Peer review file
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Reviewer A

Major comment: They should clarify information about neoadjuvant treatment for patients with stage IIIA-N2 NSCLC. Some treatment strategies are considered, such as chemoradiotherapy or chemotherapy preoperatively. After the treatment, pathological tumor size would be changed. Also, the preoperative treatment effect is reported to be a prognostic factor for those patients.
I supposed that they analyzed an extremely heterogeneous population and concluded pathological tumor size as a predictor for prognosis of patients with IIIA-N2 NSCLC after various perioperative treatments.

Reply 1: Your professional comments is very valuable to our research, neoadjuvant treatment is surely important to stage IIIA(N2) patients, we tried to include the neoadjuvant chemotherapy information in our study, but we failed to obtain the sequence information of chemotherapy and surgery. We reviewed articles about lung cancers based on SEER database, none of them contains such sequence information of chemotherapy and surgery[1-3]. We also upgraded the account authority of SSER*Stat to get access of the "radiation/chemotherapy databases", however, data in the software of SEER*Stat still does not contain such sequence information about chemotherapy. Chemotherapy was only recorded as "Yes" or "No/unknown", that is why we did not specify neoadjuvant chemotherapy and adjuvant chemotherapy in the model.

But radiation sequence information could be get from the database, actually we added this factor to our model, but the Cox regression analysis showed no differences between postoperative radiation and non-radiation group or preoperative radiation group, so we did not show this factor. Considering your comments on this section, we also think it necessary to added this factor in table 1, table 2, and table 3, even it is not statistically significant. Besides, patients with larger tumor received more preoperative radiotherapy in table 1, it reminded that better survival of smaller tumor patients was not attributed to preoperative radiotherapy. And it is consistent with the clinical experiences that larger tumor tends to be recommended with preoperative chemo or radiotherapy.

Changes in the text:

1. In the first part of results (line155-157) the following text was added "7.8% of patients received pre-operative radiotherapy, and 34.8% received post-operative radiotherapy, while the equivalent rate was 1.4% and 8.2% in the validation cohort".
2. The larger size group have "more instances of pre-operative radiotherapy (P=0.006)" was added at page 7 line 189.

Minor comment:

Page 4, line 113-114
The authors describe that “chemotherapy received before or after surgery were both recorded as an adjuvant treatment”. As I mentioned in the Major Comment, the preoperative treatment effect is reported to be a prognostic factor for patients with stage III-N2 NSCLC. They should classify them into different groups.

Reply 2:
Thanks for your advices, as we mentioned above we could not get preoperative chemotherapy information in the SEER database, and we noticed that other articles based on SEER lung cancer data also took chemotherapy into their nomogram. We did includ radiotherapy in our Cox regression model but we did not show this factor in the table because it was not statistically significant in the Cox regression model. We have added this factor in table 1-3, and small tumor size was correlated with lower rate of preoperative radiotherapy, so we speculated that the better survival of smaller tumor size group might not be caused by the preoperative radiotherapy.

Changes in the text:
Page 4, line 122 “Chemotherapy received before or after surgery were both recorded as adjuvant treatment” was deleted. Text of explaining chemotherapy and radiotherapy method was added in page 4 line 109 t0 112 with “Chemotherapy and radiotherapy treatment information was also acquired from the “radiation/chemotherapy databases” of SEER, but only the sequence of radiotherapy with surgery was recorded in the database; the sequence of chemotherapy with surgery was not available.”

Reviewer B

Comment 1: I think the biggest limiting factor for the study is that the research subjects have been around for a long time, from 2005 to 2015, and have not received the same kind of systemic treatment or radiation therapy. Over this period, these fields have made considerable progress.

Reply 1: It is undeniable that treatment of stage IIIA-N2 patients is complicated, surgery roles in such patients also experienced controversial, and preoperative chemotherapy or radiotherapy was proved to be favorable factors. To reduce the impact of systemic treatment on such patients, we tried to included chemotherapy and radiotherapy treatment method in our Cox regression model and nomogram. As showed in table 3, only chemotherapy was taken into the model to be an independent favorable factor, radiotherapy preoperative or postoperative was not independent factor in our Cox regression analysis, so we did not show the data. Now we added the radiotherapy strategy data in table 1-3 to make the results more convincible. We also tried to include preoperative chemotherapy information into our model, but sequence

of chemotherapy and surgery was not recorded in SEER, so it was a pity that preoperative chemotherapy treatment which was proved to be favorable factor could not be taken into the Cox regression analysis.

Comment 2: It would be better to discuss the data on the use of platinum based agents and RT, and if these data are not available, it would be better to specify them.

Reply 2: It is a pity that SEER data does not contain detail chemotherapy regimens, and we have added word to specify this in page 4 line 107. Information of radiotherapy was also supplemented in table 1-3.

Changes in the text:

1. Text added in page 4 line 112 “Moreover, chemotherapy regimens were not available for a more detailed analysis.”
2. Text added in page 6 line 155 “In the SEER cohort, 7.8% of patients received pre-operative radiotherapy, and 34.8% received post-operative radiotherapy, while the equivalent rates were 1.4% and 8.2% in the validation cohort.”
3. Text added in page 7 line 189, the large tumor group tended to have “more instances of pre-operative radiotherapy(P=0.006)”

Comment 3: Why don't the authors consider single N2 vs. multiple N2 in the study?

Reply 3: The lymph node information in SEER database only showed with examined nodes number and positive nodes number without the section information of the positive nodes. But the examined LNs and positive LNs were both included in our model to represent the different lymph nodes metastasis conditions. Examined nodes number and positive nodes number were both proved to be helpful in predicting survival of N2 patients.

Comment 4: This is most important, but the authors need to address future perspectives on stage IIIA NSCLC treatment based on current treatment modality. Do the categories obtained in this study, 0-2 cm, 2-4 cm, and 4-5cm, affect the treatment strategy? Please state the authors' thoughts in the text.

Reply 4:

Changes in the text: Paragraph added in discussion from line 278 to 296: “Although our results showed that the 0–2 cm group had a good 5-year OS rate after surgery in both cohorts (53.7% and 54.1% in the SEER and validation cohorts, respectively), mediastinoscopy to assess LN metastasis was still important for making treatment decisions. However, even though it is recommended in all patients with N2 NSCLC, mediastinoscopy is still far from widespread, and accurate multistation N2 assessment remains difficult before surgery. Therefore, tumor size is the most important factor to help clinicians make treatment decisions. We propose that if multiple N2 is not

confirmed or multistation mediastinal LN assessment is unavailable, the 0–2 cm group should be strongly recommended for surgery. The median survival time of the 4–5 cm group (40 and 36 months) was far from that of the 0–2 cm group (68 and 64 months) and was only slightly better than the 29 months reported in 2018 among patients receiving definitive chemoradiation; in that study, neoadjuvant treatment followed by surgery was compared with definitive chemoradiation among patients with stage IIIA-N2 NSCLC (3). The time span was similar to that of the present study, but the patients were staged according to the 7th edition TNM classification, which included more severe invasive tumors than our study. We speculate that the 4–5 cm group received limited added benefit from the surgery over the definitive chemoradiation treatment, and that the role of surgery in such patients should be assessed in randomized control trials.

Comment 5: What do the authors think about "definitive CRT + durvalumab" for resectable stage IIIA NSCLC? I think it would be easier to interpret the results if there was discussion.

Reply 5:

Changes in the text: Paragraph added in discussion from line 297 to 315: "Both adjuvant therapy and radical tumor or LN resection contributed to the prognosis after surgery in the present study. Although SEER data showed older age, higher rate of local resection, and fewer examined LNs, more patients received chemotherapy; meanwhile, the validation cohort had more central bronchus and pleural invasion, less chemotherapy treatment, but higher radical lobectomy rate and more examined LNs. As such, the survival data in each size hierarchy were similar. With the development of immunotherapy, definitive conformal radiation therapy (CRT) plus durvalumab proved superior to traditional CRT in a phase 3 PACIFIC study in patients with stage III NSCLC who showed no progression after chemoradiotherapy [4]. The PACIFIC study achieved a median survival of 43.3 months among patients with 1%–24% tumor cells expressing PD-L1, which was higher than the median survival time of patients with ≥ 25% PD-L1 expression. However, these results are still not comparable to the survival of 0–2 cm surgery group in the present study (68 and 64 months), and we believe that prognosis will be more promising if adjuvant or neoadjuvant durvalumab treatment were applied. Neoadjuvant immunotherapy with or without chemotherapy has proven effective in patients with resectable lung cancer, with a major pathological response in 40.5% to 57% of patients [5-7]. We believe that resection of the primary lesion will benefit patients with N2 NSCLC who have shown better systemic treatment outcomes among well-selected candidates."

Reviewer C

Comment 1:

Title:
Please add “surgical” in front of IIIA-N2, which could promote the reader's understanding.

Reply 1: “surgical” has been added in front of IIIA-N2

Comment 2:
Method:
Please add “surgical” in front of IIIA-N2, which could promote the reader's understanding.

Reply 2: “surgical” has been added in front of IIIA-N2 at line 113

Comment 3:
Introduction:
The authors explained the scientific background and rationale for the investigation being reported. However, the explanation for the stage of these cancers was ambiguous.
The authors need to clarify whether the cited references are in the clinical or pathological stage.

Reply 3: “pathological confirmed” was added before IIIA(N2) at line 70 and 73 page 2.

Comment 4:
Materials and methods:
P4. L114
I think that the authors described surgical IIIA NSCLC. However, their patients were diagnosed as pathological IIIA-N2 NSCLC, which could contradict the study design. Please review the data collection. Surgical stage is not often equal to pathological stage.
Furthermore, the authors need to add how to diagnose the surgical stage.
This is a serious problem to understand the aim of this study.

Reply 4: Sorry I don’t understand the difference between surgical and pathological stage, in our study all the patients in SEER and our data were classified based on the pathological information after surgery. To make it clear, we added some words to specify this in the “Methods” part.

Changes in the the text:
1. page 3 line 105 “Patients were restaged according to the 8th edition staging system using records in the Collaborative Stage Data Collection System; pathological information after surgery such as tumor size, invasion extension, LN metastasis, and distant metastasis were obtained from the Collaborative Stage

Data."

2. Page 3 line 118 "patients were extracted and restaged according to the 8th edition staging system using postoperative pathological information."

Comment 5:
Discussion:
The authors compare survival rates with reference to stage IIB-N1. However, the explanation for the stage of these cancers was ambiguous.
The authors need to clarify whether the cited references are in the clinical or pathological stage.

Reply 5:
"pathological stage" was added before IIB-N1 in the "Methods" part at line 126 page 4, line 143 page 5, and in the discussion part line 258 page 10.

Comment 6:
Discussion:
The characteristics in SEER showed elderly age, higher rate of local resection, less examined LNs, less positive LNs, less invasive central bronchus, more non-pleural invasion, and more chemotherapy than the validation cohort. Despite these differences of backgrounds, the survival curves sorted by tumor size showed similar results.
The author should consider similar survival outcomes, discussing the differences in these backgrounds.

Reply 6:

Changes in text: words were added from line 281 to 286 page12 "Both adjuvant therapy and radical tumor or lymph nodes resection contributed to prognosis after surgery. Although SEER data showed elder age, higher rate of local resection, less examined LNs, but more patients received chemotherapy, while the validation cohort got more central bronchus and pleural invasion, less chemotherapy treatment but higher radical lobectomy rate and examined more LNS, so they got similar survival data in each size hierarchy."

Comment 7:
Conclusion:
The authors described treatment strategies for surgical N2 patients.
What do you suggest about specific treatment policies and future prospects for these patients?

1. Reply 7:
2. paragraph added in the discussion part from line 278 to 296 "Although our results showed that the 0–2 cm group had a good 5-year OS rate after surgery in both cohorts (53.7% and 54.1% in the SEER and validation cohorts, respectively),

mediastinoscopy to assess LN metastasis was still important for making treatment decisions. However, even though it is recommended in all patients with N2 NSCLC, mediastinoscopy is still far from widespread, and accurate multistation N2 assessment remains difficult before surgery. Therefore, tumor size is the most important factor to help clinicians make treatment decisions. We propose that if multiple N2 is not confirmed or multistation mediastinal LN assessment is unavailable, the 0–2 cm group should be strongly recommended for surgery. The median survival time of the 4–5 cm group (40 and 36 months) was far from that of the 0–2 cm group (68 and 64 months) and was only slightly better than the 29 months reported in 2018 among patients receiving definitive chemoradiation; in that study, neoadjuvant treatment followed by surgery was compared with definitive chemoradiation among patients with stage IIIA-N2 NSCLC [8]. The time span was similar to that of the present study, but the patients were staged according to the 7th edition TNM classification, which included more severe invasive tumors than our study. We speculate that the 4–5 cm group received limited added benefit from the surgery over the definitive chemoradiation treatment, and that the role of surgery in such patients should be assessed in randomized control trials."

3. paragraph added in the discussion part from line 302 to 315: "With the development of immunotherapy, definitive conformal radiation therapy (CRT) plus durvalumab proved superior to traditional CRT in a phase 3 PACIFIC study in patients with stage III NSCLC who showed no progression after chemoradiotherapy [4]. The PACIFIC study achieved a median survival of 43.3 months among patients with 1%–24% tumor cells expressing PD-L1, which was higher than the median survival time of patients with ≥ 25% PD-L1 expression. However, these results are still not comparable to the survival of 0–2 cm surgery group in the present study (68 and 64 months), and we believe that prognosis will be more promising if adjuvant or neoadjuvant durvalumab treatment were applied. Neoadjuvant immunotherapy with or without chemotherapy has proven effective in patients with resectable lung cancer, with a major pathological response in 40.5% to 57% of patients [5-7]. We believe that resection of the primary lesion will benefit patients with N2 NSCLC who have shown better systemic treatment outcomes among well-selected candidates. "

Others:

Figure 1

The authors need to clarify whether the patients in SEER were in the clinical or pathological stage.

Figure 4

The authors need to clarify whether N2 stage in SEER was in the clinical or pathological stage.

Table 1 and 2

The authors need to clarify whether N2 stage in SEER was in the clinical or

pathological stage.

Reply : “pathological” was added before “IIIA-N2” in legend of Figure 1, Figure 4, table 1 and table 2.

[1] Demir A, Gunluoglu MZ, Kara HV*, et al.* Prognostic factors in resected T3 non-small cell lung carcinoma: perineural invasion as a new prognostic factor[J]. Thorac Cardiovasc Surg, 2008, 56(2): 93-98.

[2] Mao Q, Xia W, Dong G*, et al.* A nomogram to predict the survival of stage IIIA-N2 non-small cell lung cancer after surgery[J]. J Thorac Cardiovasc Surg, 2018, 155(4).

[3] Zhao Y, Li G, Zheng D*, et al.* The prognostic value of lymph node ratio and log odds of positive lymph nodes in patients with lung adenocarcinoma[J]. J Thorac Cardiovasc Surg, 2017, 153(3): 702-709.

[4] Paz-Ares L, Spira A, Raben D*, et al.* Outcomes with durvalumab by tumour PD-L1 expression in unresectable, stage III non-small-cell lung cancer in the PACIFIC trial[J]. Ann Oncol, 2020, 31(6): 798-806.

[5] Forde PM, Chaft JE, Smith KN*, et al.* Neoadjuvant PD-1 Blockade in Resectable Lung Cancer[J]. N Engl J Med, 2018, 378(21): 1976-1986.

[6] Shu CA, Gainor JF, Awad MM*, et al.* Neoadjuvant atezolizumab and chemotherapy in patients with resectable non-small-cell lung cancer: an open-label, multicentre, single-arm, phase 2 trial[J]. Lancet Oncol, 2020, 21(6): 786-795.

[7] Uprety D, Mandrekar SJ, Wigle D*, et al.* Neoadjuvant Immunotherapy for NSCLC: Current Concepts and Future Approaches[J]. J Thorac Oncol, 2020, 15(8): 1281-1297.

[8] Counago F, Rodriguez de Dios N, Montemuino S*, et al.* Neoadjuvant treatment followed by surgery versus definitive chemoradiation in stage IIIA-N2 non-small-cell lung cancer: A multi-institutional study by the oncologic group for the study of lung cancer (Spanish Radiation Oncology Society)[J]. Lung Cancer, 2018, 118: 119-127.