Peer Review File

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Reviewer A

Q1: The definition of MPLC is not given (page 12, line 225), which may confuse the reader. Is msPLC included in MPLC? In this study, the definition of msPSC is given (page 5, line 80-84), but it was difficult to understand the relationship between this and the MPLC proposed by Martini and ACCP (page 12, line 222-228). I would appreciate it if you could revise this as clearly as possible.

A1: Thank you for your rigorous attitude. In this study, all recruited msPSC patients were those with previously resected PSC. According to the current technical condition, it is difficult to distinguish the tumor clonality of the second lung cancer as primary lung cancer or metastatic lung cancer. The aim is to establish a prognositc model for prognostic prediction and treatment decision making, in the premise of suspending the dispute of tumor clonality. In another words, although we have established a prognostic model for those msPSC, we are still unable to answer who is primary lung cancer and who is metastatic lung cancer.

Q2: In this study, the main objective is to analyze OS2. To make it easier to understand the purpose of this study, it is better to declare this in the methods section (page 6, line 100-103 in “revised manuscript without trace”).

A2: Thank you for your kind suggestion! The manuscript has been modified according to your advice. (page 8, the last sentence in “revised manuscript without trace”)

Q3: The number of events is not shown (results, table 2), which makes it difficult to interpret the results.

A2: Thank you for your kind suggestion! The number of event has been added into Table 2.

Q4: When considering Interval survival, the time of first surgery is the start of the period (table 2). From this point of view, Node metastasis (2nd) is a future event and should not be added as a factor. Similarly, in the analysis of OS1, I think that tumor diameter (2nd), node metastasis (2nd), and extrapulmonary metastasis (2nd) should not be added as factors. It is difficult to interpret the results when these are added. Rather, I recommend indicating the values of the tumor diameter (1st), and node metastasis (1st), surgery (1st), and etc. even if the univariate P values are greater than 0.1.

A4: Thank you for your kind advice! Exactly, data analysis in a more rigorous logical manner would generate a more reliable result. According to your suggestion, node metastasis (2nd) is excluded in the analysis of interval survival; tumor diameter (2nd), node metastasis (2nd), and extrapulmonary metastasis (2nd) are excluded in the analysis of OS1. Besides, according to your suggestion, tumor diameter (1st), node metastasis (1st), and surgery (1st) were included in mulvariate analysis for OS1. However, all these parameter still missed significance after adjusting for other confounders. (Table 2) (page 11, line 4-19, and page 9, line 13-15 in “revised manuscript without trace”)

Reviewer B

Q1: What did the “interval survival mean? Please show the definition of interval survival. Did the authors mean “interval period” between initial lung cancer and second primary lung cancer?

A1: Thank you for your kind suggestion! In this study, overall survival (OS1) means the time duration between surgery date of first PSC and last follow-up or death; overall survival 2 (OS2) means the time duration between treatment date of msPSC and last follow-up or death. Interval survival is defined as OS1 minus OS2, which indicated as the time duration between surgery date of first PSC and treatment date of msPSC. (page 8, line 17-22 in “revised manuscript without trace”)

A2: Why did the authors include the patients who underwent pneumonectomy for initial lung cancer? It should be tough to perform surgery for this population.

Q2: Thank you for your rigorous attitude. Honestly, metachronous surgery for metachronous lung cancer is rarely performed for patients who have received pneumonectomy previously due to the limited lung function. However, in this study, the treatment of metachronous lung cancer involved surgery, chemotherapy and radiotherapy. This is decided by the aim of this study, which is to establish a prognostic model for msPSC to facilitate prognostic prediction and treatment decision making. I have to acknowledge that, patients who underwent pneumonectomy would encounter a more limited performance score than others, and this would further impact the prognosis. It is plausible that, the prognostic model, which involved these unavoidable cases in real world, would generate a more general clinical implication.

A3: Generally, the field cancerization theory is well known. Did the authors analyze the history of extra-pulmonary malignancy in this population?

Q3: Thank you for your rigorous attitude! In this study, we did not analyze the history of extra-pulmonary malignancy due to the limited information of SEER

database. According to your kind suggestion, we have initiated a multi-center real world analysis to validate our results and have considered field cancerization of extra-pulmonary as an important record in the data collection and database construction.

A4: Also, the information on ceasing smoking or continuing smoking after initial lung cancer should also be examined. Recent research showed it affected survival.

Q4: Thank you for your rigorous attitude! In this study, we did not analyze the information on ceasing smoking due to the limited information of SEER database. According to your kind suggestion, we have initiated a multi-center real world analysis to validate our results and have considered smoking cessation as an important record in the data collection and database construction.

Q5: Again, it was unclear why did the authors exclude adenocarcinoma cases. For adenocarcinoma, it might be much easier to differentiate the second primary cancer or metastatic disease by histology.

A5: Thank you for your rigorous attitude! In this study, we only include patients with squamous cell carcinoma for two reasons. First, the biological behaviour of lung adenocarcinoma is significantly different from that of PSC, especially in recurrence/metastatic patterns and multiple nodule models. Second, for metachronous adenocarcinoma, it is easier to differentiate the second primary cancer or metastatic disease by histology. This is not consistent with the study design, since the aim of this study is to establish a prognositc model for prognostic prediction and treatment decision making, in the premise of suspending the dispute of tumor clonality.