

Peer Review File

Article Information: <https://dx.doi.org/10.21037/tlcr-24-450>

Reviewer A

Comment 1: What was the number of patients who were excluded due to a lack of complete pathological information on LNM? This is necessary information to shed light on the effect of missing data.

Reply 1: Thank you for your rigorous comment, for which we reviewed the electronic medical records of our patients. We retrospectively reviewed the patient data and found that 33 patients had missing lymph node data, all of whom were confirmed to have lung metastases by pathology. Considering that the frozen pathological examination during surgery indicated the presence of metastases, no routine lymph node dissection/sampling was performed.

Changes in the text: No change.

Comment 2: For right sided tumors the ESTS guidelines states that: Any visible nodes in front of the superior vena cava and/or posterior to the trachea should be removed (stations 3a and 3p). Please comment.

Reply 2: Thank you very much for your valuable comments, for which we gave the following explanation. The ESTS guidelines do mention 3a/3p lymph nodes dissection, but lymph node dissection in surgical treatment of non-small cell lung cancer has not mentioned 3a/3p dissection/sampling in both the guidelines of NCCN (Version 7.2024) and CSCO (Version 2024). Therefore, we performed lymph node dissection/sampling only in some patients with 3a/3p lymph nodes visible during the operation. So, this study does not require 3a/3p station lymph node dissection/sampling.

Changes in the text: No change.

Comment 3: Was the systematic lymph node dissection, as stated in the methods section complete for all included patients?

Reply 3: Thank you for your review of the manuscript, your suggestions are helpful in improving the strictness of the study. Systematic lymph node dissection was not achieved in certain patients undergoing systematic lymph node sampling, following the current guidelines.

Changes in the text: we have modified our text as advised (see Page 8, line 125, 142)

Comment 4: Please do not use abbreviations such as ADC and SqCC, these do not enhance readability.

Reply 4: Thank you for your review of the manuscript, your suggestions are helpful in improving the readability of the study. We removed the abbreviation within the scope of the full text.

Changes in the text: we have modified our text as advised (see Page 5, line 79-80,

Page 10, line 169, 172-177, 179, 181-182, 186-187, 189, Page 11, line 196, Page 11, line 210-211, Page 13, line 241-242, 245, 246-247, Page 14, line 274, Page 16, line 303, Page 20, line 400, 405).

Comment 5: In continuance on comment 2: you do not state in the methods section that you remove 3a/3p, but mention them in the results?

Reply 5: Thanks again for your review, these comments are very helpful to improve the quality of the manuscript. According to the NCCN guidelines and CSCO guidelines, the systematic lymph node dissection/sampling standard we studied did not include the 3a/3p stations, but some patients underwent 3a/3p station lymph node dissection/sampling during surgery, so we conducted supplementary analysis on the 3a/3p data. As mentioned above, not all patients underwent pathological examination of 3a/3p station lymph nodes, so whether the 3a/3p data corresponds to the real world situation still needs further exploration.

Changes in the text: No change.

Comment 6: It would improve the results if you would be able to determine predictors for LNM. In this way you may also rule out other confounders and effect modifiers.

Reply 6: We appreciate it very much for this good suggestion. Our findings suggest that lymph node dissection should be performed according to the pathological type of lung cancer, the lobe in which the nodule is located, and the size of the tumor. The choice of lymph node dissection/sampling method should be based on the characteristics of the tumor (including pathological type, tumor size, and lobe).

Changes in the text: No change.

Comment 7: It is stated previously that: The number of removed lymph nodes is closely related to the recurrence-free survival after VATS lobectomy. Therefore, proper lymph node dissection, in terms of number and station, should be performed in VATS lobectomy despite its difficulties (<https://vats.amegroups.org/article/view/5438/html>). So shouldn't we just stick to remove as much nodes as surgically possible?

Reply 7: Thank you for your careful review of the manuscript. We carefully read this article describing the association between the number of lymph nodes dissection and recurrence-free survival. This study revealed that the removal of more than 10 up to 40 lymph nodes was associated with improved recurrence-free survival, but did not analyze the postoperative complications and length of hospital stay. In clinical work, we often need to pay attention to the short-term effect of patients while paying attention to the long-term survival of patients according to the reality. This is also the starting point of our study, for which patients are suitable for lobe-specific lymph node dissection to reduce the occurrence of surgical complications. The more thorough the dissection, the greater the risk of surgical complications.

Changes in the text: No change.

Reviewer B

Comment 1: Abstract - no SqCC results in Abstracts Results section

Reply 1: Thank you for your careful review of the manuscript. Our study found that there was no significant difference in lymph node metastasis in patients with squamous cell carcinoma from multiple angles, and the main content of the subsequent study was adenocarcinoma, so the results of the related studies in patients with squamous cell carcinoma were not described in the abstract. To demonstrate the completeness of the study results, we have added relevant descriptions of squamous cell carcinoma.

Changes in the text: we added some data of patients with squamous cell carcinoma (see Page 4, line 67-69).

Comment 2: Introduction and Discussion - International guidelines recommend both Mediastinal Lymph Node Dissection and Systematic Sampling. You forgot to mention about the sampling

Reply 2: Thank you for your rigorous comment, which was very helpful in improving the quality of the manuscript. Both the NCCN guidelines and CSCO guidelines mention systematic lymph node dissection and systematic lymph node sampling in the section of surgical treatment of lung cancer. We have added a description of lymph node sampling in this paper. Thank you again for your valuable comments.

Changes in the text: we added a description of lymph node sampling in this paper (see Page 4, line 52, Page 8, line 125, 142).

Comment 3: Methods: Were patients with lymph node sampling eligible? If not why?

Reply 3: Thank you for your rigorous comment, which was very helpful in improving the quality of the manuscript. Both the NCCN guidelines and CSCO guidelines mention systematic lymph node dissection and systematic lymph node sampling in the section of surgical treatment of lung cancer. We have added a description of lymph node sampling in this paper. Thank you again for your valuable comments.

Changes in the text: we added a description of lymph node sampling in this paper (see Page 4, line 52, Page 8, line 125, 142).

Comment 4: Methods, variables: I think in peripheral lesions group variables regarding distance to the pleura, or pleural invasions (PL status) are crucial. Subpleural lymph node drainage results in skip metastasis and metastasis outside of typical lymph node drainage. Please consider including such data.

Reply 4: Thank you for your careful review of the manuscript, your suggestions are helpful in improving the quality of the study. We described in the discussion section “Mediastinal LNM in the right middle lobe cancer was similar to that in the right upper, and all had 2R, 4R, and L7 metastasis. Left lower lobe cancer tended to metastasis in 4L, L6, and L7, and although the rate of metastasis in L7 lymph nodes is

not very high, it was most prone to jump metastasis among the mediastinal lymph nodes (40%, 4/10). This may be because the segmental and subpleural lymphatics originating from the lower lobe can drain directly to the subcarinal lymph nodes without involving the intrapulmonary or hilar lymph nodes” . According to the 8th TNM stage, visceral pleural invasion was classified as cT2, and the probability of lymph node metastasis in cT2 patients was significantly increased compared with that in cT1 patients. Therefore, we recommend systematic lymph node dissection for patients with peripheral lung cancer invading visceral pleura. The distance from visceral pleura was considered as peripheral lung cancer without visceral pleura invasion. The T stage was performed according to the tumor size, and the lymph node metastasis rate increased with the increase of tumor size.

Changes in the text: No change.

Comment 5: Results: Besides lymph nodes and lymph node metastasis - lymph node station and station metastasis count are important (e.g. several lymph nodes from a single station is not adequate lymphadenectomy). Please consider including data regarding lymph node stations

Reply 5: Thank you for your comment. The relevant data in our study include the number of lymph nodes in each lymph node station. Lymph node metastasis rate is the proportion of the number of metastatic lymph nodes in each lymph node station in the total number of lymph nodes dissection at that lymph node station. Therefore, the lymph node station and station metastasis count are included in the original data of our article.

Changes in the text: No change.

Comment 6: Abbreviation ADC is redundant - ADC and adenocarcinoma are 1-word phrases.

Reply 6: Thank you for your review of the manuscript, your suggestions are helpful in improving the readability of the study. We removed the abbreviation within the scope of the full text.

Changes in the text: we have modified our text as advised (see Page 5, line 79-80, Page 10, line 169, 172-177, 179, 181-182, 186-187, 189, Page 11, line 196, Page 11, line 210-211, Page 13, line 241-242, 245, 246-247, Page 14, line 274, Page 16, line 303, Page 20, line 400, 405).

Comment 7: Labeling stations as blue, green, etc. is confusing in the results section. I think just reporting the data would be more clear. Also, how did you set these cut-off points for certain colors?

Reply 7: Thank you for your comment. Figures are more intuitive and has an impact, and the table has more data, it is difficult to find the key at a glance. Furthermore, there are no clear and accepted cut-off points for LNM rates reported in the previous literature, so we analyzed them based on lymph node dissection data reported in the literature. To facilitate the interpretation of the data, we color coded lymph node metastases according to metastasis rates and mapped the distribution of lymph node

metastases.

Changes in the text: No change.

Comment 8: Some English Editing is needed: e.g.: "Among patients with lung lobes affected" should be rephrased.

Reply 8: Thank you for your review of the manuscript, your suggestions are helpful in improving the readability of the study. We read it carefully from beginning to end and revised the description in the full text as appropriate

Changes in the text: we have modified our text as advised (see Page 11, line 194).

Comment 9: You should elaborate more what's the importance of pT1b-cN2 phenomenon.

Reply 9: Thank you for your rigorous comment, which was very helpful in improving the quality of the manuscript. We added “ The pathological subtype was predominantly adenocarcinoma with a predominantly acinar pattern (21/34), followed by a predominantly solid/micropapillary pattern (10/34). Interestingly, we found that 7 out of 10 patients with solid/micropapillary predominance had undergone 2L/2R dissection/sampling, and 6 of them had 2L/2R metastasis (lymph node metastases/total lymph nodes (9/18); all 10 patients had undergone L7 dissection/sampling, and 6 of them had L7 metastasis (7/16). Among the 10 patients with upper left lobe adenocarcinoma, 7 had L5 metastasis (8/19).” in Results.

Changes in the text: we added a description of lymph node dissection/sampling in pT1b-cN2 patients (see Page 16, line 216-221).

Comment 10: Figures should be self-explanatory. Please explain what is upper and lower values in each colored bubble.

Reply 10: Thank you for your review of the manuscript, your suggestions are helpful in improving the readability of the study. We added the definition of upper and lower values in each colored bubble in the annotation of each figure. The numbers above the horizontal lines in each colored bubble represent the lymph node stations, while the numbers below the lines represent the rate of lymph node metastasis.

Changes in the text: we have added the definition as advised (see Page 20, line 395-396, 399-400, 404-405, 407-408).

Reviewer C

Comment 1: Section 2.6 Statistical Analysis:

o While the statistical analyses are sound, the manuscript could benefit from a more detailed explanation of the statistical tests used and their appropriateness for the data. Specifically, the manuscript mentions using Pearson's chi-square and Fisher's exact tests, but it would be helpful to explain why these tests were chosen over others.

o Multiple comparisons are made across different groups, but the manuscript could be

clearer about how the Bonferroni correction was applied to control for type I errors.

Reply 1: Thank you for your careful review of the manuscript. When n is greater than or equal to 40 and E is greater than 5, see the Pearson chi-square value; when n is less than 40 or E is less than 1, select the result of Fisher's exact test. The Bonferroni correction method is a statistical method for multiple comparisons, which aims to correct the probability of type I error due to multiple comparisons. For each comparison, we divided its significance level by the total number of comparisons, such that the actual significance level for each comparison.

Changes in the text: No change.

Comment 2: Section 4. Discussion:

o As you mentioned your findings and strategy, were there any differences from current guidelines? Please clarify any differences and strengths that distinguish your study from existing guidelines.

Reply 2: Thank you very much for your constructive comments. At present, the NCCN guidelines and CSCO guidelines mention systematic lymph node dissection / sampling, but there is no detailed introduction on the characteristics of the tumor. We studied the recommendation of lymph node dissection / sampling for different characteristics of the tumor, which can reduce the occurrence of surgical complications to a certain extent without reducing the tumor stage.

Changes in the text: No change.

Comment 3: Section 5. Limitation:

o The study acknowledges the limitations of being a single-center study with a population that may not be representative of all ethnicities or geographical areas. It would be beneficial to discuss how these limitations might affect the generalizability of the findings and consider suggesting further multicenter studies.

Reply 3: Thanks so much for your careful reading, and our study was a single-center study, as the limitations said, and the treatment population was limited to the municipal level. However, considering the influence of different regions and different living habits, the incidence rate and mortality rate of lung cancer are still different. Therefore, this study still needs to further verify and explore by expanding the sample size and cooperating with other medical institutions.

Changes in the text: No change.

Comment 4: Figures Section:

o The figures and tables included in the manuscript are informative but could be improved for clarity. For instance, some figures are labeled with abbreviations that may not be immediately clear to all readers, so including full terms or a key could help.

Reply 4: Thank you for your review of the manuscript, your suggestions are helpful in improving the readability of the study. We removed the abbreviations from the picture and added the full spell.

Changes in the text: we have modified the abbreviations as advised (see Figure 4).