Peer Review File

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Reviewer A

Comment 1: Very interesting and well described work.

Results and conclusions in line despite study limitations.

Reply 1: We would like to express our sincere appreciations of your careful review concerning our article.

Changes in the text: No changes in the text.

Reviewer B

In this retrospective, single-institution study, the authors investigated to validate the prognostic effect of the proposed R descriptor in NSCLC. They concluded that proposed residual tumor descriptors was applicable in radiologic solid and stage II-III NSCLC but was ineffective in GGO-featured NSCLC and stage I NSCLC. Although the study included a good number of patients to assess the prognosis, there are some concerns regarding this manuscript. I do not find these results to be novel or surprising.

Comment 1: One significant limitation of this study is the absence of data on pleural lavage cytology, a well-established prognostic factor. The R (un) recategorization in this study appears inadequate, and the results may be misinterpreted by readers. If pleural lavage cytology had been included as R (un) category in this study, the results might have been different.

Reply 1: We feel great thanks for your professional review work on our article. As you mentioned, and as previous study(1-5) has shown, data on pleural lavage cytology is well-established. We totally agree that this is a major limitation of the study. Due to pleural lavage is less commonly used in fact, (the percentage of available data on pleural lavage cytology on previous literature(6-10) is 12%, 0.1%, 0%, 0% and 0%)), and pleural lavage cytology is not an established practice in our institution. It is hard to add this data on our study. Lacking the results of pleural lavage cytology may let to the inadequacy of this study. It is also discussed in the limitations section of the manuscript. Thanks again for your careful review.

Changes in the text: Discussion part, paragraph 8, line 1-4.

Comment 2: The authors concluded that the proposed R descriptor was not effective in GGO-featured NSCLC. However, this is because GGO featured NSCLC typically represents indolent tumors. Especially, in small-sized GGO featured NSCLC, sublobar resection is a suitable option. Patients with GGO tumors who did not undergo LSND/SND may have been omitted because they have indolent tumors. The authors should clarify how they intend to distinguish whether to omit or perform LSND in GGO featured NSCLC based on the results.

Reply 2: We sincerely thank you for your valuable feedback that we have used to improve the quality of our manuscript. In fact, for GGO-featured NSCLC, there are two reasons why rigorous LSND/SND is not performed. The one reason is that the surgeons were planned to performed LSND/SND, but for some reason (e.g., there were less than 3 lymph nodes at certain station N1, (Discussion part, paragraph 6, line 6-10)) did not meet the criteria for rigorous LSND/SND. The other reason is exactly what you have mentioned that not performing LSND/SND is due to surgeon's choice. According to our previous study(11, 12), Segment location, ground glass opacity proportion, and absence of hilar lymph nodes involvement are reliable predictors of node-negative status in specific mediastinal regions; Consolidation tumor ratio less than or equal to 0.5, segment location, lepidic-predominant adenocarcinoma (LPA), negative hilar nodes (stations 10-12), and negative visceral pleural invasion (VPI) used separately or in combination can correctly predicted negative node status. For example, for tumor with consolidation tumor ratio <0.5, no lymph node involvement was observed, these tumors may be more inclined to consider to omit LSND/SND.

Changes in the text: Discussion part, paragraph 6, line 6-14.

Comment 3: The authors should provide the recurrence pattern according to R pattern, especially considering that the main reasons for recategorization from R0 to R(un) was the absence of LSND/SND. It would be important to know whether there were a significant the number of lymph node recurrences in the study, as this information could provide the importance of LSND/SND in NSCLC.

Reply 3: Thank you very much for your attention and constructive comment. The recurrence pattern according to R pattern is now shown on Table S6 according to your comment. It might also be noted that we classified lymph node recurrence and ipsilateral/contralateral lung recurrence as "thorax" recurrence.

Changes in the text: "Recategorization using R descriptors released by IASLC" on Results part, paragraph 2, line 9-12. "Follow-up strategy for patients" on Methods part, paragraph 1, line 7-10. Add a new Table S6.

Comment 4: There is no table of patient background differences between pure solid tumor and GGO featured tumor.

Reply 4: We sincerely appreciate the valuable comments. As suggested by the reviewer, we have added the table of patients' background differences between pure solid tumor and GGO featured tumor (Table S1). There were significant differences in sex, age, smoking status, pathology types, pathological T stage, pathological N stage, number of resected lymph node, pathological TNM stage, proposed R descriptors between GGO and solid nodule groups.

Changes in the text: "Patient Characteristics " on Results part, paragraph 1, line 7-10. Add a new Table S1.

Reviewer C

The authors have evaluated a large series of lung cancer resections and analyzed the validity of the current categories of R0, R(un), R1 and R2 in regard to survival. The study is of particular importance due to the contributions of the subset analyses of the ground glass lesions with suboptimal lymph node sampling and correlation with survival.

I have the following questions/comments:

Comment 1: An initial point is the definition of R(un) as stated on page 5 is incorrect. The authors state:

<>

Condition number three should actually be Carcinoma in situ (CIS) and not AIS (adenocarcinoma in situ). (Edwards, et al, JTO Volume 15, Issue 3, March 2020, Pages 344-359). AIS as defined by the current WHO classification refers to a tumor completely composed of carcinoma cells growing on the pre-existing alveolar framework (lepidic growth). Even if one considers lepidic growth as an in situ component of an otherwise invasive adenocarcinoma, it should not be present in a bronchial margin section which, by definition, should consists of bronchial and not alveolar tissue. Along those same lines, the three cases reclassified as R (un) indicated in supplemental table 1 require clarification. Did the authors perhaps mean squamous cell carcinoma in situ (CIS) which may indeed involve the bronchial margin?

Reply 1: We were sorry for our careless mistakes. Thank you for your review and reminder. Three cases indicated in supplemental table 1 were re-checked, and the pathological reports indicate that squamous cell carcinoma in situ were found in the bronchial margins of these three cases in pathological specimens. We have corrected the AIS (adenocarcinoma in situ) into Carcinoma in situ (CIS).

Changes in the text: "Re-classification of residual tumors descriptors" on Methods part, paragraph 1, line 15.

Comment 2: Some of the subgroup analyses could use greater detail. The authors have clearly explained the subgroup analysis of the GGO lesions alone; however, it appears that for the evaluation of stage 1 tumors vs higher stages, stage 1 included GGO plus solid tumors together. It is unclear if the solid stage 1 were compared to solid tumors of higher stages to avoid potential skewing of stage 1 by a high number of GGO lesions. Also, in the table it appears that Squamous and adeno were evaluated separately in table 3 and showed a p value of 0.0001 in the univariate analysis. This is not discussed in the text and, while a proper analysis to undertake, again, this subgroup analysis should include only radiographic solid ADC to avoid skewing of results by a high number of ground glass tumors--it is somewhat unclear what is included in this analysis.

Reply 2: We are very grateful for your review and for the valuable comments that have made us aware of the importance for appropriate subgroup analyses. Supplementary Figure 4 demonstrates that overall survival of radiographic solid adenocarcinoma in different TNM stage.

Changes in the text: Add a new Figure S4. "Subgroup analyses and survival analyses" on Results part, paragraph 1, line 13-17.

Comment 3: While a small number of cases, the category of "other" tumors needs more granularity to avoid mixing tumors of potentially indolent behavior (i.e typical carcinoid) and/or extremely aggressive behavior (i.e small cell) in the analysis.

Reply 3: Thank you for pointing this out. Small cell lung cancer was firstly excluded from the study (Figure 1). The 45 cases of other type of lung cancer were 28 adenosquamous carcinoma and 17 large cell carcinoma.

Changes in the text: "Patient Characteristics" on Results part, paragraph 1, line 6-10.

Comment 4: On page 7, the authors state: <>

Given that the authors also state that <> I am not sure this is a proper comparison given that the highest LN positive tumors are more likely of higher stage and possible also higher grade ADC given the larger number of solid tumors in the latter. Also it is not mentioned if any of these were squamous cell. The rationale for this subgroup analysis requires clarification.

Reply 4: We would like to appreciate you for your precious time in reviewing our paper and providing valuable comments. Unfortunately, what you quoted seems to be lost (inside two < > was nothing), and we don't know what part of our manuscript you quoted. We would like to explain the purpose of our subgroup analyses: the subgroup analyses were performed to explore whether different R descriptors could represent different prognoses in different subgroups. We therefore subgrouped the overall cohort. This included groupings such as pathology type, CT appearance, TNM staging, and other subgroups that are frequently used in clinical practice --- to get a succinct result.

Changes in the text: "Subgroup analyses and survival analyses" on Results part, paragraph 1, line 1-2.

Comment 5: The average number of lymph nodes resected as indicated in Table 1 (18 +/- 32.3) is quite high and I suspect that these are node fragments and not individual nodes given there is not a pathologic standard for recording mediastinal node pieces. Given the pathology would seem to be from a single institution, a comment regarding the methodology used in the department would be useful.

Reply 5: Thank you so much for your minute observation and careful review. Durning the surgery, the surgeon removed the entirety of the lymph nodes. After sending them to the pathology department, the pathologist would collect the specimen according to the standard protocol.

Changes in the text: No changes in the text.

Comment 6: While the authors have opted to use the term "GGO" for the non-solid lesions, given that AIS and MIA cases were excluded, the radiology must have included a solid component. It would be useful to have a range of total radiographic tumor size and solid tumor size, as well as what the largest solid component size was in the "GGO" group. Additionally, were the "solid" tumors completely solid or did these include any tumors which were mostly solid with a small peripheral GGO component?---additional detail on how these categories were defined would be helpful so that readers can more directly translate the findings of the paper to daily practice.

Reply 6: Thank you for your constructive suggestions. Totally, radiographic tumor size ranged from 0.9cm to 19.0cm in solid nodule group. In GGO group, the largest solid component size was 4.8cm. We also provide additional detail about "solid" and "GGO" group in the manuscript, according to the reviewer's comment.

Changes in the text: "Radiological and Pathological Evaluation" on Methods part, paragraph 1, line 2-4.

Reviewer D

The authors verified the efficacy of the R classification proposed by IASLC in 5200 patients with resected NSCLC. Patients with R(un) showed intermediate survival between those with R0 and R1. However, in patients with GGO tumors or TNM stage I disease, there was no significant difference between R0 and R(un). The authors concluded that the R classification proposed by IASLC may be ineffective in patients with GGO tumors and TNM stage I disease.

The results of this study seem reasonable to me because not performing rigorous LSND/SND may have little impact on postoperative outcomes in NSCLC patients with GGO tumors and TNM stage

I disease who have a low risk for lymph node metastasis. Thus, the main issue is whether performing rigorous LSND/SND is appropriate for deciding the R classification in NSCLCs.

Comment 1: The authors described that in patients with TNM stage I disease and GGO tumors, the main reason for reclassification from R0 to R(un) was not performing rigorous LSND/SND. Thus, the main clinical question is whether performing rigorous LSND/SND is appropriate for deciding the R classification in NSCLCs. If you investigate the prognostic impact of performing rigorous LSND/SND by the multivariate analyses in each subgroup (e.g., CT appearance, pTNM stage, and Pathology), it should be interesting for readers. The descriptor regarding rigorous LSND/SND may not have a prognostic effect on postoperative survival even for patients with solid tumors and stage II-III disease. Moreover, the other descriptors for the R classification (the highest LN resected (+), AIS at the surgical margin, and positive PLC) may be examined in the same manner.

Reply 1: We would appreciate your constructive comment to improve the quality of our manuscript. Now Table S7 and S8 illustrates the prognostic impact of performing rigorous LSND/SND and the prognostic impact of highest LN resected (+) in GGO group, solid nodule group, stage I group, stage II/III group, adenocarcinoma group and squamous group. In squamous cell carcinoma group and TNM stage II/III group, performing rigorous LSND/SND was an independent prognostic factor on OS. In all analysed subgroups, highest LN resected (+) was an independent prognostic factor on OS.

Changes in the text: "Subgroup analyses and survival analyses" on Results part, paragraph 3 , line 1-6. Discussion part, paragraph 6, line 12-14. Add new Tables S7 and S8.

Comment 2: Why did the authors exclude patients with AIS/MIA and those who underwent sublobar resection? Because the R classification is applied even for these subgroups of patients with NSCLCs, patients with AIS/MIA and those who underwent sublobar resection should be included.

Reply 2: Thanks for your valuable comment. AIS/MIA was consider to have a significant better prognosis while compared with other types of NSCLC(13, 14) and was reported to have no recurrence during 10-year follow-up after resection(15). Excluding AIS/MIA may reduce the impact of bias on the study. On the other hand, the criteria of performing rigorous LSND/SND for uncertain resection applies to lobectomy, whereas for sublobar resection, some researchers believe that it should be considered as an incomplete resection, while others classified sublobar resections based on the rest criteria, expect for performing rigorous LSND/SND, and some researchers also exclude it from the recategorization(8-10, 16). In this study, we excluded sublobar resection and AIS/MIA, referring to previous studies.

Changes in the text: No changes in the text.

Comment 3: Figure 4 seems complicated and difficult to understand.

Reply 3: We apologize for not being able to give a clear presentation of Figure 4. Figure 4 is used to illustrate the difference in the distribution of reasons that reclassified as uncertain resection between GGO and solid groups/ between stage I and stageII/III groups. A detailed explanation helps to further elucidate the meaning of Figure 4A: The pink bands (stage I) in the grey rectangle (R(un)) in the fourth column are all from the grey bands in the third column(not performed rigorous LSND/SND), and the yellow bands in the second column(Highest LN resected(+)).This bands explains that the reclassification as uncertain resection in stage I patients, was all due to not performing rigorous LSND/SND. We have also added a further explanation of Figure 4 in the manuscript.

Changes in the text: Figure legends of Figure 4.