Peer Review File

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Reviewer A

Comment 1: How were the patients categorized who developed MULTIPLE secondary pulmonary nodules?

Reply 1: Thank you for your kind suggestion! Under the current medical conditions, when the pathological type of metachronous second lung cancer is the same as the first one, it is hard to determine its origin (primary or metastatic lung cancer). Although assessment on several clinical parameters, including the location of the primary tumor and metastatic node, tumor diameter, histology, and cancer-free survival, have long been used to distinguish metachronous primary lung cancer (MPLC) from metastasis. However, these suggestions remain controversial owing to contradictory results reported by series of studies. This makes it difficult to obtain an accurate stage on a current staging system, and restrict the development of effective prognostication and appropriate treatment decision. Therefore, the purpose of this study is to establish a TNM-like risk stratification system in the premise of suspending the dispute of tumor clonality for metachronous second pulmonary adenocarcinoma (msPAD). Thus, categorization of tumor clonality is not the aim of this study.

Comment 2: How was the Grade of lung adenocarcinoma determined in non-surgical cases?

Reply 2: Thank you for your rigorous attitude! The purpose of this study is to establish a TNM-like risk stratification system in the premise of suspending the dispute of tumor clonality for metachronous second pulmonary adenocarcinoma (msPAD) patients with previously resected

PAD. With this purpose, only patients with previously resected PAD and encounter msPAD were included. Besides, this study is performed on a public medical database in the USA. The Grade information of non-surgical cases is extract from the database as well. I speculate that, for non-surgical cases, the grade information might be determined by needle biopsy. Thank you.

Comment 3: Is it appropriate to include the characteristics of the 2nd adenocarcinoma in the analysis of the interval survival? (Table 2)

Reply 3: Thank you for your careful attitude! In this study, we extracted overall survival 1 (OS1) for the primary, overall survival 2 (OS2) for the msPAD, and defined interval survival as the interval time between the first and second PAD. In our opinion, when the msPAD is found and treated in early stage, the interval survival is short; when the msPAD is found and treated in advanced stage, the interval survival is long. That is the reason why we include the characteristics of the 2nd adenocarcinoma in the analysis of the interval survival. (see modified manuscript, Page 13, line 14-17)

Comment 4: The factors in the risk classification system the author developed seem similar to the TNM system, given that the systems include tumor diameter, nodal status, and extrapulmonary metastasis. The only difference is the Grade. The authors should focus more on the validity to use the new classification rather than the TNM.

Reply 4: Thank you for your useful advice! Recently, many studies have established risk stratification on gene expression, which presenting excellent performance. Whereas, in the SEER database, these information is lacked. Therefore, we could not establish a risk stratification on various onco-gene. On the other hand, the TNM system is the most recognized

prognostication system. However, for patients with msPAD, because the tumor clonality is unclear, the TNM stage is unknown. Therefore, the purpose of this study is to establish a TNM-like risk stratification system in the premise of suspending the dispute of tumor clonality. With this purpose, the judgement criteria of the TNM stage is modified as follows. For tumor, only tumor diameter is included. For node, N2 and N3 status were combined. For distant metastasis, only extrathoracic metastasis were included. Thank you.

Comment 5: Tentative risk stratification (Table 3) is determined by the information from the second lung adenocarcinoma only. Can the OS2 be determined without considering the characteristics of the first primary lung adenocarcinoma?

Reply 5: Thank you for your kind suggestion! Honestly speaking, the characteristics of the first primary PAD should impact the OS2, since it is involved in the OS1. Therefore, in the survival analysis of OS2, characteristics of the first primary lung cancer were involved. We found that, although the T status (1^{st}) present significant association with OS2 in the univariate analysis (P=0.045), however, it missed significance after adjusting other confounders in the multivariate analysis. Thus, the tentative risk stratification system was established on the characteristics of first primary lung cancer. For this phenomenon, there is two potential explanations. The first is that, the characteristics of the msPAD play an more important impact on OS2 than PAD. The second is that, the tumor clonality of the msPAD is still unclear, therefore its association with the first primary lung cancer is still unknown, which would greatly limit the impact of first primary lung cancer on OS2. (see modified manuscript, Page 13, line 17-22; Page 14, line 1-5)

In addition, the tentative risk stratification play well performance in

predicting OS2. The median survival after msPAD for category I, II, III, and IV was 88, 58, 32, and 12 months, respectively ($P < 0.001$) (Figure 3C). However, according to the extracted stage information, survival curves were overlapped as the long-term survival of cases with stage IV was similar to that of cases with stage II ($P = 0.308$) but better than that of cases with stage III ($P < 0.001$) (Figure 3D). The AIC value for the proposed risk classification was smaller than that for the applied staging system (5890.612 vs 6015.516). The c-index value was larger for the proposed version than for the applied staging system (0.656 vs 0.572, $P < 0.001$). Meanwhile, according to the time-dependent ROC curve, the predict accuracy of the proposed risk stratification system is better than the TNM stage system at 160 months of follow-up (Figure 3E).

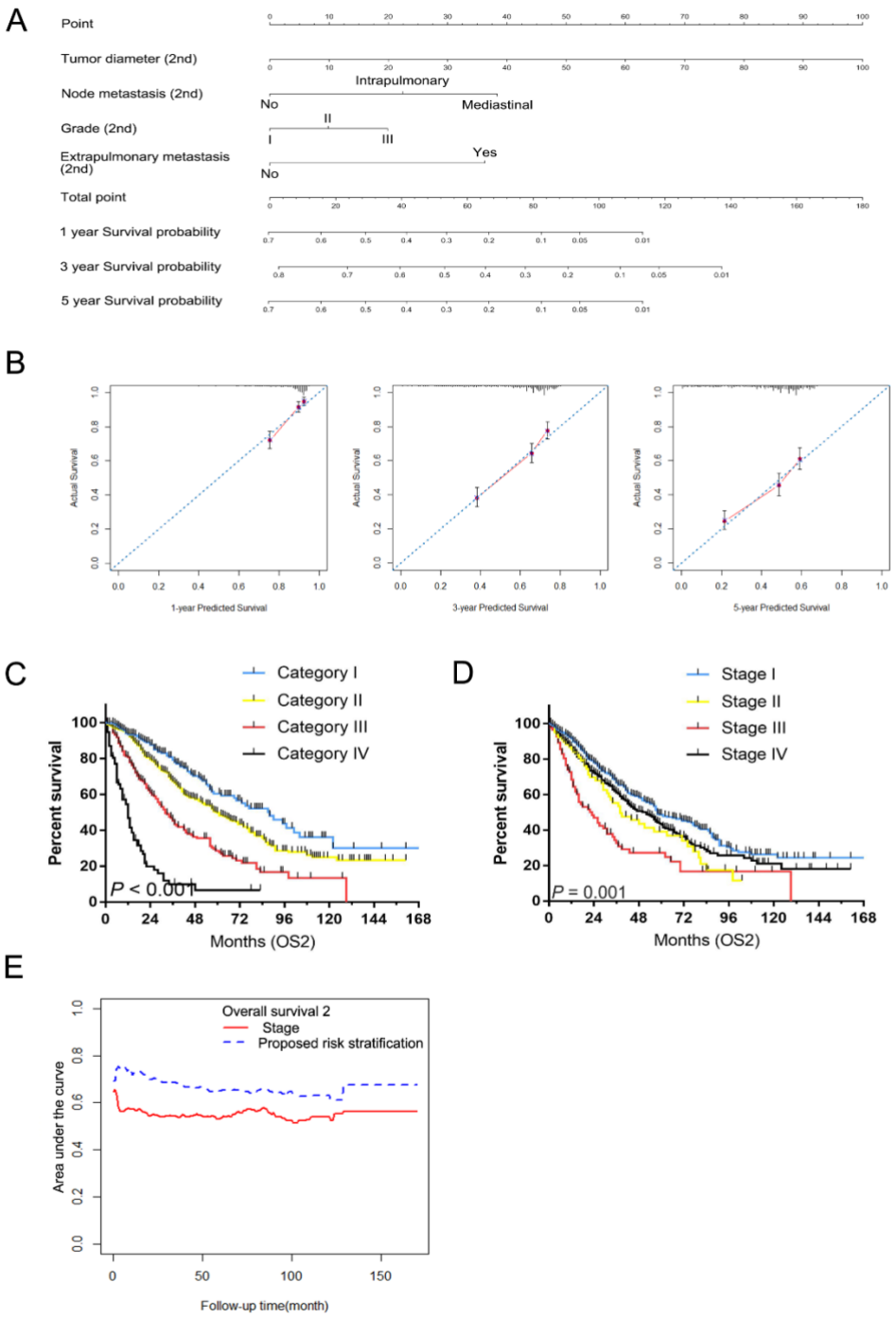

Figure 3.

Comment 6: Are any molecular biomarkers available in the analysis?

Reply 6: Thank you for your kind suggestion! This study is performed on

SEER database, which is a public medical database. There is no molecular biomarker information in the database. Thank you!

Reviewer B

The authors have presented a nomogram prognostication system and a risk stratification system for prognosis based on the patients who underwent surgery for first pulmonary adenocarcinoma and encountered metachronous second pulmonary adenocarcinoma (msPAD) from the SEER database. With the soaring incidence pulmonary adenocarcinoma, the number of patients diagnosed with msPAD is also rising. While surgery offers the best chance for potential cure of msPAD and provides the most sufficient samples for diagnosis, the prognosis of msPAD after surgery has not been studied in detail. In general, this manuscript is logical and interesting, and discussed a hot topic in pulmonary adenocarcinoma treatment. However, the following points should be addressed.

Comment 1: The authors defined msPAD as the second PAD which occurred after diagnosis of the first PAD. Patients with interval survival ≤ 1 month were excluded in this study. There are two subsets of patients with msPAD, referred to as synchronous and metachronous according to the time of occurrence of foci. How did the authors exclude synchronous second PAD? Was the interval survival ≤ 1 month acceptable for definition of msPAD worldwide?

Reply 1: Thank you for your kind suggestion! This is a very good question!

Until now, for msPAD, it is hard to distinguish the clonality. In this study, the purpose is to establish a TNM-like risk stratification system in the premise of suspending the dispute of tumor clonality for metachronous second pulmonary adenocarcinoma (msPAD). Therefore, the included msPAD involved second primary lung caner or second metastatic lung cancer. Diagnostic time window for metastatic lung cancer is 1 month. The most important evidence is that, the least recurrence-free survival of many studies on lung cancer is 1 month. That is the reason why we choose 1 month as the criteria.

Comment 2: In Table 2, independent prognostic factors such as tumor diameter (2nd), node metastasis (2nd) were identified for interval survival. The reviewer wondered whether information of 2nd tumor should not be included for analysis of independent prognostic factors for interval survival. Conversely, why did the authors not include the information of 1st tumor or interval survival as risk factors for analysis of independent prognostic factors for OS2?

Reply 2: Thank you for your careful attitude! In this study, we extracted overall survival 1 (OS1) for the primary, overall survival 2 (OS2) for the msPAD, and defined interval survival as the interval time between the first and second PAD. In our opinion, when the msPAD is found and treated in early stage, the interval survival is short; when the msPAD is found and

treated in advanced stage, the interval survival is long. That is the reason why we include the characteristics of the 2nd adenocarcinoma in the analysis of the interval survival.

Honestly speaking, the characteristics of the first primary PAD should impact the OS2, since it is involved in the OS1. Therefore, in the survival analysis of OS2, characteristics of the first primary lung cancer were involved. We found that, although the T status (1^{st}) present significant association with OS2 in the univariate analysis (P=0.045), however, it missed significance after adjusting other confounders in the multivariate analysis. Thus, the tentative risk stratification system was established on the characteristics of first primary lung cancer. For this phenomenon, there is two potential explanations. The first is that, the characteristics of the msPAD play an more important impact on OS2 than PAD. The second is that, the tumor clonality of the msPAD is still unclear, therefore its association with the first primary lung cancer is still unknown, which would greatly limit the impact of first primary lung cancer on OS2. (see modified manuscript, page 13, line 14-22; page 14, line 1-5)

Comment 3: We generally decide the treatment strategy for msPAD according to the clinical diagnosis of msPAD. It is the most important to distinguish msPAD between 2nd multiple primary lung cancer and intrapulmonary metastasis. Thus the information of 1st PAD such as stage

and presence of GGO in chest CT has a impact on decision making as well as prognosis after treatment for 2nd msPAD. While the authors established a TNM-like classification for msPAD using information of 2nd tumor, these issues should be discussed.

Reply 3: Thank you for your kind suggestion! We are strongly agreeing with your opinion. Most lung cancer with GGO in chest CT scan is primary lung cancer. Thus, this TNM-like risk stratification is not suitable for these patients. (see modified manuscript, page 14, line 20-22; page 15, line 1)

However, for those without GGO in chest CT scan, it is still hard to distinguish the tumor clonality. Although assessment on several clinical parameters, including the location of the primary tumor and metastatic node, tumor diameter, histology, and cancer-free survival, have long been used to distinguish metachronous primary lung cancer (MPLC) from metastasis. However, these suggestions remain controversial owing to contradictory results reported by series of studies. This makes it difficult to obtain an accurate stage on a current staging system, and restrict the development of effective prognostication and appropriate treatment decision. Therefore, establishing a TNM-like risk stratification system in the premise of suspending the dispute of tumor clonality for metachronous second pulmonary adenocarcinoma (msPAD) patients with previously resected PAD is still merit. (see modified manuscript, page 5, line 12-22)