Peer Review File
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Reviewer A

The authors have submitted a comprehensive review of PSC, a rare malignant subtype of lung cancer. The content covers both basic and clinical aspects and will be of interest to many readers. The reviewers recommend that the authors revise the following points:
1. The PSCs have both epithelial and sarcomatoid components, presumably arising from the original carcinoma; which component is more responsible for the "malignancy" of the PSCs? Does its predominance vary with progression, e.g., after metastasis? Is the predominance of each component associated with prognosis and treatment response?
2. Genetic characteristics should be discussed in comparison to NSCLC in general. Instead of just stating the frequency of each genetic mutation, a comparison table should be created.
3. What about mutation signatures, which would be useful in elucidating the etiology of PSC?
4. The reviewer feels that a comparison table with NSCLC in general is also necessary to understand the current status and efficiency of clinical treatment. The descriptive nature of the text may make it difficult for basic researchers to understand the therapeutic characteristics of PSC.

Reply:
We greatly appreciate your professional review of our article. Your insightful feedback has helped us identify several points that require attention. Based on your valuable suggestions, we have made revisions to our previous draft. Below, we outline the detailed corrections that have been implemented.

Comment 1: The PSCs have both epithelial and sarcomatoid components, presumably arising from the original carcinoma; which component is more responsible for the "malignancy" of the PSCs? Does its predominance vary with progression, e.g., after metastasis? Is the predominance of each component associated with prognosis and treatment response?
Reply 1: We believe that sarcomatoid components are more responsible for the "malignancy" of PSC. Database research indicates that the metastasis in patients with spindle cell and giant cell carcinoma is higher than in patients with pleomorphic carcinoma. The former two are mainly composed of sarcomatoid tumor cells, while the

latter contains more epithelial components, which may suggest a correlation between sarcomatoid components and metastasis [1]. However, other studies show that epithelial components are more enriched in metastatic lesions of carcinosarcoma and pleomorphic carcinoma patients [2]. The dynamic changes in different components between metastatic and primary lesions still require exploration with larger sample sizes. EMT is associated with chemotherapy resistance, as confirmed in other lung cancers [3]. There are a large number of sarcomatoid tumor cells with EMT processes in PSC, which may be related to chemotherapy resistance. Multivariate analysis also suggests that the sarcomatoid histological subtype is the only factor associated with early PD in first-line chemotherapy patients [4].

Comment 2: Genetic characteristics should be discussed in comparison to NSCLC in general. Instead of just stating the frequency of each genetic mutation, a comparison table should be created.

Reply 2: We have created a bar chart to visually compare the frequency of different gene mutations between PSC and NSCLC, making it easier for readers to understand and compare.

Change in the text：We have modified our text as advised (see Page 24, lines 613-620)

Comment 3: What about mutation signatures, which would be useful in elucidating the etiology of PSC?

Reply 3: P53R2, as a downstream target gene of TP53, plays an important role in tumorigenesis, DNA damage repair, and maintenance of genomic stability[5]. Immunohistochemistry indicates that the expression of P53R2 is mainly located in the cytoplasm of PSC tumor cells. The study suggests that its lack of transportation to the nucleus to participate in DNA repair may be the cause of tumorigenesis, but this is only a speculation. At present, there is no study to clearly elucidate the correlation between PSC mutation characteristics and pathogenesis.

Comment 4: The reviewer feels that a comparison table with NSCLC in general is also necessary to understand the current status and efficiency of clinical treatment. The descriptive nature of the text may make it difficult for basic researchers to understand the therapeutic characteristics of PSC.

Reply 4: We greatly appreciate your feedback. However, since the efficacy comparison of some treatment strategies has not been reported, and the study design or evaluation criteria for assessing the efficacy of different treatment strategies for PSC vary, we have added a more detailed summary of the comparison of efficacy between the two in the main text. We have also modified Figure 2 to include the current clinical treatment logic for PSC and the effectiveness assessment of different treatment modalities.

Change in the text：We have modified our text as advised (see Page 13, lines 346-347; Page 14, lines 379-381; Page 17, lines 439-441; Page 18, lines 459-461; Page 25, lines 623-628)

Reference：

1. Xiao, C., et al., Clinicopathological features and prognostic analysis of metastatic pulmonary sarcomatoid carcinoma: a SEER analysis. J Thorac Dis, 2021. 13(2): p. 893-905.
2. Pelosi, G., et al., Review article: pulmonary sarcomatoid carcinomas: a practical overview. Int J Surg Pathol, 2010. 18(2): p. 103-20.
3. Debaugnies, M., et al., RHOJ controls EMT-associated resistance to chemotherapy. Nature, 2023. 616(7955): p. 168-175.
4. Giroux Leprieur, E., et al., Clinical and molecular features in patients with advanced non-small-cell lung carcinoma refractory to first-line platinum-based chemotherapy. Lung Cancer, 2013. 79(2): p. 167-72.
5. Zhang, K., et al., p53R2 inhibits the proliferation of human cancer cells in association with cell-cycle arrest. Mol Cancer Ther, 2011. 10(2): p. 269-78.

Reviewer B

This is a comprehensive and very well-written review on the subject. Optionally the authors could consider to add a Figure (or modify Figure 2) in order to show a therapeutic algorithm for the treatment of these patients (e.g. mutation-positive -> TKI, otherwise CHT-IO etc)

Reply:

We feel great thanks for your professional review work on our article. According to your nice suggestion, we have made corrections to our previous draft, the detailed corrections are listed below.

Comment 1: This is a comprehensive and very well-written review on the subject. Optionally the authors could consider to add a Figure (or modify Figure 2) in order to show a therapeutic algorithm for the treatment of these patients (e.g. mutation-positive -> TKI, otherwise CHT-IO etc)

Reply 1: We have revised Figure 2 according to your suggestions, incorporating the current clinical treatment logic for PSC and assessments of the effectiveness of different treatment modalities, to facilitate readers' understanding.

Change in the text：We have modified our text as advised (see Page 25, lines 623-628)