



Research Article

Journal of MAR Oncology (Volume 4 Issue 3)

Cystectomy in Metastatic Bladder Cancer: Feasibility, Safety and Outcomes

I. Vitruk¹, O. Voylenko², O. Stakhovsky¹, M. Pikul¹, O. Kononenko¹, S. Semko¹,
B. Grechko¹, E. Stakhovsky¹

1. Department of Plastic and Reconstructive oncurology, National Cancer Institute, Kyiv, Ukraine

Corresponding Author: B. Grechko, Department of Plastic and Reconstructive oncurology, National Cancer Institute, Kyiv, Ukraine.

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Received Date: June 29, 2022

Published Date: August 01, 2022

Abstract

Potential clinical efficacy of cystectomy in patients with metastatic bladder cancer (mBCa) remains poorly investigated. Clinical data suggests that there could be a benefit from local treatment in selected patients with mBCa in terms of redeeming local symptoms, increasing life quality and decreasing number of potential adverse events of systemic therapy.

The aim of our study was to test safety and efficacy of cystectomy in mBCa and its impact and patients' survival, life quality and eligibility for systemic therapy. We analyzed 21 patients who underwent cystectomy in the setting of mBCa from 2008 to 2018. 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 postoperative period. During analysis no 30-d mortality events were found and 11 of 21 patients were alive at 1 yr after surgery. Main part of patients (n = 19) were eligible for standard first-line chemotherapy after surgery with 13 proceeding to second-line due to further progression with no AE higher than grade II during systemic therapy. An increase in life quality was found out by comparing pre-surgical and 3-months after surgery questionnaire data.

The benefits of cystectomy in mBCa setting are mainly hidden by life quality improvement and decreasing number of potential contraindications to systemic therapy. Potential effects that reduce adverse event during chemotherapy should prompt to estimate oncological preferences of cystectomy in advanced bladder cancer.

Introduction

Positive effects of cytoreductive cystectomy in metastatic bladder cancer (mBCa) patients remain unclear. Potential benefits are hidden behind theoretical bases of elimination of the immunosuppressive effects on the primary tumor, removal of a source of lethal clone reseeding and avoidance of local progression morbidity [1]. Local symptoms of advanced bladder cancer often promote life-threatening conditions that limit candidacy for systemic therapies and impact survival. Even in cases of metastatic disease, primary tumor elimination may lead to improvement in life quality, lower possibility of adverse events during systemic therapy and incur significant costs.

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

Potential development of novel targeted agents and check-point inhibitors prompts to seek promising ways of impacting survival and improving quality of life in patients with mBCa [5-6]. Safety of cytoreductive surgery and its combination with systemic therapy in selected group of patients is poorly described and little is also known regarding quality of life prior and after cystectomy [7-10]. Therefore, we endeavored to describe our center's 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 National Cancer institute of Ukraine from 2008 to 2018. During analysis we have selected a group of 21 (4%) patients with surgically resectable primary tumor in advanced metastatic disease prior to surgery and proceeded for further analysis. Main part of patients underwent surgery due to presence of significant local symptoms: gross hematuria, bilateral hydronephrosis, pain, sepsis and renal failure. This event impacted patients' quality of life, incurred significant costs and could result in death. All cases were discussed on multidisciplinary board including urologist, clinical oncologist and radiologist with recommendation to proceed to surgery. At the time of cystectomy 6 patients were undergoing first-line platinum based palliative chemotherapy with other 15 undergoing primary surgery due to local symptoms deterioration or presence of life-threatening conditions. Complication within 90 d were assigned Clavien-Dindo grade. Identification of metastatic sites was done by the means of CT-scan prior to surgery. Life quality was assigned prior to surgery and 3 months after surgery according to SF-36 questionnaire. Institutional review board approval to perform this retrospective analysis was obtained.

Results

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). Six patients (31%) received platinum-based chemotherapy prior to cystectomy according to standard protocols, among which four (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 is summarized in table 1.

Median operative time was 230 minutes (IQR 150 – 315) with estimated blood loss - 460 cc (IQR 200 – 980). Surgery was done in 13 cases in terms of palliative (cytoreductive) setting and in 8 as a salvage option. In seventeen cases (81%) the surgical procedure technically included standard volume of radical cystectomy with lymph node dissection, in other four cases due to lymph node invasion to iliac vessels, lymph node removal was omitted. Sixteen of 20 patients underwent unilateral ureterocutaneostomy, 4–Bricker diversion, 1 – ileal neobladder. Median length of stay was 10,5 days (ranged 5 – 13). Five patients were transfused postoperatively. Positive surgical margin rate was 26 %. Sixteen of 20 patients underwent extended lymphadenectomy with median of three (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 four patients experienced Grade I or II complications that were managed conservatively. During analysis no 30-d mortality events were found and 11 of 21 patients were alive at 1 yr after surgery.

Main part of patients (n = 19) proceeded to systemic therapy after surgery. Seventeen 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. Systemic approach was well tolerated after surgery with no AE higher than grade II and didn't include any events of kidney failure or injury. Change in therapy lines was progression dependent. Life quality improvement after cystectomy is shown in the fig 1. The decrease of local symptoms was a significant confounder of measured parameters change.

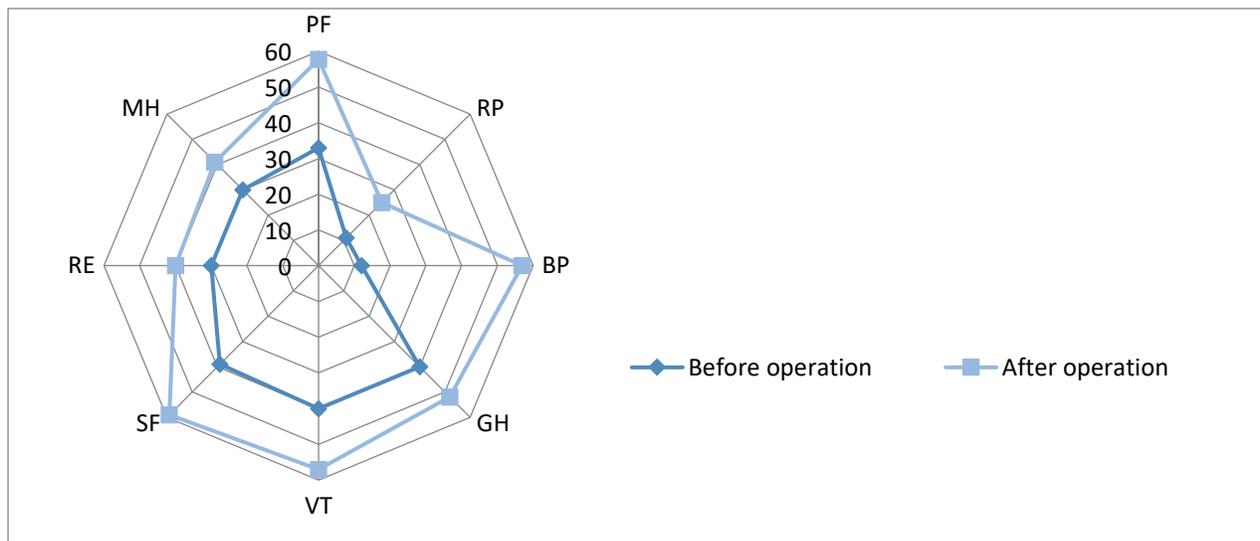


Fig 1. Life quality (SF-36 Questionnaire) prior to surgery and 3 months after surgery

Achieved 2-year survival rate equaled 24%. Exact Fischer's test have shown better survival probability in patients that underwent preoperative chemotherapy (P =0,0498) and had less than 4 metastatic lesions (P = 0,0412). Postsurgical complication probability didn't depend from metastatic burden, surgery duration, diversion type or blood transfusion.

Pt	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
1	Pre/post-surgical	Cytoreduction ^a	3	2	2	25	Alive, ECOG - 1
2	Pre/post-surgical	Low life quality ^b , cytoreduction ^a	2	2	1	36	Alive, ECOG - 2
3	Pre/post-surgical	Salvage ^c	2	4	2	14	Dead of disease
4	Pre/post-surgical	Low life quality ^b , cytoreduction ^a	4	3	1	26	Alive, ECOG - 1
5	Pre/post-surgical	Low life quality ^b , cytoreduction ^a	3	4	2	13	Alive, ECOG - 1
6	Pre/post-surgical	Low life quality ^b , cytoreduction ^a	2	2	1	26	Dead of disease
7	Pre/post-surgical	cytoreduction ^a	6	5	2	39	Dead of heart failure
8	Post-surgical	Low life quality ^b , cytoreduction ^a	3	3	2	13	Dead of disease
9	Post-surgical	Salvage ^c	2	2	1	7	Dead of disease
10	Post-surgical	Salvage ^c	9	5	3	14	Dead of disease
11	Post-surgical	Salvage ^c	2	4	3	10	Dead of heart failure
12	Post-surgical	Low life quality ^b , cytoreduction ^a	5	2	2	6	Dead of disease
13	Post-surgical	Salvage ^c	7	4	3	8	Dead of disease
14	Post-surgical	Salvage ^c	2	9	2	27	Alive, ECOG - 2
15	Post-surgical	Low life quality ^b , cytoreduction ^a	1	5	3	10	Dead of disease
16	Post-surgical	Low life quality ^b , cytoreduction ^a	3	6	2	5	Dead of disease
17	Post-surgical	Low life quality ^b , cytoreduction ^a	1	3	3	9	Alive, ECOG - 2
18	Post-surgical	Salvage ^c	2	5	1	25	Dead of disease
19	No Systemic therapy	Salvage ^c	1	2	3	5	Dead of disease
20	Post-surgical	Low life quality ^b , cytoreduction ^a	2	4	2	7	Dead of disease
21	No Systemic therapy	Salvage ^c	1	2	3	4	Dead of disease

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

Table 3 – Summary of systemic therapies, rationale for cystectomy, treatment times and follow-up

Discussion

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 seek for rationale in combining local treatment with systemic approach in mBCa. Surgery might have potential in selected group of patients in terms of redeeming from severe local symptoms thus decreasing the level of possible AE following chemo or immunotherapy. The other key point is a significant increase in quality of life in this patient due to improvement in local symptoms and reduction of concomitant medication quantity.

Surgical safety profile of cytoreductive cystectomy remains controversial, although all complications are well tolerated by patients and do not affect 30d mortality rate. Cytoreductive affect may also be inducted by extension of lymph node dissection, but the benefit of surgery enlargement remains unclear. Diversion type after bladder removal should mainly rely on the principle «the easier –the better», taking

to account several confounders. The primary one is that healthcare status of this group of patients may provoke severe complications in case of any bowel insufficiency or anastomosis leakage. The secondary is that due to low cancer specific survival rate there are no arguments in favor of proceeding to more complex procedure as the main part of patients won't meet with problems concerning ureteral stenosis. Nevertheless, diversion type should be safe in terms of acute upper urinary tract obstruction and kidney insufficiency.

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

The data received during the study proves the information that patients with metastatic urothelial carcinoma have better outcomes after cytoreductive surgery in case tumor reacts to systemic agents. Systemic effects of pre-surgical chemotherapy do not have any influence on 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 influence of tumor suppression.

The other important fact that during systemic treatment local symptoms often induce adverse events occurrence, which may require hospitalization thus delaying systemic agent infusion. One of the main parameters that often limits chemotherapeutic treatment in mBCa remains kidney function which is often affected during disease. External diversion often resolves problem of upper tract obstruction and reduces risk of kidney block between planned investigations. Although we should note that surgical profile must be good enough, so that post-surgical complications would not limit further treatment. Patient selection remains crucial and probably plays one of the main roles in potential efficacy of treatment and outcomes.

Life quality is the other promising value that can be changed by the surgery. Symptoms decrease leads to patients' perception of treatment process and inspires for social activity. Psychological understanding of combined approach is also derived to change personal attitude towards cancer eradication. Life quality remains one of the key points that prompt patients to proceed to cystectomy.

Conclusion

The role of surgery in patients with advanced solid tumors remains controversial. Approaches existing today suggest that there could be a benefit in selected cases with metastatic bladder cancer. Surgical safety profile of cytoreductive cystectomy does not radically differ from cases of locally advanced disease. Development of novel systemic agents might influence survival of these patients and require solution in terms of life quality increase. Potential effects that reduce adverse event during chemotherapy should prompt to estimate oncological preferences of cystectomy in advanced bladder cancer.

References

1. Radical Prostatectomy in Metastatic Castration-resistant Prostate Cancer: Feasibility, Safety, and Quality of Life Outcomes Chad A. Reichard a , Justin R. Gregg a , Mary F. Achim a , Ana M. Aparicio b , Curtis A. Pettaway a , Louis L. Pisters a , John F. Ward a , John W. Davis a , Brian F. Chapin a. Eur Urol-7139
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;34:3495–8.
3. Efficacy of High-Intensity Local Treatment for Metastatic Urothelial Carcinoma of the Bladder: A Propensity Score-Weighted Analysis From the National Cancer Data Base Thomas Seisen, Maxine Sun, Jeffrey J. Leow, Mark A. Preston, Alexander P. Cole, Francisco Gelpi-Hammerschmidt, Nawar Hanna, Christian P. Meyer, Adam S. Kibel, Stuart R. Lipsitz, Paul L. Nguyen, Joaquim Bellmunt, Toni K. Choueiri, and Quoc-Dien Trinh. J Clin Oncol 34. © 2016
4. Efficacy of Systemic Chemotherapy Plus Radical Nephroureterectomy for Metastatic Upper Tract Urothelial Carcinoma Thomas Seisen a , Tarun Jindal a , Patrick Karabon a , Akshay Sood a , Joaquim Bellmunt b , Morgan Roupert c , Jeffrey J. Leow d , Malte W. Vetterlein a , Maxine Sun d , Shaheen Alanee a , Toni K. Choueiri b , Quoc-Dien Trinh d , Mani Menon a , Firas Abdollah a. J Clin Oncol 34. © 2016
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.
6. Massard C, Gordon MS, Sharma S, et al. Safety and efficacy of durvalumab (MEDI4736), an anti-programmed cell death ligand1 immune checkpoint inhibitor, in patients with advanced urothelial bladder cancer. J Clin Oncol 2016;34:3119–25.

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;20:1171–8.
8. Role of Radical Cystectomy in Non-Organ Confined Bladder Cancer: A Systematic Review Roger Li, Michael Metcalfe, Janet Kukreja and Neema Navai* Department of Urology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA/ *Bladder Cancer* 4 (2018) 31–40
9. Otto T, Krege S, Suhr J, et al. Impact of surgical resection of bladder cancer metastases refractory to systemic therapy on performance score: a phase II trial. *Urology* 2001;57:55–9.
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.