

## Peer Review File

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### Review Comments

#### Reviewer A

The authors review the utility of single-dose pIVC after radical nephroureterectomy for UTUC. This paper provides a very good summary of the current status and future of single-dose pIVC and is very informative for urologic oncologists. This article also contains the latest information and is highly recommended to urologists involved in the treatment of UTUC.

Please consider the following:

What are the reported risk factors for bladder recurrence after radical nephroureterectomy? Please summarize briefly and add it to the text.

**Comment #1:** What are the reported risk factors for bladder recurrence after radical nephroureterectomy? Please summarize briefly and add it to the text.

**Reply 1:** We have included the reported risk factors for bladder recurrence after radical nephroureterectomy.

**Changes in the text:** Section 1.2 “Rationale and knowledge gap” has been updated in its entirety, including references, to reflect the comments by Reviewer A (see page 3, line 61 to page 4, line 80). We included a summary of several meta-analyses on predictors for bladder recurrence after radical nephroureterectomy. We highlighted the role of postoperative intravesical chemotherapy as a modifiable target for decreasing the risk of bladder recurrences.

#### Reviewer B

Dear Authors,

I read with interest your manuscript entitled: “Single Instillation Intravesical Chemotherapy after Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma: Current Evidence and Future Directions.

Overall, I think this article is quite interesting and provides an adequate overview of the studies underlying the inclusion of post-operative intravesical chemotherapy in the guidelines for the treatment of HG UTUC.

Actually, I cannot find a very useful take-home message. In particular, even recognizing the high value of this cross-sectional study, the lack of future perspectives leaves the sensation of an “unresolved issue”.

First of all, I think it would be useful to include further details on the results and conclusions of the cited studies. For example: how was the low utilization of pIVC explained?

Furthermore, the evaluation of pIVC use in this manuscript is based on data collected from other works with a limited number of participants, with low response rates in surveys, which could affect the representativeness of the results, and the absence of an overall consideration on these results does not add a significant value to the existing literature. I believe that Authors should try to explain

why this scenario occur (If you find an issue, try to fix it).

In this manuscript, two strong take-home messages come out:

1. Single dose pIVC is effective after RNU for UTUC in preventing BR;
2. Although official guidelines recommend it, there is still a large part of urologist who do not routinely use it.

The point 1 has been sufficiently explained.

The point 2 is touched, but this aspect is not fully explained and examined. In particular, after that European Association of Urology, National Cancer Center, Network, and American Urologic Association recommend pIVC, could we only state that “further studies on single dose pIVC are warranted to overcome the barriers to implementation” (line 206-207)? Are we sure that barriers are only “theoretical” and resolvable through clinical studies?

It seems that Authors rely on a possible solution of the issue just to wait for more published results. Please, develop this point better.

I think you should add to the conclusions a possible “future plan”, trying to answer the question of how the compliance with level 1 evidence may be promoted in the urological community.

I would suggest enriching the paragraph "understanding safety concerns" with scientific studies such as the following:

“Gulamhusein A, Silva P, Cullen D, Tran M, Mumtaz F, Patki P, Barod R, Bex A. Safety and feasibility of early single-dose mitomycin C bladder instillation after robot-assisted radical nephroureterectomy. *BJU Int.* 2020 Dec;126(6):739-744. doi: 10.1111/bju.15162. Epub 2020 Aug 9. PMID: 32638490.”

The work is well written and has a good structure. Altogether, the use of the English language is valid and only a few corrections are needed before a possible publication.

Waiting for a revised version, I thank you a lot for your scientific contribution and for considering my review report.

I remain at your disposal.

Best Regards

**Comment #1:** First of all, I think it would be useful to include further details on the results and conclusions of the cited studies. For example: how was the low utilization of pIVC explained?

**Reply 1:** The authors agree to the utility of further details on the results of the cited studies regarding pIVC utilization.

**Changes in the text:** The utilization studies were expanded upon in “Assessing Utilization” (see page 7, line 142 to page 10, line 212). Included an additional study that was previously referenced later in the paper by Kenisberg et al.

**Comment #2:** Furthermore, the evaluation of pIVC use in this manuscript is based on data collected from other works with a limited number of participants, with low response rates in surveys, which could affect the representativeness of the results, and the absence of an overall consideration on these results does not add a significant value to the existing literature. I believe that Authors should try to explain why this scenario occur (If you find an issue, try to fix it)

**Reply 2:** In the context of the weakness of this pooled analysis of the 3 studies on utilization of pIVC, we agreed that it does not add significant value to the existing literature. Thus, we do not feel the figure or description of the analysis in the text is necessary.

**Changes in the text:** Removal of Figure 1 and its associated notation within the article.

**Comment #3:** The point 2 is touched, but this aspect is not fully explained and examined. In particular, after that European Association of Urology, National Cancer Center, Network, and American Urologic Association recommend pIVC, could we only state that “further studies on single dose pIVC are warranted to overcome the barriers to implementation” (line 206-207)? Are we sure that barriers are only “theoretical” and resolvable through clinical studies?

It seems that Authors rely on a possible solution of the issue just to wait for more published results. Please, develop this point better.

**Reply 3:** We agree the need for further explanation and examination of point 2. Thus, we have expanded upon the sections regarding “Trajectory of Postoperative Intravesical Chemotherapy Use” to include the suggestion of further investigation specifically along the lines of implementation sciences, which have already been initiated for the NMIBC world. We reinforce the need for groups to identify the specific areas of improvement and outline/implement interventions with trackable outcomes. We do think that study results need to be published from the RESECT study to help guide the pIVC after RNU study group(s).

**Changes in the text:** Page 13, line 262 to page 14, line 290 have been updated to include discussion of implementation sciences.

**Comment #4:** I think you should add to the conclusions a possible “future plan”, trying to answer the question of how the compliance with level 1 evidence may be promoted in the urological community.

**Reply 4:** As discussed in reply to comment #3, we have attempted to answer the question by reference to implementation sciences that have robust evidence-based frameworks for developing interventions that may promote compliance. Given the sparse survey studies available with low response rates, the existing studies are not appropriate models to represent the urologic community as a whole. Thus, expanded survey based studies are necessary.

**Changes in the text:** Page 13, line 262 to page 14, line 290 have been updated to include discussion of implementation sciences.

**Comment 5:** I would suggest enriching the paragraph "understanding safety concerns" with scientific studies such as the following: “Gulamhusein A, Silva P, Cullen D, Tran M, Mumtaz F, Patki P, Barod R, Bex A. Safety and feasibility of early single-dose mitomycin C bladder instillation after robot-assisted radical nephroureterectomy. *BJU Int.* 2020 Dec;126(6):739-744. doi: 10.1111/bju.15162. Epub 2020 Aug 9. PMID: 32638490.”

**Reply 5:** Thank you for this reference, it has now been added to the section on understanding safety concerns.

**Changes in the text:** Page 11, line 225 to page 12, line 246.