The authors are to be congratulated for their excellent long-term results in these challenging cases. I believe however there are some issues which reduce the meritorious nature of this report.

1. The manuscript would benefit from utilizing current pathology terminology including the subtypes of "adenocarcinoma". Based on the very high survival rates in mainly nonsmoking patients, one would assume that most of the "adenocarcinoma" cases fall under the category currently designated as "adenocarcinoma with lepidic growth" (previously known as bronchoalveolar carcinoma) which include adenocarcinoma in situ, and minimally invasive adenocarcinoma, and lepidic predominant adenocarcinoma. The authors found that "identical" histology from both lungs was independently predictive of improved survival. Was there a specific subtype of "identical" adenocarcinoma (or squamous cell) which was predominately responsible for this finding? Along these same lines, the number of patients with pure (or mainly) GGO lesions was not provided and perhaps the findings of improved survival after resection of bilateral nodules with similar pathology represent a surrogate for pure (or mainly) bilateral GGO lesions?

Reply 1: First and foremost, I would like to extend my sincere gratitude for your insightful comments. Given the numerous foci in multiple primary lung cancers, individual categorization was impractical. Thus, in our study, we grouped them under the general category of lung cancer, without conducting detailed statistical analyses based on lung adenocarcinoma's pathological subtypes. However, for identifying Synchronous Multiple Primary Lung Cancers (SMPLC), we did analyze each lesion in every case based on its pathological subtype.

We acknowledge this limitation and plan to focus on this aspect in future research. Specifically, we aim to continue studying BSMPLC patients with identical pathological subtypes, to better understand why they may exhibit a relatively better prognosis.

Regarding the pure GGO cases, a significant limitation was the absence of High-Resolution Computed Tomography (HRCT) scans in the early stages of our study at our hospital. This gap in data prevented us from accurately collecting specific imaging features of the lesions, hindering our ability to determine whether they were pure GGOs or not.

We appreciate your understanding of these constraints and are committed to addressing these gaps in our subsequent studies to enhance the comprehensiveness and validity of our findings.

2. It is not clear to me what type of surgical approach (complete or non-complete) the authors of this study are advocating for which type of neoplasms. As the authors suggest in the discussion section, patients with pure GGO lesions typically experience excellence survival even without surgery. A very high number of patients (24%) in this series did not have all nodules removed. (Of note: in the manuscript Table 3 seems to have the numbers of complete vs non-complete resections erroneously transposed as compared to patient numbers in survival curves #2 and #4). The overall survival for patients who did not have all nodules removed was almost statistically superior to patients who underwent complete resections. Here again, is this finding just a surrogate for a less invasive subtype of adenocarcinoma or GGO lesions in this series? Providing specific information regarding patients who did not have all nodules removed and still demonstrated excellent long-term survival would enhance the information contained in this manuscript. What was the definition of "recurrent free survival" as again 24% of patients had incomplete nodule removal to begin with? It appears that these patients were not considered to fall under the category of "recurrent disease" for the survival analyses. Shouldn't "disease free survival" analysis be more appropriate or at least provided?

Reply 2: Thank you for the reminder. We have revised Table 2 to correctly reflect the number of cases with and without the removal of all nodes (see the table 2). This correction is appreciated and was essential for the accuracy of our study.

In the study, we observed a slightly higher overall survival rate in patients who did not have all nodes removed compared to those who did, though this difference did not reach statistical significance (p=0.054). We suspect this may be attributable to selective bias. Additionally, the uncertain pathological nature of the remaining nodules poses a challenge, particularly as some patients did not undergo HRCT scanning in the early stages of the study at our hospital. Consequently, we lack detailed imaging data for this subset of patients.

Regarding recurrence-free survival, the inability to determine the pathological nature of residual nodules led us to define it as the absence of new nodules in the same lung lobe or no usual hilar or mediastinal lymph node metastases. We realize this definition was not explicitly stated in our initial text, leading to potential misunderstandings. Therefore, we have made the necessary clarifications in the revised manuscript (see Page 6, line 184).

Thank you again for your attention to these details, which has helped improve the quality and clarity of our work.
Changes in the text:

1. We have corrected the errors in Table 2.
2. We have reformulated the definition of recurrence-free survival in the paper (see Page 6, line 184).

3. The authors should provide numbers for each category of BSMPLE on Table I in this series.   Perhaps it would be meaningful to analyze these categories with respect to long-term survival as well. Patients were followed for very long-time intervals in this study. Did any patient(s) die from non-disease causes? Twelve patients were lost to follow which was as many patients as died of disease during follow up.   Accordingly, providing more information regarding the patients lost to follow up may be meaningful.

Reply 3: Thank you for your suggestion. We have now included the number of cases for each category in the text (see Page 4-5, line 122-129). This study featured an extended follow-up period, during which we primarily tracked each patient through phone calls and clinic visits. Throughout this period, 12 patients were lost to follow-up and 12 patients passed away due to disease progression. Notably, there were no recorded deaths related to causes other than the disease during the follow-up.

Changes in the text: we have increased the number of each category (see Page 4-5, line 122-129).

4. More minor issues: Providing overall patient numbers who underwent surgery for lung cancer and were screened for inclusion as well as providing SMPLE patient numbers who were excluded from analysis would be helpful to understand the "denominator" of the cases analyzed in this report.   Did patients with EGFR positive tumors and persistent nodules which were not surgical removed receive targeted therapy to explain the excellent survival in this group?

Reply 4: Following your suggestion, we have now included in the text the total number of patients with NSCLC and SMPLC who underwent surgery at our hospital during the study period (see Page 4, line 116). Due to the inability to ascertain the pathological nature of residual nodules, and considering that EGFR status was determined based on the largest bilateral lesion, it's noteworthy that most patients with EGFR-positive residual nodules did not receive EGFR-Tyrosine Kinase Inhibitors (EGFR-TKIs) treatment. Furthermore, we did not quantify the number of EGFR-positive patients with residual nodules. In this study, we solely focused on comparing the overall survival rates of EGFR-positive versus EGFR-negative patients, which did not show a statistically significant difference ($p=0.057$).

Changes in the text: "A total of 17,389 patients with non-small cell lung cancer underwent

surgery at our hospital during this period, and 2,380 patients were diagnosed with SMPLC."

I have some comments and suggestions on the manuscript, and I thank the authors for reading and considering them.

1. Please specify why the ACCP recommendations for the surgical treatment of BSMPLC are debatable, as in your sentence in lines 51-53. Is there any publication justifying your statement?

Reply1: Thank you for your valuable feedback. We realize that our initial presentation may not have precisely conveyed the role of surgical treatment in patients with Multiple Primary Lung Cancer (MPLC). Our intention was not to question the primary role of surgery in the treatment of MPLC but to highlight that there are additional treatment options available, such as Stereotactic Ablative Radiotherapy (SABR) and local ablative therapy. We have amended the statement in the article to reflect this clarification (see Page 3, line 90-93). Your input has been instrumental in enhancing the accuracy of our discussion.

Changes in the text: We have amended the statement in the article (see Page 3, line 90-93).

2. Complete the information on preoperative diagnosis. Did you obtain a cyto-histological diagnosis in your cases before surgery? Or at surgery? If not, your recommendation on not resecting all nodules couldn't be supported, since many nodules could be benign ones.

Reply 2: Thank you for your valuable advice. In addressing the presence of residual nodules in patients with BSMPLC, we conducted a multidisciplinary discussion, involving experts in imaging, oncology, pathology, and radiotherapy, prior to surgery. We acknowledge that not all residual nodules were suspected of being malignant; some could indeed be benign, particularly as their small size precluded definitive pathological characterization.

In our treatment approach for BSMPLC, we independently evaluate each lesion to categorize them as high, intermediate, or low risk. Notably, all residual nodules in this study were classified as low risk. This finding supports our conclusion that in managing BSMPLC, after removing high and medium-risk nodules, careful consideration should be given to the patient's overall health and lung function. The aim is to avoid unnecessary lung function loss rather than pursuing the removal of all nodules, which may pose increased risks during surgical treatment for these patients.

3. Define the clinical and functional characteristics contraindicating surgical therapy. Your mean predicted postoperative FEV1% seems to be high in comparison to other published series of cases. This could be a relevant bias in case selection for surgical treatment.

Reply 3: In Table 1, the FEV1% values refer to those measured in patients with Bilateral Synchronous Multiple Primary Lung Cancer (BSMPLC) prior to their first surgery. Given that all participants in the study had bilateral lesions, a critical factor in determining their eligibility for surgery was their lung function capacity to withstand bilateral lung resections. This selection criterion may have introduced a selectivity bias, as patients with sufficient lung function were chosen for surgical treatment. We have addressed and elaborated on this potential bias in the Discussion section of our study.

4. Specify if cases were or not discussed at multidisciplinary meetings. Your results could be biased because of a highly selected for surgery population.

Reply 4: Yes, the patient group in our study underwent a comprehensive multidisciplinary evaluation, encompassing imaging, oncology, pathology, and radiotherapy, prior to undergoing surgery. Consequently, there is a potential for selection bias. We have addressed this aspect and discussed the limitations related to it in the discussion section of our study.

5. Overall survival is a quite relevant outcome indeed if death cause is known. In your series, low FEV1% is statistically correlated with low probability of OS. That could be because patients having respiratory comorbidity died because of that, not because of cancer. If you know death causes, you should conduct survival analysis with competing events. If not, you should discuss this problem in full.

Reply 5: Thank you for your suggestion, which we have indeed addressed in our paper (see Page12, line 368-375). According to our follow-up data, there were no instances of patient deaths attributable to respiratory comorbidities. However, it was observed that poorer lung function correlates with an increased risk of respiratory complications post-surgery. This aspect further emphasizes the importance of thoroughly evaluating lung function in patients undergoing surgical treatment for BSMPLC.

Changes in the text: we have indeed addressed in our paper (see Page12, line 368-375).

6. Your sentence in line 139 is non-understandable. You are comparing differences in survival distribution, not differences between variables.

Reply 6: Thank you for pointing out the need for greater precision in our wording. We have taken your reminder into consideration and accordingly revised the relevant sentence in the text (see Page 6, line 184-186).

Changes in the text: We have revised this sentence from the text (see Page 6, line 184-186).

7. In your statistical analysis, you must test the normality of the distribution of continuous variables to treat them with parametric or non-parametric tests. In fact, in lines 158 and Table 1 you are reporting median values, and I believe that mean and SD would be more correct.

Reply 7: Thank you for your suggestion, we have corrected the error (see Page 7, line 214-215).

Changes in the text: We have modified our text as advised (see Page 7, line 214-215).

The work is a priori interesting, but it contains key aspects that must be clarified:

• The high number of cases that presented SMPLC underwent bilateral lung resection is notable. It seems clear that this is a high-volume hospital. The authors do not report the total number of patients with NSCLC undergoing surgery in the same period of time. It would be interesting to know this information in order to have an estimate of the prevalence of SMPLC in the authors' casuistry.

Reply1: Thank you for your insightful suggestion. We have now included in the text the number of NSCLC patients who underwent surgery during this period, as well as the count of SMPLC patients (see Page 4, line 116-118).

Changes in the text: we have now included in the text the total number of patients with NSCLC and SMPLC who underwent surgery at our hospital during the study period (see Page 4, line 116-118).

• The pathological study includes a broad battery of biomarkers, yet PD-L1 is not analyzed. For what reason?

Reply 2: Given the extended duration of our study, PD1/PD-L1 expression was not assessed in some patients during the initial stages. Consequently, we did not include the count of patients with this biomarker in our analysis.

• Among the demographic characteristics of the population studied, the authors should have mentioned the race of the patients.

Reply 3: Thanks to your suggestion, we have added the ethnicity of these patients to the text (see Page 4, line 116).

Changes in the text: "These patients are of East Asian ethnicity."

• The authors have not included the determination of DLco in respiratory function studies; Do the authors carry out this determination in a protocolized manner in the study of patients who are candidates for surgery?The authors acknowledge as a limitation of the study: "Additionally, the exclusion of certain indicators like Forced Vital Capacity (FVC) and the FEV1/FVC ratio may have led to incomplete results." However, the DLco value is much more decisive as an indicator of functional capacity.

Reply 4: DLco is a crucial parameter in pulmonary function testing. Due to the extensive range of factors considered in our paper's univariate analyses, we had to make some omissions, including DLco. Recognizing its importance, we have now included the exclusion of DLco as a limitation in our study (see Page 14, line 423-424).

Changes in the text: "Additionally, the exclusion of certain indicators like Diffusing Capacity Of The Lungs For Carbon Monoxide (DLco), Forced Vital Capacity (FVC) and the FEV1/FVC ratio may have led to incomplete results."

• The authors report 568 surgical interventions in 293 patients, when it would be logical that there were 586 interventions. This is probably an erratum.

Reply 5: Thank you for highlighting the need for clarity in our text. Among the 293 patients in our study, 24 underwent simultaneous bilateral surgery and 269 underwent staged bilateral surgery. Additionally, 6 patients required a third surgery, amounting to a total of 568 surgical procedures.

• The authors report their results with periods of 5 and 10 years alternately. This can be confusing. They should refer the results to 5 and 10 years in all cases. All survival curves presented refer to 10 years.

Reply 6: Thank you for pointing out the need for greater clarity in our manuscript. We have specified in the text that the calculation of overall survival (OS) for the entire group was based on a 10-year period. This was done to assess the OS and recurrence-free survival (RFS) during the longest follow-up period. In other sections, we have made comparisons using a 5-year timeframe for consistency and detailed analysis.

• Another aspect that may be decisive is the use of adjuvant chemotherapy. The authors make absolutely no mention of adjuvant therapies. This is especially important when the work

concludes: "Removal of all nodules is not essential in the patient's long-term prognosis."

Reply 7: In our study, out of the 72 patients who had residual nodules, two underwent ablation while the remaining 70 did not receive any form of adjuvant therapy, as detailed in the text (see Page 8, line 228).

Changes in the text: In the text we have added the description (see Page 8, line 228).

• The authors, supported by their results, state in the Discussion: "our study revealed no statistically significant difference in OS and RFS between patients with N1 involvement and those without (N0), which could be attributed to the limited number of N1 cases in our dataset." However, in Highlight box, they state: "The prognosis of BSMPLC patients, including their overall survival (OS), was significantly correlated with the advanced pathological tumor-node-metastasis stage." The contradiction is evident, this statement in Highlight box is completely inconsistent with the results of the study.

Reply 8: Thank you for the reminder. It appears we may not have clearly conveyed our message in the Highlight box. We intended to indicate that it is already established in prior studies that the prognosis of BSMPLC patients correlates with the highest TNM stage. This point has now been accurately corrected and clarified in the text to reflect our intended meaning (see Page 16, line 472).

Changes in the text: "In previous studies it was found that the prognosis of BSMPLC patients, including their overall survival (OS), was significantly correlated with the advanced pathological tumor-node-metastasis stage."

Reviewer D

The topic is of interest for the magazine, being one of the articles with the highest number of cases on the issue. The title reflects the content of the article. The objectives and hypothesis are clear. The study is logically described and the inclusion and exclusion criteria are clearly defined. The statistical methods are suitable. Statistical significance is well-documented. The discussion is easy to read and understand. It compares its results with existing literature. However, in t a surgical study with a substantial number of cases, I miss a more detailed analysis of the results based on the type of sublobar resection: segmentectomy or wedge resection, which would be crucial in this type of article.

Reply 1: First and foremost, I would like to express my deep gratitude for the thorough review of our article. In our study, we exclusively included SMPLC patients who underwent bilateral surgical treatment. Considering the variability in surgical approaches between the two sides,

we categorized both segmental resection and wedge resection under the unified term 'sublobar resection' to simplify our statistical analysis.

congratulations for presenting a big series of 293 patients with bilateral SMPLC. Nevertheless I have some considerations:

1. Try to rewrite the abstract because results and conclusions are very similar.

Reply 1: Thank you for the suggestion, we have rewritten the abstract section (see Page1-2)

Changes in the text: The abstract of the article has been rewritten (see Page 1-2).

2. Keywords should include the word synchronous.

Reply 2: Thanks to your suggestion, we have added the keyword synchronous multiple primary lung cancer.

Changes in the text: Keyword section changed (see Page 4, line 76).

3. You did not include poor FEV1 as a exclusion criteria.

Reply 3: Thank you for your advice. In our retrospective study, we intentionally did not use poor FEV1 as an exclusion criterion to avoid selective bias, as excluding patients with poor FEV1 could have skewed our results.

4. Did you perform mediastinoscopy, EBUS or EUS in patients before surgery? I have not seen N1 or N2 as an exclusion criteria...

Reply 4: Thank you for the reminder. As our study was retrospective in nature, the staging was determined based on postoperative pathology. Consequently, we did not document whether patients underwent preoperative procedures such as mediastinoscopy, EBUS, or EUS. Regarding the exclusion of N2 patients, we specifically omitted those with bilateral pathology of the same type and mediastinal lymph node metastases. This exclusion was necessary as it was challenging to distinguish between SMPLC and metastatic disease in such cases.

Changes in the text: Patients with the same type of bilateral pathology and mediastinal lymph node metastases were excluded (see Page 5, line 135).

5. Please clarify in sublobar resections how many procedures where wedge resections and segmentectomies.

Reply 5: In our study, we exclusively included SMPLC patients who underwent bilateral surgical treatment. Considering the variability in surgical approaches between the two sides, we categorized both segmental resection and wedge resection under the unified term 'sublobar resection' to simplify our statistical analysis.

6. There are not patients with N2. Do yo have any explanation?

Reply 6: We excluded patients with N2 because the presence of patients with the same type of bilateral pathology and mediastinal lymph node metastases would have prevented us from determining whether they were SMPLC or not

7. Authors say that the presence or absence of total lesion excision did not exhibit a significant difference in OS. Can you give us the information about the number of residual nodules not operated? And can you tell us the size and the radiological characteristics?

Reply 7: Thank you for your valuable suggestions. In our current study, 72 patients were identified with residual nodules post-surgery. These cases were subjected to a preoperative multidisciplinary discussion involving oncology, pathology, radiotherapy, and imaging departments, where the nodules were collectively deemed as low-risk. Specific imaging characteristics of these residual nodules were not detailed in this study. However, we intend to monitor the progression of these nodules in future follow-up studies to derive more definitive conclusions.

<mark>Reviewer F</mark>

This paper is written quite well and the results are based on a very large series of cases even if it is a single center retrospective study. However, important data that I believe is necessary before thinking about publishing this paper is missing. The 10-year results that are well above average suggest that patients with indolent tumors or those with low biological growth and aggressiveness were treated. Were they all lung tumors with high percentage of GGO on CT scan? At least for the "dominant" tumor it would be appropriate to have the radiological picture in terms of percentage of GGO.

A total of 285 cases displayed identical bilateral pathology types, with bilateral lung adenocarcinoma emerging as the most prevalent (282 cases, 96.25%) while different bilateral pathological types were present in only 8 patients, making comparisons between these two groups unfeasible. Above all, there is no data on the subtypes of adenocarcinoma that have an

important prognostic role. All these data (percentage of GGO, subtypes of ADK...) are very important, otherwise it seems that the message of this paper is let's operate on all patients with multiple tumors because they are doing very well with surgery, when instead we know that solid bilateral synchronous tumors have a prognosis decidedly lower than that reported in this paper and an indication for much more selective surgery.

Reply 1: Thank you for your insightful advice. Due to the extensive duration of our study, some early-stage patients did not undergo High-Resolution Computed Tomography (HRCT) at our hospital, limiting our ability to obtain complete imaging characteristics for all patients' lesions. Consequently, we did not classify these lesions based on imaging findings. Notably, most cases in this study displayed consistent bilateral pathological types, with only a few exhibiting inconsistencies. This disparity raises the possibility of bias in comparing these groups, a point we have discussed in the paper. Additionally, while imaging characteristics and pathological subtypes are linked to patient prognosis. Given the numerous foci in multiple primary lung cancers, individual categorization was impractical. Thus, in our study, we grouped them under the general category of lung cancer, without conducting detailed statistical analyses based on lung adenocarcinoma's pathological subtypes. However, for identifying Synchronous Multiple Primary Lung Cancers (SMPLC), we did analyze each lesion in every case based on its pathological subtype. We acknowledge these limitations and plan to focus on these aspects in our subsequent research.

Reviewer G

In this study, the authors analyzed the prognostic factors affecting the outcome of patients with bilateral synchronous multiple primary lung cancer (BSMPLC) underwent surgical treatment, and reported some prognostic factors were associated with favorable prognosis. However, I have some serious concerns and comments listed below.

1. Methods and Results: The authors did not show their surgical strategy. Which lesion did they resect first? Because it might be necessary to change the resection method in the second surgery depending on the amount resected in the first surgery. This is my first serious concern. Therefore, they should show about their strategy in the Methods part. In addition, I thinkthey should show the order of resection amount by making the new figure or table.

Reply 1: Thank you very much for your advice. In our approach to treating patients with Multiple Primary Lung Cancer (MPLC), we recognize that the choice of surgical strategy varies significantly on an individual basis. This variability is largely due to differences in lesion location and each patient's unique physical condition, which is particularly complex when lesions are bilateral. Typically, our process begins with a multidisciplinary discussion, where we classify all lesions into high-risk, intermediate-risk, and low-risk categories. Based on this classification and the patient's specific condition, we then determine the most appropriate surgical approach.

2.Figure 1 and Table 3: The prognosis (10-year OS and DFS are 98.1% and 92.8%) was quite good in this study. In addition, 73.04% are female in sex, 96.25% are Ad-Ad in pathology and 71.33% are <2cm in largest tumor size, which might mean most of lesions could be small-sized early adenocarcinoma showing GGO containing tumor in CT. I think selection bias could affect the reliability of the data in this study even although they indicated in the limitation part. How about that?

Reply 2: The cases in our retrospective study predominantly involved female patients with small-diameter lung adenocarcinomas, which, as you rightly point out, could introduce selective bias. To mitigate this concern and obtain more robust findings, we are currently in the process of designing a randomized controlled study.

3.Table 6: Maybe I could understand they wanted to say that standard resection should be underwent for advanced lesion inpatients with BSMPLC. From their multivariate analysis, there was no preoperative oncological factor to determine which lesions are the most advanced cancers. For example, I believe SUVmax and clinical TNM staging could be indicators of malignant potential. But they did not show. How about this? How should we decide on priorities? This is also serious my concern. They should address.

Reply 3: The determination of the most appropriate surgical approach for patients with Multiple Primary Lung Cancer (MPLC), particularly those with bilateral lesions, remains a significant clinical challenge. Key issues include identifying which lesion most significantly impacts the patient's prognosis, accurately pinpointing the primary lesion, and assessing the risk level of multiple lesions. These are the critical areas we aim to address in our upcoming research. We are hopeful that our future study will provide valuable insights and solutions to these complex challenges in MPLC treatment

4. Figure 1 and Table 5: They analyzed just pathological factors such as plural invasion, pathological T/N factor, lymphovascular invasion (LVI) and others. We could not catch these information preoperatively. How should we do to decide the surgical method?

Reply 4: The selection of a surgical approach in MPLC cases cannot solely rely on the pathological features described, as this information is not available preoperatively. However, preoperative imaging does offer valuable insights. It allows us initially to determine the clinical TNM (cTNM) stage of the patients. Furthermore, preoperative pathological diagnosis and staging can be achieved through procedures like mediastinoscopy and Endobronchial Ultrasound (EBUS). These methods collectively contribute to making a more informed and rational decision regarding the surgical approach.

5.They did not show the details of recurrence pattern. They should show.

Reply 5: Thank you for the reminder about the recurrence, which is also explained in the article (see Page 10, line 295).

Changes in the text: We've added details of the recurrence (see Page 10, line 295).