Peer Review File

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Reviewer A

In this study, the authors retrospectively investigated 352 patients with pathological stage IA3 lung adenocarcinoma who underwent curative surgical treatment. They found that the absence of a GGO component was associated with higher incidences of postoperative recurrence and MIP component ≥5%, and showed different peak patterns of recurrence and death from those with the presence of GGO component.

I think that the results and conclusions of this study seem reasonable and make sense to the readers of the journal. However, similar studies have been repeatedly conducted and similar results have been reported over and over again. What is the new information that was obtained from this study? It may be interesting if the patients with the presence of GGO component and those with the absence of the GGO component are separately analyzed.

Comment 1: As mentioned above, I think that this study showed few new information regarding the role of a GGO component in patients with early-stage lung adenocarcinoma who underwent surgical resection. It is obvious that the presence of GGO component is associated with favorable outcomes in those patients. It may be interesting if the patients with the presence of GGO component and those with the absence of the GGO component are separately analyzed in the risk factor analysis and the prognostic scoring methods.

Reply 1: Thank you for the comments. We have studied the comments carefully and have made modifications and corrections which we hope to meet your approval. In this study, we found that the proportion of centrally-located tumors in the absence-GGO group was significantly higher than that in the presence-GGO group (P=0.004). Patients with absence-GGO had a higher rate of lobectomy than those with presence-GGO (P=0.016). Postoperative pathology showed that the proportion of an MIP component ≥5% in the absence-GGO group was significantly higher than that in the presence-GGO (P=0.015). Although this study is multi-center data, the population included is still relatively small. Therefore, a larger data is needed in the future to explore prognostic factors in patients with and without GGO components respectively.

Comment 2: Methods: The strategies for deciding the extent of pulmonary resection should be described. What did “radical surgery” mean?

Reply 2: Thank you for the comments. We have studied the comments carefully and have made modifications and corrections which we hope to meet your approval. The “radical surgery” means segmentectomy or lobectomy plus mediastinal lymphatic nodes dissection. These results have been showed in “**Methods**” with red color (see Page 5, line 136-137).

Comment 3： Results: The median follow-up of 40.5 months is too short to analyze postoperative outcomes in early-stage lung adenocarcinoma.

Reply 3: Thank you for the comments. We have studied the comments carefully and have made modifications and corrections which we hope to meet your approval. In our study, the majority of patients relapsed within 36 months, about 27/37(73.0%). Therefore, the median follow-up time should be sufficient for patients with pathological stage IA3 lung adenocarcinoma.

Comment 4： Conclusions: The authors described that "postoperative adjuvant therapy and more frequent follow-up strategies should be considered for patients without GGO components." What is the reason that the patient without a GGO component is a suitable subgroup for postoperative adjuvant therapy? I think that the results of this study did not support this conclusion. If you want to state that, you should show evidence that postoperative adjuvant therapy is effective in those patients.

Reply 4: Thank you for the comments. We have studied the comments carefully and have made modifications and corrections which we hope to meet your approval. In Japan, tegafur-uracil is recommended as postoperative adjuvant therapy for IA lung cancer patients with tumors >2 cm[1]. The Figure 3 showed that the total recurrence rate of patients with the presence of a GGO component was 3.0% and that of patients with the absence of a GGO component was 17.2%, with a significant difference between the two groups (P<0.001). Therefore, our study provides a reference for whether adjuvant therapy should be performed in pathological stage IA3 patients without GGO in the future.

Reviewer B

This paper demonstrated the effects of a GGO component on the recurrence and survival of patients with pathological stage 1A3 lung adenocarcinoma using data of two different medical centers (Fujian Medical University Union Hospital and First hospital of Putian).

It is well known that the good prognostic values of the presence of GGO components from some retrospective study and nationwide study in Japan. Similar results were observed in this study compared to previous studies. In addition, the authors suggested individualized and precise follow up strategy based on relapse risk curve which might be very useful in real clinical situations.

Overall this paper is well written and well organized. But there are some comments or questions.

Comment 1: Duration of the enrollment of patients: Follow up period for patients who underwent surgery between 2019 and 2020 is relatively short. Those patients could be excluded to draw more precise conclusions.

Reply 1: Thank you for the comments. We have studied the comments carefully and have made modifications and corrections which we hope to meet your approval. In this study, the recurrence of pathological stage IA3 patients within 1 year after surgery accounted for 21.6% (8/37) of all relapses. Therefore, patients who underwent surgery between 2019 and 2020 are also worthy of inclusion.

Comment 2: Is there IRB approval from first hospital of putian?

Reply 2: Thank you for the comments. We have studied the comments carefully and have made modifications and corrections which we hope to meet your approval. This study was reviewed and approved by the Institutional Ethics Review Committee of the First Hospital of Putian. The

IRB is No. 2020KJT009. These results have been showed in “Study population” with red color (see Page 4-5, line 130-131).

Comment 3: CT protocol is important to describe GGO for these kinds of studies. Please provide CT protocol from each institution.

Reply 3: Thank you for the comments. We have studied the comments carefully and have made modifications and corrections which we hope to meet your approval. In this study, 16-slice spiral CT was used as the main imaging method for the chest of patients, and the GGO component of all tumors was evaluated by the thickness of lung field imaging of 1.25mm ~ 5mm. “Lung window” is defined as window height of -500 ~ -700H and window depth of 1000 ~ 2000H. These results have been showed in “Definition” with red color (see Page 5, line 140-143).

Comment 4: In authors’ list, there are some authors not from two institution in China. Please clarify their roles and contributions for this paper.

Reply 4: Thank you for the comments. We have studied the comments carefully and have made modifications and corrections which we hope to meet your approval. The authors in the paper such as Duilio Divisi, Marcello Migliore, Stefano Bongiolatti, Marion Durand, Masaaki Sato and Hiroaki Kuroda are the AME Thoracic Surgery Collaborative Group. These results have been showed in “Study population” with red color (see Page 12-13, line 386-387).

Reference

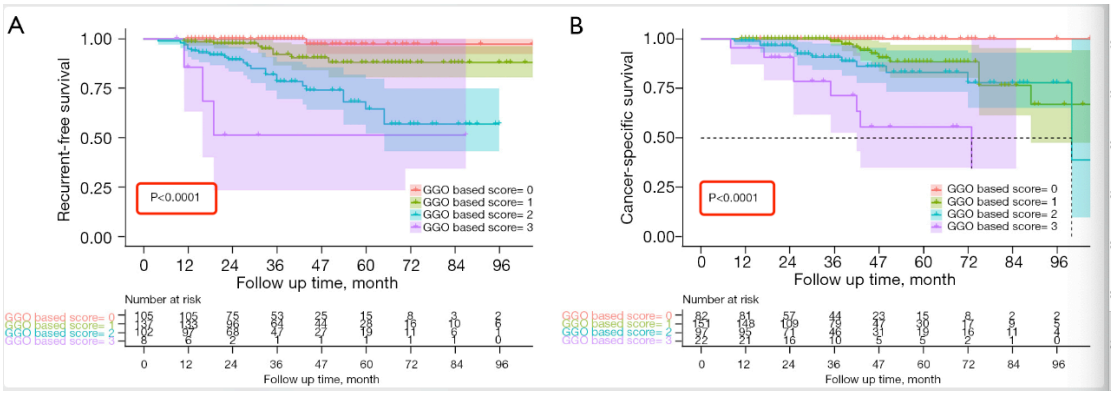
1. Tsutani Y, Imai K, Ito H, Miyata Y, Ikeda N, Nakayama H, Okada M (2022) Adjuvant Chemotherapy for High-risk Pathologic Stage I Non-Small Cell Lung Cancer. The Annals of thoracic surgery 113:1608-1616

Reviewer C

1. Figure 5

Please check the p value, they are different in the main text and figure.

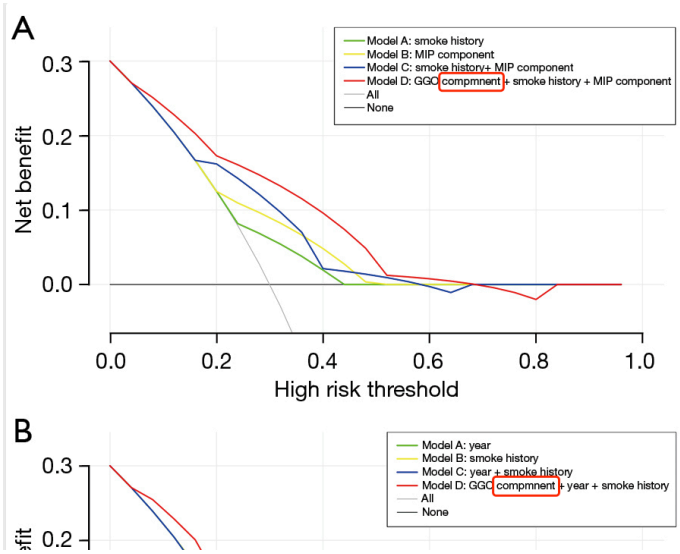
282 between these groups (P<0.001) (Figure 5A). Based on the GGO component, the predicted 5-
283 year CSS of patients with scores of 0, 1, 2, and 3 was 100%, 88.3%, 83.1%, and 55.6%,
284 respectively. Similarly, there were significant differences between the groups (P<0.001)
285 (Figure 5B).



Reply: Thank you for the comments. We have studied the comments carefully and have made modifications and corrections which we hope to meet your approval.

2. Figure 6

Please check the spelling.



Reply: Thank you for the comments. We have studied the comments carefully and have made modifications and corrections which we hope to meet your approval.

3. Figure S1

a) Please provide an editable version of the flow chart in DOC/PPT.

b) Please explain GGO in the legend.

Reply: Thank you for the comments. We have studied the comments carefully and have made modifications and corrections which we hope to meet your approval.

4. Figure S2

Please explain LRR and DM in the legend.

Reply: Thank you for the comments. We have studied the comments carefully and have made modifications and corrections which we hope to meet your approval.

5. Figure S3

Please explain GGO, LRR and DM in the legend.

Reply: Thank you for the comments. We have studied the comments carefully and have made modifications and corrections which we hope to meet your approval.

6. Figure S4

a) Please provide an editable version of the flow chart in DOC/PPT.

b) Please explain CSS, GGO, RFS, and MIP in the legend.

Reply: Thank you for the comments. We have studied the comments carefully and have made modifications and corrections which we hope to meet your approval.

7. References/Citations

There are 2 reference lists in the file, please keep the correct one and delete another one.

Reply: Thank you for the comments. We have studied the comments carefully and have made modifications and corrections which we hope to meet your approval.