**Peer Review File**

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**Reviewer A**

Your data is very thorough, and I would expect you have access to the type of approach used for resection (posterior-lateral thoracotomy, anterior muscle sparing thoracotomy, VATS, robotic). Evaluation of this parameter in survival data of this type I think would be revealing, though likely would be a better independent paper.

Also, discussion of second primary lung cancer patients that were not resected due to inoperability for two cancers would be interesting. I have had many patients that would likely benefit from surgery if they were candidates for resection of both tumors, but in the absence of this they received definitive chemo-radio-immunotherapy.

And finally, you are using lots of terms to describe multiple primary lung cancers. The literature is full of variability, but I prefer the concepts of synchronous multiple primary lung cancers (SMPLC's) and metachronous multiple primary lung cancers (MMPLC's), which I think helps inform our thinking of two or more separate primaries identified at the same time or at different times. I've had as many as 5 separate synchronous primary lung cancers (3 adeno, 2 squamous), so the term second primary lung cancers is limiting.

But overall, excellent paper. I enjoyed reading it, and look forward to seeing it published.
Reply: Thank you for your suggestions on our articles. We are also interested in the surgical modalities and prognosis of SMPLC patients. We hope to conduct this study after refining the data sample size and share the results with more surgeons.
Also, for the abbreviations you raised. We agree with your ideas and will unify the abbreviation of this article to SMPLC for readers to understand.
It is a great honor to share your clinical experience, which provides a broader idea for our subsequent research. Thank you for your time!

**Reviewer B**

1. Title – consider changing to “Establishment of a Survival Predictive Model for Patients with Two Synchronous Multiple Primary Lung Cancers.”
Reply 1: Thanks to your suggestion! We've changed the title of the article
Changes in the text: Establishment of a Survival Predictive Model for Patients with Two Synchronous Multiple Primary Lung Cancers：A Multicenter Cohorts Analysis (see Page 1, line 1-2)
2. The acronym SPLC is not commonly used. Broad and variable use of acronyms in scientific literature contributes to the lack of understanding among the readers. Consider using

“synchronous multiple primary lung cancer (SMPLC)”, and clarify in your inclusion criteria that only patients with two SMPLC are included in the present study. Use the same acronym in abstract as you use in main text.

Reply 2: Thank you for your suggestion, we think it is important to clarify a definition of multiple primary lung cancer to readers in all countries. We have changed the abbreviation for multiple primary lung cancer to SMPLC throughout the text. We have also specify the definition of sMPLC in our study.

Changes in the text: In this study, the criteria for diagnosis of SMPLC were based on the 8th edition lung cancer staging criteria of the IASLC: 1) primary lung cancer; 2) pathological report showing that the number of lung tumors was more than 2; 3) preoperative chest CT showing two different lung tumors ; 4) two tumors from the same patient that had different histological types or morphological characteristics according to comprehensive histologic assessment (CHA)12; and 5) two tumors from the same patient that had same histological types and no lymph node metastases, sMPLC was judged on the basis of molecular analysis or CHA. The exclusion criteria included induction therapy, adjuvant therapies before surgery, other lung cancer diagnoses in the past, lesions showing a ground-glass opacity (GGO) component in all tumors, and inadequate pathological or radiological information available for review. (see Page 8, line 145-154)

3. Abstract: “there is a lack of studies exploring the prognosis of patients with resected SPLC”. This is not exactly true. There are many studies exploring prognostic factors among SMPLC patients. Please revise, and explore reasons for the lack of concrete prognostic factors according to these studies.

Reply 3: It is true that we have expressed the meaning unclearly in the original text. What we were trying to describe is that the inclusion of survival outcomes of patients with multiple GGOs in the SMPLC patient population in many previous articles may have led to an overly optimistic prognosis of long-term survival in SMPLC patients. We have revised the expression in the article.

Changes in the text: The prognostic predictors of the synchronous multiple primary lung cancer (SMPLC) still remain unclear, and there is a lack of studies on the prognosis of SMPLC patients excluding those with multifocal ground-glass/lepidic (GG/L) nodules. (see Page 4, line 65-67)

4. Abstract line 27 – change to “patients presenting for lung cancer resection”. Was it with intention to cure? Did they have 2/2 lung cancers resected or did you include those who had ½ resected only.

Reply 4: Thank you for your suggestion, we have fixed it as you suggested. The patients in this study all underwent resection of both lung nodules, otherwise we would not have been able to diagnose them as SMPLC patients according to the inclusion exclusion criteria of this study.

Changes in the text: SMPLC patients presenting for lung cancer resection (see Page 4, line 70)

5. Page 2, line 53 – “greatest enemies” should be removed. Be more direct in your language, could simply state lung cancer is the leading cause of cancer mortality.

Reply 5: We have removed this unclear statement and refined this sentence.

Changes in the text: Among all the malignant tumors worldwide, lung cancer is the leading cause of cancer mortality. According to the global cancer statistics for 2022, lung cancer has the highest mortality rate among all sexes and poses a great threat to the life and health of patients (see Page 6, line 95-97)

6. Page 2, line 60 – this needs to be cited and explained briefly. Heterogeneity in survival is not why the traditional staging system is unreliable. Heterogeneity in outcomes is due to the heterogeneity of inclusion criteria and definitions deployed by studies involving SMPLC, not the TNM staging system.

Reply 6: Thank you for your advice! We have modified this expression to show that unclear criteria for SMPLC patients is the main reason for the heterogeneity of survival results in previous articles, rather than the use of TNM staging system.

Changes in the text: Due to the inconsistent inclusion criteria of studies involving sMPLC patients, there is significant heterogeneity in survival and recurrence rates across studies. Therefore, the use of the traditional Tumor Node Metastasis (TNM) staging system to predict the survival of patients with SMPLC may be inadequate or unreliable. (see Page 6, line 101-104)

7. Strongly suggest reducing the introduction into 2 paragraphs.

Reply 7: We've reduced the introduction to two paragraphs, which gives it a more concise structure

Changes in the text: (see Page 6-7)

8. Page 3 line 90 – 'complexity of smplc is enhanced by tumor heterogeneity' – I don't quite understand what this sentence means. Are you still referring to heterogeneity of outcomes?

Reply 8: We are sorry that we are not clear. What we are trying to imply is that differences in histological types of multiple tumors in SMPLC patients may lead to more complex classification requirements

Changes in the text: Considering that differences in tumour histological types add to the complexity of SMPLC, the IASLC recommends further classification of SMPLC. (see Page 7, line 130-131)

9. Page 3 line 90 – authors switch from SPLC to sMPLC. Please be consistent.

Reply 9: All occurrences of SPLC in this article have been corrected to SMPLC to avoid bias in the understanding of multiple primary lung cancers by readers in different regions.

Changes in the text: SMPLC

10. Page 3 line 95 – I agree that a prognostic categorization model is necessary. As the authors previously mention, correctly so, heterogeneity of outcomes among studies is attributed to a number of factors. The reason we need a model is because current studies and prognostic factors cant be generalized due to the lack of larger literature using consistent inclusion criteria. Thus, we have to work with what we have. But stating that the TNM classification system is not applicable to SMPLC is flawed in reasoning.

Reply 10: Thank you for your advice! That's exactly what we were trying to convey. In order to avoid misinterpretation and to highlight the research context, we have removed this part of the discussion in the introduction

Changes in the text: ~~That is we should assign different T, N, and M for the two tumors4. While this TNM classification system was valuable, it was insufficient for prognosis prediction and estimation of SPLC. Even for the patients with the same highest stage, their survival rate varies greatly when other prognostic factors (e.g., surgical mode, second tumor stage) are considered.~~

11. Page 3 line 9 – synchronous multiple primary entails the patient has two or more lung cancers. So this can be removed, but based on the title, I was under the impression that this study is only concerned with patients with two cancers.

Reply 11: Thank you for your suggestion! We have refined the inclusion criteria for patients in this study.

Changes in the text: 1) primary lung cancer; 2) pathological report showing that the number of lung tumors was more than 2; 3) preoperative chest CT showing two different lung tumors ; 4) two tumors from the same patient that had different histological types or morphological characteristics according to comprehensive histologic assessment (CHA)12; and 5) two tumors from the same patient that had same histological types and no lymph node metastases, sMPLC was judged on the basis of molecular analysis or CHA.(see Page 8, line 147-152)

12. Page 3 line 9, inclusion criteria 3 – what CT characteristics are you referring to? CT characteristics are not an inclusion criteria for SMPLC.

Reply 12: Here's where we've misrepresented ourselves and have removed the ambiguity

Changes in the text: 3) preoperative chest CT showing two different lung tumors.

13. Page 3 line 10 – did you take into account histologic subtyping or molecular analysis? Modified Martini Melamed criteria is one methodology. Did you consider them as SMPLC if two tumors were of similar histologic subtype (major and minor) if the patient did not have any evidence of lymph node involvement and tumors were arising of separate foci? Please include details regarding this in your inclusion criteria. This is of utmost importance to address the heterogeneity of data in the literature as you previously stated.

Reply 13: We agree with your point of view. For tumours with the same pathological type and no lymph node metastases, we mainly base on CHA to determine whether they are multiple primary or not. As it is a retrospective study, there are some patients who have had molecular analysis and these patients can be evaluated based on molecular analysis. For patients who had not undergone molecular analysis, we assessed them based on CHA.

Changes in the text:5) two tumors from the same patient that had same histological types and no lymph node metastases, sMPLC was judged on the basis of molecular analysis or CHA. (see Page 8, line 150-152)

14. Page 4 line 140 – classifying patients according to lobar, sublobar anatomic, non-anatomic sub-lobar would be more accurate.

Reply 14: Thank you for your advice! We have changed the use of our surgical approach.

Changes in the text: All the patients included in our cohort underwent thoracic surgery, which consisted of lobectomy, sublobar anatomic, non-anatomic sub-lobar and pneumonectomy. Among these, both sublobar anatomic and non-anatomic sub-lobar are sublobar resections. (see Page 9, line 171-173)

15. Page 4 line 164 – specify version of R used.

Reply 15: We have added this element from the original

Changes in the text: The R statistical language was adopted for all of the calculations (version 4.3.1). (see Page 10, line 199)

16. Page 5 line 76 – the % of patients with adenocarcinomas – does this include patients with 3 or more tumors?

Reply 16: In our study, this refers to the percentage of patients whose primary and secondary tumours were both adenocarcinomas. We have refined this expression.

Changes in the text: Patients with both adenocarcinomas accounted for 75.2% and 76.5% of patients in the training and validation sets, respectively. (see Page 11, line 209)

17. Change accronym IM to IPM – stick to commonly used acronyms in the literature over

creating your own.

Reply 17: We have modified this expression

Changes in the text: intrapulmonary metastasis (IPM) (see Page 13, line 268)

18. Page 7 line 265 – how does the importance of lymph node staging support the importance of radical lobectomy over other surgical options?

Reply 18: In general, for solid tumors, radical lobectomy provides a more comprehensive assessment of lymph node status than other surgical approaches, which helps to stage the tumor more precisely so that the patient can benefit from postoperative adjuvant therapy. Sublobectomy, especially wedge resection, has limited sampling of lymph nodes, especially in groups 11 and 12. We therefore consider the importance of lymph node staging support the importance of radical lobectomy over other surgical options. In a number of other articles, we find similar views (e.g. *Development and Validation of a Nomogram for Predicting Survival in Patients With Resected Non - Small-Cell Lung Cancer*). In addition, there are many patients with more than 2 tumors located in the same lobe, and for these patients, lobectomy can maximize the evaluation of the pulmonary lymph nodes so that we can exclude some potential metastases.

19. Page 7 line 267- the literature you state does not support the use of one surgical resection method over another, based on the limitations you correctly identified. Soften language when making recommendations in cases where evidence is lacking. Second, it is necessary for the reader to know how many tumors these patients had, as mentioned above. From experience and recent literature, over 20% of patients with SMPLC have 3 or more tumors. There is no consensus or evidence regarding the surgical management of these patients. Paper would strongly benefit from detailing the limitations of the recommendations made by the authors' MDT.

Reply 19: For this study, more patients with pure solid lesions were included, so there may be some bias in the selection of surgical methods. In addition, our data analysis found that about 23% of patients in the L&L group had only one lung lobe removed because both lesions were located in the same lobe, which may lead to the conclusion that the prognosis of patients in the L&L group is better than that in the L&S group. Based on the above factors, we suggested the influence of tumor location on surgical methods in the discussion, and pointed out the limitations of this study

Changes in the text: Since more patients with pure solid lesions were included in this study, there may be some bias in the selection of surgical methods. Although the results of our paper favor lobectomy of the primary tumor in patients with SMPLC, the appropriate surgical approach should be selected after discussion of the patient's nodule using MDT in the clinic. ~~Thus, our MDT suggests that radical lobectomy of the primary lung tumor followed by selectable resection (lobectomy or sublobar resection) of the secondary lung tumors may be a more beneficial surgical approach for SPLC. Simultaneously, thorough LN dissection is recommended during each surgery.~~ (see Page 14, line 289)

20. Consider specifying why/if your study presents novel findings not addressed in the following study and others who have established nomograms. Song CK, Guo ZX, Shen XY, Wang YJ, Wang QW, Yu DH, Chen C, Liu XP, Huang JY, Li S, Hu W. Prognostic Factors Analysis and Nomogram Construction of Dual Primary Lung Cancer: A Population Study. Biomed Res Int. 2020 Feb 19;2020:7206591. doi: 10.1155/2020/7206591. PMID: 32149127;

PMCID: PMC7049836.

Reply 20: Thank you for sharing this article! After reading it, we believe that the following are the most important differences between us and it:

1. This article is based on the SEER database and does not describe the image characteristics of different tumor lesions
2. 88% of the patients in this article had heterochronous double primary cancer rather than simultaneous multiple primary lung cancer
3. Not all patients in this paper were surgical patients, so the impact of other treatments on prognosis was considered

In summary, due to the complexity and diversity of multi-primary lung cancer, and considering that it is difficult to analyze various types of multi-primary lung cancer together, we only discuss specific types of concurrent multi-primary lung cancer and put forward clinical recommendations.