Peer Review File

Article information: http://dx.doi.org/10.21037/tau-20-933.

Response to Reviewer A:

Comment 1: In this study the authors performed a retrospective analysis regarding the therapeutic role of the association of neoadiuvant chemotherapy (NAC) to radical nephroureterectomy (RNU) for locally advanced upper tract urothelial carcinoma (UTUC).

They included 19 studies from 1995 to 2020 concluding that the combination of NAC and surgical treatment could provide an improvement in survival outcomes compared to surgery alone.

Reply 1: We would like to express our sincere thanks to you for reviewing this study and giving many constructive comments. The aim of this study is to provide a more comprehensive, updating and convincing study to estimate the effect of neoadjuvant chemotherapy (NAC) on upper tract urothelial carcinoma (UTUC) patients. By pooling those included studies and analyzing those data, we found that NAC treatment for patients with UTUC before RNU might provide better survival outcomes and achieve higher pathological response rates comparing with surgery only. For urologists, those results might strengthen their confidence when using NAC for UTUC patients; For UTUC patients, there might be another more suitable management, and they might obtain more benefits by NAC treatment.

Comment 2: There are some typos and grammatical errors that should be corrected;

Reply 2: Thank you very much for your constructive comment. We made a linguistic revision with help of native speakers. And we have proofread the manuscript and edited the text extensively to minimize this issue. And typos and grammatical errors are corrected in the revised manuscript. Please check the details in the revised manuscript.

Comment 3: Abbreviation of upper tract urothelial carcinoma (UTUC) should be explained also in the introduction section and not only in the abstract

Reply 3: Thank you very much for your constructive comment. We have added the explanation of the abbreviation of upper tract urothelial carcinoma (UTUC) in the introduction section.

Changes in the text: Page 3 line 2-3

Original version: UTUC are a relatively rare disease and the proportion is only 5–10% in urothelial carcinomas, about 2 cases in 100000 residents in Western

countries

Revised version: Upper tract urothelial carcinoma (UTUC) are a relatively rare disease and the proportion is only 5–10% in urothelial carcinomas, about 2 cases in 100000 residents in Western countries

Comment 4: The authors should correct EUA guideline (line 5, page 3) with EAU guideline

Reply 4: We would like to express our sincere thanks to the reviewer for this constructive comment. We also proofread the manuscript and edited the text extensively to minimize this issue.

Changes in the text: Page 3 line 5-6

Original version: According to the EUA guideline, UTUC is recommended to perform radical nephroureterectomy (RNU) with excision of ipsilateral bladder cuff

Revised version: Following the EAU guideline, UTUC is recommended in radical nephroureterectomy (RNU) with excision of ipsilateral bladder cuff.

Comment 5: I would suggest to add a reference to the third sentence of the introduction (line 9, page 3);

Reply 5: Thank you very much for your constructive comment. We have added 2 reference to support our opinion. And the 2 articles are *Margulis V, Shariat SF, Matin SF, Kamat AM, Zigeuner R, Kikuchi E, et al. Outcomes of radical nephroureterectomy: a series from the Upper Tract Urothelial Carcinoma Collaboration. Cancer. 2009;115(6):1224-33* and *Munoz JJ, Ellison LM. Upper tract urothelial neoplasms: incidence and survival during the last 2 decades. J Urol. 2000;164(5):1523-5.*

Changes in the text: Page 3 line 7-8

Original version: but high recurrence rate of advanced UTUC after standard surgery caused an unsatisfying prognosis and confusion of treatment.

Revised version: however, high recurrence rate of advanced UTUC after standard has been reported to cause an unsatisfying prognosis and inaccurate treatment (3, 4).

3. Margulis V, Shariat SF, Matin SF, Kamat AM, Zigeuner R, Kikuchi E, et al. Outcomes of radical nephroureterectomy: a series from the Upper Tract Urothelial Carcinoma Collaboration. Cancer. 2009;115(6):1224-33.

4. Munoz JJ, Ellison LM. Upper tract urothelial neoplasms: incidence and survival during the last 2 decades. J Urol. 2000;164(5):1523-5.

Comment 6: I would suggest to cite the most recent EAU guideline (not 2017) in the discussion section

Reply 5: Thank you very much for your constructive comment. Because we finished and submitted our manuscript before the publishment of the most recent EAU

guideline, we cited the guideline of UTUC (2017 update). Now, guideline of UTUC (2020 update) has published, and we compared the difference among those 2 vensions. The content that we cited from the guideline (2017 update) had no big changes compared with guideline (2020 update), and RNU plus excision of ipsilateral bladder cuff is still recommended for high-grade UTUC. We have updated the cite in the discussion part.

Changes in the text: Page 9 line9

Original version:

According to the EAU guideline (2017) of UTUC, RNU plus excision of ipsilateral bladder cuff is recommended for high-grade UTUC

Revised version:

The EAU guideline (2020) on UTUC recommends RNU plus excision of ipsilateral bladder cuff for high-grade UTUC (33)

Comment 7: TABLE 1 (1)-Please correct the country of Youssef's study (not UTUC); (2) I would suggest to add the period of follow-up of each included study; this could be useful to better understand survival results.

Changes in the text: Thank you very much for your constructive comment. We have revised Table 1 according to your suggestion. We correct the country of Youssef's study and add the period of follow-up of each included study. Please check the details in the revised manuscript.

Response to Reviewer B:

Comment 1: There sits ongoing debate on the use of NAC for patients with HG UTUC. In this study, the authors performed a pooled analysis to evaluate the effect of NAC. The study is well conducted and well done.

Reply 1: We are delighted for your praise and thankful for your comment sincerely. The aim of this study is to provide a more comprehensive, updating and convincing study to estimate the effect of neoadjuvant chemotherapy (NAC) in upper tract urothelial carcinoma (UTUC) patients. By pooling those included studies and analyzing those data, we found that NAC treatment for patients with UTUC before RNU might provide better survival outcomes and achieve pathological response comparing with surgery only. For urologists, those results might strengthen their confidence when using NAC for UTUC patients; For UTUC patients, there might be another more suitable management, and they might obtain more benefits by NAC treatment.

Comment 2: First of all, I strongly recommend linguistic revision by a native speaker.

Reply 2: Thank you very much for your constructive comment. We made a linguistic revision with the help of native speakers. And we have proofread the manuscript and edited the text extensively to minimize this issue. We are sorry for the grammatical and linguistic errors, and these have now been corrected throughout the manuscript.

Comment 3: Concerning PFS and DFS - please report the definitions of these endpoints as sometimes they are used interchangeably across studies. Better to clarify

Reply 3: Thank you very much for your constructive comment. We add the definitions of PFS and DFS in the method part for a better clarification of those two endpoints. PFS means periods from the start of treatment to disease progression or death from any cause. DFS means periods from the start of treatment to disease recurrence or death from any cause. We also add the definitions of OS (periods from the start of treatment to death from any cause) and CSS (cancer survival in the absence of other causes of death) in the method part for a better understanding.

Changes in the text: page 5, line 4-11

Original version: 4. Outcomes (O): prognosis indicators including overall survival (OS), cancer-specific survival (CSS), progression-free survival (PFS), disease--free survival (DFS)

Revised version: Outcomes (O): prognosis indicators including overall survival (OS) (periods from the start of treatment to death from any cause), cancer-specific survival (CSS) (cancer survival in the absence of other causes of death), progression-free survival (PFS) (periods from the start of treatment to disease progression or death from any cause), disease--free survival (DFS) (periods from the start of treatment to disease recurrence or death from any cause), pathological complete response (pCR) rate (achieve pT0N0 disease condition after treatment) and pathological partial response (pPR) rate (achieve ≤pT2N0 disease condition after treatment);

Comment 4: To be consistent with prior studies I suggest using the following terms and abbreviations: Pathological complete response: pCR Pathological partial response: pPR

Reply 4: Thank you very much for your comment. We changed the abbreviations according to your suggestion. Please check the details in the revised manuscript.

Comment 5: In the discussion when you mention AC and NAC, please consider discussion the findings of this recent article: PMID 32284255

Reply 5: We would like to express our sincere thanks to the reviewer for this constructive comment. We carefully read this paper (PMID 32284255). (*Neoadjuvant versus adjuvant chemotherapy for upper tract urothelial carcinoma).* Authors

compared the outcomes of patients treated with radical nephroureterectomy (RNU) who received NAC vs. those who received AC, and found no difference in outcomes between NAC+RNU vs. RNU+AC in high-grade UTUC. Comparing with AC, there was a survival advantage for patients who achieve a response after NAC, but a worse prognosis in patients without NAC response. But the results of this article are hypothesis-generating and further studies aimed at NAC are needed We cited this paper to enrich the comparison between AC and NAC in the discussion part. Please check the details in the revised manuscript.

Changes in the text: page 9, line 25- page 10, line 1

Original version: In contrast, NAC avoids this side effect and might play a more indispensable role in treatment of advanced UTUC (35, 36)…..

Revised version: On the other hand, NAC is not associated with a similar side effect and may play a more indispensable role in managing advanced UTUC (35, 36). Elsewhere, a retrospective study reported no difference in prognosis between NAC plus RNU and RNU plus AC in high-grade UTUC patients, and the study hypothesized that patients who responded to NAC showed better survival compared with AC (37).

35. Roupret M, Babjuk M, Comperat E, Zigeuner R, Sylvester RJ, Burger M, et al. European Association of Urology Guidelines on Upper Urinary Tract Urothelial Carcinoma: 2017 Update. Eur Urol. 2018;73(1):111-22.

36. Spiess PE, Agarwal N, Bangs R, Boorjian SA, Buyyounouski MK, Clark PE, et al. Bladder Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network: JNCCN. 2017;15(10):1240-67.

37. Martini A, Falagario UG, Waingankar N, Daza J, Treacy PJ, Necchi A, et al. Neoadjuvant versus adjuvant chemotherapy for upper tract urothelial carcinoma. Urol Oncol. 2020;38(8):684.e9-.e15.