Author’s response to reviews

Title: A hypothesized TNM staging system based on the number and location of positive lymph nodes may better reflect the prognosis for patients with NSCLC

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Author’s response to reviews:

Dear editor,

Thank you for your devoted efforts in conveying us the reviewers’ suggestions and your kindness in offering us such a precious opportunity to improve our manuscript entitled “A hypothesized TNM staging system based on the number and location of positive lymph nodes may better reflect the prognosis for patients with NSCLC” (BCAN-D-18-03229). We have analyzed the reviewers’ suggestions meticulously and made the corresponding replies earnestly. We have learned some flaws which we failed to notice in our manuscript, as enlightened by their illuminating remarks. We have revised the manuscript according to their insightful perceptions. And our point-to-point response to the reviewers’ comments are as follows:

Best regards!

Sincerely

Xiaoling Shang

Responses to comments of reviewer 1

Question 1: There are extensive grammatical errors throughout the paper which require a significant amount of editing. The paper is extremely difficult to read. These errors are evident even in the abstract of the paper. For example:
- Objectives: should be rephrased as: "Our study evaluated the feasibility and prognostic utility of incorporating the number of positive lymph nodes into the TNM staging system..."

- Results: "Basing on the cut-off values" should be "Based on the cut-off values"

- "And then, we drawn..." should read "And then, we drew"

- Conclusions: should read "The hypothesized TNM staging system combining locational pN stage..."

Answer: We feel great thanks for your professional review work on our article. We have revised our manuscript by a professional English language modification agency. If necessary, we can upload relevant certificates.

Question 2: The objective of the paper is to improve the TNM staging system. However, the authors used the AJCC seventh edition. This has already been replaced by the AJCC eighth edition. As I believe you would have had the information required, could you reclassify patient's stage based on AJCC 8th edition? Please defend.

Answer: Thank you for your academic comments concerning our manuscript. I have read these comments very carefully and I admit that data about the AJCC eighth edition is better to use in this study than the AJCC seventh edition. However, due to the limitation of SEER database, we couldn't get the information of the eighth edition and the latest update is the seventh edition. In addition, in this study, we mainly to investigate the impact of lymph node numbers on prognosis, but many patients did not reach the end point of survival for data of the eighth edition staging which was updated in 2017. Especially for patients after surgery, the eighth edition staging is not as accurate as the seventh edition to evaluate the 5-year OS rate. In another reason, the eighth edition staging was revised on the basis of the seventh edition staging, and mainly for T and M stages, but not for N stages. So we require further large-scale prospective clinical study to confirm these recommendations. We have noted the limitation in discussion section using “In addition, all data originated from SEER database according to the seventh edition TNM staging system rather than the eighth edition TNM staging system. This may have had some influence on the final results. These issues should be explored in future studies.”

Question 3: The first four paragraphs of the discussion belong in the introduction. Please reformat.

Answer: Thank you for your comments concerning our manuscript. And we have revised the manuscript using red word in introduction. And these do not affect our interpretation of the result.

Question 4: The sentence: "Obviously, from the view of survival prognosis, the current TNM staging system is irrational." - This is an extremely inflammatory comment, and one which I do
not believe belongs in the paper. Perhaps stating this instead as: "Improvements to the TNM staging system from the view of survival prognosis should be considered."

Answer: Thank you for your reminding. As reviewer suggested that we have changed the sentence "Obviously, from the view of survival prognosis, the current TNM staging system is irrational." into "Improvements to the TNM staging system from the view of survival prognosis should be considered." And thank your careful suggestion again.

Question 5: It is unclear to me throughout the paper whether the patient's stage should be reclassified based on the number of lymph nodes simply to improve prognostic information to the patient or provider, or whether the authors believe differences in treatment should be considered. These are very different conclusions, and I do not believe a statement of choosing different treatment interventions could be supported based on available clinical data. Any illusions to changing treatment based on this information should be removed. For example, in the discussion section, line 7 should be revised to "The results require further large-scale prospective clinical study to confirm these recommendations."

Answer: We feel great thanks for your professional review work on our article. For this question, the patient's hypothesized stage in our study was reclassified based on the number of lymph nodes to improve prognostic information to the patient. In other hand, we would like to improve the current staging in order to better guide the treatment of patients, which is also important for the prognosis of patients. We have followed the reviewer's suggestion revise line 7 in discussion into "The results require further large-scale prospective clinical study to confirm these recommendations."

Question 6: The decision to include only patients treated with surgery was not discussed enough as to how this might affect the results of this study. Many patients who have N2+ disease are treated with chemotherapy and radiation, and not surgery. This should be acknowledged as well as commented upon.

Answer: Thanks for your academic suggestion. Your suggestion means a lot to us. For this question, we looked up previous literature and added some discussion using red word in our manuscript. In this study, patients with pN2 NSCLC who account for 14.9% were treated with surgery from SEER database. We only analysed the impact of these patients on staging and did not analyse other patients who did not undergo surgical treatment. These may have an impact on phases. We need to validate this result in future studies.

Question 7: The authors extensively discuss in the section "The current TNM Stage and Survival" certain surprising OS outcomes. As an example, "The 2 year OS rate of each substage in Stage IIA-IIIB was even better than in stage IA and IB." The authors use this to essentially argue the statistical inaccuracy of the TNM staging. However, this data would not be supported by many prior publications, and additional reasons why this data might be as it is were not given. This makes me suspicious of the statistical methods used in the paper, as opposed to skeptical of
the TNM staging system. These statistical examples are also in multiple cases outside of the original intent of the paper, which is to discuss whether adding number of lymph nodes to the staging system may be of prognostic utility. Please consider revising this section.

Answer: Thanks for your academic suggestion. I'm very sorry to draw the wrong conclusion because of my personal mistake. In fact, the conclusion of this article is that the 2-year OS rate of IA and IB patients is better than that of IIA-IIIB patients, as shown in Figure 1A. We have deleted the wrong sentence of “The 2 year OS rate of each substage in Stage IIA-IIIB was even better than in stage IA and IB”. I am deeply ashamed of my carelessness and apologize for the misunderstanding and inconvenience I have caused you.

Responses to comments of reviewer 2

Question 1: The objective statement in the abstract needs some language editing. Generally, a small amount of language editing is needed for the whole manuscript.

Answer: We feel great thanks for your professional review work on our article. We have revised our manuscript by a professional English language modification agency. If necessary, we can upload relevant certificates.

Question 2: The "Patients and Methods" section of the abstract only discusses the statistical methods used, but does not at all mention which patients were included in the study. I would at least mention a querying of the SEER database for stage IA-IIIB patients between 2010 and 2015.

Answer: Thanks for your professional review work on our manuscript. We have added the sentence “we screened a total of 9539 patients with resected stage IA - IIIB non-small cell cancer between 2010 and 2015 from SEER database.” to "Patients and Methods" section using red words.

Question 3: Unless it is just worded a bit awkwardly, the introduction seems to contend that upfront surgery with possible adjuvant chemotherapy and radiation is the first line treatment for all stage IA-IIIA NSCLC. I would at least acknowledge the role of induction therapy for stage IIIA (N2) disease.

Answer: Thanks for your remending on our manuscript very much. In discussion section, we made discussion for patients with stage IIIA (N2) NSCLC. And we gave some explanations for these patients using red word.

Question 4: The authors acknowledge that "other treatment therapy affecting prognosis" was not available from the SEER database. The lack of information regarding neoadjuvant treatment for
stages IIIA and IIIB NSCLC that underwent resection is a fairly large limitation given that clinical staging information was incorporated into the inclusion criteria but pathologic information was ultimately incorporated into the prognosis and staging system. Surely a pT1aN0 NSCLC that was originally IIIA behaves differently from a pT1aN0 NSCLC for which induction treatment was not indicated.

Answer: Thank you for your academic work on our article and this is a very perfect question. Due to the limitation of the database, we did not give information on neoadjuvant therapy for stage IIIA and IIIB patients. These data also have an impact on clinical prognosis. We added this limitation in the discussion section and discussed information on neoadjuvant therapy for patients with stage IIIA-IIIB using red words. Even if this information is not available, we can reflect some problems by incorporating the number of lymph nodes into the revise staging compared with conventional staging that neoadjuvant treatment information was also not taken into account.

Question 5: Can the authors explain their thoughts on why the standard TNM staging system failed to accurately stratify survival by stage grouping in their cohort of patients? For example, how is 2-year OS better for IIIB than for IA NSCLC? This section of the paper is the crux of the argument, and I think it requires a more detailed look as to why these findings occur, as the TNM stage is a tool for stratifying survival.

Answer: Thanks for your careful suggestion. I'm very sorry to draw the wrong conclusion because of my personal mistake. In fact, the conclusion of this article is that the 2-year OS rate of IA and IB patients is better than that of IIA-IIIB patients, as shown in Figure 1A. We have revised the wrong conclusion. And I am deeply ashamed of my carelessness and apologize for the misunderstanding and inconvenience I have caused you.

Question 6: How did the authors identify 0, 1-3, and 4+ positive lymph nodes as the meaningful cutoffs for grouping?

Answer: Thanks for your reminding. In this study, we used X-tile model to screen three different cut-off values including nN=0, nN1-3 and nN4+.

Question 7: If stage IA patients do not actually have the best survival according to the conventional TNM system (as per point 5 above), how is nN=0 a favorable prognostic factor in the revised staging rubric?

Answer: Thanks for your academic suggestion. I'm so sorry to make the wrong conclusion because of my personal mistake. In fact, our manuscript also demonstrated that stage IA patients have the best survival as well as the conventional TNM system in figure 1A. In the hypothesized TNM staging system, we also showed that the 2-year OS rate of stage IA patients is the best one compared with any other stage. So, nN=0 is a favorable factor in the revised stages.