Peer Review File
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Reviewer A

Comment 1: Lines 134-140: I would move the discussion of study limitations after the discussion of the results, as it provides a description and clarification of the obtained results, and therefore it is appropriate to include it after the analysis.
Reply 1: We have moved the limitations in Discussion (see Page 26, line 421-428)
Changes in the text: N/A

Comment 2: From Table 1, it emerges that information regarding T (Tx; 14%), stage (3.7%), grade (0.4%), laterality, site of surgery (13%), and performance of lymphadenectomy (1.7%) is not available for several patients. To minimize bias and limitations resulting from a retrospective study, it would be necessary to exclude these patients with incomplete information.
Reply 2: Thank you for highlighting the importance of this aspect. We want to reiterate that prior to receiving your feedback, we had already conducted our survival analysis using completed cases. We share your commitment to minimizing bias and ensuring the robustness of our study. By excluding patients with incomplete information before analysis, we aimed to uphold the integrity of our findings. Your comment reaffirms our approach and underscores the thoroughness of our methodology.

Comment 3: Lines 172-173: Have you considered the possible reasons why the HR of tumors in the left lung and those in the upper and middle lobes of the right lung is higher compared to tumors in the main bronchus and lower lobes?
Reply 3: We have modified our text as advised (see Page 10, line 183-188)
Changes in the text: Additionally, tumor laterality and specific locations within the lung were significant predictors of outcomes. Tumors located in the left lung and in the upper and middle lobes were associated with lower hazard ratios compared to tumors in the main bronchus or the lower lobes. These differences could be attributed to anatomical variations, differences in lymphatic drainage and blood supply, impacts on pulmonary function, and variations in surgical accessibility and effectiveness.

Comment 4: Lines 196-200: This paragraph is repetitive. The content has already been expressed using the same words in Lines 183-189.
Reply 4: The repetitive paragraph has been eliminated (see Page 13, line 224-228)
Changes in the text: N/A

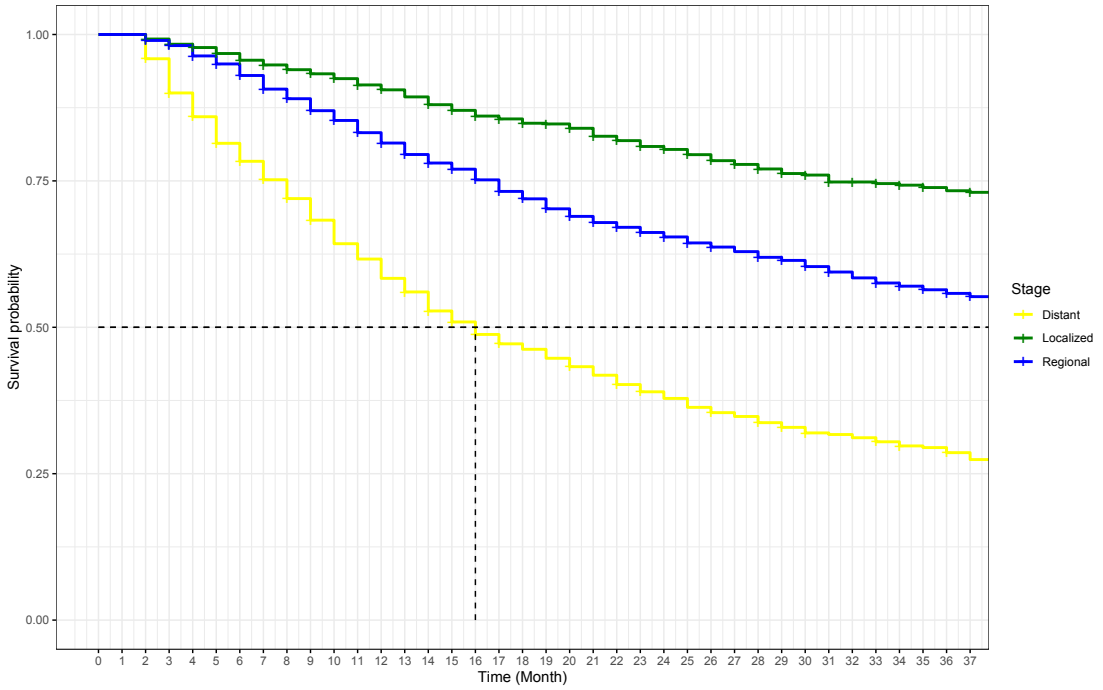
Comment 5: Table 3: The table illustrates the multivariate analysis for lung cancer-specific survival in NSCLC patients undergoing surgery. On page 12, it is mentioned that with an increase in stage, the hazard ratio decreases, indicating a lower risk of lung cancer death (contrary to what is stated in Lines 188-189). How is it possible that with an increase in stage, survival is better, considering that with increasing T, N, and M values, survival is lower?
Reply 5: This discrepancy was in careful consideration and clarification within the analysis and interpretation of the data. (see Page 12-13, line 210-223)
Changes in the text: Among these variables, lymph node dissection during surgery had a significant impact on survival. The hazard ratio for no regional lymph nodes removed or aspirated was 1 (reference), while the hazard ratios for biopsy or aspiration of regional lymph node and removal of regional lymph nodes were 0.85 (95% CI: 0.81-0.89; $p < 0.001$) and 0.43 (95% CI: 0.39-0.46; $p < 0.001$), respectively, indicating a survival benefit.. Contrary to initial expectations, an analysis mentioned that an increase in stage is associated with a lower hazard ratio, implying better survival outcomes. This counterintuitive finding may be attributed to factors such as selection bias for surgical candidates, the comprehensive treatment approaches for higher-stage patients, more aggressive surveillance and follow-up care, and stage migration

due to advances in diagnostic accuracy. These aspects highlight the complexity of treating lung cancer and underscore the necessity of a nuanced understanding of how staging, treatment interventions, and patient characteristics interplay to influence survival outcomes.

Comment 6: Tables 2-3: The concept of laterality is unclear and needs to be reviewed. The abbreviation RLN is used by the author (in both the text and tables) regarding the coijoint treatment. However, its meaning is not specified.
Reply 6: The explanation of laterality and RLN is supplemented in the paragraph in the "Results" section that introduces the impact of each variable on survival. (see Page9-10, line 180-183, 192-196)
Changes in the text: The concept of laterality was clarified that 'laterality' refers to the side of the lung (left or right) where the primary tumor is located, which impacts survival predictions. Tumors on the left and right sides may lead to differences in treatment strategies and prognoses due to anatomical differences, the feasibility of surgical treatment, and variations in lymphatic drainage patterns./ RLN in this study stands for Regional Lymph Nodes. The removal or biopsy of regional lymph nodes during surgery is a key step in assessing tumor spread and guiding subsequent treatment plans. We have paid special attention to the management of RLN within the context of conjoint treatment, including chemotherapy and radiotherapy, and their impacts on survival rates.

Comment 7: Lines 215-217: How can we talk about early-stage NSCLC while also considering M1? By definition, M1 indicates advanced stage.
Reply 7: We have modified our text as advised (see Page 15-16, line 245-253)
Changes in the text: The analysis indicated that patients with non-metastatic NSCLC, particularly those presenting with a localized stage and classified as T1 and N1, showed the most significant survival benefits from lymph node dissection. It is important to note that while the inclusion of M1 (a designation for distant metastasis) in this context may suggest a contradiction, it can be postulated that this reflects a subset of patients where the primary tumor characteristics (such as T1 and N1) are indicative of a localized disease process, but isolated metastases (M1) were also present. In such cases, comprehensive lymph node dissection may still offer a survival advantage, potentially due to the removal of metastatic deposits within accessible regional nodes, or it may reflect a survival benefit in a specific patient cohort that warrants further investigation.

Comment 8: Figure 2: It is recommended to change the colors of the graph lines to make it clearer which group they refer to.
Reply 8: Thank you for your suggestion regarding Figure 2. We have revised the colors of the graph lines to enhance clarity and improve differentiation between the various groups.
Please find the revised Figure 2 here. (see Page 17, line 258-259)
Changes in the text:



Comment 9: Lines 244-245: The sentence seems incomplete.
Reply 9: The first sentence appears to be missing a description of what the binary outcome represents in the context of the analysis. We completed the sentence by including a plausible binary outcome that the study might have been examining.
Changes in the text: We performed restricted cubic spline method to explore the relationship between a continuous variable of the number of lymph nodes examined and a binary outcome of lung cancer-specific mortality.

Comment 10: Lines 258-260: The concept is expressed in exactly the same way in lines 257-258. It should be eliminated as it is repetitive, as well as in Lines 261-266: The concept is always the same, expressed differently, so the paragraph should be rephrased to be more concise.
Reply 10: Lines 257-258 has been eliminated. We have rephrased the paragraph as advised.
Changes in the text: Data analysis identified 24-32 as the optimal number of lymph nodes to examine during dissection for enhanced survival benefits in NSCLC patients. This range, supported by a U-shaped curve, aligns with the highest survival probability, indicating its strong association with better patient outcomes (Figure 7). Such findings can inform surgical strategies, particularly emphasizing the importance of extensive lymph node dissection in early-stage patients to potentially improve prognosis.

Comment 11: Line 316: "beyond 16 nodes the prognosis worsens": considering what has been described by the author so far, the prognosis worsens after 32 lymph nodes, considering that the appropriate range of lymph nodes excised during lymphadenectomy is reported to be 24-32.
Reply 11: we have modified our text as advised (see Page 24, line 377-380)
Changes in the text: Our study delineates that the survival benefit does not extend indefinitely with more lymph nodes; instead, it plateaus and potentially declines when more than 32 lymph nodes are dissected. This suggests that excessive lymph node removal may be detrimental, thus necessitating a balanced approach to lymphadenectomy. Our findings highlight the importance of future research to validate the optimal lymph node range, especially considering previous recommendations of 10 lymph nodes, and to inform systematic lymph node dissection (SLND) protocols, which traditionally involve dissecting at least 11 lymph nodes across a minimum of 5 stations for accurate staging and prognosis, particularly regarding recurrence-free survival.

Comment 12: Paragraph 4.4 can be eliminated as it is redundant. What has been elucidated has already been described in the previous paragraph.
Reply 12: Eliminated (see Page 24-25, line 388-395)
Changes in the text: N/A

Reviewer B

Comment 1: Why was it chosen to include advanced stages of the disease in the analysis? the impact of lymphadenectomy at this stage of the disease is well known, and I believe that since this part of the sample is the largest part of the population in question (distant stage diagnosis 63%, mortality 85%), it may create several confounding factors;
Reply 1: To address the potential confounding factors, especially given the proportion of the population with a distant-stage diagnosis, the manuscript was improved by discussing these aspects：1）Methodology Section: Where you explain the inclusion criteria and how the multivariate analysis was designed to account for these potential confounders.2）Results Section: When presenting the findings, particularly the outcomes associated with lymphadenectomy in advanced stages, it would be beneficial to discuss how these were adjusted for confounders.
To provide the rationale for including advanced-stage diseases and address the confounding factors, we added a paragraph in the Discussion section, typically after presenting your main findings (after line 290 and before subsection 4.1), where the study's scope and design considerations are elaborated upon. Context to the inclusion of advanced-stage patients and how analysis methods (e.g., multivariate Cox proportional hazards modeling) account for and mitigate the influence of these confounders.
Changes in the text:
In the Methodology Section: (see Page 6, line 125-133)
Insert a paragraph after line 125 in the Statistical Methods subsection:
"Furthermore, to address potential confounding factors particularly prevalent among the patient cohort with advanced-stage disease, who comprise the largest portion of our study population, the multivariate Cox PH analysis was meticulously designed. This design accounted for the stage of the disease to differentiate the effect of lymph node dissection on survival outcomes. While it is recognized that lymphadenectomy in the context of distant-stage disease is well documented, including these patients enables a more thorough understanding of the intervention's role across the complete spectrum of the disease. This comprehensive approach facilitates the identification of stage-specific therapeutic benefits and informs nuanced treatment strategies that cater to individual patient profiles."

In the Results Section:
Insert a comment after the presentation of the outcomes associated with lymphadenectomy, around line 195:
"While the beneficial impact of lymph node dissection on survival was clear, the analysis was adjusted for confounding factors, including the predominance of patients with distant-stage cancer. By integrating the stage of the disease into the model, the analysis provided insights into the therapeutic value of lymph node dissection even in advanced stages, which is critical for developing balanced and evidence-based clinical guidelines."

In the Discussion Section:
Add a paragraph after line 299:
"Including advanced-stage disease in our analysis allowed for a comprehensive examination of lymph node dissection's impact across all stages. Despite the acknowledged efficacy of lymphadenectomy in early-stage NSCLC, its role in advanced disease has been less clear. By analyzing a full spectrum of disease stages, we aimed to clarify the survival benefits in the context of distant-stage diagnoses. While the largest part of our study population had a distant-stage diagnosis, representing 63% with a mortality rate of 85%, we accounted for this potential bias. The study design and statistical analysis, especially the use of multivariate Cox PH models,

aimed to control for confounding factors, ensuring that the observed benefits of lymph node dissection are not overestimated for advanced-stage patients. This careful consideration ensures that the study's conclusions are reliable and applicable to the wider NSCLC patient population."

Comment 2: regarding inclusion/exclusion criteria, I think it is necessary in such a study to exclude patients who have not undergone lymphadenectomy (representing the majority of the study population 84)
Reply 2: Thank you for your comment regarding the inclusion/exclusion criteria in our study. We appreciate your insights and would like to offer further clarification on our research question and study design.
Our study aimed to explore two main aspects: firstly, to investigate the survival effects of patients who did not undergo lymphadenectomy compared to those who did, and secondly, to examine the survival impacts of different levels of lymph node dissection during surgery. We intended to compare both groups to understand the relative benefits or risks associated with lymphadenectomy.
Regarding the exclusion of patients who have not undergone lymphadenectomy, it is important to note that their inclusion was intentional as it allows for a comprehensive examination of survival outcomes across different treatment approaches. By including this group, we aimed to capture the real-world scenario where not all patients undergo lymphadenectomy and understand the implications of this choice on survival.
We hope this clarifies our approach and rationale for including patients who have not undergone lymphadenectomy in our study. Your feedback is valuable, and we welcome further discussion on this matter.

Comment 3: details of the type of lymphadenectomy performed in these patients, the number of lymph nodes removed and the corresponding stations are not given, so it is unclear where the range of 24-32 lymph nodes to be removed came from
Reply 3: Thank you for your insightful comment regarding the details of lymphadenectomy in our study. We acknowledge the importance of providing clarity on this aspect. In our study, we identified the optimal range of lymph nodes (24-32) to examine during dissection based on careful analysis of our data.
Figure 7 illustrates our findings, showing a U-shaped curve that highlights the relationship between the number of examined lymph nodes and survival probability. Through this analysis, we determined that examining lymph nodes within the range of 24-32 was most strongly associated with improved survival outcomes.
The selection of this specific range was guided by the shape of the curve, indicating a significant survival advantage within this range. Therefore, our choice of 24-32 lymph nodes for examination during dissection is grounded in data-driven insights aimed at enhancing patient outcomes in NSCLC management.
We appreciate your attention to this detail, and we hope that this clarification provides a better understanding of our study's findings and their implications for clinical practice.

Comment 5: Finally, the study concludes that performing lymphadenectomy has a positive effect on survival especially in early-stage patients, who, however, on page 14 lines 215-217 are defined as patients with localised, T1, N1 and M1 disease. It is unclear to me how patients with N1 and M1 disease can be defined as early-stage?
Reply 5: Changes in the Discussion Section:Insert a paragraph after line 290
Changes in the text: Our study categorizes 'early-stage' NSCLC patients as those with localized disease, reflecting T1 and N1 classifications. However, it is crucial to address an apparent inconsistency where M1 status, indicative of distant metastases, has been associated with early-stage disease. This inclusion stems from a subset of patients with primary tumors characteristic of early-stage (T1, N1) but also present with singular metastatic sites (M1), which may still be amenable to surgical intervention and lymphadenectomy. This condition is sometimes referred to as oligometastatic disease and represents a particular clinical scenario distinct from widespread metastatic disease typically associated with advanced stages. To avoid confusion

and ensure precise communication of our findings, we will revise the text to clarify that patients with M1 disease are not categorized as early-stage, but rather, they represent a specific group where targeted surgical approaches, including lymphadenectomy, may still provide survival benefits. Further research is warranted to delineate the survival implications in this unique patient population thoroughly.