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Cytoreductive cystectomy combined with chemotherapy versus chemotherapy alone in the treatment of metastatic bladder cancer: A retrospective comparative study

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Introduction The role of cytoreductive surgery in metastatic bladder cancer remains controversial. While systemic chemotherapy is the standard of care, the potential benefit of combining chemotherapy with radical cystectomy in selected patients requires further evaluation.

Material and methods We performed a retrospective cohort study of 192 patients with metastatic urothelial carcinoma treated between 2008 and 2022. Patients were divided into two groups: treatment with four cycles of gemcitabine–cisplatin followed by cytoreductive cystectomy in selected non-progressing patients (n = 90), and treatment with chemotherapy alone (n = 102). Median follow-up was 14.2 months. Cancer-specific survival (CSS) was evaluated using Kaplan–Meier analysis and Cox regression with adjustment for baseline characteristics.

Results Median CSS was longer in the cystectomy group compared to chemotherapy alone (19.6 vs 12.6 months, p = 0.03). Treatment-related toxicity was comparable between groups. Cytoreductive cystectomy also provided symptomatic relief in patients with local complications such as hematuria, pain, and urinary obstruction.

Conclusions Cytoreductive cystectomy combined with systemic chemotherapy may be associated with improved survival in carefully selected patients with metastatic urothelial carcinoma. These findings should be interpreted with caution due to the retrospective design and potential selection bias.

Key Words: metastatic bladder cancer ‹› chemotherapy ‹› cystectomy

INTRODUCTION

Bladder cancer (BC) represents one of the most prevalent malignant urological pathologies worldwide, with a steadily increasing incidence and prevalence [1, 2]. BC ranks sixth among all cancer types in men [3]. Globally, approximately 613,791 new cases of bladder cancer and 220,349 deaths are registered annually [4]. The prognosis for patients with metastatic bladder cancer remains poor, with median overall survival (OS) of 12–15 months with platinum-based chemotherapy. Without treatment, median OS is markedly reduced to approximately 3–6 months, with five-year survival rates for metastatic disease at approximately 5%. Notably, 10%-15% of patients present with metastatic disease at initial diagnosis, and these patients experience particularly high mortality rates [3, 5].

Systemic therapeutic approaches remain the cornerstone in managing metastatic bladder cancer. The therapeutic landscape has undergone significant transformation with the integration of immune checkpoint inhibitors in first-line settings, demonstrating substantial improvements in survival

outcomes [6–8]. Maintenance therapy with avelumab following platinum-based chemotherapy has exhibited significant survival advantages compared to best supportive care, with median overall survival reaching 21.4 months vs 14.3 months (p = 0.001). Additionally, atezolizumab monotherapy has demonstrated enhanced survival outcomes in platinum-ineligible patients exhibiting programmed death-ligand 1 (PD-L1)-positive tumors [5, 9]. This therapeutic advancement represents a paradigm shift in the management of this challenging patient population. The EV-302/KEYNOTE-A39 trial demonstrated substantially improved outcomes with enfortumab vedotin plus pembrolizumab as first-line therapy for metastatic urothelial carcinoma, with a median overall survival exceeding 31 months. Despite advances in systemic therapy, optimizing local control in metastatic BC remains an unmet clinical need. Francolini et al. [10] demonstrated the feasibility and efficacy of combining local and systemic treatments in metastatic bladder cancer patients with acceptable toxicity profiles. Their approach suggests that stereotactic body radiation therapy (SBRT) may provide clinical benefit for selected patients with oligometastatic bladder cancer when integrated with systemic therapy. Supporting this concept, Leonetti et al. reported outcomes after stereotactic body radiation therapy targeting nodal metastases, with median local progression-free survival of 11.4 months. Importantly, lesions treated at higher doses (35–40 Gy) demonstrated prolonged local control compared to lower dose schedules (20–25 Gy).

While local therapeutic interventions for metastatic disease have shown increasing promise across various solid tumors, the efficacy of cytoreductive cystectomy specifically for advanced bladder cancer remains controversial. Current literature lacks comprehensive data regarding the role of local surgical treatment in combination with systemic therapy for metastatic BC [11–13]. There is particularly limited understanding of cytoreductive surgery safety and its optimal integration with modern systemic therapies in this patient population.

The integration of systemic therapies with local treatment approaches is well-established in other urological malignancies, including metastatic prostate and kidney cancers [10, 14–16]. The theoretical rationale supporting the potential benefits of cytoreductive cystectomy encompasses several mechanisms: elimination of primary tumor-mediated immunosuppression, prevention of lethal clone dissemination, and reduction of local progression-associated morbidity. Advanced bladder cancer frequently presents with local symptoms that may precipitate life-threatening complications, potentially limiting eligibility for systemic therapeutic interventions and adversely affecting survival outcomes. We hypothesize that a combined approach incorporating cytoreductive cystectomy with systemic chemotherapy may provide superior oncological outcomes compared to chemotherapy alone in metastatic bladder cancer. This approach may reduce overall tumor burden, eliminate potentially resistant tumor clones, and improve patient performance status for subsequent systemic therapy.

The primary aim of this study was to compare the safety profile and oncological efficacy of combined chemotherapy and cystectomy to chemotherapy alone in the treatment of metastatic bladder cancer.

MATERIAL AND METHODS

Study design

This retrospective cohort study included adult patients with histologically confirmed metastatic urothelial carcinoma of the bladder treated at the National Cancer Institute of Ukraine between 2008 and 2022. During this period, a total of 2,200 patients underwent radical cystectomy for bladder cancer. Following clinical, histopathologic, and imaging review, 1,540 patients with locally confined or locally advanced non-metastatic disease (T1–T4a, M0) were excluded, and 468 patients were excluded due to non-urothelial histologic subtypes, including squamous cell carcinoma, adenocarcinoma, and neuroendocrine carcinoma. The remaining 192 patients had histologically confirmed urothelial carcinoma with radiologically verified distant metastases (M1 stage, based on CT or MRI) and constituted the final study cohort. Patients were then divided into two comparative groups based on the received treatment modality: the cystectomy + chemotherapy group (n = 90), who received 4 cycles of gemcitabine–cisplatin chemotherapy followed by cytoreductive radical cystectomy (performed in patients demonstrating disease control after initial systemic therapy), and the chemotherapy alone group (n = 102).

Inclusion criteria were as follows:

- histologically confirmed muscle-invasive urothelial carcinoma of the bladder;
- radiologically confirmed metastatic disease on contrast-enhanced CT, with at least one distant metastasis;
- completion of a minimum of 4 cycles of palliative chemotherapy (Gem-Cis);
- ECOG 0–2;
- Karnofsky performance score >70.

Cytoreductive cystectomy was performed in selected patients with metastatic bladder cancer based on the following indications: local complete response/partial response/stable disease following initial systemic chemotherapy (no evidence of progression after 4 cycles), preserved performance status (ECOG 0–2), acceptable surgical risk profile, and signed informed consent for the surgery. All surgical candidates were assessed by a multidisciplinary team – comprising a urologic oncologist, medical oncologist, radiologist, and anesthesiologist – based on a risk–benefit evaluation strategy. Participating surgeons were required to have experience of at least 15 radical cystectomies per year.

Systemic treatment

All patients received systemic chemotherapy according to the standard gemcitabine-cisplatin (GemCis) regimen: gemcitabine 1,000 mg/m^2 was administered on days 1 and 8, and cisplatin 70 mg/m^2 on day 2 of a 21-day cycle. Treatment continued for up to six cycles or until the occurrence of unacceptable toxicity or radiologically confirmed disease progression. CT staging was performed after every two cycles of systemic therapy and at least once every 3 months following the completion or discontinuation of first-line chemotherapy. In cases of disease progression, patients were transitioned to second-line therapy in accordance with the prevailing guidelines at the time. In the cystectomy+chemotherapy group, 54 of 90 patients (60%) received second-line therapy: vinflunine (n = 22, 40.7%), paclitaxel-based combinations (n = 19, 35.2%), and pembrolizumab (n = 13, 24.1%), the latter predominantly from 2017 onward. The median time from completion of first-line chemotherapy to initiation of second-line therapy was 4.3 months. In the chemotherapy-alone group, 49 of 102 patients (48%) received second-line treatment: vinflunine (n = 18, 36.7%), paclitaxel-based regimens (n = 17, 34.7%), and pembrolizumab (n = 14, 28.6%), per institutional and national protocols applicable at the time. The difference in the proportion of patients receiving second-line therapy between groups (60% vs 48%) did not reach statistical significance (p = 0.09).

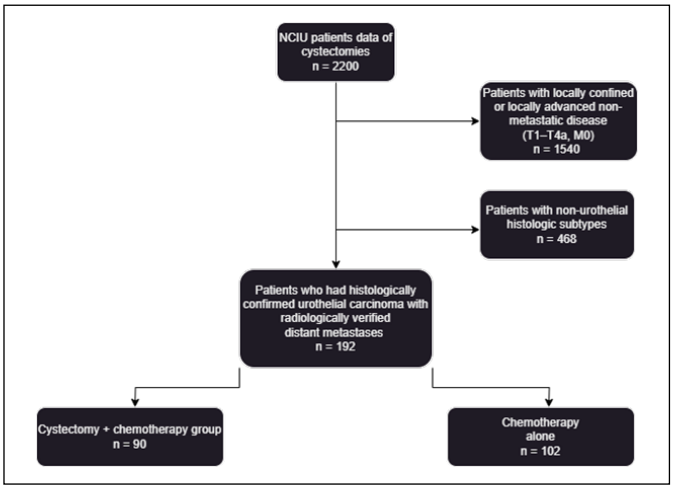

Figure 1. *Study flowchart.*

Patients undergoing cytoreductive surgery received a standard radical cystectomy with extended lymph node dissection, followed by a unilateral cutaneous ureterostomy. After cystectomy, both ureters were freed cranially closer to the kidneys. In cases of kinking, ureters were mobilized for maximum straightening. Sigmoid colon was mobilized medially by cutting fixation with parietal peritoneum on the left. Afterwards a window was created in the root of sigmoid colon mesentery, where both ureters were brought retroperitoneally: the left one penetrating the mesentery between colon vessels heading the window and the right one under visceral peritoneum (Figure 2). Then, the tunnel was formed beneath the visceral peritoneum of the mesosigmoid, which distally opened at the distance of 2 cm from the colon (Figure 2). Both ureters were passed throughout this tunnel, and their ends were exteriorized through the opening in the left abdominal wall, the anti-McBurney point. An abdominal wall channel was cut in the form of sandglass for ureteral separation. Under-skin fat was maximally excised to shorten the abdominal wall tunnel and prevent fibrous changes of the ureters. To create an extraperitoneal way of the ureters, 4 sides of the peritoneal window were anastomosed with rectal muscle aponeurosis. This maneuver separated the tunnel from the peritoneal cavity and made it shorter, thus modeling the needed length. The ends of the ureters were anastomosed with the skin in a modified X-shaped technique, forming a single-site cutaneous ureterostomy and preventing stomal stenosis (Figure 2). Ureters were reverted to form the anastomosis with skin, which also prevented stenosis. Two 6–7 French JJs were inserted and fixed to the skin, and a stoma bag was applied [17, 18]. This approach allowed safe and rapid urinary diversion, reduced operative time, and was particularly appropriate in patients with extensive metastatic disease.

Metastatic disease characteristics

Among the 192 patients with metastatic bladder cancer included in this study, 137 patients (71.4%) presented with a single metastatic site, while 55 pa-

tients (28.6%) demonstrated metastases in multiple anatomical locations. The distribution of metastatic burden was comparable between treatment groups, with single-site metastases observed in 65 patients (72.2%) in the cystectomy + chemotherapy group and 72 patients (70.6%) in the chemotherapy-alone group. Among patients with solitary metastases, the distribution pattern revealed three predominant sites of distant disease:

1. Pulmonary metastases: observed in 21 patients (32.3%) in the cystectomy + chemotherapy group and 23 patients (31.9%) in the chemotherapy-alone group.
2. Hepatic metastases: 23 patients (35.4%) in the cystectomy + chemotherapy group and 30 patients (41.7%) in the chemotherapy-alone group.
3. Osseous metastases: 21 patients (32.3%) in the cystectomy + chemotherapy group and 19 patients (26.4%) in the chemotherapy-alone group.

Distribution of multiple metastatic sites

The 55 patients with multiple metastatic sites demonstrated various combinations of organ involvement:

1. Combined pulmonary and osseous metastases: 9 patients (36% of multiple-site cases) in the cystectomy + chemotherapy group and 10 patients (33.3%) in the chemotherapy-alone group.
2. Combined pulmonary and hepatic metastases: 8 patients (32% of multiple-site cases) in the cystectomy + chemotherapy group and 10 patients (33.3%) in the chemotherapy-alone group.
3. Combined hepatic and osseous metastases: 8 patients (32% of multiple-site cases) in the cystectomy + chemotherapy group and 10 patients (33.3%) in the chemotherapy-alone group.

Outcome assessment

The primary endpoints were safety outcomes, including treatment-related complications assessed using the Clavien-Dindo classification (for surgical patients) and chemotherapy-related toxicity evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The secondary endpoint was cancer-specific survival, defined as the time from treatment initiation to death from bladder cancer or last follow-up between groups. Follow-up was performed as already mentioned in section 2.2.

Statistical analysis

Descriptive statistics were used to summarize patient characteristics. Continuous variables were expressed as median with range or interquartile range, and categorical variables as frequencies and percentages. Differences in patient characteristics between groups were assessed using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. Survival probabilities were estimated using the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate Cox proportional hazards regression analyses were performed to identify prognostic factors associated with cancer-specific survival. Variables included in the multivariate model were selected based on clinical relevance and statistical significance in univariate analysis ($p \leq 0.10$), and comprised age, ECOG performance status, Charlson Comorbidity Index, ASA score, body mass index, tumour stage, metastatic burden, and treatment modality. The proportional hazards assumption was assessed using Schoenfeld residuals and log-log survival plots and was not violated for any covariate. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. To address potential selection bias due to baseline differences between treatment groups, propensity score adjustment was performed, incorporating key variables including age, ECOG performance status, Charlson Comorbidity Index, ASA score, BMI, tumour stage, and metastatic burden.

Bioethical standards

Information about patients was received from the National Cancer Registry of Ukraine, therefore no recruitment process was performed. Data were anonymised prior to analysis. A standard of care treatment was used for all the patients. Therefore no new intervention comparison was done. The current study did not require registration according to the Helsinki Declaration in the clinical trial registry.

RESULTS

Patient characteristics

The baseline characteristics and clinical outcomes of 192 patients with metastatic bladder cancer, who received either combined operative and chemotherapy treatment (cystectomy + chemotherapy, n = 90) or chemotherapy alone (n = 102) are summarized in Table 1. The median age of patients in both groups was similar (67.3 vs 67.2 years, p = 0.178), with a predominance of male patients in both cohorts (male-to-female ratio 9:1 and 8.3:1, respectively). Significant differences were observed in several baseline characteristics between the two treatment groups. Patients in the chemotherapy-

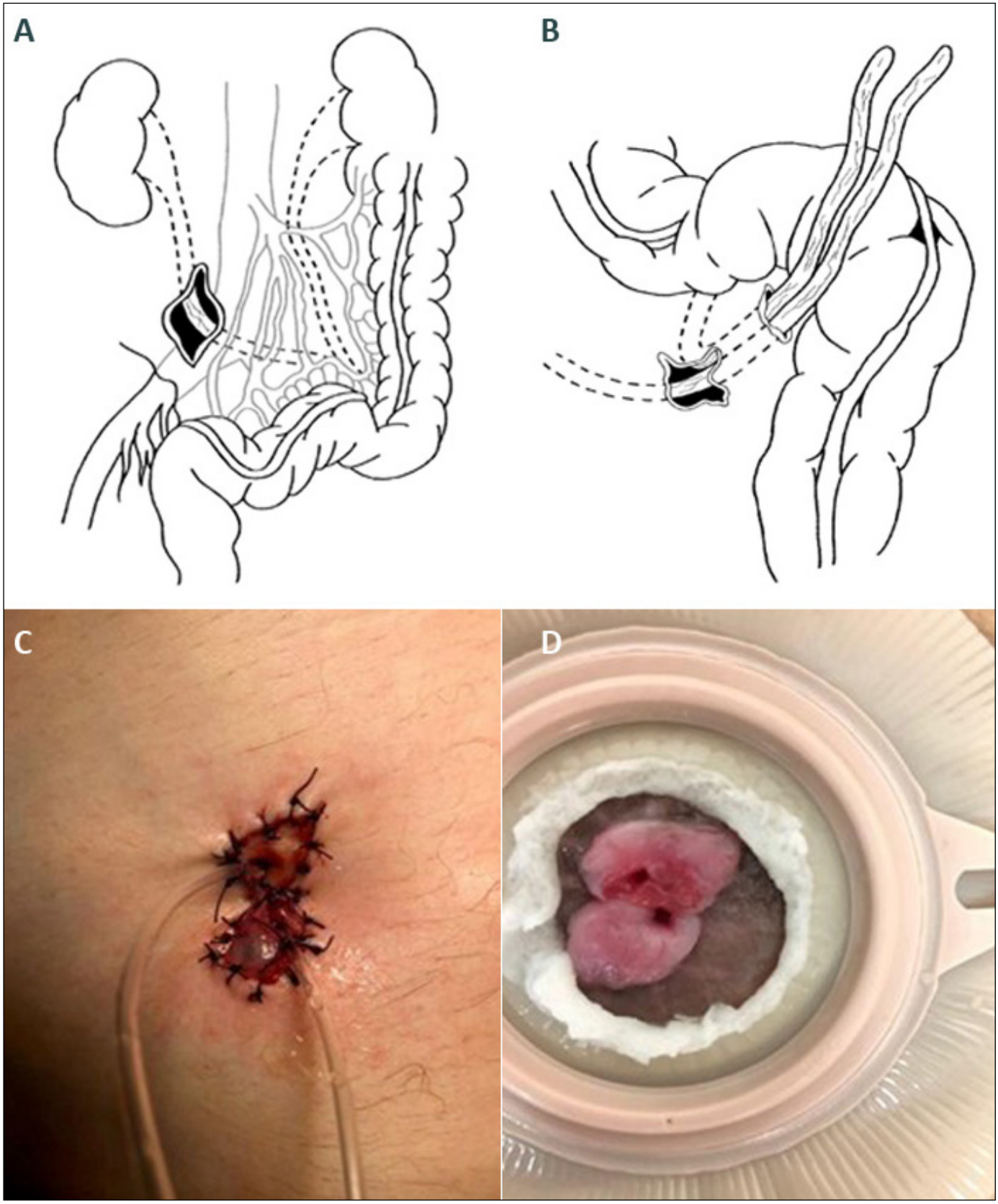

Figure 2. A) *Transperitoneal transposition of the right ureter to the left side.* **B)** *Exteriorization of the distal ends of both ureters with formation of a cutaneous ureterostomy.* **C)** *Early postoperative appearance of the cutaneous ureterostomy with ureteral stents in place.* **D)** *Mature cutaneous ureterostomy one year after surgery.*

alone group had a higher median body mass index (27.1 vs 24.0 kg/m², p <0.001), and a higher proportion were classified as ASA III (57 vs 43 patients, p = 0.008). Of the 192 patients included, 137 (71.4%) presented with a single metastatic site, while 55 (28.6%) had multiple metastatic sites. The distribution was similar between treatment groups: Single-site metastases were seen in 72.2% in the cystectomy + chemotherapy group and in 70.6% in the chemotherapy-only group.

Among solitary metastases, the most frequent locations were as follows:

- lung: 32.3% (cystectomy + chemotherapy) vs 31.9% (chemotherapy only);
- liver: 35.4% vs 41.7%;
- bone: 32.3% vs 26.4%.

Among patients with multiple metastatic sites (n = 55), the most common combinations were as follows:

- lung + bone: 36% (cystectomy + chemotherapy) vs 33.3% (chemotherapy only);
- lung + liver: 32% vs 33.3%;
- liver + bone: 32% vs 33.3%.

The median Charlson comorbidity index was identical in both groups (9.5, IQR 7–12); however, the distribution within this range differed, with a higher proportion of CCI ≥11 in the chemotherapy-only group (p = 0.041, Mann-Whitney U test). Multivariate analysis confirmed this parameter as a significant independent predictor of cancer-specific survival (HR 1.23, 95% CI: 1.12–1.35, p <0.001). Renal function parameters demonstrated notable differences between the groups. Baseline serum creatinine was higher in the cystectomy + chemotherapy group compared to the chemotherapy alone group (113 vs 103.4 μmol/l, p = 0.001), while baseline glomerular filtration rates were similar (60.2 vs 63.4 ml/min/1.73 m², p = 0.586). Importantly, patients who underwent the combined approach showed improvement in renal function parameters after treatment (creatinine decreased to 92.9 μmol/l and GFR increased to 71.9 ml/min/1.73 m²). Regarding disease characteristics, there was a trend toward a higher proportion of stage 3 tumors in the chemotherapy alone group (59 vs 44 patients, p = 0.055). The distribution of metastatic burden was similar

Table 1. *Patient baseline characteristics and clinical parameters*

Indicator/group		Cystectomy + chemotherapy (n = 90)	Chemotherapy alone (n = 102)	HR	95% CI	P-value
Age		67.3 (59–75)	67.2 (57–77)	1.02	[0.99–1.05]	0.178
Men/women ratio		81/9	91/11			
Body mass index		24.0 (18.7–27.4)	27.1 (20–33.4)	1.44	[1.36–1.52]	<0.001
ECOG	2 3	47 43	48 54	1.30	[0.97–1.74]	0.077
Karnofsky peformance scale index		80 (70–90)	80 (70–90)	0.995	[0.98–1.01]	0.631
Charlson comorbidity index		9.5 (7–12)	9.5 (7–12)	1.23	[1.12–1.35]	0.041
Serum creatinine		Before cystectomy 113 (95–130) After cystectomy 92.9 (80–105)	103.4 (85–125)	1.04	[1.03–1.06]	0.001
Total glomerular fltration rate		Before cystectomy 60.2 (39.4–76.13) After cystectomy 71.9 (47.1–91.4)	63.4 (39.6–84.4)	1.00	[0.98–1.02]	0.586
ASA score	II III	47 43	45 57	1.49	[1.11– 2.01]	0.008
Tumor stage	3 4	44 46	59 44	0.79	[0.62 – 1.01]	0.055
Metastatic sites	1 2>	65 25	72 30			0.840

ASA – American Society of Anesthesiologists physical status classification: ASA II – mild systemic disease without functional limitation; ASA III – severe systemic disease with functional limitation; CI – confidence interval; ECOG – Eastern Cooperative Oncology Group performance status; GFR – glomerular filtration rate; HR – hazard ratio

P-values for group comparisons derived from Mann-Whitney U test (continuous variables) or Fisher's exact test (categorical variables). HR and 95% CI from univariate Cox proportional hazards regression.

between groups, with approximately 70% of patients in each group presenting with single-site metastases (72.2% vs 70.6%, p = 0.840, Fisher's exact test). Hepatic metastases were the most common in the chemotherapy alone group (30 patients), while metastases were more evenly distributed among lung, liver, and bone in the cystectomy + chemotherapy group.

Chemotherapy-related adverse events

Chemotherapy-related adverse events are presented in Table 3. No statistically significant differences were identified between groups regarding incidence of adverse events (all p >0.05), indicating similar tolerability of chemotherapy. The most common toxicities were hematological, including anemia (87.8% vs 83.3%), lymphopenia (84.4% vs 86.3%), and neutropenia (88.9% vs 81.4%). Grade II–III events occurred in small proportions of patients. Importantly, chemotherapy did not negatively impact feasibility or timing of subsequent surgery; surgical interventions were typically performed within 3 to 4 weeks after completion of chemotherapy.

Surgical outcomes and complications

A total of 90 patients underwent cytoreductive cystectomy. Urinary diversion was performed using cutaneous ureterostomy in 83 patients (92.2%), ileal conduit in 6 patients (6.7%), and neobladder reconstruction in 1 patient (1.1%). Among patients with ≥2 metastatic sites, 13 (23.6%) required surgery due to urgent local complications, including severe hematuria (n = 7), intractable pelvic pain (n = 4), and bilateral hydronephrosis with deteriorating renal function (n = 2). Intraoperative data are summarized in Table 2. Blood loss >500 ml occurred in 6 patients (6.7%), and >1,000 ml in 2 cases (2.2%). Mean operative time was 165 ±35 min, and median hospital stay was 11,3 ±3.8 days. No intraoperative deaths occurred. A total of 10 patients (11.1%) experienced significant postoperative events. The most clinically relevant postoperative complications and their classification according to the Clavien–Dindo system were as follows: Rectal injuries (n = 3; 3.3%) were intraoperatively identified and managed with primary suture repair and protective urinary diversion; all were classified as Grade IIIb due to the need for surgical intervention under general anesthesia. Iliac vessel injuries (n = 2; 2.2%) were controlled intraoperatively using vascular suturing techniques and were categorized as Grade IIIb. Cutaneous ureterostomy strictures (n = 5; 5.6%) were primarily treated with percutaneous nephrostomy placement (Grade IIIa); one case required surgical revision under general anesthesia (Grade IIIb). Minor complications (Clavien–Dindo Grade I–II), including transient fever, mild wound infection, or ileus, were observed in 6 patients (6.7%) and resolved with conservative measures. No Grade IV–V complications or perioperative deaths were recorded. These data demonstrate that the overall complication profile was acceptable, with most events being manageable and reversible, supporting the feasibility of cytoreductive surgery in a selected metastatic population.

Table 2. *Intraoperative and postoperative complications in patients undergoing cytoreductive cystectomy*

Complication	Cystectomy + chemotherapy
Operative time, min	165 ±35 (95–230)
Average blood loss, ml	320 ±140 (180–460)
Adjacent organ injury	1 (1.1)
Rectal injury	3 (3.3)
Iliac vessel injury	2 (2.2)
Clavien–Dindo any complication	16 (17.7)
Clavien–Dindo III–IV grade	10 (11.1)
Postoperative stay, days	11.3 ±3.8 (7.0–17.0)
90-day hospital readmission rate	2 (2.2)
Long-term complications	7 (7.77)

Data are presented as mean ± standard deviation (min-max) or n (%), unless otherwise indicated.

Table 3. *Comparison table of side effects after chemotherapy*

Complications after chemotherapy	Cystectomy + chemotherapy	Chemotherapy alone	p-value
Anemia	79 I – 64 II – 12 III – 3	85 I – 65 II – 16 III – 4	0.5
Leukopenia	55 I – 44 II – 11	60 I – 47 II – 13	0.86
Lymphopenia	76 I – 63 II – 13	88 I – 73 II – 15	0.87
Neutrophils/granulocytes	I – 80	I – 83	0.21
Thrombocytopenia	I – 22	I – 26	1
Hypertension	I – 31	I – 34	0.99
Fatigue	I – 46	I – 49	0.77
Alopecia	I – 17	I – 20	1
Dry skin	I – 79	I – 83	0.3
Nausea	I – 73	I – 85	0.83
Vomiting	I – 38	I – 40	0.78
Diarrhea	I – 14	I – 18	0.84
Hypercreatinemia	I – 45	I – 49	0.89

Survival outcomes

Median CSS was significantly higher in the cystectomy + chemotherapy group compared to chemotherapy alone (19.6 vs 12.6 months, p = 0.03; HR = 0.68, 95% CI: 0.48–0.96). Kaplan-Meier curves are presented in Figures 3 and 4. In subgroup analysis based on metastatic burden: patients with single-site metastases demonstrated a median cancer-specific survival of 16.7 months, while those with two or more metastatic sites showed a median CSS of 14.9 months. Because the vast majority of deaths in this metastatic cohort were cancer-related, CSS closely approximates overall survival in this context. At 16 months, survival rates were 50% for single-site vs 36% for two-site metastases. Across follow-up duration, patients with limited metastatic involvement consistently exhibited higher probability of survival.

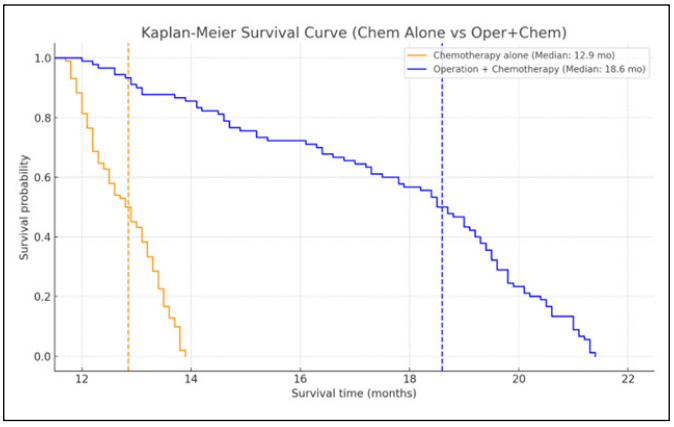

Figure 3. *Kaplan-Meier survival curves comparing combined treatment (cytoreductive cystectomy plus chemotherapy vs chemotherapy alone (chem) in patients with metastatic bladder cancer.*

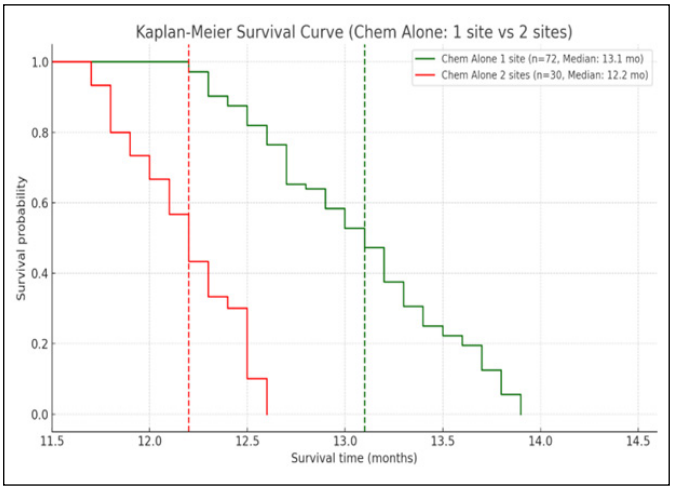

Figure 4. *Kaplan-Meier survival curves comparing cancer-specific survival according to metastatic burden (1 tumor site vs 2 tumor sites) in patients receiving chemotherapy alone.*

DISCUSSION

Metastatic bladder cancer (mBC) continues to pose a major therapeutic challenge, with limited survival outcomes despite recent progress in systemic therapies. In this retrospective cohort study, we demonstrated that cytoreductive radical cystectomy combined with platinum-based chemotherapy was associated with improved cancer-specific survival compared to chemotherapy alone in carefully selected patients with mBC. These findings support the growing body of evidence suggesting a beneficial role for local tumor control in metastatic settings, consistent with strategies employed in metastatic renal and prostate cancers [12, 13, 17]. The oncological rationale for cytoreductive surgery in metastatic disease is multifaceted. First, resection of the primary tumor may reduce tumor-mediated immunosuppression, enhance systemic treatment efficacy, and eliminate potentially resistant clones. Second, controlling the local tumor burden may prevent severe complications such as bleeding, pain, or urinary obstruction, which can compromise performance status and delay or preclude systemic therapy. Third, our findings suggest an improvement in renal function parameters after surgery, which could contribute to greater tolerance and continuity of systemic treatment. It is important to note that in our study, cytoreductive cystectomy was performed following 4 cycles of Gem-Cis chemotherapy, not as an upfront procedure. Patients were selected for surgery only after demonstrating disease control (complete response, partial response, or stable disease) and maintaining adequate performance status, evaluated by a multidisciplinary team. This sequential approach mirrors the strategy employed in metastatic renal cell carcinoma, where systemic therapy precedes cytoreductive nephrectomy to identify chemotherapy-sensitive patients and exclude early progressors from major surgery [12, 16]. Importantly, to address the inherent selection bias of this retrospective design, multivariate Cox proportional hazards regression was adjusted for ECOG performance status, Charlson Comorbidity Index, ASA score, BMI, tumour stage, and metastatic burden. Cystectomy remained independently associated with improved survival after adjustment (HR = 0.68, 95% CI: 0.48–0.96, p = 0.03). Propensity score analysis incorporating the same covariates yielded consistent results, supporting the robustness of the observed effect beyond patient selection

alone. Potential selection bias, unmeasured confounders, and heterogeneity in systemic therapy regimens should nevertheless be acknowledged. In addition, the impact of newer immunotherapy agents was not evaluated in this cohort, although maintenance avelumab has now become a standard component of first-line treatment. Future research should focus on prospective trials evaluating the integration of local and systemic therapies, especially in the era of immune checkpoint inhibitors. Biomarker-driven patient selection, health-related quality of life (HRQoL) assessments, and comparisons with alternative local treatments such as stereotactic radiotherapy would provide further clarity Systemic therapy remains fundamental in metastatic bladder cancer management. While our study utilized the gemcitabine-cisplatin regimen, the therapeutic landscape has evolved considerably with the integration of immune checkpoint inhibitors. Maintenance avelumab following platinum-based chemotherapy has demonstrated substantial survival advantages compared to best supportive care (median OS 21.4 vs 14.3 months, p = 0.001) [5, 9]. Future research should explore the potential synergistic effects of cytoreductive surgery with these novel immunotherapeutic approaches. Local radiotherapy represents another emerging modality for primary tumor management in metastatic settings. A large-scale meta-analysis of approximately 5,000 metastatic cancer patients demonstrated significant survival advantages with radiotherapy directed at primary tumors (HR = 0.67, 95% CI: 0.52–0.85), with particular efficacy in patients with minimal metastatic burden. Comparative studies between surgical and radiotherapeutic approaches for local tumor control would provide valuable insights for clinical decision-making. Despite the limitations inherent to retrospective analyses, our findings contribute meaningfully to the evolving understanding of multimodal approaches in metastatic bladder cancer. The potential survival benefit associated with cytoreductive cystectomy, alongside an acceptable safety profile, suggests that surgical intervention should be considered within a comprehensive treatment strategy for selected patients. Future research directions should include prospective randomized trials specifically designed to evaluate the role of cytoreductive surgery in the era of immunotherapy, comprehensive quality of life assessments, and identification of biomarkers to optimize patient selection. Additionally, comparison of different local control strategies, including surgery and radiotherapy, would further refine clinical decision-making algorithms.

This study has several limitations inherent to its retrospective design. Most importantly, the two treatment groups are not directly comparable due to selection bias, as patients undergoing cytoreductive cystectomy were required to demonstrate non-progressive disease after initial chemotherapy and maintain adequate performance status. This introduces both selection bias and potential immortal time bias. Although multivariate Cox regression and propensity score adjustment were performed, residual confounding cannot be excluded. In particular, response to chemotherapy was not included as a covariate, as it represents the primary selection criterion for surgery, and thus remains an important unmeasured confounder.

Additionally, this single-center study spans a long period (2008–2022), during which systemic treatment strategies evolved, and the impact of modern immunotherapy was not assessed. Finally, quality of life outcomes were not systematically evaluated.

CONCLUSIONS

Our data support cytoreductive cystectomy combined with systemic chemotherapy as a feasible and potentially advantageous approach for selected patients with metastatic bladder cancer. This combined strategy significantly improves survival outcomes compared to systemic chemotherapy alone, highlighting the necessity of careful patient selection and integration into comprehensive multidisciplinary treatment protocols.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

FUNDING

This research received no external funding.

ETHICS APPROVAL STATEMENT

The study was approved by the Institutional Review Boards and the Local Ethics Committees (Local Ethics Committee agreement 198, Kyiv, 26.03.2022) and was conducted according to the Declaration of Helsinki and the Good Clinical Practice guidelines. The databases used in the study are the intellectual property of the National Cancer Institute of Ukraine.

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