

The association between thoracic sarcopenia and survival is gender specific in early-stage lung cancer

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Background: Sarcopenia, as measured at the 3rd lumbar (L3) level, has been shown to prognosticate survival in cancer patients. However, many patients with early-stage non-small cell lung cancer (NSCLC) do not undergo abdominal imaging. We hypothesized that preoperative thoracic sarcopenia is associated with survival in patients undergoing lung resection for early-stage NSCLC.

Methods: Patients who underwent anatomic resection for NSCLC between 2010–2019 were retrospectively identified. Exclusion criteria included induction therapy, less than 90 days of follow-up, and absence of computed tomography (CT) imaging. Cross sectional skeletal muscle area was calculated at the fifth thoracic vertebra (T5), twelfth thoracic vertebra (T12), and L3 level. Gender-specific lowest quartile values and previously defined values were used to define sarcopenia. Overall survival and disease-free survival were assessed using the Kaplan-Meier method.

Results: Overall, 221 patients met inclusion criteria with a median body mass index (BMI) of 26.5 kg/m² [interquartile range (IQR), 23.3–29.9 kg/m²], age of 69 years (IQR, 62.4–74.9 years), and follow-up of 46.9 months (IQR, 25.0–70.7 months). At the T5 level, sarcopenic males demonstrated worse overall survival [median 41.0 (IQR, 13.8–53.7) *vs.* 42.0 (IQR, 23.1–55.1) months, P=0.023] and disease-free survival [median 15.8 (IQR, 8.4–30.78) *vs.* 34.8 (IQR, 20.1–50.5) months, P=0.007] when compared to non-sarcopenic males. There was no difference in survival between sarcopenic and non-sarcopenic females when assessed at T5. Sarcopenia at T12 or L3 was associated with worse overall survival (P<0.05).

Conclusions: Sarcopenia at T5 is associated with worse survival in males, but not females. When using upper thoracic vertebral levels to assess for sarcopenia, it is necessary to account for gender.

Keywords: Sarcopenia; thoracic sarcopenia; non-small cell lung cancer (NSCLC); early stage; anatomic lung resection

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Introduction

Lung cancer is the leading cause of cancer related deaths worldwide, with more than 131,000 deaths projected for 2021 in the United States (1). Surgical resection remains the gold standard therapy for patients presenting with early-stage non-small cell lung cancer (NSCLC), with 5-year survival rates reported to range from 25–73% (2-5). Unfortunately, early detection alone does not ensure long-term survival, as 1 in 5 patients with stage IA NSCLC will die from disease recurrence within 5 years of surgery and adjuvant chemotherapy offers no survival advantage in unselected populations (6,7). Methods capable of selecting subsets of patients with aggressive disease at the time of resection could aid clinicians in determining if adjuvant chemotherapy or closer surveillance is likely to provide a benefit.

Sarcopenia, or the physiologic state of reduced muscle mass and function, has recently emerged as a prognostic factor in the outcomes of patients with malignancy (8,9). It has been shown to be highly prevalent in lung cancer patients, with rates as high as 56%, and been associated with major perioperative complications and reduced overall survival (OS) (10-13). Similarly, thoracic sarcopenia, or reduced thoracic muscle mass, has been associated with impaired respiratory status and has been found to be a prognostic factor in the outcomes of cardiothoracic surgeries (14,15). Although there have been multiple investigations into the association between sarcopenia and outcomes of patients with lung cancer, few have examined the implications of measuring sarcopenia at various vertebral levels (10,12,16-20). Since a majority of patients with early-stage lung cancer do not receive abdominal computed tomography (CT) imaging, it is important to understand the relationship between thoracic sarcopenia and outcomes in this population. Therefore, we investigated the association between sarcopenia, measured at three separate vertebral levels, and survival in patients with earlystage lung cancer who underwent surgical resection. Our hypothesis was those with sarcopenia would have worse outcomes including OS and disease-free survival (DFS). We present the following article in accordance with the STROBE reporting checklist (available at https://jtd. amegroups.com/article/view/10.21037/jtd-22-273/rc).

Methods

After Institutional Review Board approval was obtained, a retrospective review of an institutional database was

conducted. Inclusion criteria included patients who underwent anatomic lung resection for pathologic T1–T2, N0, M0 NSCLC (AJCC 8th edition) between 2010–2019. All patients had histologic confirmed adenocarcinoma, R0 resection, thoracic lymphadenectomy and no history of induction therapy. Exclusion criteria included less than 90 days of follow-up or technically inadequate preoperative CT chest or abdominal imaging. Because arm position (raised *vs.* by the side) has been shown to alter the total muscle area obtained from a single-slice CT scan, patients unable to raise their arms over their head were classified as technically inadequate.

Demographic, treatment, and outcome data were collected. Sarcopenia was assessed by measuring skeletal muscle cross-sectional area (SMA) at the 5th thoracic level (T5), 12th thoracic level (T12), and 3rd lumbar level (L3) utilizing staging CT scans performed within 90 days prior to surgery (Figure 1). Chest CT scans were utilized for obtaining body composition analysis at T5 while CT abdomen/pelvis scans were utilized for obtaining body composition analysis at the L3 level. Both CT chest and CT abdomen/pelvis scans were utilized for obtaining body composition analysis at the T12 level. SliceOMatic v5.0 revision 8 (TomoVision, Magog, Canada) was utilized for sarcopenia analysis. All CT scans were assessed by two operators trained on the software. Sarcopenia at L3 was defined using skeletal muscle index (SMI) cut-off values of $<41 \text{ cm}^2/\text{m}^2$ for females, $<43 \text{ cm}^2/\text{m}^2$ for males with a body mass index (BMI) <25 kg/m², and <53 cm^2/m^2 for males with a BMI ≥ 25 kg/m², based on previous reports (1). Sarcopenia at T5 and T12 were defined as gender-specific lowest quartile values.

Statistical analysis

Baseline demographic and treatment data were compared between patients with and without sarcopenia at each of the three vertebral levels. Patients with missing outcome data were excluded from analysis. Differences in baseline demographic and treatment data were assessed with Student's *t*-test for parametric continuous variables and Wilcoxon-Ranked Sum for non-parametric continuous variables and Chi-square tests and Fisher's Exact test for dichotomous and categorical variables. Primary outcomes included OS and DFS. Secondary outcomes included postoperative complications, hospital length-of-stay (LOS), and 30-day readmission rate. OS and DFS were examined using Kaplan-Meier survival analysis curves. Cox Proportional Hazard



Figure 1 Kaplan-Meier curves for OS and DFS at T5. (A,B) Kaplan-Meier curves for OS and DFS between patients with sarcopenia (red line) and non-sarcopenia patients (blue line) as assessed at 5th thoracic vertebral level. (C-F) Kaplan-Meier curves for OS and DFS between male (C,D) and female (E,F) patients with sarcopenia (red line) and non-sarcopenia (blue line). OS, overall survival; DFS, disease-free survival.

regression was utilized to perform adjusted survival analysis and to model which variables were independently associated with OS and DFS. Variables found to either be significant on univariate analysis or those previously reported in the literature were included in the Cox proportional hazard regression model. A proportional hazards assumption test was conducted for all Cox proportional hazard regression models. Results with alpha ≤0.05 was considered statistically significant for all analysis. All statistical analyses were performed using STATA/IC software (version 16.1, StatCorp, College Station, TX, USA).

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Rush University Medical Center institutional review board (IRB number 19121401), and individual consent for this retrospective analysis was waived.

Results

Overall, 296 patients that underwent anatomic lung resection for early-stage NSCLC met inclusion criteria

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during the study period. Patients were excluded from analysis for having less than 90 days of follow-up (n=30) and incomplete or missing CT imaging (n=45). Overall, 221 patients met inclusion criteria with 70% (154/221) being female, a median BMI of 26.5 kg/m² [interquartile range (IQR), 23.3–29.9 kg/m²], age of 69 years (IQR, 62.4– 74.9 years), and follow-up of 46.9 months (IQR, 25.0– 70.7 months) (*Table 1*).

Upper thoracic skeletal muscle analysis

A total of 193 patients were analyzed at T5 with 68% (131/193) being female, a median BMI of 26.4 kg/m² (IQR, 22.7-29.9 kg/m²), age of 68.8 years (IQR, 62.3-74.7), and follow-up of 47.4 months (IQR, 25.8-68.6 months). At T5, 26% (51/193) patients were determined to have sarcopenia with a median upper thoracic SMI of 42.2 cm^2/m^2 (IQR, $39.5-46.6 \text{ cm}^2/\text{m}^2$) compared to $54.3 \text{ cm}^2/\text{m}^2$ (IQR, 49.6–61.7 cm^2/m^2) in the non-sarcopenic group (P<0.001). BMI was found to be lower in the sarcopenic group, with a median value of 23.9 kg/m² (IQR, 21.2–26.7 kg/m²) compared to 27.5 kg/m² (IQR, 24.0-31.9 kg/m²) in the non-sarcopenic group (P<0.001). There were no differences in height, age, race/ethnicity, smoking status, medical comorbidities, or pathologic stage between groups. With a median follow-up of 47.4 months, patients with upper thoracic sarcopenia at time of lung resection had similar OS [median 45.5 (IQR, 26.3-75.6) vs. 47.7 (IQR, 25.7-66.8) months, P=0.257) and DFS (median 31.3 (IQR, 15.9-72.2) vs. 36.6 (IQR, 20.1-58.3) months, P=0.296] compared to patients without sarcopenia (Figure 1A,1B). However, sarcopenic males had worse OS [median 41.0 (IQR, 13.8-53.7) vs. 42.0 (IQR, 23.1-55.1) months, P=0.023] and DFS [median 15.8 (IQR, 8.4-30.8) vs. 34.8 (IQR, 20.1-50.5) months, P=0.007] when compared to non-sarcopenic males (Figure 1C,1D). No difference in OS or DFS was identified between sarcopenic and nonsarcopenic females when assessed at T5 (Figure 1E, 1F).

Lower thoracic skeletal muscle analysis

Overall, 221 patients were analyzed at T12 with 70% (154/221) female, a median BMI of 26.6 kg/m² (IQR, 23.4–30.0 kg/m²), age of 68.9 years (IQR, 62.3–74.7 years), and follow-up of 47.4 months (IQR, 25.4–72.1 months). Fifty-three patients (24%) were determined to have sarcopenia at this vertebral level with a median lower thoracic SMI of 23.9 cm²/m² (IQR, 22.3–24.9 cm²/m²) compared to

 $33.2 \text{ cm}^2/\text{m}^2$ (IQR, 29.4–38.4 cm²/m²) in the non-sarcopenic group (P<0.001). BMI was found to be significantly lower in the sarcopenic group, with a median value of 22.2 kg/m² $(IQR, 20.3-25.1 \text{ kg/m}^2)$ compared to 27.7 kg/m² (IQR, 24.6–31.6 kg/m²) in the non-sarcopenic group (P=0.002). There were no differences in height, age, race/ethnicity, smoking status, medical comorbidities, or pathologic stage between groups. With a median follow-up of 47.4 months, patients with lower thoracic sarcopenia at time of lung resection had worse OS [median 38.8 (IQR, 23.8-72.6) vs. 49.1 (IQR, 25.7–69.9) months, P=0.013] (Figure 2A). There was no difference in DFS between those with and without sarcopenia at T12 (Figure 2B). When stratifying based on gender, sarcopenic females were similar to non-sarcopenic females in regards to OS and DFS (Figure 2C, 2D) and sarcopenic males were similar to non-sarcopenic males in regards to OS and DFS (Figure 2E, 2F).

Lumbar skeletal muscle analysis

Overall, 178 patients were analyzed at L3 with 65% (116/178) female, a median BMI of 26.2 kg/m² (IQR, 22.9–29.9 kg/m²), age of 69.2 years (IQR, 62.1–75.0 years), and follow-up of 46.2 months (IQR, 26.5-66.5 months). One hundred and eight patients (61%) were determined to have sarcopenia at the third vertebral level with a median SMI of 38.6 cm^2/m^2 (IQR, 35.4–41.9 cm^2/m^2) compared to 47.1 cm²/m² (IQR, 44.0–53.6 cm²/m²) in the non-sarcopenic group (P<0.001). BMI was found to be significantly lower in the sarcopenic group, with a median value of 25.7 kg/m² (IQR, 22.1-28.1 kg/m²) compared to 27.2 kg/m² (IQR, 24.2-32.3 kg/m^2) in the non-sarcopenic group (P=0.003). Increased age was also significantly associated with sarcopenia with a median value of 72.2 (IQR, 65.0-77.3) vs. 67.0 (IQR, 60.3-72.9) years in the nonsarcopenic group (P=0.003). There was no difference in height, race/ethnicity, smoking status, medial comorbidities, or pathologic stage between groups. With a median follow-up of 46.2 months, patients with L3 sarcopenia had worse OS [median 43.3 (IQR, 25.9-63.9) vs. 48.8 (IQR, 26.9-75.0) months, P=0.042] (Figure 3A). There was no significant difference in DFS between those with and without sarcopenia at L3 and when comparing genders for OS or DFS. (Figure 3B-3F).

Discussion

Gender-specific differences in the association between sarcopenia at various vertebral levels and survival in

| Table 1 Patient demographics | Upper thor | acic level | Lower tho | racic level | Lumba | ir level | |
|--|--|--|---|-------------------------------|--------------------------|-----------------------------|----------|
| Characteristics | T5 sarcopenic (n=51) | T5 non-sarcopenic (n=142) | T12 sarcopenia (n=53) | T12 non-sarcopenic (n=168) | L3 sarcopenia (n=108) | L3 non-sarcopenia (n=70) | P value |
| Age, years, median (IQR) | 71.3 (64.5–75.2) | 68.4 (61.0–73.8) | 69.7 (65.2–75.4) | 68.4 (61.9–74.3) | 72.2 (65.0–77.3) | 67.0 (60.3–72.9) | 0.001 |
| Sex | | | | | | | |
| Female | 34 [67] | 97 [68] | 38 [72] | 116 [69] | 74 [69] | 42 [60] | 0.075 |
| Height, cm, median (IQR) | 161.3 (149.9–168.5) | 160.0 (134.6–165.1) | 160.0 (142.2–165.1) | 160.0 (134.6–165.1) | 160.0 (147.3–166.4) | 160.0 (144.8–165.1) | 0.566 |
| BMI, kg/m², median (IQR) | 23.9 (21.2–26.7) | 27.5 (24.0–31.9) | 22.2 (20.3–25.1) | 27.7 (24.6–31.6) | 25.7 (22.1–28.1) | 27.2 (24.2–32.3) | 0.001 |
| SMI, cm²/m², median (IQR) | 42.2 (39.5–46.6) | 54.3 (49.6–61.7) | 23.9 (22.3–24.9) | 33.2 (29.4–38.4) | 38.6 (35.4–41.9) | 47.1 (44.0–53.6) | 0.001 |
| Tobacco use | | | | | | | 0.070 |
| Current | 8 [16] | 25 [18] | 9 [17] | 29 [17] | 20 [19] | 14 [20] | |
| Former | 33 [65] | 97 [68] | 33 [62] | 116 [69] | 72 [67] | 48 [69] | |
| Never | 10 [20] | 20 [14] | 11 [21] | 23 [14] | 16 [15] | 8 [11] | |
| DM | 10 [20] | 24 [17] | 6 [11] | 32 [19] | 22 [20] | 16 [23] | 0.225 |
| CAD | 6 [12] | 20 [14] | 9 [17] | 20 [12] | 18 [17] | 10 [14] | 0.748 |
| Race/ethnicity | | | | | | | 0.397 |
| Caucasian | 39 [76] | 113 [80] | 42 [79] | 129 [77] | 90 [83] | 51 [73] | |
| African American | 9 [18] | 17 [12] | 6 [11] | 28 [17] | 12 [11] | 12 [17] | |
| Hispanic | 1 [2] | 1 [1] | 1 [2] | 1 [1] | 0 [0] | 0 [0] | |
| Asian | 1 [2] | 4 [3] | 3 [6] | 3 [2] | 1 [1] | 2 [3] | |
| Other | 1 [2] | 7 [5] | 1 [2] | 7 [4] | 5 [5] | 5 [7] | |
| Pathologic stage | | | | | | | 0.795 |
| IA1 | 21 [41] | 65 [46] | 22 [42] | 70 [42] | 51 [47] | 35 [50] | |
| IA2 | 10 [20] | 34 [24] | 6 [17] | 43 [26] | 22 [20] | 16 [23] | |
| IA3 | 2 [4] | 6 [4] | 1 [2] | 7 [4] | 3 [3] | 2 [3] | |
| B | 16 [31] | 30 [21] | 17 [32] | 41 [24] | 28 [26] | 12 [17] | |
| IIA | 2 [4] | 7 [5] | 3 [6] | 8 [5] | 4 [4] | 5 [7] | |
| All data presented as n [%], mass index; SMI, skeletal m. | unless otherwise indicat uscle index; DM, diabete | ed. T5, 5th thoracic vest mellitus; CAD, coron | ertebra; T12, 12th thoi lary artery disease. | acic vertebra; L3, 3rd I | lumbar vertebra; IQR, | interquartile range; BN | MI, body |

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Figure 2 Kaplan-Meier curves for OS and DFS at T12. (A,B) Kaplan-Meier curves for OS and DFS between patients with sarcopenia (red line) and non-sarcopenia patients (blue line) as assessed at 12th thoracic vertebral level. (C-F) Kaplan-Meier curves for OS and DFS between female (C,D) and male (E,F) patients with sarcopenia (red line) and non-sarcopenia (blue line). OS, overall survival; DFS, disease-free survival.

patients with resected early-stage NSCLC patients is not well understood. The current data suggest that sarcopenia is associated with OS and DFS at upper vertebral levels in males, but not females. To our knowledge, this is the first report of a gender-specific difference in the ability to prognosticate survival based on skeletal muscle mass at the upper vertebral levels. The ability for physicians to preoperatively risk-stratify patients with lung cancer for OS and DFS is of paramount importance as this can identify patients that could potentially benefit from closer surveillance or adjuvant cancer therapies. As early-stage lung cancer is often identified with low dose CT chest screening programs it will be important to understand how thoracic sarcopenia in particular should be interpreted in this patient populations.

Upper thoracic vertebral levels are increasingly being used to assess for sarcopenia in lung cancer patients (14,15). However, differences have been noted in the ability of

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Figure 3 Kaplan-Meier curves for OS and DFS at L3. Kaplan-Meier curves for OS and DFS between patients with sarcopenia (red line) and non-sarcopenia patients (blue line) as assessed at 3rd lumbar vertebral level (A,D). Kaplan-Meier curves for OS and DFS between male (B,E) and female (C,F) patients with sarcopenia (red line) and non-sarcopenia (blue line). OS, overall survival; DFS, disease-free survival.

thoracic vs. lumbar vertebral levels to assess for generalized sarcopenia. Some authors have reported L3 to be superior given the large percentage of skeletal muscle and absence of ribs at this level (21). However, early-stage lung cancer patients do not always undergo CT abdominal imaging, making it difficult to assess L3 in these patients. Thus, it is necessary to evaluate how measurements at different vertebral levels will impact survival to help clinicians prognosticate outcomes for their patients.

There has been growing consensus that sarcopenia

negatively impacts patients with lung cancer. A recent meta-analysis including 13 studies reported sarcopenia in 50% in lung cancer patients and found it was a predictor of reduced OS but not DFS in patients with NSCLC (12). Although this study demonstrated the association between sarcopenia and outcomes in patients with lung cancer, the studies reviewed used different methods to assess for sarcopenia. For example, one studied included in the review assessed sarcopenia via dual-energy X-ray absorptiometry (DXA) (22). It remains unclear how evaluating sarcopenia

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with DXA compares to CT scans, as there have been no direct comparisons in lung cancer patients. Furthermore, of the studies reviewed that assessed sarcopenia at L3, two computed psoas musculature cross-sectional area (PMA) to assess for presence of generalized sarcopenia (10-19). Utilizing PMA to assess for generalized sarcopenia has been recently reported to not be as accurate as assessing total SMA at L3 (23,24).

Another issue complicating the comparison of different lung cancer sarcopenia studies from the review by Yang et al. was the various definitions adopted by authors in determining which patients met criteria for sarcopenia (12). The most utilized cut-off values used to define sarcopenia were referenced by Prado et al. and Martin et al.; both very large retrospective reviews of patients with gastrointestinal and lung malignancies (8,21). However, 2 studies utilized a cut-off value in which the patient population studied was those with colorectal liver metastasis and another study utilized cut-off values which assessed SMI in health adults (25.26). We utilized L3 cut-off values from Martin et al. in our study, which accounts for the impact obesity may have on sarcopenia values. There are currently no generally accepted cut-off values for upper thoracic vertebral levels and thus we utilized gender specific lowest-quartile cut-off values at T5 and T12 to account for this. Further research is needed to determine uniform cut-off values at these levels for cancer patients who routinely undergo CT chest imaging.

Another recent meta-analysis was performed that included studies of patients that had surgically treated NSCLC (13). It demonstrated that sarcopenia was an independent prognosticator of worse OS in patients with resected NSCLC and only those with early-stage disease had a reduction in DFS. However, no studies included in this meta-analysis assessed sarcopenia at the upper thoracic levels. With the emergence of data associating reduced upper thoracic musculature with short and longterm outcomes in cardiothoracic surgery, there is a need to investigate differences between vertebral levels when assess for sarcopenia.

This study has limitations. First, although our sample size was adequate for a robust survival analysis, we had a larger proportion of females than males, perhaps confounding the results. In addition, the retrospective design of the study allows the potential for unrecognized bias. Future investigations into the role sarcopenia, as measured at various vertebral levels, and outcomes of cancer patients should be performed in prospective manner. Furthermore, utilizing gender-specific lowest quartiles to define sarcopenia at T5 and T12 may underreport the prevalence of sarcopenia at these levels. Unlike the widely used definitions for sarcopenia at the L3 vertebral level there is no consensus on the definition of sarcopenia at thoracic vertebral levels in patients with early-stage lung cancer. This study attempts to provide some guidance for clinicians to understand how to compare thoracic sarcopenia in lung cancer patients that may not have CT abdominal imaging to use the gold standard L3 level for sarcopenia analyses. Finally, almost half of patients reviewed at L3 met definition of sarcopenia whereas only a quarter of those at T5 and T12 met criteria.

Conclusions

The current study represents one of the largest analyses comparing thoracic and lumbar vertebral levels in the assessment of sarcopenia in lung cancer patients. Our data suggest that sarcopenia is associated with worse OS at T12 and L3, however sarcopenia at T5 was associated with worse OS and PFS in males, but not females. Sarcopenia measured at the L3 vertebral level remains the gold standard for prognosticating survival in patients with early-stage lung cancer. However, in cases when abdominal imaging is not available, it is important to understand how to best interpret sarcopenia as measured at higher thoracic levels. Further prospective research is required to better understand what role sarcopenia, measured at various vertebral levels, has on the outcomes of patients with lung cancer.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd. amegroups.com/article/view/10.21037/jtd-22-273/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.

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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 was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Rush University Medical Center institutional review board (IRB number 19121401), and individual consent for this retrospective analysis was waived.

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