Author’s response to reviews

Title: Presence of transient hydronephrosis immediately after surgery has a limited influence on renal function 1 year after ileal neobladder construction

Authors:
Takuma Narita (pure.drive.m@gmail.com)
Shingo Hatakeyama (shingoh@hirosaki-u.ac.jp)
Takuya Koie (goodwin@hirosaki-u.ac.jp)
Shogo Hosogoe (hosogoe_06m@yahoo.co.jp)
Teppei Matsumoto (shingohatake@gmail.com)
Osamu Soma (shingohacchi@gmail.com)
Hayato Yamamoto (yamahaya10@yahoo.co.jp)
Tohru Yoneyama (keacpvcpo2004@mac.com)
Yuki Tobisawa (tobisawa@hirosaki-u.ac.jp)
Takahiro Yoneyama (uroyone@hirosaki-u.ac.jp)
Yasuhiro Hashimoto (bikkuri@opal.plala.or.jp)
Chikara Ohyama (coyama@hirosaki-u.ac.jp)

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Responses to the Reviewers

List of revisions in BURO-D-15-00143

Presence of transient hydronephrosis immediately after surgery has a limited influence on renal function 1 year after ileal neobladder construction
Reviewer #1:

1. In the ethics statement, the authors have mentioned that "the participants in this study provide their verbal informed consent, and it was recorded in medical chart". How in a retrospective study, the participants could provide consent?

Response:

Thank you for comments. We have explained about using clinical data for clinical research when being hospitalized (before operation), and we enrolled study only the patients who could obtain consent. This part was added in revised manuscript.

Page 5, line 7

The participants in this study provide their verbal informed consent when hospitalized, and it was recorded in medical chart.

2. In the patient selection, the authors describe as "137 patients without serum Creatinine levels and/or computed tomography (CT) imaging within one year after surgery......... were excluded". Did all 64 patients who were included in the study have their CT scans at one month and one year post operatively? Moreover, if so, were all scans done in same machine/scanner. Was it multi-detector (MDCT) or were these different ones (like 4 slice, 16 slice, 64 slice etc). If different machines were used at different times (from 1996-2013), there is a potential difference in diagnostic accuracy (sensitivity and specificity) of scanners. How was this potential difference corrected?

Response:

Thank you for comments. Yes, all patients we enrolled this study has CT scans at one month and one year post operatively. We didn’t scan in same machine from 1996 to 2013.

Nevertheless, we think the difference of computed tomography imaging machine didn’t influence the accuracy of the classification of a hydronephrosis.

3. Why the hydronephrosis grading measured by single urologist? Why not by a radiologist or multiple observers?

Response:

Thank you for comments. At first, we tried to include a radiologist in the present study. However, we could not include them. Therefore, we analyzed it by ourselves. We understand our
method is complicated, and need improvement. Our future study will address more simple strategy to evaluate post-operative renal function including radiologist.

4. In patients' follow up, the authors mentioned that "Ureteral stents were removed 1 week after surgery under radiographic guidance to confirm absence of stricture". How did subsequent formation of uretero-intestinal stricture excluded? as it can also contribute to worsening of HN or renal function deterioration.

Response:

Thank you for comments. We agree with the reviewers comment. In the case of severe hydronephrosis patients, we routinely follow up hydronephrosis by ultrasound whether patient developed severe hydronephrosis or not. When patients developed it, we suspected and investigated subsequent formation of uretero-intestinal stricture. However, in the present study no patient experienced subsequent uretero-intestinal stricture. This point is a limitation of the present study. It was included in the revised manuscript.

This part was collected in revised manuscript.

Page 8, line 16 to 17
Subsequent formation of uretero-intestinal stricture was suspected and investigated when hydronephrosis was worsening.

Page 14, line 12 to 15
In addition, we were unable to control all variables, including selection bias, operative duration, influence of neoadjuvant chemotherapy, split renal function, status of neobladder-urethral anastomosis, reservoir capacity, continence status, uro-dynamic testing data, and other unmeasurable confounding factors.

5. "Patients were discharged 4-6 weeks after surgery" What was the mean duration of hospitalization?

Response:

Thank you for comments. In Japan, national medication care system covered hospitalization more than one month. All Japanese citizen were included in this national medication care system. Therefore, discharge 4 to 6 weeks after surgery is common in Japan.
6. In the patient's follow up, it is mentioned that "each patient was assessed every 3 months using ultrasonography to monitor for hydronephrosis" and later as "CT was performed every 6-12 months for the early detection of tumor recurrence". What was the investigation done to grade the hydronephrosis and its comparison at one and 12 months?

Response:

Thank you for comments. Because of retrospective nature, it was difficult to evaluate all hydronephrosis grades at the same timing. We evaluated one month and one year after the surgery as a represented data. Ultrasound was mainly used to evaluate hydronephrosis worsening. Therefore, we included hydronephrosis grading by CT imaging at 1 month and 1 year after surgery.

This part was added in revised manuscript.

Page 8, line 12 to 13

We performed CT 1 month and 1 year after surgery as a routine work, and patients were discharged 4-6 weeks after surgery.

7. In the results portion, the authors described as "Sixty-one patients (95%) received carboplatin-based neo adjuvant therapy". Was neo adjuvant chemo a routine protocol at authors' institute since 1996? How many cycles of carboplatin-based chemo were given and what was the time interval b/w neo-adjuvant chemo and surgery?

Response:

Thank you for comments. We apologize for the confusing for neoadjuvant therapy. We used cisplatin or carboplatin based on baseline of renal function.

We performed neoadjuvant chemotherapy as a routine protocol since 2004. Two cycles of platinum-based chemotherapy was done, and cystectomy was done within 1 month after chemotherapy. The patient included in the present study underwent radical cystectomy after 2006.

We fixed it.

Page 10, line 4 to 7

Sixty-one patients (95%) received 2 cycles of platinum-based neoadjuvant chemotherapy, and cystectomy was done within 1 month after neoadjuvant chemotherapy.
8. In the table 1, the authors have stratified hydronephrosis into control, low, intermediate and high groups. Lower down they have mentioned about hydronephrosis graded before surgery, one month after surgery and 1 year after surgery. It appears from the result that none of the patients had pre-operative hydronephrosis while mean grade increased in all stratified groups at one month and then again hydronephrosis came down at one year. What is the plausible explanation for this phenomenon?

Response:

We apologize the confusion and pointed question. The reason for transient hydronephrosis may be caused by edema at anastomosis and compliance of the neobladder.

This part was added in revised manuscript.

Page 13, line 16 to 19

Transient hydronephrosis may be caused by transient edema at anastomosis and compliance of the neobladder. However, it is difficult to prove our hypothesis in the present study design. Further prospective study is necessary to verify our findings.

9. The authors have mentioned complication rate of 25%. Kindly stratify them according to some standardized grading system like Modified Clavien grade.

Response:

Thank you for comments.

We added number of complications classified by Clavien-Dindo classification in revised table 1.

10. The Figure 1 describing the grade and hydronephrosis stratification. Is it the original art work and copyright protected? If not, whether prior permission was taken if it was reproduced?

Response:

Thank you for comments. Yes, this is our original art work.

11. In a continent reservoir, many other factors can affect renal function such as status of neobladder-urethral anastomosis. What was the mean reservoir capacity? What was the continence status? How many patients had uro-dynamic testing done to determine the neobladder pressure during voiding which could contribute to hydronephrosis and hence
renal function deterioration in a non-refluxing uretero-intestinal anastomosis. How many of patient required CISC / indewelling catheter after the surgery?

Response:

Thank you for constructive comments. There are no patient need indwelling catheter or clean intermittent catheterization. One patient required urethral bougie only once because of neobladder-urethral anastomotic stricture. We doesn’t have data of reservoir capacity, continence status, and uro-dynamic testing. These limitation should be written in manuscript, so we added in revised manuscript.

Result:

Page 10, line 6 to 9

There were no patients required clean intermittent catheterization or indwelling catheter after the surgery. One patient required urethral bougie only once because of neobladder-urethral anastomotic stricture.

Limitation:

Page 14, line 12 to 15

In addition, we were unable to control all variables, including selection bias, operative duration, influence of neoadjuvant chemotherapy, split renal function, continence status, uro-dynamic testing data, and other unmeasurable confounding factors.

Reviewer #2:

1) There are minor grammatical and syntax issues that would benefit from careful editing from an native English editor.

Response:

Thank you for comments. This manuscript is already proofread by native English editor. If there are any correction points, please instruct us.

2) How do the authors explain the transient hydronephrosis that exists at post operative month #1. Do they think this is due to residual edema at the ureteroileal anastomosis or perhaps less
compliance of the neobladder or of patient unfamiliarity with rigid emptying of the neobladder?

Response:

Thank you for comments. As the reviewer pointed, the transient hydronephrosis may be caused by edema at anastomosis and compliance of the neobladder.

This part was added in revised manuscript.

Page 13, line 16 to 19

The reason for transient hydronephrosis may be caused by transient edema at anastomosis and compliance of the neobladder. However, it is difficult to prove our hypothesis in the present study. Further prospective study is necessary to verify our findings.

3) The authors have not directly compared preoperative eGFR to post operative eGFR at year 1. They do look significantly different, but would not know without statistical analysis. I think this is an important point to ascertain, especially if GFR losses persist despite recovery of radiologic hydronephrosis.

Response:

Thank you for comments. The median rate of renal function deterioration from pre to post operation (1 year) in control group, low group, intermediate group, high group were 10.8%, 24.2%, 11%, 0.0%, retrospectively. Renal function deterioration wasn’t seen in high group, this phenomenon may be due to low renal function before the surgery.

Although we strongly agree with reviewer’s comment, number of cases of each group was not enough to investigate the difference.

This part was added in revised manuscript.

Page 10, line 11 to 13

the median decrease in 1-year eGFR was 12% in all patient. (control group : 10.8%, low group : 24.2 %, intermediate group : 11.0%, high group : 0.0%)

Reviewer #3:

Urinary tract infection, either in the form of non-symptomatic bacteriuria, or a symptomatic infection may be one of the key factors leading to loss of kidney function. Although they define
acute pyelonephritis in M&M, I do not see infection stated anywhere else. It should be one of the main factors assessed, especially when they perform a refluxing technique.

Response:

Thank you for comments. We strongly agree with reviewer’s comments. Nevertheless, only one patient experienced UTI after radical cystectomy with neobladder construction. Therefore, it isn’t feasible to investigate UTI in statistical way.

In the ideal world, each kidney, that is each one of the 128 renal units, should be analyzed individually. Even if one kidney loses significant function, this may not be obvious in the total renal function. This could be performed by nuclear scans to measure split renal function. I believe they do not have this data. They should at least mention this in discussion.

Any thoughts for transient hydronephrosis? Edema, reflux etc…?

Response:

Thank you for comments. We strongly agree with comments and thank for kind suggestion. Unfortunately, we didn’t perform nuclear scan to measure split renal function. As the reviewer pointed, the transient hydronephrosis may be caused by edema at anastomosis and compliance of the neobladder. Therefore, we added in revised manuscript as a limitation of this study.

Page 14, line 12 to 15

In addition, we were unable to control all variables, including selection bias, operative duration, influence of neoadjuvant chemotherapy, split renal function, continence status, uro-dynamic testing data, and other unmeasurable confounding factors.

I find the results of the 4 different groups quite confusing, despite my best efforts to understand in detail. Maybe they can find a way to present their results in a more simple manner.

Response:

We strongly agree with comments and thank for kind suggestion. Our hypothesis is that the post-operative transient hydronephrosis has limited impact on renal function. Therefore, we developed this complicated stratification. We apologize for the inconveniences.

Although not a concern for this specific manuscript, I would like comment on some of their routine:
95% received neoadjuvant chemotherapy and that is to be congratulated! However, they received carboplatinum based chemotherapy. Many medical oncologists would state that unless cisplatinum is given, neoadjuvant will be useless…

Response:

We strongly agree with comments, and apologize for the confusing. Sixty-one patients (95%) received 2 cycles of platinum-based neoadjuvant chemotherapy, and cystectomy was done within 1 month after neoadjuvant chemotherapy.

We already state the point that the influence of neoadjuvant chemotherapy was unclear in this manuscript.

What is exactly checked for under radiographic guidance, when removing the catheters? A stricture will not be visible at that time.

Response:

Thank you for comments. We have done retrograde pyelography when removing ureteral stents. If contrast medium outflow to bladder was smooth, we removed ureteral stents. We were checking early stenosis at this time. However, we could not detect subsequent formation of uretero-intestinal stricture in this practice. Therefore, in the case of severe hydronephrosis patients, we routinely followed up hydronephrosis by ultrasound whether patient developed severe hydronephrosis.

This part was collected in revised manuscript.

Page 8, line 16 to 17

Subsequent formation of uretero-intestinal stricture was suspected and investigated when hydronephrosis was worsening.

Page 14, line 12 to 15

In addition, we were unable to control all variables, including selection bias, operative duration, influence of neoadjuvant chemotherapy, split renal function, continence status, uro-dynamic testing data, and other unmeasurable confounding factors.
4-6 weeks hospitalization is very long; in fact the longest I have read so far…

Response:

Thank you for comments. In Japan, national medication care system covered hospitalization more than one month. All Japanese citizen were included in this national medication care system. Therefore, discharge 4 to 6 weeks after surgery is common in Japan.

Urethroscopic examination is again interesting; I am not aware of many centers that perform this. The more common would be cytology.

Response:

Thank you for comments. We have checked urine cytology too at 3 month intervals. However, sensitivity and specificity of urine cytorogy after neobladder construction are quite low. Therefore, we have performed urethroscopic examination at 3-month intervals for first 2 years. We added this part in methods part.

Page 8, line 16 to 17

Urethroscopic examination and urine cytology was performed at 3-month intervals for 2 years.