

Peer Review File

Article information: <http://dx.doi.org/10.21037/tau-20-1086>.

Reviewer A

This is a well thought out article with possible implications on choosing patients for neoadjuvant chemotherapy. In this article, the authors discuss differences in pathological response in smokers to neoadjuvant chemotherapy. This is an interesting finding.

Comment 1: However, it would be interesting to note how much pathological response occurred after neoadjuvant chemotherapy. Specifically, patients typically are considered muscle invasive anything T2 and above on TURBT specimen, thus this study should look at patients that had some response with final pathology as T1 or less and complete clinical response (T0). I am not sure that this captures that based on Table 2 or the results which discuss outcomes at T0 or T2.

Reply 1: We would like to express our sincere thanks to you for reviewing this article and giving many constructive comments. The aim of this analysis is to try to find the relationship between smoking status and patients undergoing neoadjuvant chemotherapy for bladder cancer. Hence, the number of pathological responses occurred after neoadjuvant chemotherapy cannot be obtained since only four articles that we involved reported the patients' number of no response (pT2-4 or pN+).

Changes in the text: -

Comment 2: This study should define partial response as anything less than T2 and also look at complete response as T0.

Reply 2: We are sorry for our unclear definition of pT2. We use the definition "anything less than T2" as partial response and we make a clear definition in our new version. (Changes in the text: Page 6, Line 112 & Page 9, Line 185).

Changes in the text: Page 6, Line 112 & Page 9, Line 185

Comment 3: In this study, it would also be interesting to note the differences in medical comorbidities of smokers vs. non-smokers if looking at overall survival. Do most of these patients just end up dying from their bladder cancer or from some other condition? I would imagine that smokers should have decreased OS compared to non-smokers since they likely have more other medical issues. Perhaps the study should also compare disease specific survival.

Reply 3: Actually, we also consider that it will be better to collect the data about the medical comorbidities of smokers vs. non-smokers. However, most of the articles that

we involved in do not show the data that we need, probably because the median follow-up time is not enough to observe the outcome and the data of disease specific survival also cannot be obtained. Definitely, it will make our article better with these data. Thanks again for your constructive comments.

Changes in the text: -

Reviewer B

An interesting manuscript, yet I have some points:

Comment 1: The most cited article on the relationship of pathological response and OS in NAC is following: (Rosenblatt et al, 2012): <https://pubmed.ncbi.nlm.nih.gov/22189383/>. The concept of the relationship of pathological response and OS in NAC and the principals of this concept, needs to be expanded in the INTRODUCTION and the mentioned reference should be included.

Reply 1: We are delighted for your praise and thankful for your comment sincerely. For the first question, we download the article that you mentioned and figure that it can indeed help us to prove our article. Thus, we make a modification and cite this article in our introduction part (Changes in the text: Page 3, Line 52).

Changes in the text: Page 3, Line 52

Comment 2 & 3: The authors have designated pT2 and more as partial response. I think that is incorrect. I suggest that they instead use following outcomes: CR (Complete Response): pT0N0, PR (Partial Response): pTa, pTis & pT1 [all with pN0], SD (Stable Disease): pT2, T3, T4a and finally PD (Progressive Disease) any pTN1-3 and/or pT4b. Following that, I suggest that the investigators perform a new analysis. If to small groups I would suggest pooling CR+PR, having SD separate and having PD separate. Maybe the outcomes will become significant in terms of correlation to OS with mentioned grouping.

Reply 2: For the second point and the third point, we are sorry for the wrong expression of our designation of pT2. We make a clear definition in our modification about partial response (anything less than T2). For the new classification that you suggested in the comment, we are really thankful and willing to try it. However, the articles that we involved in did not separate the patients by this way and it is hard for us to classify them. Some articles only separate the patients into three group (CR (Complete Response): pT0N0, PR (Partial Response): pTa, pTis & pT1 [all with pN0], NR (No Response): pT2, T3, T4a and any pTN1-3 and/or pT4b) or two group (CR and no CR). We also believe if we can do the analysis with the new standard of classification, probably we can conclude with a more powerful and meaningful outcome.

Changes in the text: -

Reviewer C

Thank you for the opportunity to review an interesting paper: Smoking status and pathological response to neoadjuvant chemotherapy among patients with bladder cancer: A pooled analysis.

The paper is a systematic review, the authors investigate the influence of smoking status on pathological response and oncological outcomes among patients with muscle invasive bladder cancer (MIBC) who underwent neoadjuvant chemotherapy (NAC) and radical cystectomy. The paper is clear and well written, the authors should be complimented for their effort.

However interesting, several comments should be explained before possible publication.

Comment 1: Results section line 136

Why was the partial response to NAC defined as pT2? Among patients with MIBC after NAC complete response is defined as ypT0N0 and partial response as downstaging to non-MIBC (ypTis/Cis/T1 N0). What was the rationale to use pT2? Was the lymph node status taken under the consideration? Or maybe the authors meant <pT2?

Reply 1: Thank you for your constructive comment sincerely. We are so sorry for the unclear definition of partial response. We make a modification about the definition about partial response (anything less than T2) (Changes in the text: Page 3, Line 52).

Changes in the text: Page 3, Line 52

Comment 2: How were the data obtained? Where the authors of 10 original papers contacted? It should be specified- not in all 10 original papers data concerning the number of complete responders and partial responders depending on smoking status were published!

Reply 2: Thank you for your positive comments. We obtained the data following the PRISMA guideline, searching all the article from PubMed, Web of Science, Embase, Cochrane Library, and Google Scholar. We find out the data that we need by two authors, separately. Because all the number of the data can be found clearly from the original article and there is no interest conflict, we did not contact with the authors. We make a clarification in our results part after modification (Changes in the text: Page 6, Line 111). Thanks again for your constructive comments.

Changes in the text: Page 6, Line 111

Comment 3: The discussion is too long; I think the manuscript would benefit from shortening of this section

Reply 3: We are grateful for your comments. According to your advice, we delete some sentence of our discussion part. (Changes in the text: Page 9, Line 185 & Page 10, Line 205)

Changes in the text: Page 9, Line 185 & Page 10, Line 205

Comment 4: The reference number should be stated in brackets before the punctuation mark (in the same sentence that it refers to) look at line 72,72,75,76...etc.

Reply 4: Thank you for your constructive comments. We revise all the wrong positions of the reference number.

Changes in the text: -

Comment 5:

Line 247-248: Obese patients with bladder cancer showed a higher risk of developing bladder cancer. (35)

I think the authors meant: Obese patients showed a higher risk of developing bladder cancer (35).

Reply 5: Sorry for the confusing expression. We make the modification in the new version. Thank you for your comments.

Changes in the text: -