ORIGINAL CONTRIBUTION

EXPERIMENTAL ONCOLOGY

https://doi.org/10.15407/exp-oncology.2024.04.345

B. HRECHKO *, O. VOYLENKO, M. PIKUL, Iu. VITRUK, O. STAKHOVSKY, O. KONONENKO, S. SEMKO, D. KOSHEL, A. TYMOSHENKO, O. BUYVOL, E. STAKHOVSKY

Department of Plastic and Reconstructive Oncourology, Nonprofit Organization "National Cancer Institute", Kyiv, Ukraine

* Correspondence: Email: bogdangrechko@gmail.com

CYSTECTOMY IN METASTATIC BLADDER CANCER: FEASIBILITY, SAFETY AND OUTCOMES

Background. Potential clinical efficacy of cystectomy in patients with metastatic bladder cancer (mBCa) remains poorly investigated. The clinical data suggest that there could be a benefit from the local treatment in selected patients with mBCa in terms of redeeming local symptoms, increasing quality of life (QoL), and decreasing the number of the potential adverse events of systemic therapy. **The aim** of our study was to test safety and efficacy of cystectomy in mBCa and its impact on patients' survival, QoL, and eligibility for systemic therapy. **Materials and Methods**. Retrospective cross-sectional analysis of 524 patients treated with cystectomy due to bladder cancer in the National Cancer Institute of Ukraine from 2008 to 2019 is presented. We selected a group of 21 (3.6%) patients with surgically resectable primary tumors and advanced metastatic disease prior to the surgery and proceeded for further analysis. Patients were analyzed in terms of pre- and postoperative performance status, metastatic burden, surgical complexity and complications (Clavien-Dindo grade), clinical benefits of systemic therapy, and cancer specific survival. **Results**. Six patients underwent preoperative systemic therapy with partial response (n = 4) and stable disease (n = 2) according to RECIST 1.1. There were no severe intraoperative complications, although 2 patients experienced Clavien Grade III events that needed surgical correction in the postoperative period. During the analysis, no 30-day mortality events were found, and 11 of 21 patients were alive 1 year after surgery. Most patients (n = 19) were eligible for standard first-line chemotherapy after surgery, with 13 proceeding to second-line chemotherapy due to further progression with no AE higher than grade II during systemic therapy. An increase in QoL was found out by comparing the questionnaire data before and 3 months after surgery. **Conclusion**. The benefits of cystectomy in mBCa setting are mainly hidden by QoL improvement and the decreasing number of the potential contraindications to the systemic therapy. Potential effects that reduce adverse events during chemotherapy should prompt to estimate oncological preferences of cystectomy in advanced bladder cancer.

Keywords: metastatic bladder cancer, chemotherapy, cystectomy.

The positive effects of cytoreductive cystectomy in metastatic bladder cancer (mBCa) patients remain unclear. The potential benefits are hidden behind theoretical bases of the elimination of the immunosuppressive effects on the primary tumor, the removal of the source of lethal clone reseeding, and

Citation: Hrechko B, Voylenko O, Pikul M, Vitruk U, Stakhovsky O, Kononenko O, Semko S, Koshel D, Tymoshenko A, Buyvol O,, Stakhovsky E. Cystectomy in metastatic bladder cancer: feasibility, safety and outcomes. *Exp Oncol.* 2024; 46(4): 345-350. https://doi.org/10.15407/exp-oncology.2024.04.345

the avoidance of local progression morbidity [1]. The local symptoms of advanced bladder cancer often promote life-threatening conditions, which limit candidacy for the systemic therapies and impact the survival. Even in cases of the metastatic disease, the primary tumor elimination may lead to the improvement in the quality of life (QoL), lower possibility of adverse events during systemic therapy, and incur significant costs.

Evidence from several studies on advanced bladder cancer local treatment suggests that there could be a benefit from combining it with chemotherapy [2, 3]. A cytoreductive surgery has already proved its efficacy in terms of patients with metastatic upper urinary tract cancer who responded to primary chemotherapy [4]. Nevertheless, an appropriate selection remains crucial and not every case might experience the advantages of such an approach.

Potential development of novel targeted agents and check-point inhibitors prompts to seek promising ways of impacting survival and improving QoL in patients with mBCa [5, 6]. The safety of cytoreductive surgery and its combination with systemic therapy in a selected group of patients are poorly described, and little is also known regarding QoL prior and after cystectomy [7—10]. Therefore, we endeavored to describe our experience with cytoreductive cystectomy in the setting of mBCa.

Materials and Methods

We have done a retrospective cross-sectional data analysis of 524 patients treated with cystectomy due to bladder cancer in the National Cancer Institute of Ukraine from 2008 to 2018. During the analysis, we selected a group of 21 (4%) patients with surgically resectable primary tumors in advanced metastatic disease prior to surgery and proceeded for further analysis (Table 1). Most of these patients underwent surgery due to the presence of significant local symptoms such as gross hematuria, bilateral hydronephrosis, pain, sepsis, and renal failure. These events impacted patients' QoL, incurred significant costs, and could result in death. All cases were discussed at a multidisciplinary board including a urologist, clinical oncologist, and radiologist with the recommendation to proceed to surgery. At the time of cystectomy, 6 patients were undergoing first-line platinum-based palliative chemotherapy while the other 15 patients were undergoing primary surgery due to local symptoms deterioration or the presence of life-threatening conditions. Complications within 90 days were assigned by the Clavien-Dindo grade. The identification of metastatic sites was done by CT-scan prior to surgery. QoL was assigned prior to surgery and 3 months after surgery according to the SF-36 questionnaire. The Institutional review board approval to perform this retrospective analysis was obtained.

Results

The median patient age was 60 years (interquartile range [IQR] 33—78 years). ECOG-status ranged from 0 to 1. Median number of metastatic lesions was 7 (interquartile range [IQR] 4—14). 6 patients (31%) received platinum-based chemotherapy prior to cystectomy according to standard protocols, among whom 4 (66%) obtained overall partial response and two (34%) stable disease (per RECIST 1.1). Rationale for cystectomy, systemic therapy regimen, treatment times, and follow-up data of patients are summarized in Table 2.

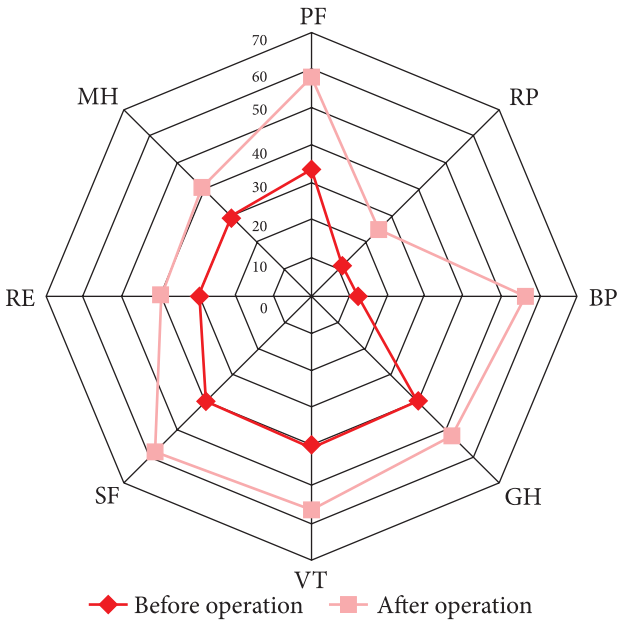
The median operative time was 230 minutes (IQR 150–315) with estimated blood loss 460 cc (IQR 200—980). Surgery was done in 13 cases of palliative (cytoreductive) setting and in 8 as a salvage option. In 17 cases (81%), the surgical procedure technically included the standard volume of the radical cystectomy with lymph node dissection, in the other 4 cases, due to lymph node invasion to the iliac vessels, lymph node removal was omitted. 16 of 20 patients underwent unilateral ureterocutaneostomy, 4 — Bricker diversion, 1 — ileal neobladder. The median length of stay was 10.5 days (ranged 5—13). 5 patients were transfused postoperatively. The positive surgical margin rate was 26%. 16 of 20 patients underwent extended lymphadenectomy with a median of 3 (IQR 1—5) positive lymph nodes out of 28 (IQR 11—32) removed. Intraoperative complications included rectal injury (n = 2) and external iliac vessel trauma (n = 1), with no severe intraoperative outcomes. There were two postoperative Clavien Grade III complications that needed surgical correction, while 4 patients experienced Grade I or II complications, who were managed conservatively. During the analysis, no 30-day mortality events were found and 11 of 21 patients were alive 1 year after surgery.

The main part of patients (n = 19) proceeded to systemic therapy after surgery. 17 patients met eligibility criteria and received 3—6 cycles of further gemcitabine-cisplatin (no dose reduction) regimen, which was switched to second-line chemotherapy in 11 cases and to immunotherapy in 2 cases. The systemic approach was well tolerated after surgery with no AE higher than grade II and did not include any events of kidney failure or injury. The change in the therapy lines was progression-dependent.

QoL improvement after cystectomy is shown in Figure. The decrease in local symptoms was a significant confounder of measured parameters change.

The achieved 2-year survival rate equaled 24%. The exact Fisher's tests showed better survival probability in the patients who underwent preoperative chemotherapy ($p = 0.0498$) and had less than 4 metastatic lesions ($p = 0.0412$).

Postsurgical complication probability did not depend on the metastatic burden, surgery duration, diversion type, and blood transfusion.



QoL (by SF-36 Questionnaire) prior to surgery and 3 months after surgery: PF — physical functioning; VT — life activity; RP — physical function-based role functioning; SF — social functioning; BP — pain intensity; RE — role functioning conditioned by emotional state; GH — general health; MH — mental health

Table 1. **Summary of the characteristics of patients**

Variable	Overall (n = 21)
Median age	60% (IQR 33—78)
Gender:	
Female	20
Male	1
Median GFR	55.9 mL/min/1.73 m^2
Median operative time	230 (IQR 150—315)
ASA	3.2 (1—4)
pT stage	
T1	3
T2	12
T3	6
Megaureter	85.7%
Diversion:	
Unilateral ureterocutaneostomy	16
Bricker	4
Ileal neobladder	1

Discussion

The advanced cancer treatment results remain unsuccessful across different types of solid tumors. Although new therapeutic agents are being investigated, the levels of objective response prompt to search for rationale in combining local treatment with systemic approach in mBCa. Surgery might have potential in a selected group of patients in terms of redeeming from severe local symptoms thus decreasing the level of possible AE following chemo- or immunotherapy. Another key point is a significant increase in QoL in such a patient due to the improvement in local symptoms and the reduction of the concomitant medication.

The surgical safety profile of cytoreductive cystectomy [1] remains controversial, although all complications are well tolerated by patients and do not affect the 30-day mortality rate. The cytoreductive effect may also be inducted by the extension of lymph node dissection but the benefit of surgery enlargement remains unclear. A diversion type after bladder removal should mainly rely on the principle «the easier the better», taking into account several confounders. The primary one is that the healthcare status of this group of patients may provoke severe complications in case of any bowel insufficiency or anastomosis leakage. The secondary one is that due to the low cancer-specific survival rate, there are no arguments in favor of proceeding to more complex procedures as the main part of patients cannot meet problems concerning ure-

teral stenosis. Nevertheless, a diversion type should be safe in terms of the acute upper urinary tract obstruction and kidney insufficiency.

Some observative articles [2—4] suggest the potential benefits of undergoing systemic therapy after local symptoms removal and reduced probability of the upper tract obstruction. The surgery also plays a cytoreductive role reducing the number of targets for systemic agents thus increasing its potential efficacy. There also exists a high possibility of the improvement in performance status, which also affects eligibility for chemotherapy. Nevertheless, we should always keep in mind that patients have an oncological benefit from surgery if they respond to preoperative chemotherapy.

The data obtained from this study prove that patients with metastatic urothelial carcinoma have better outcomes after cytoreductive surgery in case a tumor reacts to systemic agents. Systemic effects of pre-surgical chemotherapy do not have any influence on the surgical complication rate; in fact, it can reduce tumor size and make surgery less complex. The other benefit might be hidden by the fact that surgery does not promote fast progression when it is done under tumor suppression.

Another important fact is that during systemic treatment, local symptoms often induce adverse events, which may require hospitalization thus delaying systemic agent infusion [5, 7]. One of the main parameters that often limits chemotherapeutic

Table 2. **Diagnostic performance of methylated genes-candidates**

Setting of first-line systemic therapy (Gem – Cis)	Rationale for cystectomy	Time from diagnosis to cystectomy (mo)	Number of metastases	Number of metastatic sites[d]	Follow-up	Status at last follow up
Pre/post-surgical	Cytoreduction [a]	3	2	2	25	Alive, ECOG - 1
Pre/post-surgical	Low QoL [b], cytoreduction	2	2	1	36	Alive, ECOG - 2
Pre/post-surgical	Salvage [c]	2	4	2	14	Dead of disease
Pre/post-surgical	Low QoL , cytoreduction	4	3	1	26	Alive, ECOG - 1
Pre/post-surgical	Low QoL , cytoreduction	3	4	2	13	Alive, ECOG - 1
Pre/post-surgical	Low QoL , cytoreduction	2	2	1	26	Dead of disease
Pre/post-surgical	Cytoreduction	6	5	2	39	Dead of heart failure
Post-surgical	Low QoL, cytoreduction	3	3	2	13	Dead of disease
Post-surgical	Salvage	2	2	1	7	Dead of disease
Post-surgical	Salvage	9	5	3	14	Dead of disease
Post-surgical	Salvage	2	4	3	10	Dead of heart failure
Post-surgical	Low QoL, cytoreduction	5	2	2	6	Dead of disease
Post-surgical	Salvage	7	4	3	8	Dead of disease
Post-surgical	Salvage	2	9	2	27	Alive, ECOG -2
Post-surgical	Low QoL, cytoreduction	1	5	3	10	Dead of disease
Post-surgical	Low QoL, cytoreduction	3	6	2	5	Dead of disease
Post-surgical	Low QoL, cytoreduction	1	3	3	9	Alive, ECOG - 2
Post-surgical	Salvage	2	5	1	25	Dead of disease
No systemic therapy	Salvage	1	2	3	5	Dead of disease
Post-surgical	Low QoL, cytoreduction	2	4	2	7	Dead of disease
No systemic therapy	Salvage	1	2	3	4	Dead of disease

Notes: [a] — elimination of immunosuppressive effects on the primary tumor and removal of the source of lethal clone reseeding; [b] — obstructive LUTS and retention, suprapubic tube, bilateral nephrostomy, pain syndrome, and other conditions requiring frequent hospitalization; [c] — elimination of life-threatening conditions (mainly progressive anemia due to hematuria); [d] — by site one organ system is mentioned (lymph nodes are measured as one system).

treatment in mBCa remains the kidney function, which is often affected during disease. An external diversion often resolves the problems of the upper tract obstruction and reduces risk of kidney block between the planned investigations. We should note that a surgical profile must be good enough, so that the post-surgical complications would not limit further treatment. Patient selection remains crucial and probably plays one of the main roles in the potential efficacy of treatment and outcomes.

QoL is another promising value that can be changed by surgery. The decrease in symptoms leads to patients' perception of the treatment process and inspires their social activity. The psychological understanding of the combined approach is also derived to change personal attitudes toward cancer eradication. QoL remains one of the key points that prompt patients to proceed to cystectomy.

To sum up, the role of surgery in patients with advanced solid tumors remains controversial. The current approaches suggest that there could be a benefit in selected cases of metastatic bladder cancer. The surgical safety profile of cytoreductive cystectomy does not radically differ from cases of the locally advanced disease. The development of novel systemic agents might influence the survival of such patients and require a solution in terms of the QoL increase. The potential effects that reduce adverse events during chemotherapy should prompt an estimate of the oncological preferences of cystectomy in advanced bladder cancer.

Conflict of interests

On behalf of all authors, the corresponding author states that there is no conflict of interest.

REFERENCES

1. Reichard CA, Gregg JR, Achim MF, et al. Radical prostatectomy in metastatic castration-resistant prostate cancer: feasibility, safety, and quality of life outcomes. *Eur Urol*. 2018;74(2):140-143. https://doi.org/1016/j.eururo.2018.03.031
2. Galsky MD, Domingo-Domenech J, Sfakianos JP, Ferket BS. Definitive Management of primary bladder tumors in the context of metastatic disease: who, how, when, and why? *J Clin Oncol*. 2016;34(29):3495-3498. https://doi.org/10.1200/JCO.2016.68.3714
3. Seisen T, Sun M, Leow JJ, et al. Efficacy of high-intensity local treatment for metastatic urothelial carcinoma of the bladder: a propensity score-weighted analysis from the national cancer data base. *J Clin Oncol*. 2016;34(29):3529-3536. https://doi.org/10.1200/JCO.2016.66.7352
4. Seisen T, Jindal T, Karabon P, et al. Efficacy of systemic chemotherapy plus radical nephroureterectomy for metastatic upper tract urothelial carcinoma. *Eur Urol*. 2017;71(5):714-718. https://doi.org/10.1016/j.eururo.2016.11.012
5. Shariat SF, Chade DC, Karakiewicz PI, et al. Combination of multiple molecular markers can improve prognostication in patients with locally advanced and lymph node positive bladder cancer. *J Urol*. 2010;183:68-75. https://doi.org/10.1016/j.juro.2009.08.115
6. Massard C, Gordon MS, Sharma S, et al. Safety and efficacy of durvalumab (MEDI4736), an anti-programmed cell death ligand-1 immune checkpoint inhibitor, in patients with advanced urothelial bladder cancer. *J Clin Oncol*. 2016;34:3119-3125. https://doi.org/10.1016/j.juro.2017.11.024
7. Urakami S, Yuasa T, Yamamoto S, et al. Clinical response to induction chemotherapy predicts improved survival outcome in urothelial carcinoma with clinical lymph nodal metastasis treated by consolidative surgery. *Int J Clin Oncol*. 2015;20:1171-1178. https://doi.org/10.1007/s10147-015-0839-y
8. Li R, Metcalfe M, Kukreja J, Navai N. Role of radical cystectomy in non-organ confined bladder cancer: a systematic review. *Bladder Cancer*. 2018;4(1):31-40. https://doi.org/10.3233/BLC-170130
9. Otto T, Krege S, Suhr J, Rübben H. Impact of surgical resection of bladder cancer metastases refractory to systemic therapy on performance score: a phase II trial. *Urology*. 2001;57:55-59 https://doi.org/10.1016/s0090-4295(00)00867-0
10. Apolo AB, Ostrovnaya I, Halabi S, et al. Prognostic model for predicting survival of patients with metastatic urothelial cancer treated with cisplatin-based chemotherapy. *J Natl Cancer Inst*. 2013;105:499-503. https://doi.org/10.1093/jnci/djt015

Submitted: October 04, 2024

Б. Гречко, О. Войленко, М. Пікуль, Ю. Вітрук, О. Стаховський,
О. Кононенко, С. Семко, Д. Кошель, А. Тимошенко, О. Буйвол, Е. Стаховський

Державне некомерційне підприємство "Національний Інститут раку",
науково-дослідне відділення пластичної та реконструктивної онкоурології, Київ, Україна

ЦИСТЕКТОМІЯ ПРИ МЕТАСТАТИЧНОМУ РАКУ СЕЧОВОГО МІХУРА: МОЖЛИВОСТІ ВИКОНАННЯ, БЕЗПЕЧНІСТЬ ТА РЕЗУЛЬТАТИВНІСТЬ

Ефективність цистектомії у пацієнтів з метастатичним раком сечового міхура залишається недостатньо дослідженою. Клінічні дані говорять про те, що хірургічне лікування пацієнтів із метастатичним раком сечового міхура ефективне для покращення уродинаміки за ВСШ, купування симптомів нижніх сечових шляхів, зменшення больового синдрому, підвищення якості життя та зменшення кількості побічних дій системної терапії. Метою нашого дослідження було перевірити ефективність цистектомії в пацієнтів з метастатичним раком сечового міхура, її вплив на якість життя та придатність до системної терапії. Ми проаналізували 21 пацієнта, яким було проведено цистектомію в умовах Національного Інституту раку в період з 2008 по 2019 рік. Шість пацієнтів пройшли передопераційну системну терапію з частковою відповіддю (n = 4) та стабілізацією захворювання (n = 2) згідно з RECIST 1.1. Важких інтраопераційних ускладнень не було, хоч у 2 пацієнтів спостерігалися ускладнення Clavien - Dindo Grade III ступеню, які потребували хірургічної корекції в післяопераційному періоді. Основна частина пацієнтів (n = 21) отримали можливість проведення хіміотерапії першої лінії після операції, а 13 з них перейшли до другої лінії через подальше прогресування без ускладнень. Підвищення якості життя встановлено шляхом порівняння даних за допомогою опитувальника SF-36 до хірургічного втручання та через 3 місяці після операції. Переваги цистектомії при метастатичному раку сечового міхура суперечливі: від покращення якості життя до зменшення протипоказань щодо системної терапії. Потенційні ефекти, що зменшують несприятливі явища під час хіміотерапії, мають підвищити оцінку онкологічних переваг цистектомії при запущених формах раку сечового міхура.

Ключові слова: метастатичний рак сечового міхура, цистектомія, хіміотерапія.