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ORIGINAL ARTICLE

The role of metastatic burden in cytoreductive/consolidative radical cystectomy

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Abstract

Purpose To describe our institutional experience with cytoreductive/consolidative radical cystectomy (CCRC) for metastatic urothelial carcinoma (UC) and to investigate clinicopathologic features predicting prolonged cancer specific survival (CSS) following CCRC.

Methods We performed IRB-approved review of our cystectomy database, and identified 43 patients with metastatic UC who underwent CCRC. Baseline demographics, chemotherapy regimen, clinicopathologic features, and perioperative complications were collected. Progression-free survival (PFS) and CSS were estimated from the time of CCRC. Univariate and multivariate Cox regression models were used to identify predictors of improved CSS after CCRC.

Results Of the 43 patients, 32 (74.4%) had clinical evidence of distant metastases, while 11 harbored occult metastases on the surgical specimen. The most common site of metastasis was the retroperitoneal lymph nodes, found in 30 patients. Solitary metastases were found in 22 patients (51.1%). Forty-one (95%) patients received chemotherapy prior to CCRC. Disease progression was detected in 35 patients after CCRC (median PFS 5.9 months), and 34 died of metastatic cancer (median CSS 12.3 months). On multivariate analysis, patients with solitary metastases were found to have improved CSS compared to those with multiple metastases (HR 2.62, 95% CI 1.16–5.90, $p = 0.02$), with median CSS of 26.0 months vs. 7.9 months ($p < 0.001$). Median postoperative length of stay was 10 days. Overall, 56% suffered postoperative complications, including one perioperative mortality.

Conclusions CCRC is feasible in the setting of metastatic UC. Patients with solitary metastasis demonstrated longer CSS than those with multiple metastases, and should be considered candidates for future trials evaluating the role of CCRC for metastatic UC.

Keywords Metastatic bladder cancer · Radical cystectomy · Cytoreductive surgery · Consolidative surgery · Metastatic burden

Abbreviations

CCRC	Cytoreductive/consolidative radical cystectomy
RC	Radical cystectomy
UC	Urothelial cancer
PFS	Progression-free survival
CSS	Cancer-specific survival
TCGA	The Cancer Genome Atlas Project
MIBC	Muscle invasive bladder cancer
BMI	Body mass index
ASA	American Society of Anesthesiologists score

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LVI	Lymphovascular invasion
CIS	Carcinoma in situ
LOS	Length of stay
OS	Overall survival
RPLN	Retroperitoneal lymph nodes
FPTV	Fractional percentage of tumor volume removed
NCDB	National Cancer Data Base

Introduction

Urothelial cancer (UC) is associated with over 165,000 global deaths annually and a 5-year survival of approximately 5% in the metastatic setting [1, 2]. Cisplatin-based chemotherapy provides overall survival benefit and has been a mainstay in the treatment of metastatic UC over the last quarter century [3]. Response rates range between 39 and 65%, and overall survival between 12.5 and 14.8 months [3–5]. Despite the poor survival associated with metastatic UC in general, a small subset of patients has been observed to demonstrate superb chemosensitivity and prolonged survival. It is unknown whether surgical consolidation of the primary disease site can extend survival in this subset of patients.

Cytoreductive surgery in the metastatic setting is performed for a few malignancies [6, 7]. Theoretically, such an approach can limit disease progression by suppressing the source of tumor growth factors and new metastases. Moreover, it provides the added benefit of quality-of-life improvement by eliminating the significant adverse effects brought on by local disease progression, including persistent gross hematuria, hydronephrosis and impaired kidney function, urinary tract infections, and cancer-associated pain. Historically, interest in applying this treatment to metastatic UC has been stifled by the unacceptably high perioperative morbidity associated with RC. However, with the advent of enhanced recovery pathways, perioperative complications have been reduced [8]. As a result, many have begun to investigate potential survival benefits that may be derived from a less morbid CCRC. In this study, we retrospectively reviewed our institutional experience with CCRC and attempted to identify clinicopathologic features associated with improved CSS.

Patients and methods

After institutional review board approval, we retrospectively searched the UT MD Anderson Cancer Center RC database. Of 1766 patients undergoing RC between Jan. 1997 and Dec. 2011, 45 had distant metastases at the time of surgery. Two patients were excluded from analysis due to non-UC pathology (spindle cell pleomorphic sarcomatoid neoplasm and adenocarcinoma with signet ring features). Of the remaining patients, 32 had clinical evidence of distant metastatic disease prior to RC, while 11 patients had occult metastatic disease discovered on pathologic evaluation of the surgical specimen. Of the patients with clinical metastatic disease, 15 were verified on presurgical biopsy. Thirty-one patients' tumors originated from the bladder, and one patient had metastatic urethral UC.

Collected demographic and clinicopathologic features included age at RC, gender, ASA, date of initial diagnosis, site of metastasis, number of metastatic foci, chemotherapy regimen, response to chemotherapy, interval from diagnosis to RC, clinical and pathologic TNM staging according to the American Joint Committee on Cancer 2010 classification, the presence of lymphovascular invasion (LVI), carcinoma in situ (CIS), the presence of variant histology, and lymph node yield. Perioperative hospital length of stay (LOS) as well as 30- and 90-day complications as per the Clavien–Dindo classification scheme [9] were captured by retrospective chart review. Disease progression was defined by clinical or radiographic evidence of increasing metastatic burden postoperatively. PFS and CSS were calculated from the time of RC.

Statistical methods

Statistical analysis was performed using STATA/SE version 14.1 statistical software (Stata Corp. LP, College Station, TX). Continuous variables were summarized using the mean and standard deviation, and categorical variables using frequency count and percentage. PFS and CSS were estimated using the Kaplan–Meier methods and compared using the log-rank test. Multivariate analysis was performed using the Cox regression model. Stepwise elimination was used for multivariate regression. All tests were two-sided and $p < 0.05$ was considered statistically significant.

Results

Clinicopathologic features are shown in Table 1. Mean age was 61.8 years and 30 (69.8%) patients were males. On preoperative evaluation, 5 (11.6%) were classified as ASA 1, 25 (58.1%) as ASA 2 and 13 (30.2%) as ASA 3. On clinical staging, 32 (74.4%) patients had MIBC, 23 (53.5%) had nodal disease, and 32 (74.4%) had clinically evident distant metastases. The most common site of metastasis was the retroperitoneal lymph node (RPLN), found in 30 patients; this was followed by lung (5) and bone metastases (5). Twenty-two patients had solitary metastasis on preoperative cancer staging and/or pathologic evaluation of the RC specimen, while 21 patients had multiple metastatic lesions. Median

Table 1 Clinicopathologic features

Age at cystectomy, med (SD)	61.8 (11.4)
Gender	
M	30 (69.8)
F	13 (30.2)
ASA	
1	5 (11.6)
2	25 (58.1)
3	13 (30.2)
Clinical staging[a]	
T staging	
≤ T1	10 (23.3)
T2	18 (41.9)
T3	6 (14.0)
T4	8 (18.6)
Unknown	1 (2.3)
N staging	
N0	20 (46.5)
N +	23 (53.5)
M staging	
M0	11 (25.6)
M +	32 (74.4)
Clinical/pathologic site of metastasis	
Retroperitoneal nodes	30 (69.8)
Lung	5 (11.6)
Bone	5 (11.6)
CNS	2 (4.7)
Penis[b]	2 (4.7)
Uterus, vagina[b]	2 (4.7)
Distant lymph nodes	2 (4.7)
Liver	1 (2.3)
Adrenal	1 (2.3)
Peritoneum	1 (2.3)
Metastatic burden	
Single	22 (51.2)
Multiple	21 (48.8)
Neoadjuvant chemotherapy	
Yes	40 (93)
No	3 (7)
Pathologic staging[a]	
T staging	
≤ T1	10 (23.3)
T2	5 (11.6)
T3	18 (41.9)
T4	10 (23.3)
N staging	
N0	15 (34.9)
N +	27 (62.8)
Nx	1 (2.3)
M staging	
M0	10 (23.3)
M1	23 (53.5)
Mx	10 (23.3)
Postoperative chemotherapy	
Adjuvant	7 (16.3)
Salvage	9 (20.9)
Pallivative	7 (16.3)

[a]Clinical and pathologic tumor staging classified according to the 7th AJCC Cancer Staging manual

[b]Tumor foci in penis, uterus, and vagina were non-contiguous from primary disease, and were deemed metastatic

time from diagnosis of MIBC to RC was 12.7 months (SD 14.3 months).

A total of 41 (95%) patients received between 1 and 4 regimens of chemotherapy. Of these, 38 received cisplatin-based chemotherapy. Most commonly administered regimens were gemcitabine/cisplatin-based regimens (21 patients) and adriamycin/gemcitabine-based regimens (20 patients). The traditional regimen of methotrexate, vinblastine, adriamycin and cisplatin was used in 19 patients. Complete or partial response to chemotherapy was observed in 32 patients, while the others had stable disease.

All RC were performed for maximal local control, via the open surgical approach, with ileoconduits as the urinary diversion. No tumor was deemed unresectable. On pathologic evaluation, three patients were staged pT0 and seven others had non-muscle invasive disease in the bladder. Twenty-eight patients (65%) were found to have locally advanced disease (≥ pT3). Sixteen patients had variant histology, including seven with mixed squamous differentiation and six with micropapillary features. Average nodal yield was 28 (range 0–69). Twenty-seven patients (62.8%) were found to have pathologic pelvic nodal metastases. A total of 18 patients received additional chemotherapy after RC.

Survival

Disease progression was detected in 35 patients after RC, with a median PFS of 5.9 months (95% CI 2.6–8.1 months). Thirty-four of the 43 patients died of metastatic bladder cancer, with median CSS of 12.3 months (95% CI 5.6–16.9 months) from the time of RC. One-, two- and five-year CSS were 53.5%, 34.9%, and 19.9%, respectively. On univariate analysis, metastatic burden was found to be a significant predictor for CSS (HR 4.49, 95% CI 2.16–9.33, $p < 0.001$) and PFS (HR 3.06, 95% CI 1.51–6.21, $p = 0.002$) (Table 2). On the other hand, CSS and PFS were not affected by other variables examined: between patients with metastases to the RPLN vs. other sites (CSS $p = 0.80$, PFS $p = 0.20$), patients harboring occult metastases vs. clinically evident metastases (CSS $p = 0.15$, PFS $p = 0.29$), patients with perioperative complications vs. no complications (CSS $p = 0.74$,

Table 2 Univariate and multivariate Cox proportional hazard regression analysis for CSS

	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age at cystectomy	1.01	0.97–1.04	0.75	–		
Female vs. male	1.07	0.52–2.21	0.85	–		
Biopsy proven	1.35	0.68–2.70	0.40	–		
Other mets vs. RPLN	1.10	0.55–2.20	0.80	–		
Multiple vs. single metastasis	4.49	2.16–9.33	**< 0.001**	2.62	1.16–5.90	**0.02**
Time from diagnosis to cystectomy	1.00	0.97–1.02	0.71	–		
NAC	1.95	0.47–8.18	0.36	–		
Response to NAC	0.81	0.39–1.66	0.56	–		
Number of nodes removed	1.01	0.99–1.04	0.21	–		
Clinical met vs. occult	0.58	0.27–1.21	0.15	–		
Any complication	0.89	0.44–1.78	0.74	–		
pT stage (pT > 2 vs. pT ≤ 2)	3.37	1.50–7.56	**0.003**	2.68	1.18–6.08	**0.02**
pN stage (pN + vs. pN0)	5.83	2.32–14.64	**< 0.001**	2.77	1.01–7.64	**0.05**
Variant histology	1.25	0.63–2.48	0.52	–		
Post-surgical chemotherapy	1.19	0.60–2.35	0.62	–		
ASA (2 vs. 1)	2.02	0.60–6.83	0.26	–		
ASA (3 vs. 1)	2.34	0.65–8.45	0.20	–		

Bolded *p* values denote statistical significance, with $p < 0.05$

Table 3 Univariate and multivariate Cox proportional hazard regression analysis for PFS

	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age at cystectomy	1.01	0.98–1.05	0.52	–		
Female vs. male	0.91	0.45–1.87	0.81	–		
Biopsy proven	1.56	0.78–3.11	0.21	–		
Other mets vs. RPLN	1.55	0.79–3.06	0.20	–		
Multiple vs. single metastasis	3.06	1.51–6.21	**0.002**	1.79	0.81–3.95	0.15
Time from diagnosis to cystectomy	1.00	0.98–1.03	0.72	–		
NAC	1.77	0.42–7.46	0.43	–		
Response to NAC	0.69	0.34–1.41	0.30	–		
Number of nodes removed	1.00	0.98–1.02	0.84	–		
Clinical met vs. occult	0.67	0.32–4.40	0.29	–		
Any complication	1.02	0.52–2.04	0.94	–		
pT stage (pT > 2 vs. pT ≤ 2)	3.08	1.42–6.66	**0.004**	2.17	0.98–4.84	0.06
pN stage (pN + vs. pN0)	3.94	1.65–9.40	**0.002**	2.15	0.80–5.81	0.13
Variant histology	1.03	0.52–2.02	0.94	–		
Post-surgical chemotherapy	1.46	0.74–2.86	0.27	–		
ASA (2 vs. 1)	2.15	0.64–7.22	0.22	–		
ASA (3 vs. 1)	2.64	0.73–9.57	0.14	–		

Bolded *p* values denote statistical significance, with $p < 0.05$

PFS $p = 0.94$), and patients receiving additional postoperative chemotherapy vs. those who did not (CSS $p = 0.62$, PFS $p = 0.27$). On multivariable analysis, metastatic burden remained a significant predictor of CSS (HR 2.62, 95% CI 1.16–5.90, $p = 0.02$) (Table 3). When categorized by metastatic burden, patients with solitary metastases were found to have longer median PFS (10.4 months vs. 3.5 months, $p = 0.001$) and CSS (26.0 months vs. 7.9 months, $p < 0.001$) than patients with multiple metastatic lesions (Fig. 1).

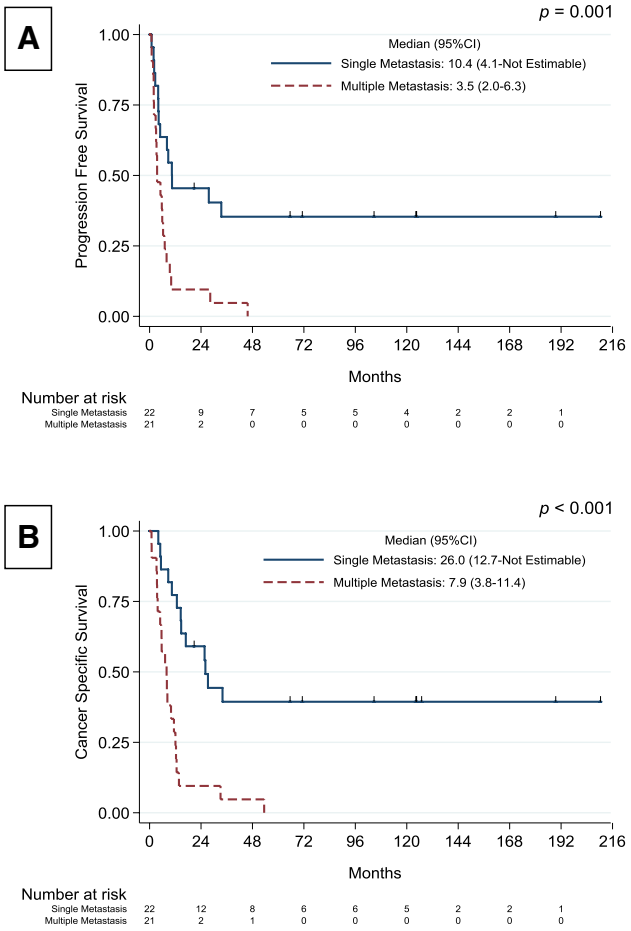

Fig. 1 The effect of metastatic burden on PFS (**a**) and CSS (**b**) from the time of cytoreductive/consolidative radical cystectomy

Complications

Median postoperative hospital LOS was 10 days. In all, 37 complications occurred in 24 patients (56%) within 30 days of RC, including one perioperative mortality (2.3%) subsequent to aspiration pneumonia (Table 4). Of these, 27 were classified as minor (Grades I–II), while 10 were classified as major (Grade III or above). The most common major complication was wound infection ($n = 3$). Five other complications requiring invasive procedural interventions were pneumonitis requiring bronchoscopy, ascites requiring IR-guided drainage, post-surgical abscess requiring IR-guided drainage, anastomotic stricture requiring endoscopic dilation, and a case of incidental gangrenous cholecystitis requiring cholecystectomy. Two patients suffered life-threatening complications requiring ICU admissions for postoperative pulmonary failure and aspiration pneumonia.

In addition, four complications occurred in the 30–90 days period after RC (Table 5). One patient suffered acute renal failure that was corrected with dialysis. Three additional patients were diagnosed with urine leak, enterocutaneous fistula, and anastomotic stricture, requiring surgical correction.

Table 4 30-day complication

Clavien–Dindo I	*n*
Ileus	3
Wound infection	2
Diarrhea	1
Post-surgical delirium	1
Hypernatremia	1
Clavien–Dindo II	
Ileus	7
Cardiovascular	6
UTI	2
Post-surgical delirium	1
DVT	1
AKI	1
Wound infection	1
Clavien–Dindo III	
Wound infection	3
Pneumonitis	1
Ascites	1
Abscess	1
Anastomotic stricture	1
Gangrenous cholecystitis	1
Clavien–Dindo IV	
Pneumonia	1
Clavien–Dindo V	
Aspiration pneumonia	1

Table 5 90-day complication

Clavien–Dindo II	
Acute renal failure	1
Clavien–Dindo III	
Urine leak	1
Enterocutaneous fistula	1
Anastomotic stricture	1

Discussion

We report our single-centered experience with RC in the setting of metastatic UC originating from the lower urinary tract. Patients with solitary metastasis were found to have an 18-month CSS advantage over those with multiple metastatic lesions, independent of the site of metastasis. Additionally, although early perioperative complications occurred more frequently than in other RC series (56% vs. 28%), perioperative mortality rates were similar (2.3% vs. 2.5%) [7]. As such, we demonstrate the feasibility of RC in

the metastatic setting as well as the paramount importance of patient selection.

The lack of association between the site of metastasis and survival was somewhat surprising. In subgroup analyses of previous postchemotherapy RC series, patients harboring solitary visceral metastases seemingly fared worse than those found to have extraregional lymph node metastases [10]. Five of the 11 patients with extraregional lymph node metastases were free of disease at the time of RC, and two of them survived beyond 5 years postoperatively. In comparison, only one of the seven patients in the visceral metastasis group was staged pT0N0M0 and survived beyond 5 years from surgery. Furthermore, the presence of visceral metastases (i.e., lung, liver, bone or other non-lymph node metastasis) was found to be a poor prognosticator in patients with metastatic UC treated with cisplatin-based chemotherapy [11]. The lack of difference in survival between patients with RPLN and visceral metastases in the current study may be due to the small sample size.

On the other hand, the finding that low metastatic burden was associated with prolonged CSS is a concept familiar to urologic oncologists. In the treatment of metastatic renal cell carcinoma, the number of metastatic sites, but not the location of metastasis, dictated the overall survival [12]. In regard to cytoreductive nephrectomy, several groups have introduced and popularized the concept of "fractional percentage of tumor volume removed" (FPTV), as an indirect measure of the metastatic burden at the time of surgery [13–15]. In the recent literature, $>90\%$ FPTV has been linked to improved PFS and OS [13, 15]. Similarly, in the oligometastatic setting, cytoreductive radical prostatectomy led to a remarkable 7-year CSS of 82% [16]. In other surgical oncology literature, quantitative measures of metastatic burden such as the peritoneal cancer index [17] have been utilized to refine patient selection.

With regard to metastatic UC, Galsky et al. found the number of visceral metastatic sites to be prognostic of patients treated with cisplatin-based chemotherapy [18]. Moreover, higher volume of metastatic disease has also been associated with poor prognosis following pulmonary metastasectomy [19]. In line with these findings, results from the current study proved oligometastatic disease to be a favorable prognosticator in UC patients undergoing CCRC. It follows that if CCRC is truly beneficial, its effect may be most evident in the oligometastatic population.

The abysmal median survival in metastatic bladder cancer patients, coupled with the morbidity of RC, make it doubly important to select patients who will not only tolerate the surgery, but also gain survival benefit. Our study suggests that patients with multiple metastases benefitted minimally from RC. In the group with solitary metastases, however, the median interval from diagnosis of MIBC to RC was 7.1 months, in addition to the 26.0 months median CSS after RC. The total CSS of 32.1 months from the time of diagnosis compares favorably to historic chemotherapy series (8.2–16 months) [20] as well as the emerging data from the recently completed immunotherapy series (15.9 months) [21].

Contrary to the prevailing perception of the inexorable morbidity associated with RC, 18/43 (41.9%) patients went on to receive chemotherapy after CCRC. Although not specifically queried in this study, clinicians are undoubtedly familiar with UC patients with crippling hematuria and/or pelvic pain, whose symptoms may actually improve after CCRC. In a study of 70 patients with metastatic UC, Otto et al. reported an improvement in the performance scores of symptomatic patients who underwent surgical resection [22]. Such patients may thus be rendered eligible for systemic therapy as a result of CCRC. It should be pointed out, however, that the perioperative outcomes may have been artificially improved by the careful selection of patients who underwent CCRC.

However, the importance of selection bias cannot be overstated. Although ASA score was not found to be a significant predictor of PFS or CSS, factors not measured in the current study, such as Charleson comorbidity and Karnofsky performance indices, may play vital roles in the survival after CCRC. To properly investigate potential benefits derived from CCRC, a prospective randomized trial is warranted.

Although potentially hampered by biases inherent in a population study, the most compelling data in support of such a trial were compiled from the National Cancer Data Base (NCDB) [23]. Of 3753 patients receiving systemic chemotherapy for metastatic UC, those receiving high-intensity local therapy, as defined by RC or ≥ 50 Gy radiotherapy, had significantly longer median OS (15 vs. 10 months, $p<0.001$). Furthermore, the subgroup receiving consolidative surgery (i.e., RC after chemotherapy), achieved even higher OS of 17.7 months. These findings corroborated with results from earlier series [10]. In a small cohort with clinical extraregional lymph node and visceral metastases, 5-year survival was achieved by 15% after RC. Those who achieved complete response after chemotherapy and surgery fared equally well as those achieving complete response after chemotherapy alone.

Inferences for the benefit of CCRC can also be made from literature demonstrating the benefit of RC in the setting of regional nodal metastases. In another NCDB analysis, combination of chemotherapy and RC led to higher 5-year OS (31% for NAC + RC, and 26% for RC + AC) than chemotherapy (14%) alone [24]. Furthermore, a multi-institutional study of 304 cN + patients undergoing combination NAC + RC showed median overall survival of 22 months (IQR 8.0–54 months) [25].

We believe the results of the current study not only provide further support for a trial assessing the role of CCRC,

but can also be used towards patient selection. In addition to patients with solitary metastasis, other selection criteria may include response to chemotherapy, surgically resectable primary tumor, and a period of disease stability with no evidence of rapid progression. Recent advances in immunotherapy [26] and perioperative management following RC [8] have not only prolonged average survival in metastatic UC patients, but also reduced the morbidity of extirpative surgery. It would be critically important to assess whether these advances have tipped the balance in favor of surgical control of the primary tumor in the metastatic setting.

To that end, another important finding in the current study was the acceptable perioperative morbidity. The 56% complication rate was on par with those recently reported in the randomized clinical trial comparing robot-assisted laparoscopic and open RC [27]. The mortality rate of 2.3% in the current series was also similar to figures from recent as well as historic RC series [7, 27]. As shown herein, the vast majority of the patients (65.2%) were found to have locally advanced disease, adding complexity to surgical extirpation. As such, CCRC should be limited to high volume, tertiary centers to optimize perioperative outcomes [28].

This study was not without limitations. As CCRC has been heretofore untested in the clinical setting, only few cases were available in our RC database. The small sample size limited the power of the analysis with regard to several potentially vital factors. Although no difference in survival was apparent in comparing patients with different sites of metastasis, occult vs. clinically detected metastases, variable postoperative recovery, and different post-surgical chemotherapy regimens, no definitive conclusions can yet be made. More importantly, to answer whether CCRC can improve upon the results of systemic chemotherapy and immunotherapy series, prospective randomized trials should be considered to control for potential confounders as previously mentioned. Without the results of such trials, the practice of CCRC should strictly be regarded as experimental, as the potential downside to this treatment can be devastating. Finally, although no patient underwent minimally invasive CCRC in the current series, robot-assisted RC has previously been demonstrated to be feasible for locally advanced tumors [29]. Whether minimally invasive CCRC can further reduce perioperative morbidity in the metastatic setting remains to be explored.

Conclusions

We present our single-centered experience on CCRC in the setting of metastatic cancer originating from the lower urinary tract. Compared to patients with multiple metastatic lesions, patients with solitary metastases were found to have an 18-month survival benefit from the time of CCRC. Multiple metastases should be an exclusion criterion in future trials investigating the role of CCRC.

Author contributions RL: protocol/project development, data collection or management, data analysis, manuscript writing/editing; JEBK: data collection or management; MAS: data collection or management, data analysis, manuscript writing/editing; FGP: data collection or management, manuscript writing/editing; MTC: manuscript writing/editing; JVN: data collection or management, manuscript writing/editing; GMNG: data analysis, manuscript writing/editing; AMK: manuscript writing/editing; LLP: manuscript writing/editing; PD: manuscript writing/editing; NN: protocol/project development, data collection or management, data analysis, manuscript writing/editing.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals Institutional Review Board approved.

Informed consent No informed consent as this was a retrospective study.

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