Peer review file
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Reviewer A

Comment:
In this manuscript, the Authors describe the results of a study comparing three-dimensional computed tomography (3D-CT) and high resolution computer tomography (HRCT) in the prediction of the invasiveness of Stage IA lung adenocarcinoma. One hundred ninety-five lesions were examined in the trial, 57 classified as difficult to be evaluated due to irregular margins and hazy shapes (Hazy lezions), and 138 typical lesions (TL). The results of the study show that when the whole population is analyzed, similar results were observed with the two CT scan techniques both in the evaluation of total and solid tumor volume, without significant advantages with the use of the 3D CT assessment. However, when the analysis was focused on the group of hazy lesions, 3D-CT had a higher sensitivity that HRCT in the measurement of the solid component of the tumor, and therefore showed a better correlation with tumor invasiveness, although statistical significance was not reached ($p = 0.070$).

The increased accuracy of 3D-CT in the evaluation of irregular lesions seems mainly due to a lower interobserver variability related to the use of a semi-automatic tumor volume assessment, as shown by the fact that interobserver agreement in the measurements of solid tumor size with HRCT was lower in the HL group (ICC = 0.561) than in the TL group (ICC = 0.965).

The topic is of interest, considering the need of improving the capacity of preoperatively determining tumor invasiveness to select patients for a differentiated surgical treatment with lobar and sublobar resections. However, probably due to the low statistical power of the study, the Authors failed in observing statistically significant advantages with the use of 3D-CT. Nevertheless, the results, to be confirmed in larger studies, seem to show a possible role of 3D assessment in the evaluation of radiologically complex lesions. The manuscript could therefore be of interest.

The Authors should however provide further comments on the limits of the study, and in particular on the fact that although the use of 3D-CT improved the radiological evaluation

of radiologically complex lesions, the sensitivity remained relatively low. Another point that needs a further comment concerns the limits concerning the reproducibility of the technique.

Reply:
We acknowledge the comment on this point. As Reviewer A pointed out, the sensitivity remained relatively low in HL group, but we cannot provide a clear explanation. We might need to revise the cut-off. Accuracy improvement of software constructing 3D-CT might be also necessary. About the reproducibility of the technique, we also explained in the discussion part.

In accordance with the comments, we have added comments in the discussion part of manuscript.

Changes in the text:
We added "About the sensitivity, we could not show the superiority of the solid tumor volume in HL group. We cannot provide a clear explanation, but the reason for this result might be that 3D CT categorizes solids and non-solid regions using -300 HU as a cutoff value uniformly." in the discussion part, in page 10, paragraph 3 in the revised manuscript.

We also added "We did not evaluate the reproducibility of 3D CT analysis. However, interobserver and intraobserver errors will remain minimal because we just need to do the simple task, tracing both ends of the tumor in a straight line in axial plane for 3D-CT analysis." in the discussion part, in page 12, paragraph 1 in the revised manuscript.

Reviewer B

Comment:
In this work, the Author deal with this important issue about the predicting value of 3D-CT for invasive adenocarcinoma. Predicting the invasiveness of lung ADC also in CT scan "hazy" lesions is very useful for the surgical planning, in a better choice between lobar vs sublobar resection.

The article is clear and well-written, and the results obtained about specificity of the 3D-CT in predicting the invasiveness of lung ADC are quite interesting, adding new

predictive approach, especially for the surgical planning. The results obtained in the ROC curve in predicting the invasive ADC based on the solid tumor volume (AUC 0.881), demonstrates that the accuracy of the test is quite good.

For more completeness, in the patient characteristics (Table 1) I would insert the type of surgical procedure performed.

Reply:
We wish to thank for this comment. As Reviewer B pointed out, the type of surgical procedure is import data in interpreting the results of the study.
We have added it to patient characteristics (Table 1).

Changes in the text:
We have added the detail information about “surgical procedure” in Table 1 in the revised manuscript.

Reviewer C

This study is interesting, there is not enough paper for the three-dimensional (3D) CT in literatures. To publication this article, please explain and clarify the followings.

Comment 1:
Please add the explain and introduce of this software in the methods section.
(mechanism and practical examples of this program for analysis of lung nodule.

Reply1:
We wish to thank for this comment. We used the Synapse Vincent software (Fujifilm Corporation, Tokyo, Japan) in this study, which is commercially available and broadly used for 3D analysis of lung nodule. We searched some of the previous studies on lung nodule analysis based on Synapse Vincent. However, none of them described a specific mechanism or process. Probably, the mechanism and algorithm of the program for analysis will be industrial secrets. So, we are sorry but it is difficult to describe how the workstations actually perform nodule recognition and qualitative assessment.

Comment 2:

Do you identify HL only through the lung window setting? (Figure.1) Have you measured the boundary of solid part in the mediastinal window setting?

Reply 2:
We only use the lung window setting to identify HL. As Reviewer C pointed out, the mediastinal window setting may be useful to identify HL in some cases. However, there are also some problems to be resolved in the mediastinal window setting. For example, the extent and shape of lung nodule are easily changed depending on the window setting. In the 8th TNM classification, only the lung window setting is used to determine T factor classification. Thus, in this study, we only used the lung window setting.

Comment 3:
What are the reason for separating solid and non-solid regions with -300 HU? Is there any relevant guidelines?

Reply 3:
We acknowledge the comment on this point. We reviewed the literature for several previous studies. However, we did not recognize any mention of cut-off value of HU which distinguish solid and non-solid regions. This is the standard setup for a Synapse Vincent.

Comment 4:
According to our experience, when Synapse Vincent software analyzes nodules, blood vessels or pleura may be mistaken as nodules. Have you ever had this kind of situation? How do you deal with it? If you did something, please describe this.

Reply 4:
As Reviewer C pointed out, in the present study, blood vessels and pleura were mistaken as nodules in some cases. With the current version of Synapse Vincent, manual modification is required for advanced discrimination such as vessel removal. Since we conducted this study to verify the advantages of semi-automated analysis, we did not perform manual modifications. That is one of the study limitations.

Comment 5:
I think the unit of volume in Table 2 should be mm3, please confirm it.

Reply 5 and Change in the text:
We wish to thank for this comment. We have corrected the unit value in Table 2 in the revised manuscript.

Comment 6:
Please correct mm3 at Results section of abstract.

Reply 6 and Change in the text**:**
We wish to thank for this comment. We have corrected mm3 at Results section of abstract, adequately.

Comment 7:
In first phrase of introduction, add the "the" at 'useful for evaluation of pathological malignant grade'; useful for the evaluation.

Reply 7 and Change in the text:
We have corrected the first phrase of introduction, adequately.

Comment 8. Correct 'in 8 the Edition' to 'in the 8th Edition'.

Reply 8 and Change in the text:
We have corrected the phrase, adequately.

Reviewer D
SUMMARY
The current retrospective study from a single institute's experience is aimed to clarify the solid tumor size in clinical stage IA adenocarcinoma via HRCT and 3D-CT for predicting invasive adenocarcinoma. They divided the lesions into hazy and typical lesions (HL vs. TL). The relationships between the size of the solid tumor region on HRCT, the solid tumor volume on 3D CT, and following pathologic diagnoses were analyzed. In general, this manuscript is well-written and interesting. Some minor concerns should be addressed by the authors.

Comment 1:
Introduction:

Page 6, Line 4: As authors mentioned, the 3D CT is a semi-automatic modality; how the author could minimize this bias between the observers?

Reply 1:
We wish to thank for this comment. About 3D CT analysis, the two observers work and decide together. So, we cannot assess about interobserver bias for 3D-CT. However, it would be not matter too much for us, because we just need to trace both ends of the tumor in a straight line in a axial plane for 3D-CT analysis. It is not so complex work and does not provide large bias.

Changes in the text:
We added "We did not evaluate the reproducibility of 3D CT analysis. However, interobserver and intraobserver errors will remain minimal because we just need to do the simple task, tracing both ends of the tumor in a straight line in axial plane for 3D-CT analysis." in the discussion part, in page 12, paragraph 1 in the revised manuscript.

Comment 2:
Methods:
P6, Line 14: Since the current study is conducted to predict the invasiveness of adenocarcinoma of lung by 3D-CT, please provide more information to the readerships that are all 195 patients included in the study with preoperative diagnosis or not? If not, how do authors expect all the lesions were adenocarcinomas of lung, other pathologies of NSCLC, or benign lesions preoperatively?

Reply 2 and Change in the text:
We wish to thank for this comment. All 195 lung lesions were peripheral small lesions, which is difficult to be obtained pathological diagnosis by preoperative biopsy. So, the number of cases diagnosed preoperatively is small (N=22).
This is a retrospective study and we analyzed 195 lesions which were all pathologically diagnosed as adenocarcinoma. The lesions with other histological diagnosis were excluded from the study.
In accordance with the comments, we have changed the result part of manuscript which describe the number of cases with a preoperative histological diagnosis in Table 1.

Comment 3.
Results:
P8, Line 18: Please refrain from using the word "enrolled", which is reserved for prospective trials, and this retrospective database study. Please also refrain from using this word in the body of the manuscript

Reply 3 and Change in the text:
As you pointed out, we changed the word “enrolled” to “investigated” with changes highlighted.