Utility of robot assisted radical cystectomy with intracorporeal urinary diversion for muscle invasive bladder cancer

Review Article

Utility of robot-assisted radical cystectomy with intracorporeal urinary diversion for muscle-invasive bladder cancer

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Abbreviations & Acronyms
BCa = bladder cancer
CDDP = cisplatin
CMV = cisplatin, methotrexate and vinblastine
DFS = disease-free survival
EBL = estimated blood loss
ECNB = extracorporeal ileal neobladder reconstruction
ECUD = extracorporeal reconstruction of urinary diversion
ICNB = intracorporeal ileal neobladder reconstruction
ICUD = intracorporeal reconstruction of urinary diversion
IQR = interquartile range
IRCC = International Robotic Cystectomy Consortium
LOS = length of hospital stay
LRC = laparoscopic radical cystectomy
MIBC = muscle-invasive bladder cancer
MIE-RC = minimum-incision endoscopic radical cystectomy
MVAC = methotrexate, vinblastine, doxorubicin and cisplatin
NAC = neoadjuvant chemotherapy
ORC = open radical cystectomy
OS = overall survival
RARC = robot-assisted radical cystectomy
RC = radical cystectomy

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Abstract: Radical cystectomy remains the gold standard for treatment of muscle-invasive bladder cancer. Robot-assisted radical cystectomy has technical advantages over laparoscopic radical cystectomy and has emerged as an alternative to open radical cystectomy. Despite the advancements in robotic surgery, experience with total intracorporeal reconstruction of urinary diversion remains limited. Most surgeons have carried out the hybrid approach of robot-assisted radical cystectomy and extracorporeal reconstruction of urinary diversion, as intracorporeal reconstruction of urinary diversion remains technically challenging. However, intracorporeal reconstruction of urinary diversion might potentially proffer additional benefits, such as decreased fluid loss, reduction in estimated blood loss and a quicker return of bowel function. The adoption of intracorporeal ileal neobladder reconstruction has hitherto been limited to high-volume academic institutions. In the present review, we compare the totally intracorporeal robot-assisted radical cystectomy approach with open radical cystectomy and robot-assisted radical cystectomy + extracorporeal reconstruction of urinary diversion in muscle-invasive bladder cancer patients.

Key words: intracorporeal urinary diversion, muscle-invasive bladder cancer, neoadjuvant chemotherapy, radical cystectomy, robot-assisted surgery.

Introduction

RC remains the gold standard of treatment for MIBC and for high-grade, recurrent non-muscle-invasive tumors. ORC is associated with high morbidity, with historical rates of postoperative complications between 30% and 60% in large pelvic oncology centers.[1–3] Minimally invasive surgical techniques have been widely used in a variety of surgical procedures.[4] LRC might proffer benefits in terms of EBL, analgesic requirements and reduced scarring.[5] However, LRC is not widely adopted, because it is a challenging procedure.[6] Conversely, RARC has technical advantages over LRC, such as magnified 3-D vision with a surgeon-controlled camera, mechanical wrists with seven degrees of motion, motion scaling and tremor reduction.[7] Therefore, RARC has emerged as a better alternative to ORC because of its possible reduction in EBL, blood transfusion rate and postoperative analgesia, and quicker recovery of bowel function.[8,9]

Although robotic surgery has advanced, experience in total ICUD, including intracorporeal ileal conduit or neobladder reconstruction, remains limited. Most surgeons have carried out the hybrid approach of RARC and ECUD, as ICUD, especially ICNB, remains technically challenging.[10,11] However, ICUD might have potential benefits, including decreased fluid loss, reduced EBL and a quicker return of bowel function.[12] The adoption of ICNB has hitherto been limited to high-volume academic institutions, and several surgical techniques for ICNB have been reported with promising functional outcomes.[4,13–18]

In the present review, we compare the totally intracorporeal RARC approach with ORC and RARC + ECUD in MIBC patients, focusing on perioperative morbidities and oncological outcomes.

Table 1 Pathological outcomes

	RARC cohort	MIE-RC cohort	P
No. patients	29	196	
Pathological stage, n (%)			
T0	10 (34.5)	42 (21.4)	0.644
T1	11 (37.9)	45 (23)	
T2	1 (3.4)	67 (34.2)	
T3	6 (20.7)	35 (17.9)	
T4	1 (3.4)	7 (3.6)	
Lymph node involvement, n (%)	3 (10.3)	16 (8.2)	0.164
Positive surgical margins	0	1 (0.5)	>0.999
Median lymph node yield, n (IQR)	15 (12–18)	18 (12–28)	0.747

Fig. 1 Kaplan–Meier analysis of OS in patients with muscle-invasive BCa who underwent RARC or MIE-RC. The 5-year OS rate was 80.8% in the RARC group and 84.6% in the MIE-RC group (P = 0.647).

RARC

Perioperative morbidities

Although RC surgical technique and perioperative care have improved in recent years, ORC still has a perioperative mortality ranging from 0% to 8% and a morbidity ranging from 48% to 74%.[1–3,19] The Canadian Urological Association investigated the quality of surgical care for MIBC patients who underwent RC in Quebec from 2000 to 2009.[19] A total of 2778 RC procedures were carried out in 48 hospitals by 122 urologists.[19] Of the patients treated, 30.6% had at least one postoperative complication and 12.6% had more than one complication.[19] The overall mortality rates at 30, 60 and 90 days were 2.8%, 5.3% and 7.5%, respectively.[19] The 30-, 60- and 90-day mortality rates in high-volume centers were significantly less than those of small hospitals.[19] Therefore, minimally invasive surgical approaches have been rapidly adopted for the treatment of MIBC worldwide.[10]

RARC has emerged as an alternative to ORC due to its possible reduction of perioperative morbidities, including EBL, blood transfusion rate, postoperative analgesia and quicker recovery of bowel function.[8,12,20] Matsumoto et al. reported a mean EBL of 1700 mL for the ORC group, 961 mL for the LRC group and 450 mL for the RARC group (P = 0.004), and only the ORC group required blood transfusion (P = 0.003).[6] Gandaglia et al. reported the perioperative outcomes of RARC and ORC in patients with BCa who were treated in two high-volume centers.[21] The median operative time was significantly longer in patients who underwent RARC than in those who underwent ORC (330 vs 185 min, respectively; P < 0.001).[21] Patients treated by RARC had a shorter LOS (13 vs 20 days, respectively; P < 0.001).[21] The rates of overall and low-grade complications were also significantly higher in the RARC patients (all P ≤ 0.01).[21] Li et al. carried out a systematic review and meta-analysis of available literature comparing RARC and ORC in BCa patients.[22] Based on data pooled from nine studies involving 668 MIBC patients, RARC had significantly longer operative time, lower EBL and shorter LOS than ORC (all P < 0.001).[22] Although there were no significant differences in intraoperative and postoperative complication rates between the two groups, major
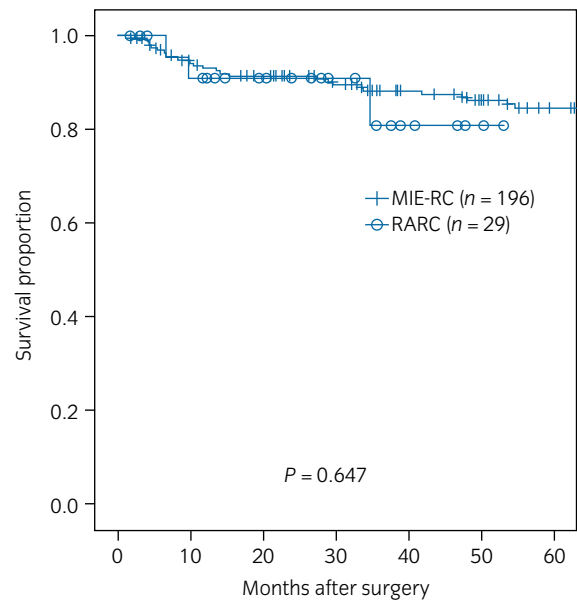
complications were significantly lower in the RARC group than in the ORC group (P = 0.002).[22]

In contrast, Al-Daghmin et al. investigated the RARC outcomes and predictors of readmission.[23] Of the participating patients, 25.5% were readmitted within 90 days and the causes of readmission were mostly infection-related.[23] Four patients (1.4%) required reoperation (two patients for appendicitis and adhesive small bowel obstruction, and two for ureteroenteric stricture), and six (2.2%) required percutaneous procedures (three patients for pelvic fluid collections, two for ureterocutaneous fistula and one for anastomotic leak).[23] On multivariate analysis, body mass index (P = 0.004) and female sex (P = 0.014) were independent predictors of readmission within 90 days.[23] Indeed, RARC can be safely carried out with acceptably low risk of EBL, blood transfusion and LOS. However, we should always keep the risk of postoperative complications, including readmission or reoperation, in mind.

Oncological outcomes

In recent years, several authors have described the feasibility of robotic approaches for BCa patients undergoing RC.[8,10,20] Yuh et al. carried out a systematic review and cumulative analysis of oncological and functional outcomes of RARC.[24] At 1, 3 and 5 years, the OS rates were 82–90%, 61–80% and 39–66%, respectively.[24] The corresponding DFS rates were 79–96%, 67–76% and 53–74%, respectively.[24] However, just six out of 18 series (33%) reported a mean follow-up period >36 months.[24] In contrast, Raza et al. reported the long-term oncological outcomes using the IRCC database.[11] At a median follow-up period of 67 months, the OS and DFS rates

Table 2 Perioperative outcomes

Study	No. patients	Median age (years)	Median operative time (min)	Median EBL (mL)	Positive surgical margins (%)	Clavien–Dindo 3–5 complications		Mortality rate (%)
						Early	Late	
Koie et al.[13]	22	67	430	300	0	0	4.5	0
Simone et al.[14]	45	65	305	210	0	17.8	35.5	0
Parekh et al.[26]	148	70	428	300	6	22	Not evaluated	3
Lenfant et al.[38]	74	66	320	400	8.1	20	64.3	0
Tytitzis et al.[39]	70	59.8	420	500	1.5	31.4	18.3	1.4
Simone et al.[40]	64	62.5	Not evaluated	Not evaluated	0	6.3	Not evaluated	0
Tan et al.[41]	59	69	330	300	8.5	16.9	30.2	0
Butt et al.[42]	4	61.8	522	237	0	25	Not evaluated	0
Schwentner et al.[43]	62	63.6	476.9	385	6.4	25.8	Not evaluated	0
Desai et al.[44]	132	60	456	430	0.8	15.2	12.9	1.5

were 50% and 67%, respectively.[11] Gandaglia *et al.* reported the perioperative and oncological outcomes for MIBC patients who underwent ORC and RARC at two high-volume centers with a median follow-up period of 54 months.[21] After patient categorization according to the surgical approach used, no differences were observed in the 5-year OS and DFS rates between the ORC and RARC groups (58.4 *vs* 59.2% and 57.1 *vs* 54.2%, respectively).[21] Likewise, Bochner *et al.* reported that there were no significant differences in DFS or OS between ORC and RARC.[4] However, in that randomized study, it appeared that the patient population was skewed toward earlier stage disease given the percentage of patients with organ-confined disease.[4] In retrospective RARC series or prospective series without adequate controls, patient selection introduces bias, which makes it difficult to directly compare oncological outcomes between two surgical techniques.[4]

A long-term analysis of survival of 1100 chemotherapy-naïve ORC patients showed 10-year cancer-specific survival and OS rates of 67% and 44%, respectively.[3] Moschini *et al.*

described the recurrence patterns and characteristics related to survival for 1110 BCa patients who underwent RC at a single institution after a median follow-up period of 8.4 years.[25] Overall, 29.2% of the patients experienced recurrences, and 31.2% died from BCa.[25] The 5-year cancer-specific and overall mortality-free rates were 59% and 54%, respectively.[25] These reports showed that RARC and ORC provide similar oncological outcomes, including OS and DFS.[4,10,11,21] Although the RC surgical technique and perioperative care have improved in recent years, the oncological outcomes, especially OS, for MIBC patients who underwent RC alone were still low.

Patterns of recurrence after RC

RARC is reported to increase the risk of peritoneal carcinomatosis, port site recurrences and extrapelvic lymph node metastases, which might be caused by tumor seeding associated with pneumoperitoneum, excessive manipulation of the cystectomy specimens and breach of the specimen bag.[25]
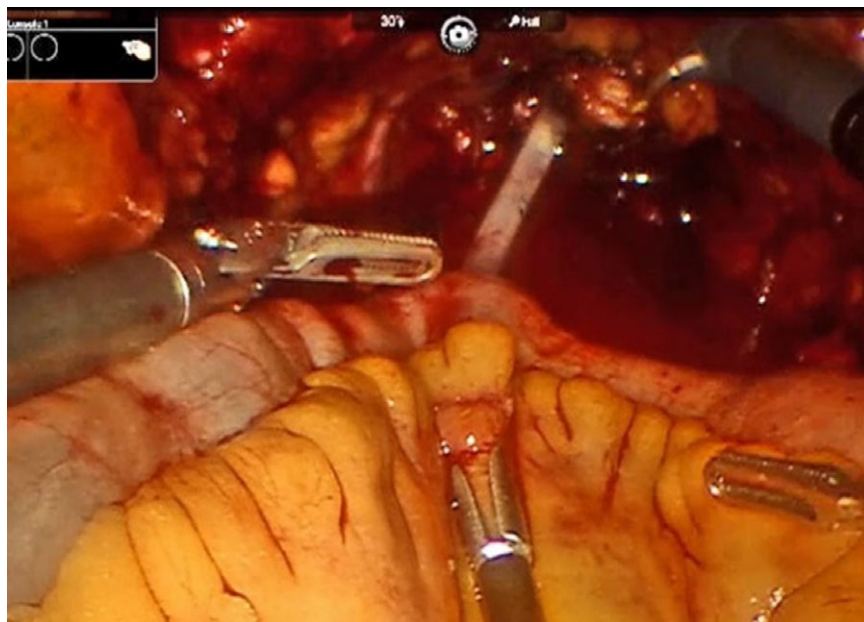

Fig. 2 Selection of the appropriate portion of ileum that reaches the urethra without tension. A 40-cm bowel segment is chosen for the neobladder. A 14-Fr urethral catheter is inserted through the urethra to irrigate the ileum.

According to the Randomized Open versus Robotic Cystectomy trial, which was carried out to investigate whether RARC was non-inferior to ORC for the treatment of BCa, the proportion of patients with local recurrences was similar between the RARC and ORC groups (4% and 3%, respectively; $P = 0.54$).[26] Local recurrence in the cystectomy bed was also similar in both groups (4% and 1%, respectively; $P = 0.17$).[26] No port site recurrences were reported.[26] In a recent prospective randomized trial comparing RARC with ORC, there were no statistically significant differences between the groups, even though the ORC group tended toward higher overall rates of distant recurrence as their first site of recurrence than the RARC group (27.6% and 16.7%, respectively; $P = 0.077$).[4] However, the ORC group showed significantly less local/regional recurrence than the RARC group (10.3% and 16.7%, respectively; $P = 0.035$).[4]

MIBC is a systematic disease with distant metastases, lymph node involvement and local recurrence often caused by micrometastases at the time of diagnosis. Therefore, early systemic therapy is important for eradication of the risk of micrometastases outside the surgical field.[9]

Role of NAC before RC

NAC followed by RC is recommended for MIBC patients according to the guidelines of the European Urological Association and National Comprehensive Cancer Network.[27,28] The most commonly referenced NAC trial is the Southwestern Oncology Group 8710 trial, in which neoadjuvant MVAC followed by RC was compared with RC alone.[29] Although the difference in 5-year OS was not statistically significant ($P = 0.06$), the results of that study have been used as evidence of the superiority of NAC over RC alone.[29] A meta-analysis of randomized trials showed that CDDP-based NAC including MVAC and CMV improves OS by 5% in T2–T4a

BCa patients.[29,30] In our previous studies, the oncological outcomes were significantly improved in MIBC patients who received NAC followed by immediate RC compared with patients who underwent RC alone.[31–33] The 5-year OS rate was 79.5–98.6% in MIBC patients who received NAC followed by immediate RC, and 53.8–66.6% in those who underwent RC alone ($P < 0.001$).[31–33] The 5-year DFS rate was 75.5–100% in MIBC patients who received NAC followed by immediate RC, and 55.4–69.7% in those who underwent RC alone ($P < 0.001$).[31–33]

In contrast, few studies have investigated the utility and efficacy of NAC in patients with MIBC who underwent RARC.[9,34] Hinata *et al.* compared the perioperative and oncological outcomes after RARC in MIBC patients who received three cycles of CDDP-based NAC (optimal NAC) with those who failed to complete three cycles of NAC or received a decreased dosage of CDDP-based regimen (suboptimal NAC), or did not receive NAC (no NAC).[34] The optimal NAC group had better 1- and 3-year recurrence-free survival rates (85.4% and 75.2%, respectively) in comparison with the suboptimal group (55.3% and 33.2%, respectively) and the no NAC group (55% and 39%; $P < 0.01$).[34] They also had better OS at 1 and 3 years (95% and 89%, respectively), compared with the suboptimal (64% and 49%, respectively) and the no NAC group (76% and 50%, respectively; $P < 0.01$).[34] Multivariate analysis showed that recurrence-free survival in the suboptimal NAC and no NAC groups were significantly lower than in the optimal NAC group ($P = 0.001$, $P = 0.001$, respectively).[34] In addition, there were no significant differences in DFS and OS between the suboptimal NAC and no NAC groups.[34] In our previous study, we evaluated 29 MIBC patients who received NAC followed by RARC and compared results with those of patients treated by MIE-RC.[9] In the RARC cohort, four patients (13.8%) showed a complete response, four (13.8%)
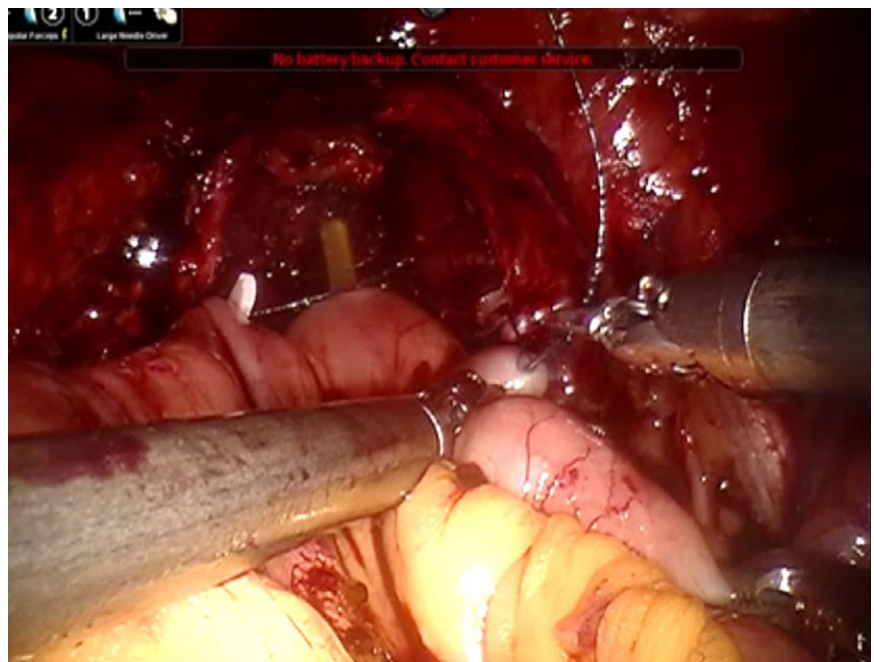

Fig. 3 The ileal loop is fixed to the pelvic floor to facilitate ease of handling and the neobladder-urethral anastomosis.

showed a partial response and two (6.9%) showed stable disease (Table 1). In the MIE-RC cohort, 27 patients (13.8%) showed a complete response, and 80 (40.8%) showed a partial response. Table 1 lists the histopathological details. By the end of the follow-up period, 10.3% and 11.7% of the patients in the RARC and MIE-RC groups, respectively, had died of BCa.[9] The 5-year OS rate was 80.8% in the RARC group and 84.6% in the MIE-RC group (Fig. 1; $P = 0.647$).

Combination therapy with NAC and RARC might result in favorable and acceptable oncological outcomes in patients with MIBC.

ICUD after RARC

With increasing surgical experience, ICUD is gradually being adopted, thereby affording potential benefits including
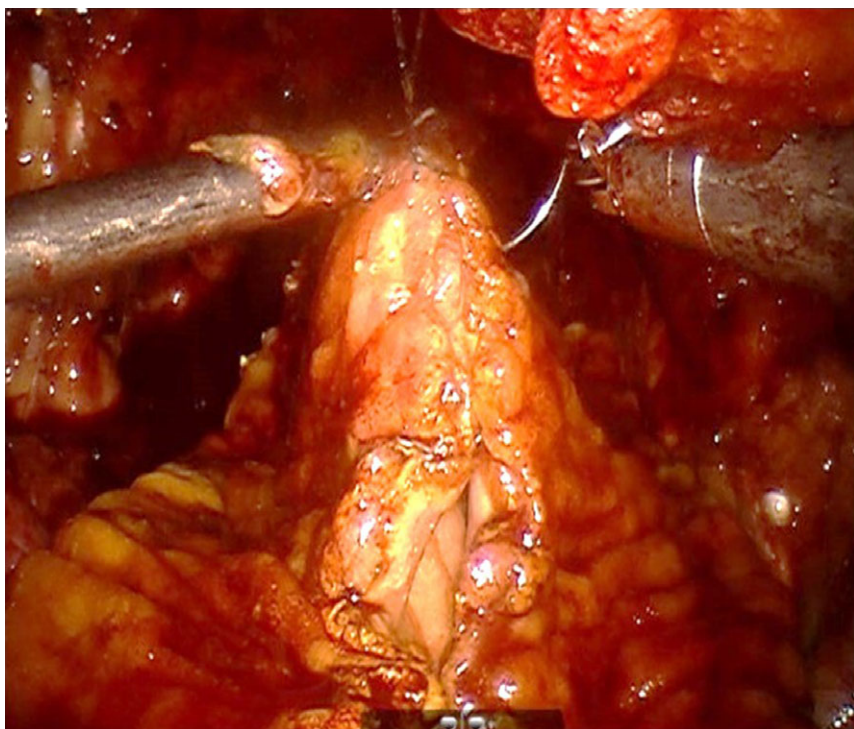

Fig. 4 The detubularized ileal loop is arranged in an inverted U-shape and the inner opposite borders are over-sewn with a single-layer seromuscular running suture.
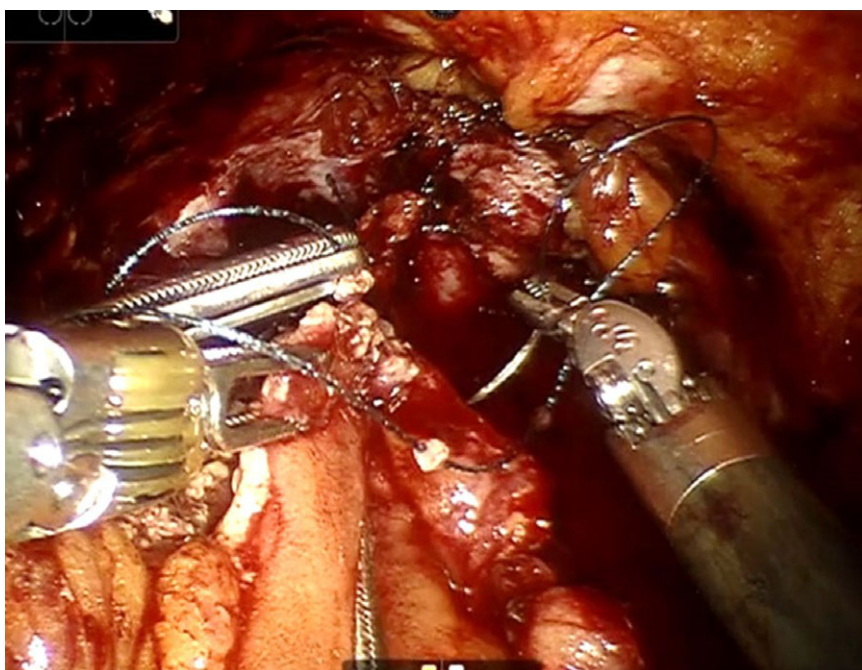

Fig. 5 After the ureteral anastomosis, the U-flap is cross-folded to make a pouch.

Table 3 Perioperative complications

Type of complication, n (%)	RARC + ICNB		MIE-RC + ECNB	
No. patients	22		131	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Surgical site infection	2 (9.1)	0	18 (13.7)	0
Urinary leak	2 (9.1)	0	11 (8.4)	0
Ileourethral anastomotic stricture	1 (4.5)	1 (4.5)	5 (3.8)	5 (3.8)
Ileus	3 (13.6)	0	4 (3.1)	1 (0.8)
Ileal anastomosis leak	0	0	1 (0.8)	1 (0.8)
Readmission for complications	0	0	0	0

decreased fluid loss, reduced EBL, less pain, smaller surgical incisions, quicker return of bowel function and fewer anastomotic strictures.[12] The urinary reconstruction probably has more impact on postoperative morbidity and complications than RC.[35] The rationale for ECUD is the shorter operative time and the pre-existing need for an extraction site for the specimens.[35] Therefore, most surgeons still consider ECUD a safer option, and carry out the hybrid approach of RARC and ECUD.[36,37] On review of the literature, we identified 10 studies with RARC followed by ICUD (Table 2).[13,14,26,38–44] The IRCC study retrospectively compared the perioperative outcomes in 935 patients undergoing ICUD ($n = 167$) and ECUD ($n = 768$) followed by RARC.[37] Although there were no statistically significant differences in the 90-day complication rates, the ICUD group tended to have fewer overall complications ($P = 0.059$), significantly fewer gastrointestinal complications ($P < 0.001$) and lower transfusion rates ($P = 0.02$).[37] Lenfant *et al.* investigated the perioperative outcomes and complications of ECUD and ICUD in patients undergoing RARC at five referral centers in France.[38] Overall, the operative time, LOS, positive margin rate and number of lymph nodes removed did not differ significantly between the two cohorts.[38] EBL and transfusion rates were significantly higher in the ECUD group.[38] The early and late surgical complications did not differ significantly between the ECUD and ICUD groups.[38]

In our previous study, we compared the oncological and functional outcomes of 22 MIBC patients who underwent RARC with U-shaped ICNB or MIE-RC with ECNB.[13] Our surgical technique for RARC has been described in detail previously.[13] Briefly, the first step is to identify the most mobile ileum that reaches the urethra without tension (Fig. 2). A 40-cm bowel segment is chosen for the neobladder. The second step is to fix the ileal segment at the pelvic floor using a 3-0 V-Loc suture (Covidien, Mansfield, MA, USA) (Fig. 3). The third step is to make the ileourethral anastomosis. After the anastomosis is complete, the ileal loop is arranged in an inverted U-shape and the inner opposite borders are over-sewn with a single-layer seromuscular running suture (Fig. 4). The fourth step is to make the ileoureteral anastomosis. Two small enterotomies are created in the U-flap and the ureters are introduced into the future neobladder. A 4-0 braided polyglactin

suture is used to make an anastomosis with interrupted sutures. After ureteral anastomosis, the U-flap is cross-folded to make a pouch (Fig. 5). The operative time in the ICNB group was significantly longer than in the ECNB group.[13] The median EBL was less and the transfusion rate was significantly lower in the ICNB group than in the ECNB group ($P < 0.001$).[13] In contrast, the rate of postoperative ileus in the ICNB group was relative higher than in the ECNB group. Several steps have been shown to have a causative role in postoperative ileus. However, there were no statistically significant differences in the major complications between the two groups (Table 3).[13] In addition, the rate of postoperative ileus was not high in our series.[13] Indeed, totally ICUD technique increased the complexity of the procedure. However, the surgical outcomes and complication rates after RARC with ICUD might improve with more experience if the ICUD surgical techniques are standardized.

Acknowledgments

Conflict of interest

None declared.

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Editorial Comment

Editorial Comment to Utility of robot-assisted radical cystectomy with intracorporeal urinary diversion for muscle-invasive bladder cancer

Koie *et al.* reviewed the usefulness of robot-assisted radical cystectomy (RARC) with intracorporeal urinary diversion (ICUD) for muscle-invasive bladder cancer.[1] The authors described the oncological outcome, morbidities, pattern of