Peer Review File

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Reviewer A

Comment: This is a new statistical analysis of the SEER database trying to propose a way to select patients for PORT. There are now two large scale phase III trials showing no benefit from PORT after adjuvant chemotherapy. The main limitation of the current analysis is the quality of the information recorded in the SEER database: no data is given regarding the chemotherapy (drugs and number of cycles) neither on the radiotherapy (dose, quality, technique...). We have no information on the time interval between surgery and radiotherapy and the only information is I guess a R0 resection according to the IASLC definition. The most interesting information is the impact of the number of positive nodes but is it the number of the ratio? The only value of the paper is to suggest perhaps the coordinators of the two randomized trials to join their database and to look in the prospective trial on the role of your normgram.

Reply: Thank you very much for your comments. It is very correct that our article has some limitations, specifically including information on radiation and chemotherapy. This is mentioned in our article. In addition, our study is limited by its retrospective design, which represents an unavoidable bias. The only way to solve this issue is through a well conducted phase III trial. However, our data is a result of exactly the world. This model may help to identify a subset of patients who might benefit from PORT.

The number of positive nodes is not the ratio, it is only the number.

Changes in the text: Furthermore, our study lacks data on some relevant molecular factors, chemotherapy regimen and cycle, tumor recurrence, DFS, radiotherapy details, surgical margin status, and comorbidity (line295-297).

Reviewer B

Comment: Thank you for the opportunity to review the submitted manuscript. I will

provide an assessment of the manuscript. “x/10” functions as a rating scale from 1 (very poor) to 10 (very good). Additionally, respective tasks that need to be performed in my opinion to improve the manuscript are introduced by the symbol “->”

Title (8/10)
“Association of Post-Operative Radiotherapy With Survival in Resected N2 Non-Small Cell Lung Cancer Patients” The title is appropriate.

Abstract (8/10)
The abstract seems to be concise.

Introduction (6/10)
The introduction could have been more elaborated considering the available literature. For example, there is no mentioning the subgroup analysis of the “ANITA” trial.

Methods (8/10)
Seems to be sufficient.

Results (8/10)
The results are presented precisely.

Discussion (4/10)
Please also see “Introduction”
-> I could not find the discussion of the “Lung-Art” Trial, which is -next to the PORT-C trial - one of the most important studies in this field! Moreover, both studies mention (at least in the supplementary material) prognostic models considering the disease-free survival, which partly overlap with your detected prognostic factors and could therefore be used to underscore the importance of your (retrospective) data!

Conclusion (8/10)
The conclusion seems sufficient.

Limitations (8/10)
The limitations are addressed sufficiently.

Quality of written English (8/10)
The writing is fluent and understandable. However, small spelling/grammar mistakes need to be corrected.

Quality of figure and tables (8/10)
The tables and figures are adequate.

Quality of references (5/10)
See “discussion”

Added value/relevance in the field/ Key message of the manuscript (8/10)
Two prospective phase-III studies could demonstrate, that PORT "in general" for the III-N2 situation does not significantly improve overall survival. This leaves however more questions than before: Which patients benefit from PORT nonetheless? Your addressed topic -though retrospective- is highly important!

Overall impression
My overall impression is a "minor revision".

Reply: Thank you very much to the positive comments.
Introduction (6/10): Thank you for the suggestion.
Discussion (4/10): "A randomized controlled trial (NCT00410683) of ESMO congress and the most recent phase 3 clinical trial(12) announced the results that postoperative radiotherapy has no PFS or OS benefit for R0 resection N2 (IIIA) of NSCLC. Our study obtained the same result for OS based on a large population of SEER database (line 234-238)". A randomized controlled trial (NCT00410683) is the "Lung-Art" Trial. The most recent phase 3 clinical trial(12) is the "The PORT-C trial -"
Changes in the text: The subgroup investigation of "Lung-Art Trial" verified that PORT can decrease the local recurrence rate for these patients (line 80-81).
A randomized controlled trial (Lung-Art Trial, NCT00410683) of ESMO congress and the most recent phase 3 clinical trial(12) announced the results that postoperative radiotherapy has no PFS or OS benefit for R0 resection N2 (IIIA) of NSCLC. Moreover, both studies mention prognostic models considering the disease-free survival and suggest that further studies discovering patients benefit from PORT are required. (line 234-239)

Reviewer C

Comment: The authors established a practical nomogram that can produce an individualized estimate of the net survival difference with or without PORT for patients with completely resected pathologic N2 NSCLC treated with chemotherapy.

Can you provide specifics from this study as to what cases PORT is effective?

In a randomized controlled trial of postoperative chemotherapy versus postoperative chemoradiation for stage III N2 patients, Shen et al. reported that recurrence-free survival was significantly better in PORT group (18 months vs. 28 months, HR of the former to the latter 1.49, 95% CI: 1.01-2.20, P=0.04), and median OS also tended to be better in PORT group. (Radiother Oncol. 2014 Jan;110(1):120-5). So, Is the

nomogram you have established valid for DFS?

Reply: Thank you very much for your comments. For an individual patient, first use nomogram A to calculate the expected OS with PORT; then use nomogram B to calculate the expected OS without PORT. The difference between the two estimates represents the expected net survival difference from the addition of PORT. **(line 204-207)** This means that a patient can get the overall survival rate with and without PORT according to their clinical situation. PORT is effective when patients with PORT have better survival.

SEER only has the data of OS and cancer-specific survival (CSS), and the externally validated cohort also lacks the data of DFS, so we cannot judge whether it is also valid for DFS at present. In the furture, we can try it when we have DFS data through the idea of this article.

Changes in the text: Furthermore, our study lacks data on some relevant molecular factors, chemotherapy regimen and cycle, tumor recurrence, DFS, radiotherapy details, surgical margin status, and comorbidity (line295-297).