

## Peer Review File

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### Review Comments

#### Reviewer A

This paper well summarized the current status of the excision of distal ureter and bladder cuff in nephroureterectomy including open, endoscopic, laparoscopic, and robotic technique.

#### Comment 1:

One critique that could improve this manuscript. The authors postulate "tetrafacta" outcomes especially in robotic nephroureterectomy. This is interesting, but I think that lymphadenectomy need not be performed in all UTUC patients. If the authors include lymphadenectomy in "tetrafacta" outcomes, it is necessary to present strong evidence that lymphadenectomy contributes to improved prognosis in UTUC patients.

#### Reply 1:

Achieving "tetrafacta" outcomes, in terms of radical nephroureterectomy, has been previously described [Soria F. et al. *Eur Urol Open Sci* 2022 PMID:35911084]. The authors propose that performing a Lymph Node Dissection according to EAU guidelines is an important aspect in achieving "tetrafacta" outcomes. This notion is supported in the literature where patients with pNx were found to have worse prognosis than pN0 in pT2-4 tumors [Roscigno M et al. *J Urol* 2009 PMID: 19371878]. Performing a LND during RNU provides valuable staging information and can serve as a prognostic tool.

As the main emphasis of the paper is about the optimal management of the distal cuff and not the role in LND at the time of RNU, we have chosen to only include the above sources in our manuscript.

#### Reviewer B

This article provides a concise summary of the extensive literature available on this subject. It aims to assist readers interested in the topic by offering a brief overview of the existing literature. Additionally, it serves as a valuable resource for staff in training, helping them comprehend the intricacies of this procedure due to its numerous variations and combinations.

I have no additional comments at this time. I made some minor suggestions regarding the form in which it was presented.

Comment 1. Add reference in line 26.

Reply 1: Added

Comment 2. Replace written numbers "twenty percent" for "20-75%"

Reply 2: Modified

Comment 3. Same in in line 31, replace written numbers for values.

Reply 3: Modified

Comment 4. Line 48. Avoid using rhetorical questions in academic writing.

Reply 4: Changed

Changes in text:

Increased utilization, however, may not necessarily translate to superior oncologic outcomes.

Comment 5. Line 60. Replace written numbers for values.

Reply 5: Replaced

Comment 6. Line 87 to 94. Add reference.

Reply 6: Added

Comment 7. In addition, I would include a note in line 157 emphasizing that many studies on this topic have been conducted in diverse risk populations and with varying approaches ( general approach and bladder cuff excision combinations) , making it challenging to homogenise and establish definitive evidence at this stage. However, it is important to note that this does not imply any inferiority in the robotic approach.

Reply 7: Agree with the reviewer on his remark.

Changes in text:

[Line 173-176] The data comparing these approaches is largely retrospective and comprise of inhomogenous populations and varied surgical techniques thereby making direct comparisons between open vs. laparoscopic vs. robotic is difficult. It is important to note that no data has suggested or implied any inferiority with the robotic approach.

Comment 8: Line 164. Avoid using rhetorical questions in academic writing.

Reply 8: Agree with author.

Changes in text:

[Line 181-182]The advantages afforded by the robotic technique should not compromise oncologic outcomes. In fact,

Comment 9. Improve references 1 and 2 with the proper format

Reply 9: Modified

## **Reviewer C**

Authors have described the various approaches in performing a bladder cuff excision and provided technical commentary supporting the advantages and disadvantages of each technique.

-These techniques with their advantages and disadvantages have been well described earlier and I am not sure if this paper is highlighting any new information. I would like to make few points.

Comment 1: Endoscopic techniques: Authors have mentioned 'Pluck' and 'stripping technique'. These are historical techniques and rarely used nowadays. They have not mentioned other endoscopic techniques which have been described in recent time. I have provided some of the references.

-Gill IS, Soble JJ, Miller SD, Sung GT: A novel technique for management of the en bloc bladder cuff and distal ureter during laparoscopic nephroureterectomy. JUrol 1999;

Reply 1: This was included in the original manuscript but is now citation # 32

Comment 2:-Agarwal DK, Khaira HS, Clarke D, Tong

R: Modified transurethral technique for the management of distal ureter during laparoscopic assisted nephroureterectomy. Urology 2008;71:740–743 161:430–434.

Reply 2: Added this reference

Comment 3: -Agarwal DK. Agarwal PolyLoop Ligation Technique for the Management of the Distal Ureter during Laparoscopic Assisted Nephroureterectomy. Curr Urol. 2020 Jan;13(4):209-213

Reply 3: The above reference only has 6 patients and the main application of this particular device is in gastroenterology. After careful consideration, we feel it does not add to the crux of the paper.

Comment 4. Authors have provided few oncological data about the various techniques. The main focus of this paper is critical analysis of various techniques with their advantages and disadvantages. They should have provided a more detailed account of oncological data of various techniques.

Reply 4: The following oncologic data is included in the manuscript

- A. Inadequate management of the distal ureter and bladder cuff can directly result in a 1.25-1.45 times greater disease-specific mortality
- B. The recurrence rate of UTUC can be quite high and sub-optimal dissection of the distal ureter may yield a ureteral remnant with recurrence rates of 33-75% [6]
- C. The laparoscopic and robotic approaches have resulted in improved perioperative factors compared to open surgery [8, 9]; though, oncologic outcomes are a bit more inconclusive [10] [11].
- D. A recent systematic review sought to compare oncologic outcomes between open and laparoscopic surgery and found inferior outcomes associated with laparoscopy, especially in high-risk patients with pure laparoscopic management of the bladder cuff [3].
- E. However, in older series, a single incision (compared to dual incision) was associated with a 50% likelihood of retaining a ureteral stump [14]

- F. When comparing the open transvesical vs. extravesical approaches, one study found that the transvesical approach had improved recurrence free survival and intravesical recurrence free survival [6].
- G. These endoscopic techniques permitted potential spillage of tumor or urine within the abdomen leading to increased retroperitoneal or bladder recurrence [18]
- H. One study found the mean rate of intravesical recurrence at 19.3% for ‘stripping’ and 24% for ‘plucking’ [20].
- I. Although several publications indicate the endoscopic approach is non-inferior with respect to oncologic outcomes [22] [23], lack of long-term data, level I evidence, or meta-analyses make comparing approaches problematic.
- J. When examining laparoscopic extravesical stapling of the bladder cuff, an increased incidence of positive surgical and inferior local recurrence-free survival was noted [30].
- K. In a meta-analysis examining over 250 patients in 9 distinct studies, patients undergoing laparoscopic bladder cuff excision had a higher rate of distant metastases while the open approach was associated with a higher incidence of intravesical recurrence [32]. For bulky distal ureteral tumors, high grade and pT3/T4 tumors, pure laparoscopic excision resulted in inferior oncologic outcomes [8].
- L. In fact, positive surgical margins are found to be less frequent when adopting the robotic approach [14]. Overall and cancer-specific survival are comparable if not slightly improved compared to the open/laparoscopic approach in certain series [9] [38]
- M. In fact, the fate of residual ureteral stump directly translates to inferior rates of overall survival, cancer-specific survival, distant recurrence-free survival and bladder recurrence-free survival [7].

## **Reviewer D**

The authors presented an interesting study about optimal management of the distal ureter and bladder cuff at the time of nephroureterectomy. The topic is certainly still debated in the literature and results are inconclusive.

The article is well written, the procedures are clearly described.

I have no important comments to point out except little suggestions:

Comment 1. The authors may consider to enclose Figures or tables that can briefly and easily describe each technique with its advantages/disadvantages, especially for open incisions and robotic approach.

Reply 1: We agree with the reviewer that the introduction of visuals would be easier to understand each technique. However, all techniques are cited and any images would infringe on copyright laws making this difficult. We, however, did include a Figure outlining some of the main techniques.

Changes in text: Addition of Figure 1

Comment 2. Hand-assisted laparoscopic nephroureterectomy may be mentioned as an alternative approach.

Reply 2: we agree with the reviewer that hand-assisted nephroureterectomy should be mentioned in the manuscript given the favorable perioperative outcomes and minimal compromise to oncologic outcomes.

Changes in text:

[Line 118-120] In one systematic review and meta-analysis, both laparoscopic and hand-assisted nephroureterectomy were found to have improved peri- and post-operative outcomes with similar oncologic outcomes {Nouralizadeh, 2018 #48}

Comment 3. Can the authors better clarify the utilization of simultaneous pneumocystoscopy? I understand that ureteral orifice would be easier to identify, but they state that Co2 can prevent spillage of bladder contents; shouldn't it be the opposite?

Reply 3: The reviewer brings up a good point. The utilization of CO2 pneumocystoscopy obviates the need to use intravesical saline which may lead to spillage intra-abdominally. By using Co2, instead of saline, this risk can be mitigated. There has been no reports in the literature of aberrant metastasis as a result of using insufflation with respect to upper tract urothelial carcinoma.

Comment 4. Line 173- "that achieving "tetrafecta" outcomes need to be achieved are a defined as the following". Please provide grammar/punctuation revision.

Reply 4: The authors postulate that to achieve "tetrafecta" outcomes, the surgeon must adequately perform the following:

Changes in text:

[Line 190-191] The authors postulate that to achieve "tetrafecta" outcomes, the surgeon must adequately perform the following: 1) adequate bladder cuff excision, 2) lymphadenectomy [45] [46], 3) no complications and 4) negative surgical margins.

## **Reviewer E**

I commend the authors for providing an overview on a still debated issue.

The article is well written and provides a granular description of the available techniques to manage the bladder cuff during nephroureterectomy. Despite this some shortcomings have been noticed:

Comment 1:- the title lets the reader assume the authors will provide the answer, but this is not the case. I would change it;

Reply 1: We have changed the title to the following:

Management of the distal ureter and bladder cuff at the time of nephroureterectomy:  
An overview of open, laparoscopic and robotic approaches

Comment 2: - line 32-33 I suggest to provide a reference regarding the sentence such as the following one [10.1007/s00345-019-03020-1](https://doi.org/10.1007/s00345-019-03020-1);

Reply 2: We have added the above reference.

Comment 3: - paragraph from line 40 to 48 describes the surgical approaches available, but being this article focused on bladder cuff excision I suggest the authors to consider to remove it or to rephrase it focusing on bladder cuff management;

Reply 3: We removed certain sentences and rephased to emphasize that that inadequate bladder cuff excision can directly lead to inferior oncologic outcomes  
Change in text: [Line 51-55] After initial publications of the laparoscopic approach [13], the robotic approach has gained significant traction [10]. A recent systematic review sought to compare oncologic outcomes between open and laparoscopic surgery and found inferior outcomes associated with laparoscopy, especially in patients with pure laparoscopic management of the bladder cuff [3].

Comment 4: - I suggest to update the reference related to sentence line 139-140 (10.23736/S2724-6051.21.04247-8);

Reply 4: We have added this reference

Comment 5: sentence line 173-174 is not that clear. It should be rephrased;

Reply 5: We agree with the comment made by the reviewer. We have changed to the following: Incomplete distal ureteral dissection can lead to a residual ureteral stump, which translates to inferior rates of overall survival, cancer-specific survival, distant recurrence-free survival and bladder recurrence-free survival [8].

Changes in text:

[Line 185-187] Incomplete distal ureteral dissection can lead to a residual ureteral stump, which translates to inferior rates of overall survival, cancer-specific survival, distant recurrence-free survival, and bladder recurrence-free survival [8].

Comment 6: - several surveys demonstrated an underuse of bladder instillation due to the concern of drug spillage from bladder closure. The authors should underline this issue;

Reply 6: We agree with the authors and made the following addition to our manuscript:

Adequate exposure to the bladder cuff can also lead to a water-tight cystorrhaphy curtailing fears of drug spillage from bladder closure and perhaps increasing adherence to guideline-based practice [41]

Changes in text: [Lines 161-163] Adequate exposure to the bladder cuff can also lead to a water-tight cystorrhaphy curtailing fears of drug spillage from bladder closure and perhaps increasing adherence to guideline-based practice [41]

Comment 7:- please provide the correct reference stile for reference 1 and 2;

Reply 7: completed

Comment 8:- references 8 and 12 are the seme.

Reply 8: changed