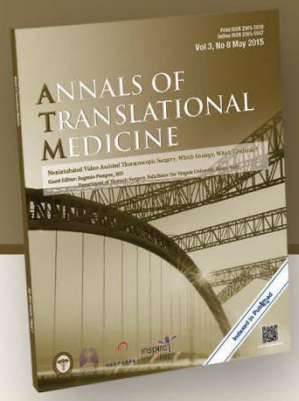
ANNALS OF TRANSLATIONAL MEDICINE



Peer Review File

Article information: http://dx.doi.org/10.21037/atm-20-4380.

Reviewer A

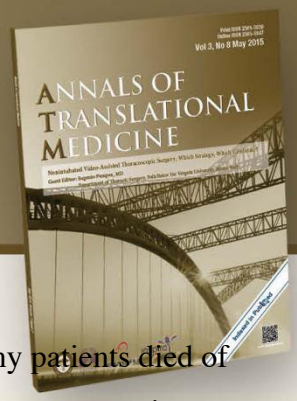
Major Comment

Comment 1: As described in the Discussion, the definition and the cut-off values of sarcopenia is not well established to date. This study arbitrarily defined sarcopenia as the lowest sex-specific quartile in the average of both psoas muscle area. This definition was not standard, not common among the many past studies, and has not been validated as a definition of sarcopenia. The lowest quartiles defined as sarcopenia in men and women were 770mm2 and 495mm2 of psoas muscle area (PMA) in Ref 13 by Okamura H, 567.4 and 355.8 mm2/m2 of psoas muscle index (PMI) in Ref 72 by Fujikawa H, and 564.2 and 414.5 mm2/m2 of PMI in Ref 73 by Amini N, respectively. The study of Ref 74 by Ganapathi AM did not use psoas muscle area (PMA), but total psoas muscle volume (TPV). The studies cited by the authors used much different measurement methods and cut-off values.

Thus, I am afraid that this study might define some non-sarcopenic patients as sarcopenic, and vice versa. According to the definition used in this study, so-called 'sarcopenia' defined in this study was only relatively sarcopenic. The authors should carefully mention it.

Reply 1: We thank the Reviewer A for the helpful comment. We agree that our "sarcopenia group" may include some of just relatively sarcopenic patients in this study. Also, our measurement methods and definition are non-standard and arbitrary. There are many previous studies which had used various measurement methods and cut-off values in these studies. We had already described that our measurement method and cut-off cvalue are potentially arbitrary in the Discussion section of the original manuscript (page 18, Lines 14-17).

Changes in the text: We added the following sentence "Previous studies used various measurement methods … evaluating "pre-sarcopenia" even in early-stage NSCLC." On page 15, lines 2 - 8, in the Discussion section.



Comment 2: The authors should show the outcomes of the patients. How many patients died of cancer progression or non-cancer events, lost follow-up and still survived? How many patients experienced recurrence?

Considering the high 5-year survival rates, I am afraid of too small number of death events, compared with many explanatory variables (N=9) in multivariate Cox-regression analysis in Table 5.

Reply 2: Thank you for the kind comment as well. We have observed 38 cancer related- and 29 non-cancer related deaths during the follow-up period in this study. It seems sufficient to perform multivariable Cox-regression analysis with using 6 variables in the revised version of Table 5. Notably, we have already present patients at risk in the Figure 3.

Changes in the text: We thus added these numbers of the patients in accordance with the comment as follows, "Consequently, we have observed 38 cancer related- and 29 non-cancer related deaths during the follow-up period in this study. Also, 54 patients have experienced recurrence." (on page 11, lines 8 - 10)

Minor Comment

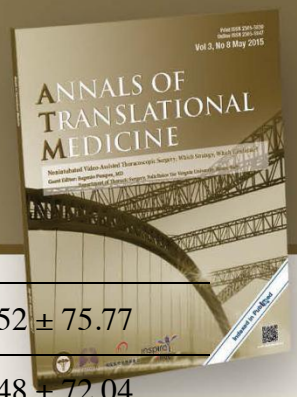
Comment 1: In the cited study of Ref 13 by Homare Okamura, psoas muscles were measured at the level of the top of the iliac crest by Ziostation. On the other hand, in another cited study of Ref 24 by Raghavendra Paknikar, 'The psoas muscles were outlined at the inferior border of the fourth lumbar vertebrae.' Was there any reason why the authors cite slightly different measurement site of psoas muscle?

Reply 1: Actually, we measured psoas muscle area at the level of the top of the iliac crest which is different from some of the previous studies as above. We thus compared the psoas muscle area between the two methods. As shown in the Reviewer Response Table 1-1, there is no significant difference. Thus, slight difference of measurement methods may result in no clinically significant difference of psoas muscle mass area.

Reviewer Response Table 1-1:

Comparison of psoas muscle area between the current method and Paknikar's method

Methods	Median psoas muscle area (± QD, mm^2)



The current study	Male: 675.3 ± 166.12	Female: 525.52 ± 75.77
Paknikar et al.	Male: 683.2 ± 131.28	Female: 509.48 ± 72.04
p-value	0.842	0.714

Comment 2: When was the data cut-off?

Reply 2: The data cut-off was 14 December 2019.

Changes in the text: We thus added the sentence, "The data cut-off was Decembe r 2019." (see page 9, lines 8 – 9 in the Methods section)

Comment 3: Considering Fig.2, psoas muscle area in this study was limited only to right? This study did not use average of both psoas muscles?

Reply 3: Actually, we have measured bilateral psoas muscle areas and calculate average as described page 8, lines 7 – 8 in the Methods section. We have revised Figure 2 to avoid the misunderstanding as well.

Comment 4: The red curves of 'Sarcopenia 1' have many black censored bars. Can these lines and bars be unified in the same color?

Dose 'Sarcopenia 1' and 'Sarcopenia 0' mean non-sarcopenia and sarcopenia, respectively?

The dotted curves mean 95% CI curves?

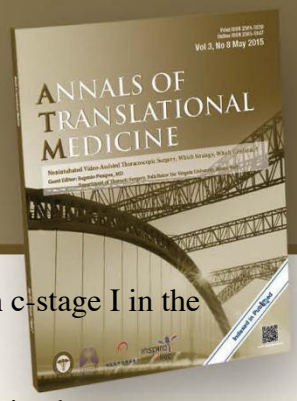
The X-axis of 1000, 2000, 3000, 4000days should be changed to years.

Reply 4: Unfortunately, we cannot change the color of censored bars on the R software. In accordance with the comment, however, we have revised Figure 3 and the legends.

Comment 5: Mistaken calculation? In Table 1, the total number of never-smoker (127) and ex-smoker (206) is 333, not 323. The total number of histology is also 333, not 323.

Reply 5: We would like to apologize the mistakes in the Table 1, we have revised some numbers in the Table 1.

Comment 6: In Table 1, the range of FEV1 is 0.94 to 4.76L. I was surprised by the fact that the patients with FEV1<1.0L had received lobectomy, not partial resection or stereotactic



radiotherapy. Were there any indication criteria of lobectomy for patients with c-stage I in the authors' institution?

Reply 6: In Table 1, the case with 0.94L of FEV1 was excluded as the tumor histology was large ell neuroendocrine carcinoma in accordance with the comment 7. Actually, the patients have undergone tight middle lobectomy because of the predicted postoperative FEV1 of 0.85L. Our criterion for lobectomy of the predicted postoperative FEV1 was greater than 0.8L.

Changes in the text: We thus added the sentence, "Our operative indication of lobectomy is predicted postoperative FEV1 larger than 0.8L." (see page 7, line 15 in the Methods section)

Comment 7: In Table 6, despite of very small number of patients, carcinoid (N=4), LCNEC (N=3) and SCLC (N=1) were included in this study. This histology is characteristically different in prognosis and treatment strategy from typical NSCLC. Why did this study include this minor histology together with NSCLC?

Even if a patient with stage 1 of LD-SCLC had received curative lobectomy, adjuvant chemotherapy of platinum-based CPT-11 or VP-16 should have been completed after the surgery.

Reply 7: We agree the comment and we have excluded 8 cases from the revised version in accordance with the comment.

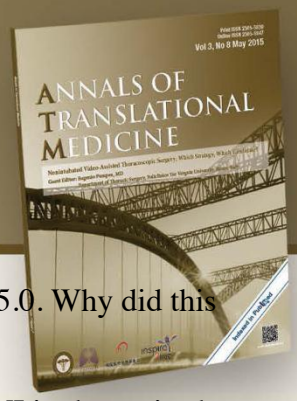
Changes in the text: We thus added these numbers of the patients in accordance with the following sentence, "5) those carcinoid or large cell neuroendocrine carcinoma." (see page 7 line 9

Comment 8: Table 5 keeps revision records.

Reply 8: We would like to apologize for the mistake. We have removed the revision records.

Comment 9: In Table 5 of Cox-regression analysis, BMI was divided by 25.0, which is the cut-off value of normal and overweight. Was 18.5, which is cut-off value of normal and underweight, more suitable in the study of sarcopenia?

In Table 4 of logistic regression analysis of risk factor of post-surgical complications, BMI was used as an explanatory variable by continuous variable. On the contrary, in Table 5, BMI was



used as an explanatory variable by dichromatised variable, that is ≥25.0 vs <25.0. Why did this study use BMI as an explanatory variable in different ways?

Reply 9: We also agree with the comment. We used the cut-off of 18.5 for BMI in the revised version. We have also changed to use dichotomized variables consistently in both Table 4 and 5.

Comment 10: In Supplemental Figure 1, '# of patients' means 'number of patients'?

Reply10: We have revised the description into "Number of Patients" in the Supplementary Figure 1.

Reviewer B

In my opinion the authors should be acknowledged for their work. I've appreciated authors aim and as an oncologist, the paragraph dedicated to post-operative complications and sarcopenia. I mean, of course sarcopenia is a prognostic factor overall, but it might be particularly useful to predict post-operative complication, rather than survival, in the stage I setting.

I've just a couple of question for the authors:

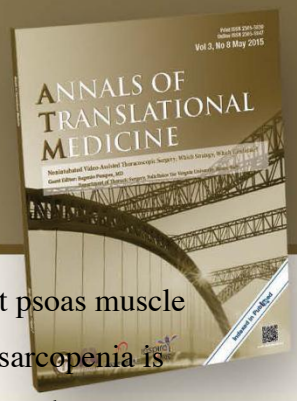
I would like that they add a clearer explanation of sarcopenia evaluation. E.g. the role of contrast media: recent experience has shown that contrast media and slice thickness may have a strong effect on the evaluation of body composition (Montano-Loza AJ, J Cachexia Sarcopenia Muscle 2016;7:126–35. Mourtzakis M, Appl Physiol Nutr Metab 2008;33:997–1006) Morsbach et al. (Nutrition 2019) have shown that average skeletal muscle index (SMI) increased by up to 2.8% after contrast media injection and decreased by 1.9% on average when increasing slice thickness from 2 to 10 mm. Muscle attenuation did not change significantly with reconstruction thickness but increased after contrast media injection depending also by the time (arterial or early portal-venous) scan

Moreover, I appreciated the sex-specific cut-off. Could they explain why they did not adjusted for patients' height the muscle area?

After this minor points, in my opinion the manuscript deserves publication.

Reply: Thank you very much for the valuable comments and suggestions which may give us an opportunity to improve our manuscript.

We should be aware that there is no consensus regarding measurement methods and



normalization methods in evaluating sarcopenia. That is why we did not adjust psoas muscle area with height. On the other hand, sex-specific cut-off is usually used when sarcopenia is defined as psoas muscle mass lower than the lowest quartile within the patients cohort.

In addition, we have added the description regarding the effect of contrast media and CT slice thickness on evaluation of skeletal muscle area as below.

Changes in the text: We thus added the sentence, "Third, the current measurement method … may methodological errors in evaluating sarcopenia." on page 18, line 14 – page 19, line 2.

Reviewer C

Interesting study.

However, novelty of study claimed in the introduction must be mitiged.

Authors cite different studies reporting similar results in the discussion section: stating in the introduction that data on resected NSCLC are scarce is contradictory.

Display of tables and figures should be improved (cf. characters in the figure of CT scan, the corrections in the headings of some tables, etc; the sum of histologic types which is inconsistent with the total number of patients).

With respect to statistical analysis, I suggest removing EGFR status: this has no value in squamous cell type and there are several missing data. Anyway, multivariable analyses should be redone: they included EGFR status and because of missing data, corresponding patients were not included in the model: what about results when taking into account the whole population?

Reply: Thank you very much for the kind comments and suggestions.

We agree that EGFR status might have inaccurate impact on the results because of the considerable missing data. In accordance with the comment, we have removed EGFR status from the Cox-regression analysis in the revised version.

Also, we have corrected Tables and Figures in accordance with the comment.