

Peer Review File

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Reviewer A

The authors present a series of patients undergoing ureteral reconstruction and stratify rates of "complex repair" based on radiation history.

There are some methodologic flaws of this study that prevents publication in its current form. I ask the following questions:

Comment A1: Doesn't the etiology of ureteral injury in the non-radiated affect the type of repair the patient ultimately receives? For example, if a nonradiated patient undergoes a ureteral avulsion at the UPJ, then isn't that automatically an ileal ureter (and by your definition, a complex repair)?

Reply A1: We agree the mechanism of ureteral injury impacts the chosen repair type. However, to borrow your example, an avulsion injury can also occur in the distal or mid ureter where the type of repair would likely differ from a UPJ injury. Therefore, we report both etiology and repair type as these are often related but not interchangeable.

Changes in the text: none

Reviewer B

In this study, the author evaluated the outcomes of ureteral reconstruction in irradiated and non-irradiated fields, and highlighted that the former is associated with more complex urinary reconstruction. Overall, there was no difference in the mid-term complication rate between the two groups.

Comment B1: The main limitation of this study is the small sample size of 47 patients. Were there patients who undergone nephrectomy instead of a ureteral reconstruction? These patients maybe included to increase the study number. Alternatively, the authors may consider recruiting patients from other surgeons or a multicenter study to provide greater reliability and reproducibility of the results.

Response B1: We agree that sample size limits interpretation of these data. Our study design reviewed hospital billing data to identify and include patients having surgical reconstruction of ureteral injuries. We agree that this fails to capture patients who elected nephrectomy or supravescical diversion, either because reconstruction was not feasible or they were unwilling to tolerate associated morbidity. Further, our study design does not capture those patients with ureteral injuries managed with chronic renal drainage. We

included text in the discussion in the submitted manuscript to address this and have added additional text to make the specific limitations Reviewer B cited explicit.

Changes in the text B1: added text to discussion, page 13, lines 318-319.

Comment B2: A greater effort should be attempted to explain the reasons for a more complex ureteral reconstruction in irradiated patients. The mechanism of radiation and devascularization could be elaborated. The decision for a more complex ureteral reconstruction maybe ultimately a subjective one (based on surgeon) rather than an objective one and this should be highlighted.

Response B2: We agree that selection of a complex ureteral reconstruction, which we defined as ileal ureter or renal autotransplantation, is subjective and driven by both patient characteristics and both patient and surgeon preferences. Pelvic radiotherapy has two main effects relevant to ureteral reconstruction: 1) microvascular injury to the ureter which may increase risk of failure, and 2) decreased compliance, functional capacity, and mobility of the bladder. While both of these contribute to selection of ureteral reconstruction repair we feel the impact on the bladder is most likely to drive selection of a complex repair in order to avoid bothersome storage symptoms following an anatomically successful repair. We have added text to the introduction with additional references to make this point more clear and reiterate this in the discussion as written.

Changes in the text B2: Added text to the introduction, page 4, lines 104-106

Comment B3: 7 patients required immediate reconstruction and would unlikely undergo the preoperative nephrostogram/pyelogram or VUDS to assess bladder capacity. In these patients, the algorithm does not appear clinically relevant. Furthermore, urologists are often involved intra-operative as a multidisciplinary surgical team in complex advanced pelvic malignancies that required multi-organ resection (eg.exenteration). Again, this preoperative algorithm may not be applicable.

Response B3: In our series 14% of patients underwent immediate reconstruction at the time of recognized surgical injury and therefore could not be evaluated using our proposed framework. Conversely, this means 86% of patients underwent delayed reconstruction in which our approach was utilized. Clearly, our proposed evaluation protocol cannot be universally applied. However, we feel strongly that careful and accurate fluoroscopic assessment of the ureteral injury in conjunction with preoperative evaluation of the functional status of the bladder facilitates appropriate selection of surgical technique and improved patient counseling. The high success rate reported with the full gamut of ureteral reconstruction techniques supports this conclusion.

Changes in the text B3: Text added to discussion, page 14, lines 321-326

Comment B4: Unfortunately, the algorithm provided in Fig 1 may not be clinically relevant, unless the authors suggest that all patients should undergo some form of VUDS and fluoroscopic assessment prior to any ureteral reconstruction. The small numbers and a single surgeon experience represent significant sample and selection bias for the acceptance of this manuscript.

Response B4: As stated in response B3, we do propose that patients undergoing delayed ureteral reconstruction should have careful evaluation of their ureteral injury/anatomy as well as their bladder function. In our practice we find the most efficient way to do this is with combination of antegrade/retrograde pyelography with video urodynamics. Clearly this is not feasible for every patient, however we do feel it is a key component of our high success rate even among radiated repairs.

Changes in the text B4: None

Reviewer C

Comment C1: "...selection of surgical technique was similar for radiated and non-radiated repairs" This statement is contradictory to the hypothesis that "radiated patients will require more complex techniques."

Response C1: We have clarified that statement to highlight the differences in radiated and non-radiated patients. Specifically that Boari flaps were avoided in radiated patients with bladder volumes <300mL and/or persistent urge incontinence requiring more than one pad per day 4-6 weeks after ureteral stent removal.

Changes in the text C1: Methods page 7, line 160

Comment C2: Result

Length of stricture and site of stricture are crucial determinant factors for reconstruction technique. However, the length of stricture was not included in the data.

Response C2: During our initial data collection we made great efforts to measure length of ureteral stricture. However, we found that these measurements were difficult to obtain and had low inter-observer consistency. Therefore, we chose a reproducible metric of distal versus proximal injury as defined by the relation of the proximal extent of the ureteral injury to the common iliac vasculature. We feel this is both more consistent and clinically relevant as distal injuries can nearly universally be repaired with reimplantation +/- psoas hitch or Boari flap while proximal injuries are more likely to require substitution repair or autotransplant (defined as complex in our series).

Changes in the text C2: none

Comment C3: The actual reasons for each complex repair were unclear. Obviously not all patients followed the algorithm suggested in Fig.1 as many proximal strictures were managed by non-complex methods. Were there insufficient length of residual ureter or excessive ischemic tissue? Were the underlying reasons directly or indirectly related to radiation?

Response C4: As stated in response C2 we defined proximal versus distal ureteral injuries by their relation to the common iliac vasculature. As a result, some proximal strictures (extending above the iliac vasculature) were reconstructed using non-complex methods (reimplant with Boari flap). As highlighted in the discussion (paragraph 1) we speculate that decreased bladder capacity and/or presence of preoperative LUTS (specifically urge incontinence) in the radiated cohort drove increased use of ileal ureter repairs which accounted for the difference in selection of surgical technique.

Changes in the text C4: none

Comment C5: Radiated patients had lower preoperative bladder capacity. From the data presented, it is unclear whether LUTS and bladder capacity actually affected the decision of surgical technique.

Response C5: Indeed the retrospective nature of our study limits our ability to determine the prospective effect of diminished bladder capacity on selection of surgical technique. However, we do note that radiated patients had lower bladder capacity and those undergoing ileal ureter had the lowest capacities. Therefore in the context of our limited data, we speculate that decreased bladder capacity did indeed impact selection of surgical technique – specifically selection of ileal ureter in radiated patients with low bladder capacity.

Changes in the text C5: none

Comment C6: Discussion

The authors suggested the decreased bladder capacity hindered the use of Boari flap and increase the use of ileal ureter or psoas hitch. However, the 300 mL cut-off volume (not actually contracted) for bladder capacity seems arbitrary for the major decision. Why didn't the authors use bladder compliance or other UDS parameters for the decision?

Response C6: We agree and our motivation to submit this manuscript is to address the scant literature addressing appropriate selection of ureteral reconstruction techniques – especially in radiated fields. In an attempt to make our approach generalizable we used readily available anatomic (bladder capacity) and functional (presence of UI requiring more than one pad/day and/or pharmacologic treatment) information from patients. We based our bladder capacity cutoff on a combination of prior urodynamic data regarding radiated bladders as well as our clinical experience as outlined in the changes to the text

below.

Changes in the text C6: paragraph added to discussion, pages 11-12, lines 272-283.

Reviewer D

This is a very interesting study with good methodology. However, I would suggest addressing some issues:

Comment D1: The title of the work does not quite match the content of the article. This is an original work comparing the postoperative results of radiated and non-radiated patients undergoing ureteral reconstruction. The current title suggests that this is a review that assesses preoperative management of radiated patients only.

Response D1: we agree and have changed the title to: “A systematic approach for successful repair of radiated and non-radiated ureteral injuries.”

Changes in the text D1: title changed as above

Comment D2: I suggest moving the sentence “The purpose..” to a new paragraph

Response D2: Agree

Changes in text D2: inserted paragraph break in introduction

Comment D3: The term injury is not exactly defined. Does it involve only ureteral disruption or also ureteral stricture? The abstract uses the term "ureteral stricture / injury", but the materials and methods contain only information about "injury", and the discussion discusses ureteral strictures

Response D3: Agree. We choose the term “injury” as this reflected the full gamut of ureteral pathology included in our series. In recognition of this ambiguity, we were careful to define the types of ureteral injuries (Methods paragraph 2) as external trauma, surgical injury, radiotherapy, endoscopic stone treatment, or other. These are also summarized in Table 1. In the discussion, we used “stricture” as this was the term used by the papers we include in our literature review.

Changes to the text D3: none

Comment D4: The description of the procedure is confusing. Did all patients undergoing delayed reconstruction have stents? Has everyone had the stent removed and a nephrostomy performed, and then the bothersome LUTS were evaluated? After reconstruction and removal of the stent, were bothersome LUTS assessed in all patients after a minimum of 4 weeks? I

suggest adding a second figure showing management before and after the reconstruction.

Response D4: Agree. We added text to the methods section to clarify our standardized approach to preoperative assessment.

Changes to the text D4: text added to methods, page 5-6, lines 135-137.

Comment D5: Figure 1 is too small, and it is very difficult to read

Response D5: Agree, we will work with the submission office to ensure this figure is printed at a legible resolution.

Changes in the text D5: none

Comment D6: Figure 1 legend repeats the information from the text and information contained in the figure. In my opinion, such a long legend is not necessary.

Response D6: Agree, the text was shortened.

Changes in the text D6: text removed from Figure 1 legend

Comment D7: the PCN abbreviation on line 152 is not explained

Response D7: Thank you. We defined this abbreviation with the first use of percutaneous nephrostomy tube (PCN).

Changes in the text D7: as above (page 5, line 135)

Comment D8: The abbreviations used in the tables are not explained

Response D8: Thank you. The abbreviations have been defined appropriately in updated tables.

Changes in the text: as above

Comment D9: A reference is missing for lines 240-245

Response D9: Thank you, this has been rectified.

Changes in the text D9: reference added (#13).

Reviewer E

Comment E1: Primary outcome should include more than just hardware free. It should include further evidence of success whether radiologic or functional.

Response E2: We agree. In order to facilitate statistical analysis we defined primary outcome as freedom from operative intervention. In recognition of other clinically relevant endpoints we defined secondary outcomes as 1) unplanned need for upper tract drainage within 90 days, 2) worsening renal function, 3) persistent urge incontinence, and 4) persistent hydronephrosis after ureteral stent removal. (Methods paragraph 5).

Changes to text E2: None

Comment E3: your sample size is too small to draw such strong conclusions that radiated patients have fewer complications long term.

Response E3: We agree that small sample size is a major limitation of our data and we clearly state this in the discussion. However, we might also point out that in our literature review of comparable studies sample sizes ranged from n=13 to n=54. Therefore, we feel our series provides a meaningful contribution to the literature.

Changes in the text E3: none

Comment: E3 figure 1 is too small to read and does not contribute to the results or discussion of your topic.

Response E3: please see response D5 and D6 above.

Comment E4: the data does not include length of the strictures. This is an important consideration when deciding reconstruction approach. stricture location can be further categorized between proximal, mid and distal. location can affect reconstruction choice. stratifying at just the iliacs is too broad.

Response E4: please see response C2 above.

Comment E5: Provide further details regarding choice of repair. why was autotransplant used instead of ileal ureter in some cases.

Response E5: Choice of ureteral reconstructive technique is complex and nuanced. We propose a systematic framework based on patient anatomic and functional factors which

guides selection of reconstruction. However, no framework can capture all relevant factors – especially patient and surgeon preferences guiding choice of complex reconstructions such as ileal ureter versus autotransplant. In recognition of this, we have added text to the discussion to point out this limitation of our data and propose future study.

Changes in the text E5: added text to discussion, page 14, lines 328-334.

Comment E6: operative time is not comparable across the entire groups. there are too many different types of surgeries to compare OR times just across these two groups.

Response E6: Agree, we have omitted these data.

Changes in the text E6: operative times removed from Table 1.

Comment E7: please provide details for each patient that required intervention within 90 days.

Response E7: Agree

Changes in the text E7: added text to results section, page 9, lines 208-214

Comment E8: what is the surgeons experience and history.

Response: The primary surgeon is fellowship trained in genitourinary reconstructive surgery and practices at a tertiary referral center.

Changes in the text: added text to methods, page 5, lines 119-120.

Comment E9: why not consider buccal graft or appendiceal onlay for complicated or long strictures. tell us more about decision making for choice of reconstruction.

Response E9: Agree.

Changes in the text E9: discussed this limitation in the discussion section, page 14, lines 332-335.

Comment E10: The data is interesting and promising but the conclusions are strongly worded. With only 17 cases, it can't be concluded that radiated patients will have similar outcomes to non-radiated patients.

Comment E10: Agree, we added additional language to the conclusions section to temper

the strength of our conclusions given limited data.

Changes to text E10: added text to conclusions section, page 14-15, lines 344-343.

Comment E11: You need to take a deeper dive into your data. can you provide a table or further information regarding all the complications and regression analysis to see if complications were associated with history of radiation or not.

Response E11: Thank you for the comment. We used the Clavien system to categorize surgical complications and then classified them as low and high grade. These are reported in Table 1 along with the results of a Chi Square analysis which did not find a significant difference in frequency of complications with respect to radiated and non-radiated groups. We do not see how performing a regression analysis would add additional meaning to these data as reported, but would welcome a statistical review if the Editorial Board feels his is appropriate.

Changes in the text E11: none