**Peer Review File**
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**Reviewer A**

Abstract:

Comment 1- Results: total patients in cohort should be mentioned here.

Reply: This change has been made

Change in text: “Out of 227 patients presenting for lung cancer resection, 47 patients…”. Please see abstract, results, line 41.

Comment 2- Conclusion: not only radiographic, but also histopathological reports apparently?

Reply: We have edited this line.

Change in text: “radiographic and histopathologic staging”. Please see abstract, conclusion, line 51.

Key findings:

Comment 3- SMPLC "as assessed by the Martini and Melamed guidelines from 1975" should be added for clarification.

Reply: We have included this change

Change in text: “as assessed by the Modified Martini-Melamed criteria” as you suggested. However, the original Martini-Melamed criteria from 1975 has been continuously adjusted, most recent changes are reflected in the IASLC publication in 2016. Line 61.

Comment 4- one fifth of patients are presented with two or more lesions...

Reply: In a recent study we conducted, along with similar research, it was found that the occurrence of SMPLC can be as high as 20%. To put it differently, this means that one out of every five patients undergoing lung cancer resection may have SMPLC. It's important to note that this percentage doesn't encompass all patients presenting with two or more lesions, which would be implied if we were to use the term 'two or more' lesions.

Comment 5- patients with SMPLC are at risk of being incorrectly staged ... in this center

Reply: We have made this change.
Change in text: “Patients with SMPLC are at risk of being incorrectly staged in this center”. Line 65.

Introduction:

Comment 6- Martini et al. (1975), it is more clear to add the year after every reference mentioned in my opinion.

Reply: We have added the year after every reference mentioned throughout the manuscript.

Changes in text:
“Martini and Melamed (1975) were first to …”, line 74.
“According to a meta-analysis by Nie et al (2021) …” line 78.
“A large retrospective study (2023) of patients presenting for lung cancer …”, line 84.
“… reported as low as 0.5% by Zuin et al (2013)”, line 88.
“Our recently published (2020) incidence ….” line 179.
“Based on the IASLC database (2016)…”, line 187.
“This is strongly supported by a study by Finley et al (2010) …”, line 233.
“ … although the IASLC (2016) has published their recommendation.” line 243.

Comment 7- A little more information about what is known about this cohort would give the reader more insight into the necessity.

Reply: We have added a few lines to the Introduction, outlining the outcomes of patients with SMPLC, highlighting the importance of an accurate diagnosis and stage-based treatment.

Change in text: “When accurately diagnosed and managed, survival in patients with SMPLC is promising. According to a meta-analysis by Nie et al (2021), 5-year overall survival in patients with SMPLC is approximately 62%, a significant improvement from 5-year overall survival in patients with IPM (1). Thus, failure to recognize SMPLC among patients with multiple pulmonary lung cancers results in suboptimal staging which leads to inappropriate management and poor outcomes.

Change in text: The incidence of SMPLC has steadily risen (4). A large retrospective study (2023) of patients presenting for lung cancer resection reported a significant rise in the incidence of SMPLC, from 1.35% in 2015 to 15.4% in 2021 (2). In our latest study, we reported an incidence of 20.5% among a contemporary cohort of patients who underwent lung cancer resection (1). However, the incidence of SMPLC widely varies in the literature, reported as low as 0.5% by Zuin et al (2013) (3). We suspect that A lack of understanding, awareness, and application of diagnostic criteria likely results in

a lower reported incidence of SMPLC." Line 77 – 89.

Methods:

Comment 8- the authors assume that when two lesions have been identified and no lymph node involvement was found, that the patient has SMPLC. Later on, they state that Finley et al. found that 80% of an IPM cohort turned out to be SMPLC, which means that a 1 on 1 correlation between 2 lesions and SPMLC can also not be made.

Reply: You have a very good point, and we agree. That is why we use the strictly defined Martini-Melamed criteria. Cancer-specific survival data supports that these lesions are not IPM.

Comment 9- How were the lymph nodes assessed? How many lymph nodes were resected on average and how many HE-slices were made of them? Has possible error in the N-stage therewith been taken into account?

Reply: These variables are important and obviously can influence staging and outcomes. Nearly all patients underwent staging based on NCCN guidelines including but limited to preoperative invasive mediastinal staging. All surgical patients underwent lymph node sampling or lymphadenectomy based on surgeon preference intraoperatively. We don't have control over the number of HE slices, and it varies depending on the pathologist. We spoke to the pathologists, and some say they have a standard and others say they do not have a standard of slices.

Our previously published CSS data suggests that we are fairly accurate in nodal staging but I'm sure we are not perfect. We have modified our results section to provide more information on lymph node assessment to the readership.

Change in text: "All patients were staged according to the National Comprehensive Cancer Network (NCCN) guidelines (4), including but not limited to preoperative invasive mediastinal staging and intraoperative lymph node sampling or lymphadenectomy." Line118-122.

Comment 10- The used criteria are somewhat old and new diagnostic measurement tools have become available in most academic centers. Consider exploring molecular analysis or clonal comparison to evaluate whether the Martini and Melamed criteria are still valid to determine whether or not SMPLC is as big a problem as stated here. Most academic centers use these techniques and will distinguish between IPM and SMPLC when a patient with two lesions is presented.

Reply: We use Next-generation sequencing (NGS) as well and have added a paragraph to address the issue. See below. We would love to elaborate on this broad topic, but

unfortunately, even when we test metastatic tumors NGS is not always concordant in known metastases. We are hoping to stay on point without overelaborating since the purpose of the study is to report accuracy of preoperative staging.

While the original Martini-Melamed Criteria is old and rarely used, the modified Martini-Melamed Criteria is commonly used for diagnosing SMPLC. This new criterion was suggested in 2010 to include a comprehensive histologic assessment. This addition to the original Martini-Melamed Criteria has improved the accuracy of diagnosis SMPLC significantly better (Tian S et al. Differential Diagnostic Value of Histology in MPLC and IPM: A Systematic Review and Meta-Analysis. doi: 10.3389/fonc.2022.871827).

Change in text: "While next-generation sequencing technology shows potential for enhancing the detection of SMPLC (4), this approach is costly and is still in its early stages. Further, it has several limitations including frequent discordance (5) among tumors with the same histology and identical driver genes, recently reported in 7.5% of cases (2, 4). While continued efforts are necessary to determine the role of molecular analysis in the management of patients with multiple suspicious lung nodules, current endeavors should also focus on refining the existing approach for patients with multiple suspicious lung nodules until this technology becomes more widely available." Line 253 – 258.

Results:
Comment 11- Sentence in line 90-92 is the same twice.
Reply: Thank you for your careful review. We have removed the duplicate sentence.
Change in text: Line 147.

Comment 12- Is 2 primary tumors compared to a metastases always of a lower stage? Consider mentioning whether IPM or SMPLC was wrongly assumed.

Reply: You are correct it is not always a lower staged. We have added that both IPM and SMPLC can be diagnosed in error.

Change in text: "The fundamental problem is that having the same histology does not rule out SMPLC, nor does it guarantee IPM." Line 246.

Comment 13- Was molecular analysis or clonal comparison of tumor samples performed in any of the patients? Did this give a different result (IPM or SMPLC)?

Reply: We have added a paragraph regarding NGS in response to your comment. Please see above (line 253 – 258). Unfortunately, clarity and value of concordance and discordance is outside of the scope of this Preoperative staging Accuracy paper.

Comment 14- How are histopathological reports incorrect compared to clinical

assessment by a board or surgeon?

Reply: In short, bad pathology. One example is 1 cm bilateral adenocarcinomas with in situ disease which were labelled M1a. We have added a sentence to our discussion to clarify this point.

Change in text: "Histopathology reports, when incorrect, most often over-staged in 7 (87.5%) of 8 patients, by reporting T4, M1a, or 'likely metastatic disease' in the absence of positive intervening lymph nodes". Line 167 – 168.

Comment 15- How many patients had a different morphology in both tumors in the cohort mentioned?

Reply: We have included a sentence in the results to address your question.

Change in text: "Histologically distinct tumors were found in 38 (80.9%) patients, while the same histological subtype was found in 9 (19.1%)" line 137 – 140.

Comment 16- How many patients were considered to have SMPLC based on which of the 5 criteria?

Reply: In our results, we have now included this information to address your question.

Change in text: "Among the 47 patients with SMPLC, 12 (25.5%) had tumors with distinct histology (Criteria I), 26 (55.3%) had tumors of similar histology but with different histologic subtypes (Criteria II), 6 (12.8%) had tumors with similar histologic subtype in the same lobe, originating from separate foci (Criteria III), and 3 (6.4%) had tumors with similar histologic subtype in different lobes, without any intervening lymph node stations (Criteria IV)." Line 118 – 123.

Discussion:
Comment 17- How many radiologists and nuclear physicians were involved? Was there a difference in their assessment?

Reply: You make an excellent point; however, it is difficult to address this in the manuscript. We have 4 thoracic radiologists at our institution alone, however, more than 50% of cases have imaging from outside institutions. To further add complexity, some of our thoracic radiologists may occasionally read at outside institutions. Without going through it, I would imagine at least 20 different radiologists and nuclear physicians were involved. Yes, our radiologists are much more familiar with the SMPLC than their community counterparts. This is one of the reasons we wanted to explore this area.

Comment 18- PET/CT overall sensitivity and specificity for detecting one nodule or detecting lymph node metastasis is compared to detection of a second primary lung

cancer vs metastatic disease, which cannot be correlated one on one.

Reply: We do not entirely understand the question. We believe that in our manuscript, what we are trying to relay is that while there is data on single tumors, there are no data on SMPLC or even assumed IPM in the absence of distant metastasis. And we agree that we cannot correlate the speceficity/sensitivity of radiographic imaging for detecting one nodule "one on one", and we have not attempted to do so our manuscript.

Comment 19- Sentence in line 147-148 is wrong, should end with surgeons.

Reply: Thank you for your careful review. The sentence has been adjusted.

Change in text: "Only 21.3% of patients were incorrectly staged by surgeons." Line 215.

Comment 20- How many surgeons were involved in the staging of patients and was there a difference in how well the patients were staged by surgeon A, B, etc.?

Reply: Four surgeons were involved in the care of these patients. We would concede that patients are likely treated differently between all surgeons and their own tendencies. We have added to our results to address this point.

Change in text: "Overall, four surgeons were involved in the staging and treatment of patients with SMPLC." Line 161.

Comment 21- The authors call upon more awareness about SMPLC, but they also state that most overstaging pathology reports do mention the possibility of SMPLC, so you would say there is enough awareness.

Reply: You raise an excellent question: I don't think the problem is with the pathologists we work with, as we work with them quite frequently during our daily practice. The problem with awareness is with PCP, radiologist, oncologist, and surgeons undertreating and making the assumption that are M1a. This happens in our practice where we are asked, for example, to put a port-a-Cath in someone with metastatic lung cancer to find out that the patient does not have metastatic disease.

Comment 22- Can these results be correlated to other centers that use the same cohort (if that has been reported on)?

Reply: That is an excellent question. We believe that our results are generalizable to other centers, but it is ultimately it's up to the reader to decide. Practice varies widely from region to region, institution to institution and surgeon to surgeon. Our institution incorporates patients referred from hundreds of miles and over 2.5 million population.

We see this as a strength in the data and assessment as it relates to correlation. We also concede that others may perceive this as a weakness.

While our findings are undoubtedly constrained by the absence of a comparative analysis, we aim to encourage further research in this critical area to enhance the care provided to our patients.

Comment 23- Line 161, what is meant by relatively uncommon? Are they numbers known about the incidence of IPM vs SMPLC?

Reply: Yes, the percentage of SMPLC at our institution is published, which we have cited in this paper (~20% in Smith et al 2020). We do not know the incidence of IPM, but we believe that it has been historically overreported. Clinically we don't see a lot of IPM in the absence of extra thoracic disease and are actively pursuing research on this topic to address that issue. We have softened our language in the text.

Change in text: "Our data here supports that IPM may be relatively uncommon and pulmonary metastases in different lobes (T4 and M1a) even less common." Line 229-230.

Comment 24- How do biopsies create confusion? (line 172) You would suppose they add knowledge.

Reply: Thank you we have added to the paper to clarify that comment and we agree it's an important issue.

Change in text: "The fundamental problem is that having the same histology does not rule out SMPLC, nor does it guarantee IPM. Preoperative biopsies have several imitations. First, their sensitivity and specificity are not particularly high. Second, biopsy techniques often yield insufficient tissue, making it challenging or even impossible to differentiate histologic subtypes. Third, biopsies frequently fail to sample key tumor components, such as tumors arising from in situ disease. Ultimately, the major drawback of relying on biopsies in these patients is that having the same histology does not always entail the presence of IPM." Line 246-251.

Comment 25- It is true that tumors of the same histology do not equate to IPM, but they also do not equate to SMPLC as boldly as stated here. Let's say around 80% of NSCLC is AC and 80%*80% means at least 64% of patients with two lesions would receive two AC diagnosis; regardless whether it is a second primary or metastatic disease.

Reply: We agree – same histology does not always entail IPM, nor does it always entail SMPLC. We have softened our language to address this point.

Change in text: “The fundamental problem is that having the same histology does not rule out SMPLC, nor does it guarantee IPM.” Line 244-245.
Conclusion:
Comment 26- What would really be an add on here is when it would be mentioned how the surgeons base their staging and how the other disciplines can learn from their way of staging SMPLC.

Reply: We have added to our conclusion several recommendations regarding how healthcare professionals, including radiologists and pathologists can improve the accuracy of staging in patients with SMPLC.

Change in text: “Improving the accuracy of staging for patients with two or more suspicious lung nodules can be achieved by implementing a MDTB and raising awareness of SMPLC among healthcare professionals, including thoracic oncologists, primary care physicians, radiologists, pathologists, and thoracic surgeons. Radiologists are advised to report all suspicious nodules, rather than solely focusing on the primary high-index lesion, and to refrain from prematurely “labeling” lung nodules as malignant unless there is evidence of extrapulmonary metastasis.” Line 252-257.

**Reviewer B**

Tabrizi and colleagues describe the staging of patients scheduled for resection with post-resection determined Synchronous Multiple Primary Lung Cancer (SMPLC) from their institution in a 21-month retrospective cohort. The groups find a rather astounding 20% prevalence of SMPLC.

Comment 27. A number of methodological issues make this paper not ready for publication. First and foremost, bias by indication is a problem. You are reporting various imaging modalities with surgical/pathological modalities. A radiologist is not on the team and as such, the conservative directives used by the authors to determine SMPLC do not reflect standard of care for radiologist report, such that stating on nodule is likely cancer and the second or third may be cancer or could not be ruled out or simply mentioning it's location and size, especially if in the same lobe, leaves it to the proceduralist to determine it's importance and their operative plan.

Reply: Very good point but we don’t agree that a “proceduralist” determines the importance alone. Many mischaracterized patients never meet a surgeon and are simply referred to medical oncologists who may or may not be able to interpret images.

We do not use radiologist reports in making our determination of stage or therapy, but we believe many other physicians do. We wouldn’t argue regarding “the standard of care” but I think the medical oncologist would be surprised to hear it is not the standard of care. An incidence of 20% is astounding, which we have cited in our text. This increase is further supported by the IASCL data that is remarkable as well.

Here we have shown that even in those who are referred to thoracic surgery, inaccurate staging is not uncommon. We agree that bias by indication is a limitation. We are hoping to raise awareness and inspire more robust studies in the future to optimize the care of these patients.

Comment 28 - Nothing is mentioned about other pathological determination, like nav. bronch, which would also impart defining information and may enrich the population under study for incorrect imaging. Generally, the CT information is incomplete as is evidenced by almost 100% PET imaging per patient. Finally, the extent of resections and types of operation as well as reporting how the surgical plan had to be changed or failed (improper, post-hoc resection given post-surgical staging) and what may be driving those mistakes (missed N2) seeming more interesting and informative.

Reply: Yes, none of our patients had N2 disease. One patient staged as IIIA had N1 disease and tumors of different histology. We believe the absence of N2 disease demonstrates our strict adherence to NCCN staging criteria. The numerator of this study is patients resected with SMPLC. As we learn more, we can assess in a preoperative fashion and have an ongoing study doing this. We have added to our results information about staging and lymph node involvement as recommended by reviewer A.

Change in text: “All patients were staged according to the National Comprehensive Cancer Network (NCCN) guidelines (9), including but not limited to preoperative invasive mediastinal staging and intraoperative lymph node sampling or lymphadenectomy.” Line 124 – 127.

Change in text: “Of the 119 SMPLC, 6 (5.0%) had N1 disease and none had N2. Based on the highest pathologic stage of the tumor, 34 (72.3%) patients were diagnosed with stage IA disease, 7 (14.9%) patients had stage IIB disease, 4 (8.5%) patients had stage IB disease, 1 (2.1%) patient had stage IIA disease, and 1 (2.1%) patient had stage IIIA disease.” Line 140 – 143.

Comment 29 - Some significant issues: 47 patients with 113 SMPLC's were reported in the results but only 119 in the abstract.

Reply: Thank you for your thorough review. This was an error. 119 SMPLCs were discovered. The sentence in the abstract and main manuscript results have been edited.

Change in text: “Of these, 47 patients with 119 SMPLCs were identified”. Line 41 and line 118.

Comment 30 - No histology is reported or it's association with either SMPLC complexity or nodule distribution (size, location etc.).

Reply: That is an excellent point. We have added information regarding tumor distribution, nodule distribution, histology, and staging.
Changes in text:
Tumor distribution: “Ipsilateral tumors were found in 24 (51.1%) of 47 patients, of which 14 (58.3%) patients had tumors located in the same lobe and 10 (41.7%) patients had at least 1 tumor in a different lobe. Bilateral tumors were found in 23 (49.4%) patients”. Line 132 – 134.

Tumor histology: “Of 47 patients, at least one tumor was composed of adenocarcinoma in 40 (85.1%) patients, followed by squamous cell carcinoma in 10 (21.3%), carcinoid in 7 (14.9%), and large cell carcinoma in 2 (4.3%). Histologically distinct tumors were found in 38 (80.9%) patients, while the same histological subtype was found in 9 (19.1%)”. Line 136 – 139.

Nodal distribution: “Among the 47 patients, 36 (76.6%) had no nodal involvement. Five (10.6%) patients had N1 disease and in 6 (12.8%) patients, regional lymph nodes could not be ascertained”. 140-141.

Staging of patients as a representative of tumor size and nodal status: “Based on the highest pathologic stage of the tumor, 34 patients (72.3%) were diagnosed with stage IA disease, 7 patients (14.9%) had stage IIB disease, 4 patients (8.5%) had stage IB disease, 1 patient (2.1%) had stage IIA disease, and 1 patient (2.1%) had stage IIIA disease.” Line 141 – 143.

Comment 31 - CT is reported and greatly inflates the results. Nothing is reported on lymphademopathy or other likely FDG-PET/imaging related

Reply: Thank you. We have added pathologic lymphadenopathy in the manuscript. Additionally, we would like to point out that this cohort consists of a surgically treated group of patients. We hope it’s clear that if a patient is referred with two malignant nodules and N2 disease they are not going to the OR. Those patients were staged appropriately with invasive mediastinal staging and treated non-surgically and therefore not reported here.

Change in text: “Of the 119 SMPLC, 6 (5.0%) had N1 disease and none had N2”. Line 140.

**Reviewer C**

Strengths:

Comment 32 - Topic Relevance: The accurate identification of Synchronous Multiple Primary Lung Cancer (SMPLC) is crucial for treatment and prognosis. Addressing the accuracy of its detection is fundamental.

Reply: Thank you for your thorough review.
Comment 33 - Study Design: The retrospective review is appropriate for this kind of research. As long as data is collected rigorously and consistently, this methodology can provide valuable insights. Use of Modified Martini-Melamed Criteria: This criterion is a classic tool for the identification of SMPLC.

Reply: Thank you. Each patient was thoroughly reviewed by at least 2 thoracic surgeons to ensure accurate adoption of the modified martini-melamed criteria.

Comment 34 - Comprehensive Comparison: The study isn't limited to just one diagnostic modality but looks into CT, PET-CT, surgeon's clinical evaluation, and histopathological reports, providing a more comprehensive picture of the diagnostic scenario. Detailed Description of Results: The differentiation between under-staging and over-staging in CT and PET-CT reports is valuable.

Reply: We are glad you enjoyed our work.

Weaknesses:

Comment 35 - Sample Size: With 47 patients identified with SMPLC, the sample size is relatively small. This could limit the generalizability of the results. Short Study Period: The study spans just over a year. A longer period might have provided a larger sample and potentially more robust findings.

Reply: We agree. We believe that perioperative staging accuracy in patients presenting with multiple lung nodules is best carried out with a prospective multi-institutional study to improve generalizability, include all patients with multiple lung nodules (IPM and SMPLC), utilize molecular analysis, and demonstrate long-term survival data. We hope that our findings inspire more robust and large studies in the future.

Comment 36 - Lack of Contextual Information: While the paper points out there are inaccuracies in staging, there's no information provided on the clinical consequences of these mistakes. Did they result in inappropriate treatments or adverse outcomes?

Reply: We believe patients are frequently labelled as stage 4 and treated with chemotherapy or now targeted therapies without the intention of cure.

We hypothesize that patients with multiple lung nodules, and preoperative CT/PET-CT indicating “evidence of metastatic disease”, may not be referred to thoracic surgeons. This cohort of patients may be wrongfully referred to thoracic oncology who may rely on CT/PET-CT findings. Unfortunately, it is difficult to study the patient population that is never referred to thoracic surgeons. However, we have shown here that even in those who are referred to thoracic surgery, inaccurate staging is not uncommon. Further

studies are warranted to understand the role of radiographic staging in patients with multiple nodules.
This is stated in the discussion “One critical limitation that holds significance for future investigations is the fate of those who undergo staging but aren’t subsequently referred to surgeons. The findings presented in this study only pertain to patients who have been referred to thoracic surgeons at a tertiary referral center. Certainly, there are additional patients with SMPLC who receive treatment based on radiographic assessments only that incorrectly stage them as having IPM and referred elsewhere.” Line 269 – 276.

Comment 37 - Limitation in Approach: Even though the focus is on staging accuracy, it might be useful to consider other factors that could influence accuracy, such as the experience of the radiologist, the equipment used, etc.

Reply: We agree that staging accuracy is multifactorial and have added a sentence to our conclusion to reflect this point. We believe that imaging systems are at this point in our community not particularly variable. We have added the below sentence thank you.

Change in text: “The high prevalence of under-staging by preoperative imaging is a cause for concern and may be attributed to the radiologists' emphasis on the primary nodule in question, which may be further influenced by their education and experience with lung cancer.” Line 281.

Conclusion:
Comment 38 - The study addresses a relevant topic and provides findings that could be of concern to the thoracic community. However, the mentioned weaknesses might limit the generalizability of the findings and their impact. It would be ideal to conduct additional studies with a larger sample and over an extended period to confirm and expand these findings. Also, analyzing the clinical consequences of staging errors would be valuable.

Reply: We agree and hope to inspire further investigation into the matter in the future.

**Reviewer D**

In this study, the authors investigated the rate of misdiagnosed cases of multiple synchronous primary lung cancers (MSPLC) at different level of work-up and surgical and pathological staging. This is a monocentric cohort of 47 patients with MSPLC. Apparently, all patients have been operated upon insofar as all of them have had a pathological staging. The authors used the modified Martini and Melamed criteria and follow the STROBE guidelines in analysing their cohort.

Reading this manuscript rises two main comments:

Comment 39 - I - The study is insufficiently informed on several points regarding:

First - The management of surgery and histological access for patients who had lung cancer in both lungs. Was one side surgically treated and the other one receiving surgical alternatives such as SBRT or radiofrequency ablation?

Reply: All SMPLC were surgically resected except for three patients. We have added to our results to address this point.

Change in text: “Three patients (6.4%) underwent surgical resection of at least 1 SMPLC but failed to undergo planned resection for subsequent tumors. Of these cases, 1 patient developed hypertensive crisis intraoperatively, thus the case was aborted. The remaining 2 patients denied subsequent contralateral surgical intervention and were included with intention to treat.” Line 170 – 173.

Comment 40 - Second - The accurate differences in pathological diagnoses between different primary lung cancers: ADC vs. SQC? ADC differing by their respective histologic grade (for instance one with lepedic features (gr I), another one with solid features (gr III)? And so on.

Reply: Yes, major histologic subtype was used to differentiate between same vs. different histology in patients with all adenocarcinomas (lepidic vs. mucinous) and all squamous cell carcinomas (keratinizing vs. non-keratinizing).

Comment 41- II - The use modified Martini Melamed criteria, with a first proposal dating 1974, is debatable in the molecular biology era. There are many reports suggesting that multiple pulmonary nodules, despite meeting classic criteria for intrapulmonary or hematogenous metastases, in fact, carry distinct mutations. Even more notable, a marked absence of shared mutations in individual patient tumors was demonstrated and instead assert that distinct lung tumors in the same individual are distinct MSPLC whatever the results of the work-up investigation and histologic features (see for instance Stiles BM, J Thorac Dis 2017;9(1): E87-E88). The lack of genetic profiling in the herein study limits any conclusion.

Reply: While genomic profiling is ideal, unfortunately this method of staging is not particularly well vetted for concordance and discordance. It will clearly play a role moving forward. We have added a paragraph to address your concerns. Thank you.

Change in text: “While next-generation sequencing technology shows potential for enhancing the detection of SMPLC (4), this approach is costly and is still in its early stages. Further, it has several limitations including frequent discordance (5) among tumors with the same histology and identical driver genes, recently reported in 7.5% of cases (15). While continued efforts are necessary to determine the role of molecular analysis in the management of patients with multiple suspicious lung nodules, current endeavors should also focus on refining the existing approach for patients with multiple suspicious lung nodules until this technology becomes more widely available.” Line

258 – 265.

**Reviewer E**

Comment 42- Overall, this is a well-written manuscript investigating an important clinical issue - the accurate staging of synchronous multiple primary lung cancers (SMPLC). The objective is clearly stated, the methods are appropriate, and the results support the conclusions. The discussion situates the findings in the context of prior literature and highlights the clinical implications. I have some suggestions to further strengthen the manuscript:

Reply: Thank you for your thorough review.

Introduction:
Comment 43 - The introduction effectively establishes the background and motivation for studying staging accuracy in SMPLC. To further enhance this section, consider citing recent epidemiologic data on the increasing incidence of SMPLC.

Reply: We have added more background information in the introduction.

Change in text: "The incidence of SMPLC has steadily risen (4). A large retrospective study (2023) of patients presenting for lung cancer resection reported a significant rise in the incidence of SMPLC, from 1.35% in 2015 to 15.4% in 2021 (2). In our latest study, we reported an incidence of 20.5% among a contemporary cohort of patients who underwent lung cancer resection (1). However, the incidence of SMPLC widely varies in the literature, reported as low as 0.5% by Zuin et al (2013) (3). We suspect that A lack of understanding, awareness, and application of diagnostic criteria likely results in a lower reported incidence of SMPLC." Line 77 – 90.

Methods:
Comment 44 - The methods are clearly described, allowing reproducibility. Using a multidisciplinary tumor board to definitively classify lesions as SMPLC or metastatic is a strength.
Provide a bit more detail on the criteria used to categorize the radiology, surgeon, and pathology reports as correct, under-staged, or over-staged. For instance, were specific imaging features or reporting terms evaluated? This will aid interpretation of the results.

Reply: We considered the report to be over-staged if there was any indication of metastatic disease. We have included the key terms in the methods.

Change in text: "under-staged if they failed to identify all suspicious or malignant nodules, or if they identified all nodules but incorrectly identified one or more nodules as "likely benign" or "not concerning for neoplasm/malignancy," and C) over-staged if all suspicious nodules were identified but incorrectly reported to be "concerning for

metastatic disease," "consistent with metastasis," or "likely metastatic." Line 103 – 106.

Results:
Comment 45 - The results are presented in a logical manner. The high rate of incorrect staging, particularly under-staging, is clinically concerning.
Reply: Thank you.

Discussion:
Comment 46 - The discussion provides good context for the results in relation to past studies on staging accuracy. The limitations are acknowledged.
Reply: Thank you.

Comment 47 - Consider expanding on the clinical implications and next steps. For example, how could staging accuracy be improved for SMPLC patients? What changes in evaluation or reporting could help address this issue?

Reply: We have added a paragraph in our discussion to provide our recommendations to improve the accuracy of staging in this patient cohort.

Change in text: "Improving the accuracy of staging for patients with two or more suspicious lung nodules can be achieved by implementing a MDTB and raising awareness of SMPLC among healthcare professionals, including thoracic oncologists, primary care physicians, radiologists, pathologists, and thoracic surgeons. Radiologists are advised to report all suspicious nodules, rather than solely focusing on the primary high-index lesion, and to refrain from prematurely "labeling" lung nodules as malignant unless there is evidence of extrapulmonary metastasis." Line 252 – 257.

Comment 48 - Overall this an interesting study addressing an important clinical problem. With minor revisions to further strengthen the presentation of methods and results, as well as expanding the clinical implications, this manuscript would make a valuable contribution to the thoracic surgery literature.

Reply: Thank you. We have made every effort to address these changes in the most recent version of the manuscript.