Efficacy of the Addition of Robot-assisted Radical Cystectomy with Extracorporeal Urinary Diversion after an Enhanced Recovery Protocol

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Research Article

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Abstract

Background: Evaluation of the benefits to postoperative outcomes of introducing robot-assisted radical cystectomy (RARC) to enhanced recovery after surgery (ERAS) is limited, especially in RARC with extracorporeal urinary diversion (eRARC). We assessed whether eRARC, when added to ERAS, provided additional efficacy in terms of patient outcomes during its initial implementation.

Methods: We retrospectively identified 143 patients undergoing radical cystectomy with urinary diversion between June 2010 and December 2021 at a single center. The patients were assigned to three groups based on the type of surgical procedures and perioperative recovery protocols used. Length of hospital stay (LOS) and 90-day postoperative complication rates were compared between the groups. Regression analyses were performed to evaluate how ERAS and eRARC affected outcomes. Whereas, multivariate analysis was used to detect LOS predictors.

Results: The median LOS was shorter with ERAS and eRARC (28.0 vs. 20.0 vs. 17.0 days, $P < 0.001$). In the linear regression model, ERAS was associated with a significantly shorter LOS (10.4 days, $P < 0.001$); eRARC was also associated with a shorter LOS, but the difference was nonsignificant (4.10 days, $P = 0.14$). Neither ERAS nor eRARC was associated with a significant improvement in complications. Following multivariate analysis, ERAS was found to be independently associated with shorter LOS (OR 0.23, $P < 0.001$), but eRARC showed no such association (OR 0.29, $P = 0.096$).

Conclusion: ERAS was significantly associated with shorter LOS. Although a desirable trend was evident, eRARC did not contribute to additional efficacy. Neither ERAS nor eRARC improved complications.

Introduction

Radical cystectomy (RC) is the standard of care for muscle-invasive bladder cancer and non-muscle-invasive bladder cancer refractory to bladder-instillation therapy [1]. The complex procedures of RC include organ extirpation and urinary tract reconstruction, which are associated with a relatively high morbidity [2].

Enhanced recovery after surgery (ERAS) is a multimodal program that aims to hasten postoperative recovery and improve perioperative outcomes. After gradual uptake, ERAS is widespread in RC [3,4]. ERAS provides the advantage of a shortened length of hospital stay (LOS); however, lower complication rates and faster bowel recovery have also been reported [4,5]. In addition, robot-assisted radical cystectomy (RARC) is widely used as a minimally invasive surgery and is recognized as comparable to open radical cystectomy (ORC) for oncologic and perioperative outcomes [3,6-8]. Similar to ERAS, RARC provides the advantage of shortened LOS, faster bowel recovery, and less intraoperative blood loss [7,9].

Given the initial findings, the individual efficacy of ERAS and RARC have been demonstrated. However, concurrent analyses of those techniques remain scarce. A previous study that analyzed both considered only RARC with intracorporeal urinary diversion (iRARC) [10]. Other studies evaluated the benefits of iRARC after ERAS, but none evaluated RARC with extracorporeal urinary diversion (eRARC) in a similar setting [11-13]. The learning curve for the complicated surgical skills of urinary reconstruction in iRARC suggests that the surgeon and hospital volume might be associated with complication rates [2,14]. Hence, adopting iRARC is challenging in non-high-volume centers, and eRARC might play an indispensable role in the transition from ORC to RARC.

Recently, we sequentially introduced the use of both ERAS and eRARC. Subsequently, we assessed whether eRARC provided additional efficacy in postoperative patient outcomes when added to ERAS.

Methods

Study design

We retrospectively identified 143 patients who underwent RC with ileal conduit creation between June 2010 and December 2021 at a single institution. We excluded patients who underwent additional procedures related to concomitant malignancies, such as upper tract urothelial carcinoma and colorectal cancer, and those with surgical complications. ERAS was adopted in July 2017, and eRARC in June 2018 [15]. ERAS was used in all patients undergoing eRARC. Fig. 1 depicts the timing of the changes in perioperative protocol and surgical approach.

We allocated the patients to the following three groups: group A comprised 75 patients who underwent ORC with conventional recovery after surgery (CRAS) between June 2010 and June 2017, group B comprised 47 patients who underwent ORC with ERAS starting in July 2017, and group C comprised 21 patients who underwent eRARC with ERAS starting in June 2018. The institutional review board approved the study (approval number 712).

Surgical procedures

ORC

After a suprapubic to infraumbilical skin incision, a retrograde and retroperitoneal approach was taken, with the peritoneum being opened just before specimen removal. The prostate and seminal vesicles in men and the uterus and anterior vaginal wall in women were also extracted. Pelvic lymph node dissection, whose extent was determined at the surgeon’s discretion, was ordinarily performed below the level of the common iliac artery. The surgeon’s experience varied from fellowship to expert, but at least one well-experienced surgeon attended each operation.

RARC

RARC was performed with a da Vinci Si, X, or Xi surgical robot (Intuitive Surgical, Sunnyvale, CA, USA) and six ports. The surgical maneuvers were identical to those in ORC, but an antegrade and transperitoneal approach was used. Before attempting RARC, every surgeon had performed over 30 robot-assisted radical prostatectomies. All patients were operated on consecutively starting with the initial implementation of RARC.

Urinary diversion

To construct an ileal conduit, a 60 mm Endo GIA stapler (Covidien, Dublin, Ireland) was used to isolate a 15–20 cm segment of the ileum 10–15 cm from the oral side of the cecum valve. The stapler was also used to create the functional end-to-end ileal–ileal anastomosis; the Nesbit or Wallace method with ureteral stents was used to create the ureteroileal anastomosis. In RARC, an extra 5 cm skin incision was added to extirpate the specimen and construct the ileal conduit.

Perioperative protocol

ERAS was formally introduced in July 2017 [15]. However, parts of its preoperative counseling, education, and medical optimization had been applied before that. No anesthesiologist was dedicated to RC procedures; therefore, intraoperative anesthesia was managed by the attending anesthesiologist in each case. Table 1 lists the changeover from conventional recovery to ERAS.

Data extraction

The demographic data collected for patients included age, sex, body mass index (BMI), American Society of Anesthesiologist physical status (ASAPS), prior abdominal surgery, prior pelvic radiotherapy, and neoadjuvant chemotherapy. Operative data, such as operation time and use of transfusion were also extracted.

Complications were graded using the Clavien–Dindo classification version 2.0, with a complication greater than grade 3 defined as a major complication. All patients were followed postoperatively for at least 90 days.

Outcome measures

The primary endpoint was LOS. The secondary endpoint was the 90-day postoperative complication rate, including overall complications, major complications, paralytic ileus, and miscellaneous gastrointestinal (GI) complications, such as bowel obstruction and anastomosis failure.

Statistical analysis

The Fisher exact test was used to compare categorical variables. Whereas, the Kruskal–Wallis test was used to compare continuous variables. Categorical variables are reported as frequencies and percentages, and continuous variables are reported as medians with an interquartile range.

In outcome analyses, LOS and complication rates were first compared between the groups.

Next, pairs of groups were compared (group A vs. group B and group B vs. group C) to estimate the outcome improvement resulting from ERAS and eRARC individually. Specifically, the differences in LOS after ERAS or eRARC were evaluated in a linear regression model. The odds ratios (OR) for complications were evaluated in logistic regression models, comparing values from, before, and after implementing ERAS or eRARC. Finally, univariate and multivariate analyses were performed to assess the contributions of ERAS and eRARC to outcomes.

All statistical analyses were performed using the EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R software (The R Foundation for Statistical Computing, Vienna, Austria) [16]. All *P* values are two-sided, and *P* < 0.05 was considered statistically significant.

Results

Table 2 presents the patient characteristics; patients' age was the only significant difference between the groups (group A vs. group B vs. group C: 70.0 vs. 73.0 vs. 75.0 years, *P* = 0.005). Table 2 also presents the operative parameters, where the median operative time was significantly the shortest in group C, (group A vs. group B vs. group C: 469.0 vs. 429.0 vs. 407.0 min, *P* = 0.003). During eRARC, none of the patients received an intraoperative transfusion. However, during ORC, 27.9% of the patients (34/122) were transfused intraoperatively.

Table 3 presents the perioperative outcomes of LOS and complication rates, and Fig. 2 presents a box plot of LOS for each study group. Median LOS declined with the introduction of ERAS and eRARC (group A vs. group B vs. group C: 28.0 vs 20.0 vs 17.0 days, *P* < 0.001). In the entire cohort, overall complications and major complications occurred in 63.6% (91/143) and 30.1% of the patients (43/143), respectively. The overall complication rates were comparable between the groups; individual complication rates tended to decline after introducing ERAS (groups B and C), but without any significant differences. Mortality was seen in two patients due to perioperative complications only in group A.

Table 3 also presents the evaluation of the individual efficacies of ERAS and eRARC (group A vs. group B and group B vs. group C, respectively). LOS was significantly shorter after implementing ERAS [−10.4 days, *P* < 0.001, 95% confidence interval (CI) −15.6 to −5.12 days], and although a tendency toward a shorter LOS was observed after implementing eRARC, the decline was not significant (−4.10 days, *P* = 0.14, 95% CI −9.52 to 1.32 days). No significant improvements in complications were evident after implementing either ERAS or eRARC. However, nonsignificant but favorable trends in major complications, paralytic ileus, and miscellaneous GI complication were observed after implementing ERAS. Thus, no additional benefit of eRARC over ERAS was observed for complications.

We aimed to identify LOS predictors using univariate and multivariate analysis. In this study, the median LOS was 23 days. Therefore, this number was used as a cut-off. Table 4 presents the results of the relevant analyses. In univariate analysis, major complications and paralytic ileus were factors associated with significantly longer LOS (major complications: OR 4.54, *P* < 0.001, 95% CI 1.99–10.3; paralytic ileus:

OR 3.40, $P = 0.017$, 95% CI 1.24–9.31), and ERAS and eRARC were factors associated with significantly shorter LOS (ERAS: OR 0.16, $P < 0.001$, 95% CI 0.077–0.34; eRARC: OR 0.14, $P = 0.002$, 95% CI 0.038–0.49). In multivariate analysis, the major complication was an independent factor predicting significantly longer LOS, and ERAS was an independent factor predicting shorter LOS (major complication: OR 4.74, $P = 0.001$, 95% CI 1.83–12.3; ERAS: OR 0.23, $P < 0.001$, 95% CI 0.098–0.53). Contrastingly, eRARC was not an independent predictor of either longer or shorter LOS (OR 0.29, $P = 0.096$, 95% CI 0.21–2.96).

Discussion

After the sequential implementation of ERAS and eRARC, we assessed whether eRARC, when added to ERAS, provided additional efficacy in terms of patient outcomes. To our knowledge, this is the first study to evaluate both eRARC and ERAS concurrently. The results revealed that LOS was shorter in patients receiving ERAS (groups B and C) than in those receiving CRAS (group A). Moreover, ERAS was found to be an independent predictor of shorter LOS.

Recent meta-analyses evaluating the utility of ERAS for RC also reported shortened LOS [4,5]. ERAS implementation has not been standardized and has differed between institutions. However, some theoretical advantages of each element of ERAS have been suggested. For instance, early resumption of oral intake can promote faster bowel function recovery and maintain metabolism, preoperative carbohydrate loading might improve insulin resistance and maintain muscle mass, and omitting a nasogastric tube might facilitate faster pulmonary recovery and early mobilization [4,5,17]. By acting synergistically, these practices might contribute to shortened LOS.

In this study, no difference in LOS between groups B and C was observed. Moreover, eRARC was not a significant predictor of shortened LOS in multivariate analysis. Chen et al. and Schiavina et al. demonstrated additive efficacy for RARC after ERAS, but their analyses were limited to patients undergoing iRARC [12,13]. The evidence for the superiority of iRARC compared with eRARC has emerged mainly from high-volume academic centers [18,19]. Furthermore, hospital and surgeon volume correlations with postoperative outcomes have been reported [2,14]. Notably, Kimura et al., in LOS, reported that the randomized study group did not show RARC superiority in contrast to the nonrandomized study group [20]. Considering the preceding findings, the contribution of RARC to LOS remains uncertain, but any potential positive efficacy might not be observed in a non-high-volume community center and a retrospective study, such as in this study.

In this study, a major predicted complication was longer LOS. A meta-analysis evaluating morbidity in RC reported a range of 36%–86% for 90-day overall complications and 8.6%–35% for major complications—comparable to our results [20]. With ERAS, we observed a favorable trend in major complications (OR 0.57, P = 0.18). Concerning the potential advantages of ERAS, Feng et al. suggested that ERAS can promote early GI function recovery, thus, facilitating wound healing, which might help avoid severe morbidity [21]. In contrast, we found that eRARC was not associated with improvement in major complications—resembling the findings of several prospective studies of iRARC after ERAS [12,13].

Multiple factors, such as surgical experience, specific operative procedures, and patient characteristics could affect perioperative outcomes [14,22,23]. Therefore, the surgical approach might not be the definitive factor for reducing complications [12].

Our study has several limitations. First, it is a retrospective, nonrandomized study conducted at a single center with a small patient sample. The feelings and preferences of both patients and surgeons might have affected the selection of the surgical approach. Moreover, we did not adjust for observed differences in stratifying the patient groups, but we did confirm that those differences were minor. Second, the LOS for patients in our study was much longer than those in European and American studies, regardless of the surgical approach [20]. That finding might reflect the universal health reimbursement provided through employee- and community-based social health insurance in Japan and the existing local traditions [24]. In previous Japanese studies, Muto et al. reported median LOSs of 25.5 days with ORC and 19.0 days with RARC (comparable to results in the present study), and Gondo et al. reported even longer median LOSs (ORC: 35.0 days; RARC: 39.0 days) [25,26]. Third, ERAS implementation at our institution involved only a few potential ERAS elements. The ERAS protocol has not yet been standardized, so the number of elements to be performed and the method of performing them have not yet been established [5]. However, previous studies suggest that at least 15 elements should be implemented to maximize the benefit [27]. Our simplified ERAS implementation might have left room for further improvement. Nevertheless, our limited implementation was found to yield a consistent effect. Finally, the study comparisons spanned different eras, with differences in maturity between the surgical team and the individual surgeon, thus potentially influencing outcomes. Considering the preceding limitations, further prospective investigation in a larger population with adjustments for patient and surgeon characteristics will be needed. Identification of the optimal implementation of the ERAS protocol will also be desirable.

Conclusions

To summarize, we assessed whether eRARC, when added to ERAS, provided additional efficacy in patient outcomes. The implementation of ERAS was associated with a significant shortening of LOS, but no significant shortening of LOS was observed with the implementation of eRARC. Multivariate analysis revealed that ERAS was a significant predictor of shorter LOS but that eRARC had no significance as a LOS predictor. With respect to complications, neither ERAS nor eRARC was associated with any significant improvement.

Declarations

Funding

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Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

Conceptualization: Jun Nagayama and Yushi Naito; Data curation: Jun Nagayama; Formal analysis and investigation: Jun Nagayama; Methodology: Jun Nagayama and Akiyuki Yamamoto; Project administration: Jun Nagayama; Supervision: Akiyuki Yamamoto; Validation: Akiyuki Yamamoto, Yushi Naito, Hiroki Kamikawa, Hideyuki Kanazawa, Akiyuki Asano, Norie Sho and Yasuhiro Terashima; Writing – original draft preparation: Jun Nagayama; Writing – review and editing: Jun Nagayama and Akiyuki Yamamoto.

Ethics approval

Ethical approval requirement was waived by the Institutional Reviewer Board of Toyohashi Municipal Hospital (approval number: 712) in view of the retrospective nature of the study and because all the procedures being performed were part of routine care.

Consent to participate

Informed consent was obtained in the opt-out form on the institutional web-site. The patients who subject to the study could refuse to participate in case they did not consent.

Consent to publish

Informed consent was obtained in the opt-out form on the institutional web-site. The patients who subject to the study could refuse to publish in case they did not consent.

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Tables

Table 1 The change points of perioperative protocol from CRAS to ERAS

	CRAS	ERAS
Mechanical bowel preparation	Take magnesium citrate orally on the day before the operation	Omit any mechanical bowel preparation
Preoperative carbohydrates loading	Fasting from 24 h before the operation	Taking liquid containing carbohydrates 2 h before the surgery
Preoperative fasting	Fasting from 24 h before the operation	Take a meal by the night before surgery
Resection site drainage	Perianastomotic and pelvic drains Removal of drain decided by attending surgeon	Only pelvic drain Drain was principally removed in postoperative day 2
Preoperative fluid management	Loading 2L electrolyte solution from 48 h before the operation	Omit preoperative hydration
Nasogastric intubation	Removal of the nasogastric tube at postoperative day 1	Remove nasogastric tube at the end of the operation
Early oral diet	Resumption of oral intake decided by the surgeon	Resumption of liquid taking in postoperative day 1 and taking meal on postoperative day 2

CRAS-conventional recovery after surgery

ERAS-enhanced recovery after surgery

Table 2 Patient characteristics and operative parameters

Variables	Group A (CRAS+ORC) (n = 75)	Group B (ERAS+ORC) (n = 47)	Group C (ERAS+eRARC) (n = 21)	p value
Patient characteristics				
Age (year) median (IQR)	70.0 (66.5, 74.5)	73.0 (69.0, 76.0)	75.0 (73.0, 78.0)	0.005
Gender, male n (%)	61(81.3)	37 (78.7)	18 (85.7)	0.79
BMI (kg/m²) median (IQR)	22.8 (21.2, 24.8)	22.9 (21.3, 25.1)	24.3 (22.3, 26.6)	0.28
ASAPS n (%) 1	24 (32.0)	16 (34.0)	6 (28.6)	0.50
2	39 (52.0)	22 (46.8)	8 (38.1)	
3≦	12 (16.0)	9 (19.1)	7 (33.3)	
NAC n (%)	27 (36.0)	20 (42.6)	6 (28.6)	0.52
Prior abdominal surgery n (%)	23(30.7)	12 (25.5)	2 (9.5)	0.15
Prior pelvic radiotherapy n (%)	7 (9.3)	3 (6.4)	0 (0.0)	0.33
Operative parameters				
Operation time(min) median (IQR)	469.0 (424.0, 512.5)	429.0(352.0, 453.0)	407.0(375.0, 501.0)	0.003
Intraoperative transfusion rate n (%)	23 (30.7)	11(23.4)	0(0.0)	0.014

ASAPS: American Society of Anesthesiologist physical status

BMI: body mass index

CRAS: conventional recovery after surgery

ERAS: enhanced recovery after surgery

IQR: interquartile range

NAC: neoadjuvant chemotherapy

Table 3 LOSs and complication rates, and comparison of postoperative outcomes after the implementation of ERAS and eRARC

	Group A (n = 75)	Group B (n = 47)	Group C (n = 21)		p value
LOS days(median), IQR	28.0 (23.0, 36.3)	20.0(16.0, 25.0)	17.0(14.0, 22.0)		<0.001
mortality due to complication n (%)	2 (2.7)	0 (0.0)	0 (0.0)		0.39
Overall complication n (%)	48 (64.9)	30 (63.8)	13(61.9)		0.97
Major complication n (%)	27 (36.0)	11 (23.4)	5 (23.8)		0.27
Paralytic ileus n (%)	17 (22.7)	6 (12.8)	2 (9.5)		0.22
Miscellaneous GI complication n (%)	9 (12.0)	3 (6.4)	2 (9.5)		0.29
	Post ERAS (Group A vs. B) reference Group A	p value	Post eRARC (Group B vs. C) reference Group B	p value	
Reduction of LOS days, 95%CI	-10.4 (-15.6, -5.12)	<0.001	-4.10 (-9.52, 1.32)	0.14	
Overall complication OR, 95% CI	0.99(0.46, 2.13)	0.97	0.95(0.33, 2.76)	0.93	
Major complication OR, 95% CI	0.57(0.24, 1.31)	0.18	1.13(0.33, 3.83)	0.85	
Paralytic ileus OR, 95% CI	0.46(0.16, 1.38)	0.17	0.86(0.15, 4.86)	0.87	
Miscellaneous GI complication OR, 95% CI	0.45(0.16, 1.24)	0.12	1.57(0.39, 6.28)	0.53	

CI: confidence interval

ERAS: enhanced recovery after surgery

eRARC: robot-assisted radical cystectomy with extracorporeal urinary diversion

GI: gastrointestinal

IQR: interquartile range

LOS: length of hospital stay

OR: odds ratio

Table 4. Univariate and multivariate analysis for predictors of LOS≦23days

	Univariate analysis (OR, 95%CI)	p value	Multivariate analysis (OR, 95%CI)	p value
Age	1.03 (0.98, 1.09)	0.19		
BMI	1.02 (0.92, 1.12)	0.73		
ASAPS≧3 (ref 1-2)	0.50 (0.12, 2.09)	0.34		
Major complication	4.54 (1.99, 10.3)	<0.001	4.74 (1.83, 12.3)	0.001
Miscellaneous GI complication	1.95 (0.55, 7.01)	0.30		
Paralytic ileus	3.40 (1.24, 9.31)	0.017	2.35 (0.72, 7.61)	0.16
eRARC (ref ORC)	0.14 (0.038, 0.49)	0.002	0.29 (0.21, 2.96)	0.096
ERAS (ref CRAS)	0.16 (0.077, 0.34)	<0.001	0.23 (0.098, 0.53)	<0.001

ASAPS: American Society of Anesthesiologist physical status

BMI: body mass index

CI: confidence interval

CRAS: conventional recovery after surgery

ERAS: enhanced recovery after surgery

eRARC: robot-assisted radical cystectomy with extracorporeal urinary diversion

GI: gastrointestinal

IQR: interquartile range

OR: odds ratio

ORC: open radical cystectomy

ref: reference

Figures

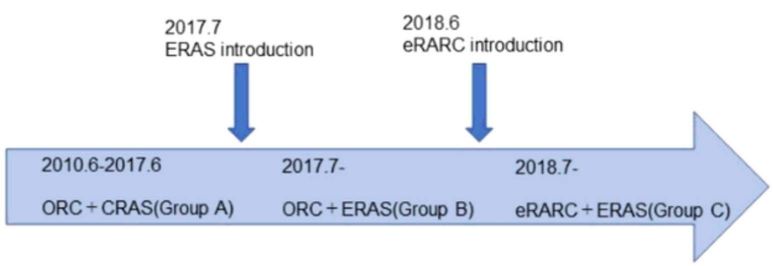

Figure 1

The time sequence of the changes in perioperative protocol and surgical approach

Enhanced recovery after surgery (ERAS) was introduced in July 2017 and robot-assisted radical cystectomy with extracorporeal urinary diversion (eRARC) was also introduced in June 2018. In the present study, the patients were allocated as following: Group A) conventional recovery after surgery (CRAS) with open radical cystectomy (ORC), Group B) ERAS with ORC, Group C) ERAS with eRARC

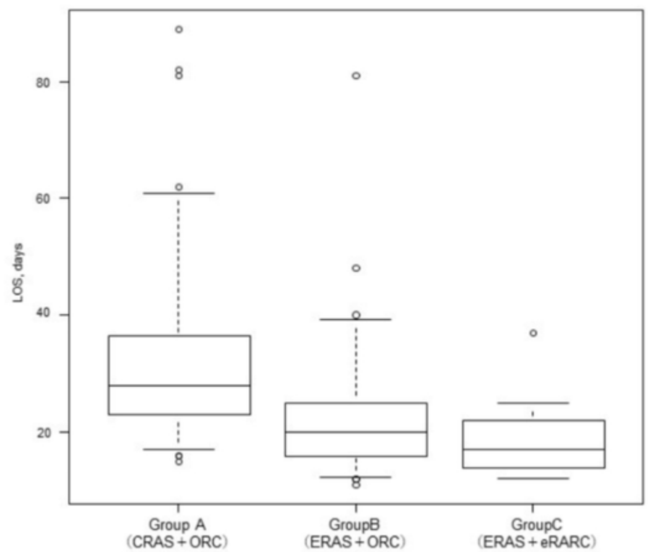

Figure 2

The box plot depicts the median LOSs of the groups

The actual days of median LOSs for each group are shown in Table 1