Author’s response to reviews

Title: Prediction of lymph node status in completely resected IIIa/N2 small cell lung cancer: Importance of subcarinal station metastases

Authors:
rong qiao (qiaoxkyy@hotmail.com)
Runbo Zhong (13761156937@139.com)
Jianlin Xu (xujianlin1018@163.com)
Yanwei Zhang (zhangyw198691@163.com)
Bo Zhang (zb1063253078@163.com)
Shuyuan Wang (18817519225@163.com)
yuqing lou (Louyq@hotmail.com)
Dongfang Chen (cdf94827@sina.com)
qing chang (c.qing819@foxmail.com)
yizhuo zhang (zhyz920916@126.com)
baohui han (18930858216@163.com)

Version: 1 Date: 12 Feb 2019

Author’s response to reviews:
Response to Editor and Reviewers

Dear Professor Vipin Zamvar and reviewers,

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled “Prediction of lymph node status in completely resected IIIa/N2 small cell lung cancer: Importance of subcarinal station metastases” (ID: JCTS-D- 18-00306). We have studied the reviewers’ comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the paper. The main corrections in the paper and the responds to the reviewer’s comments are as following. Again, we thank all the reviewers for their positive and constructive comments and suggestions. If the reviewer or the editor has any further comments or advice, we will be happy to address accordingly.
Thanks for all the help.

Best wishes,

Dr. Baohui Han

Reviewer Comments:

Reviewer #1:

This study by Qiao and colleagues is a single center retrospective analysis of 163 small cell lung cancer patients with N2 disease who underwent lobectomy of pneumonectomy. The study aims to define the prognostic role the extent of N2 disease, including multistation and subcarinal and skip-N2 without N1 disease. Their results show that both multilevel N2 and subcarinal lymph node metastases are associated with a worse prognosis. The study is unusual by its large number of patients who underwent resection small cell lung cancer with nodal disease. As expected, the prognosis of these patients is overall poor, but the data provides information on prognostic differences within stage IIIaN2 patients. My comments are meant to be used to improve the manuscript

Major issues:

Comment 1. As eluded to in the introduction, the presented patients were discovered to have small cell lung cancer or nodal disease based on the surgical pathology report. Essentially, the majority these patients therefore reflect failures in workup given the omission of a preoperative PET scan and invasive mediastinal staging (>2/3 of tumors >3cm). Please acknowledge this clearly in the manuscript and describe in detail how patients were selected for an operation and how were patients staged preoperatively.

Response: Thank you for your comments. In my study, all of the patients had a bronchoscopy examination with bronchial brushing. 102 (62.5%) patients underwent preoperative biopsy by CT-guided transthoracic needle aspiration and/or bronchoscopy. 40 (24.5%) patients were preoperatively diagnosed with SCLC, 37 (22.7%) patients were diagnosed with other types of cancer (included unclassified carcinoma), and 86 (52.8%) patients received CT-guided transthoracic needle aspiration and/or bronchoscopy (including EBUS) with negative results. In the revised manuscript, we describe those in detail(page 6, paragraph 2, highlighted in red). Surgery for small cell lung cancer is rare and non-standard in our institution, occurring mostly in those rare patients who had lobectomy for suspected lung cancer and small cell was found incidentally, which may explain most of the patients (52.8%) failed to be diagnosed with cancer. Before surgery, patients with mediastinal lymph nodes received EBUS. If the biopsy of mediastinal lymph nodes is negative, patients were selected for an operation. In the current study, only 63 (38.7%) patients receive PET-staged to assess the mediastinal lymph nodes. In the
revised manuscript, we discussed this in the limitation section(page 11, paragraph 3, highlighted in red).

Comment 2. The interpretation in discussion and conclusion is problematic. Please expand on how the additional prognostic information should be used to guide adjuvant treatment. My interpretation of the findings is the poor outcomes of small cell lung patients with nodal disease, which points to the need for accurate staging to direct patients to the most effective treatments. Per consensus guidelines, these patients should have been treated with chemoradiation and not surgery. It is important to discuss the findings in the correct context to help the reader understand the significance of the findings.

Response: Thank you for your critical comments and we totally agree with your suggestions which might be of great help to improve the quality of our manuscript. We greatly accept the reviewer’s suggestions that we should expand on how the additional prognostic information should be used to guide adjuvant treatment. So we have made more explanations on this point in the Discussion section of the revised version of the manuscript (page 10, paragraph 2, highlighted in red).

Comment 3 In the discussion, please discuss outcomes as they compare to established outcomes of Stage IIIaN2 patients treated with chemoradiation.

Response: Thank you very much for your comments. We are sorry for the unclear descriptions in our previous manuscript. This point has been made clearer in the revised version of the manuscript (page 10, paragraph 2, highlighted in red). The National Cancer Data Base (NCDB) analysis found that compared to chemotherapy-based non-surgical treatment, surgery was associated with longer survival for SCLC patients with stage IIIA (median OS 21.7 vs. 16.0 months, p< 0.0001) and node positivity(N2+ 20.1 vs. 14.6 months p =0.007) [ Lung Cancer. 2017; 109: 78-88]. Because of the worse prognosis, more potent treatment modalities, such as a combination of PORT and chemotherapy, may be necessary for patients with subcarinal LN metastasis.

Comment 4 In the discussion, "accurate pre-operative diagnosis is difficult" Please explain how this statement. The crux of this study is that preoperative diagnosis is essential given the prognostic implication of nodal disease in small cell and importance to establish the correct diagnosis and stage preoperatively.

Response: Thank you very much for your comments. I have paid attention to this issue, and we had removed this sentence in the revised manuscript. The study indicated that preoperative accurate diagnosis and stage were important to establish the best treatment strategy, and may influence survival of patients with SCLC. I am sorry for the misleading explanation, our purpose was to emphasize the essentiality of preoperative accurate diagnosis.
Comment 5 In results, please report differences in survival times in addition to hazard ratios.

Response: Thank you very much for your comments. We have added hazard ratios in survival times in the Results section of the revised manuscript (page 7, paragraph 2 and 3, highlighted in red).

Comment 6 The multivariate analysis of factors associated with subcarinal nodal disease does not include all associated factors from table 1. Please explain why you chose to leave tumor size out or explain how variables were selected.

Response: We thank the reviewer’s valuable suggestions, which is very helpful to us for strengthening our manuscript. All of the patients were classified into the subcarinal node (-) group and the subcarinal node (+) group, we used a χ2 test for categorical variables and an unpaired t-test for continuous variables and found that tumor location, tumor size, and node levels were associated with subcarinal LN metastasis (p < 0.05). According to the results of univariate analysis, logistic binary regression model was used to evaluate tumor location, tumor size and node levels, the results showed that tumor location and node levels were independent predictors of subcarinal node metastasis (Table 2), as mentioned in the manuscript, the tumor size was not statistically significant independent risk factors predicting subcarinal LN involvement (p > 0.05).

Comment 7 The multivariate survival analysis includes 17 factors, which is a lot for the small number of patients and may resulted in larger confidence intervals and some factors not reaching statistical significance. Please consider a systematic approach for inclusion of variables.

Response: Thank you very much for your further instructions, and we entirely agree with your comment that 17 factors in the multivariate survival analysis is a lot for the small number of patients and may resulted in larger confidence intervals.

The univariate logistic and Cox regression model was built using variables felt a priori to be important confounders for survival, namely, patient age, sex, smoking status and tumor characteristics (histology, tumor endoscopy, visceral pleura invasion, lymphovascular invasion, tumor size, node levels, node-spreading patterns, subcarinal LN metastasis). Procedural details, such as PET scan, cycles of chemotherapy, PORT to the lung and PCI were included, because these may have a significant effect on overall survival. So in the Table 3 of revised manuscript, PET scan was added in the univariate analysis, but the difference was not significant (p = 0.681) (page 5, paragraph 4, highlighted in red and page 18, Table 3).

For multivariate logistic and Cox regression model, variables were categorized based on clinical experience and statistical analysis. Baseline characteristics of the patients such as age, sex, smoking status were included by our clinical experience which maybe potentially correlated with survival outcomes. Moreover, variables that were significant upon univariate analysis (p < 0.05) were included. In the revised manuscript (page 20, Table 4), we left out histology, visceral pleura invasion, cycles of chemotherapy and node-spreading patterns which were not significant.
upon univariate analysis (p > 0.05). In the end, there remains only 10 factors in the multivariate survival analysis.

- Please provide additional details on adjuvant therapy. Did all patients receive adjuvant chemotherapy? What was the time to additional therapy?

Response: We entirely agree with your comment, which is beneficial for strengthening our manuscript. All patients received adjuvant chemotherapy within 28-45 days after surgery. Different chemotherapy regimens were used: 96 patients received cisplatin plus etoposide, 60 patients received etoposide plus carboplatin, and only 7 patients received etoposide alone. This point has been added in the Results section of the revised manuscript. (page 6, paragraph 2, highlighted in red). The detail of chemotherapy agents were shown in supplement Table 1.

Supplemental Table 1. The regimens of adjuvant chemotherapy

<table>
<thead>
<tr>
<th>Chemotherapy agent</th>
<th>n = 163</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etoposide + Cisplatin</td>
<td>96</td>
</tr>
<tr>
<td>Etoposide + Carboplatin</td>
<td>60</td>
</tr>
<tr>
<td>Etoposide</td>
<td>7</td>
</tr>
</tbody>
</table>

Minor Comments:

- Title page- There should be only one corresponding author

- Title page- Please add word count

- Abstract: -median OS does not match the reported OS for entire group in manuscript.

- Abstract: typo-"Systemic" lymphadenectomies

Response: Thank you for your review. I have carefully made corrections in the revised Title page and Abstract respectively (highlighted in red).

Reviewer #2: 1.January 2006 and June 2014 were enrolled. You retrospectively analyzed the potential clinicopathologic factors that influenced survival, including the node levels (single or multiple-station) and the node-spreading patterns (skip N2 or non-skip N2). The prognostic significance was examined by Cox regression analysis. The research work had taken a long time, were rich in content and had clinical significance.
Response: Thank you for your positive comments.

2. Whether different post-operative adjuvant therapies could influence survival of patients with pathologic N2 (pN2) stage IIIA SCLC in different lymph node status?

Response: Thank you for your careful review. According to the reviewer’s suggestions, we have added the details on adjuvant chemotherapy as following. Different chemotherapy regimens were used: 96 patients received cisplatin plus etoposide, 60 patients received etoposide plus carboplatin, and only 7 patients received etoposide alone. This point has been added in the Results section of the revised manuscript (page 6, paragraph 2, highlighted in red). The different regimens were not associated with the overall survival (p=0.549).