Reviewer A

The manuscript would investigate an interesting issue about lung cancer: the impact of the lymph node dissection on the ICI therapy response.

The data presented are interesting and significant even if they refer to a single-center study.

There are many minor language mistakes.

Comment: Minor language mistakes.

Reply: We are immensely grateful for your meticulous and constructive feedback. In response, we have carefully revised our manuscript, correcting grammatical errors and refining expressions throughout. These amendments have been distinctly highlighted in yellow to facilitate your review. We trust that these revisions have enhanced the clarity and precision of our text.

Changes in the text: We corrected English mistakes in manuscript (yellow highlighted).

Reviewer B

I congratulate with the authors for the original idea, but the manuscript needs major revisions.

In the statistical analysis you told about the propensity score but in the results there is no mention. Have you used is or not?

Figure 2 and 3 are inverted.

I believe that the statistical analysis needs to be improved (univariate, multivariate analysis and COX regression...) with more emphasis on the survival analysis and the correlation with ICI.

Comment1: In the statistical analysis you told about the propensity score but in the results there is no mention. Have you used is or not?

Reply1: I appreciate your insightful comment. We used propensity score for IPTW. As you pointed out, describing the weights obtained from IPTW based on propensity score is important to ensure the robustness of this study.

Changes in the text1: We included a statistical summary of the weights obtained by IPTW using propensity score in the Results section.

Comment2: Figure 2 and 3 are inverted.

Reply2: Thank you for your important remarks. As you pointed out, Figure 2 and Figure 3 are interchanged.

Changes in the text2: Re-submitted with Figure2 and Figure3 replaced.

Comment3: I believe that the statistical analysis needs to be improved (univariate, multivariate analysis and COX regression...) with more emphasis on the survival analysis and the correlation with ICI.

Reply3: I appreciate your insightful recommendation. Ad you pointed out, we must reconsider the statistical analysis about efficacy of ICI and lymph node dissection.

Changes in the text3: We added the multivariate analysis for ICI-PFS to the result section (Table 3).

Reviewer C

Dear author and co-authors, the work you have presented is interesting, but it requires major revisions before potential publication.

Abstract:

Comment1: - Line 15: "134 patients were analyzed who HAD (not were)"

Reply1: I appreciate your comment. We believe that the sentence as you have indicated is more appropriate.

Changes in the text1: Corrected L15 to "134 patients were analyzed who had".

Comment2:

- The conclusions of the abstract need improvement: the lack of difference in prognosis between surgical patients with recurrence and patients with advanced lung cancer is not correlated with the different response to ICI in patients undergoing surgery with or without systematic lymph node dissection, while the current approach suggests a correlation.

Reply2: Thank you for helpful pointing this out. As you pointed out, the comparison of prognosis between patients with postoperative recurrence and patients with advanced lung cancer does not imply a difference in response to ICI. We believe that we have made it difficult to understand by stating the results of two different studies as the same conclusion. We thought that the two studies should be separated and described separately.

Changes in the text2: we modified the conclusions of abstract. "In the IPTW-adjusted base, there was no difference in the prognosis between patients with postoperative recurrence and those with advanced lung cancer. However, in patients with postoperative recurrence, the extent of lymph node dissection was a predictor of ICI-PFS. This result might suggested that lymph node dissection may affect the effectiveness of ICI. "

Introduction: Needs improvement to better highlight the rationale of the study.

Comment3: Line 45-48: The concept you want to convey is not clear.
Reply3: I appreciate your comment. The clinical trials of ICI were primarily in unresectable stage IV lung cancer, and our clinical question was as to whether the same efficacy could be expected in a different population of patients with postoperative recurrence. We have made a correction to make the statement clearer and easier to understand.

Changes in the text3: we modified L45-48 "Such clinical trials for ICI have been conducted primarily in patients with unresectable stage IV advanced lung cancer. It is unclear whether the same efficacy can be expected in patients with postoperative recurrence as in patients with advanced lung cancer.

"

Comment4: The sentence "Notably...study" in line 45-46 does not have any meaningful significance.
Reply4: I appreciate your comment. As you pointed out, we thought we should do a defensive formation as described in comment 3.
Changes in the text4: We removed the sentence "Notably...study" in L45-46.

Materials and Methods:
Comment5:   - Is there a study protocol? If so, please include it.
Reply5: I appreciate the opportunity to clarify this aspect of our work. I regret to inform you that a formal study protocol was not developed prior to the commencement of this study. The research was conducted based on retrospective observational study. However, we acknowledge the importance of a study protocol in ensuring the rigor and reproducibility of scientific research. We will take this valuable feedback into consideration for our future studies and will strive to incorporate a more structured approach, including the development of a study protocol, in our subsequent research endeavors.
Changes in the text5: There was no correction.

Comment6:- It is essential to accurately specify what is meant by systematic and selective lymph node dissection, and specify why certain patients underwent systematic dissection or sampling: is there a rationale for the choice? Since the number of patients is small, it would also be useful to compare the number of lymph nodes removed in each patient and specify which lymph node stations were sampled.

Reply6: Thank you for your insightful comments. We recognize the importance of clearly defining 'systematic' and 'selective' lymph node dissection and the rationale behind the choice of procedure for each patient. We addressed this by adding a detailed description of our surgical policy to the Methods section. This addition clarifies the criteria for selecting the type of dissection. Some patients were operated on at other hospitals and the number of dissected lymph nodes were not known, so number of dissected lymph nodes were not used in the prognostic analysis.

Changes in the text6: We added detailed description of our surgical policy about lymph node dissection to the Methods section.

We added surgical procedure and number of dissected lymph nodes to Table1.

Comment7:- Line 84-85: "Survival outcome and measurement of tumor response". This sentence does not contain a verb and needs to be completely restructured.

Reply7: I appreciate your comment. As you pointed out, Thera was grammatical mistakes.

Changes in the text7:

Results7: L84-85: We reconstructed the sentence from "Survival outcome and measurement of tumor response" to "The survival results and tumor response to ICI were analyzed to determine the effect of ICI."

Comment8:- Table 1: include the value of "p" in the histology variable.

Reply8: I appreciate your comment. We apologize for our lack of attention.

Changes in the text8: We Added p-value to histology variable in Table 1.

Comment9: - Line 121-122: The phrase "although...lesions" is not clear. Perhaps it was meant to say that only 65% of the surgery group patients had measurable lesions?

Reply9: Thank you for pointing out the ambiguity in the manuscript. You are correct; the intention was to communicate that while all patients in the non-surgery group had measurable lesions, only 65% of the patients in the surgery group had measurable lesions. This has been clarified in the revised text for better comprehension.

Changes in the text9: We modified "although...lesions" to "In the non-surgery group, all 108 patients (100%) presented with measurable lesions. In contrast, within the surgery group, only 17 of 26 patients (65%) had measurable lesions (P<0.001)." in L121-

Comment10:   - Figure 1: In the figure description, also specify that two subgroups were created from the surgery group based on the performed lymph node dissection.

Reply10: I appreciate your attention to detail. The figure legend should indeed have included an explanation that two subgroups were formed from the surgery group based on the type of lymph node dissection performed. This will be corrected to provide a clear understanding of the figure. Thank you for your guidance.

Changes in the text10: we added the sentence "Surgery group was further divided into two groups according to the extent of lymph node dissection: Systematic group (n=16) and a Selective group (n=10).

" To the Figure legends (Figure 1).

Comment11: - Figures 2 and 3: The Kaplan-Meier curves have been inverted: what appears as Figure 2 is described in Figure 3 and vice versa.
Reply11: Thank you for your important remarks. As you pointed out, Figure 2 and Figure 3 are interchanged.

Changes in the text11: Re-submitted with Figure2 and Figure3 replaced.

Comment12: - Table 3: Specify in the description that the table refers solely to the group of 26 patients who underwent surgery.
Reply12: I appreciate your comment. We should have emphasized in the description of Table 3 that this is an analysis for the Surgery group.
Changes in the text12: We added the describe "in Surgery group" to L141 and title of Table 3.

Discussion:

Comment13：- Line 176-177: One of the reasons why prognosis tends to be better in

the surgery group may also be the earlier stage of the tumor at diagnosis. Perhaps this should be added to the considerations.
Reply13: I appreciate your insightful comment. As you pointed out, we believe that the stage at which the diagnosis is reached greatly affects the prognosis. We have described the small tumor volume in the Surgery group, but we thought we should mention the stage as well.
Changes in the text13: We added "Surgery group is diagnosed at an earlier stage compared to non-Surgery group, and with it" to L176.

Comment14- The discussion reveals that systematic lymph node dissection reduces the response to ICI in case of disease recurrence. Could it be indicated in selected patients, possibly based on PD-L1 expression, to perform a more selective lymphadenectomy in order to ensure a more effective ICI treatment in the event of disease recurrence? This aspect should be further investigated.
Reply14: I appreciate your insightful recommendation. Although our current review does not allow us to make any definitive statements, we believe that a study to reduce the extent of lymph node dissection in order to increase the effectiveness of ICI should be considered as a future prospect. Clinical trials on the extent of lymph node dissection are underway, and we have determined that this should be added to the discussion.

Changes in the text14: We add the sentence "For the selected patient population from these results, a treatment strategy that reduces the extent of lymph node dissection to increase the effectiveness of ICI at the time of recurrence may also be considered. A randomized phase III trial is undergoing for early stage NSCLC with a range of LND (27). Since ICI is the key drug in the treatment of patients with postoperative

recurrence, it is anticipated that patients enrolled in this trial will also receive ICI at recurrence. We believe that the results of this trial will provide important insights into the efficacy of ICI in patients with postoperative recurrences."

Reviewer D

The author reported on the impact of ICI on postoperative recurrence, which is an interesting study. However, it has several problems that need to be corrected.

Major comments

Comment1: 1. I think the reason why there was no significant difference between surgery group and non-surgery group is due to the lack of sufficient number of cases. This should be mentioned in the limitation.
Reply1: I appreciate your comment. As you pointed out, we should have mentioned about the small-sample size.
Changes in the text1: we added the sentence "and this study included only 26 patients in Surgery group. This study design and small-sample size may have introduced selection bias."
To limitation in L158-.

Comment2: 2. Between which groups were the backgrounds matched using the IPTW method? Please describe in the text.
Reply2: I appreciate your comment. We also thought that describing the subjects with matched patient backgrounds was a way to make the design of this study more understandable.
Changes in the text2: We added "between Surgery group and non-Surgery group" in Statistical analysis (Methods section)

Comment3: 3. Tumor stage may also influence the effect of ICI; it would be better to add stage as a variable in the IPTW method or as a variable in a multivariate analysis.
Reply3: I appreciate your helpful comment. As you indicated, stage may have an impact on prognosis, and we believe that this variable should be added to the prognostic analysis.
Changes in the text3: We added clinical stage as a variable to the Cox-Hazard analysis in Table 3.

Comment4: 4. Systematic dissection group may have included more advanced lung cancers, which may have affected the PFS. Please describe the criteria used to determine the extent of lymph node dissection in the text.
Reply4: Thank you for your insightful comments. We recognize the importance of clearly defining 'systematic' and 'selective' lymph node dissection and the rationale behind the choice of procedure for each patient. We addressed this by adding a detailed description of our surgical policy to the Methods section. This addition clarifies the criteria for selecting the type of dissection.

Changes in the text4: We added detailed description of our surgical policy about lymph node dissection to the Methods section.

Comment5: 5. Of the 134 cases in the multivariate population, only 26 had lymph node dissection. Is it a correct method statistically to add a factor that is a missing data in the majority of cases to the variables in a multivariate analysis?

Reply5: My apologies for the confusion caused by the unclear expression in the manuscript. To clarify, the Cox-Hazard analysis was conducted exclusively on the Surgery group and did not include all 134 patients. This analysis was intended to assess outcomes within the subgroup of Surgery group, taking into account the types of lymph node dissection performed. I regret any misunderstanding this may have caused and will ensure that the text is amended to accurately reflect this information. Thank you for bringing this to my attention.

Changes in the text5: We added the describe "in Surgery group" to L141 and title of Table 3.

Comment6: 6. In order to evaluate the adequacy of the IPTW analysis, please describe the weights obtained from the IPTW analysis in the text or supplement.

Reply6: I appreciate your insightful comment. As you pointed out, describing the weights obtained from IPTW is important to ensure the robustness of this study.

Changes in the text6: We included a statistical summary of the Weights obtained by IPTW in the Results section.

Minor comments

Comment7: 1. I don't understand the meaning of the sentence in line121-122 on page 5. I think "in the surgery group" is missing. Please confirm.

Reply7: Thank you for pointing out the ambiguity in the manuscript. You are correct; "in the surgery group" is missing. We apologize for confusing describe.

Changes in the text7: We modified "although...lesions" to "In the non-surgery group, all 108 patients (100%) presented with measurable lesions. In contrast, within the surgery group, only 17 out of 26 patients (65%) had measurable lesions (P<0.001)." in L121-

Comment8: 2. Figures 2 and Figure 3 appear to be reversed. Please confirm.

Reply8: Thank you for your important remarks. As you pointed out, Figure 2 and Figure 3 are interchanged.

Changes in the text8: Re-submitted with Figure2 and Figure3 replaced.

Comment9: 3. Number at risk in Figure 3 is 129 for the surgery group and 134 for the non-surgery group. Please check the consistency with Table 1 and Table 2.

Reply9: We appreciate your insightful observation regarding the divergence between

the actual and the adjusted sample sizes post- IPTW application. Upon reflection, we recognize that our manuscript did not sufficiently elucidate this aspect. We apologies for this oversight.

To clarify, IPTW aims to create a balanced pseudo-population in which the distribution of covariates is similar across treatment groups. This method assigns weights to each individual based on their probability of receiving the treatment, calculated from the propensity scores. As a result, while the actual number of participants remains unchanged, the weighted analysis reflects a pseudo-sample size, which is the sum of the weights rather than a count of individuals. This pseudo-sample size can deviate substantially from the actual sample size, especially in the presence of extreme weights. The sample size you pointed out is the sample size after adjustment by IPTW. To address this, we have modified the manuscript to include a detailed explanation of the IPTW process.

Changes in the text9: We have described in the results section the apparent sample size after adjusting for IPTW.