

Predictors of postoperative complications after robot-assisted radical cystectomy with extracorporeal urinary diversion

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Purpose: Robot-assisted radical cystectomy (RARC) is known to have less postoperative morbidity and complications than open radical cystectomy. However, various complications not yet have been reported after RARC. In this study, we aimed to identify the predictors of complications following RARC.

Patients and methods: From August 2008 to November 2017, we retrospectively reviewed 126 patients who underwent RARC with extracorporeal urinary diversion. Overall perioperative complications were examined, and factors that may affect complications were analyzed using a logistic regression model. Complications were classified according to the Clavien-Dindo system.

Results: Overall postoperative complications occurred in 78 (61.9%) of 126 patients. Whereas the rate of minor complications was 58.0% (grade I=15.9% (n=20), grade II=42.1% (n=53)), the rate of major complications was very low (grade IIIa=1.6% (n=2), grade IIIb=2.4% (n=3)). No fatal complications more than grade IV were developed. Notably, transfusions (27.0%), urinary tract infection (15.9%), anastomosis site leakage (14.3%), and ileus (10.3%) were the most common complications after RARC. In the multivariate regression model, previous intravesical instillation (odds ration [OR]=3.374), preoperative hemoglobin (OR=0.751), and estimated blood loss (EBL) (OR=3.949) were identified as the predictors of postoperative complications.

Conclusion: In sum, our data showed the rates of major complications were comparable after RARC with extracorporeal urinary diversion compared as reported in previous studies and lower major than minor complications following RARC. Moreover, we identified the independent predictors of postoperative complications, such as preoperative hemoglobin, intravesical instillation, and EBL.

Keywords: bladder cancer, complications, cystectomy, predictor, robotic surgery

Introduction

Bladder cancer is one of the most common genitourinary cancers in the world and is associated with a high morbidity and mortality rate. Because of its aggressiveness, many studies focus on the optimal treatment of bladder cancer.¹ According to the European Association of Urology guidelines, radical cystectomy is recommended not only for patients with muscle-invasive bladder cancer, but also for patients with non-muscle invasive bladder cancer who are at highest risk of progression and patients with BCG (bacillus calmette-guérin)-refractory bladder cancer.^{2,3} However, radical cystectomy is one of the most complex urological surgical procedures, with higher complication rates.

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Minimally invasive robot-assisted radical cystectomy (RARC) is the most advanced surgical approach to reduce the incidence of complications.⁴ Postoperative morbidity and mortality after RARC are lower than those in open radical cystectomy (ORC), while the oncologic outcomes are comparable.^{5–8}

While the proportion of overall postoperative complications after RARC has decreased compared with complication rates of ORC (57–74%) due to advances in surgical methods and techniques, it still remains high at 35–63%. Similarly, RARC is associated with fewer major complications more than grade III or more than ORC (about 22%), but the rate of major complications is still high 10%.^{9–11}

To reduce the incidence of complications following surgery, it is important to predict and prevent factors associated with the occurrence of complications. High American Society of Anesthesiologists (ASA) score, estimated blood loss (EBL), Charlson comorbidity index (CCI), and obesity are well-known predictors of perioperative complications in patients undergoing ORC.^{12,13} However, there is still a lack of research in postoperative complications and associated risk factors were still limited in patients underwent RARC.

Here, we evaluated postoperative complications following RARC with extracorporeal urinary diversion, and identified predictive factors for these complications following RARC with extracorporeal urinary diversion.

Material and methods

We retrospectively reviewed 126 consecutive patients who underwent RARC with extracorporeal urinary diversion from August 2008 to November 2017. Age at the time of surgery, sex, body mass index (BMI), ASA score, preoperative hemoglobin, history of previous abdominal surgery, history of intravesical instillation, history of neoadjuvant chemotherapy, pathologic stage, operative time, EBL, and type of urinary diversion were included as demographic data and perioperative data. This study was approved by the International Review Board of Samsung Medical Center (approval number: 2018–05-146) with the Declaration of Helsinki. For this type of study, formal consent was not required and data were anonymous.

Complications were classified according to the modified Clavien-Dindo system.¹⁴ Major complications were defined as Clavien-Dindo grade III or greater, while minor complications were defined as Clavien-Dindo grade II or less. Multiple complications were defined as the presence of more than one complication in the same patient.

The following descriptive statistics were used for continuous data: mean, standard deviation, and 95% confidence interval (CI) or median and interquartile range (IQR). Predictive factors for complications after RARC were determined using a multivariate logistic regression model and calculating the odds ratio (OR) and 95% CI. Multivariate analyses were performed with only significant factors as judged by univariate analysis.

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R 3.4.3 (Vienna, Austria; <http://www.R-project.org/>). Values of $p < 0.05$ were considered statistically significant.

Results

Patient characteristics

Baseline demographics of patients are presented in Table 1. The mean age of patients with RARC was 61.7 ± 10.7 . RARC was performed primarily in males (91.3%, $n=115$). Mean preoperative hemoglobin was 13.4 ± 1.8 , and patients who had previously undergone abdominal surgery comprised 15.9% ($n=20$). Among patients with RARC, 20.6% ($n=26$) underwent intravesical instillation (except for three patients who received epirubicin intravesical instillation), and all patients underwent BCG intravesical instillation, while 15.1% ($n=19$) of patients underwent neoadjuvant chemotherapy. T3 pathology was the most common (37.3%, $n=47$), and LN (lymph node) metastasis was confirmed in 27.8% ($n=35$) of patients (Table 1).

Perioperative data

Perioperative data are shown in Table 2. Median overall operation time was 500 minutes (IQR, 435–585), median EBL was 400 mL (IQR, 300–600), median hospital stay was 23 days (IQR, 17–32), and median follow-up was 22.4 months (IQR, 8.0–43.0). The diversion type of RARC was preferred to ileal conduit (68.3%, $n=86$) compared to neobladder formation (31.7%, $n=40$). In patients with ileal neobladder, longer operative times (527 minutes [IQR, 465–655] vs 445 minutes [IQR, 372–526]) and longer hospital stays (25 days [IQR, 20–33] vs 17 days [IQR, 16–21]) were recorded than patients with ileal conduit. However, EBL did not significantly differ between ileal neobladder and ileal conduit (450 minutes [IQR, 300–600] vs 400 minutes [IQR, 300–600]). Transfusions were performed in 34 patients (27%), most of which were performed postoperatively (30 patients, 23.8%), with intraoperative transfusions performed in 8 patients (6.3%) (Table 2).

Table 1 Patient demographics

Variable	Value
Age, year	61.7±10.7
Sex, n (%)	
Male	115 (91.3)
Female	11 (8.7)
BMI, n (%)	
<18.5	5 (4.0)
18.5–22.9	50 (39.7)
23.0–24.9	26 (20.6)
≥25.0	45 (35.7)
Preoperative hemoglobin	13.4±1.8
CCI, n (%)	
3 or lower	44 (34.9)
4	41 (32.5)
5	24 (19.0)
6 or higher	17 (13.5)
ASA score, n (%)	
1	37 (29.4)
2	84 (66.7)
3	5 (4.0)
Previous abdominal surgery, n (%)	
Yes	20 (15.9)
No	106 (84.1)
Intravesical instillation, n (%)	
Yes*	26 (20.6)
No	100 (79.4)
Neoadjuvant chemotherapy, n (%)	
Yes	19 (15.1)
No	107 (84.9)
Pathologic stage, n (%)	
T0	7 (5.6)
Ta	1 (0.8)
Tcis	10 (7.9)
T1	23 (18.3)
T2	26 (20.6)
T3	47 (37.3)
T4	12 (9.5)
LN metastasis, n (%)	35 (27.8)

Notes: *Except for 3 (epirubicin intravesical instillation), all patients underwent BCG intravesical instillation.

Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; ASA, American Society of Anesthesiologists; LN, lymph node; BCG, bacillus calmette–guérin.

Complications

Complications occurred in 78 patients (61.9%). Total 95 minor complications occurred in 73 patients (57.9%), 5 major complications occurred in 5 patients

Table 2 Perioperative data

Variable	Value
Median overall operation time, min	500 (435–585)
Ileal conduit	445 (372–526)
Neobladder (studer)	527 (465–655)
Median EBL, mL	400 (300–600)
Ileal conduit	400 (300–500)
Neobladder (studer)	450 (300–600)
LN removal, n (%)	
Yes	120 (95.2)
Mean LN removal	20.1±8.9
No	6 (4.8)
Type of urinary diversion, n (%)	
Ileal conduit	40 (31.7)
Neobladder (studer)	86 (68.3)
Transfusion, n (%)	34 (27.0)
Intraoperative	8 (6.3)
Postoperative	30 (23.8)
Surgical margin positive, n (%)	
Yes	9 (7.1)
Ureter	6 (4.8)
Perivesical tissue	2 (1.6)
Vas deferens	1 (0.8)
No	117 (92.9)
Median hospital stays, day	23 (17–32)
Ileal conduit	17 (16–21)
Neobladder (studer)	25 (20–33)
Time to flatus, day	3.6±3.2
Median follow up, month	22.4 (8.0–43.0)
Ileal conduit	18.3 (7.8–42.3)
Neobladder (studer)	26.1 (9.1–43.0)

Abbreviations: EBL, estimated blood loss; LN, lymph node.

(4.0%), and multiple complications occurred in 22 patients (17.5%).

Grade I complication occurred in 27 patients (21.4%), grade II complication occurred in 68 patients (54.0%), grade IIIa complication occurred in 2 patients (1.6%), and grade IIIb complication occurred in 3 patients (2.4%). Complication of grade IV or higher did not occur (Table 3).

Detailed complications following RARC are listed in Table 4. The most frequent complications were transfusion (27.0%, n=34), febrile urinary tract infection (15.9%, n=20), anastomosis site leakage (14.3%, n=18), and ileus (10.3%, n=13). A classification of complications and specific complications according to diversion type and pathologic results are listed in Tables S1 and 2. In addition, a classification of

Table 3 Clavien-Dindo classifications of complications following RARC

	No. (%)
Patients with complications, n (%)	78 (61.9)
Patients with minor complications, n (%)	73 (57.9)
Patients with major complications, n (%)	5 (4.0)
Patients with multiple complications, n (%)	22 (17.5)
Total number of complications	100
Grade I complications, n (%)	27 (27.0)
Grade II complications, n (%)	68 (68.0)
Grade III a or greater complications, n (%)	5 (5.0)
Highest complications grade, n (%)	
No complications	48 (38.1)
Grade I	20 (15.9)
Grade II	53 (42.1)
Grade IIIa	2 (1.6)
Grade IIIb	3 (2.4)
Grade IV	0 (0)
Grade V	0 (0)

Abbreviations: RARC, robot-assisted radical cystectomy; EBL, estimated blood loss; LN, lymph node.

Table 4 Detailed complications following RARC

Complications	No. (%)
Transfusion	34 (27.0)
UTI (febrile)	20 (15.9)
Anastomosis site leakage	18 (14.3)
Ileus	13 (10.3)
Wound problem	5 (4.0)
Grade I	2 (1.6)
Grade IIIa	2 (1.6)
Grade IIIb	1 (0.8)
Lymphocele	2 (1.6)
Bowel injury	2 (1.6)
Operation site fluid collection	2 (1.6)
Grade I	1 (0.8)
Grade IIIa	1 (0.8)
Scrotal edema	2 (1.6)
Anastomosis site stricture	1 (0.8)
Pulmonary thromboembolism	1 (0.8)

Abbreviations: RARC, robot-assisted radical cystectomy; UTI, urinary tract infection.

complications and specific complications according to intravesical instillation are also listed in [Table S3](#).

Predictors of complications

In univariate analysis, intravesical instillation (OR=3.168, 95% CI=1.10–9.07, $p=0.0318$) and EBL (OR=3.159, 95%

CI=1.452–6.876, $p=0.0037$) were significant predictors associated with complications following RARC. In multivariate analysis, intravesical instillation (OR=3.374, 95% CI =1.116–10.197, $p=0.0312$), EBL (OR=3.949, 95% CI=1.682–9.27, $p=0.0016$), and preoperative hemoglobin (OR=0.751, 95% CI=0.588–0.96, $p=0.022$) were significant predictors associated with complications following RARC ([Table 5](#)).

Discussion

In this study, we investigated complications following RARC and factors affecting the occurrence of complications after RARC. We found that preoperative hemoglobin, EBL, and intravesical instillation were significant predictors of complications following RARC.

Previous studies have shown that overall complication rates after RARC vary from center to center. According to Al-Daghmin et al in RARC with mainly extracorporeal conduit diversion, the overall complication rate is 77%, the low-grade complication rate is 58%, and the high-grade complication rate is 19%.¹⁵ According to Yuh et al in RARC with mainly extracorporeal continent diversion, the overall complication rate is 82%, the low-grade complication rate is 45%, and the high-grade complication rate is 37%.¹⁶ According to Nazmy et al in RARC with mainly extracorporeal continent diversion, the overall complication rate is 77%, the low-grade complication rate is 45%, and the high-grade complication rate is 32%.¹⁷ In contrast, we found that the incidence of overall complications after RARC was lower (61.9%) in our study. While rates of low-grade (Clavien-Dindo grade 1 or 2) complications after RARC (57.9%) were similar, rates of high-grade complications (Clavien-Dindo grade 3 or 4) were much lower than those in previous reports (4%).

Many previous studies have explored predictors of complications following RARC. According to Nazmy et al, ASA, preoperative hematocrit, and diversion type contribute to any grade of complications after RARC.¹⁷ Yuh et al identified age, ASA, preoperative hematocrit, operation time, EBL, and diversion type as predictors of complications after RARC.¹⁸ However, according to Abe et al there were no significant differences in overall complications according to diversion type,¹⁹ while according to Tan et al preoperative anemia is not associated with increased preoperative complications in patients treated with RARC.²⁰ Notably, we identified intravesical instillation (OR=3.374) as a novel unfavorable predictive factor for complications after RARC, in addition to preoperative

Table 5 Logistic regression model to identify predictive factors for postoperative complications following RARC

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age	0.996 (0.963–1.031)	0.8333		
Sex				
Male		Reference		
Female	1.714 (0.432–6.803)	0.4438		
BMI				
<25		Reference		
≥25	0.763 (0.362–1.609)	0.4775		
Preoperative hemoglobin	0.816 (0.661–1.008)	0.0594	0.751 (0.588–0.96)	0.022
ASA score		0.7174		
1		Reference		
2	0.807 (0.322–2.018)	1		
3	1.652 (0.144–18.944)	1		
Abdominal surgery history				
No		Reference		
Yes	1.531 (0.545–4.3)	0.4187		
Urinary diversion type				
Conduit		Reference		
Neobladder	1.778 (0.828–3.821)	0.1402		
Intravesical instillation				
No		Reference		Reference
Yes	3.168 (1.106–9.078)	0.0318	3.374 (1.116–10.197)	0.0312
Neoadjuvant chemotherapy				
No		Reference		
Yes	0.821 (0.305–2.212)	0.6964		
EBL	3.159 (1.452–6.876)	0.0037	3.949 (1.682–9.27)	0.0016
LN removal	0.971 (0.935–1.009)	0.1305		
Operation time	1.001 (0.999–1.004)	0.3373		
Operation year	0.92 (0.812–1.042)	0.1913		

Abbreviations: RARC, robot-assisted radical cystectomy; OR, odds ratio; CI, confidence interval; BMI, body mass index; ASA, American Society of Anesthesiologists; EBL, estimated blood loss; LN, lymph node.

hemoglobin (OR=0.751) and EBL (OR=3.949). Because intravesical instillation was a significant factor for complications following RARC, more careful procedures are needed when operating on patients with intravesical instillation history. Additionally, preoperative hemoglobin control through anemia correction or nutritional support and careful bleeding control during surgery are necessary to reduce complications after RARC.

We hypothesized that there are unknown effects of intravesical instillation resulting in complications, including anatomical modifications such as mucosal changes in the bladder and deterioration of immunity after performing

transurethral resection of the bladder several times before intravesical instillation or intravesical instillation. In fact, bladder contracture or necrosis has been reported with local side effects after BCG intravesical instillation,²¹ and a previous study found that BCG intravesical instillation causes modulation of peripheral immune mechanisms in addition to local immune activation.²²

There are some limitations of this study. First, the study was retrospective and analyzed a relatively small quantity of data. Second, we conducted the study in a single tertiary center and cannot rule out selection bias. Third, we included only RARC with extracorporeal urinary diversion, so it is

difficult to generalize our results to RARC as a whole. Fourth, our analysis did not reflect the improvement of the surgeon's RARC technique over time. More accurate results would be obtained by analyzing the learning curve of the surgeon. Finally, our results may reflect minor complications rather than major complications, because few major complications occurred. Additionally, in this study we do not adjust enhanced recovery after surgery (ERAS) protocol to all patients because the ERAS protocol introduced in urologic surgery relatively recently.

Briefly mention about ERAS protocol, it is a multimodal perioperative care pathway designed to achieve early recovery for patients undergoing major surgery.²³ ERAS protocol was applied first at colorectal surgery to decrease complications after surgery and introduced in urologic surgery especially in radical cystectomy relatively recently.²⁴ There is a meta-analysis of the effect of ERAS protocol on perioperative outcomes after radical cystectomy that shows reduction in length of the index hospitalization, decrease in the rate of low-grade complications, and improvement of the time-to-bowel function, so the benefit of applying the ERAS protocol to radical cystectomy is expected to be substantial.²⁵ We expect the further reduction of complications by applying ERAS protocol to RARC, especially in ileus.

Nevertheless, our study has strength in relatively large amount of RARC cases from single institution. And it is significant that our study reemphasizes existing predictors of complications following RARC and presents new predictors, such as history of intravesical instillation.

Conclusion

We detected that the rates of major complications were comparable after RARC with extracorporeal urinary diversion compared as reported in previous studies and lower major than minor complications following RARC in our study. The predictors of postoperative complications following RARC were intravesical instillation, preoperative hemoglobin, and EBL during surgery. Our results offer valuable information that may help clinicians to reduce complications following RARC.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Clavien-Dindo classifications of postoperative complications and specific complications following RARC according to type of urinary diversion

	Ileal conduit (N=40)	Ileal neobladder (N=86)
Patients with complications, n (%)	21 (52.5)	57 (66.3)
Patients with minor complications, n (%)	19 (47.5)	54 (62.8)
Patients with major complications, n (%)	2 (5.0)	3 (3.0)
Patients with multiple complications, n (%)	7 (17.5)	15 (17.4)
Total number of complications	29	71
Minor complications, n (%)	27 (93.1)	68 (95.8)
Major complications, n (%)	2 (6.9)	3 (4.2)
Highest complications grade, n (%)		
No complications	19 (47.5)	29 (33.7)
Grade I	4 (10.0)	16 (1.6)
Grade II	15 (37.5)	38 (44.2)
Grade IIIa	1 (2.5)	1 (1.2)
Grade IIIb	1 (2.5)	2 (2.3)
Specific complications, n (%)		
Transfusion	15 (37.5)	19 (22.1)
UTI (febrile)	1 (2.5)	19 (22.1)
Anastomosis site leakage	1 (2.5)	17 (19.8)
Ileus	4 (10.0)	9 (10.5)

Abbreviations: RARC, robot-assisted radical cystectomy; UTI, urinary tract infection.

Table S2 Clavien-Dindo classifications of postoperative complications and specific complications following RARC according to pathologic results

	T0, Tcis, Ta, T1, T2 (N=67)	T3, T4 (N=59)
Patients with complications, n (%)	44 (65.7)	34 (57.6)
Patients with minor complications, n (%)	39 (58.2)	34 (57.6)
Patients with major complications, n (%)	5 (7.5)	0 (0.0)
Patients with multiple complications, n (%)	14 (20.9)	8 (13.6)
Total number of complications	58	42
Minor complications, n (%)	53 (91.4)	42 (100.0)
Major complications, n (%)	5 (8.6)	0 (0.)
Highest complications grade, n (%)		
No complications	23 (34.3)	25 (42.4)
Grade I	9 (13.4)	11 (18.6)
Grade II	30 (44.8)	23 (39.0)
Grade IIIa	2 (3.0)	0 (0.0)
Grade IIIb	3 (4.5)	0 (0.0)
Specific complications, n (%)		
Transfusion	18 (26.9)	16 (27.1)
UTI (febrile)	12 (17.9)	8 (13.6)
Anastomosis site leakage	10 (14.9)	8 (13.6)
Ileus	8 (11.9)	5 (8.5)

Abbreviations: RARC, robot-assisted radical cystectomy; UTI, urinary tract infection.

Table S3 Clavien-Dindo classifications of postoperative complications and specific complications following RARC according to intravesical instillation

	Intravesical instillation (N=26)	No intravesical instillation (N=100)
Patients with complications, n (%)	21 (80.8)	57 (57.0)
Patients with minor complications, n (%)	27 (103.8)	68 (54.0)
Patients with major complications, n (%)	1 (3.8)	4 (4.0)
Patients with multiple complications, n (%)	6 (23.1)	16 (16.0)
Total number of complications	28	72
Minor complications	27 (96.4)	68 (94.4)
Major complications	1 (3.6)	4 (5.6)
Highest complications grade, n (%)		
No complications	5 (19.2)	43 (43.0)
Grade I	4 (15.4)	16 (16.0)
Grade II	16 (61.5)	37 (37.0)
Grade IIIa	1 (3.8)	1 (1.0)
Grade IIIb	0 (0)	3 (3.0)
Specific complications, n (%)		
Transfusion	10 (38.5)	24 (24.0)
UTI (febrile)	7 (26.9)	13 (13.0)
Anastomosis site leakage	3 (11.5)	15 (15.0)
Ileus	3 (11.5)	10 (10.0)

Abbreviations: RARC, robot-assisted radical cystectomy; UTI, urinary tract infection.

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