

Peer review file

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Reviewer A

Comment 1: Other studies have looked at the association between sarcopenia as measured by psoas muscle area. The authors should make a stronger argument how their chosen anthropometric metric of sarcopenia adds value. Is it easier to measure? Does it more comprehensively measure a patient's sarcopenia rather than psoas muscle area, which just focuses on one muscle?

Reply 1: We agree with the reviewer's comments. We have added text to the manuscript describing the limitations of psoas muscle area as a measure of sarcopenia. To date, there are limited data comparing psoas muscle area and skeletal muscle area, however, a report from Rutten et al. (reference 29) demonstrated that psoas muscle does not correlate with total muscle area or overall survival, while total skeletal muscle area is associated with survival. For this reason, our group uses total skeletal muscle area for sarcopenia analyses.

Changes in the text: In lines 184-186 the following text was added: Although PMA may offer some benefits, such as quicker assessment of muscle mass, a recent study of patients with ovarian cancer demonstrated that PMA poorly correlates with SMA ($r = 0.52$) and is not associated with overall survival.

Comment 2: Do you have any data on change in sarcopenia pre and post-treatment? Does change in sarcopenia have a greater impact on outcomes than a static value post-neoadjuvant therapy?

Reply 2: Thank you for the great question. We did not have access to enough pre-neoadjuvant therapy scans to perform a meaningful analysis on change in skeletal muscle area pre and post-treatment since many patients were referred from outside our system and only had scans within 30 days of surgery.

Changes in the text: No changes were made.

Comment 3: State your hypothesis at the end of the Introduction.

Reply 3: We agree with the suggestion and added a hypothesis to the Background section.

Changes in the text: On lines 86-90 the following text was changed: We hypothesized that sarcopenic patients with LAEC who received induction CRT followed by surgery would have reduced overall and progression free survival when compared to non-sarcopenic patients.

Comment 4: Were all CT scans obtained at the primary institution? It's not uncommon to have patients referred to a tertiary center who received treatment neoadjuvant therapy in the community and obtained imaging locally.

Reply 4: Thank you for this question. Many patients included were referred to our center from outside institutions. However, all patients included in the current study had CT scans obtained at our institution within 30 days of surgery.

Changes in the text: On line 106 the following text was added; obtained at our institution.

Comment 5: You indicated that two radiologists reviewed all CT scans. Is there potential for variability when using the same software by two different individuals? If so, what was the product-moment correlation coefficient?

Reply 5: We agree this is an important point to make. There is potential for variability when using this software and it is important to ensure interobserver variability is at a minimum. We performed Pearson correlation coefficient of the two observers measurements and it was determined they were in adequate agreement with a Pearson correlation coefficient of 0.87.

Changes in the text: On lines 117-118 the following text was added: Interobserver correlation between the two operators who analyzed CT scans was assessed with Pearson correlation coefficient (r). On lines 141-142 the following text was added: Interobserver agreement between both operators on measurements of skeletal muscle area was determined to be good with a Pearson coefficient of 0.87.

Comment 6: Clarify how variables were selected for inclusion in your multivariable model? Did you use forward or backward selection? Did you have a statistical cutpoint from the univariable model for inclusion in the multivariable model (eg, $p < 0.1$).

Reply 6: Thank you for the question. We used stepwise selection for the cox proportional hazard multivariate models. Variables were selected with alpha value < 0.1 on univariate analysis or those found through prior reports to be significantly associated with overall survival or progression free survival after esophagectomy.

Changes in the text: On lines 123-127 the follow text was added: Independent variables were selected for inclusion in the multivariate regression using stepwise selection and those found to have $\alpha < 0.1$ on univariate analysis or those previously reported in the literature to be significantly associated with esophagectomy outcomes were included in the Cox Proportional Hazard regression model.

Comment 7: Which test did you use to assess violations of the proportional hazards assumption (line 115).

Reply 7: We agree this is important and added that we performed a proportional hazards assumption test utilizing Schoenfeld residuals to test for violations.

Changes in the text: On line 128 the following text was added: utilizing Schoenfeld residuals.

Comment 8: Clarify that you used two-sided statistical testing for all analyses.

Reply 8: We agree and clarified that two-sided statistical testing was used for all analyses.

Changes in the text: On line 128-129 the following text was added: Two-sided statistical testing was utilized for all analyses and results with $\alpha \leq 0.05$ was considered statistically significant for all analysis.

Comment 9: Based on your data, should patients found to be sarcopenic on their pretreatment CT scan undergo more aggressive intervention, such as exercise therapy and nutritional optimization, with a J tube if needed?

Reply 9: Thank you for this important question. We suspect that sarcopenic patients may benefit from more aggressive interventions in the preoperative period to mitigate the poor outcomes observed in multiple reports. However, there is a lack of prospective, level I data demonstrating improved outcomes among patients who undergo more aggressive nutritional or physical conditioning regimens.

Changes in the text: On line 239-243 the following text was added: Patients found to be sarcopenic in the preoperative period may require more aggressive physical and nutritional optimization to mitigate these findings. However, this is yet to be confirmed in a prospective study and further research is needed to determine whether prehabilitation programs and enhanced ERAS protocols can improve the poor outcomes seen in this patient population.

Comment 10: Do you have data on visceral protein levels, such as prealbumin or albumin, in your cohort and their association with sarcopenia.

Reply 10: Thank you for the thoughtful question. Unfortunately, we obtained albumin levels on <50% of our cohort within 30 days of surgery and thus did not report this data point in the manuscript. Similarly, our institution did not routinely collect prealbumin levels during the study period.

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

Comment 11: The 13% of missing data from patients being lost to follow-up is a potential limitation.

Reply 11: We agree that patients excluded for having missing data secondary to lost to follow-up is a limitation and added this to the limitations section of the discussion.

Changes in the text: On lines 233-235 the following text was added: Finally, 7 patients had to be excluded for being lost to follow up which could potentially confound survival analysis results.

Comment 12: For your Kaplan-Meier curves add the number at risk along the x-axis, and add 95% confidence intervals.

Reply 12: We agree. The Kaplan-Meier curve for overall survival and progression free survival was changed to include both number at risk along x axis and the 95% confidence intervals.

Changes in the text: No changes to the text were made. Please see Figure 2 and 3 for updates.

Comment 13: Were there any postoperative deaths? I realize you excluded patients who had less than 90 days of follow-up, but sarcopenia may be associated with perioperative mortality which would be valuable data to add to your study.

Reply 13: Thank you for the great feedback as we too feel perioperative mortality would be important to consider in sarcopenia. There were no patients who experienced perioperative mortality. Those excluded because of less than 90 days of follow up were lost to outside health networks with incomplete survival data.

Changes in the text: On lines 135-136, the following text was added; There were no patients who expired in the immediate postoperative period.

Reviewer B

Comment 1: The authors state in rows 89-90: " Induction CRT regimens were administered at the discretion of the treating team, however generally consisted of a cisplatin-based doublet and 41.4-50 Gy external beam radiation" The authors should describe the different regimens of CRT given to the patients in further detail.

Reply 1: Thank you for the excellent feedback. We too feel this important to further clarify and have added 2 references and further information of the neoadjuvant regimen to the manuscript.

Changes in the text: On lines 95-100 the following text was added: Induction CRT regimens were administered at the discretion of the treating team in accordance with previously reported protocols. (10, 11). Neoadjuvant radiation treatment consisted of 41.4-50 Gy external beam radiation administered in 25 to 28 fractions over a period of 5 weeks. Neoadjuvant chemotherapy was administered concurrently and included biweekly administration of 5-fluorouracil in combination with platinum based agent for up to 6 cycles or weekly administration of carboplatin and paclitaxel for up to 6 cycles.

Comment 2: It would also be interesting to in more detail what were the surgical approaches used, as now in Table 1, only "minimally invasive" and "Open" are described.

Reply 2: Thank you, we agree and have added information on the surgical approaches used in the results section.

Changes in the text: On lines 148-151 the following text was added; Open operative approaches consisted of Ivor Lewis approach technique in 31 patients (60%), modified McKeown (3-hole esophagectomy) in 7 patients (13%), transhiatal approach in 2 patients (4%). Minimally invasive esophagectomy Ivor Lewis esophagectomy was performed in the remaining 12 patients (23%).

Comment 3: I would also like to hear some insight in to the rate of minimally invasive surgery vs. Open, the percentage of MIE seems to be low, is there a reason for this.

Reply 3: Our group did not begin performing minimally-invasive esophagectomies until 2016, therefore a majority of patients underwent open approaches during the study period. Since 2018, nearly all of our esophagectomies have been performed in a minimally-invasive fashion.

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