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ORIGINALPAPER – UROLOGIC ONCOLOGY

Long-Term Outcomes Following Partial Versus Complete Cystectomy in Advanced Colorectal Cancer with Regarding to the Extent of Bladder Invasion

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ABSTRACT

Background. Two procedures widely performed to treat locally advanced colorectal cancer adherent to the urinary bladder are total cystectomy (as part of pelvic exenteration) and partial cystectomy; however, little is known about outcomes following partial cystectomy.

Methods. A retrospective database of patients with colorectal cancer involving the urinary bladder who underwent R0 or R1 resection at our institution from 2001 to 2015 was constructed. The histological extent of bladder invasion and long-term outcomes were examined.

Results. Of the 89 consecutive patients, 49 underwent partial cystectomy and all had negative margins of the bladder. Tumor invasion to the urinary bladder was confirmed histologically in 19 of 49 patients (coincidence rate of diagnosis, 39%): invasion only to the bladder serosa ($n = 3$), invasion to the bladder muscle ($n = 4$), and invasion beyond the bladder muscle without ($n = 1$) and with ($n = 11$) exposure to the bladder lumen. The 5-year recurrence-free and overall survival rates were 63.2% and 70.2% in the partial cystectomy group, and 66.2% and 72.7% in the total cystectomy group ($p = 0.567$ and 0.648), respectively. Except for the remnant bladder, recurrence sites were very similar to sites observed in patients who underwent total cystectomy. Intravesical recurrence occurred in four patients 3–13 months after the initial surgery, all of whom showed bladder lumen exposure to the tumor.

Conclusions. With regard to long-term outcomes and low diagnostic concordance rates of clinical and pathological bladder invasion, partial cystectomy seems a generally acceptable treatment option. However, when the bladder lumen is exposed to a colorectal tumor, surgeons should be cognizant of possible intravesical recurrence and act accordingly.

Total cystectomy is the standard surgical procedure for muscle-invasive urinary bladder cancer.[1,2] For locally advanced colorectal cancer involving the bladder, partial cystectomy is also performed as part of the en bloc resection.[3–6] If invasion to other organs is clinically suspected (preoperatively or intraoperatively) with locally advanced colorectal cancer, en bloc resection to leave no residual cancer tissue is highly recommended.[7, 8] However, because the concordance rate for clinical versus pathological invasion is approximately 40–50%,[3–6,9,10] and organ preservation is important, total cystectomy for all patients with suspected bladder invasion might represent excessive medical treatment. Partial cystectomy is a bladder-sparing procedure that also preserves patients' quality of life, primarily because a stoma is not required.

A difference between total and partial cystectomy is the potential for intravesicular recurrence. The rate of intravesicular recurrence is used to assess the oncological validity of partial cystectomy for locally advanced colorectal cancer. Pathological invasion into the urinary bladder is an independent predictor of intravesicular recurrence and distant metastasis after partial cystectomy among patients with locally advanced colorectal cancer.[3]

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Urinary bladder invasion is classified by histological extent of invasion, categorized as invasion to the bladder serosa only, bladder muscle, beyond the bladder muscle without exposure to the bladder lumen, and beyond the bladder mucosa with exposure to the bladder lumen. No previous studies have investigated the histological degree of bladder invasion in bladder-involving colorectal cancer, which might affect the long-term oncological outcomes. We hypothesized that the risk of intravesicular recurrence after partial cystectomy in colorectal cancer differs by degree of infiltration into the bladder wall. We investigated the histological extent of bladder invasion and evaluated the long-term outcomes following partial versus complete cystectomy in patients with advanced primary colorectal cancer.

PATIENTS AND METHODS

Patient Selection

We retrospectively included patients with primary colorectal cancer and urinary bladder involvement (cT4b, bladder invasion) referred to the National Cancer Center Hospital from January 2001 to November 2015. We investigated the long-term postoperative outcomes and only included patients who underwent R0 (negative margins) or R1 (positive margins) resection, and excluded those with R2 resection (residual tumor) or no bladder resection and with a histological diagnosis other than adenocarcinoma (squamous cell carcinoma). In cases in which the bladder was safely separated from the primary tumor in a partial serosal- or mucosal-sparing fashion during intraoperative dissection of the bladder from the primary colonic mass, there was usually no histological cancer invasion to the bladder. Thus, we considered that these cases were not cT4b (bladder), but were cT3 or cT4 with inflammation and/or abscess, and therefore did not include them in this study. In other words, we only included patients who underwent cystectomy of all layers of the bladder for intraoperative cT4b (bladder). At the time we intraoperatively confirmed bladder involvement by colorectal cancer, all layers of the bladder wall were resected, keeping the macroscopic surgical margin at least 1 cm from the infiltrated portion. A ureteral stent was inserted either preoperatively or intraoperatively when needed.

Criteria for Selecting Partial Versus Total Cystectomy

Partial versus total cystectomy was based on preoperative computed tomography (CT) and magnetic resonance imaging findings, as well as cystoscopy. We chose total cystectomy for patients with tumors that were difficult to resect with clear margins and those with tumors involving the bladder sphincter or the trigone because cancer in these locations increases the difficulty of partial resection.

Data Collection

Parameters assessed included age, sex, tumor location, major operative method, partial versus total cystectomy, composite resection, sites of tumor invasion, estimated blood loss, surgical time, length of hospital stay, histological type, and lymph node metastasis. The extent of primary tumor invasion (T), regional lymph node metastasis (N) and tumor stage were assessed by Union for International Cancer Control (UICC) TNM staging (8th edition).[11] This study was approved by the Institutional Review Board (IRB) of the National Cancer Center Hospital (IRB code 2017-437) and met our governmental agency's guidelines. Patient consent to participate in this study was waived due to its retrospective design.

Follow-Up

Postoperative follow-up consisted of serum tumor marker measurements every 3 months for the first 2 years, then every 6 months for 3 years; hepatic imaging (ultrasonography or CT) and chest x-rays every 3–6 months; and colonoscopy every 2–3 years. Follow-up data were recorded prospectively until the patient's death or the study cut-off date of January 2018, whichever came first. Complete follow-up was conducted for the entire patient cohort, with a median follow-up time of 71 months (range 0–167 months) for survivors.

Statistical Analysis

We used Fisher's exact test to evaluate categorical variables and the Wilcoxon rank-sum test for comparisons of continuous variables. Data are expressed as numbers of patients and ratios (%). A p-value < 0.05 was considered statistically significant. Data were analyzed using the R program version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria; www.R-project.org) and JMP13 (SAS Institute Japan, Tokyo, Japan).

RESULTS

Patient Characteristics

Patient characteristics are summarized in Fig. 1. Of 5689 patients with primary colorectal cancer referred to the National Cancer Center Hospital from January 2001 to November 2015, 114 patients (2.0%) with primary colorectal cancer and involvement of the urinary bladder met the inclusion criteria. Of these, we excluded 7 patients who

underwent R2 resection, 17 patients without bladder resection, and 1 patient with histological diagnosis of squamous cell carcinoma, resulting in a final study population of 89 patients who underwent R0 or R1 resection for colorectal adenocarcinoma with involvement of the urinary bladder (Fig. 1). All these patients underwent open surgery (not laparoscopic surgery); 49 patients underwent partial cystectomy, and 40 underwent total cystectomy as part of pelvic exenteration (total pelvic exenteration, $n = 34$; anterior pelvic exenteration, $n = 6$). In men, total pelvic exenteration involved excising the bladder, prostate, seminal vesicles, and rectum, whereas in women, total pelvic exenteration involved excising the uterus, bladder, and rectum. Anterior pelvic exenteration involved removing the reproductive structures and bladder while preserving the rectum, in both men and women.

Patient characteristics are shown in Table 1. The median age was 60 years (range 19–80 years), and 77 patients (87%) were men and 12 (13%) were women. In the partial cystectomy group, the primary tumor location was the sigmoid colon and upper rectum ($n = 45$, 92%) versus the rectum and anal canal in the total cystectomy group ($n = 36$, 89%; $p < 0.001$). Nine patients (two in the partial cystectomy group and seven in the total cystectomy group) underwent neoadjuvant treatment prior to colon surgery and cystectomy. Nineteen patients in the partial cystectomy group and 18 patients in the total cystectomy group showed histological invasion to the bladder (concordance rates for clinical versus pathological invasion: 39% and 45% for partial cystectomy and total cystectomy, respectively). Six patients (12%) in the partial cystectomy group underwent lateral lymph node dissection on the pelvic side wall, compared with 37 patients (92%) in the total cystectomy group ($p < 0.001$).

Patient Clinicopathological Features and Short-Term Postoperative Outcomes

Patient clinicopathological features are shown in Table 2. Bladder tumor margins were negative in all patients undergoing partial cystectomy. Histological samples were evaluated by three different pathologists from our center. Mean operative time (partial: 324 min, vs. total: 547 min; $p < 0.001$) was significantly longer, and blood loss volume (partial: 480 ml, vs. total: 1247 ml; $p < 0.001$) was significantly higher in the total cystectomy group. Mean length of hospital stay (partial: 19 days, vs. total: 26 days; $p < 0.001$) was significantly longer in the total cystectomy group. Postoperative complications tended to occur more frequently in the total cystectomy group (partial: $n = 6$ (12%), vs. total: $n = 20$ (50%); $p = 0.06$), but this difference was not significant. No perioperative deaths occurred.

Recurrence Following Partial Versus Total Cystectomy

Five-year recurrence-free survival rates in our study were similar between the total (66.2%) and partial (63.2%) cystectomy groups ($p = 0.567$) [Fig. 2a], while 5-year overall survival rates were 70.2% and 72.7% in the partial

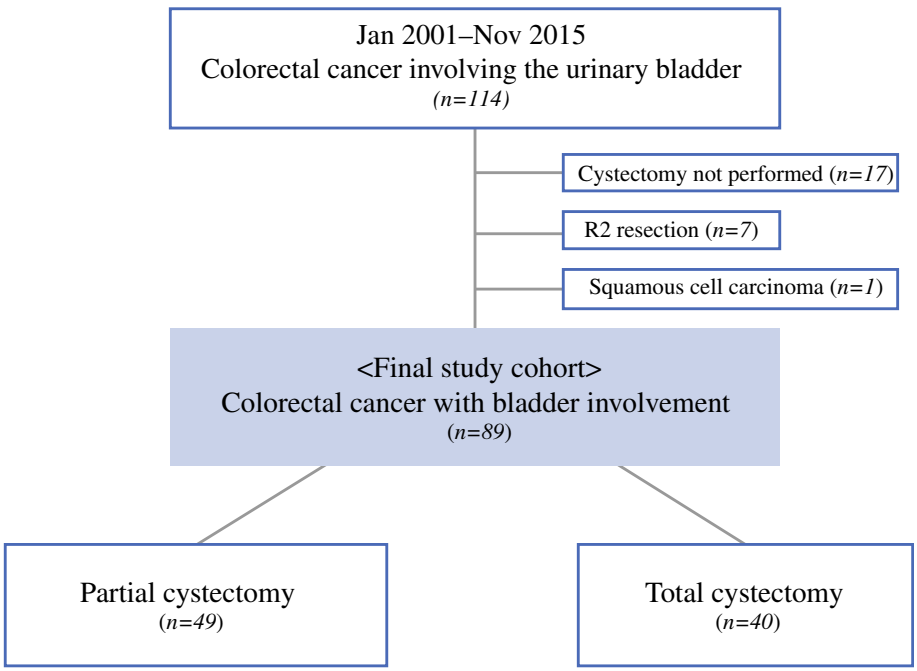

FIG. 1 Study cohort. After excluding patients with no bladder resection ($n = 17$), R2 resection ($n = 7$), and squamous cell carcinoma ($n = 1$) from the initial 114 patients diagnosed with colorectal cancer involving the urinary bladder, the final study population comprised 89 patients

TABLE 1 Patient characteristics

Variable	Partial cystectomy [$n = 49$]	Total cystectomy [$n = 40$]	Overall [$n = 89$]	p-Value
Age, years [median (range)]	64 (32–79)	58 (19–80)	60 (19–80)	0.09
Sex				0.21
Male	40 (82)	37 (93)	77 (87)	
Female	9 (18)	3 (7)	12 (13)	
Tumor location				< 0.001
Cecum	3 (6)	1 (3)	4 (5)	
Sigmoid colon to rectosigmoid	40 (82)	12 (30)	32 (36)	
Upper rectum	5 (10)	10 (25)	35 (39)	
Lower rectum to anal canal	1 (2)	17 (42)	18 (20)	
Preoperative therapy	2 (4)	7 (18)	9 (10)	1.00
Chemotherapy	1 (2)	4 (10)	5 (6)	
Chemotherapy + radiotherapy	1 (2)	3 (8)	4 (4)	
Major operative method				< 0.001
ICR/sigmoidectomy/Hartmann	3 (6)/20 (41)/5 (10)	–	3 (3)/20 (23)/5 (6)	
HAR/LAR/ULAR	6 (12)/14 (29)/1 (2)		6 (7)/14 (16)/1 (1)	
APE/TPE	–	6 (15)/34 (85)	6 (7)/34 (38)	
Histologically invasive sites				0.07
Bladder	19 (39)	18 (45)	37 (42)	
Uterus/vagina	1 (2)/0	0/1 (3)	1 (1)	
Prostate/seminal vesicle	0	5 (13)/3 (8)	5 (6)/3 (3)	
Rectum/sigmoid colon	3 (6)/2 (4)	1 (3)/1 (3)	4 (4)/3 (3)	
Small intestine	5 (10)	3 (8)	8 (9)	
Appendix	1 (2)	0	1 (1)	

Data are expressed as n (%) unless otherwise specified

ICR ileocecal resection, *HAR* high anterior resection, *LAR* low anterior resection, *ULAR* ultra-low anterior resection, *APE* anterior pelvic exenteration, *TPE* total pelvic exenteration

and total cystectomy groups ($p = 0.648$), respectively, with a median follow-up time for survivors of 71 months (range 0–167 months) [Fig. 2b].

During the study period, recurrence after R0 or R1 surgery occurred in 32 patients (36%) [partial cystectomy, $n = 18$ (37%) vs. total cystectomy, $n = 14$ (35%)]. Recurrence sites were similar between groups (Table 3), except remnant bladder recurrence, which occurred in four partial cystectomy patients (8%). No significant group-dependent differences were reported for the number of patients with recurrence in different sites when comparing partial cystectomy with total cystectomy (Table 3).

Infiltration of Locally Advanced Colorectal Cancer into the Bladder Wall

Urinary bladder invasion is categorized by extent of tumor invasion. In this study, specific categories included invasion to the bladder serosa only, invasion to the bladder muscle, invasion beyond the bladder muscle without exposure to the bladder lumen, and invasion beyond the bladder mucosa with exposure to the bladder lumen (Fig. 3).

Of 49 patients who underwent partial cystectomy, tumor invasion to the urinary bladder was confirmed histologically in 19 patients (concordance rate 39%). Thirty patients experienced no tumor invasion to the bladder. We observed invasion only to the bladder serosa in three patients, invasion to the bladder muscle in four patients, invasion beyond the bladder muscle with no exposure to the bladder lumen in one patient, and invasion beyond the bladder mucosa with exposure to the bladder lumen in 11 patients (Fig. 4).

Intravesicular Recurrence After Partial Cystectomy for Locally Advanced Colorectal Cancer

Intravesicular recurrence occurred in four patients, all of which were in the bladder lumen exposure group. No intravesicular recurrence occurred in patients experiencing histological extent of invasion shallower than the bladder mucosa ($p = 0.002$) [Fig. 4]. The characteristics and prognoses of the four patients (three men and one woman)

TABLE 2 Patient clinicopathological features

Variable	Partial cystectomy [$n = 49$]	Total cystectomy [$n = 40$]	p-Value
Estimated blood loss, ml [median (range)]	480 (14–4570)	1247 (249–4217)	< 0.001
Surgical time, min [median (range)]	324 (107–709)	547 (340–1060)	< 0.001
LOS, day [median (range)]	19 (9–46)	26 (17–67)	< 0.001
Complication (Clavien–Dindo grade III, IV)	3 (6)	8 (20)	0.06
Tumor size, cm [median (range)]	8 (3.5–15.5)	8 (1.6–13.5)	0.85
Histopathological type			0.10
Well/mod	23 (47)/22 (45)	23 (58)/13 (32)	
Muc	4 (8)	1 (2)	
Poor	0	3 (8)	
Lymph node metastasis			0.39
Positive	17 (35)	18 (45)	
Negative	32 (65)	22 (55)	
Residual tumor			0.2
R1	0	2 (5)	
R0	49 (100)	38 (95)	

Data are expressed as n (%) unless otherwise specified

LOS length of hospital stay, *Well* well-differentiated adenocarcinoma, *mod* moderately differentiated tubular adenocarcinoma, *Muc* mucinous adenocarcinoma, *Poor* poorly differentiated adenocarcinoma

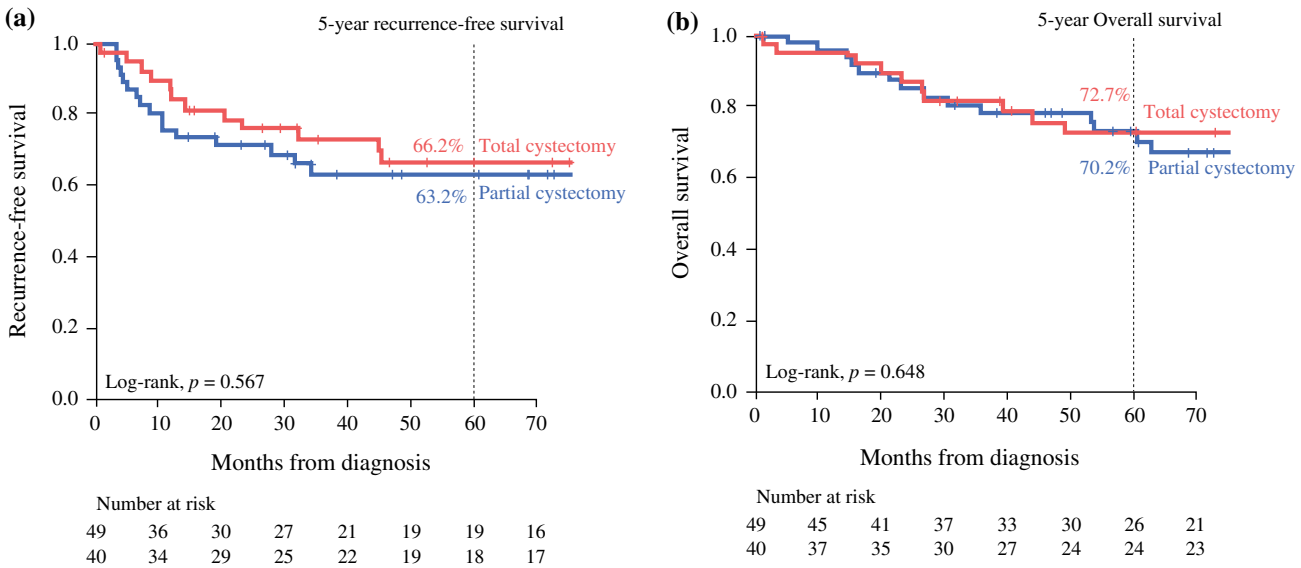

FIG. 2 **a** Comparison of recurrence-free survival curves following partial versus total cystectomy ($p = 0.567$). Five-year recurrence-free survival rates were similar between the total cystectomy (66.2%) and partial cystectomy (63.2%) groups. **b** Comparison of overall survival curves following partial versus total cystectomy ($p = 0.648$). Five-year overall survival rates were similar between the total cystectomy (72.7%) and partial cystectomy (70.2%) groups

with intravesicular recurrence are shown in Table 4. Recurrence was detected by the presence of urinary opacity or fecaluria (feces in urine), follow-up cystoscopy revealing a visible tumor, and follow-up CT revealing a mass inside the remnant bladder. The interval between initial surgery for colorectal cancer and intravesicular recurrence ranged from 3 to 13 months (median 6.5 months). No distant metastases were seen at bladder cancer recurrence (data not shown). With regard to treatment, transurethral resection of the bladder tumor (TUR-Bt) was performed in two patients, TUR-Bt and repeat partial cystectomy was performed in one patient, and total pelvic exenteration was performed in one patient. Three of four patients survived without additional recurrence (median survival time

TABLE 3 Recurrence following partial versus total cystectomy

Recurrence site	Partial cystectomy [$n = 49$] (%)	Total cystectomy [$n = 40$] (%)	p-Value
Bladder	4 (8)	–	–
Peritoneum	1 (2)	2 (5)	0.44
Hematogenous (liver, lung, bone)	10 (20)	7 (18)	0.73
Distant lymph node	2 (4)	1 (3)	0.68
Local	1 (2)	4 (10)	0.11

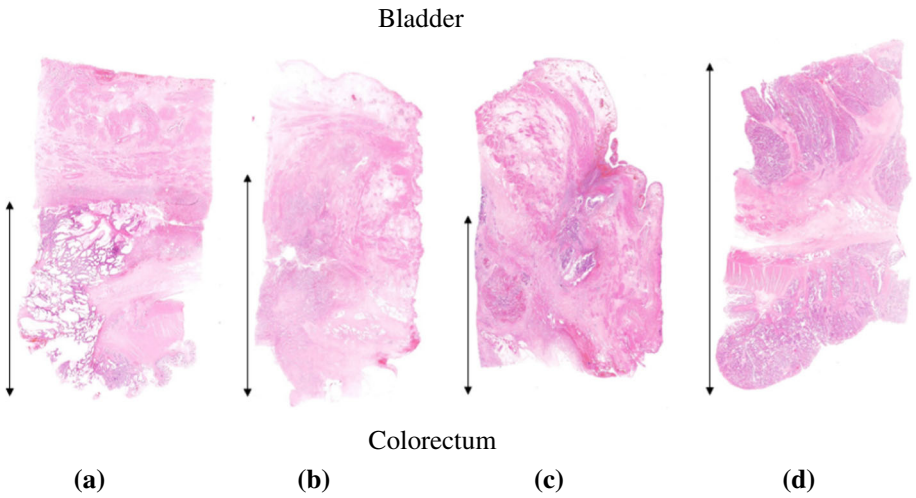

FIG. 3 Histopathological findings in representative patients with colorectal cancer involving the urinary bladder. **a** Invasion to the bladder serosa; **b** invasion to the bladder muscle; **c** invasion beyond the bladder muscle without exposure to the bladder lumen; and **d** invasion beyond the bladder mucosa with exposure to the bladder lumen. The extent of colorectal cancers are indicated by the arrows (hematoxylin and eosin stain; magnification, ×10)

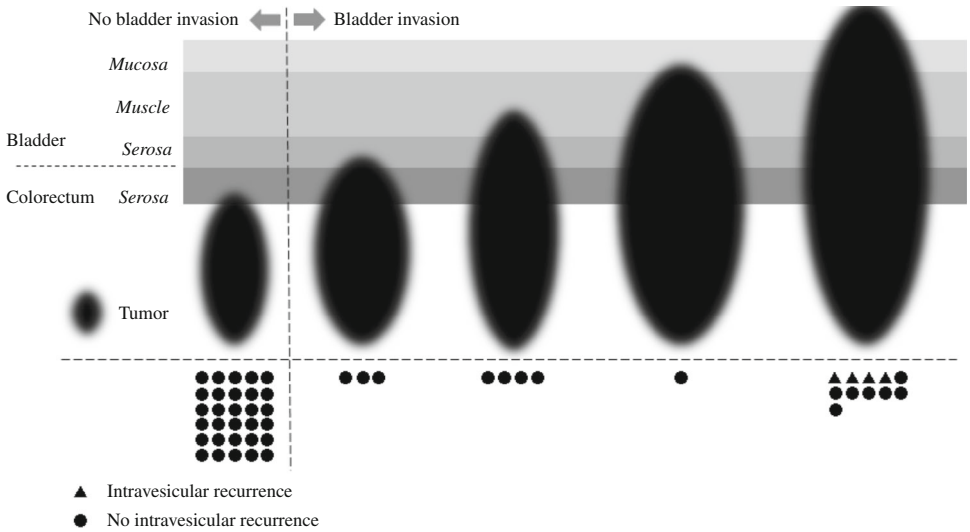

FIG. 4 Patients who underwent partial cystectomy were categorized by the histological extent of bladder invasion. In each patient, the presence (filled triangle) or absence (filled circle) of intravesicular recurrence is shown

65.5 months; range 22–165 months), and one patient died of primary cancer.

DISCUSSION

This study is the first to investigate locally advanced primary colorectal cancer involving the urinary bladder with regard to the histological extent of bladder invasion. Considering long-term outcomes and low diagnostic concordance rates for clinical versus pathological bladder invasion, partial cystectomy for colorectal cancer involving the urinary bladder is an acceptable treatment option, especially when the bladder lumen is not exposed to the colorectal tumor. Furthermore, as a single factor, bladder lumen exposure to the tumor can lead to intravesicular recurrence after partial cystectomy.

TABLE 4 Cases of intravesicular recurrence

Patient	Sex	Age, years	Reason for discovery	p Stage	Extent of bladder invasion	Intravesicular recurrence time after initial operation (months)	Surgical treatment	Prognosis
1	M	57	Fecaluria	IIIC	Exposed to bladder lumen	3	TUR-Bt	Dead (22 months)
2	M	53	Urinary opacity	IIC	Exposed to bladder lumen	7	TUR-Bt	Alive (47 months)
3	F	64	CT	IIIC	Exposed to bladder lumen	13	Partial cystectomy after TUR-Bt	Alive (84 months)
4	M	59	Cystoscopy	IIIC	Exposed to bladder lumen	6	TPE	Alive (165 months)

M male, *F* female, *TUR-Bt* transurethral resection of the bladder tumor, *CT* computed tomography, *TPE* total pelvic exenteration

Comparing long-term outcomes following partial versus total cystectomy, the 5-year overall survival rates in our study were similar between the total (72.7%) and partial (70.2%) cystectomy groups (Fig. 2b). Recurrence sites were also similar between cystectomy groups, with the exception of remnant bladder in the partial cystectomy group. Even with intravesicular recurrence after partial cystectomy, TUR-Bt and/or salvage surgery may be curative if no other distant metastases are present.

Intravesicular recurrence was observed in 36% of our patients with bladder lumen exposure to the colorectal tumor, even though surgically resected bladder margins showed no tumor invasion. In contrast, no intravesicular recurrence was found in patients experiencing bladder invasion by colorectal cancers that were shallower than the bladder mucosa. Our findings indicate that the primary factor causing intravesicular recurrence after partial bladder resection is bladder lumen exposure to the tumor. Using multivariate analysis, Luo et al. reported that histopathological invasion of the urinary bladder was an independent predictor of intravesicular recurrence and distant metastasis.[3] If partial cystectomy is performed when the bladder lumen has been exposed to a colorectal tumor, close follow-up with CT as well as cystoscopy is strongly recommended for the first 2 years after initial surgery.[12]

In the present study, bladder surgical margins were free from cancer invasion in all patients who underwent partial cystectomy. Nonetheless, intravesicular recurrence occurred in four patients, and all had colorectal cancer exposure to the bladder lumen because of invasion beyond the bladder mucosa. This suggests that the mechanism of intravesicular recurrence after partial bladder resection is not recurrence from the resected margin but implantation of tumor cells inside the bladder lumen. Intravesicular seeding could lead to intravesicular recurrence because viable tumor cells remain in the bladder lumen. This is similar to anastomotic recurrence after rectal cancer surgery using the double-stapling technique, the rates of which may be reduced by intraluminal lavage.[13] Therefore, when performing partial cystectomy for colorectal cancer that has invaded the bladder, high-volume saline flushing of the bladder is a potential countermeasure. Our concordance results comparing clinical invasion with pathological invasion were similar to other reports with low values.[3] This is a concern when choosing partial versus total cystectomy given the risk of complications, especially with invasive total cystectomy. In our study, >50% of patients undergoing total cystectomy had no histological evidence of tumor invasion into the bladder. Inflammation and/or abscess makes tissue planes difficult to discern, which resulted in total cystectomy being performed for bulky tumors located near the trigone of the bladder. These patients also experienced Clavien–Dindo grade III or IV complications, possibly from the cystectomy procedure. We based our choice of partial versus total cystectomy on preoperative CT and magnetic resonance imaging, as well as cystoscopy. Even when using these tools, it was difficult to completely distinguish between inflammation and cancer.

This study has some limitations. First, due to its retrospective design, bias may exist when choosing the cystectomy method (partial vs. total). Second, the sample size of patients with intravesicular recurrence was small ($n = 4$). However, this is the first study to investigate locally advanced colorectal cancer involving the urinary bladder, specifically evaluating the histological extent of bladder invasion. Our findings warrant further consideration and validation in a larger population of patients with colorectal cancer involving the urinary bladder.

CONCLUSION

Considering the long-term outcomes and low diagnostic concordance rates for clinical versus pathological bladder invasion, partial cystectomy for locally advanced colorectal cancer involving the urinary bladder is an acceptable treatment option. However, surgeons must consider the risk of intravesicular recurrence when the bladder lumen has been exposed to a colorectal tumor. When partial cystectomy is performed, close follow-up with CT and cystoscopy is strongly recommended for the first 2 years after initial surgery. Our findings will help in the decision-making process during surgical planning, and help to establish an appropriate follow-up protocol.

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