dissection of the adhesion and control the complications like air leakage and bleeding induced by the dissection. Many of these patients had chronic intrathoracic inflammation due to COPD and other respiratory diseases. Therefore, they probably had poor prognosis postoperatively. We must consider such confounding factors. Further research examining the relationship between operation time and postoperative sarcopenia is needed.

Based on our results, the measures against sarcopenia in heavy smokers undergoing the lobe resection for lung cancer would involve shortening of the operating time for high-risk patients with a past history of other cancers, especially gastric cancer, or low FEV1.0 or both. The indication for limited surgery for heavy smokers might include these factors and a low BMI. However, among the risk factors for postoperative sarcopenia and mortality examined in our study, there were many factors that remained fixed preoperatively and only a few factors that could be improved perioperatively. Therefore, there is a need for clinical trials to be performed to assess the impact of perioperative anti-sarcopenia treatments to improve long-term prognosis. As the postoperative reduction of SMI as a continuous variable
was a risk factor for long-term prognosis in this study, measures to maintain muscle mass for all heavy smokers, especially in those with a low preoperative BMI, could be considered in order to prolong survival. As described in a previous study (14), current treatments for sarcopenia do not improve long-term prognosis in these patients, despite trials that have evaluated several nutritional therapies, rehabilitative techniques, and pharmacological methods (6,15-17). The reason for these failures may be that patients with advanced cancer might have advanced sarcopenia, that is refractory to treatment. Many of our patients were not sarcopenic or were in the early phases when clinical symptoms were absent [i.e., presarcopenia defined by European Working Group on Sarcopenia in Older People (3)]; moreover, these patients were cancer-free after the complete resection, albeit temporarily. In future studies, we would like to assess whether treatment of muscle loss for such patients could improve sarcopenia and long-term prognosis. There have been few trials investigating the association of postoperative rehabilitation and nutritional support with long-term prognosis after the resection of lung cancer. We found only one observational study with small number of patients investigating the association (34). Hence, we need to plan well-designed clinical trials including physical exercise and nutritional support. The trial should incorporate requirements to cease smoking. Unfortunately, we could not obtain and compare information regarding perioperative nutritional support and exercise training, which could be important factors to ameliorate muscle loss. There were some patients who maintained SMI despite risk factors for postoperative sarcopenia. It could be worth researching postoperative lifestyles of such patients to obtain clues regarding effective anti-sarcopenia therapies.

This study has several limitations that were similar to those of our previous study (14). First, the study might be biased for sarcopenia because patients with recurrence, death, and severe postoperative complications during the 6-month postoperative period were excluded. However, risk factors and countermeasures for sarcopenia for such patients should be considered separately. Second, variables indicating changes during the postoperative 6-month period other than SMI were limited. Third, this study was performed with a retrospective single-center design with small number of patients, which highlights the importance of prospective data accumulation at multiple centers. Fourth, we only considered Japanese patients. Our findings may not be generalizable to non-Japanese patients. Fifth, this study did not include those patients who underwent complete thoracoscopic surgery. The effects of less invasive surgery on postoperative sarcopenia would be an interesting issue for further investigation.

In conclusion, among patients who underwent complete lung cancer resection, a decrease in SMI during the 6-month postoperative follow-up period significantly predicted poor long-term prognosis in heavy smokers. Moreover, we identified risk factors for postoperative progression of sarcopenia. This generated clues regarding countermeasures. Nevertheless, thoracic surgeons should further investigate approaches to prevent perioperative sarcopenia in future studies, including clinical trials.

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Footnote
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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study’s protocol complied with the Declaration of Helsinki and was approved by the institutional review board of Kanagawa Cancer Center (ID 2018-103). The need for patient consent was waived because all data in this study were completely anonymized.

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| Variables                        | P value<sup>a</sup> | HR (95% CI)   |
|---------------------------------|----------------------|---------------|
| SMI rate of change<sup>b</sup>  | 0.15                 | 0.97 (0.92–1.01)<sup>d</sup> |
| Age<sup>b</sup>                 | 0.012*               | 1.04 (1.01–1.08)<sup>d</sup> |
| Preoperative albumin<sup>b</sup>| 0.011*               | 0.31 (0.12–0.77)<sup>d</sup> |
| Pathological stage of ≥II<sup>c</sup> | 0.002*             | 2.72 (1.43–5.18) |
| Histopathology<sup>c,e</sup>    | 0.0005*              | 3.02 (1.63–6.00) |
| Lymphovascular invasion<sup>c</sup> | 0.0017*            | 2.66 (1.44–4.92) |
| Past histories of other cancers<sup>c</sup> | 0.0032*           | 2.51 (1.36–4.66) |

<sup>a</sup>, Cox proportional hazards analysis. <sup>b</sup>, continuous variable. <sup>c</sup>, categorical variables. <sup>d</sup>, hazard ratio per one-unit increase. <sup>e</sup>, adenocarcinoma in situ, minimal invasive adenocarcinoma and lepidic pattern predominant invasive adenocarcinoma had significantly better prognosis than the others. *, statistically significant. HR, hazard ratio; CI, confidence interval; SMI, skeletal muscle index.
| Variables | Males with BI <600 (N=225) | Females with BI ≥600 (N=34) |
|-----------|-----------------------------|-------------------------------|
| SMI rate of change (%) | -3.31 (–19.6 to 14.3) | -5.00 (–12.6 to 17.9) |
| Preoperative SMI (cm²/m²) | 46.2 (27.7–71.4) | 37.7 (29.4–49.6) |
| Postoperative SMI (cm²/m²) | 45 (23.7–69.3) | 37.0 (29.0–46.8) |
| Preoperative BMI (kg/m²) | 22.8 (15.5–33.9) | 20.9 (16.9–34.5) |

**Patient factors and comorbidities**

- Age (years): Male 70 [20–88], Female 67.5 [54–82]
- Brinkman index:
  - Male: 0, 1–599, 850 [600–1,720]
  - Female: 75 [33], 150 [67]
- Current smoker: Male 4 [2], Female 1 [3]
- Albumin (mg/dL): Male 4.3 (3.3–5.5), Female 4.2 (3.3–4.7)
- C-reactive protein (ng/mL): Male 0.07 (0.01–9.96), Female 0.1 (0.01–1.62)
- Pulmonary disease:
  - Preoperative: Male 30 [13], Female 850 [600–1,720]
  - Current smoker: Male 0, Female 75 [33]
- Cardiac disease: Male 27 [12], Female 4 [12]
- Arrhythmia: Male 15 [7], Female 2 [6]
- Cerebrovascular disease: Male 12 [5], Female 2 [6]
- Diabetes mellitus: Male 28 [12], Female 8 [24]
- Other cancers: Male 38 [17], Female 9 [26]

**Respiratory functions**

- VC (L): Male 3.48 (1.52–5.58), Female 2.33 (1.62–3.11)
- % VC (%): Male 106 (64.9–155), Female 104.5 (79.8–133)
- FEV 1.0 (L): Male 2.71 (1.42–4.38), Female 1.87 (1.16–2.38)
- FEV 1.0% (%): Male 77.8 (53.8–90), Female 73.3 (55.9–84.9)
- PaO₂ (Torr): Male 86.7 (68.2–110), Female 62.7 (65.4–124)

**Tumor factors**

- Pathological stage:
  - I: Male 169 [75], Female 25 [73]
  - II: Male 35 [16], Female 6 [16]
  - III, IV: Male 21 [9], Female 3 [9]
- Histopathology:
  - Ad: Male 199 [88], Female 15 [44]
  - AIS: Male 10 [4], Female 0
  - MIA: Male 7 [3], Female 1 [3]
  - Lepidic: Male 74 [33], Female 1 [3]
  - Acinar: Male 52 [24], Female 4 [12]
  - Papillary: Male 25 [11], Female 1 [3]
  - Micropapillary: Male 4 [2], Female 0
  - Solid: Male 14 [6], Female 7 [20]
  - Micronodular: Male 10 [4], Female 0
  - Others: Male 3 [1], Female 1 [3]
  - Sq: Male 13 [6], Female 15 [44]
  - Others: Male 13 [6], Female 4 [12]
- Pleural invasion:
  - Male 40 [18], Female 11 [32]
- Lymphovascular invasion:
  - Male 74 [33], Female 23 [98]
- CEA of >5.0 mg/mL:
  - Male 37 [16], Female 12 [35]

**Operative factors**

- Resected lobe:
  - Male: RUL 79 [35], RML 18 [8], RLL 49 [22], LUL 47 [21], LLL 32 [14], Female: RUL 14 [41], RML 2 [8], RLL 8 [23], LUL 6 [16], LLL 4 [72]
- Lymph node dissection:
  - Male: Sampling 10 [4], Hilar 7 [3], Mediastinal 52 [24], Complications 47 [21], Operation time (min) 170 [75], Bleeding (mL) 40 [18], Male: CEA of >5.0 mg/mL 32 [14], Female: CEA of >5.0 mg/mL 4 [72]
- Operative therapy:
  - Preoperative therapy 10 [29], Male: Postoperative therapy 61 [27], Female: Postoperative therapy 4 [2]

### Notes

- Continuous variables are presented as median (range).
- Categorical variables are presented as number (percentage).
- History of other cancers that were cured or were under control at the time of operation for lung cancer.
- Non-systemic sampling of lymph nodes.
- Systemic dissection to the extent of hilar lymph nodes, systemic dissection to the extent of upper or lower mediastinal lymph nodes.
- Short-term postoperative complications (all types and grades of short-term postoperative complications in the medical records).
- Skelatal muscle index; BMI; body mass index; VC; vital capacity; %VC; vital capacity percentage; FEV 1; forced expiratory volume in one second; FEV 1.0%; forced expiratory volume in one second percentage; PaO₂; partial pressure of oxygen in arterial blood; Ad; adenocarcinoma; AIS; adenocarcinoma in situ; MIA; minimally invasive adenocarcinoma; Sq; squamous cell carcinoma; CEA; carcinoembryonic antigen; LUL; left upper lobe; LLL; left lower lobe; RUL; right upper lobe; RML; right middle lobe; RLL; right lower lobe.
### Table S3

Clinicopathological characteristics and univariate analyses of mortality from postoperative six months in 445 females with Brinkman index <600.

| Variables | Females with BI <600 (N=445) | P value |
|-----------|-------------------------------|---------|
| SMI rate of change (%) | −3.21 (−18.6 to 14.7) | 0.031* |
| Preoperative SMI (cm²/m²) | 36.2 (22.6–52.8) | 0.65 |
| Postoperative SMI (cm²/m²) | 35.3 (21.8–50.9) | 0.17 |
| Preoperative BMI (kg/m²) | 22.8 (15.5–33.9) | 0.99 |

**Patient factors and comorbidities**

- **Age (years)**: 68 [36–88] (P < 0.001*)
- **Brinkman index**: 0.63
- **Current smoker**: 364 [82] (P = 0.47)
- **Albumin (mg/dL)**: 4.3 (3.3–5.0) (P = 0.002*)
- **C-reactive protein (ng/mL)**: 0.05 (0.01–4.31) (P = 0.35)
- **Interstitial pneumonitis**: 5 [1] (P = 0.58)
- **Cardiac disease**: 26 [6] (P = 0.86)
- **Amythymia**: 24 [6] (P = 0.71)
- **Cerebrovascular disease**: 18 [4] (P = 0.46)
- **Diabetes mellitus**: 28 [6] (P = 0.29)
- **Other cancers**: 71 [16] (P = 0.029*)

**Respiratory functions**

- **VC (L)**: 2.47 (1.34–3.75) (P < 0.001*)
- **% VC (%)**: 108 (57.9–153) (P = 0.11)
- **FEV 1.0 (L)**: 1.9 (0.87–3.16) (P = 0.008*)
- **FEV 1.0% (%)**: 78.3 (58.6–92.4) (P = 0.47)
- **PaO₂ (Torr)**: 85.2 (82.3–137.7) (P = 0.15)

**Tumor factors**

- **Pathological stage**<0.001**: Stage I was significantly different from the other categories.**
- **Histopathology**:<0.001**: Adenocarcinoma in situ, minimal invasive adenocarcinoma and lepidic pattern predominant invasive adenocarcinoma had significantly better prognosis than the others.**
- **Pleural invasion**:<0.001**: Stage I was significantly associated with poor prognosis.**
- **Lymphovascular invasion**:<0.001**: Stage I was significantly different from the other categories.**
- **CEA of >5.0 ng/mL**:<0.001**: Stage I was significantly different from the other categories.**

**Operative factors**

- **Resected lobe**: 0.034**
- **Sampling**: 12 [6] (P = 0.21)

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**Notes:**

- **Cox proportional hazard analyses were performed for continuous and categorical variables.**
- **Continuous variables are presented as median (range).**
- **Categorical variables are presented as number [percentage].**
- **history of other cancers that were cured or were under control at the time of operation for lung cancer.**
- **stage I was significantly different from the other categories.**
- **adenocarcinoma in situ, minimal invasive adenocarcinoma and lepidic pattern predominant invasive adenocarcinoma had significantly better prognosis than the others.**
- **LUL was significantly associated with poor prognosis.**
- **non-systemic sampling of lymph nodes**
- **systemic dissection to the extent of hilar lymph nodes.**
- **systemic dissection to the extent of upper or lower mediastinal lymph nodes.**
- **short-term postoperative complications (all types and grades of short-term postoperative complications in the medical records).**
- **BI: Brinkman index; N: number; SMI: skeletal muscle index; BMI: body mass index; VC: vital capacity; %VC: vital capacity percentage; FEV 1.0: forced expiratory volume in one second; FEV 1.0%: forced expiratory volume in one second percentage; PaO₂: partial pressure of oxygen in arterial blood; Ad: adenocarcinoma; AIS: adenocarcinoma in situ; MIA: minimally invasive adenocarcinoma; Sq: squamous cell carcinoma; CEA: carcinoembryonic antigen; LUL: left upper lobe; LLL: left lower lobe; RUL: right upper lobe; RML: right middle lobe; RLL: right lower lobe.**
Table S4 Clinicopathological characteristics and univariate analyses of mortality from postoperative six months in 391 males with Brinkman index ≥ 600

| Variables                                           | n (%) or median (range) | P value*
|-----------------------------------------------------|-------------------------|----------
| SMI rate of change (%)                               | –3.68 (–18.6 to 14.7)   | 0.003*
| Preoperative SMI (cm²/m²)                            | 45.2 (28.3–64.9)        | 0.11     
| Postoperative SMI (cm²/m²)                          | 43.3 (27.2–63.5)        | 0.007**  
| Preoperative BMI (kg/m²)                            | 22.8 (15.2–33.9)        | 0.025*   

**Patient factors and comorbidities**

| Variable                              | n (%) or median (range) | P value*
|---------------------------------------|-------------------------|----------
| Age (years)                           | 69 (23–87)              | 0.002*
| Brinkman index                        | 940 (600–3,390)         | 0.000*
| Current smoker                        | 8 (2)                   | 0.79     
| Albumin (mg/dL)                       | 4.2 (2.8–5.0)           | 0.003*
| C-reactive protein (mg/mL)            | 0.13 (0.01–15.4)        | 0.64     
| Pulmonary disease                     | 121 (31)                | 0.000**  
| Intestinal pneumonitis                | 25 (8)                  | 0.000**  
| Cardiac disease                       | 59 (15)                 | 0.53     
| Amythymia                             | 26 (7)                  | 0.84     
| Cerebrovascular disease               | 22 (8)                  | 0.81     
| Diabetes mellitus                     | 74 (19)                 | 0.88     
| Other cancers                         | 87 (22)                 | 0.031*   

**Respiratory functions**

| Variable                              | n (%) or median (range) | P value*
|---------------------------------------|-------------------------|----------
| VC (L)                                | 3.44 (1.85–5.16)        | 0.004**  
| % VC (%)                              | 103 (69.9–151)          | 0.045**  
| FEV 1.0 (L)                           | 2.44 (0.75–4.64)        | 0.00008  
| FEV 1.0 % (%)                         | 73.2 (42.1–99.1)        | 0.022**  
| PaO₂, (Torr)                          | 83.4 (59.2–216)         | 0.0098*  

**Tumor factors**

| Variable                              | n (%) or median (range) | P value*
|---------------------------------------|-------------------------|----------
| Pathological stage                    | <0.0001**               |          
| I                                     | 254 (85)                |          
| II                                    | 92 (24)                 |          
| III, IV                               | 45 (11)                 |          
| Histopathology                        | 0.032**                 |          
| Ad                                    | 237 (60)                |          
| AIS                                   | 6 (2)                   |          
| MIA                                   | 3 (1)                   |          
| Lepidic                               | 52 (13)                 |          
| Acinar                                | 77 (19)                 |          
| Papillary                             | 23 (9)                  |          
| Micropapillary                        | 5 (1)                   |          
| Solid                                 | 51 (13)                 |          
| Mucinous                              | 9 (2)                   |          
| Others                                | 12 (3)                  |          
| Sq                                    | 101 (26)                |          
| Others                                | 53 (14)                 |          
| Pleural invasion                      | 137 (35)                | 0.0003*  
| Lymphovascular invasion              | 209 (53)                | 0.0001*  
| CEA of >5.0 ng/mL                     | 124 (32)                | 0.40     

**Operative factors**

| Variable                              | n (%) or median (range) | P value*
|---------------------------------------|-------------------------|----------
| Resected lobe                         | 0.73                    |          
| RUL                                   | 142 (39)                |          
| RML                                  | 19 (5)                  |          
| RLL                                  | 64 (16)                 |          
| LUL                                  | 111 (29)                |          
| LLL                                  | 55 (14)                 |          
| Lymph node dissection                 | 0.48                    |          
| Sampling                              | 11 (3)                  |          
| Hilar                                 | 83 (21)                 |          
| Mediastinal                           | 297 (76)                |          
| Complications¹                       | 93 (24)                 | 0.11     
| Operation time (minutes)              | 170 (68–467)            | 0.37     
| Bleeding (mL)                         | 30 (10–2105)            | 0.57     
| Preoperative therapy                  | 19 (5)                  | 0.65     
| Postoperative therapy                 | 126 (32)                | 0.055*   

¹ Cox proportional hazard analyses were performed for continuous and categorical variables. "continuous variables are presented as median (range), " categorical variables are presented as number (percentage). " History of other cancers cured or under control at the time of operation for lung cancer. " stage III & IV was significantly different from the other categories. ¹ adenocarcinoma in situ, minimal invasive adenocarcinoma and lepidic pattern predominant invasive adenocarcinoma had significantly better prognosis than the others. ¹ non-systemic sampling of lymph nodes ¹ systemic dissection to the extent of hilar lymph nodes ¹ systemic dissection to the extent of upper or/and lower mediastinal lymph nodes ¹ short-term postoperative complications (all types and grades of short-term postoperative complications in the medical records). ¹ statistically significant, n, number; SMI, skeletal muscle index; BMI, body mass index; VC, vital capacity; %VC, vital capacity percentage; FEV 1.0, forced expiratory volume in one second; FEV 1.0%, forced expiratory volume in one second percentage; PaO₂, partial pressure of oxygen in arterial blood; Ad, adenocarcinoma; AIS, minimal invasive adenocarcinoma; Sq, squamous cell carcinoma; CEA, carcinoembryonic antigen; LUL, left upper lobe; LLL, left lower lobe; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe.
Table S5  Deaths in the four groups

| Variables                  | Males with BI ≥600 (N=391) | Males with BI <600 (N=225) | Females with BI ≥600 (N=34) | Females with BI <600 (N=445) |
|----------------------------|----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Deaths                     | 110 (28%)                  | 28 (12%)                    | 6 (18%)                     | 53 (12%)                    |
| Cause of death             |                            |                             |                             |                             |
| Recurrence                 | 59 (54%)                   | 17 (61%)                    | 3 (50%)                     | 34 (64%)                    |
| Respiratory disease        | 20 (18%)                   | 2 (7%)                      | 1 (17%)                     | 2 (4%)                      |
| Other cancers              | 8 (7%)                     | 3 (11%)                     | 0                           | 5 (9%)                      |
| Other diseases             | 10 (9%)                    | 1 (3%)                      | 0                           | 1 (2%)                      |
| Unknown                    | 13 (12%)                   | 5 (18%)                     | 2 (33%)                     | 11 (21%)                    |
| Death without recurrence   | 43 (39%)                   | 10 (36%)                    | 2 (33%)                     | 16 (30%)                    |

BI, Brinkman index.

Table S6  Details of past histories of other cancers

| Cancers                                | N (%)   | P value  |
|----------------------------------------|---------|----------|
| Stomach                                | 32 (8.3)| 0.08     |
| Head and neck and esophagus            | 15 (3.8)| 0.29     |
| Head and neck                          | 9 (2.3) | 0.65     |
| Esophagus                              | 6 (1.5) | 0.26     |
| Urinary system                         | 17 (4.3)| 0.50     |
| Kidney                                 | 8 (2.0) | 0.64     |
| Urinary bladder                        | 9 (2.3) | 0.62     |
| Colorectal                             | 18 (4.6)| 0.33     |
| Prostate                               | 17 (4.3)| 0.18     |
| The others                             | 10 (2.6)| 1.0      |

* these responses were obtained from 87 patients among 391 heavy-smoking males. Some patients had more than one response.  
  b, percentage in relation to 391 heavy-smoking males;  
  c, Fisher's exact test for the association with postoperative change of SMI ≤−10%. N, number; SMI, skeletal muscle index.

Table S7  Association of additional procedures with operating time and postoperative sarcopenia

| Additional procedures              | N     | ≥200 min (N=123), N (%) | <200 min (N=268), N (%) | P value* for op time | P value* for sarcopenia |
|------------------------------------|-------|--------------------------|--------------------------|----------------------|------------------------|
| Partial resection                  | 39    | 18 [15]                  | 21 [8]                   | 0.046*               | 0.68                   |
| Segmentectomy                      | 10    | 5 [4]                    | 5 [2]                    | 0.30                 | 0.067                  |
| Bronchoplasty                      | 4     | 3 [2]                    | 1 [<1]                   | 0.094                | 1.00                   |
| Arterioplasty                      | 16    | 11 [9]                   | 5 [2]                    | 0.002*               | 0.74                   |
| Resection of adjacent organ        | 32    | 21 [17]                  | 11 [4]                   | <0.0001*             | 0.80                   |
| Resection of chest wall            | 11    | 9 [7]                    | 2 [1]                    | 0.007*               | 1.00                   |
| Any of the above                   | 89    | 50 [41]                  | 39 [15]                  | <0.0001*             | 1.00                   |

* these responses were obtained from 89 patients among 391 heavy-smoking males. Some patients had more than one additional procedures.  
  a, percentage in relation to 123 patients;  
  b, percentage in relation to 268 patients;  
  c, Fisher's exact test for the association with operating time ≥200 minutes.  
  d, Fisher's exact test for the association with postoperative change of SMI ≤−10%.  
  e, statistically significant. N, number; op, operation; SMI, skeletal muscle index.