

TRANSLATIONAL ANDROLOGY AND UROLOGY

Peer Review File

Article Information: Available at <http://dx.doi.org/10.21037/tau-20-713>

Review Comments

Reviewer A

The authors compare their institutional complications of ileal conduits versus neobladders. Few comments:

Comment 1: The NB and IC groups are rather disparate at baseline. Perhaps the authors ought to do a case-matched analysis in order to more fairly compare the groups.

Reply 1: We agree with the reviewer that the groups are rather disparate as shown by the differences in many of the baseline characteristics. We also agree with the suggestion that a case-matched analysis would allow us to more fairly compare the two groups. In fact, we attempted to perform a case-matched analysis and also a propensity score matching. However, groups after matching were too small for reliable statistical analysis. Therefore, we decided to proceed without a matching procedure. We acknowledge that this is a limitation of our study, and we added this to the Discussion.

Change in the text: The baseline characteristics of the IC and NB populations were quite different. We attempted to perform case-matched analysis and propensity score matching, however, the remaining populations in both groups were too small for reliable statistical analysis. Therefore, we used multivariate analysis correcting for possible confounders. However, we accept that multivariate analysis cannot fully adjust for the differences. Therefore, our results would be interpreted with caution. Ideally a formal matched analysis should be done in a larger multicenter population.

Comment 2: How does h/o radiation impact complication rates?

Reply 2: We thank the reviewer for the suggestion. However, only 5.4% of the total patients received preoperative irradiation. Moreover, patients were unequally divided between groups (7% vs. 1.3% in IC vs. NB, respectively), impeding comparison between groups. There is an apparent selection bias for urinary diversion type when a patient receives preoperative radiotherapy. We observed complications more frequently when a patient has been preoperatively irradiated. However, the small number in the NB group prevents us to compare groups. Our patients have been included in a recent paper (Gontero P et al., World J Urol 2019, doi: 10.1007/s00345-019-02982-6) which demonstrated that previous radiation increased the relative risk of experiencing any complication after radical cystectomy.

Change in the text: There is an apparent selection bias for urinary diversion type when a patient receives preoperative radiotherapy. Only 5.4% of the total patients in this cohort received preoperative irradiation. Moreover, patients were unequally divided between groups

TRANSLATIONAL ANDROLOGY AND UROLOGY

(7% vs. 1.3% in IC and NB, respectively), impeding comparison between the groups. Our patients have been included in a recent paper which demonstrated that previous radiation increased the relative risk of experiencing any complication after RC (27).

Comment 3: It might make more sense to analyze predictors of complications for each UD type (in addition to lumping them together).

Reply 3: We do not completely agree with the suggestion of the reviewer. Firstly -referring to our answer to the first comment- ideally a matched analysis should be used. However, this was impossible in our series. Secondly, if matching is not possible, the next best thing to do is to include diversion type as a variable in a multivariate analysis correcting for all possible confounders. However, we accept that multivariate analysis cannot fully adjust for the differences, thus the results might be somehow flawed. This is exactly what we did. From this multivariate analysis, it became clear that the type of diversion is a predictor of long-term complications (Table 3).

Change in the text: No change has been made in the text for this comment.

Comment 4: Does NB type impact complications? The authors used an N-pouch for their NBs, but the most common types are Studer and Hautmann neobladders. How generalizable are the NB results in these contexts?

Reply 4: In our former publications (Eur Urol 2005; 47: 666-72 and SpringerPlus 2016; 5: 646), we demonstrated that the Leuven N-pouch combines the features of two commonly performed neobladders, namely the Studer neobladder and the Hautmann neobladder, and has a good capacity with an active anti-reflux mechanism. Moreover, the complication rates in our neobladder cohort are similar to that of Studer and Hautmann neobladders. Therefore, we think that our complication rates can be generalized to these two popular neobladder types as there are various common features between them.

Change in the text: No change has been made in the text for this comment.

Comment 5: Do recurrence rates differ between the IC and NB?

Reply 5: The analyses of oncological outcomes are the subject of another paper that has been submitted and is under review.

Change in the text: No change has been made in the text for this comment.

Comment 6: What about long-term follow-up data? Surely the authors must have >1 or >2 years complication data available for a sizable proportion of patients if the database captures patients since 1996.

Reply 6: We followed the EAU Guidelines recommendations on surgical complication reporting for this paper, therefore, long-term diversion-related complications were outside of the scope of this paper. We modified the sentence in the Materials and Methods section and added the relevant reference to clarify the above-mentioned point.

TRANSLATIONAL ANDROLOGY AND UROLOGY

Change in the text: Complications were also categorized as short-term (≤ 30 days), intermediate-term (31-90 days), or long-term (>90 days), based on the European Association of Urology (EAU) Guidelines recommendations on reporting surgical complications (14).

Comment 7: Why was the mean length-of-stay upwards of 3 weeks?

Reply 7: We strictly follow ERAS guidelines since almost 5 years and since then there is an apparent decline in duration of hospitalization of the patients. However, all patients included in this analysis date before the implementation of ERAS guidelines. This has been mentioned as a limitation in the Discussion section.

Change in the text: The patients included in this analysis date from before the implementation of ERAS guidelines in our institution, which explains the long stay of the patients.

Reviewer B

As authors data appear on the first page, this is not blinded review.

The paper assesses complications after various urinary diversion options of RC. Author present large, retrospective analysis of patients operated by two urologists during 20 years period. The study is interesting, well written, and easy to follow. Also, it My recommendation will be accept as it is.

Some very minor issues that might be addressed:

Comment 1: I would suggest using term urothelial, rather than transitional carcinoma.

Reply 1: We thank the reviewer for the nice comments and accepting our paper. The term transitional has been changed with urothelial (page 5, line 96).

Change in the text: Eligible patients received RC+UDs for urothelial carcinoma.

Comment 2: Could you describe the protocol of perioperative patient care? Do you follow strictly ERAS guidelines? If no, what are the differences, and when on the study timeline did you implement them.

Reply 2: We implemented the ERAS guidelines almost 5 years ago and since then we strictly follow them. However, patients included in this analysis date from before the implementation of ERAS guidelines in our institution, which explains the long stay of the patients. This has been mentioned as a limitation in the Discussion section.

Change in the text: The patients included in this analysis date from before the implementation of ERAS guidelines in our institution, which explains the long stay of the patients.

TRANSLATIONAL ANDROLOGY AND UROLOGY

Comment 3: Did you analyze influence of adjuvant chemotherapy on long-term complications.

Reply 3: In our cohort, 102 patients received neo-adjuvant chemotherapy, which is standard of care in our institution. Adjuvant chemotherapy is only very rarely administered in our institution. We recently published on the effect of neo-adjuvant chemotherapy on short-term complications (Milenkovic et al., World J Urol 2019; 37: 1857-66). The number of patients receiving adjuvant chemotherapy was really too small to do relevant analysis.

Change in the text: No change has been made in the text for this comment.

Reviewer C

The manuscript debates an interesting, even if not innovative, topic concerning the complication rate associated with the most common urinary diversions (ileal conduit and ileal neobladder). The manuscript is well written and structured. However, it needs of some changes:

Comment 1: The authors should insert epidemiological data about bladder cancer:

Bladder carcinoma is the seventh most common cancer in the world, with 430,000 newly diagnosed cases annually and more than 165,000 cancer-related deaths (Immediate Radical Cystectomy for Massive Bleeding of Bladder Cancer.

Cochetti G, Barillaro F, Boni A, Mearini E. Biomed Res Int. 2015;2015:154392.

Expression of inflammasome-related genes in bladder cancer and their association with cytokeratin 20 messenger RNA. Poli G, Brancorsini S, Cochetti G, Barillaro F, Egidi MG, Mearini E. Urol Oncol. 2015;33(12): 505.e1-7.). Cancer mortality is significantly affected by progression rates of high-risk NMIBC and by cure rates of muscle invasive ones. (Expression of urinary miRNAs targeting NLRs inflammasomes in bladder cancer. Mearini E, Poli G, Cochetti G, Boni A, Egidi MG, Brancorsini S. Onco Targets Ther. 2017; 22; 10:2665-2673.)

Reply 1: We thank the reviewer for the nice comments and accepting our paper. We also thank for the suggestion and we added the sentence about epidemiological data into Introduction section and one of the suggested references (page 5, line 73).

Change in the text: Bladder cancer (BC) is the 10th most common type of cancer in both sexes worldwide (1,2).

Comment 2: In material and methods, the authors should replace the term transitional with urothelial.

Reply 2: The term transitional has been changed with urothelial (page 5, line 96).

Change in the text: Eligible patients received RC+UDs for urothelial carcinoma.

Comment 3: The authors should describe briefly the Leuven N-pouch technique.

Reply 3: We described the Leuven N-pouch briefly in the Methods section (page 6, lines 102-105).

Change in the text: Briefly, Leuven N-pouch was created with a 50-cm segment of

TRANSLATIONAL ANDROLOGY AND UROLOGY

preterminal ileum that was folded into four equally long parts. Three parts formed the N-shaped pouch while the most proximal part remained intact to form the afferent isoperistaltic limb onto which the ureters were anastomosed in an end-to-end fashion.

Reviewer D

The authors provide a retrospective comparison of complications of radical cystectomy with neobladders vs. ileal conduits from a high-volume center. This is a subject already well covered, especially in the era of open cystectomy. The comparison is limited by significant bias between the 2 groups, since many patient and operative variables that affect the outcome are statistically significant.

Comment 1: Multivariable analysis cannot fully adjust for the differences; thus the result might be flawed. Also, the authors adjust for age and for age-adjusted CCI, so they adjust for age twice.

Reply 1: First, we checked for all variables in univariate analysis. Then, we took only the variables with a p value of <0.05 for multivariate analysis. And age was not a predictor in any univariate analysis, but age-adjusted Charlson comorbidity index was. Therefore, we did not adjust for age twice. We removed all hyphens in the table in order to make it clear that those variables were not included in the multivariate analysis. And we added the limitation of a multivariate analysis in the Discussion section.

Change in the text: Therefore, we used multivariate analysis correcting for possible confounders. However, we accept that multivariate analysis cannot fully adjust for the differences.

Comment 2: In a minor notice, the paper could be strengthened, if the authors tried to present and focus on the significant data of the cohort. For example, Figure 1 is too busy and difficult to follow.

Reply 2: We agree with the reviewer that Figure 1 seems a little bit busy, however, it contains all the important information from our multivariate analysis. Besides, no other reviewers commented on this figure.

Change in the text: No change has been made in the text for this comment.

Comment 3: Tables 2a, 2b, 2c could be given as supplementary.

Reply 3: We are aware that these tables seem to have too much data, but we wanted to show the kinds of the complications and their distribution to the reader, as supplementary documents are not always checked.

Change in the text: No change has been made in the text for this comment.