Peer Review File

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Reviewer A

This paper attempts to address our understanding of the clinicopathological features of SWI/SNF complex deficient pulmonary neoplasms, and potential prognostic implications.

Comment 1:
p4 line 25 - do the authors mean ten gene PCR "variant" detection? (Include variant)
Figure 1 - the term "variant" is preferred over "mutation" in the context of somatic DNA alterations in tumours. Please replace all instances of mutation with variant, in figure and legend. Consider changing the key to "variant present" "no variant present".
Reply 1: Thank you for your suggestion. We have modified our text as advised, replacing "mutation" with "variant" for better accuracy. (See Page 2 Line11, Line 14, Line20; Page 5 line 26, line 27; Page 6 line 19-21; Page 8 line 22, line 24; Page 9 line11, line22, line 26; Figure1, Supplementary Figure1, Supplementary Figure2, Supplementary Table3).
Changes in the text: Page 2 Line11, Line 14, Line20; Page 5 line 26, line 27; Page 6 line 19-21; Page 8 line 22, line 24; Page 9 line11, line22, line 26; Figure1, Supplementary Figure1, Supplementary Figure2, Supplementary Table3.

Comment 2:
Also, the figure key mentions that these are "driver mutated genes" - if the authors mean "driver variants", how were the variants curated for oncogenicity? e.g., to include only variants with an oncogenic function, as opposed to synonymous variants or variants of uncertain significance. This would need to be stated in the methods. A supplementary table listing all variants would be very useful.
Reply 2: Thank you for your valuable comment. We have revised the manuscript to clarify that the identified gene variants are those with potential clinical significance, rather than exclusively driver mutations. We have included a description in the methods section on how these variants were curated to include only those with potential implications for cancer progression, treatment response, or resistance, excluding synonymous variants and variants of uncertain significance. Additionally, we have provided a supplementary table listing all identified variants from the ten gene PCR detection(see Page 4 line 1-9, Supplementary Table 1, legend of Figure1,Supplementary Figure1, Supplementary Figure2 and Supplementary Table3).

Changes in the text: Page 4 line 1-9, Supplementary Table 1, legend of Figure1,Supplementary Figure1, Supplementary Figure2 and Supplementary Table3.

Comment 3:
p6 line 31 - include "those in" TP53.... mutations (variants) occur in genes, they are not genes.
Reply 3: Thank you for your suggestion. We have modified our text as advised: “our research indicates that common variants in SWI/SNF-d pulmonary neoplasms include those in TP53, STK11, CDKN2A, KRAS, APC, and EGFR, among others, with TP53 being the most prevalent.” (See Page 9 line 11-13)
Changes in the text：Page 9 line11-13.

Comment 4: p3 line 8 - pulmonary neoplasms WERE defined as....
Reply 4: Thank you for your suggestion. We have modified our text as advised:“SWI/SNF complex-deficient pulmonary neoplasms were defined as cases with deficient for immunoexpression in at least one of the four representative SWI/SNF complex subunits (ARID1A, SMARCA2, SMARCA4 and SMARCB1).” (See Page 3 line 13)
Changes in the text: Page 3 line 13.

Comment 5: p3 line 10 - what does this mean? "SWI/SNF-d pulmonary neoplasm was only cancer and the first primary cancer."? edit for clarity
Reply 5: Thank you for the suggestion. We have rewritten this section to make it clearer： “SWI/SNF-d pulmonary neoplasm was the only type of cancer observed and was identified as the first primary cancer in these patients.” (See Page 3 line 15-16)
Changes in the text: Page 3 line 15-16.

Comment 6: p4 line 23 - 31 cases were conducted NGS - edit for clarity
Reply 6:Thank you for the reminder.We have rewritten this section to make it clearer:"Of the 101 patients with SWI/SNF-d pulmonary neoplasms, Next-Generation Sequencing was performed on 31 cases, and ten gene (ALK /ROS1 /RET /EGFR /KRAS /NRAS /BRAF /HER2 /PIK3CA /MET) PCR detection was conducted on 18 cases (Figure 1)." (See Page 5 line 23-25)
Changes in the text: Page 5 line 23-25.

Comment 7: p5 line 10 onwards - e.g., for patients WHO received radiotherapy, etc.
Reply 7: Thank you for the reminder.We have rewritten this section to make it clearer:“As shown in Figure 3B, overall survival was significantly better for patients who received radiotherapy. The 3-year OS was 30.7% for those who did not receive radiotherapy, compared to 61.7% for those who did (p=0.012).”(see Page 6 line 26-28)

Changes in the text: Page 6 line 26-28.

Reviewer B

This is a well written manuscript describing clinical studies of SWI/SNF-d pulmonary neoplasms, although the manuscript has a few typos involving spaces and periods. The authors analyzed 101 SWI/SNF-d pulmonary neoplasms from 675 SWI/SNF-d cancer patients. They found that immunotherapy improved 3-year OS rates from 20.8% to 68.4%, but KRAS-mutated patients on immunotherapy showed a lower 1-year survival rate. Radiotherapy increased 3-year OS rates to 61.7% from 30.7%. Of 38 patients treated with immunotherapy, 16 benefited from radiotherapy (median OS 31.4 months vs NE), with an average 17.2 days between radiotherapy and immunotherapy.

Comment 1: These findings are interesting. However, this reviewer has some relevant questions which are not addressed by the authors. For example, what is the benefit of identifying mutations in SWI/SNF? The data seem to show that cancers with these mutations are more susceptible to immunotherapy and/or radiotherapy than other types of lung cancers. If so, the authors may explain it more clearly. As SWI/SNF mutations are not common, it would be useful to justify the identification of such uncommon mutations for clinical applications.

Reply 1: Thank you for your insightful comments. We have revised the manuscript to more clearly explain the benefits of identifying SWI/SNF deficiency. Specifically, we have highlighted those cancers with SWI/SNF deficiencies are more susceptible to immunotherapy and/or radiotherapy in comparison with other treatment, which can help develop more effective personalized treatment plans and improve patient outcomes for these specific patients' group. Additionally, identifying this deficiency provides valuable data for future research, contributing to a better understanding of their roles and mechanisms in different populations and cancer types. We believe these revisions address your concerns and strengthen our discussion.(see Page 8 line 13-18, Page 11 line 17-20)

Changes in the text: Page 8 line 13-18, Page 11 line 17-20.

Comment 2: The discussion on page 7 about the molecular mechanisms involving interferon signaling and endogenous retrovirus are too speculative. The effect of radiotherapy on enhancing immunotherapy efficacy has been previously shown, and those studies should be included in the discussion instead.

Reply 2: Thank you for your insightful comments. We have revised the manuscript to address your concerns. Specifically, we have removed the speculative discussion on interferon signaling and endogenous retroviruses and have included more references to existing studies that demonstrate the effect of radiotherapy on enhancing immunotherapy efficacy. We believe these changes have strengthened our discussion and made our conclusions more robust. (See Page 10 line 10-25)
Changes in the text: Page 10 line 10-25.

Comment 3: The statement "These findings highlight the SWI/SNF complex's crucial role in modulating T cell activation and exhaustion, …" is not supported by the data shown in this manuscript and should be deleted, revised, or toned down.
Reply 3: Thank you for the suggestion. We have revised this section to tone down the statement and better reflect our research data. The revised paragraph is as follows: "While our findings do not directly demonstrate the SWI/SNF complex's role in modulating immune responses, the observed better responses to immunotherapy in patients with SWI/SNF deficiencies suggest that more research is needed."(see Page 9 line 7-10)
Changes in the text: Page 9 line 7-10.