Peer Review File

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Reviewer A

Comment 1: Thank you for your interesting paper on a very actual topic.
With the intrinsic limitations of a retrospective study, you provide a credible statistical analysis, but more importantly, you point out the importance of patient stratification in order to achieve a valid tailored surgery that can effectively benefit the follow-up.
Our colleagues, recently, had published the results of two randomized trials addressing the same issue (https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02333-3/fulltext ; https://www.nejm.org/doi/10.1056/NEJMoa2212083), they may be worth mentioning.
Another meta-analysis addresses the same questions (https://www.mdpi.com/2072-6694/14/24/6157) about the results limited resections can obtain compared to lobectomy.
Reply 1: We are grateful for your insightful and constructive feedback on our manuscript. Your comment highlights the importance of our statistical analysis and our novel contribution to the field of patient stratification for tailored surgery. We concur with your reference to two recent randomized trials that investigated the same issue of patient stratification for tailored surgery (Saji et al., 2023; Nasser et al., 2023) and one meta-analysis that establish whether minimally invasive anatomical segmentectomy and lobectomy had comparable perioperative and survival outcomes in early-stage NSCLC patients (Luca et al., 2022). These articles demonstrate the efficacy of sublobar resection as an alternative to lobectomy. We updated the outcome of all 1,566 patients in our study and our result corroborates the evidence on the efficacy of sublobar resection in stage IA adenocarcinomas by conducting a retrospective analysis of a large cohort of patients. Furthermore, to enhance the persuasiveness of our conclusion, we revised our manuscript with a propensity score matching (PSM) to balance the bias between the limited resection group and the lobectomy group.
Changes in the text: We acknowledge the relevance of the recent randomized trials published by your colleagues and we have incorporated a paragraph to discuss them in the revised manuscript. The revised text is as follows on page 4, lines 82-84: Moreover, we balanced the bias between groups by using PSM, as shown on page 7, lines 172-178; the characteristics between groups are presented on page 8, lines 194; and the updated survival curves after PSM are illustrated in Figure 2, 3, 4.

Comment 2: In your paper, though, it's not clear what limited resections really mean: the proportion of wedge resections and anatomic segmentectomy is not indicated. Based on your assumptions of tumor spreading through airways, should be interesting to analyze the differences in endpoints between wedge and segmentectomy, considering that the majority of the studies highlight the superiority of segmentectomies over wedges.
This, nevertheless, could be addressed in a more specific article.
Reply 2: We appreciate your constructive comment on our manuscript. In our study, we categorized any type of sublobar resection, including wedge resections and anatomic segmentectomies, as limited resections. We have specified this categorization in the revised manuscript. Moreover, the proportion of wedge resection to segmentectomy in the limited resection group in the matched cohort was 43:59. We concur that it would be worthwhile to

examine the differences in outcomes between wedge and segmentectomy. We conducted a survival analysis on these two types of resections and found no significant difference in terms of RFS and OS. However, as you pointed out, this could be the subject of a more focused article. Therefore, we did not compare the clinicopathologic variables between groups or perform subgroup analysis in our study. We have acknowledged this limitation in the revised manuscript.
Changes in the text: We have added the definition of limited resection on page 5, line 118. The additional survival analysis on wedge resection and segmentectomy can be found on page 9, lines 226 and supplementary Figure 2.

Reviewer B

The authors show that there is no difference in prognosis between lobectomy and sublobar resection in stage I lung adenocarcinoma patients, with many subgroup analyses including the presence of STAS and postoperative adjuvant chemotherapy. This is a very interesting article, but there are a few major concerns to be accepted for publication in JTD.

Comment 1: Major
1. Confounding factors, such as pathologic stage and histologic subtype, must be considered in analyzing prognosis. In addition, statistical analysis of various subgroups can be misleading. Although the authors have performed univariate and multivariate analyses, it would be clearer and more correct to adjust for background factors by propensity score matching.
Reply 1: We thank the reviewer for raising this important point. We agree that confounding factors, such as pathologic stage and histologic subtype, can affect the prognosis of patients. Therefore, we updated the outcome of all 1566 patients in our study and performed propensity score matching (PSM) to balance these factors between the groups. Other balanced factors include age, sex, smoking history, ECOG PS, pleural invasion and lymphovascular invasion. We have added the details of the propensity score matching method and the results of the matched cohort analysis in the revised manuscript. The results showed that after PSM, the overall survival (OS) of patients who underwent limited resection was inferior to those who underwent lobectomy in stage I STAS-positive patients, which was inconsistent with the results before PSM. We have accordingly updated the discussion section and conclusion section to reflect the findings from the matched cohort analysis and subgroup analysis. We hope that these revisions will address the reviewer's concern and enhance the clarity and validity of our study.
Changes in the text: We added the details of PSM on page 7, lines 172-178. We presented the characteristics between groups on page 8, lines 190-195; and we illustrated the different survival curves after PSM in Figure 2, 3, 4. We revised the discussion section on page 11, lines 280-286. We also modified the conclusion on page 13, lines 355-357.

Comment 2: 2. Many patients are receiving postoperative adjuvant chemotherapy even though they are stage I. What is the regimen?
Reply 2: We appreciate the reviewer's question. As the literature suggests, postoperative adjuvant chemotherapy can improve survival by reducing the risk of recurrence in patients with stage IB NSCLC who have high-risk factors, such as STAS, lymphovascular invasion, visceral pleural invasion, or poorly differentiated tumors (Jeong et al. 2022). Moreover, previous studies have demonstrated that adjuvant chemotherapy was a favorable prognostic

factor in stage IB STAS-positive patients and stage IA STAS-positive patients who underwent segmentectomy (Chen et al. 2020). The choice of postoperative adjuvant chemotherapy regimen for stage I patients was made by the attending physician based on the patient's condition and preference. However, due to the lack of clear criteria for adjuvant chemotherapy in every patient and in order to follow the guidelines for ACT in stage I patients and evade the impression of over treatment, we have revised our survival analysis of adjuvant chemotherapy from stage I to stage IB patients. In our study cohort, the most frequently used regimen was platinum-based doublet chemotherapy, such as cisplatin plus vinorelbine (55.6%) or pemetrexed (33.3%).
Changes in the text: We performed a survival analysis of adjuvant chemotherapy for stage IB patients and reported the results on page 10, line 252-258. We also specified the adjuvant chemotherapy regimens on page 10, line 259-261.

Comment 3: Minor
What is the ratio of wedge resection to segmentectomy in limited resection?
Reply 2: In our study, we categorized any type of sublobar resection, including wedge resections and anatomic segmentectomies, as limited resections. The ratio of wedge resection to segmentectomy was 72.9% (43/59). In order to compare the differences in endpoints between wedge and segmentectomy. We also performed subgroup based on extent of resection in limited resection group and found no significant difference in the recurrence-free survival and overall survival between wedge resection and segmentectomy.
Changes in the text: We add ratio of wedge resection to segmentectomy in limited resection in page 9, line 226. The additional survival analysis on wedge resection and segmentectomy can be found on page 9, line 227-228 and supplementary Figure 2.

Reviewer C

This manuscript presents very interesting data on the validity of limited resection for the early-stage lung adenocarcinoma with spread through air spaces. The study provides an important contribution to operative procedure for pathological stage I lung adenocarcinoma. I would recommend it for acceptance after the minor points listed below.

Comment 1: ① line 58 findings of radiologic noninvasiveness patterns
This sentence has the same repetition on line 59, and I suggest it would be easier to understand if it was deleted.
Reply 1: We agree that the sentence on line 58 is redundant and confusing. We have revised it as you suggested.
Changes in the text: The revised sentence now reads at page 4, line 78-81.

Comment 2: ② The first paragraph of Introduction describes the recent trend of limited resection, but since none of the references are limited to adenocarcinoma, I think it is better to list NSCLC instead of ADC. Regarding STAS in the second paragraph, it cites research based on adenocarcinoma, and I think it can be left as it is.
Reply 2: Thank you for your feedback on paragraphs of the Introduction. We understand your suggestion to list NSCLC instead of ADC since none of the references specifically mention limited resection for adenocarcinoma. We have revised the first paragraph accordingly and keep the second paragraph unchanged to maintain accuracy.
Changes in the text: We have modified our text as advised (see Page 4, line 78-87)

Comment 3: ③ When comparing lobectomy and limited resection, ECOG PS and smoking indices are also important and fundamental factors in patient characteristics. Is it possible to add it? If you decide that it is unnecessary, please tell me why.

Reply 3: Thank you for your feedback and suggestion to include ECOG PS and smoking indices as important factors. I agree that Eastern Cooperative Oncology Group Performance Status (ECOG PS) and smoking indices are fundamental aspects of patient characteristics that can significantly impact treatment outcomes. Including them in our analysis will provide a more comprehensive understanding of the factors influencing the choice between lobectomy and limited resection. In our revised manuscript, we have incorporated these factors into the study. We also updated the outcome of all 1,566 patients in our study and performed propensity score matching (PSM) to balance factors including ECOG PS and smoking history between the limited resection group and lobectomy group. These two characteristics were effectively balanced between both groups after matching.

Changes in the text: We have incorporated these factors into the study (see Page 5, line 125-126). Moreover, a detailed comparison between the groups before and after PSM can be observed in Table 1.

Comment 4: ④ Looking at the Supplement Table, chemotherapy is also given to StageIA1 and IA2, giving the impression of over treatment. What is the indication of adjuvant chemotherapy for early-stage lung adenocarcinoma in your institution? In addition, although there is insufficient clinical information on ACT modality in limitation, considering the trend of drug treatment in recent years, the use of EGFR-TKI is an important point. Furthermore, if the result is that the RFS was bad despite using EGFR-TKI, it may be clinically important information, so I think it should be described about ACT modality as far as it can be understood.

Reply 4: We appreciate your insightful comments and suggestions. As the literature suggests, postoperative adjuvant chemotherapy can improve survival by reducing the risk of recurrence in patients with stage IB NSCLC who have high-risk factors, such as STAS, lymphovascular invasion, visceral pleural invasion, or poorly differentiated tumors (Jeong et al. 2022). Moreover, previous studies have demonstrated that adjuvant chemotherapy was a favorable prognostic factor in stage IB STAS-positive patients and stage IA STAS-positive patients who underwent segmentectomy (Chen et al. 2020). The choice of postoperative adjuvant chemotherapy regimen for stage I patients was made by the attending physician based on the patient's condition and preference. However, in order to follow the guidelines for ACT in stage I patients and reduce the impression of over treatment as you suggest, we have revised our survival analysis of adjuvant chemotherapy from stage I to stage IB patients. And new survival analysis revealed that ACT did not confer any survival benefit in our stage IB patients. Regarding the use of EGFR-TKIs, we acknowledge their importance in the treatment of lung adenocarcinoma, particularly in cases with EGFR mutations. We identified 31 of 74 patients present with EGFR mutation and 20 of them received EGFR-TKIs. However, due to the primary focus on surgical interventions of our study and limited space, we will not provide specific subgroup analyses on it. Besides, in our study cohort, the most frequently used regimen was platinum-based doublet chemotherapy such as cisplatin plus vinorelbine (55.6%) or pemetrexed (33.3%).

Changes in the text: We performed a survival analysis of adjuvant chemotherapy for stage IB patients and reported the results on page 10, line 252-258 and Figure 4. We also specified the adjuvant chemotherapy regimens on page 10, line 259-261.

Comment 5: ⑤ There are some easy mistakes in the use of abbreviations and figures. I recommend proofreading, but please correct the following parts that I found.
line24 ADC→ adenocarcinoma(ADC)
line26 adenocarcinoma→ ADC
line30 OS→ overall survival (OS)
line189 adenocarcinoma→ ADC
line219,220 adenocarcinoma→ ADC
line260 adjuvant chemotherapy→ ACT
line155,156 Figure2 C and D are opposite.
(Also, "C" is missing in the Figure Legend of Figure2)
line178,179
If the notation is in the order of Figure4A and B, it should be written in the order of RFS and OS, instead OS and RFS.
Reply 5: Thank you for your feedback. We have made the following changes to address your comment.
Changes in the text: We have corrected line 24 from ADC to adenocarcinoma (ADC). (see Page 5, line 121)
We have corrected line 26 from adenocarcinoma to ADC. (see Page 2, line 34)
We have corrected line 30 from OS to overall survival (OS). (see Page 2, line 41)
We have corrected line 189 from adenocarcinoma to ADC. (see Page 10, line 271)
We have corrected lines 219 and 220 from adenocarcinoma to ADC. (see Page 12, line 306-307)
We have corrected line 260 from adjuvant chemotherapy to ACT. (see Page 13, line 359)
We have redrawn Figure 2 and corrected Figure 2C and D as per your suggestion to 2F and E. (see Page 9, line 223, 225)
We have also added "C" in the Figure Legend of Figure 2. (see Page 17, line 494)
We have changed the order of RFS and OS in order of Figure 4A and B. (see Page 10, line 255)

Reviewer D

The authors have retrospectively evaluated 1348 patients underwent surgical intervention with pathologic stage I lung adenocarcinoma. They suggested that patients underwent limited resection of pathological stage I ADC had a relative good prognosis.
Although this paper was well written and indicated important association of limited resection for stage I lung adenocarcinoma, I disagree that the outcomes in patients who have undergone limited resection are comparable to those of lobectomy. This is because some important data are not presented and Insufficient analysis of the data may have led to erroneous conclusions.

Comment 1: The authors did not describe the procedure for lung cancer. A clear description of the surgical technique is needed for lobectomy or limited resection. The technique of lymph node dissection or sampling should also be described because Clinical stage I lung cancer is often found to have progressed postoperatively. Whether mediastinal lymph node dissection improves the prognosis is currently unknown, but it is necessary for accurate staging. For example, it is inappropriate not to pathologically evaluate the presence of lymph node metastases in stage IB (over 3cm in consolidation!) lung cancer patients who have undergone surgical reduction.

Reply 1: Thank you for your valuable feedback. We apologize for the lack of clarity in our manuscript regarding the surgical technique for lobectomy or limited resection. We have added a clear description of the surgical technique and the technique of lymph node dissection or sampling as suggested. We concur with your highlight of the importance of mediastinal lymph node dissection on advanced tumor. We have reviewed patients with tumors larger than 3 cm and found that all of them received a lobectomy or anatomic segmentectomy along with mediastinal lymph node dissection or sampling. Therefore, we confirmed that lymph node metastases have been well evaluated in those patients.
Changes in the text: We added definition of lobectomy and segmentectomy at Page 5, line 120-123. We also add lymph node dissection status and present details in Table 1.

Comment 2: There is no mention of whether limited resection means segmentectomy or wedge resection. The percentage of these procedures should also be stated. The indication of limited resection was also not described (for patients with poor risk or for patients expected to have low malignancy tumors?).
Reply 2: We appreciate your insightful and constructive comment on our manuscript. In our study, we categorized any type of sublobar resection, including wedge resections and anatomic segmentectomies, as limited resections. We have specified this categorization in the revised manuscript. Moreover, the proportion of wedge resection to segmentectomy in the limited resection group in the matched cohort was 43:59. We also conducted a survival analysis on these two types of resections and found no significant difference in terms of RFS and OS. Limited resection is indicated for patients with stage I NSCLC who are not candidates for lobectomy due to poor lung function or other comorbidities. However, the specific indication of limited resection may vary depending on the patient's condition and the surgeon's preference.
Changes in the text: We have added the definition of limited resection on page 5, line 118. The additional survival analysis on wedge resection and segmentectomy can be found on page 9, lines 226 and supplementary Figure 2. We describe the indication to perform limited resection in Page 5, line 123-125.

Comment 3: Patient characteristics suggest that lobectomy was performed in patients with more advanced disease (pathological stage, lymphatic and vascular invasion). Thus, inverse probability of treatment weighting (IPTW) or propensity score matching should be performed to confirm that the results of limited resection are not inferior to those of lobectomy.
Reply 3: We thank the reviewer for raising this important point. We agree that confounding factors, such as pathologic stage lymphatic and vascular invasion, can affect the prognosis of patients. Therefore, we updated the outcome of all 1,566 patients in our study and performed propensity score matching (PSM) to balance these factors between the groups. Other balanced factors include age, sex, smoking history, ECOG PS and histologic grade. We have added the details of the propensity score matching method and the results of the matched cohort analysis in the revised manuscript. The results showed that after PSM, the overall survival (OS) of patients who underwent limited resection was inferior to those who underwent lobectomy in stage I STAS-positive patients, which was inconsistent with the results before PSM. We have accordingly updated the discussion section and conclusion section to reflect the findings from the matched cohort analysis and subgroup analysis. We hope that these revisions will address the reviewer's concern and enhance the clarity and validity of our study.
Changes in the text: We added the details of PSM on page 7, lines 172-178. We presented

the characteristics between groups on page 8, lines 190-195; and we illustrated the different survival curves after PSM in Figure 2, 3, 4. We revised the discussion section on page 11, lines 280-286. We also modified the conclusion on page 13, lines 355-357.

Comment 4: There are no indications or methods of adjuvant chemotherapy. In addition, it is necessary to look at local recurrence in the postoperative follow-up period to evaluate whether STAS is involved in postoperative recurrence. Please provide specific data on local recurrence.

Reply 4: Thank you for your insightful comments and suggestions. As the literature suggests, postoperative adjuvant chemotherapy can improve survival by reducing the risk of recurrence in patients with stage IB NSCLC who have high-risk factors, such as STAS, lymphovascular invasion, visceral pleural invasion, or poorly differentiated tumors (Jeong et al. 2022). Moreover, previous studies have demonstrated that adjuvant chemotherapy was a favorable prognostic factor in stage IB STAS-positive patients and stage IA STAS-positive patients who underwent segmentectomy (Chen et al. 2020). The choice of postoperative adjuvant chemotherapy regimen for stage I patients was made by the attending physician based on the patient's condition and preference. However, in order to follow the guidelines for ACT in stage I patients and reduce the impression of overtreatment, we have revised our survival analysis of adjuvant chemotherapy from stage I to stage IB patients. Our new survival analysis revealed that ACT did not confer any survival benefit in our stage IB patients. We have also provided specific data on recurrence in the revised manuscript and found that 48 of the 77 patients who experienced recurrence had local recurrence in STAS-positive patients, while 16 of the 33 had local recurrence in STAS-negative patients. These results suggest that STAS may hold potential risk for local recurrence.

Changes in the text: We performed a survival analysis of adjuvant chemotherapy for stage IB patients and reported the results on page 10, line 252-258 and Figure 4. We also specified the adjuvant chemotherapy regimens on page 10, line 259-261. We added detailed recurrence data on page 8, line 199-200.

Comment 5: Several Abbreviations are not indicated in figures. Please indicate appropriate abbreviations (for example ACT, STAS, RFS and OS).

Reply 5: Thank you for your feedback. We have revised the figures and indicate the appropriate abbreviations.

Changes in the text: We add abbreviations to the Figure Legends. (see Page 17, line 492, 496, 501, 505)