Peer Review File
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Reviewer A

This manuscript was summarized about the association of thoracic sarcopenia and their prognosis. It is interesting to read. This manuscript needs some revision to publish.

Minor points
Comment 1: Authors should propose the best way to predict prognosis in sarcopenia patients based on your results and previous literature.

Reply 1: We agree, and have added a statement to the conclusion stating that 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.

Changes in the text: We added the following text to the conclusion, "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."

Comment 2: (In line 117-118, page8)
I suspect that authors should interchange "48.8" and "43.3".

Reply 2: We agree, and have interchanged 48.8 and 43.3.
Changes in the text: The text now reads, "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] vs. 43.3 [IQR 25.9-63.9] months, p= 0.042)"

Reviewer B

Comment 1:
https://link.springer.com/article/10.1245/s10434-021-11034-6

The paper of Dr. Shah, also a co-author of this paper, Chest CT-Derived Muscle Metrics for Sarcopenia: Choosing the Right Target, discusses the differences in the values obtained when the arms are raised against arms that are on the side.

Can you define how the CT scans were obtained? Were all "arms raised" or were all "arms by the side"?

Reply 1: Thank you for this comment. All patients in this study had their arms raised. Patients who had their arms by their side were excluded, as these CTs scans were deemed "technically inadequate." However, this was not a common issue as most patients included obtained scans as an outpatient and had a good performance status. This is in contrast to many inpatients and critically ill patients who often cannot raise arms above their head.
Changes in the text: We have added the following changes to the methods section: "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."

Comment 2:
What will explain the difference in N between T5 (52+142) population and T12 (52+ 169) population? Is T5 not routinely seen on CT scan that some patients' scan do not include information on it?

Reply 2: The reason more patients (169 vs 142) had T12 available is because both CT chest and CT abdomen pelvis scans include T12 as part of our institution protocol. Thus some patients with just CT abdomen pelvis scans had T12 available and nearly all with CT chest scans had T12 available for analysis.
Changes in the text: The following changes were made to the text; "Chest CT chest scans were utilized for obtaining body composition analysis at the T5 thoracic vertebral level while CT abdomen/pelvis scans were utilized for obtaining body composition analysis at the T12 and L3 level. Both CT chest and CT abdomen/pelvis scans were utilized for obtaining body composition analysis at the T12 level."

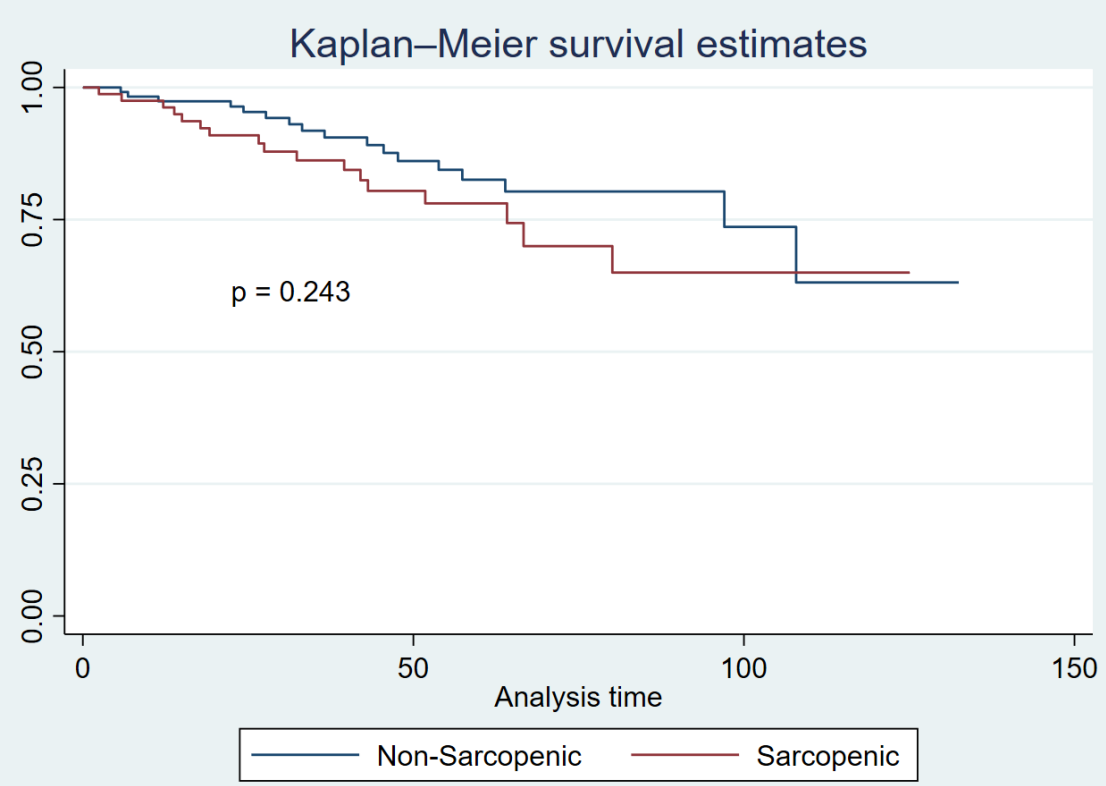
Comment 3:
Since at baseline, there is already a major gender difference in the population, how can we conclude that the outcome is due to sarcopenia and not due to the baseline characteristic of the population?

Reply 3: The association between sarcopenia, as measured at T5, and survival appears to be gender-specific, however, the same was not observed when measured at T12 and L3. This suggests that that a patient's gender alone is not the driving factor for survival in this analysis.

Changes in the text: No changes in the text were made.

Comment 4:
Is there a difference in survival if presence of any sarcopenia value is considered sarcopenia, regardless of level. ie, survival if sarcopenia in T5, L1 or L3 vs no sarcopenia at all.

Reply 4: We performed the requested analysis using patients with CT data at T5, T12, and L3 (n=199) and sarcopenia at any level was not associated with overall survival. Future studies including a larger study cohort would be required to examine the association between sarcopenia and survival, stratified by the number of sarcopenic vertebral levels.



Changes in the text: No changes to the text was made.

Reviewer C

This study attempts to demonstrate significance of sarcopenia based on measuring skeletal muscle area on various vertebral levels in surgically treated NSCLC. It seems to expand utility in general practice of thoracic surgery. However, several issues in the study and the manuscript should be revised in the current form.

Comment 1: In the Introduction section, there seems to be absence of several relevant references. For instance, " Takahashi Y, et al. Ann Transl Med. 2021" and "Shinohara S, et al. Ann Surg Oncol. 2020" should be cited.

Reply 1: Thank you for this suggestion. We have included both of these relevant references in the introduction.

Changes in the text: Both references were added

Comment 2: Please add inclusion and exclusion criteria more clearly. Exact number of patients who met the criteria would be shown in the Methods and Results section, hopefully as a CONSORT diagram.

Reply 2: We have clarified the inclusion and criteria in the methods section, per the reviewer's request. Because there were only 2 exclusion criteria, we did not include a CONSORT diagram, as we felt the numbers excluded seem clear to the readership from the body of the results section.

Changes to the text: Inclusion criteria included patients who underwent anatomic lung resection for pathologic T1-T2, N0, M0 NSCLC (AJCC 8th edition) between 2010-2019. All patient had primary lung adenocarcinoma, an 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.

Comment 3: The study design seems inappropriate since the grouping based on the three different definition of sarcopenia may be confusing.

Reply 3: Thank you for this comment. Unfortunately, there is no universally accepted definition of sarcopenia at the thoracic levels. The definition of sarcopenia at L3 has been well established in the cancer literature (Martin et al), therefore this definition was used in our analysis. However, given the lack of established definition for sarcopenia at the thoracic levels, we utilized gender-specific lowest quartile which has been reported in other populations.

Changes to the text: No changes to the text were made.

Comment 4: In the Figures 1 - 3, the number of patients at risk should be added because there may be shortage of patient numbers.

Reply 4: We agree this is important information and have added it to Figures 1-3.

Changes to the text: Please see figures 1-3 updated.

Comment 5: In the Discussion section, the clinical utility of the current study should be more clearly described.

Reply 5: We agree that the clinical utility of the current study should be more clearly described.

Changes to the text: The following text was added to lines 194 through 199 of the discussion section "The ability to preoperatively risk-stratify patients with lung cancer for OS and DFS is of paramount importance as this can help clinicians identify subsets

of patients that could potential benefit from closer surveillance or adjuvant cancer therapies. Since lung cancer is increasingly being identified through low dose chest CT lung cancer screening programs, it will be important to understand how thoracic sarcopenia should be interpreted in this patient population."

Comment 6: Actually, various definition of "Sarcopenia" result significant difference of the proportion of "sarcopenic patients" in the current study. How do they explain the significant difference and difference of survival significance of the sarcopenia?

Reply 6: We agree that this needs to be clarified further. The difference seen in the proportion of sarcopenic patients may be related to the different definitions of sarcopenia used. For L3 level we utilized the established definition based off Martin et al. for sarcopenia that is widely used in cancer literature. However, there is no established definition of sarcopenia at T12 or T5, thus we utilized gender-specific lowest quartile cut offs for these levels. However, it is unclear how sarcopenia can vary between the various vertebral levels. The main purpose of the study was to investigate the limitations of utilizing the upper thoracic vertebra for sarcopenia analyses, as few clinicians are likely to perform dedicated abdominal CT scans in every patient with early-stage lung cancer.

Changes to the text: The following text was added to lines 246-251 in the discussion section; "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 interpret thoracic sarcopenia in lung cancer patients that may not have CT abdominal imaging to assess the gold standard L3 level for sarcopenia analyses."

Reviewer D

Sarcopenia, measured at the L3 level, has been shown to be associated with survival in cancer patients, but many NSCLC patients do not undergo abdominal imaging. The authors examined the association between sarcopenia measured at different levels and prognosis in 259 patients undergoing surgery for early-stage NSCLC and concluded that gender should be considered when assessing sarcopenia using the upper thoracic spine level.

Comment 1: In discussion, authors' attitude towards sarcopenia measurement levels is unclear. Whether the T5 level is recommended or not, the T12 level may be imaged, but is it useless? L3 level is more reliable, really? Readers will have these questions.

Reply 1: Thank you for this comment. Overall, the main purpose of this study was to understand how thoracic sarcopenia may relate to the gold standard L3 level used to obtain sarcopenia. Early stage lung cancer patients provide a unique challenge to

physicians who perform sarcopenia research, as not all of these patients undergo CT abdominal imaging thus L3 is not routinely available. Although the L3 is the gold standard the T12 and T5 may be beneficial alternatives with the knowledge that there may be gender differences seen at thoracic levels when compared to L3.

Changes in the text: The following text was added to the conclusion section to lines 259-263; "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."

Comment 2: In abstract line 48, "Sarcopenia at T12 or L3 was associated with worse overall survival in both males and females ($p < 0.05$)." This is not correct as far as Figures 2 and 3 are shown. In addition, in order to evaluate the value of sarcopenia as a prognostic factor, this study requires a multivariate analysis that includes age, stage, and ... as variables.

Reply 2: Thank you for the observation. There was an error in this statement as it is supposed to read sarcopenia at T12 or L3 among the combined groups (Figure 2A and 2D, and Figure 3A and 3D) was associated with worse overall survival. This is in comparison to saying the significance held for both males and females.

Changes in the text: The follow text was removed from line 48 of the abstract; "in both males and females".

Comment 3: There is no information about histological type. Squamous cell carcinoma and adenocarcinoma may have different relationships with sarcopenia.

Reply 3: Thank you for this comment. All patients included in this study had histologic confirmed primary lung adenocarcinoma. Patients with squamous cell carcinoma were excluded.

Changes in the text: The following text was added to lines 100-102 to the patients and methods section; "All patient had histologic confirmed primary lung adenocarcinoma, an R0 resection, thoracic lymphadenectomy and no history of induction therapy."