

Peer Review File

Article information: <https://dx.doi.org/10.21037/tau-21-758>

Reviewer A

Comment 1: The hypothesis of this article that the authors are going to prove does not seem to be clear in the introduction session.

Reply 1: Thanks for reviewer's important and helpful suggestion. Currently, the impact of previous, simultaneous, or subsequent bladder cancer on the prognosis of UTUC is controversial. We aimed to investigate whether UTUC patients with previous, simultaneous bladder cancer or IVR were prognostic factor affecting the prognosis of UTUC based on a large population-based cohort from the Surveillance, Epidemiology and End Results database (SEER) database. The introduction has been rewritten to show the current debate of the impact of bladder cancer on UTUC, and to make the objective of the study clear (see Page 3, line 40 to 59)

Comment 2: It is very well known that UTUC patients with previous bladder cancer history have different pathogenesis and prognosis in comparison with simultaneous bladder cancer or IVR cases. Many simultaneous bladder cancer with UTUC could be a consequence of delayed diagnosis itself rather than the aggressive nature of the disease. However, in the case of previous bladder cancer, the development of UTUC may have different tumorigenesis or biological behavior. The IVR after RNU is quite a common phenomenon because it develops about half of the cases managed by RNU. Therefore, I think you should distinguish all these three categories of bladder cancer, before the identification on the UTUC, with the identification on the UTUC, and after the identification on the UTUC. As you addressed in the result session, you already have data for 820 cases with previous bladder cancer and 60 cases with simultaneous cases. Please compare those two groups as well as the IVR groups.

Reply 2: We appreciate this suggestion. We have compared the impact of previous bladder cancer history and simultaneous bladder cancer on the prognosis of UTUC. As shown in Supplementary Figure S1, no significant difference was detected between the two groups (see page 6, line 110-111). After PSM, the simultaneous bladder cancer showed a tendency of declined CSS, but did not reach statistically significant ($P=0.30$). Due to the small sample size of UTUC patients with simultaneous bladder cancer, and further study are still warranted.

Comment 3: Why do we need to discriminate IVR with MIBC and NMIBC in the case of UTUC? Any different reports from IVR especially with UTUC? What I mean is that, regardless of UTUC, MIBC has a distinctively notorious prognosis in comparison with NMIBC. What makes MIBC after UTUC makes different from other cases without UTUC?

Reply 3: Currently, the impact of IVR on the prognosis of UTUC prognosis remains debatable. Xylinas et al. (1) reported that existence of IVR, which included NMIBC and MIBC, was not correlated with recurrence free survival or cancer specific survival (see page 9, line 172-175). As a result, we explored the impact of IVR with

MIBC and NMIBC on the prognosis of UTUC. In contrast, we found UTUC with subsequent MIBC recurrence had significant poorer survival than UTUC-only group. We agree with the reviewer that MIBC has a distinctively notorious prognosis than NMIBC, we thus suggest stringent follow UTUC patients with cystoscopy to avoid IVR progression to MIBC.

Reference

1. Xylinas E, Colin P, Audenet F, et al.: Intravesical recurrence after radical nephroureterectomy for upper tract urothelial carcinomas: predictors and impact on subsequent oncological outcomes from a national multicenter study. *World J Urol.* 2013; 31: 61-8.

Reviewer B

The authors did a SEER review evaluating the prognostic risk of bladder cancer for CSS after RNU for UTUC. The authors should be commended on obtaining a large sample size and utilizing appropriate statistical evaluation of propensity score matching given the significantly different comparison groups.

However, there are several factors that should be addressed.

Comment 1: Overall grammar and syntax needs to be addressed throughout the paper, including in the title.

Reply 1: Many thanks to this pertinent advice, our manuscript have been revised by an English teacher to address grammar and syntax mistakes throughout the paper (see page 5, line 96).

Comment 2: I recommend changing "Bca-UTUC" to "UTUC-Bca" to be in line with the other acronyms

Reply 2: We have changed "Bca-UTUC" to "UTUC-Bca" according to advice (see page 5, line 96).

Comment 3: Introduction: Delete first sentence. "Subsequence" should be changed to "subsequent." Lines 44-47 should be rephrased for clarity. Lines 56-63 are more of a discussion than introduction. Would remove from this section

Reply 3: We have changed the manuscript according to suggestion (see page 3, line 42). Previous Lines 44-47 and Lines 56-63 have been deleted.

Comment 4: Major revisions are needed in the discussion section. The authors do not highlight their own results. The authors should start with a paragraph stating the results of their study and then move on to discussion points of how this fits into the current literature. As of now, the discussion reads as if this were a review paper.

Reply 4: Thanks for reviewer's important and helpful suggestion. We have revised the discussion to highlight our own results, and compared them to the previous study (See page 7-10, lines 143-210).

Comment 5: The authors state that patients with MIBC after UTUC prior to UTUC have worse outcomes than those with NMIBC. Could this just be a statement about

the MIBC itself? I presume that SEER data does not have enough granularity to be able to answer this question

Reply 5: We agree with the opinion of the reviewer. The data from the SEER could not be able to answer this question since MIBC was an aggressive tumor with 5 year CSS around 50% after cystectomy. As a result, we compared the UTUC patients with NIMBC or MIBC history to UTUC-only cohort, which revealed that UTUC patients with bladder cancer, regardless of tumor stage, were predictor of poorer survival (Figure 3D-F).

Comment 6: The authors also state that effort should be made to prevent MIBC recurrence. How do the authors propose this is done?

Reply 6: In the present study, we revealed that UTUC patients with MIBC had poorer survival, which may be due to MIBC itself as the reviewer said. In any case, it is important to prevent MIBC after UTUC. As a result, it is necessary to apply intravesical chemotherapy or bacillus calmette-guerin instillation to prevent early recurrence after RNU, and stringent follow UTUC patients with cystoscopy to avoid IVR progression to MIBC (see page 10, lines 195-198).

Comment 7: Furthermore, the authors cite the EAU guidelines for intravesical therapy after RNU, yet are using a database from the USA. At least, the authors should cite AUA/SUO guidelines if utilizing a seer database. Further, this brings up a broader question of how many patients actually were undergoing intravesical chemotherapy.

Reply 7: Thanks for this suggestion. We have gone through the AUA guidelines; however, they do not have an independent chapter like EAU to guide the treatment of UTUC in details. In NCCN guidelines, early intravesical installation (24-48h) was not done in all centers, some centers are delaying intravesical instillation by up to one week to administer a cystogram confirming there is no perforation (see page 10, lines 206-207). How many patients actually were undergoing intravesical chemotherapy cannot be determined in the SEER database, we thus regarded this as a limitation of this study (see page 10, lines 199-212).

Comment 8: It would be interesting to include grade/pathology of recurrence. The authors state that high grade upper tract cancers had better prognosis if they had low grade recurrence. This could give perspective on seeding vs field effect.

Reply 8: Thanks to this helpful suggestion, we have analyzed the impact of bladder tumor grade on the prognosis of UTUC (Figure 3 and Figure 5). Both low- ($P=0.03$) or high-grade ($P<0.01$) bladder cancer history had significantly adverse effect on the prognosis of UTUC (see page 6, lines 116-119). The prognosis for patients with subsequent low grade bladder cancer ($P=0.01$) or NMIBC ($P<0.01$) was better than the UTUC-only cohort (see page 7, lines 137-138).

Comment 9: There should be more discussion of the biologic basis for these findings. While they can not be confirmed using the SEER database, it is worthy of mention in

the discussion section. Is a worse prognosis of CSS with previous bladder ca because of aggressive bladder cancer moving to the upper tracts? The overall take away from this paper is that CSS is dependent on the bladder (ie MIBC has worse prognosis than NMIBC).

Reply 9: We have revised the discussion according to suggestion. UTUC with subsequent MIBC recurrence had significant poorer survival than UTUC-only group. Meanwhile, those with shorter interval between UTUC and IVR was associated with significant worse prognosis. Interestingly, UTUC patients with low grade or NMIBC IVR was associated with favorable survival outcomes. Intraluminal seeding theory and field effect theory have been proposed to explain the potential pathophysiological mechanisms after RNU. The phenomena in this study may be explained by the theories of intraluminal seeding, because the heterogeneity of IVR reflected the aggressiveness and prognosis of UTUC tumor. Several genetic studies also showed a monoclonal origin of recurrence bladder tumors and primary UTUC with intraluminal seeding (see page 9-10, lines 185-195).

Comment 10: Overall, adding more granularity will help this paper tremendously. What were pathology results within the bladder among the patients who had previous bladder cancer? The paper needs to be clearer in what question they are answering and how it is adding to the literature.

Reply 10: Thanks to this helpful suggestion, we have added more granularity per advice. We analyzed the impact of bladder tumor grade on the prognosis in the UTUC-Bca cohort and UTUC-IVR cohort. (Figure 3 and Figure 5). The introduction has been rewritten to show the current debate of the impact of bladder cancer on UTUC, and to make the objective of the study clear (see Page 3, line 40 to 59).