

Peer Review File

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Reviewer A

Can you please elaborate on the following –

Comment 1:

All participants are female - is there a reason for that ? What was the reason for radiotherapy that resulted in these strictures ?

Reply 1:

- 1) Thanks for your good question. We believe there are two reasons for this result. First, bilateral ureteral stenosis due to radiotherapy after gynecologic oncology accounted for the majority (7/9) of our reported cases. These patients were all female. Second, the remaining 2 patients underwent IUR for recurrent bilateral ureteral stones and multiple ureteral polyps, respectively. No special selection was made and coincidentally, both patients were female. Overall, due to the small sample size, there are no valuable findings yet.
- 2) Bilateral ureteral stenosis caused by postoperative radiotherapy for gynecologic tumors has been reported in our center [1]. Radiotherapy treatment of tumors is inevitably accompanied by damage to normal tissues. Radiotherapy injury refers to the degradation and subsequent remodeling of the connective tissue matrix, leading to radiation-induced fibrosis[2]. Radiation ureteral injury has different characteristics at different times. In the short term, the pathological changes are mainly characterized by inflammatory exudation and in the long term by fibrosis[3]. Radiation-induced ureteral apoptosis with inflammation eventually leads to ureteral scarring and narrowing. The incidence of ureteral stenosis has been reported to be 1.0%, 1.2%, 2.2%, 2.5%, and 3.3% at 5, 10, 15, 20, and 25 years after radiotherapy, respectively [4]. Given that postoperative radiotherapy has been used as a common tool in postoperative gynecologic oncology, the number of patients with bilateral ureteral stenosis due to radiotherapy injury is rising in recent years based on our center's experience.

Comment 2:

What size stents were used? What is the need for two stents in each segment ?When was the stents removed after surgery ? The authors mention stitching the stents in for prevention of migration - what size and suture were they stitched in with ? Did that impede stent removal ?

Reply 2:

Thank you very much for your question, which mentioned some key points that we were not able to describe in detail. We have added them in the latest manuscript.

- 1) We usually use F7 DJ stents, 26 or 28 cm in length.
- 2) We place two DJ stents to drain the urine from the bilateral renal pelvis and to support the bilateral ureteral-ileal anastomoses.
- 3) Due to the large mobility of the ileal segment, we usually fix the DJ stents in the

anastomotic position using a 4-0 Vicryl suture to prevent the stents from displacement.

- 4) The ureteral stents were removed 2 months after surgery. Mentioned in the text. (Page 6, line 134)
- 5) Since the sutures we use are absorbable and are theoretically absorbed by 2 months postoperatively, removal of the stents should not be difficult. In fact, we have not experienced any difficulty in removing the stents so far.

Changes in the text:

To provide more detail, we have added a description of the sutures and fixation (Page 5, line 112, Page 6, line 117).

Comment 3:

Please mention limitations of these study - one being short term follow up, given the very small number of patients made it to 1 year - it would be difficult to evaluate long term risks of metabolic side effects, subsequent stone formation and long term recurrences.

Reply 3:

Thank you very much for your valuable suggestion. The short-term follow-up is indeed an obvious limitation. We have added the above-mentioned limitations in the updated manuscript.

Changes in the text:

We modified our manuscript and add the limitations (Page 13, line 265-266).

Reference:

1. Li, X., et al., Bilateral ileal ureter substitution for patients with ureteral strictures secondary to gynecological tumors radiotherapy: a multi-center retrospective study. *Transl Androl Urol*, 2021. 10(8): p. 3226-3238.
2. Kochueva, M., et al., Quantitative assessment of radiation-induced changes of bladder and rectum collagen structure using optical methods. *J Biomed Opt*, 2018. 23(9): p. 1-8.
3. Lobo, N., et al., Urologic Complications Following Pelvic Radiotherapy. *Urology*, 2018. 122: p. 1-9.
4. Levenback, C., et al., Hemorrhagic cystitis following radiotherapy for stage Ib cancer of the cervix. *Gynecol Oncol*, 1994. 55(2): p. 206-10.

Reviewer B

Comment:

This is very impressive technique and outcomes. It will be difficult to get a much larger sample size elsewhere in the world. I think this technique can only be replicated in a very high volume tertiary center instead of being commonplace. Perhaps robotic assistance may replicate your technique and make it more reproducible in other lower volume center. The manuscript has sufficient details in its technical description and illustrations. The results and discussion are

well written. I do not have any major criticism except a minor suggestion that total laparoscopic surgery will be hard to be replicated.

Reply:

- 1) Thank you very much for your comments and suggestions, which we fully agree with. This case series presented in this study is rare and challenging. All procedures were performed in two high-volume centers by an experienced surgeon. The completion of these procedures requires a high level of skill and experience.
- 2) Replicating this technique on a robotic surgical platform may be easier with advantages in terms of suturing and visualization. Robotic bilateral IUR has been performed at our center but was not included for comparison due to the small sample size and short follow-up period. Longer-term results regarding robotic versus laparoscopic bilateral IUR may be reported in the future.
- 3) Totally intracorporeal laparoscopic bilateral IUR is difficult. Extracorporeal construction of the ileum is an alternative and may help surgeons gain experience and eventually attempt a totally intracorporeal approach.

Reviewer C

The figure legend for figure 1 and 2 do not match with the figure they are switched, please correct.

This is excellent work. Congratulations on your study. Just a few recommendations. In the discussion section I recommend that you begin the first paragraph by reviewing the open ileal ureteral experience (Launer, B., Redger, K., Koslov, D., Sax-Bolder, A. Higuchi, T., Windsperger, A.P, and Flynn, B. J.: Long-term follow-up of ileal ureteral replacement for complex ureteral strictures: Single institution Study. *Urology* 2021. PMID:34310914. <https://doi.org/10.1016/j.urology.2021.07.012>.). We have published this recently and review the entire open experience. We are gradually converting to a minimal invasive approach but it's important to understand the contributions of the open surgeons. This will allow you to make a better argument on why laparoscopic.

Then compare and contrast why you prefer the minimally invasive approach compared to the open approach. Also, discuss the robotic approach and compare and contrast laparoscopic to robotic. Did you choose the laparoscopic approach because you did not have the robotic platform available or is this truly your preference.

You make a good argument for why you doing the bowel work extracorporeal, but this does add to the morbidity in hospital stay. Do you believe in the future you can do the entire case intracorporeal

Comment 1:

The figure legend for figure 1 and 2 do not match with the figure they are switched, please correct.

Reply 1:

Thank you very much for pointing out our mistakes. We are very sorry for this unwarranted error. We have corrected the error in the order of the Figure legend in the updated text.

Comment 2:

I recommend that you begin the first paragraph by reviewing the open ileal ureteral experience. Then compare and contrast why you prefer the minimally invasive approach compared to the open approach. Also, discuss the robotic approach and compare and contrast laparoscopic to robotic.

Reply 2:

Thank you very much for your valuable suggestions. We fully agree that a full understanding of the development of open IUR is indeed more helpful in understanding our choice of a more minimally invasive approach. We rewrote the first paragraph of the discussion and reviewed the development and the main advantages and disadvantages of open IUR. We also discuss the advantages and disadvantages of laparoscopic and robot-assisted laparoscopic IUR. (page 8-9, line 171-183).

Change in the text:

We added some information about the main advantages and disadvantages of open IUR and compared laparoscopic and robot-assisted approaches in the first paragraph of the discussion (page 8-9, line 171-183).

Comment 3:

Did you choose the laparoscopic approach because you did not have the robotic platform available or is this truly your preference.

Reply 3:

- 1) Thanks for your question. Laparoscopic bilateral IUR was performed earlier at our center before robotic surgery. Robotic bilateral IUR has been performed but was not included for comparison due to the small sample size and short follow-up period. Long-term results regarding robotic versus laparoscopic bilateral IUR may be reported in the future.
- 2) It is undeniable that the robotic platform has significant advantages over laparoscopies in terms of stability and visualization. However, according to our initial experience, laparoscopic bilateral IUR is still a valuable technique. It has a lower overall cost and is an alternative surgical option in centers with no robotic platform available.
- 3) Both laparoscopic and robotic-assisted laparoscopic IUR are good options, and the decision should be based on the individual patient, the availability of different surgical platforms and the personal experience of the surgeon.

Comment 4 :

You make a good argument for why you doing the bowel work extracorporeal, but this does add to the morbidity in hospital stay. Do you believe in the future you can do the entire case intracorporeal.

Reply 4:

- 1) Thank you for your question. Our center is going through the same conversion from an open to a minimally invasive approach like you mentioned. We are performing increasingly complex minimally invasive procedures in recent years. Total intracorporeal bilateral IUR is already an option at our center. Although it is more minimally invasive, we are very careful in selecting our patients. On the one hand, we need more surgical experience, and on the other hand, to prevent unanticipated complications.
- 2) Nowadays, we are trying more and more total intracorporeal approaches. Nevertheless, we believe that the laparoscopic IUR technique, as currently presented, is still valuable, especially in the process of conversion from open to minimally invasive, to gain experience and to improve the safety of the procedure.

Reviewer D

The authors describe their experience and results of a case series of nine laparoscopic bilateral ileal ureter replacements. The results of their series for this challenging surgical procedure are very good. This is the largest series reported for this very rare surgical indication. Technically feasible the laparoscopic approach does not necessarily imply any advantages over an open or laparoscopic robot-assisted approach. For such rare and challenging operations it is the surgeon's experience that renders the best outcome independent of the surgical approach applied. This is an interesting series of a very challenging laparoscopic operation for a very rare surgical procedure.

Comment 1:

Technically feasible the laparoscopic approach does not necessarily imply any advantages over an open or laparoscopic robot-assisted approach.

For such rare and challenging operations it is the surgeon's experience that renders the best outcome independent of the surgical approach applied.

Reply 1:

- 1) Thank you very much for your comments. The authors fully agree with your comments regarding the importance of the surgeon's experience for the outcome of the procedure. This is a challenging procedure and all procedures in this study were done by a very experienced surgeon.
- 2) The main advantage of laparoscopic IUR over open IUR is the smaller incision and faster postoperative recovery. In our experience, the length of the surgical incision and postoperative recovery are important factors influencing the patient's surgical choice. Aesthetics is also a consideration for this series of patients, who are predominantly young and middle-aged with a high proportion of women. Therefore, we believe that laparoscopic bilateral IUR offers significant minimally invasive and aesthetic advantages compared to open surgery.
- 3) Robotic-assisted laparoscopic bilateral IUR was also performed at our center. It shows good

advantages in suturing and visualization but is not without drawbacks. For example, bilateral IUR requires anastomosis of three different sites and may require 2 or even 3 docking to obtain surgical space and visualization, which prolongs the operative time.

- 4) Although there is no direct comparison between laparoscopic and robot-assisted IUR in this article, we believe that both are valuable minimally invasive approaches. The choice of a surgical platform requires a combination of factors including the patient's condition, the surgeon's personal experience, the availability of the surgical platforms and the overall costs.