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Review Comments

Reviewer A

This is a literature review on nephron sparing surgical management of UTUC. I feel this manuscript is well written, but there are some points to be addressed.

Thanks for reviewing our manuscript. We appreciate your comments and have made changes as appropriate.

Major:

1. The structure of Chapter 5 is odd.

The first paragraph discusses the oncological outcome of SU and RNU. 5.1 discuss the comparative result of SU, TU, and RNU. Maybe the authors can combine these discussions into one paragraph. Furthermore, 5.2 discuss the management of distal UTUC, comparing DU and RNU. Are 5.1 and 5.2 mutually exclusive? I feel the 5.1 include DU for UTUC. Am I wrong?

5.3 discusses management of distal UTUC again, and 5.4 suddenly refer to age of patients. The authors should reconstruct the paragraph to clearly discuss the oncological results between proximal ureterectomy, distal ureterectomy, TU, and RNU. In the current form, it seems that they just introduce the result of individual reports.

Response 1: We tried to provide a brief introduction regarding the oncological outcomes (SU vs RNU) from previously published literature based on large databases/multi-institutional studies. This was done to establish a foundation. We further incorporated smaller studies in subsections to shed light/discuss specific scenarios such as segmental vs total ureterectomy, distal ureterectomy vs RNU for distal ureteral tumors, options for distal ureteral tumors (distal ureterectomy with BCE vs segmental ureterectomy).

The subsections 5.1 and 5.2 were not mutually exclusive, but these sections were created to extract evidence/suggestions for the larger question of the utility of Nephron Sparing surgical procedures in terms of oncological outcomes. This section is followed by renal function outcomes to establish the apparent benefit of such procedures in terms of eGFR benefit.

Changes in the text: Edited and reorganized the subsections to 5.1, 5.2.1, 5.2.2 and 5.3

Minor:

1. Please spell out the abbreviations at the first appearance in the manuscript. Abstract and Main body should be separately considered.

2. Line 130 “This a non-systematic… “ means “This IS a non-systematic…”?

3. Line 131 “with in” means “within”?

Response 2: Thanks a lot for highlighting these issues. We made the changes as advised.

Changes in the text: **Highlighted in section 2**

Reviewer B

132 Although nephron sparing management also include endoscopy guided procedures through
133 antegrade or retrograde approach, we are primarily highlighting nephron sparing alternatives with 134 surgical resection of UTUC for the sake of this review

(*) The apparent presence of selection bias indicates that it should be addressed within the article, particularly in terms of comparing patient selection and considering that those chosen for radical treatment or surgery were likely in a sufficiently fit condition for it.

Response: Thanks a lot for reviewing our manuscript. We completely agree with your assessment. Considering the rarity of disease condition (UTUC), current evidence is open to selection bias. The aim of this manuscript as stated in the introduction was to provide a comprehensive review (narrative/non-systematic review) of the nephron sparing surgical management (excluding the endoscopic procedures as it will be addressed in another article of this review series). Each study included in this narrative review was marred by selection bias as they included heterogenous patient populations (although majority were high grade in each study). All the studies published till date are retrospective and no set criteria was stated to include/exclude the patients from those studies.

Changes in the text: Highlighted in section 3

135 PubMed was performed

(*) Does there exist a supplementary file illustrating the number of results obtained from the PubMed search and the specific search terms used?

Response: Since this was a narrative/non-systematic review, we looked through all the studies that could be found on the PubMed using the terms in different combinations as mentioned in the Methods (upper tract urothelial carcinoma, nephron sparing surgery, segmental ureterectomy, total ureterectomy, partial nephrectomy, ileal ureter etc.). We do have a file for our own use which includes all the relevant studies pertaining to this narrative review.

Changes in the text: N/A

204 In a study by Pedrosa et al. (2015), a total of 141 patients were included, of which 35 & 96 patients 205 underwent SU & RNU respectively

(*) In my opinion, it is more suitable to use the word "and" instead of the symbol "&".

Response: Thanks a lot for highlighting this issue. Addressed as advised.

Changes in the text: Highlighted in section 5.1

217 (0.22) between distal ureterectomy and RNU [9]. Our senior author

(*) While I understand your desire to improve and acknowledge one of the authors, it is generally more accepted to present the results as "our group results/our department results" or utilize abbreviated forms of the surgeon's name.

Response: Thanks a lot for highlighting this issue. We have made changes as advised.

Changes in the text: Highlighted in section 5.2.1

280 7. Role of Lymph Node Dissection

(*) I believe that this particular chapter does not align with the primary objective of the article, which is focused on nephron sparing. Therefore, it should either be omitted or its title and abstract should be modified.

Response: The objective of this manuscript is to provide a comprehensive review of the nephron sparing surgical options for the management of UTUC. The role of LND is evolving even in patients undergoing Radical Nephroureterectomy. We highlighted its role & underutilization, and the outcomes with RNU. When it comes to surgical decision making, considering a hypothetical scenario of localized high grade invasive tumor (on ureteroscopic biopsy) involving a 2 cm segment of distal ureter, RNU with BCE and LND would be the appropriate management. We

would suggest if the patient underwent distal ureterectomy for a HG UTUC or possibility based on imaging, LND should be included (considering the same rationale, as at time of RNU). Again, based on the rarity of the disease and paucity of established literature on outcomes specifically pertaining to LND at segmental/distal ureterectomy, no reasonable conclusions/suggestions can be made at this time. Therefore, we included this segment in our comprehensive review. We have included this in our abstract as well.

Changes in the text: N/A, Highlighted in section 7

316 8. Role of peri-operative chemotherapy

(*) I believe it is crucial to raise this matter for review, with a specific emphasis on reaching conclusions regarding the utilization of chemotherapy after the operation and the necessity of its use in patients selected for nephron sparing.

Response: We agree with your assessment. Again, systemic chemotherapy is largely underutilized in patients with UTUC as highlighted in our manuscript. Its role is still evolving in patients receiving RNU and currently it is still largely underutilized. Therefore, no reasonable conclusions can be drawn at this time. However, intra or perioperative intravesical chemotherapy could be utilized such as Gemcitabine or Mitomycin instillation based on the same rationale as for its utilization at the time of RNU. At our institute we use Gemcitabine.

Changes in the text: N/A, Highlighted in section 8

256 6. Functional Outcomes

(*) To avoid any confusion with regards to patient functioning, it is suggested to rename the chapter as "Renal Function Outcomes" instead of "Renal Function".

Response: Thanks a lot for highlighting this issue. We have made the changes as advised.

Changes in the text: Changed the section 6 heading to Renal Function Outcomes

Other comments (Reviewer B)

The main concept of the paper, which focuses on preserving renal function for UTUC, is crucial and captivating. However, it is essential to compare the risks of recurrence and death with the benefits of renal preservation in terms of years. Furthermore, the article lacks a thorough discussion on patient selection, which should be a key aspect to be reviewed.

Response: As highlighted above, the evidence is open to selection bias. Each patient presents with a unique set of challenges. Main objective is to preserve the renal function when it is desired and appropriate but without compromising oncologic outcomes. With rarity of this condition, and plethora of management options RNU, Nephron Sparing Endoscopic Management, Nephron Sparing Segmental Ureterectomy with/without BCE, Partial Nephrectomy etc. are reported in the literature and no one treatment fits all. Perhaps patient tailored approach with a shared decision making is reasonable at this time which we follow at our institute.

Regarding the organization of the article, there is room for improvement to enhance its coherence and readability. I suggest reorganizing the content by including a chapter that outlines the various treatment options along with a table summarizing their outcomes. Additionally, separate chapters should be dedicated to presenting the combined results of distal ureter, middle ureter, proximal and kidney procedures, and a specific chapter should be allocated to discussing the bladder cuff.
Response: We have made the changes in the oncological outcomes section to make it more coherent. Again, due to rarity of the disease (UTUC) and dearth of literature addressing each individual scenario, although difficult, we have tried to provide evidence in different ways/subsections, including a detailed Table 1 elaborating the oncological outcomes.

To better address the topic of renal function, it would be beneficial to include a chapter that compares the eGFR levels among different cases and examines whether the differences observed in the provided studies are clinically significant, particularly in terms of years.
Response: We have **highlighted** the evidence **(section 6),** specifically addressing your query.

Considering the uniqueness of single kidney cases and special scenarios, it might be helpful to allocate a separate chapter to discuss these specific situations.
Response: These are unique scenarios, and there is paucity of published/available evidence barring a few case reports which lacks oncological and renal function outcomes. Again, each patient presents with a unique set of challenges. Main objective is to preserve the renal function when it is desired and appropriate.

The aspect that remains unaddressed is the limitations of this review, and I strongly urge you to include it, at the very least, in the summary/conclusions chapter.

Response and changes in the text: Included and highlighted in the section 9 (Summary)