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Modified Ileal Conduit for Urinary Diversion After Radical Cystectomy: Perioperative and Oncological Outcomes

Running title: Ileal conduit for urinary diversion

Precis

We conducted the largest scale chart review of outcomes post radical cystectomy with ileal conduit in bladder cancer patients. We found that, through use of a modified technique, overall complications can be managed satisfactorily.

Abstract

Background: To evaluate the surgical effects and oncological outcomes of modified ileal conduit (IC) after RC for bladder cancer.

Methods: A retrospective study was conducted on bladder cancer patients in our hospital. A single center cohort of 211 consecutive bladder cancer patients who underwent RC + Modified IC from September 2012 to August 2019 was analyzed. Demographic data, perioperative results, complications 30 and 90 days after surgery, and oncological outcomes were recorded. Kaplan-Meier method for specific survival results. The 5-year recurrence-free survival (RFS) and overall survival (OS) rate was calculated. Univariate and multivariate Cox regression analyses assessed the predictive effects of comorbidities, tumor stage, grade, and lymph node status on survival rate.

Results: 136 (64.4%) underwent laparoscopic radical cystectomy (LRC) and 75 (35.5%) underwent open radical cystectomy (ORC). The median postoperative first exhaust time (PFET) and postoperative hospital stay (PHS) were 4 days (IQR, 3-5 days) and 16 days (IQR, 14-21 days). There was a total of 103 (48.8%) complications. There were 35, 54, 11, and 2 cases of grade I, II, III, and IV complications, respectively; of which 89 cases were grade I and II, accounting for 87.3%. There were 38 cases of preoperative hydronephrosis and 22 cases of postoperative hydronephrosis. There were 19, 24, 108, 40, and 20 cases of PT0, T1, T2, T3, and T4, respectively, in postoperative pathological stages, and there were 47, 147, and 17 cases of low-grade and high-grade urothelial carcinoma and non-urothelial carcinoma, respectively. The median lymphadenectomy was 14 (IQR, 6–18), and 18 patients had lymph node positivity. The median follow-up time was 26 months (IQR, 13–43), with a total survival of 177 (83.9%), a recurrence-free

survival of 171 (81%), and 34 deaths. Fourteen patients had local recurrence, 31 patients had distant metastasis, and 6 patients had both local recurrence and distant metastasis. The estimated 5-year OS and RFS rates were 76.80% and 79.10%. Preoperative comorbidities, pathological stage, grade and lymph node involvement were the significant predictors of RFS and OS. Preoperative comorbidities, pathological stage, grade, and lymph node involvement were important influencing factors for OS, while preoperative comorbidities and high pathological grade were important influencing factors for RFS.

Conclusions: Modified IC after RC not only can achieve lower postoperative complications, especially the lower incidence of uretero-ileal anastomosis and stoma related complications, but also can achieve the established oncological outcomes of critical radical surgery, and our outcomes were encouraging.

1 . Introduction

Bladder cancer is one of the most common malignant tumors in the urinary system, ranking the 9th among all malignant tumors in the world(1), and the 7th among male malignant tumors in the Chinese population(2). About 20%–30% of bladder cancer patients were diagnosed as muscular invasive bladder cancer (MIBC) at the initial consult(3, 4) and even if patients were initially diagnosed as non-muscular invasive bladder cancer (NMIBC), 10%–30% of patients progress to MIBC(5). The overall incidence in China follows an upward trend compared to previous years(2, 6). Radical cystectomy (RC) as a standard treatment for MIBC and high-risk NMIBC, such as in repeated recurrence and in failure of Bacillus Callmette-Guerin (BCG)

treatment, has been validated in open(7) and in minimally invasive procedures(8-10). RC is also recommended by current guidelines(11, 12). After RC however, there is an important problem: urinary diversion (UD), which has been controversial regarding the surgical method of choice, with no consensus currently reached. There are many types of urinary diversion techniques. Currently, the commonly used methods include: orthotopic neobladder (ONB), ileal conduit (IC) and ureterocutaneostomy(12). As of writing, IC is the most widely used and applied diversion method in the world(13, 14). In 1950, Bricker used the ileum as the output channel for urinary diversion(15). Because of its good therapeutic effect, it has been widely promoted and applied. The Bricker ileal conduit has also been regarded as the gold standard for incontinent urinary diversion(16). The common complications of the classic Bricker IC are ureteral ileum anastomosis and stoma-related complications. It was reported that the incidence of ureter-ileal anastomosis-related complications was 2%–14%, most of which occurred on the left side(17), which was an important cause of renal insufficiency in postoperative patients(18-21). In view of this, some scholars have made improvements on the ileal conduit (IC), such as peritoneal externalization of the IC(22), or pulling the input end of the IC under the mesosigmoid towards the left(23), all of which had achieved good perioperative results. However, up to now, there have been few reports of large cases or oncological outcomes of modified IC after RC. Since September 2012, our hospital has adopted a modified IC technique for urinary diversion after RC, which is similar to, but slightly different from the previously reported methods(22, 23), with a total number of 211 cases that had not been systematically evaluated or analyzed. In this study, the data of patients undergoing modified IC after RC in our hospital for around 8 years were retrospectively analyzed to evaluate the perioperative and oncological outcomes.

2. MATERIALS AND METHODS

2.1 Patients

The medical records database of our institution has had an established electronic medical record homepage system since 2012, including: demographics, diagnosis, treatment (including surgery) and pathology information. It is a continuous database populated with data directly from the patient's electronic medical records and follow-up information. This system is also linked to electronic medical records, which can easily query all inpatient diagnosis and treatment information, under authorization by the institution. After approval by the institutional review Committee, all patients who underwent modified ileal conduit after radical cystectomy (RC+MIC) were reviewed between September 2012 and June 2019. Patients followed up for less than 6 months were excluded, except for those who died.

2.2 Surgical Technique

During the study period, four teams of surgeons performed urinary tract reconstruction. An identical technique was adopted in all IC for Urinary Diversion. The steps taken were as follows:

Firstly, after radical cystectomy and bilateral pelvic lymphadenectomy, an ileal segment was separated from the proximal ileocecal valve approximated 15–20 cm in length. As previously reported(23), the length of the IC was decided by the patient's abdominal condition and the small intestinal mesentery anatomy, ranging from 20–25 cm in length, which is slightly longer than the classical Bricker IC(15). After continuity of the small intestine was restored, the ileal segment was washed with diluted Iodophor to remove residual material in the small intestine.

Secondly, retroperitoneal placement of IC and uretero-ileal anastomosis were performed. At the level of the sacral promontory, behind the sigmoid mesocolon, a tunnel was obtusely

dissociated. After the input end was closed with 3-0 absorbable sutures, the proximal IC was pulled towards the left retroperitoneum without significant tension. At the intersection of the left IC and the left ureter, a redundant part of ureteral stump was removed, which was about 8-10 cm long (Fig 1). Then, the left ureter was anastomosed almost in situ to the ileum by end-to-side anastomosis, and a single J tube was placed inside the ureter-ileum as an internal stent for drainage. Moreover, the proximal IC was fixed to the left psoas major aponeurosis(24). At the promontory of the sacrum, a retroperitoneal channel was separated towards the right (Fig 2), and the outlet end of the conduit was passed from the retroperitoneum to the right side, and led out from the prepositioned skin stoma. The right redundant ureter was resected, the right ureter was anastomosed to the conduit in the same way, then a single J tube was placed inside for drainage (Fig 3). After removing the excess part, both ureters underwent almost in situ end-to-side uretero-ileum anastomosis, ensuring that the blood supply of the ureters would be good after the anastomosis.

Finally, construction of ileal cutaneous stoma was done. A round stoma, about 3 cm in diameter, was made over the right abdominal wall area and the anterior and posterior sheaths of rectus abdominis around the stoma were sutured together. Then, the IC was drawn from the retroperitoneum and fixed to the rectus abdominis sheath. A papillary stoma was created at the output end of the IC, which was similar to a method previously reported(22, 25), leaving the papillary stoma partially exposed and protruding about 2–3 cm away from the skin(Fig 4).

2.3 Follow-up

The patients were followed-up every 3 months for the first year, every 6 months for the second year, and once yearly thereafter. Routine follow-up included: physical exam, serologic

testing, and imaging examination, including: electrolyte, creatinine, liver function test, and abdominal/pelvic ultrasonography. Chest X-ray and abdominal/pelvic CT were performed 6 months after surgery, and then annually, as needed.

Follow-up data were obtained by reviewing medical records or by directly calling patients. Three of the authors (Zhang Yimu, Zhou Zhengyu and Bai Jiyan) performed telephone interviews. In addition, all complications, especially those related to ureteral-ileal anastomosis, were recorded in detail during follow-up. For patients followed up in other places, relevant records were obtained through telephone interviews.

2.4 Data collection

Demographic and preoperative variables were recorded as followed: age, gender, body mass index, smoking history, drinking history, Charlson comorbidity index, preoperative upper urinary tract collection system status, neoadjuvant chemotherapy, and bladder cancer surgery history (including partial cystectomy and TURBT).

The operation-related variables were written down as followed: operative time (OT), estimated intraoperative blood loss (EBL), intraoperative blood transfusion, postoperative first exhaust time (PFET), postoperative hospital stay (PHS), postoperative complications within 30 days, 90 days, and long-term complications. Long-term complications were defined as surgery-related complications encountered up to 90 days after operation. Postoperative uretero-ileal anastomose-related complications, including postoperative urinary leakage and hydronephrosis, as well as stoma related complications, including intestinal obstruction, intestinal leakage, parastomal hernia, and IC or stoma necrosis, were separately recorded.

Primary tumor invasion and lymph node involvement recorded in the pathological reports

were classified according to the 2010 AJCC TNM staging system(26),. If no cancer cells were found in postoperative pathological specimens, the staging was defined as T0, and the pathological grading referred to results of the preoperative cystoscopy biopsy or TURBT.

2.5 Statistical analysis

Continuous variables were recorded as median and interquartile ranges. Qualitative variables were reported as n (%). Survival times were defined as the time elapsed from procedure to the date of recurrence (RFS), or death (OS). Kaplan-Meier method was used to plot the stage specific survival results. The 5-year survival rate was calculated, and the statistical significance among groups was evaluated by log-rank test. Univariate and multivariate Cox regression analyses were used to assess the predictive effects of comorbidities, tumor stage, grade, and lymph node status on survival rate. A two-sided P value of ≤ 0.05 was considered statistically significant. All statistical analyses were adopted with the IBM SPSS Statistics ver. 25.0 (SPSS Inc., Chicago, IL, USA).

3 Results

3.1 Patient demographic data

During the study period, of 259 patients who underwent radical cystectomy in our department, 211 (81.5%) underwent modified IC, 42 (16.2%) underwent ureterocutaneostomy, and 6 (2.3%) received orthotopic neobladder (ONB). Of the 211 patients who received IC, 136 (64.4%) underwent laparoscopic surgery and 75 (35.5%) underwent open surgery.

Of the 211 modified IC patients in this study, 183 were male and 28 were female. The

demographic, perioperative and pathologic data are summarized and shown in Table 1. The median age of the patients was 61 years. Among them, 110 (52.1%) had a history of smoking and 31 (14.7%) had a history of alcoholism. Eighty-seven patients had comorbidities: 65 patients with hypertension, 27 patients with diabetes, and 63 patients with other comorbidities, including 16 patients with multiple system comorbidities. Seventy seven (36.5%) had bladder cancer surgery, including transurethral resection of bladder tumor (TURBT) with partial cystectomy, or multiple tumor resection. There were 15 cases with other system operation history, including 13 cases of abdominal open operation. Thirty-one patients received 2–3 courses of neoadjuvant chemotherapy.

3.2 Hydronephrosis.

Cases of hydronephrosis before and after operation was analyzed and compared. There were 38 cases of hydronephrosis before operation, including 17 cases of left hydronephrosis, 12 cases of right hydronephrosis and 9 cases of bilateral hydronephrosis.

Postoperatively, there were 22 cases of hydronephrosis, including 10 cases of left hydronephrosis, 4 cases of right hydronephrosis, and 8 cases of bilateral hydronephrosis.

When patients with hydronephrosis were examined and compared, it was found that disease in 22 patients with preoperative hydronephrosis had reduced or disappeared postoperatively, with 16 still having hydronephrosis postoperatively. Six patients without preoperative hydronephrosis developed postoperative hydronephrosis, including 5 cases on the left side, 1 case on the right side and 1 case on bilaterally. In these 6 patients with postoperative hydronephrosis, renal function was normal or mildly abnormal by the last follow-up. The longest

follow-up time was 83 months. By the end of review, there were no cases of postoperative renal failure requiring dialysis.

3.3 Perioperative data

No intraoperative death or Severe complications occurred during the period observed. The surgical and follow-up data are presented in Table 3. The median OT was 315 minutes (IQR, 260-375 minutes), 342.5 minutes and 270 minutes for LRC and ORC technique, respectively. The median EBL was 500 ml(IQR, 300–900 ml), with median EBL for the LRC and ORC groups at 400 and 700 ml, respectively. The differences between OT and EBL were consistent with previous reports(27, 28). A total of 96 (45.5%) patients received a transfusion during the perioperative period. The median PFET was 4 days (IQR, 3–5 days),and median PHS was 16 days (IQR, 14–21 days).

3.4 Complications

Postoperative complications were divided into 30-day, 90–day, and long-term postoperative complications. All of them were graded according to the Clavien-Dindo classification system(29) and the organ system classification(30). The total number of postoperative complications noted was 102 (48.3%), including 87 cases of complications within 30 days, 9 cases within 90 days, and 6 cases of long-term postoperative complications. Among them, 10 cases (4.7%) had IC-related complications and 11 cases (5.2%) had ureteral ileum anastomose-related complications according to the Clavien–Dindo classification system. The specific breakdown of complications is shown in Table 4. Grade 1, 2, 3, and 4 complications were seen in 35, 54, 11, and 2 cases,

respectively, of which, 89 cases of grade 1 and 2 complications accounted for 87.3 % of all complications. There were 11 patients with two or more complications at the same time or successively, which were cured after comprehensive treatment.

Shown in Table 5., there were 25, 23, and 16 cases of wound, infection and gastrointestinal system occupying the top three positions according to the classification of organ system,

3.5. Oncologic outcomes

The oncologic outcomes are shown in Table 6, and consist of the following: postoperative pathological staging, positive resection margin, positive lymph nodes, number of lymph nodes removed, median follow-up time, local recurrence or distant metastasis, RFS rate, and OS Rate. There were 18, 23, 109, 40, and 21 patients with PT0, T1, T2, T3, and T4 stages, respectively. All patients with PT0 underwent TURBT before surgery. None of the patients had a positive surgical margin. Cases divided into low-grade, high-grade urothelial carcinoma and non-urothelial carcinoma. According to the WHO 2004 pathological classification method(31), with 47, 147, and 17 cases respectively. Of the 211 patients analyzed, the median lymph node resection count was 14 (IQR, 6–18), with 18 (8.5%) patients being found lymph node positive. There were 14 patients with local recurrence, 31 patients with distant metastasis, and 6 patients with both local recurrence and distant metastasis. The median follow-up time was 26 months (IQR, 13–43). We noted 177 patients (83.9%) survived, and 171 patients (81%) survived without recurrence.

Kaplan–Meier method was used to plot the stage-specific survival results, and the 5-year RFS and OS rate were 79.10% and 76.80%, respectively. Log-rank test was used to evaluate the statistical significance among each group. Pathological stage (T4 vs T0, P=0.003; T4 vs T1, P=0.03;

T4 vs T2, P=0.001; T3 vs T0=0.032; T3 vs T1=0.050), grade (low grade vs high grade, P=0.006; low grade vs non urethral epithelial carcinoma, P=0.002), preoperative CCI (CCI=0 vs CCI⩾ 1, P=0.000), and lymph node status (negative LN vs positive LN, P = 0.000) had significant influence on survival rate, but the surgical method did not. Univariate Cox regression analysis showed that preoperative comorbidities, pathological stage, grade and lymph node involvement were the significant predictors of RFS and OS. Multivariate Cox regression analysis showed that preoperative comorbidities, pathological stage, grade, and lymph node involvement were important influencing factors for OS, while preoperative comorbidities and high pathological grade were important influencing factors for RFS, as shown in Table 7.

4. Discussion

RC combined with bilateral pelvic lymph node dissection (PLND), as the standard treatment for radical bladder cancer, has been validated clinically with multiple studies demonstrating similar oncologic results versus both open and minimally invasive procedures. However, the most important issue after RC is performing a proper urinary diversion or reconstruction as only when this link is completed, can the radical operation for bladder cancer be considered as over. Radical resection of bladder cancer combined with urinary diversion is considered as one of the most complex and difficult surgeries in the field of surgery due to the large amount of surgical trauma caused, the extensive resection needed, and the complexity of the surgical procedure, including resection and reconstruction, as well as the involvement of intestinal tract. It is not difficult to infer therefore, that the rate of surgical complications is very high. The high complication rates in RC have been confirmed by many studies, with an overall complication rate of approximately 30–

70%(28, 32). A high incidence of complications is associated with urinary tract reconstruction or diversion, with a reported duct-related complication rate of up to 32.7%(33). IC urinary diversion is currently the most widely used technique, accounting for the highest proportion of all urinary diversion surgery.

The main problem with classic IC is in the placement of ileal segment and uretero-ileal anastomosis. With classic IC, the left ureter is widely dissociated and pulled towards the right side for anastomosis with ileum, which increases the potential risk for complications related to uretero-ileal anastomosis. This complication has also been reported by many others(18, 24). To avoid such complications, many scholars have modified the Bricker IC. One method is to make the stoma extraperitoneal to avoid stomata-related complications. Another one is to pull IC from the posterior sigmoid colon towards the left side to reduce complications of left ureteral ileal anastomosis. Combining the advantages of the two above procedures, we externalized the peritoneum of the stoma and pulled the input side of IC towards the left, significantly reducing the incidence of ileal conduit-related complications and ureteral ileal anastomose-related complications. In this study, 103 cases (48.8%) had complications, including 16 cases (7.6%) of ileal conduit-related complications and 12 cases (5.7%) of ureteral anastomotic complications, which was lower than the previous reports. It is noteworthy that no cases of parastomal hernia occurred. Hussein AA et al(34). reported that the incidence of parastomal hernia after RC and IC was as high as 20%, of which 15% required surgery. The absence of parastomal hernia in this study was mainly due to our modifications.

In order to reduce the complications associated with ostomy and ureteral ileal anastomosis, to improve surgical safety, and to improve postoperative quality of life, we optimized and

modified surgical procedures for urinary diversion after RC, with some parts completely changed. Based on an experience with 211 cases of modified IC over 8 years, we suggest the following: 1) If both ends cannot be taken into consideration, the outlet end of IC should be guaranteed first. Since IC enters the retroperitoneum from anterior sacrum, it needs a relatively long ileum and mesentery. Some obese patients, or people with short mesenteries, have difficulty taking care of both sides. After the peritoneal extraperitoneum of the IC, the position of uretero-ileal anastomosis should be preliminarily estimated under the condition that the exit is long enough. At this time, the left side of the IC may not be able to be pulled to the left ureter, but it can be as close to it as possible. That is, the position of uretero-ileal anastomosis can be slightly adjusted according to the specific length of the IC; 2) At the skin stoma, the aponeurosis of rectus abdominis should be sutured intermittently with 1-0 silk thread. The suture should be retained and used to fix the ileostomy. This can not only prevent the stoma from retraction or protrusion, but can also prevent parastomal hernia. Extraperitoneal stoma, suture choice, and fixation of the outlet are the key techniques to avoid parastomal hernia; 3) Uretero-ileal anastomosis does not require anti-reflux. Continuous suture can be performed directly with 4-0 absorbable suture. The single J tubes were routinely placed inside as the stent for internal drainage, thus reducing the chance of urine leakage and anastomotic stenosis; 4) Under tension-free conditions, remove as much of the residual ureter as possible to ensure a good blood supply to the remaining ureter, preventing lower ureter and anastomotic ischemia, thereby reducing the occurrence of anastomotic stenosis and hydronephrosis.

To ensure negative surgical margins as far as possible, we have a wide range of resected area. Since Bricker IC does not need to consider the issue of urinary control, extended resection is

feasible. The bladder was dissociated on both sides of the pelvic floor fascia and placed in the extraperitoneal space. The neurovascular bundle was generally not retained unless the patient requested it. After a cystectomy, the pelvic floor was almost skeletonized. In this study, none of the patients had a positive surgical margin. In addition, since IC was pulled towards the left retroperitoneum, the left ureteral stump was excised 8–10 cm, further ensuring a negative margin.

The ideal extent for lymph node dissection has not been determined. Some scholars reported that enlarged lymph node dissection yielded more lymph nodes and had a higher positive rate than standard lymph node dissection. In patients with lymph node positivity, the five-year recurrence free survival rate after expanded lymph node dissection was significantly higher than that after localized lymph node dissection(35, 36). However, a randomized phase 3 clinical trial yielded the opposite result. The study included 198 patients with extended lymph node dissection and 203 patients with limited lymph node dissection. The former had no significant advantage in terms of 5-year RFS, CSS and OS(37). The current guidelines recommend a minimum of standard lymph node dissection, defined as the removal of lymphoid fat tissue below the bifurcation level of the iliac vessels. Guidelines also recommend that at least standard lymph node dissection should be performed, which is the removal of adipose tissue below the level of iliac vascular bifurcation(12). In this study, standard lymph node dissection was used, and the median number of harvested lymph nodes was 14 (IQR, 6–18), and 16 (7.6%) patients were lymph node positive. Although the scope of lymph node resection has not yet been agreed upon and is still being debated, the impact of lymph node involvement on tumor prognosis is clear(38). Patients with lymph node metastasis had worse RFS and OS than those without lymph node

metastasis and that difference was statistically significant. Univariate and multivariate regression analysis further confirmed that lymph node positivity was an independent predictor of the prognosis in radical cystectomy(8, 39, 40).

The prognosis of bladder cancer after radical resection has been verified via long-term clinical practice(7, 8, 41). The introduction of minimally invasive surgery in the latest two decades, such as laparoscopic radical cystectomy and robot-assisted radical cystectomy for bladder cancer, have not only improved perioperative parameters, but have also achieved similar oncologic results as open surgery(42). This has been further demonstrated in recent randomized clinical trials(9, 10, 27). In this study, a modification of IC significantly reduced associated complications, especially those related to ureteral ileum anastomosis and the stoma. The tumor prognosis was also encouraging. This study further confirmed that the most accurate predictors of tumor recurrence and death were the pathological stage of the primary tumor and regional lymph node status. Through univariate and multivariate regression analyses, the study also found that preoperative comorbidities had significant effects on RFS and OS, with poorer RFS and OS outcomes for patients with CCI⩾1. This was consistent with the poor physical status mentioned in the RAZOR trial as an important predictor of 36-month progression-free survival(28).

Minimally invasive treatment of tumors has become widely used in practice and it is most widely used in the field of urology. Minimally invasive surgery provides many important advantages, such as reducing intraoperative bleeding, accelerating recovery, shortening hospital stay and reducing wound complications(14, 28). However, in addition to these perioperative advantages, there is scant evidence that these methods have better oncological outcomes, with outcomes still depending largely on the local tumor stage, the biological characteristics of the

disease, and perhaps also on the surgeon's experience(9). In fact, it is not difficult to speculate that, in a sense, minimally invasive surgery only achieve the same range of results as open surgery through less invasive methods, and in some aspects, with less resection under certain refined procedures, such as uterus preservation. In this study, there were 136 (64.5%) cases of minimally invasive surgery, compared with 75 (35.5%) cases of open surgery, RFS and OS were comparable, which was the same as previous reported results(9, 10, 27).

At present, although the application of robotic surgery in large medical centers is accelerating around the world, its high cost hinders further popularization. Although our hospital is a cancer treatment center in central China, Da Vinci robotic surgery has just recently started. Therefore, it is reasonable to speculate that laparoscopic surgery will remain the main form of minimally invasive surgery for some time to come. It is worth mentioning that open surgery is known for its relatively short operating time. For patients with a history of abdominal surgery, extensive intestinal adhesions, or cardiopulmonary diseases that do not allow long-term surgery with high CO_2 pressure in the abdominal cavity, open surgery will continue to play an irreplaceable role for quite a long time.

Since the current Guidelines for bladder cancer in China are based on the 2010 TNM staging, which has not been updated, we refer to the seventh edition of TNM staging system for clinical and pathological staging. The prognosis of patients with higher stages was significantly worse than that of patients with lower stage.

So far, as far as we know, although this is the largest single-center study of modified IC after RC, it still has some inherent limitations. This study is retrospective, so there are selection biases and differences in care. Inconsistent follow-up and lack of multicenter results limit the

applicability of this study. The OS and RFS of this study were higher than those reported before, which may be related to the relatively large number of patients who were lost follow-up. In the past 20 years, China's economic and social development has been in a transitional period. Some patients, especially those in rural areas, have frequently changed their address and mobile phone number. Further, some patients living in remote areas may have not received regular follow-up, resulting in some mild complications that were not recorded. In addition, under our country's current medical system, a three-level referral system is not yet complete. Also, patients can seek medical treatment anywhere, which poses challenges to follow-up work. The number of complications may thus be less than the actual number of occurrences, and some may not have been recorded. We did not calculate the cancer-specific survival rate, mainly because a considerable number of patients died at home and the cause of death was unknown. However, except for a few deaths, the follow-up time was more than half a year, which showed that the complication reports within 180 days were accurate. Therefore, the results of the incidence of postoperative complications are reliable. However, most of the patients lost to follow-up were mainly concentrated before 2014, and these patients were lost to follow-up due to changes of their phone numbers and addresses. There were relatively few patients lost to follow-up after 2015, so the 3-year and 5-year RFS and OS were basically unaffected. In addition, the proportion of total patients lost to follow-up is still within the statistical range, so the impact of loss to follow-up on survival rate is limited.

Conclusions

To the best of our knowledge, this is the largest single institution study of modified IC after RC to date. We evaluated the postoperative complications and oncological outcomes in detail.

Modified IC after RC not only can achieve lower postoperative complications, especially the lower incidence of uretero-ileal anastomosis and stoma related complications, but also can achieve the established oncological outcomes of critical radical surgery, and our outcomes is encouraging. This requires longer-term follow-up and prospective randomized controlled studies for further verification.

Table Legends:

Table 1:

Table depicts patient baseline characteristics.

Table 2:

Table depicts comparison of pre- and post-operative hydronephrosis.

Table 3:

Table depicts perioperative results.

Table 4:

Table depicts surgical complications stratified by the Clavien-Dindo classification system.

Table 5:

Table depicts a summary of complication types encountered.

Table 6:

Table depicts a summary of oncologic outcomes.

Table 7:

Table depicts univariable and multivariable logistic regression analyses to identify predictors of RFS and OS after RC with IC.

Figure Legends:

Tables:

Table 1 Baseline characteristics of patients (n=211)	
No. of patients	211
Sex, no.	
male	183 (86.7%)
female	28 (13.3%)
Median age (IQR), y	61 (53-67)
Smoking history	110 (52.1%)
History of alcoholism	31 (14.7%)
comorbidity	87 (41.2%)
Hypertension	65
Diabetes	27
Other comorbidities	63
Bladder cancer surgical history	77 (36.5%)
Other surgical history	15
Abdominal and gastrointestinal surgical history	7
Other urological surgical history	3
History of hysterectomy	3
Orthopedic surgical History	2
Perioperative NAC	31 (14.7%)

Table 2 Comparison of preoperative and postoperative hydronephrosis

	preoperative	postoperative
Total	38	22
left side	17	10
right side	12	4
bilateral	9	8

Table 3 Perioperative results	
Modalities, no.	
LRC+IC	136(64.5%)
ORC+IC	75(35.5%)
OT (median, IQR), min	315(260-375)
LRC group	342.5
ORC group	270
EBL (median, IQR), ml	500(300-900)
LRC group	400
ORC group	700
Transfusions, no.	96 (45.5%)
PFET (median, IQR), d	4(3-5)
PHS (median, IQR), d	16(14-21)

Table 4 Surgical complications stratified by the Clavien-Dindo classification system

Grade	Complication	No. of cases	Management
Early (≤30d after surgery)			
I	Incisional haematoma	1	Drainage
I	Wound fat liquefaction	8	Change the dressing and medication
I	Wound infection	12	Change the dressing and antibiotics
I	fever	7	Symptomatic treatment
II	Bowel ileus	7	Conservative
II	Delirium and agitation	2	Sedative
II	lymphatic leakage	11	Drainage and support therapy
II	Urinary leak	3	Stent drainage, antibiotics and supportive treatment
II	Pelvic infection	9	Two cases were treated with puncture and drainage, and 7 cases were treated with anti-infection
II	urinary tract infection	9	Antibiotics
II	pneumonia	4	Antibiotics
II	hydrothorax	2	Antibiotics and pleural puncture drainage
II	stress ulcer	1	Hemostasis and acid inhibition
IIIa	wound dehiscence	4	Suture with local anesthesia
	Small intestinal leakage	2	Reoperation
	Deep venous thrombosis	3	The thrombus filter was surgically installed
IVa	Congestive heart failure	1	ICU monitoring and treatment
IVb	multiple organ dysfunction	1	ICU monitoring and treatment
Late (>30d after surgery)			
I	hematuresis	2	Conservative
I	Mild hydronephrosis	5	observation
II	adhesive intestinal obstruction	3	Conservative
II	Recurrent urinary tract infection	3	Antibiotics

Table 4 (Continued)

IIIa	hydronephrosis	1	One case of left hydronephrosis underwent percutaneous drainage

			A case of partial intestinal necrosis with intestinal obstruction was anastomosed after partial
IIIb	Bowel ileus	1	intestinal resection
Multiple complications		11	Comprehensive treatment

Table 5 Summary of complication types and categories

Category (% of Total102)	Complication	Frequency
Wound (24.5%; n=25)	Wound seroma	1
	Wound infection	12
	Wound dehiscence	4
	Wound fat liquefaction	8
Infectious (22.5%; n =23)	fever of unknown origin	7
	Abscess	5
	urinary tract infection	4
	Sepsis/Urosepsis	2
	Pyelonephritis	3
	Gastroenteritis	2
Gastrointestinal(15.7%; n =16)	Ileus	8
	Constipation	3
	Anastomotic bowel leak	2
	Gastrointestinal bleeding	1
Genitourinary (11.8%; n = 12)	Renal failure	1
	Ureteral obstruction/RUT	6
	Urinary leak	3
	Hematuria	2
Cardiac (8.8%; n=9)	Arrhythmia	2
	Congestive heart failure	2
	Angina	2
	Hypotension	3
Pulmonary (7.8%; n=8)	Atelectasis	4
	Pneumonia	4
	Pleural effusion	2
Bleeding (3.9%; n=4)	Anemia requiring transfusion	2
	Postoperative bleed other than gastrointestinal	1
	Wound hematoma	1
Thromboembolic (2.9%; n =3)	Deep venous thrombosis	3
Neurological (2.0%; n = 2)	Delirium/Agitation	2

Table 6 Oncologic outcomes

Postoperative pathological stage	
pT0	18(8.5%)
pT1	23(10.9%)
pT2	109(51.7%)
pT3	40(19.0%)
pT4	21(10%)
Positive surgical margin, n	0
Negative surgical margin, n	211
Postoperative pathological grade	
low grade	47（22.3%）
high grade	147（69.7%）
non-urothelial carcinoma	17（8.1%）
Lymph node involvement	
no positive lymph node	195（92.4%）
positive lymph nodes	16（7.6%）
Lymph nodes removed(median,IQR)	14（6-18）
Recurrence or metastasis	40（19.0%）
local recurrence	14（35%）
distant metastasis	31（77.5%）
Local recurrence and distant metastasis coexist	6（15%）
follow-up months (median, IQR)	26（13-43）
overall survival, n	177（83.9%）
recurrence-free survival, n	171（81%）
5-year RPS	79.10%
5-year OS	76.80%

Table 7 Univariable and multivariable logistic regression analyses to identify predictors of RFS and OS after RC with IC

	Univariable analysis				Multivariable analysis			
	HR	95% CI		p value	HR	95% CI		p value
		Lower	Higher			Lower	Higher	
RFS								
Sex	0.411	0.098	1.723	0.224				
Smoking history	0.551	0.273	1.109	0.095				
Drinking history	1.942	0.872	4.328	0.104				
Comorbidity	3.382	1.638	6.982	0.001	3.214	1.506	6.859	0.003
Bladder cancer surgical history	1.368	0.685	2.73	0.374				
Surgical modality	0.648	0.297	1.413	0.276				
Postoperative pathological stage	1.831	1.27	2.641	0.021				0.192
T0								
T1	1.556	0.141	17.193	0.718	2.031	0.181	22.823	0.566
T2	2.487	0.326	18.961	0.379	2.821	0.364	21.875	0.321
T3	4.501	0.569	35.601	0.154	5.162	0.644	41.39	0.122
T4	9.41	1.151	76.907	0.036	6.935	0.796	60.382	0.079
Postoperative pathological grade				0.044				0.116
low grade	reference				reference			
high grade	5.607	1.328	23.68	0.019	4.553	1.058	19.605	0.042
non-urothelial carcinoma	7.928	1.447	43.439	0.017	5.231	0.895	30.556	0.066
Lymph node involvement	4.575	1.964	10.657	0.000	2.129	0.834	5.435	0.114
OS								
Sex	0.421	0.1	1.767	0.237				
Smoking history	0.559	0.278	1.127	0.104				
Drinking history	1.901	0.853	4.236	0.116				
Comorbidity	3.402	1.648	7.024	0.001	3.176	1.5	6.727	0.003
Bladder cancer surgical history	1.374	0.689	2.741	0.367				
Surgical modality	0.634	0.29	1.387	0.254				
Postoperative pathological stage				0.011	1.627	1.117	2.371	0.041
T0	reference				reference			
T1	1.56	0.141	17.229	0.717	2.478	0.22	27.951	0.463
Table 7 (Continued)								
T2	2.496	0.328	19.017	0.377	3.164	0.405	24.708	0.272

T3	4.488	0.567	35.494	0.155	4.882	0.61	39.103	0.135
T4	10.548	1.291	86.207	0.028	8.962	1.034	77.711	0.047
Postoperative pathological grade				0.032	2.276	1.159	4.472	0.017
low grade	reference				reference			
high grade	5.788	1.371	24.434	0.017	4.732	1.097	20.421	0.037
non-urothelial carcinoma	9.134	1.667	50.064	0.011	6.589	1.119	38.801	0.037
Lymph node involvement	4.958	2.123	11.58	0.000	2.462	1.003	6.048	0.049