

Peer review file

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Reviewer A

Comment 1. Because isolated organ metastasis could be single metastasis or multiple metastasis in a specific organ. Could author have a more clear definition of surgical treatment for isolated metastasis? Is there any difference between the surgical treatment for single isolated organ metastasis and multiple metastasis in a single organ? Because author had used 8th edition of lung cancer staging, I believe author could answer this question.

Reply 1: Thanks for the reviewer's comments to help us improve the first manuscript. The study mainly focused on the surgery in single-organ metastasis and multi-organ metastasis, and we added the definition of the classification of metastasis sites (see Page 5, line 87). However, the database cannot list how many metastatic lesions are in a single organ, which was the limitation of this study, so it is impossible to study the impact of the metastasis number. At present, the principal contradiction in the local treatment of stage IV lung cancer is whether to perform surgery. Meanwhile, the lack of information on the number of metastases led to no subdivision of surgical procedures in the SEER database. The primary tumor resection (PTR) mentioned in this paper includes sub-lobectomy, lobectomy, and pneumonectomy. We hope to have more comprehensive data or prospective studies for further analysis in the future.

Changes in the text: see Page 5, line 87 and Page 12, line 236.

Comment 2. Because there must have selection bias of patients receiving surgical treatment for advanced lung cancer either primary tumor resection or metastasectomy, author should use propensity score matching to exclude the selection bias for selection of these patients. (This should be done for patients receiving primary tumor resection and also for patients receiving brain surgery)

Reply 2: We appreciate the reviewer's suggestions. We divided the data into surgery and no-surgery groups and reanalyzed the data after 1:1 PSM to eliminate confounders (see Page 5, line 100 and table 2). We still found that the surgery group had better survival benefits (see figure 1). Before comparing whether different metastasis sites

should be operated on, we re-performed 1:4PSM (see supplementary table) for each metastasis site (PTR or MTR). We concluded that patients with lung metastasis and multiple metastases could benefit from PTR but not in MTR (see figure 3 and figure 4).

Changes in the text: see Page 5, line 100, table 2, and supplementary table 1-8.

Comment 3. Radiation therapy was also had survival benefit for advanced lung cancer. Could author identify which organ metastasis receiving radiotherapy could have survival benefit? Did radiation to the primary tumor also have survival benefit?

Reply 3: I am sorry that the first manuscript ignored the possible influence of radiotherapy on the analysis of the efficacy of the surgical intervention, because radiotherapy can partially replace surgery. Unfortunately, we were unable to determine whether radiotherapy was targeted at lung lesions or metastatic lesions and its specific purpose in the SEER database. In order to avoid the interference of radiotherapy in our study of surgical intervention for advanced lung adenocarcinoma, we excluded these patients.

Changes in the text: see Page 12, line 238.

Comment 4. Was there any survival difference if patient received primary tumor resection and radiation therapy for distant metastasis?

Reply 4: Thanks to reviewer for asking such insightful questions. As mentioned above, we were unable to determine whether radiotherapy was targeted at lung lesions or metastatic lesions and its specific purpose in the SEER database. In clinical practice, most brain metastases of lung cancer choose gamma knife treatment locally. To our knowledge, few studies focused on local treatment of primary tumor resection and radiation therapy. We hope more prospective clinical trials can be conducted in the future.

Changes in the text: see Page 12, line 238.

Comment 5. What is the true meaning of lymph nodes dissection affecting the survival of advanced lung cancer

Reply 5: Thanks for the reviewer's question. Lung cancer is prone to lymph node metastasis, especially for advanced lung adenocarcinoma. Therefore, we added a

prognostic analysis of lymph node dissection and found that surgery combined with lymph node dissection improved patients' OS and LCSS significantly (see figure 2).

Changes in the text: see Page 8, line 150, and figure 2.

Reviewer B

Comment 1. I would recommend that the authors explain any conceivable reason for the interesting results. The authors should add the interpretation of the following results (a. and b.) in the Discussion.

a. Our study found that PTR for isolated bone metastases, brain metastases, lung metastases, and MOM could prolong the survival time of patients. Moreover, the OS and LCSS of LUAD patients were higher than those of NS patients regardless of PTR, MTR, or PMTR (Lines 191-194).

b. In our study, significant benefits were observed in LUAD patients who underwent surgical resection of isolated brain metastases and MOM, but no survival benefits were observed in patients with isolated bone metastases and lung metastases (Lines 210-213).

Reply 1: We appreciate the reviewer's advice. We used PSM to eliminate confounding factors and reanalyzed the data. The conclusion was slightly different from the first manuscript, and we added our interpretation of the results. For example, we found that surgical interventions for patients with LUM and MOM could prolong survival time to a certain extent. These results may be related to the reduction of tumor burden in patients with advanced LUAD by surgical intervention on the basis of comprehensive treatment. However, the effect was not significant for patients with BRM and BOM. Due to the small sample size and the possible confounding factors, prospective studies should be conducted in the future. Patients with LUM, BOM, or MOM did not benefit from MTR in our research. We believe that surgical intervention for metastases without resection of the primary tumor cannot fundamentally reduce the tumor burden of patients, nor can the potential risk of metastasis and recurrence be excluded. Therefore, MTR is not recommended for general use.

Changes in the text: see Page 10, line 189.

Comment 2. The authors suggested a survival benefit of some factors such as female, earlier T and N stage, receiving radiotherapy, chemotherapy, and lymph node resection. In previous reports, propensity score matching is performed to reduce potential selection bias from patient selection. Presentation of matching analysis could increase the value of this paper.

Reply 2: We appreciate the reviewer's suggestions. We divided the data into surgery and no-surgery groups and reanalyzed the data after 1:1 PSM to eliminate confounders (see Page 5, line 100 and table 2). We still found that the surgery group had better survival benefits (see figure 1). Before comparing whether different metastasis sites should be operated on, we re-performed 1:4PSM (see supplementary table) for each metastasis site (PTR or MTR). We concluded that patients with lung metastasis and multiple metastases could benefit from PTR but not in MTR (see figure 3 and figure 4).

Changes in the text: see Page 5, line 100, table 2, and supplementary table 1-8.

Reviewer C

Comment 1. For staging, SEER does not recommend intentionally changing the stage. This is because it is likely to be misclassified, and in fact some may have problems converting the 7th to the 8th edition unless they look at the pathology report. If only the 7th edition stage was performed, whether the tumor size was seen, or the tumor size was taken as the standard, the 8th edition was specifically based on the invasive size. How did you approach the problem?

Reply 1: Thanks to the reviewer's comments on the stage adjustment. We reclassified the T stage according to the eighth edition of the American Joint Committee on Cancer (AJCC) TMN stage based on the information of "CS Tumor size" and "CS Extension." The N stage of the eighth edition is consistent with that of the seventh edition. However, the database cannot list how many metastatic lesions are in a single organ, and the M stage was not subdivided. This method is the commonly used method for stage adjustment in the SEER data at present, thus ensuring the accuracy of stage adjustment.

Changes in the text: see Page 4, line 80.

Comment 2. Isolated metastasis may not actually be isolated metastasis.

In SEER, there are only four columns of metastasis site: liver, bone, brain, and lung, so the patient may have meta that is not in the columns such as liver + adrenal gland, lung + pleura, so it is impossible to know whether it is a single metastasis or not. Also, common sites are mediastinal lymph node or supraclavicular lymph node, but it is unknown. what do you think about this issue?

Reply 2: We appreciate the reviewer's questions about the metastatic site. We have added a detailed definition of the metastatic site in the article. Metastatic sites were divided into (I) lung metastases only (LUM) without bone, brain, or liver metastases, (II) bone metastases only (BOM) without lung, brain, or liver metastases, (III) brain metastases only (BRM) without lung, bone, or liver metastases, (IV) liver metastases only (LIM) without lung, bone, or brain metastases, (V) multiple organ metastases (MOM): two or more metastatic organs among lung, liver, brain, and bone, and (VI) other metastases (OTM): no metastases to lung, bone, brain, and liver. Therefore, if there are two or more known organ metastases, all are classified as "MOM". However, we cannot list how many metastatic lesions are in a single organ due to the limitations of the database. The study mainly focused on the impact of surgical intervention on the prognosis of different metastatic organs. As for lymph node metastasis, Mediastinal lymph node or supraclavicular lymph node are included in the information of the N stage, which is accurate in the SEER database. Multivariate Cox proportional hazards regression analysis revealed that the advanced N stage was an independent risk factor for patients (table 3). Surgery combined with lymph node dissection improved patients' OS and LCSS significantly in K-M analysis (figure 2).

Changes in the text: see Page 5, line 87

Comment 3. Surgical intervention alone is rarely used and additional Tx modality is added. If a group is divided into PTR, MTR, and PMTR only, the ratio of chemotherapy or RT varies depending on the group, so it cannot be concluded that it is the effect of surgery alone. If you really want to see the role of surgery, you should do it after the other two modality are at least evenly distributed. I recommend you reanalyze the data.

Reply 3: We appreciate the reviewer's suggestions. We divided the data into surgery and no-surgery groups and reanalyzed the data after 1:1 PSM to eliminate confounders (see Page 5, line 100 and table 2). We still found that the surgery group had better

survival benefits (see figure 1). Before comparing whether different metastasis sites should be operated on, we re-performed 1:4PSM (see supplementary table) for each metastasis site (PTR or MTR). We concluded that patients with lung metastasis and multiple metastases could benefit from PTR but not in MTR (see figure 3 and figure 4).

Changes in the text: see Page 5, line 100, table 2, and supplementary table 1-8.

Comment 4. To what extent does PTR mean surgery? Does it include Lobectomy, Segmentectomy, or Wedge?

Reply 4: Thanks to the reviewer for comments on the surgery. The PTR mentioned in this paper includes all surgical operations that can remove the primary lung tumor. Such as sub-lobotomy, lobotomy, pneumonectomy, and so on.

Comment 5. You need to consider the possibility of difference in tumor burden: In the PMTR group, brain tumor resection + lobectomy may have been performed in the form of isolated brain meta + lung lesion, and in the case of PTR or MTR, the tumor burden may have been high overall, so It is not known whether surgical intervention has a greater effect on LCSS. Address your ideas more.

Reply 5: Thanks to reviewers' suggestions. We have added to this article some of our views on the tumor burden after surgical interventions. We found that surgical interventions for patients with LUM and MOM could prolong survival time to a certain extent. However, the effect was not significant for patients with BRM and BOM. Due to the small sample size and the possible confounding factors, prospective studies should be conducted in the future. On the other hand, patients with LUM, BOM, or MOM did not benefit from MTR in our research. We believe that surgical intervention for metastases without resection of the primary tumor cannot fundamentally reduce the tumor burden of patients, nor can the potential risk of metastasis and recurrence be excluded. Therefore, MTR is not recommended for general use. Unfortunately, the number of patients undergoing PMTR is relatively small, so we could not analyze these patients further. But in the multivariate Cox proportional hazards regression analysis, PMTR is not an independent risk factor for patients in the surgery cohort, which may be related to the impact of multi-organ surgery on patients' poor physical state and postoperative complications.

Changes in the text: see Page 10, line 189, and Page 11, line 209.

Comment 6. What does "other" mean in the metastatic site in the table?

Reply 6: We appreciate the reviewer's question. In SEER, there are only four columns of metastasis site: lung, bone, brain, and liver. We divided metastatic sites into (I) lung metastases only (LUM) without bone, brain, or liver metastases, (II) bone metastases only (BOM) without lung, brain, or liver metastases, (III) brain metastases only (BRM) without lung, bone, or liver metastases, (IV) liver metastases only (LIM) without lung, bone, or brain metastases, (V) multiple organ metastases (MOM): two or more metastatic organs among lung, liver, brain, and bone. The remaining patients with the M1 stage were classified into other metastases without metastases to lung, bone, brain, and liver.

Changes in the text: see Page 5, line 92.

Comment 7. What does "The cohort of patients who underwent PMTR was not evaluated due to fewer patients" mean on Line 148? PMTR is also included in Cox analysis.

Reply 7: Thanks for the reviewer's reminder. In our revised manuscript, we reclassified the data in a more organized way. 66 (4.8%) patients had PMTR, and few patients had PMTR to different metastatic sites. The number of patients who underwent PMTR for bone, brain, liver, lung, and MOM metastases was 6, 15, 1, 11, and 4, respectively. Therefore, we did not include these patients in the K-M analysis of different metastatic organs.

Changes in the text: see Page 8, line 165.

Reviewer D

Authors analyzed the correlation between the metastatic sites and survival rate of stage IV LUAD patients registered within SEER database and they suggested that surgical intervention can be an option to improve the survival of LUAD (lung adenocarcinoma) patients with different metastatic sites after highly individualized patients based on their analyses.

Given low morbidity and mortality rates after surgery and high efficacy of targeted agents or immunotherapy, the role of surgical resection should be reconsidered for patients with advanced lung cancer. The authors suggested that surgical treatment in which patients could help improve overall survival rates.

There are some comments or questions to be addressed.

Comment 1. It appears that the statistical comparison in Table in is incorrect. For example, in NS groups, the distribution of age should be 16.5% (5445/32834) under the age 55, 58.9% (19370/32834) between 56 and 75 and 24.4% (8017/32834) over age 76. I think the proportions of all parameter should be corrected.

Reply 1: Thanks for the reviewer's reminder. We have modified the ratio of the data to a more appropriate column percentage (see table 1).

Changes in the text: see table 1.

Comment 2. I think that there are some discrepancies in basic demographics between surgery group and non-surgery group which was not negligible. To suggest the role of surgery, the benefit of surgery should be proved through the comparison between surgery group and non-surgery group using Kaplan Meier curve and multivariate Cox regression analysis.

Reply 2: We appreciate the reviewer's suggestions. We divided the data into surgery and no-surgery groups and reanalyzed the data by K-M analysis and COX regression analysis after 1:1 PSM to eliminate confounders (see Page 5, line 100 and table 2). We still found that the surgery group had better survival benefits (see figure 1). Before comparing whether different metastasis sites should be operated on, we re-performed 1:4PSM (see supplementary table) for each metastasis site (PTR or MTR). We concluded that patients with lung metastasis and multiple metastases could benefit from PTR but not in MTR (see figure 3 and figure 4).

Changes in the text: see Page 5, line 100, table 2, and supplementary table 1-8.

Comment 3. Gamma knife surgery (GKS) is one of popular treatment modality for patients with brain metastasis. I am wondering if GKS was classified as radiation therapy or surgery.

Reply 3: Thanks for the reviewer's comments. In clinical practice, most brain

metastases of lung cancer choose gamma knife treatment locally. Unfortunately, the SEER database lacks more detailed information about metastatic tumor resection. This part of the patients who were treated with the gamma knife should be classified as radiotherapy according to our understanding. Therefore, Given that radiotherapy cannot be well distinguished from surgery, we excluded patients treated with radiotherapy.

Changes in the text: see Page 10, line 204.