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Original Article

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Impact of postoperative complications on long-term survival in bladder cancer patients

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Abstract

Objective: To determine the impact of postoperative complications on long-term survival outcomes in patients with bladder cancer undergoing radical cystectomy.

Methods: This retrospective multi-institutional study included 766 bladder cancer patients who underwent radical cystectomy between 2011 and 2017. Patient characteristics, perioperative outcomes, all complications within 90 days after surgery and survival outcomes were collected. Each complication was graded based on the Clavien-Dindo system, and grouped using a standardized grouping method. The Comprehensive Complication Index, which incorporates all complications into a single formula weighted by their severity, was utilized. Overall survival and recurrence-free survival (local, distant or urothelial recurrences) were stratified by Comprehensive Complication Index (high: $\geq$26.2; low: $<$26.2). A multivariate model was utilized to identify independent prognostic factors.

Results: The incidence of any and major complications ($\geq$Clavien-Dindo grade III) was 70 and 24%, respectively. In terms of Comprehensive Complication Index, 34% (261/766) of the patients

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had ≥26.2. Patients with Comprehensive Complication Index ≥ 26.2 had shorter overall survival (4-year, 59.5 vs. 69.8%, respectively, log-rank test, $P = 0.0037$) and recurrence free survival (51.9 vs. 60.1%, respectively, $P = 0.0234$), than those with Comprehensive Complication Index < 26.2. The Cox multivariate model identified the age, performance status, pT-stage, pN-stage and higher CCI (overall survival: HR = 1.35, $P = 0.0174$, recurrence-free survival: HR = 1.26, $P = 0.0443$) as independent predictors of both overall survivial and recurrence-free survival.
Conclusions: Postoperative complications assessed by Comprehensive Complication Index had adverse effects on long-term survival outcomes. Physicians should be aware that major postoperative complications can adversely affect long-term disease control.

Key words: postoperative complication, radical cystectomy, bladder cancer, survival

Introduction

Radical cystectomy (RC) in conjunction with regional lymph node dissection (LND) and urinary diversion is the mainstay of treatment for muscle-invasive or treatment-refractory non-muscle-invasive bladder cancers (BCs). However, it is well known that RC is correlated with significant perioperative morbidity (approximately 50–70%) (1–3). Recently, our group collected data on 90-day postoperative complications in patients treated by RC at Hokkaido University Hospital and our affiliated hospitals between 2011 and 2017 (recent cohort, n = 838), and compared the perioperative outcomes with those of our previous cohort (n = 919, 1997–2010). We observed that RC has remained correlated with significant postoperative morbidity [overall complications: 69% (580/838) in the recent cohort vs. 68% (629/919) in the previous cohort, and major complications (Clavien-Dindo, CD, grade ≥ III): 25% (211/838) in the recent cohort vs. 22% (201/919) in the previous cohort, respectively] over the past two decades (4).

Recent studies involving colorectal, gastric and esophagogastric cancer, or hepatocellular carcinoma resection have shown an adverse impact of postoperative morbidities on long-term survival outcomes (5–8), which remains unknown after RC. In the present study, we aimed to clarify the impact of postoperative complications on the long-term survival impact after RC.

Materials and methods

The Institutional Review Board approved this study (No. 017-0038). We reviewed the medical records of 838 patients with muscle invasive or treatment-refractory non-muscle-invasive BC who underwent RC at Hokkaido University Hospital and 19 affiliated institutions between 2011 and 2017. As mentioned before, in terms of the current landscape of postoperative complications after RC, we previously published a paper (4). In the present study, we updated the survival information. Excluding patients with distant metastasis (n = 29) at the time of RC, who died within 90 days after surgery (n = 38), in order to highlight the long-term survival effect, with the final pathology of lymphoma (n = 1), with advanced prostate cancer (n = 1), no follow-up data (n = 2) and treated for disease palliation (n = 1), 766 patients were included in the current survival analysis.

During the study period (2011–2017), the type of urinary diversion (i.e. ileal conduit, ileal neobladder or cutaneous ureterostomy) was performed based on the patients' and surgeons' decisions, and the region of LND was determined by each surgeon. Laparoscopic RC was performed mainly without robotic assistance, and urinary diversion was performed extracorporeally via a small incision (extracorporeal urinary diversion) in all patients. Perioperative systemic chemotherapy was also administered based on the patients' and surgeons' decisions.

Patient characteristics, perioperative outcomes and all complications within 90 days of surgery were reviewed. Tumor staging was performed according to the Union for International Cancer Control TNM classification ^{7th} edition, and the tumor grade was assessed according to the 2004 WHO classification. Postoperative complications were also assessed. Each complication was graded according to the CD system (9) by co-authors at each hospital, and grouped according to a standardized grouping method, consisting of the 11 complication categories reported by Shabsigh et al. (1). If there was any contradiction between CD grading and the management for each complication, two authors (YS and TA) asked co-authors to review the medical charts, and corrected the misgrading. Furthermore, in order to examine the cumulative postoperative morbidity, the Comprehensive Complication Index (CCI), which incorporates all complications into a single formula weighted by their severity, was calculated for each patient by one author (YS), who was blinded to the final survival outcomes (10). CCI ranged from 0 (no complications) to 100 (death). According to previous studies, we utilized CCI of 26.2 as the cut-off point (equivalent to one grade IIIa complication by the CD system) (11,12).

In terms of postoperative follow-up, in general, computed tomography was performed every 6 months for the first two years. Subsequently, follow-up examinations were performed every 6–12 months. The primary outcome of the current study was the impact of any or major complications on long-term survival after RC. Regarding the definition of a major complication for the subsequent analyses, both the highest CD grade of ≥III in each patient and CCI ≥26.2 were utilized. The secondary outcome was the survival effect of each complication category. Any urine leak event was also evaluated separately, which may be associated with tumor dissemination if cancer cells remained within the urinary tract. Overall survival (OS) was defined as the interval between the date of surgery and that of death. Recurrence-free survival (RFS) was calculated from the date of surgery to disease recurrence or death from any cause. Local, distant and urothelial recurrences were included in the study.

Statistical analysis

OS and RFS were estimated using the Kaplan–Meier method, and the log-rank test was used to compare survivals between the groups. Univariate and multivariate Cox models were utilized to determine independent survival predictors in the current cohort. The significant

Table 1. Patients' characteristics

Characteristics	*n* = 766
Sex	
Male	567 (74%)
Female	199 (26%)
Age at radical cystectomy (years), median (range)	72 (34–93)
Body mass index (BMI) (kg/m ^{2}), median (range)	22.7 (13.5–34.5), *n* = 761
Average annual cystectomy volume	
High (≥10 per year)	257 (34%), 3 hospitals
Moderate (5 ≤ – < 10 per year)	371 (48%), 8 hospitals
Low (<5 per year)	138(18%), 9 hospitals
Performance status	
0	661 (86%)
1	82 (11%)
2	14 (2.0%)
3	2 (0.3%)
Unknown	7 (0.9%)
No. neoadjuvant chemotherapy	95 (12%)
No. adjuvant chemotherapy	79 (10%)
No. form of urinary diversion	
Illeal conduit	516 (67%)
Neobladder	55 (7%)
Ureterocutaneostomy	182 (24%)
Nephrostomy	3 (0.4%)
Not performed	10 (1.3%)
Type of neobladder	
Hautmann	46 (84%)
Studer	6 (11%)
Unknown	3 (5%)
Pathological T-stage	
pT0	92 (12%)
pTa-is	110 (14%)
pT1	107 (14%)
pT2	148 (19%)
pT3	239 (31%)
pT4	70 (9%)
Pathological N-stage	
pN+	133 (17%)
pN0	603 (79%)
pNx	30 (4%)
Histology	
Pure urothelial carcinoma	687 (90%)
Others	79 (10%)
Grade	
high	551 (72%)
low	98 (13%)
unknown	117 (15%)
Operative time (minutes), median (range)	390 (75–820), *n* = 764
Estimated blood loss (mL), median (range)	1000 (0–9230), *n* = 760
Surgical approach	
Open	568 (74%)
Laparoscopic	198 (26%)

predictors in the univariate model were included in the multivariate model. The variables analyzed were sex, age (continuous), body mass index, average annual cystectomy volume (high: ≥10 per/year vs. moderate: 5 ≤ <10 per/year vs. low: <5 per/year), performance status (PS, 0 vs. 1 vs. 2 vs. 3), neoadjuvant chemotherapy (yes vs. no), adjuvant chemotherapy (yes vs. no), pathological T-stage (pT0-1 vs. pT2 vs. pT3-4), pathological N-stage (pN0 vs. pN+ vs. pNx), histology (pure urothelial carcinoma vs. urothelial carcinoma with variant histology), tumor grade (low vs. high), operative time (continuous), estimated blood loss (continuous), surgical approach (open vs. laparoscopic) and complications (none vs. minor/major, none/minor vs. major or CCI < 26.2 vs. CCI ≥ 26.2). All calculations were performed using JMP® Pro, version 16.0.0 (SAS Institute, Cary, NC, USA). Significance was set at $p < 0.05$.

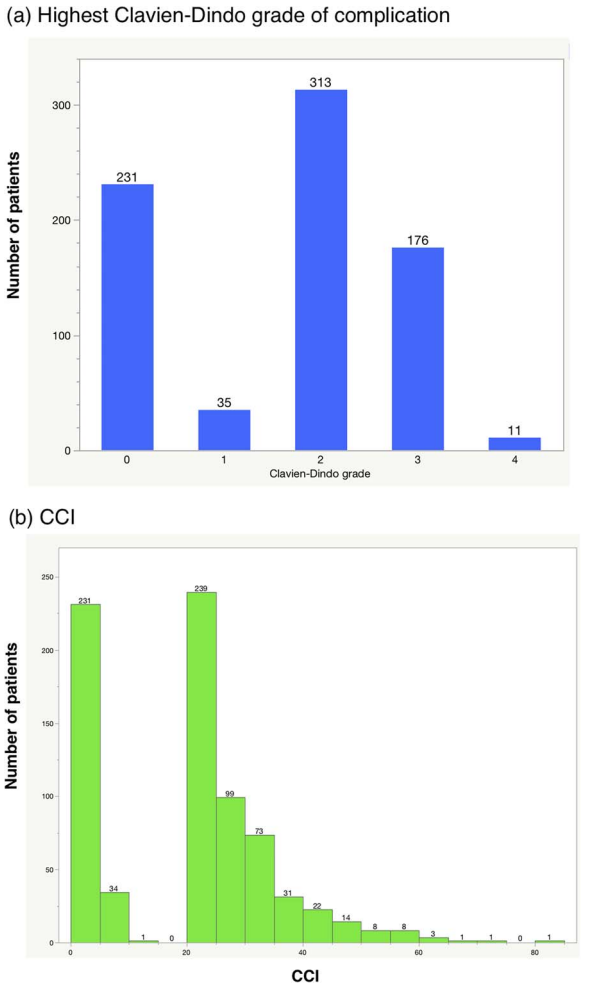

Figure 1. Distribution of the highest Clavien-Dindo (CD) grade of complication and Comprehensive Complication Index (CCI) in an independent patient population.

Results

Table 1 shows a summary of the patient characteristics. The median patient age was 72 years (range, 34–93). Neoadjuvant chemotherapy was administered to 12% (95/766) of patients. In terms of urinary diversion, two-thirds of the patients (67%, 516/766) received an ileal conduit. Seventeen % (133/766) of patients had node metastasis on pathology.

Complications

Table 2 summarizes the postoperative complications. The most common complications were infectious (39%, 300/766), followed by gastrointestinal (26%, 201/766), wound-related (18%, 136/766) and genitourinary (10%, 73/766) complications. Urine leakage was observed in 31 patients. Figure 1 shows the distribution of the highest CD grade complication per patient (a), and CCI (b). The incidences of any and major (≥CD grade III) complications were 70 (535/766) and 24% (187/766), respectively. In terms of CCI, 34% (261/766) of the patients had CCI ≥ 26.2.

Survival analyses

The median follow-up duration for the entire cohort was 53 months. Four-year OS and RFS rates were 66.4 and 57.4%, respectively.

Table 2. Summary of postoperative complications

Category	No. of all patients (%)	Clavien-Dindo grade		Events	No. of patients
		≤II	≥III		
Gastrointestinal	201 (26%)	115	86	Ileus	174
				Bowel anastomosis leak/fistula	15
				Gastrointestinal ulcer/bleeding	9
				Enterocolitis	14
				Gastrointestinal perforation	3
Infection	300 (39%)	259	41	UTI	218
				FUO	27
				Sepsis	14
				Other site infection	69
Wound	136 (18%)	102	34	SSI	79
				Wound dehiscence	65
Genitourinary	73 (10%)	29	44	Hydronephrosis	30
				Urine leak	31
				Renal failure	13
				Ileal conduit injury/necrosis	3
				Others	2
Cardiac	6 (0.8%)	5	1	Arryhythmia	5
				Hypotension	1
Pulmonary	16 (2%)	12	4	Pneumonia	14
				Respiratory distress	1
				Asthma attack	1
Bleeding	8 (1%)	5	3	Postoperative bleeding	3
				Uretero-arterial fistula	3
				Hematoma (wound)	1
				Urinary tract bleeding	1
Thromboembolic	7 (0.9%)	6	1	Vascular thrombosis	6
				Pulmonary embolism	2
Neurological	24 (3%)	22	2	Cerebrovascular event	2
				Peripheral neuropathy	2
				Delirium/Agitation/Dementia	17
				Vertigo	2
				Insomnia	1
Miscellaneous	52 (7%)	39	13	Lymphocele	7
				Dermatitis	2
				Liver dysfunction	17
				Electrolyte abnormality	5
				Compartment syndrome	3
				Drug eruption	2
				Loss of appetite	2
				Other rare complication	15
Surgical	12 (2%)	2	10	Rectal injury	8
				Incisional hernia	2
				Intestinal injury	1
				Obturator nerve injury	1

UTI = urinary tract infection
FUO = fever of unknown origin
SSI = surgical site infection

The effects of complications on OS and RFS are shown in Fig. 2. There was no significant difference in OS or RFS between patients with and without any complications (Fig. 2a and c). Major complications (≥CD grade III) were also not significantly correlated with poorer OS or RFS (Fig. 2b and d). In contrast, considering CCI, patients with CCI ≥ 26.2 had shorter OS (4-year, 59.5 vs. 69.8%, respectively, log-rank test, P = 0.0037, Fig. 3a) and RFS (51.9 vs. 60.1%, respectively, P = 0.0234, Fig. 3b), than those with CCI < 26.2.

Table 3 demonstrates the univariate and multivariate analyses of OS. Older age, higher PS, adjuvant chemotherapy, pT3-4, pN+, high grade and CCI ≥ 26.2 were significant adverse prognostic factors in univariate analyses. On multivariate analyses, age, PS, pT3-4, pN+ and CCI ≥ 26.2 remained independent predictors of OS. Table 4

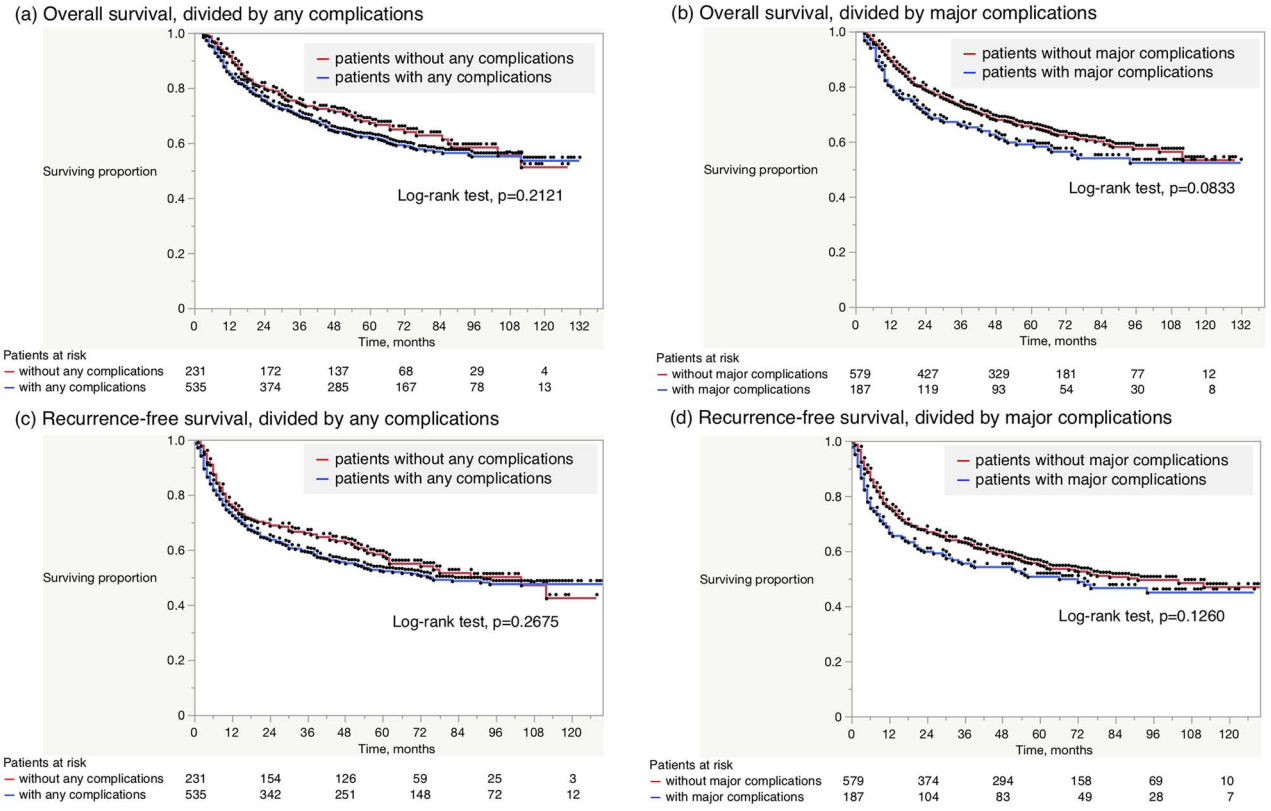

Figure 2. Kaplan–Meier estimates for overall and recurrence-free survival according to (a), (c) any complication, and (b), (d) major complications (≥CD grade III). There was no significant difference in overall survival (OS) or recurrence-free survival (RFS) between patients with and without any complications (a, c). Major complications were also not significantly correlated with poorer OS or RFS (b, d).

presents the univariate and multivariate analyses data for RFS. Older age, higher PS, adjuvant chemotherapy, higher pathological T-stage, pN+ and CCI ≥ 26.2 were significant adverse prognostic factors in univariate analyses. In multivariate analyses, age, PS, pT3-4, pN+ and CCI ≥ 26.2 remained independent predictors of RFS.

Supplementary Tables 1 (OS) and 2 (RFS) summarize univariate analyses in terms of the survival impact of each category of complication according to the CD grading [(a) any grading, and (b) ≥ CD grade III]. After adjusting for other independent survival predictors including age, PS, pathological T-stage, and pathological N-stage, thromboembolic and neurological complications remained significant predictors of OS, both in any and major categorizations (Table 5). Regarding RFS, any thromboembolic or neurological complication, or major infectious complications remained significant predictors of RFS (Table 5). Urine leak was not associated with poorer OS (4-year survival estimates, without urine leak: 66.3% vs. with urine leak: 67.6%, $P = 0.89$) or RFS (without urine leak: 57.3% vs. with urine leak: 59.1%, $P = 0.76$).

Discussion

This study investigated the prognostic impact of postoperative complications on long-term survival outcomes after RC for BC. When considering the most severe event in each patient, neither any nor CD grade ≥ III was associated with OS or RFS. Rather, when considering all events together with their respective severity with the use of CCI, which Slankamenac and colleagues created in order to assess cumulative postoperative morbidity (10), CCI was independently associated with both OS and RFS. Patients with CCI ≥ 26.2 had shorter OS (4-year, 59.5 vs. 69.8%, respectively, log-rank test, $P = 0.0037$) and RFS (51.9 vs. 60.1%, respectively, $P = 0.0234$), than those with CCI < 26.2. For the first time, we identified that postoperative complications assessed using CCI could impair long-term survival outcomes after RC. To date, the negative impact of postoperative complications on long-term survival outcomes beyond the postoperative periods has been reported in several cancers, such as colorectal, gastric and oesophagogastric cancer, or hepatocellular carcinoma (5–8). Taken together with these previous observations, postoperative complications could compromise long-term disease control after major cancer surgery.

To date, the CD Classification, a grading system based on the necessary treatment for proper management, has been widely utilized to report postoperative complications. CD Classification only accounts for the most severe complications in each patient, for example, patients with a single Grade 2 complication and those with multiple Grade 2 complications are categorized into the same category, 'minor complication.' However, infections requiring antibiotic treatment for a long time, or readmission for ileus, especially when multiple low-grade complications occur simultaneously in one patient, could significantly delay a patient's full recovery to daily life. This is because, during the healing process, physicians may be reluctant to perform adjuvant chemotherapy, which could influence long-term disease control, as described below. In the present study, when using CCI to identify cumulative postoperative morbidity, the proportion of patients with major complications (CCI ≥ 26.2) increased to 34% (261/776) as compared with 24% (187/766)

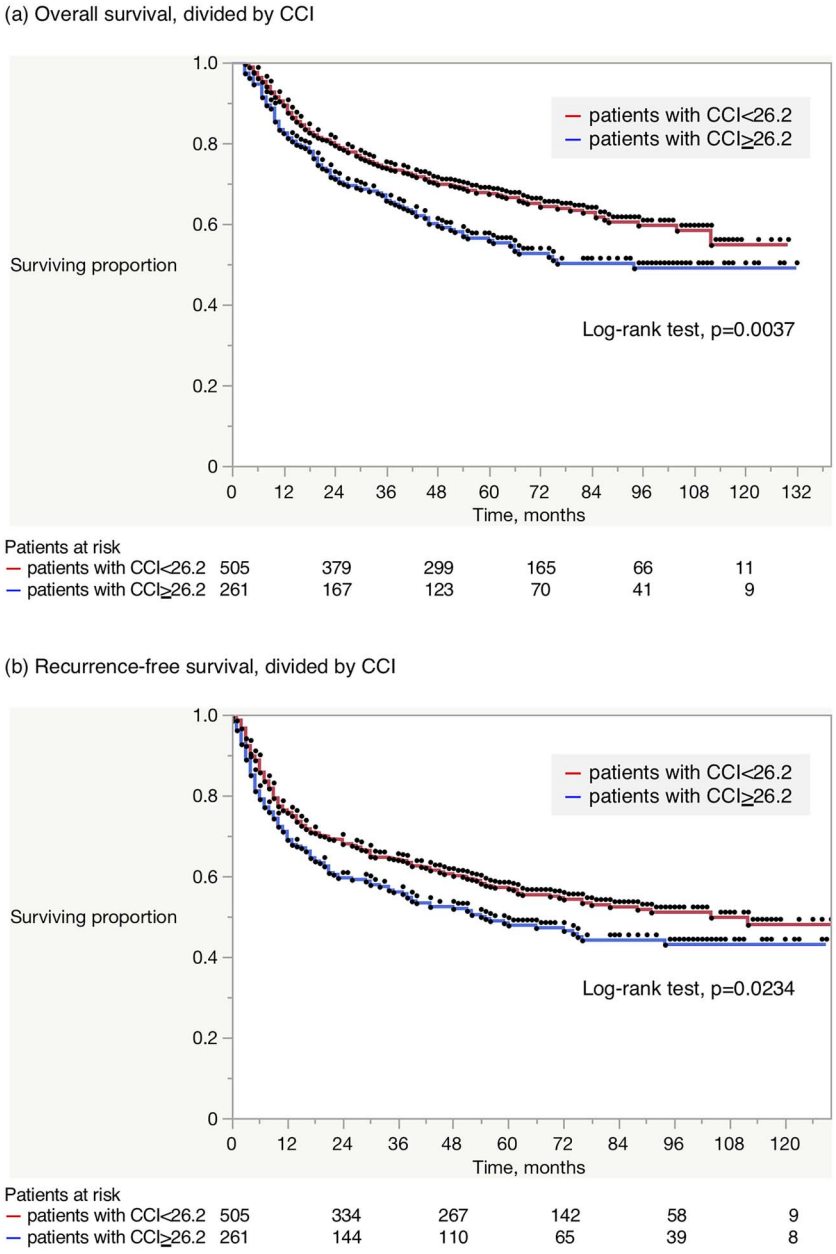

Figure 3. Kaplan–Meier estimates for (a) OS and (b) RFS according to CCI. Patients with CCI ≥ 26.2 had shorter OS (4 years, 59.5 vs. 69.8%, respectively, log-rank test, $P = 0.0037$) and RFS (51.9 vs. 60.1%, respectively, $P = 0.0234$), than those with CCI < 26.2.

when considering only the highest-grade complications (≥CD grade III). Other researchers have also observed higher cumulative postoperative morbidity after RC than the CD Classification (13,14). Consistent with the present study, the prognostic impact of CCI has been reported for other malignancies (11,12,15). For example, Yamashita et al. observed that CCI ≥ 26.2 was independently associated with cancer-specific survival after resection of colorectal liver metastases (11).

Although the mechanism has not yet been fully clarified, one hypothesis is that the growth of residual cancer cells is fueled by inflammatory cytokines and growth factors that are stimulated by surgical stress (16–18). Another hypothesis is that an attenuated host immunological response during postoperative illness may promote tumorigenesis (19). In addition, the prolonged postoperative period required to recover from major complications could preclude adjuvant chemotherapy, which may result in a poorer long-term survival outcome. For example, Jin et al. observed that, in the US Gastric Cancer Collaborative ($n = 824$), patients with postoperative complications were less likely to undergo adjuvant chemotherapy (odds ratio = 0.5, $P < 0.001$), and such patients had a significantly increased hazard of death (HR-2.3, $P < 0.001$) (20). The delay in adjuvant chemotherapy (oral fluoropyrimidine derivative monotherapy) was also associated with shorter recurrence-free survival in gastric cancer patients (21). In the present cohort, after excluding patients without information on adjuvant chemotherapy ($n = 7$), among the pTanypN+ or pT3-4pNany patients ($n = 335$) who were considered to be candidates for adjuvant chemotherapy, those with CCI ≥ 26.2 were less likely to receive adjuvant chemotherapy

Table 3. Univariate and multivariate analyses of prognostic factors for overall survival (OS)

Variables	OS Univariate analysis Hazard ratio (95% CI)	p-value	OS Multivariate analysis Hazard ratio (95% CI)	p-value
Sex				
Male	1			
Female	0.78 (0.59–1.04)	0.089		
Age, year				
Continuous	1.05 (1.03–1.06)	**<0.0001**	1.03 (1.02–1.05)	**<0.0001**
Body mass index (BMI) (kg/m ^{2}), median (range)	0.97 (0.93–1.00)	0.062		
Average annual cystectomy volume				
High (>10 per year)	1			
Moderate (5 < − < 10 per year)	0.92 (0.71–1.19)	0.52		
Low (<5 per year)	0.95 (0.67–1.34)	0.76		
Performance Status				
0	1		1	
1	1.70 (1.22–2.38)	**0.002**	1.29 (0.91–1.82)	0.16
2	4.03 (2.13–7.62)	**<0.0001**	3.36 (1.74–6.51)	**0.0003**
3	3.31 (0.82–13.33)	0.093	1.53 (0.36–6.51)	0.57
Unknown	8.16 (3.56–18.69)	<0.0001	5.22 (2.19–12.44)	**0.0002**
Neoadjuvant chemotherapy				
No	1			
Yes	1.15 (0.81–1.62)	0.44		
Adjuvant chemotherapy				
No	1		1	
Yes	1.72 (1.24–2.38)	**0.001**	0.88 (0.60–1.29)	0.52
Unknown	1.77 (0.44–7.13)	0.42	0.85 (0.21–3.52)	0.82
Pathological T-stage				
pT0-1	1		1	
pT2	1.42 (0.97–2.08)	0.069	1.19 (0.80–1.77)	0.39
pT3-4	4.03 (3.04–5.34)	**<0.0001**	2.96 (2.14–4.08)	**<0.0001**
Pathological N-stage				
pN0	1		1	
pN+	3.09 (2.28–4.02)	**<0.0001**	2.08 (1.54–2.81)	**<0.0001**
pNx	1.16 (0.61–2.18)	0.66	0.84 (0.42–1.67)	0.62
Histology				
Pure urothelial carcinoma	1			
Others	1.29 (0.90–1.86)	0.17		
Grade				
Low	1		1	
High	1.54 (1.06–2.26)	**0.026**	0.98 (0.65–1.47)	0.93
Unknown	0.96 (0.59–1.57)	0.87	0.89 (0.54–1.48)	0.66
Operative time (minutes), median (range)	0.99 (0.99–1.00)	0.18		
Estimated blood loss (mL), median (range)	1.00 (0.99–1.00)	0.19		
Surgical approach				
Open	1			
Laparoscopic	1.15 (0.88–1.49)	0.3		
Complications				
None	1			
Minor/major	1.18 (0.91–1.53)	0.21		
None/minor	1			
Major	1.26 (0.97–1.64)	0.085		
CCI 26.2 low	1		1	
high	1.42 (1.12–1.80)	**0.004**	1.35 (1.05–1.72)	**0.017**

than patients with CCI < 26.2 (25 vs. 15%, respectively, χ^2 test, P = 0.0235, Supplementary Fig. 1a), which might result in poorer survival in patients with CCI ≥ 26.2. Furthermore, in patients who received NAC (n = 95), there was no significant difference in OS or RFS between patients with CCI ≥ 26.2 and those with CCI < 26.2 (4-year OS: 57.7 vs. 60.5%, log-rank test, P = 0.91, and 4-year RFS: 55.4 vs. 49.2%, log-rank test, P = 0.52, Supplementary Fig. 1b and c). Based on these observations, we believe that NAC could be a promising treatment option because it is not influenced by postoperative complications.

Table 4. Univariate and multivariate analyses of prognostic factors for recurrence-free survival (RFS)

Variables	RFS Univariate analysis Hazard ratio (95% CI)	p-value	RFS Multivariate analysis Hazard ratio (95% CI)	p-value
Sex				
Male	1			
Female	0.92 (0.72–1.17)	0.47		
Age, year				
Continuous	1.03 (1.02–1.04)	**<0.0001**	1.02 (1.00–1.03)	**0.023**
Body mass index (BMI) (kg/m ^{2}), median (range)	0.98 (0.95–1.01)	0.17		
Average annual cystectomy volume				
High (≥10 per year)	1			
Moderate ($5 \leq - < 10$ per year)	0.95 (0.75–1.20)	0.67		
Low (<5 per year)	1.17 (0.88–1.57)	0.29		
Performance status				
0	1		1	
1	1.46 (1.07–1.98)	**0.017**	1.13 (0.82–1.55)	0.46
2	2.73 (1.49–4.99)	**0.001**	2.11 (1.14–3.91)	**0.018**
3	4.11 (1.02–16.57)	**0.047**	1.97 (0.46–8.43)	0.36
Unknown	4.84 (2.14–10.93)	0.0001	3.00 (1.24–7.27)	0.015
Neoadjuvant chemotherapy				
No	1			
Yes	1.17 (0.86–1.59)	0.31		
Adjuvant chemotherapy				
No	1		1	
Yes	1.94 (1.45–2.59)	**<0.0001**	0.96 (0.68–1.35)	0.81
Unknown	1.56 (0.50–4.88)	0.44	0.75 (0.23–2.39)	0.62
Pathological T-stage				
pT0-1	1		1	
pT2	1.51 (1.09–2.11)	**0.015**	1.34 (0.96–1.88)	0.088
pT3-4	4.11 (3.20–5.27)	**<0.0001**	3.17 (2.42–4.16)	**<0.0001**
Pathological N-stage				
pN0	1		1	
pN+	3.04 (2.41–3.85)	**<0.0001**	1.97 (1.50–2.59)	**<0.0001**
pNx	1.30 (0.76–2.22)	0.34	1.02 (0.56–1.87)	0.95
Histology				
Pure urothelial carcinoma	1			
Others	1.31 (0.94–1.81)	0.11		
Grade				
Low	1			
High	1.30 (0.94–1.78)	0.11		
Unknown	0.87 (0.57–1.32)	0.51		
Operative time (minutes), median (range)	0.99 (0.99–1.00)	0.53		
Estimated blood loss (mL), median (range)	1.00 (0.99–1.00)	0.15		
Surgical approach				
Open	1			
Laparoscopic	1.11 (0.88–1.40)	0.39		
Complications				
None	1			
Minor/major	1.14 (0.90–1.43)	0.27		
None/minor	1			
Major	1.20 (0.95–1.52)	0.13		
CCI 26.2 low	1		1	
high	1.28 (1.03–1.58)	**0.025**	1.26 (1.01–1.57)	**0.044**

Among postoperative complications, infectious complications were the most frequently reported as adverse prognostic factors in patients with hepatocellular, gastric, lung or colorectal cancers (8,22–24). As shown in Table 5, a major infectious complication (≥CD grade III) remained an independent adverse factor for RFS, but this was marginal (P = 0.0681) for OS. Although thromboembolic and neurological complications remained significant for OS and RFS, we could not draw a definitive conclusion because of the low number of events. A larger study is warranted to gain further insight into the survival impacts of each complication category.

Table 5. Summary of hazard ratio of each complication category, after adjusting for age, PS, and pathological T-stage and N-stage

Categories	OS Hazard ratio after adjusting (95% CI)	*p*-value	Categories	RFS Hazard ratio after adjusting (95% CI)	*p*-value
Cardiac, any			**Cardiac, any**		
No	1		No	1	
Yes	1.70 (0.75–3.87)	0.21	Yes	1.56 (0.69–3.54)	0.29
Thromboembolic, any			**Thromboembolic, any**		
No	1		No	1	
Yes	3.38 (1.50–7.64)	**0.003**	Yes	2.64 (1.17–5.95)	**0.019**
Neurological, any			**Neurological, any**		
No	1		No	1	
Yes	1.71 (0.99–2.95)	0.056	Yes	1.63 (1.01–2.64)	**0.018**
Infection, major			**Infection, major**		
No	1		No	1	
Yes	1.53 (0.97–2.40)	0.068	Yes	1.56 (1.03–2.37)	**0.035**
Cardiac, major			**Cardiac, major**		
No	1		No	1	
Yes	2.10 (0.28–15.59)	0.47	Yes	2.47 (0.34–18.22)	0.37
Thromboembolic, major			**Thromboembolic, major**		
No	1		No	1	
Yes	50.62 (6.17–415.2)	**0.0003**	Yes	6.83 (0.93–50.37)	0.059
Neurological, major			**Surgical, major**		
No	1		No	1	
Yes	5.60 (1.38–22.76)	**0.016**	Yes	1.92 (0.90–4.12)	0.093
Surgical, major					
No	1				
Yes	1.81 (0.80–4.12)	0.16			

Categories	RFS Univariate analysis Hazard ratio (95% CI)	*p*-value	Categories	RFS Univariate analysis Hazard ratio (95% CI)	*p*-value
Gastrointestinal, any			**Gastrointestinal, major (≥Clavien-Dindo grade III)**		
No	1		No	1	
Yes	1.209 (0.963–1.517)	0.1013	Yes	1.061 (0.767–1.468)	0.7196
Infection, any			**Infection, major**		
No	1		No	1	
Yes	1.089 (0.885–1.341)	0.4208	Yes	1.727 (1.167–2.556)	**0.0063**
Wound, any			**Wound, major**		
No	1		No	1	
Yes	1.020 (0.784–1.327)	0.8814	Yes	0.947 (0.582–1.541)	0.8266
Genitourinary, any			**Genitourinary, major**		
No	1		No	1	
Yes	1.084 (0.765–1.536)	0.6505	Yes	1.339 (0.892–2.010)	0.1588
Cardiac, any			**Cardiac, major**		
No	1		No	1	
Yes	2.329 (1.039–5.221)	**0.0401**	Yes	7.380 (1.029–52.91)	**0.0467**
Pulmonary, any			**Pulmonary, major**		
No	1		No	1	
Yes	1.327 (0.628–2.805)	0.4581	Yes		0.9992
Bleeding, any			**Bleeding, major**		
No	1		No	1	
Yes	1.131 (0.422–3.031)	0.806	Yes		0.9991
Thromboembolic, any			**Thromboembolic, major**		
No	1		No	1	
Yes	2.348 (1.047–5.265)	**0.0384**	Yes	9.762 (1.358–70.19)	**0.0236**
Neurological, any			**Neurological, major**		
No	1		No	1	
Yes	2.028 (1.291–3.184)	**0.0021**	Yes	3.108 (0.774–12.49)	0.11
Miscellaneous, any			**Miscellaneous, major**		
No	1		No	1	
Yes	1.318 (0.907–1.915)	0.1473	Yes	0.856 (0.354–2.069)	0.7295
Surgical, any			**Surgical, major**		
No	1		No	1	
Yes	1.630 (0.771–3.443)	0.2008	Yes	2.376 (1.124–5.021)	**0.0235**

In colorectal cancer, it was reported that long-term disease control was impaired by anastomotic leakage (25,26). It has been proposed that anastomotic leakage can lead to extraluminal dissemination of the remaining cancer cells. Based on this hypothesis, we compared survival curves between patients with and without urinary leakage. As described above, we did not observe significant differences in survival between patients with and without urine leak (4-year OS: without urine leak 66.3% vs. with urine leak 67.6%, $P = 0.887$ and 4-year RFS: without urine leak 57.3% vs. with urine leak 59.1%, $P = 0.76$).

Our study had several limitations. First, because of its retrospective design, some complications and comorbid conditions may not have been recorded. Second, variability among the participating hospitals regarding surgical techniques and postoperative management was another limitation. External validation is necessary to confirm the generalizability of the present findings. Nevertheless, this study is the first to demonstrate that postoperative morbidity can impair long-term disease control after RC, just as with other major cancer surgery. Physicians should be aware that major postoperative complications can impair long-term disease control.

Conclusions

Postoperative complications assessed by CCI independently had an adverse impact on long-term survival outcomes after RC. It is vital to mitigate postoperative complications, not only for early convalescence, but also for improving long-term disease control.

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Conflict of interest statement

The authors declare that they have NO affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

Ethics statement

This study received Institutional Review Board Approval (No. 017-0038).

Author Contributions

T.A., S.Y. and H.K. designed the research. T.A., S.Y., H.K., A.S., H.K., H.S., I.T., K.M., K.M., K.T., N.T., S.M., S.S., T.Y., T.M., T.A., Y.S., Y.S., N.M., T.K., J.F., H.M., R.M. and S.M. collected the data. T.A. and S.Y. analyzed the data or performed statistical analysis. T.O. and N.S. supervised the project. T.A. wrote the paper. All authors read and approved the final manuscript.

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