Assessment of Feasibility of Robot-assisted Radical Cystectomy in Patients With Advanced Bladder Cancer Treated With Maintenance Hemodialysis Therapy

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Abstract. *Background/Aim: To clarify the perioperative and oncological outcomes of robot-assisted radical cystectomy (RARC) in advanced bladder cancer (BC) patients treated with maintenance hemodialysis (HD) therapy. Patients and Methods: We retrospectively evaluated patients receiving HD therapy who had undergone RARC or open radical cystectomy (ORC) for BC between April 1988 and December 2021 at two affiliated institutions. We compared the surgical outcomes and survival after radical cystectomy between patients treated with RARC and those treated with ORC. Results: Thirty-six patients were evaluated, and eight (22%) and 28 (78%) received RARC and ORC, respectively. RARC was more frequently conducted than ORC in elderly patients (median: 75.5 vs. 68.2 years, p<0.05). Regarding postoperative surgical outcomes, the estimated blood loss volume (median: 75 ml vs. 627 ml, p<0.05) was significantly lower in the RARC group than that in the ORC group. A lower blood transfusion rate (25% vs. 67%, p=0.170) was observed. Moreover, there were no differences in operative time (median: 255 vs. 294 min, p=0.232) or complication rate (Clavien-Dindo grade, any grade: 50% vs. 46%, p=0.858; grade 3 or more: 13% vs.* 14%, p=0.897). The |1-year overall survival rate did not differ between the two groups (88% vs. 74%, p=0.365). Conclusion: The perioperative outcomes of RARC in patients undergoing HD therapy were comparable to those of ORC. RARC is a potentially feasible surgical option even in patients with high comorbidities.*

The number of patients undergoing maintenance hemodialysis (HD) as a treatment for end-stage renal disease (ESRD) is increasing worldwide (1, 2). In ESRD patients, an impairment in immune system and DNA repair mechanisms, a reduction in antioxidant defenses, and an accumulation of carcinogenic compounds due to reduced renal excretion, chronic infections, and inflammation have been reported to promote malignant transformation (3, 4). Indeed, multiple studies showed that the cancer risk was higher in patients undergoing HD therapy than that in the general population, especially in genitourinary cancers such as bladder cancer (BC) or renal cell carcinoma (5-7). Specifically, the risk of BC is reported to be increased by 1.5-2.5 times in patients undergoing HD therapy.

As for BC, advanced disease, including muscle-invasive BC, was more frequently observed in patients receiving HD therapy than it was in the general population (33% *vs.* 24%) (8). For these patients, radical cystectomy, the gold standard treatment option for advanced BC, is considered. However, radical cystectomy harbors a high risk of postoperative morbidity and mortality. Therefore, such risks may increase in patients receiving HD therapy because they are likely to harbor multiple complications, including HD-related complications and ESRD itself (9-11).

The surgical approach to radical cystectomy has dramatically changed over recent years, and robot-assisted radical cystectomy (RARC) is currently accepted.

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Randomized controlled trials demonstrated that RARC resulted in a reduction in blood transfusion rate and shortened the length of postoperative hospitalization compared to open radical cystectomy (ORC) in exchange for increased operative time (12-16). These findings suggest that RARC has the potential to be a more feasible and safer surgical approach than ORC. Thus, RARC may be suitable for patients with ESRD undergoing HD. Further, as these trials were conducted in a cohort comprising strictly selected patients, data on the feasibility of RARC in patients receiving HD therapy are limited.

In this context, we aimed to clarify the feasibility of RARC in advanced BC patients treated with maintenance HD therapy for ESRD in this retrospective study.

Patients and Methods

Study design and patients. The medical records of 403 BC patients who underwent radical cystectomy at our two affiliated institutions (Tokyo Women's Medical University and Tokyo Women's Medical University Adachi Medical Center) from April 1988 to December 2021 were retrospectively reviewed. Among 403 patients, 36 were treated with maintenance HD therapy at the time of radical cystectomy.

Until March 2018, we generally performed radical cystectomy using the open surgery approach. Following the approval from the Japanese health insurance system (April 2018), we performed RARC. Among the 36 patients, 28 underwent ORC, whereas eight patients underwent RARC.

We compared the perioperative outcomes between patients who underwent ORC and those who underwent RARC. TNM staging was performed according to the Union for International Cancer Control classification (8th edition). Postoperative complications were assessed according to the Clavien-Dindo system (17).

All clinical and laboratory data were obtained from electronic databases and medical records. The study protocol was approved by the Institutional Ethics Review Board of Tokyo Women's Medical University (approval ID: 2020-0108), and performed in accordance with the principles outlined in the 1964 Declaration of Helsinki and its later amendments. The requirement for informed consent was waived owing to the retrospective observational nature of this study.

Surgical approach. ORC was performed *via* a middle abdominal incision, and an extraperineal approach was performed to the maximum intent. RARC was performed using a six-port transperitoneal approach using the Da Vinci X/Xi system (Intuitive Surgical, Sunnyvale, CA, USA). Lymph node dissection was performed to a limited extent, which was determined by the patient's general condition and operator's discretion. Urinary diversion was performed in patients whose urinary volume was >500 ml/day.

Statistical analysis. All statistical analyses were performed using JMP version 15.0.0 (SAS Institute, Cary, NC, USA). Continuous variables were analyzed using the Mann-Whitney U-test, whereas categorical variables were analyzed using the χ^2 test or Fisher's exact test, as appropriate. Overall survival (OS) and relapse-free

Table I. *Clinical characteristics.*

	RARC (n=8)	ORC (n=28)	p-Value
Male sex	6 (75%)	19 (68%)	1.000
Age, years			
Median (IQR)	75.5 (68.9-81.1)	68.2 (58.4-73.0)	<0.05
Smoking history	2 (25%)	13 (46%)	0.247
Clinical symptoms			0.258
Gross hematuria	4 (50%)	19 (68%)	
Other symptoms	0	4 (14%)	
No symptoms	4 (50%)	5 (18%)	
Urine cytology			0.617
Positive	4 (50%)	17 (61%)	
Negative	1 (13%)	4 (14%)	
Not performed/ unknown	3 (37%)	7 (25%)	
Diameter of the main tumor			0.926
>3 cm	2 (25%)	9 (32%)	
<3 cm	5 (62%)	16 (57%)	
Unknown	1 (13%)	3 (11%)	
Multiplicity (number of tumors)			0.243
>1	4 (50%)	20 (71%)	
1	4 (50%)	6 (22%)	
Unknown	0	2 (7%)	
Clinical T stage			0.289
Ta, Tis, T1, T2	8 (100%)	21 (75%)	
≥T3	0	5 (18%)	
Unknown	0	2 (7%)	
Charlson Comorbidity Index			0.522
High (3-4)	4 (50%)	2 (7%)	
Very high (5-)	4 (50%)	4 (14%)	
Unknown	0	22 (61%)	
Duration of dialysis before surgery, months*			
Median (IQR)	65 (5-217)	115 (55-405)	0.482
Etiology of ESRD			0.674
Chronic glomerulonephritis	3 (37%)	3 (11%)	
Diabetic nephropathy	1 (13%)	2 (7%)	
Nephrosclerosis	3 (37%)	1 (4%)	
ADPKD	0	1 (4%)	
Upper urinary tract tumor	1 (13%)	1 (4%)	
Unknown	0	20 (71%)	
Follow-up after surgery, months			
Median (IQR)	18.0 (6.8-30.2)	27.5 (10.3-51)	0.402

*Analyzed in 11 patients with eligible data in the ORC group. RARC: Robot-assisted radical cystectomy; ORC: open radical cystectomy; IQR: interquartile range; ESRD: end-stage renal disease; ADPKD: autosomal dominant polycystic kidney disease.

survival (RFS) were calculated using the Kaplan-Meier method and compared using the log-rank test. Statistical significance was set at $p<0.05$.

Table II. *Operative and postoperative characteristics.*

	RARC (n=8)	ORC (n=28)	*p*-Value
Urinary diversion procedure			0.630
Ileal conduit	0	3 (11%)	
Ureterostomy	0	1 (4%)	
Nephrostomy	0	1 (4%)	
No urinary diversion	8 (100%)	22 (78%)	
Unknown	0	1 (4%)	
Lymph node dissection			0.0717
Presence	2 (25%)	16 (57%)	
Absence	6 (75%)	10 (36%)	
Unknown	0	2 (7%)	
Urethrectomy			0.292
Presence	2 (25%)	11 (40%)	
Absence	6 (75%)	13 (46%)	
Unknown	0	4 (14%)	
Nephroureterectomy			0.261
Presence	1 (13%)	8 (29%)	
Absence	7 (87%)	16 (57%)	
Unknown	0	4 (14%)	
Operative time, min*			
Median (IQR)	255 (174-279)	294 (220-355)	0.231
Console time, min			
Median (IQR)	193 (141-216)	NA	NA
Estimated blood loss, ml*			
Median (IQR)	75 (30-237)	627 (542-798)	<0.05
Blood transfusion*	2 (25%)	8 (67%)	0.170
Perioperative complications			
Clavien-Dindo grade			
I	1 (13%)	1 (4%)	
II	3 (38%)	9 (32%)	
III	1 (13%)	2 (7%)	
IV-V	0	2 (7%)	
Any grade complications per patient	4 (50%)	13 (46%)	0.858
Complications classified by system			
Infectious			
Intra-abdominal collection	1 (13%)	2 (7%)	
Urinary tract	1 (13%)	3 (11%)	
Surgical site	1 (13%)	4 (14%)	
Gastrointestinal			
Ileus	0	1 (4%)	
Cardiac			
Aneurysm	1 (13%)	0	
Cardiac failure	0	1 (4%)	
Bleeding			
Postoperative hemorrhage	1 (13%)	2 (7%)	
Neurologic			
Obturator nerve disorder	0	1 (4%)	
Grades III-IV complications per patient	1 (13%)	4 (14%)	0.897
Postoperative hospitalization, days			
Median (IQR)	10 (7-35)	9 (7-19)	0.937

*Analyzed in 12 patients with eligible data in the ORC group. RARC: Robot-assisted radical cystectomy; ORC: open radical cystectomy; IQR: interquartile range.

Table III. *Pathological characteristics.*

	RARC (n=8)	ORC (n=28)	*p*-Value
Pathological stage			0.324
T0-2	6 (86%)	18 (66%)	
T3-4	1 (14%)	9 (33%)	
Pathological lymphatic invasion			
Presence	2 (29%)	10 (43%)	0.725
Pathological vascular invasion			
Presence	2 (29%)	10 (43%)	0.725
Surgical margin status			
Positive	0	1 (3%)	0.794

RARC: Robot-assisted radical cystectomy; ORC: open radical cystectomy.

Results

Patient background. Table I summarizes the characteristics of patients and tumors. The proportion of elderly patients was significantly higher in the RARC group than in the ORC group [median: 75.5 years (interquartile range {IQR}=68.9-81.1) *vs*. 68.2 years (58.5-73.0), *p*<0.05]. However, there were no differences in sex, smoking history, clinical symptoms, positive cytology rate, size of the main tumor, tumor multiplicity, presurgical clinical T stage, Charlson Comorbidity Index, or duration of HD therapy before radical cystectomy between the two groups (all, *p*>0.05). No patients received neoadjuvant chemotherapy because they were considered chemo-unfit cases due to kidney dysfunction. The median follow-up period after radical cystectomy was 18.0 months (IQR=6.8-30.2) and 27.5 months (IQR=10.3-51.0) in the RARC and ORC groups, respectively.

Operative and postoperative outcomes. The median operative time did not differ significantly between the RARC and ORC groups [median: 255 min (IQR=174-279) *vs*. 294 min (IQR=220-355), *p*=0.231] (Table II). The urinary diversion procedure was absent in all RARC group patients but was conducted in a patient subset in the ORC group (19%). Lymph node dissection (25% *vs*. 57%, *p*=0.0717), urethrectomy (25% *vs*. 40%, *p*=0.292), and synchronous nephroureterectomy (13% *vs*. 29%, *p*=0.261) were performed more frequently in the ORC group, but the difference was not significant. The estimated blood loss volume was significantly lower [median: 75 ml (IQR=30-237) *vs*. 627 ml (IQR=542-798), *p*<0.05] and the blood transfusion rate tended to be lower (25% *vs*. 67%, *p*=0.170) in the RARC group than those in the ORC group.

The rate of postoperative complications did not differ between the RARC and ORC groups (any grade: 50% *vs*. 46%, *p*=0.858; grade ≥3: 13% *vs*. 14%, *p*=0.897) (Table II). The number of days of postoperative hospitalization was not different [median: 10 days (IQR=7-35) *vs*. 9 days (IQR=7-19),

Table IV. *Operative characteristics of RC without nephroureterectomy and urinary diversion.*

	RARC (n=7)	ORC (n=15)	p-Value
Operative time, min			
Median (IQR)*	254 (154-267)	281 (193-336)	0.405
Estimated blood loss, ml			
Median (IQR)*	50 (30-250)	610 (525-800)	<0.05
Blood transfusion*	2 (28%)	5 (71%)	0.286
Postoperative hospitalization, days			
Median (IQR)*	11 (7-43)	8 (7-9)	0.517
Perioperative complications			
Clavien-Dindo grade			
I	0	1	
II	3	3	
III	1	0	
IV-V	0	0	
Any grade	4 (57%)	4 (27%)	0.342
Grades III-V	1 (14%)	0	0.318

*Analyzed in seven patients with eligible data in the ORC group. RC: Radical cystectomy; RARC: robot-assisted radical cystectomy; ORC: open radical cystectomy; IQR: interquartile range.

p=0.937]. The pathological findings were also compared between the two groups (Table III). Infiltration into the extravesical tissues was less frequently observed in the RARC group (14% *vs*. 33%, p=0.324). A positive surgical margin was observed in one patient in the ORC group, but not in the RARC group. Surgical-related death was observed in two patients due to heart failure and intra-abdominal hemorrhage, but in no patient in the RARC group.

The rates of urinary diversion and concurrent nephroureterectomy were lower in the RARC group than in the ORC group (Table I). Therefore, this difference in the surgical approach might affect postoperative outcomes. Thus, we further compared the postoperative outcomes between the RARC (n=7) and ORC groups without urinary diversion or concurrent nephroureterectomy (n=7). This additional analysis showed comparable operative time [median: 254 min (IQR=154-267) *vs*. 281 min (IQR=193-336), p=0.405], significantly lower blood loss [median: 50 ml (IQR=30-250) *vs*. 610 ml (IQR=525-800), p<0.05], and tendency of lower rate of blood transfusion (28% *vs*. 71%, p=0.286) (Table IV).

Survival analysis. Finally, we compared survival after radical cystectomy between the RARC and ORC groups. During follow-up, 12 (33%) and six (17%) patients died and experienced recurrence of BC, respectively. The 1-year OS rate did not differ between the two groups (88% *vs*. 74%, p=0.365) (Figure 1). In addition, the 1-year RFS rate did not differ (75% *vs*. 70%, p=0.667) (Figure 2).
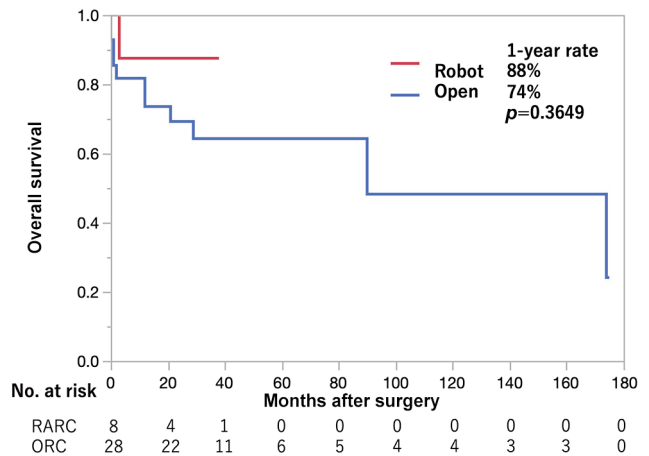

Figure 1. *Overall survival difference between RARC and ORC. RARC: Robot-assisted radical cystectomy; ORC: open radical cystectomy.*
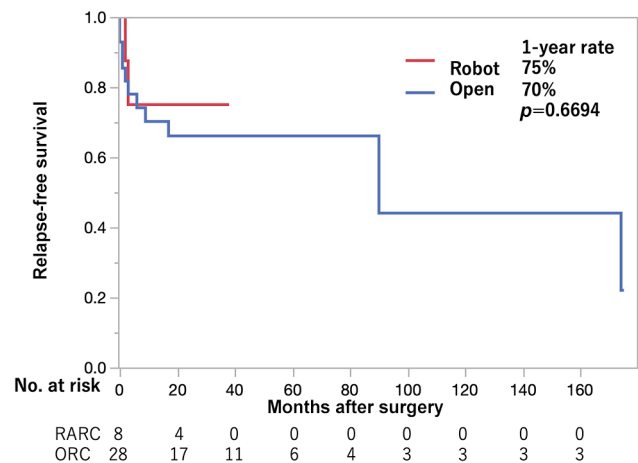

Figure 2. *Relapse-free survival difference between RARC and ORC. RARC: Robot-assisted radical cystectomy; ORC: open radical cystectomy.*

Discussion

In this retrospective study, we evaluated the feasibility of RARC in advanced BC patients treated with maintenance HD therapy for ESRD and compared it with that of ORC. RARC was more frequently performed in elderly patients undergoing HD therapy. Nevertheless, the blood loss volume was lower and the transfusion rate tended to be low. Moreover, the operative time and complication rates were comparable between the RARC and ORC groups. Furthermore, the oncological outcomes were equivalent between the two groups. To our knowledge, this study is the first to report the surgical and oncological outcomes after RARC in patients who have undergone HD therapy for ESRD.

Several studies have indicated that ORC for patients treated with HD therapy induces a high frequency of postoperative mortality and complications. A study using data from the United States Renal Data System database revealed complication and mortality rates of 43.1% and 9.3%, respectively (11). Another case series study showed that two of four patients died postoperatively after total urinary exenteration, including radical cystectomy using an open approach (10). We also reported surgery-related deaths in two of the 17 BC patients (9). These data suggest that ORC is an effective surgical approach, but always harbors a high risk of declining postoperative outcomes.

RARC for patients undergoing HD therapy was associated with less blood loss, a lower blood transfusion rate, and comparable postoperative complication rate and length of postoperative hospitalization compared to ORC. These findings regarding lower blood loss and blood transfusion rates in the RARC conformed with the findings from previous clinical trials conducted in the general population (12-16). Additionally, our data revealed a similar operative time between RARC and ORC. Notably, these findings were observed even though RARC was more frequently conducted in elderly patients than in ORC patients. Furthermore, a feasible outcome of RARC could be observed regardless of the presence of urinary diversion or concurrent nephroureterectomy. Cumulatively, RARC is potentially feasible for patients undergoing HD therapy, which can be accepted in real-world clinical practice.

This study had several limitations. First, it was conducted retrospectively using data from a small sample size from only two institutions. Therefore, any findings were affected by inevitable selection bias. Second, the relatively short follow-up time in the RARC group may make the survival data difficult to interpret. Third, the lack of some data in the ORC group might have affected the analyses. Fourth, the modality and accuracy of imaging examinations steadily increased throughout the study period, and this nonsurgical effect could have influenced the outcomes. Furthermore, advancements in surgical devices may improve postoperative outcomes.

In conclusion, the perioperative outcomes of RARC in patients undergoing HD for ESRD were comparable to those of ORC. Therefore, this surgical approach is potentially feasible and applicable on these high-risk patients in a real-world setting. Further prospective studies with larger sample sizes are required to confirm our findings.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Koichi Nishimura, Hiroki Ishihara, Tsunenori Kondo, Makoto Toguchi, Kazunari Tanabe and Toshio Takagi were involved in study design and data interpretation. Koichi Nishimura, Hiroki Ishihara were involved in data analysis. All Authors critically revised the manuscript, approved the manuscript to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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