Peer Review File

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Reviewer A

Mizuno et. al. describes a cohort of radiologically defined low-grade adenocarcinoma (264 pure GGO or part solid tumors <3 cm cN0) and compare traditional radiologic total/solid sizes and automated volumetric/density metrics to pathologic diagnosis after excision of invasive adenocarcinoma. The relevance of this study leans on the work of JCOG studies demonstrating limited resection is adequate management for small radiologically indolent lung adenocarcinoma defined by CTR, pointing out the pre-operative determination of adenocarcinoma risk is critical to risk-stratifying patients to parenchymal sparing surgical approaches. The authors nicely demonstrate solid size (SS) is generally adequate at predicting pathologically invasive adenocarcinoma with solid volume being slightly better for larger tumors (2.1-3 cm). While a very reasonable approach, the major weakness is the authors assumption that pathologic invasive adenocarcinoma (defined in this study as not AIS/MIA) is reproducible among pathologists in small subsolid lung adenocarcinoma. Unfortunately, several studies have shown this is not true (most recent and significant PMID 36503176). Still, the approach is reasonable but additional validation would be useful to support the authors conclusions.

Major

Comment 1: I would recommend further validating the findings to include not just IAD but also IAD with any of pl+, ly+, v+, or pN+ (aggressive IAD). From Table 2 there looks to be ~20 or so such cases out of the entire cohort. Sensitivity will likely be low but if specificity is good for SS or Solid volume or HU, that would support your conclusion. This is in keeping with other studies approaches cited in your discussion (your reference 5 Suzuki K JTO 2011 6:751-6).

Reply 1: In our cohort, we identified 23 patients with termed aggressive IAD. We investigated diagnostic abilities of solid volume comparing with SS. We did not observe either high sensitivity nor specificity, and did high negative predictive value due to the limited number of aggressive IAD. Those results were presented in Supplement Table 3.

Changes in the text: We added the sentences about analyses in aggressive IAD diagnoses in line 15-18, page 8. Supplemental Table 3 was presented.

Comment 2: I would also recommend validating the finding looking at recurrence free survival (RFS). Your cohort is from 2017-2020 and thus you should be able to generate a Kaplan Meier curves with at least 3-year RFS thresholds for the radiologic cutoffs studied. I would focus on the TS 2.1-3 cm group since tumors <2 cm are unlikely to recur but I would leave that to your discretion. Most NSCLC recur in the first 3 years

after surgery.
Reply 2: In the present cohort, we identified only 4 patients with recurrence, 7 patients died of other causes and no patients died of lung cancer. Three-year RFS of patients with nodules sized less than 5mm and 5mm or more was 98.2% and 97.8%, respectively (p=0.75). And those of solid volume less than 300mm^3 and 300mm^3 or more were 100% and 97.1%, respectively (p=0.18) Due to those extremely favorable cohort, we did not stratify survivals by radiological findings. We described those numbers of recurrence and death in the manuscript.
Changes in the text: We presented the limited number of recurrence and death in line 17-18, page 7 and did not the results of survival analyses.

Comment 3: Your methods state you collected CTR on all cases, but you don't report the CTR or compare your findings to the CTR values. Why?
Reply 3: As the reviewer commented, we have collected CTR data. We have presented analyses of CTR in Table 3, though those presentation were missed in Table 1. We modified Table 1 and have commented the results in the manuscript.
Changes in the text: We presented CTR data in Table1 and Table3 and commented about the data in univariate analyses in line 6, page 8.

Minor
Comment 1: Abstract (page 3, line 5) "subcentimeter". This not true since most of your tumors are > 1cm.
Reply 1: We had mistaken to use a wrong word. We modified it in the Abstract.
Changes in the text: We replace the word "small sized" in the Abstract, page 2, line 8.

Comment 2: Introduction (page 4, line 18-19): You discuss the subjectivity of radiologic assessment of solid size but you don't mention subjectivity of assessment of invasive size by pathologists (PMID 36503176).
Reply 2: We completely agree with the reviewer's comment. The subjectivity in diagnosis of IS is an important issue in comparison of radiological and pathological findings. We have discussed about it in the discussion section.
Changes in the text: We discussed about subjectivities and reproductivities in IS measurement citing the previous reports from line 20, page 9 to lime 2, page10.

Comment 3: Methods (page 5, line 10): You use IS (>5 mm) but I think you are referring to SS. It is important to keep the radiologic term (solid size) distinct from pathologic terms (invasive size).
Reply 3: I understand the reviewer referred to the description in page 6, line 10. We intended to explain that we described ROC curves for max HU, mean HU and solid volume to evaluate how those parameters diagnosed more than 5mm of IS (IAD). Definition of the clinical T descriptor was used for SS.
Changes in the text: We changed IS to 3D parameters in line 10-11, page 6 in the revised manuscript.

Comment 4: Discussion (page 9, line 16-17): The statement “This proposal was validated by physicians” seems odd. What are you trying to say?
Reply 4: This sentence meant that extremely favorable survival of AIS or MIA was confirmed by previous studies after proposal by IASLC/ATS/ERS. We replaced physician to researches.
Changes in the text: We replaced physician to researches in line 1, page 11.

Comment 5: Discussion (page 10, line 6-7): In our cohort… This sentence might be expanded based upon the follow up validation recommended. The fact that you missed 45.7% of IAD in lesions radiologically defined as cTis-T1mi may not be relevant if they don’t show any aggressive features (PL, LY, VI, pN+). Such lesions also have a low risk of recurrence and have been defined pathologically as “low-malignant potential adenocarcinoma” (PMID 33177339). Expanding this portion of the discussion may be useful.
Reply 5: On page 10, line 6-7 in the original manuscript, we documented limitation and low negative predictive value in IAD diagnosis by SS. As the reviewer commented, cases of false negative seemed to be speculated as low-malignant potential adenocarcinoma. Only one out of our 44 patients with false negative by SS experience pulmonary metastases.
Changes in the text: We added the sentence “Among those 44 cases, we observed only one patient with recurrence and two patients of aggressive IAD, most of false negative cases might be less aggressive IAD with favorable prognosis (13).” in line 4-6, page 9.

Comment 6: Table 1: Recommend including proportion of never smokers. I think this data is useful for western institutions seeking to apply data to their own populations with low-rates of never smokers.
Reply 6: We had presented numbers of former and current smoker in Table1, remaining number, 128 patients were never smoker. We change the description of the variable to never smoker.
Changes in the text: Numbers of never smokers were presented in Table 1 instead of smoking history.

Comment 7: Table 1: Indicate p values represent comparison of 2 groups stratified by size (I assume that is the case).
Reply 7: As the reviewer pointed out, *P* value represent the result of statistical tests of 2 groups by size. We described about it at the bottom of Tables.
Changes in the text: The sentence “*P* value represents the result of statistical tests of 2 groups stratified by size.” was added at the bottom of Tables.

Comment 8: Table 2: The SD is too high for whole tumor size for the 0-2.0 cm group. 15 +/- 15 would put the range above 2 cm. Is this a typo? Is the SD really 5.6?
Reply 8: The SD value was a typo. Although we should modify it to 3.56, those values in Table2 have presented in median and IQ range according to the suggestion of reviewer 3.

Changes in the text: We did not use SD values in Tables.

Comment 9: Table 2: Indicate p values represent comparison of 2 groups stratified by size (I assume that is the case).
Reply 9: As the reviewer pointed out, *P* value represents the statistical results of 2 groups by size. We described it at the bottom of Table 2 as we have done in Table 1.
Changes in the text: The sentence "*P* value represents the result of statistical tests of 2 groups by size." was added at the bottom of the Tables.

Comment 10: Figure 2: IS: invasive size – might be good to specify pathologic invasive size. This is a nice figure but could be a supplement if you decide to look at RFS and want to add a KM-curve as another figure.
Reply 10: We have already described the values of IS for respective cases in the figure legend. As we described above, survival analyses did not provide useful information concerning to the present theme. We have left present Figure 2 in this revised version.
Changes in the text: The ISs were presented in the Figure legend.

Reviewer B

Comment 1: Authors demonstrated the association with solid volume and invasive size but they did not analyze the OS or DFS using entire volume or solid volume.
Reply 1: According to the Reviewer B and A suggestions, we carried out analyses about OS and RFS. As we replied to the major comment 2 of reviewer A, we identified only 4 case of recurrence, 6 dead cases of other causes and no lung cancer death. We could not provide informative data from our survival analyses.
Changes in the text: We could not present informative results of survival analyses.

Comment 2: According to the figure 2, solid volume could be calculated even though the pathologic AIS. and solid volume was 324 for 11mm of IS. I thought that the cut off value of solid volume (300) was too high.
Reply 2: In figure 2A, the short cord shadow in the dorsal side of the nodule was evaluated as solid volume by the application, meanwhile the shadow was judges as a vessel shadow not being evaluated as solid part by us. In figure2C-D, we can explain SS was underestimated by conventional measurement based on our subjectivity. If we decrease the cut off CT value of solid volume, the cut off value of solid volume elevate responding it. So we performed analyses based on the set cut-off value to measure solid volume used in previous reports and the default setting in the application.
Changes in the text: Replying as above, we did not change the cut off value of solid volume and descriptions.

Comment 3: I wondered overall survival according to the IS, solid size, solid volume and TV (TNM staing system)
Reply 3: As we commented above, we identified extremely limited number of events

in our cohort. We could not obtain informative results from survival analyses.
Changes in the text: We did not present the results of overall survival.

Reviewer C

Following are some suggestions to improve the article.
Comment 1: Reporting Checklist
The STARD guidelines would be more appropriate for a Diagnostic Accuracy Study than the SPIRIT guidelines. We suggest authors fill out and submit the "STARD Checklist" (https://cdn.amegroups.cn/static/public/7-STARD-2015-Checklist.pdf). The relevant page/line and section/paragraph number in the manuscript should be stated for each item in the checklist.
A statement "We present the following article in accordance with the STARD reporting checklist" should be included at the end of the "Introduction". The manuscript should also include a Reporting Checklist statement in the footnote: "The authors have completed the STARD reporting checklist."
Reply 1: We had submitted the STARD reporting check list following the suggestion by Editorial Office at the last submission. We modified the check list responding this manuscript revision.
Changes in the text: We resubmitted the modified STARD check list.

Comment 2: Title
"predicting": We suggest the authors could specify it. For example, "diagnostic sensitivity".
Reply 2: We agreed with the reviewer's comment. We changed the title to "Diagnostic sensitivity of solid volume for pathological invasion in non-solid lung adenocarcinoma ".
Changes in the text: We changed the title in line 2-3, page 1.

Comment 3: Abstract
(1) The Abstract is too short and not informative enough (200-350 words max). It is suggested to refine it, e.g., what are the knowledge gaps in the field?
Reply 3(1): We agreed with the reviewer's comment. We extended and refined it.
Changes in the text: We extended the abstract to 277 words following the reviewer's suggestion in page 2. And we added the description about discrepancies between cT and pT descriptors in line 2-4, page 2.

(2) Please also specify the eligibility criteria for participants and settings where the data were collected in the abstract.
Reply 3(2): We have specified the eligibility criteria and described the data were collected at Shizuoka Cancer Center.
Changes in the text: We added the following sentences "We enrolled consecutive 246 patients who underwent pulmonary resection at Shizuoka Cancer Center. Patients with

lung adenocarcinomas which were radiologically non-solid, node negative and sized ≤3 cm were eligible." See line 9-11, page 2.

(3) Please identify whether participants formed a consecutive, random, or convenience series in the abstract.

Reply 3(3): We described participants formed consecutive series in the abstract.

Changes in the text: We added following sentence "We enrolled consecutive 246 patients・・・." See line 9, page 2.

(4) Please present all key results with precise data and their precisions instead of vaguely stating "significantly associated" or "facilitated".

Reply 3(4): We presented key results with precise data and their precisions

Changes in the text: We added the sentences "In multivariate analyses, the total and solid sizes were significantly associated with invasive adenocarcinoma (p=0.006, 0.001, respectively), whereas three-dimensional parameters were not (p=0.804). In radiological adenocarcinoma (2.1–3.0 cm), solid volume >300 mm3 diagnosed invasive adenocarcinoma with a higher sensitivity than that of the solid size (0.93 and 0.83, respectively)." in line 16-21 page 2.

(5) Please indicate whether the study was registered. If yes, present the registration number and name of registry in the abstract too.

Reply 3(5): We indicated that this study was not registered.

Changes in the text: We added a following sentence "This study was not registered ." in line 15, page 2.

Comment 4: Introduction

Lines 59-60: "Varieties of small-sized lung cancer images are obtained using novel innovations of high resolution-computed tomography (HR-CT)". We suggest the authors

- Add traditional diagnostic methods and their advantages and disadvantages.
- Introduce existing methods for assessing pathological invasion before surgery, clarify what are the advantages of volume analyzing application and its related studies, and clarify the innovation of this study by comparison.

Reply 4: Concept of comparison of radiological findings and pathological invasive size had developed after we started to use HR-CT in clinical practice. SS measurement is a traditional method. Actually, we often experience discrepancy between SS measured using HR-CT and pathological IS, other authors reported about that issue. One of the explanations is subjectivity induced by physician selecting specific slice of CT image and measuring the size of the shadow. The volume analyzing application enables us to measure 3D data semi-automatically without selecting specific slice. One of advantages is exclusion of subjectivity in measurement and selecting slice by physician.

Changes in the text: We described about SS measurement in HR-CT slice as a conventional method, and 3D measurement with potential advantage in line 11-13, 18-19, page 4, and line 2-3, page 5.

Comment 5: Methods

(1) We suggest authors also specify the study design (“This a retrospective diagnostic study") at the beginning of the Methods.

Reply 5(1): We described our study as a retrospective diagnostic study.

Changes in the text: The words “this retrospective diagnostic study” were added in line 2, page 7.

(2) We suggest authors specify the inclusion criteria for each one, not simply by stating “884 patients underwent pulmonary resection for lung adenocarcinoma at Shizuoka Cancer Center” (Lines 83-84). The same goes for the exclusion criteria.

Reply 5(2): We had described the inclusion and the exclusion following the sentence (Line 11-15, Page 5) in the original manuscript. We include those description in modified Figure 1.

Changes in the text: We add the following sentences “Patients with cN0 disease radiologically sized ≤ 3 cm and pure or part solid GGO lesion were eligible. 294 patients with pure solid nodules were excluded.” in line 11-13, page 5. And see revised Figure 1.

(3) Please indicate whether the selection of participants was consecutive, random, or a convenience series.

Reply 5(3): We indicated that we enrolled consecutive patients in the Methods section.

Changes in the text: We added “consecutive” in line 10, page5.

(4) We suggest the authors also add more details about the measurement of SS and IS: who and how? Whether the operators are blind to each other.

Reply 5(4): SS measurement were performed and confirmed in our surgical cancer board, IS measurement was done by two pathologists. The operators and the pathologist were not blind.

Changes in the text: We add the description about SS measurement in line 4-5, page 6, about IS in line 21-22, page 5.

(5) Lines 85-88: "Altogether, 294 patients ... wedge resection, respectively". The final number of included individuals and the analysis results should be presented in the Results.

Reply 5(5): We presented 246 patients were enrolled for analyses in the Result rection.

Changes in the text: We described “The remaining 246 patients with non-solid nodules were enrolled in this study (Figure 1).” in line 15, page 5, and “enrolled 246 patients” in line 8, page 7.

(6) Please describe all the statistical methods in detail, including how quantitative variables were handled, how to control for confounding, and how missing data were addressed.

Reply 5(6): We described that we compared continuous variables using Mann–Whitney U test, no missing data observed and confounding were adjusted by the multivariate

analysis.
Changes in the text: We added the sentences “Continuous variables were compared using Mann–Whitney U test. Univariate and multivariate logistic regression analyses were performed to identify factors predicting IAD, with P <0.05 indicating statistical significance. Confounding factors were adjusted by the multivariate analysis.” from line 20, page 6 to line1, page7.

(7) We suggest authors perform normality test to determine which statistical analysis to be applied. For author’s reference, in table 1, the SD value of Solid Volume is larger than the mean value (820, 933), which might indicate the data was skew distribution and the normality test is necessary. The authors should determine if the mean difference is normal, if not, then use medians with interquartile ranges and rank sum test. Please check through all the tables to address similar concerns.

Reply 5(7): We performed normality tests for 3D-CT data, observing not normal distribution. According to the reviewer’s suggestion we used medians with IQ ranges and rank sum test.
Changes in the text: Mean ± SD was changed to median [IQ range] in Table 1,2.

Comment 6: Results
(1) We suggest authors use a flow diagram to state the numbers of individuals in the screening and analysis stages of this study. Besides, give reasons for non-participation, not just in the text (Lines 83-91). Accordingly, report the numbers of inconclusive results at each stage in the context too. For authors’ reference, here is an example: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5128957/ (Figure 2)
Reply 6(1): According to the reviewer’s suggestion, we modified flow diagram of Figure 1 presenting evaluation of the accuracy of solid volume for diagnosis of invasive adenocarcinoma.
Changes in the text: We added the sentences “Among 160 patients with solid volume>300 mm3, 143 patients (89.3%) were diagnosed with IAD, meanwhile 42 patients (48.8%) out of 86 patients with SV≤300 mm3 were diagnosed with IAD (*Figure 1*).” in line 3-5, page 8. And we also modified Figure 1 following the comment.

(2) Please disclose any adverse events through the study. If not, please also state it.
Reply 6(2): We disclosed no adverse event from this retrospective study.
Changes in the text: We added the following sentences “No adverse events were reported during this retrospective diagnostic study.” in line 19, page 8.

(3) A cross tabulation of SS against IS should be listed. And actual numbers are suggested to be included.
Reply 6(3): We listed cross tabulations of SS against IS and SV against IS in Supplemental Table 1,2.
Changes in the text: We added Supplemental Table 1 and 2.

(4) We suggest the authors could present and analyze key results in the Results. For

example, in Table 1, which indicators differed in the assessment of TS tumor.
Reply 6(4): We presented and analyzed key results in the Results section following the reviewer's comment.
Changes in the text: We added the following sentences about Table 1 "In larger TS tumor of 2.1-3.0cm, TS, SS, max HU and solid volume were significantly higher comparing to the smaller tumor. And more patients with radiological invasive adenocarcinoma (SS>5mm) were included significantly." in line 12-15, page 7.

Comment 7: Discussion
(1) It is necessary and important to transparently discuss the study's LIMITATIONS in the Discussion. A separate paragraph is highly suggested.
Reply 7(1): We discussed the study's LIMITATIONS in the Discussion section using a separate paragraph.
Changes in the text: We made a paragraph for study limitations in the Discussion section. See from line 13, page 9 to line 5, page 10.

(2) We suggest the authors could discuss the results of this study in depth. For example, when discussing the inconsistent results of similar studies, the authors may consider discussing, from an objective perspective, which are more trustworthy while others are not? Authors may also compare the results of this study with other assessment methods to help readers have a more comprehensive understanding.
Reply 7(2): We discussed the results of this study comparing other studies. As described in the manuscript, our inclusion and exclusion criteria were different form other studies. Exclusion of non-solid tumor and inclusion of more cases of lobectomy were considered to be reasons of our favorable disease control.
Changes in the text: We cited and explained several reports using 3D data describing respective inclusion criteria in line 12-17, page 11.

Comment 8: Conclusions
Please add a separate section about "Conclusions".
Reply 8: We add a separate section about conclusion following the suggestion.
Changes in the text: We add a separate section about conclusion line 9-13, page 12.

Comment 9: Other Information
(1) The title page should also include the word count and the number of figures and tables.
Reply 9(1): We included the word count and the number of figures and tables.
Changes in the text: We included the word count and the number of figures and tables from line 15-16, page 1.

(2) Similar to the points on comment 2(4), please indicate whether the study was registered.
Reply 9(2): We described our study was not registered.
Changes in the text: We described that our study was not registered in line 3, page 7.

(3) We understand that authors do not want to share data. Could you please mention at the end of the article (in the "Footnote-Data Sharing Statement") whether the reader can access the data from the corresponding author if needed?

Reply 9(3): We mentioned that the reader can access the data on request at the in the Footnote-Data Sharing Statement.

Changes in the text: We stated that the reader can access the data on request in the Data Sharing Statement.

Comment 10: Format

Due to the recent editorial update on the regulations of manuscripts,

(1) Please use a structured Introduction to increase readability: a) Background, b) Rationale and knowledge gap, c) Objective.

Reply 10(1): We used a structured Introduction following the editorial update.

Changes in the text: We used a structured Introduction from line 2, page 4 to line 7, page 5.

(2) We recommend that authors use a structured Discussion to increase the readability: a) Key findings, b) Strengths and limitations, c) Comparison with similar researches, d) Explanations of findings, e) Implications and actions needed.

Reply 10(2): We modified the Discussion section using a structured form.

Changes in the text: We used a structured Discussion in the revised Discussion section from line 21, page 8 to line 8, page 12.

(3) A highlight box is strongly recommended to highly summarize the key findings/recommendations, innovation and potential implications of the study.

Reply 10(3): We made a highlight box following the recommendation.

Changes in the text: We made a highlight box and included it in the main text, page 3.

(4) The P-value should be formatted following the JTD Author's Instructions (https://jtd.amegroups.com/pages/view/guidelines-for-authors, content-4 STATISTICAL REQUIREMENTS). Also, please keep the same decimal places of each mean ± SD value in the tables and the main text.

Reply 10(4): We formatted the *P*-value following the Author's Instructions.

Changes in the text: We formatted the *P*-value following the Author's Instructions in the manuscript and tables. Mean±SD was changed to median and IQ range.

(5) Lines 169-171: "Sakao et al., Sakakura et al., and Samejima et al. reported the usefulness of predicting IS using the tumor diameter in the mediastinal window setting (7, 8, 21)". Suggest put "[21]" after "Sakao et al.".

Reply 10(5): We modified descriptions of the reference citation.

Changes in the text: We put the citation number (26) after Sakao in 1ine 5, page 11.