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Reviewer A:

This is an interesting manuscript. The authors have extracted good data from the SEER database. There is not new information since this has been reported previously even from the same database. However, the approach taken by the authors including a comprehensive literature review and adding numbers to this controversial and rare scenarior make it worth publishing but with major revisions. I strongly believe this manuscript will add a lot to literature and is worthy of publications after revisions. My specific questions, concerns and recommendations are.

1. While the data is interesting, there is a lot of room to craft this manuscript in a way to make it more interesting and gramatically and strcturally correct. I advice authors to send this to review to their collegues and send us back a more crisp version of the paper. If the authors wish to publish in this high IF journal, the manuscript needs to be in a good shape.

Reply 1:

We appreciate your professional comments. After the receipt of your suggestions, we immediately get in touch with the thoracic surgeons in our department, the oncologists, radiologists, and interventional physicians in our center to making the manuscript more concise, rigid and convincing. First, the English language, grammar, punctuation, spelling, and overall structure of this manuscript are re-edited by two doctors who received their PhD degrees in the United States. Second, the presentations of statistical methods and results, and the narrative structure of the discussion and conclusion section are revised based on our colleagues' professional suggestions. Finally, all authors read the revised manuscript and approved the resubmission.

2. Why an age cut-off of 60 years, why not use age as a continous variable.

Reply 2:

Age at diagnosis was used as a continuous variable in the comparison between the no lung resection group and lung resection group, and presented as mean ± standard deviation (SD). However, all continuous variables should be transferred into categorical variables in the univariate and multivariate Cox regression analysis; therefore, in accordance with the previous retrospective cohort studies and survival analyses (1-5), patients was grouped into two groups according to the WHO

recommendations on physical activity for health: non-elderly (≤ 60 years old) and elderly (> 60 years old) patients in the present study.

3. As far as I know, SEER data reports inconsistencies in the radiation therapy and chemotherapy data, therefore, if the authors are using that data, they should add a statement in the limitations that there might be inconsistencies in the SEER RT and chemo data.

Reply 3:

<SEER program coding and staging manual 2018> reports that radiation therapy, chemotherapy, or interventional therapy documented in the SEER additional treatment fields is given as main part of the first-course treatment. However, a multidisciplinary therapy should be considered for patients with metastatic or recurrence disease to obtain long-term survival; therefore, the above therapies can be performed in a sequential or concurrent sequence. To avoid selection bias in the subgroup analysis, all patients who received the above therapies for resectable second lung tumor after previous pneumonectomy are classified into "no lung resection" group in the present study.

However, individual radiotherapy techniques, doses and fractions, chemotherapy regimens, and interventional ablation techniques, which may affect the therapeutic efficacy, are not available within the SEER database, and therefore this limitation should be stated in the discussion section.

Changes in the text:

Third, individual radiotherapy techniques, doses and fractions, chemotherapy regimens, and interventional ablation techniques, which may affect the therapeutic efficacy, are not documented in the SEER database as well. (see page 6, lines 248-250)

4. Make discussion section more concise and interesting.

Reply 4:

We apologize for our unclear description. To make the Discussion section more concise and interesting, the narrative structure has been changed slightly and the repeated contents have been expurgated based on our colleagues' professional suggestions. The main intention is to discuss the therapeutic options and effects (i.e. surgical resection, chemotherapy, SBRT, and interventional therapy) for patients with postpneumonectomy SLT based on evidence-based medicine and the present results. In addition, a compreshensive literature review on patients with postpneumonectomy SLT is performed to conduct horizontal and longitudinal comparisons in the Discussion section. What's more, the present study is a case series in design which

has many drawbacks, and thus the limitations are discussed thoroughly in the section.

5. Need some strengths. something like they have added more numbers, did a compreshensive literature review, validate previous studies.

Reply 5:

Thanks for your professional comments. All reported cases with second lung tumor (SLT) after previous pneumonectomy in history have been collected in the Table 4 to conduct a longitudinal comparative analysis. Before 2009, surgical resection was performed in all patients, including 80 wedge resections (77.7%), 16 segmentectomies (15.5%), and 7 lobectomies (6.8%). However, in the recent ten years, most of the patients (296/365, 81.1%) with postpneumonectomy SLT received non-surgical therapy, i.e. chemotherapy, radiotherapy, and interventional therapy.

Changes in the text:

Before 2009, surgical resection was performed in all reported patients with postpneumonectomy SLT, including 80 wedge resections (77.7%), 16 segmentectomies (15.5%), and 7 lobectomies (6.8%). However, in the recent ten years, most of the patients (296/365, 81.1%) received non-surgical therapy, i.e. chemotherapy, radiotherapy, and interventional therapy (Table 4). (see page 5, lines 188-192)

6. Very weak conclusion.

Reply 6:

In this SEER database analysis, the median follow-up time for the whole patients diagnosed with resectable SLT after previous pneumonectomy was 60 months with 5-year cancer-specific survival (CSS) and overall survival (OS) rates of 60.8% and 53.7%, respectively. Separately, there was no statistically significant difference between no lung resection and lung resection in both CSS (P=0.633) and OS (P= 0.635). And so the aggressive treatment, no matter surgical resection or not, should be considered for this population to obtain long-term survival.

However, pathologic evaluation from surgical excision can accurately classify the histologic subtype of the lung cancer, determine the extent of invasion, determine whether it is a second primary lung cancer or metastatic cancer, establish the cancer involvement status of the surgical margins, and do molecular diagnostic studies to determine whether certain gene alterations (eg, EGFR, ALK, ROS1, PD-1 receptor…) are present. Moreover, we found that in the lung resection subgroup analysis, the sublobar resection (SLR) group had better CSS in statistics (P=0.030), and better OS in trend (P=0.051) than the lobectomy group; additionally, interval time greater than 53 months (P=0.003 for CSS; P=0.001 for OS) and early stage of SLT (I-II; P=0.026

for CSS; P=0.011 for OS) were significantly associated with longer survival in the multivariate Cox regression models. Therefore, we concluded that SLR can be a reasonable therapeutic option for patients with early-stage disease (I-II) and interval time to development of SLT longer than 4 years.

Changes in the text:

SLR or non-surgical resection is reasonable therapeutic option for patients with resectable SLT after previous pneumonectomy to achieve long-term survival, with acceptable treatment related mortality. (see page 1, lines 38-40)

Aggressive treatment, no matter surgical resection or not, should be considered for patients with resectable SLT after previous pneumonectomy. Moreover, more accurate diagnosis of pathology, advanced molecular and genomic detections, and long-term survival can be obtained with limited resection, especially in patients with early-stage disease (I-II) and interval time to development of SLT longer than 4 years. (see page 6, lines 256-260)

7. What TNM/AJCC staging did the authors use?

Reply 7:

In the present study, the SEER summary TNM stage is recategorized according to the eighth edition of the American Joint Committee on Cancer Staging Manual.

Changes in the text:

In addition, we recategorized the Tumor-Node-Metastasis (TNM) staging documented in the SEER database according to the eighth edition of the TNM classification for lung cancer. (see page 3, lines 93-95)

8. Why a time interval of 53 months? why tumor size cut-off of 33 mm? isn't 2 cm a cut off between t1a and 1b? then why 33mm?

Reply 8:

Currently, the commonly used statistical methods for estimating best cutoff prognostic value include receiver operating characteristic curve (ROC) analysis and X-tile software, but there is no universally accepted or standard method. In the present study, the X-tile software (version 3.6.1, copyright Yale University 2003) is used to determine the optional cutoff values for interval time (53 months) and tumor size (33mm) of SLT.

However, as you mentioned, the 8th edition of the TNM classification of lung cancer describes that the 30mm cutoff points still separates T1 from T2 tumors. We also realize that it is not proper to determinate a new cutoff point for tumor size based on our small sample data. Therefore, patients enrolled in this study are redivided into two groups: ≤3cm and >3cm.

Changes in the text:

Table 2:

Tumor size of second lung tumor					
≤30 mm	65	61.4 %	0.883	51.6%	0.251
>30 mm	34	59.9 %		57.8%	

Table S2:

Tumor size of second lung tumor					
≤30 mm	61	61.1%	0.485	51.8%	0.166
>30 mm	15	64.2%		59.3%	

9. Table 4. When using et al. Use author's last name, note first

Reply 9:

Thanks for your professional suggestion. The first author of each published paper on therapeutic options for SLT after previous pneumonectomy is listed in the Table 4 by using author's last name.

Despite all above concerns and questions, I feel the authors have good data and have put in a lot of effort on the data part. This just needs to be reflected in good writing. A very carefull and thoughfull written revision and this should be worthy of publication.

Reviewer B:

Review comment:

Authors selected cases in SEER database that developed second lung cancer after pneumonectomy for the initial lung cancer. They primarily focused on the difference in survival between lung resection vs. non- lung resection groups.

Major comments

1. Despite using one of the largest cancer databases in the world, they were able to find only 99 cases that developed second lung cancer after pneumonectomy for the first lung cancer. Of those, only 23 cases were non-resection group. Because of very small sample size, comparison between lung resection and non-resection groups does not seem to reach valid conclusion.

Reply 1:

To our knowledge, there is no special focus on the comparison between non-surgery and surgery for patients with resectable SLT after previous pneumonectomy. In the present study on patients with resectable postpneumonectomy SLT, compared with those received non-surgical treatment, patients received secondary lung resection had similar treatment-related mortality and long-term survival. However, surgical specimens could help oncologists to more accurately evaluate the genetic mutations and tumor microenvironment to guide the subsequent targeted therapy and immunotherapy (6,7). For the extent of resection, almost all literatures on patients received surgery for postpneumonectomy SLT demonstrated that patients in SLR group had a higher OS than those in lobectomy group in trend (Table 4). Similar result was verified in this population-based study, and the significant difference was firstly found. In addition, a compreshensive literature review on patients with postpneumonectomy SLT was performed to conduct horizontal and longitudinal comparisons, which support our results and conclusion.

Undeniably, the conclusion based on small sample size was an obvious limitation of this study. Even so, the chance of long-term survival obtained from the aggressive treatment had been demonstrated, and future directions of clinical practice regarding SLR or non-surgical resection therapy for postpneumonectomy SLT have also been proposed.

Changes in the text:

First, this retrospective, small sample cohort study is abstracted from a national database and the year of diagnosis spans nearly twenty years, which inevitably cause selection bias. (see page 6, lines 246-248)

2. Among 400 cases with second cancer, surgery was not recommended for 270 cases. It is common sense to avoid further resection after pneumonectomy. There must be significant selection bias for cases selected for surgery.

Reply 2:

As you mentioned, surgery is even more arduous if the previous resection was pneumonectomy which usually has a significant negative impact on pulmonary reserve. Very few patients undergo additional resection after pneumonectomy, and morbidity is not negligible. Even a limited resection on the contralateral lung has a negative impact on pulmonary function. Up to date, only approximately 169 cases received subsequent lung resection on a single remaining lung were reported in the literatures (Table 4). Grodzki et al. reported that the percentage of patients had the chance of secondary lung resection for postpneumonectomy SLT was 18.0% (18 of 100) in their single center (8). Another study based on the SEER database revealed

that about 13.7% of patients (63/459) who underwent previous pneumonectomy for initial lung cancer went on to secondary lung resection during a 25-year period, which was the largest series in the published literatures (9). Similar proportion (76 of 400, 19.0%) was observed in present study as well.

This study aims to compare the short- and long-term outcomes of different treatment patterns in patient with resectable postpneumonectomy SLT, who documented as "surgery was recommended" in the SEER database. We speculate that patients recommended for surgery for postpneumonectomy SLT may have satisfactory pulmonary function reserve, good performance status, and early-stage SLT; therefore, they could well tolerate the treatment related complications to obtain long-term survival. Among the 130 patients recommended for surgery for postpneumonectomy SLT in the SEER database, more than half of them (76/130, 58.5%) received surgical resection.

Undeniably, although utilizing a population database, this study is subject to potential bias due to its retrospective nature and small sample size. We stated this limitation in the discussion section.

Changes in the text:

First, this retrospective, small sample cohort study is abstracted from a national database and the year of diagnosis spans nearly twenty years, which inevitably cause selection bias. (see page 6, lines 246-248)

3. Authors did not provide TNM staging version. This study included cases initially diagnosed from 1998 to 2016, and TNM staging has been revised a few times over the period. I am aware that most cases have information for only one or two staging versions, and impossible to stage all the cases with the same staging version.

Reply 3:

Thanks for your professional comments. As you mentioned, the TNM staging for lung cancer had been revised three times (fifth edition in 1997, sixth edition in 2002, and seventh edition in 2009) between 1998 and 2016. In the present study, to unify the different staging versions, the SEER summary TNM stages are recategorized according to the eighth edition of the American Joint Committee on Cancer Staging Manual.

Changes in the text:

In addition, we recategorized the Tumor-Node-Metastasis (TNM) staging documented in the SEER database according to the eighth edition of the TNM classification for lung cancer. (see page 3, lines 93-95)

4. Information of radiation and chemotherapy from SEER database remain very limited at this time. I wonder these treatments were truly given for second cancer and not as adjuvant treatment for the first cancer.

Reply 4:

Thanks for your professional comments. Information on radiation and chemotherapy given for the first cancer and second cancer are documented separately. Moreover, the second therapy is administered after documented treatment failure according to the <SEER Program Coding and Staging Manual 2018>. Therefore, the fields in the "second cancer" section record whether chemotherapy or radiation was given for patients with postpneumonectomy SLT, which in accordance with the previous studies on second lung cancer from SEER database (9,10).

Minor comments

1. X axis of survival figures reports "Time". I assume its month.

Reply 1:

Thanks for your professional suggestion. The X axis of survival figures have been renamed "months".

Changes in the text:

Figure 2 and Figure 3.

2. 10-34% of histology for second cancer were reported as unknown.

Reply 2:

As you mentioned, 16 patients (16/99, 16.2%) with postpneumonectomy SLT were only recorded as "lung cancer" in the "Histology" field.

3. Staging and therapeutic technique must have improved over the study period. Tables 2-3 must include time of diagnosis for first and/or second cancer as another variable.

Reply 3: Year of first and second lung tumor diagnosis were included in the univariate Cox regression analyses as variable. However, the CSS and OS did not show significant differences between different years, which may be limited by the number of patients.

Changes in the text:

Table 2:

	Cancer-specific survival (CSS)	Overall survival (OS)

Variables	N	5-year CSS rate (%)	P value	5-year OS rate (%)	P value
Year of first lung tumor diagnosis					
1998-2003	53	58.6%		52.6%	
2004-2009	39	63.4%	0.978	55.5%	0.995
2010-2014	7	71.4%		57.1%	
Year of second lung tumor diagnosis					
1998-2003	19	41.4%		36.1%	
2004-2009	51	60.0%	0.078	51.0%	0.091
2010-2014	29	71.4%		61.7%	

Reference:

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