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BLADDER SPARING SURGERY IN HIGH-GRADE BLADDER CANCER

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The gold standard for managing muscle-invasive bladder cancer is radical cystectomy (RCE). The RCE is a treatment, which carries high burden of perioperative morbidity and mortality. As biomolecular markers make muscle-invasive high-grade bladder cancer (HGBC) an entity different from non-invasive papillary disease, we tested a hypothesis that alternative bladder preserving surgery (BPS) approaches, such as partial cystectomy and transurethral resection of the bladder would not compromise the oncological results of treating HGBC in selected patients. *Aim:* To study the cancer specific survival of HGBC patients depending on the mode of surgical treatment — RCE, partial en-block cystectomy, and transurethral resection of the bladder in the practice of the Departments of Urology and Oncology of Bogomolets National Medical University, and to assess the prevalence of bladder sparing surgical management of HGBC in local practice as a part of trimodal treatment approach to bladder preservation. *Materials and Methods*: Retrospectively we studied the medical records of 3597 urothelial bladder cancer patients, of whom 346 (10%) had high-grade disease and who underwent surgical treatment in 2004–2017. All patients were studied with contact computed tomography of the chest, abdomen, pelvis, and biopsy of the tumor. Based on the results of the diagnostic workup the choice of surgical treatment between RCE, partial cystectomy and transurethral resection was made considering the size of the tumor, location of the tumor in the bladder in relation to the bladder neck, and technical and oncological feasibility of performing the bladder sparing surgery. Kaplan — Meier survival curves were built to compare the results of survival per cancer stage and type of surgical treatment. Survival data of the patients were collected from the cancer registry maintained at the Kyiv Municipal Clinical Oncological Center. Results of data analysis were controlled for confounding parameters, such as adjuvant treatment: perioperative radiotherapy, and chemotherapy. *Results*: Median follow-up was 93 months (1–226 months). Males were 276 (80%). Average age at diagnosis was 62 ± 4.5 years. By the time of the study 61% of patients have died due to the progression of the disease. All patients with stage I disease (7% or 24 patients) were managed with bladder-sparing surgery. In muscle-invasive disease (309 patients), the RCE was performed in 109 (35.3%) patients, partial cystectomy was performed in 79 (25.6%) patients, and transurethral resection — in 121 (39.1%) patients. The overall 5-year survival of HGBC patients after radical surgical treatment (RCE/BPS) for stage I patients was 0%/83%, for stage II — 43%/58%, for stage III — 37%/42%, and for stage IV — 10%/40%. A total of 44 patients (12.7% of all treated, and 19.6% of treated with bladder sparing) received postoperative radiotherapy after bladder-sparing surgery. A total of 14 patients (4% of all treated) received postoperative chemotherapy. *Conclusion*: Bladder sparing surgery (partial en-block cystectomy, and transurethral resection of the bladder) in selected patients is not inferior to RCE in terms of cancer-specific survival when treating patients with HGBC of all stages. The bladder sparing surgery was performed in 64.7% of patients with high grade bladder cancer. Utilization of adjuvant treatment is low, 12.7% for postoperative radiotherapy, and 4% for perioperative chemotherapy

Key Words: **high-grade bladder cancer, bladder sparing surgery, survival, adjuvant treatment.**

The gold standard for managing muscle-invasive bladder cancer is radical cystectomy (RCE) [1–7]. RCE is a treatment, which carries high burden of perioperative morbidity and mortality [5, 7–9], which prompts the search for alternative treatment approaches, including bladder sparing, which would not compromise the oncological results of treatment.

Trimodal bladder sparing approach emerged as an alternative for treating muscle-invasive bladder cancer. It includes transurethral resection of all visible bladder tumor and postoperative chemo-radiotherapy [9–12]. The reported success rates of this trimodality treatment is compared or even higher than that of RCE, which makes it a viable alternative [9–24]. Nevertheless, mentioned trimodality approach possesses one significant disadvantage, namely, high local recurrence rate, which is estimated in the range of 30–70% of cancer persistence during repeated TURB [7]. The incomplete TURB during the initial surgery could not be considered a contributor to success of bladder sparing tri-modal treatment approach. Partial cystectomy could be considered as an option to minimize abovementioned downsides of the TURB. Thus research and development of treatment schedules and regimens, including optimal surgical bladder sparing modality which would bear lower recurrence rate and acceptable oncological outcomes are much needed [25].

Purpose: To study the cancer specific survival of HGBC patients depending on the type of surgery — RCE, partial en-block cystectomy (PCE), and transurethral resection of the bladder (TURB) in the practice of the Departments of Urology and Oncology of Bogomolets National Medical University, and to assess the prevalence of bladder sparing surgical management of high-grade bladder cancer (HGBC) in local practice as a part of trimodal treatment approach to bladder preservation.

MATERIALS AND METHODS

Retrospectively we studied the medical records of 3597 urothelial bladder cancer patients, of whom 346 (10%) had urothelial high-grade disease and who

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Abbreviations used: BPS – bladder preserving surgery; CT – computed tomography; HGBC – high-grade bladder cancer; PCE – partial en-block cystectomy; RCE – radical cystectomy; TURB – transurethral resection of the bladder.

underwent surgical treatment in 2004–2017 with adjuvant treatment as was recommended by multidisciplinary oncological board. All patients were studied with contact CT of the chest, abdomen, pelvis, and biopsy of the tumor. The stage of the bladder cancer was established based on American Joint Committee on Cancer, Urinary Bladder TNM Classification (7th ed., 2010) [26].

Based on the results of the diagnostic workup the choice of the surgical treatment between RCE, PCE and TURB was made considering the size of the tumor, location of the tumor in the bladder in relation to the bladder neck, status of the regional and distant lymph nodes as judged by preoperative CT scan, and technical and oncological feasibility of performing the bladder sparing surgery. Indication for the organ-sparing surgery in HGBC patients was solitary clearly defined tumor away from the bladder neck amenable for resection with sufficient margin of healthy urothelium without compromising continence and bladder capacity [3, 4]. Invasion of the ureteric orifice with resulting ureterohydronephrosis in this setting was considered an indication for the PCE with re-implantation of the ureter. The choice between TURB and PCE was based on size and depth of the tumor, with bulkier tumor and/or tumor invading the ureteric orifice being managed by PCE. The regional lymph node dissection was performed along with PCE, and if preoperative CT scan was suspicious of regional lymph nodes metastatic involvement, no TURB was performed. The indication for the RCE was total, subtotal of multifocal tumorous lesion of the bladder.

Patients who underwent only the tumor biopsy and were unfit for definitive treatment due to advanced tumor stage or poor health status, and were subjected to the palliative symptomatic treatment, were excluded from the analysis in our work.

Kaplan — Meier survival curves were built to compare the survival per cancer stage and type of surgical treatment. Survival data were collected from the cancer registry maintained at the Kyiv Municipal Clinical Oncological Center. Statistical workup included log-rank, Wilcoxon and Tarone — Ware statistics, that were applied to test the equality of survival distribution functions with the level of significance equaling 0.05.

Results of data analysis were controlled for confounding parameters, such as adjuvant treatment: perioperative radiotherapy and chemotherapy.

All patients prior to this study had signed the informed consent on processing their data. The study protocol had been endorsed by the Ethics committee of the Bogomolets National Medical University.

RESULTS

Median follow-up in our study was 93 months (1–226 months). During the study period 346 patients, or 10% of all bladder cancer patients submitted to the surgical treatment were graded as having HGBC (G3–G4). Males were 276 patients (80%), median age at the diagnosis was 62.0 ± 4.5 years. The difference in age and gender distribution between patients in groups of surgical treatment in each stage of bladder cancer was not statistically significant. The distribution of HGBC patients per stage, surgery performed, and survivorship status (survivors, %) by the time of our study presented in Table 1. By the time of our study 62.1% of operated patients died due to progression of the disease.

As we can see from the Table 1, non-muscle-invasive disease (stage I) was diagnosed in 7% of HGBC patients. Remaining 322 out of 346 HGBC patients (93%) had muscle-invasive disease: stage II in 151 (44%) patients, stage III in 108 (31%), and 63 (18%) patients had stage IV disease. This latter group of HGBC patients included pT4 in 32 (9%) patients, N1–3 in 28 (8%), and M1 in 5 (1.4%).

All patients with stage I disease were managed with bladder-sparing surgery. In muscle-invasive disease (total of 309 patients), the RCE was performed in 109 (35.3%) patients, PCE was performed in 79 (25.6%) patients, and transurethral resection — in 121 (39.1%) patients.

A total of 44 patients (12.7% of all treated, or 19.6% of treated with bladder sparing) received postoperative radiotherapy after bladder-sparing surgery. Distribution of these patients per cancer stage I, II, IIIA and IIIB–IV was 2, 18, 18 and 6, respectively. Survivors among patients with adjuvant radiotherapy after bladder-sparing surgery was 9 (out of 44) with median time of survival 69 months. Cancer specific survival among remaining part of patients receiving palliative radiotherapy after bladder-sparing surgery was 17 months (range: 1–87 months).

A total of 14 patients (4% of all treated with muscle-invasive bladder cancer) received postoperative chemotherapy. Distribution of these patients per cancer stage II, IIIA and IIIB–IV was 6, 6 and 2, respectively. There are 4 survivors after adjuvant chemotherapy with median time of 89 months (range: 47–135 months), two of whom were treated with RCE, and two — with bladder sparing approach. The cancer specific survival of other 10 patients with palliative adjuvant chemotherapy was 7.9 months (range: 2.4–20.8 months), among whom 2 were treated with RCE, and 8 others with bladder sparing approach.

Results of the cancer specific survival among patients with HGBC stage I are presented in Table 2, survival Kaplan — Meier curves presented in Fig. 1.

Test of hypothesis about equality of two survival functions (after TURB and PCE) was performed with three statistical criteria at the significance level equaling 0.05. In all results there were no statistical significant differences in survival as observed *p*-value was

Table 1. Distribution of HGBC patients per stage, surgery, and survivorship status by the time of the study

Surgery/survivors	Stage I, N (%)	Stage II, N (%)	Stage III, N (%)	Stage IV, N (%)	**Total**
TURB	18 (61)	62 (53)	36 (22)	23 (21)	**139**
PCE	6 (67)	41 (51)	33 (37)	5 (21)	**85**
RCE	–	46 (41)	33 (39)	30 (13)	**109**
Biopsy of the bladder	–	2 (0)	6 (0)	5 (0)	**13**
Total	**24**	**151**	**108**	**63**	**346**

> 0.05. As it could seem that the survival curves on the Fig. 1 differ from one another, the small amount of patients in the analyzed group (only 24 cases) made the confidence intervals for the survival curves too wide.

Results of the cancer specific survival among patients with stage II HGBC are presented in Table 3, survival Kaplan — Meier curves presented in Fig. 2.

Test of hypothesis about equality of three survival functions in patients with stage II HGBC (after TURB, PCE and RCE) was performed with three statistical criteria at the significance level equaling 0.05. In all results there were no statistical significant differences in survival as observed *p*-value was > 0.05.

Results of the cancer specific survival among patients with stage III HGBC are presented in Table 4, survival Kaplan — Meier curves presented in Fig. 3.

Test of hypothesis about equality of three survival functions in patients with stage III HGBC (after TURB, PCE, and RCE) was performed with three statistical criteria at the significance level equaling 0.05. In all results there were no statistical significant differences in survival, as observed *p*-value was > 0.05.

Results of the cancer specific survival among patients with stage IV HGBC are presented in Table 5, survival Kaplan — Meier curves presented in Fig. 4.

Test of hypothesis about equality of three survival functions (after TURB, PCE, and RCE) in patients with stage IV HGBC was performed with three statistical criteria at the significance level equaling 0.05. In all results there were no statistical significant differences in survival, as observed *p*-value was > 0.05. It could seem that the curve of the PCE is drawn higher than curves of TURB and RCE, but statistically this difference is not proven.

Based on Kaplan — Meier survival curves we calculated overall 5-year survival of surgically treated HGBC patients depending on cancer stage.

Overall survival at 5-years interval after radical surgical treatment (RCE/BPS) for stage I patients was 0/83%, for stage II — 43%/58%, for stage III — 37%/42%, and for stage IV — 10%/40%. Table 6 presents the 5-year overall survival of HGBC patients depending on cancer stage and type of surgery.

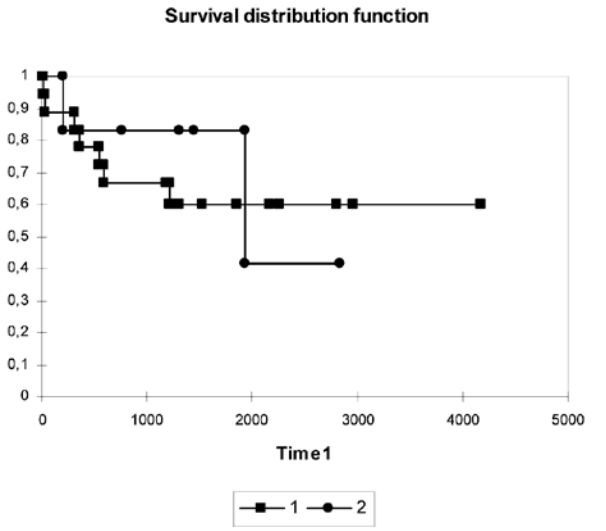

Fig. 1. Kaplan — Meier survival curves for stage I HGBC patients. 1 — TURB, 2 — PCE

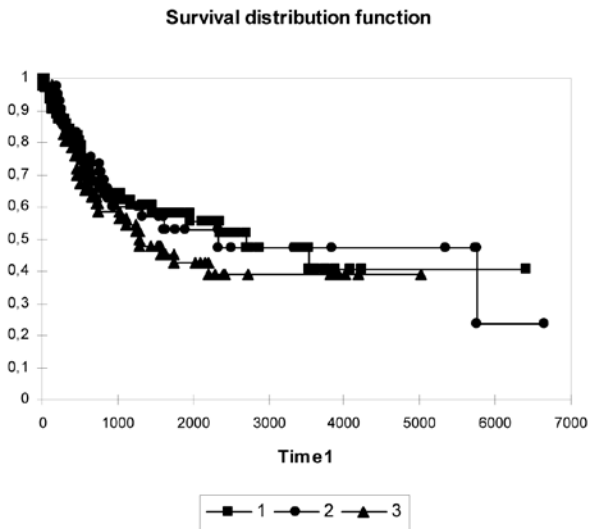

Fig. 2. Kaplan — Meier survival curves for stage II HGBC patients. 1 — TURB, 2 — partial cystectomy, 3 — RC

DISCUSSION

Muscle-invasive bladder cancer in a lethal progressive disease with poor survival prognosis. The gold standard for managing muscle-invasive bladder cancer is RCE [1, 3–5, 7]. Diagnostic tools for risk stratification,

Table 2. Stage I HGBC patients: summary of statistics (events) and Test of equality of the survival distribution functions

Surgery type	Total patients observed	Total patients died	Total number of survivors	Time steps in Kaplan – Meier function
TURB	18	7	11	18
PCE	6	2	4	6
Test of equality of the survival distribution functions				
Statistic	Observed value	Critical value	*p*-value	Alpha
Log-rank	0.084	3.841	0.772	0.050
Wilcoxon	0.348	3.841	0.555	0.050
Tarone – Ware	0.238	3.841	0.626	0.050

Table 3. Stage II HGBC patients: summary of statistics (events) and Test of equality of the survival distribution functions

Surgery type	Total patients observed	Total patients died	Total number of survivors	Time steps in Kaplan – Meier function
TURB	62	29	33	61
PCE	41	20	21	41
RCE	46	27	19	43
Test of equality of the survival distribution functions				
Statistic	Observed value	Critical value	*p*-value	Alpha
Log-rank	0.000	7.815	1.000	0.050
Wilcoxon	0.000	7.815	1.000	0.050
Tarone – Ware	0.000	7.815	1.000	0.050

Table 4. Stage III HGBC patients: summary of statistics (events) and Test of equality of the survival distribution functions

Surgery type	Total patients observed	Total patients died	Total number of survivors	Time steps in Kaplan – Meier function
TURB	36	28	8	35
PCE	33	21	12	33
RCE	33	20	13	32
Test of equality of the survival distribution functions				
Statistic	Observed value	Critical value	*p*-value	Alpha
Log-rank	0.000	7.815	1.000	0.050
Wilcoxon	0.000	7.815	1.000	0.050
Tarone – Ware	0.000	7.815	1.000	0.050

Table 5. Stage IIIB–IV HGBC patients: summary of statistics (events) and Test of equality of the survival distribution functions

Surgery type	Total patients observed	Total patients died	Total number of survivors	Time steps in Kaplan – Meier function
TURB	23	18	5	23
PCE	5	4	1	5
RCE	30	26	4	30
Test of equality of the survival distribution functions				
Statistic	Observed value	Critical value	*p*-value	Alpha
Log-rank	0.000	7.815	1.000	0.050
Wilcoxon	0.000	7.815	1.000	0.050
Tarone – Ware	0.000	7.815	1.000	0.050

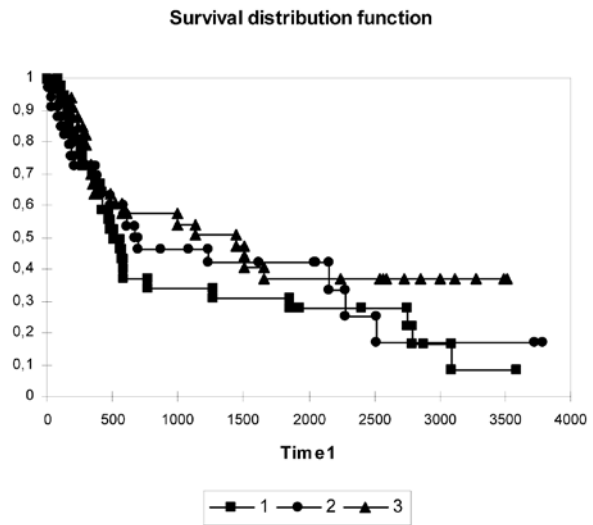

Fig. 3. Kaplan — Meier survival curves for stage III HGBC patients.1 — TURB, 2 — PCE, 3 — RC

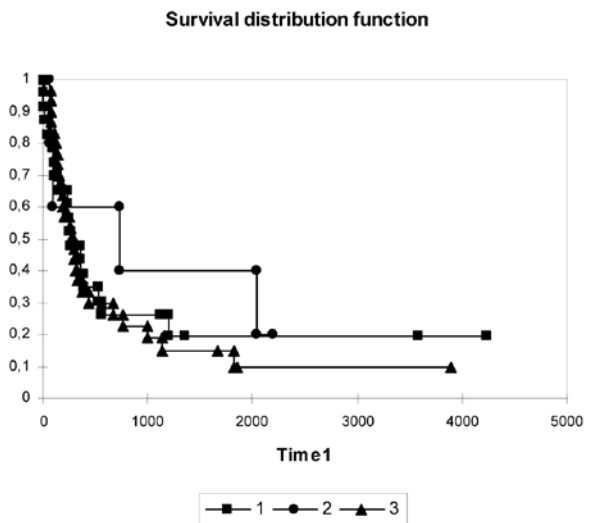

Fig. 4. Kaplan — Meier survival curves for HGBC patients stage IV. 1 — TURB, 2 — PCE, 3 — RE

better treatment approaches to improve oncological results of treatment, and quality of life of patients are currently being sought and developed [25, 27].

The results of molecular biology studies shed light onto the complexity of the bladder cancer as a nosology.

Table 6. 5-year overall survival of HGBC patients per cancer stage and surgery

Stage of cancer	Surgery		
	TURB, %	PCE, %	RCE, %
I	60	83	–
II	58	53	43
III	27	42	37
IV	19	40	10

From the histomorphological standpoint the bladder cancer is divided into two subgroups based on its recurrence and progression potential. Low grade (G1–G2 bladder cancer) prone to multifocality and local recurrence, and high grade (G3–G4 bladder cancer), which possesses more aggressive features resulting in metastatic progression [28–32]. Recent genetic and molecular studies have demonstrated that bladder cancer is even more diverse pathology, which can be broken into 5 subtypes — luminal papillary, basal squamous, luminal infiltrated, luminal, and neuronal, among which former two are the most frequent entities observed in clinical setting [33].

Urothelial carcinomas may evolve along two different pathways with distinct biological behavior and clinical prognosis that present as heterogeneous group of tumors [31]. Molecular signatures can accurately classify urothelial carcinoma into two distinct groups regardless of morphology [34]. The high-grade urothelial muscle-invasive tumors are heterogeneous and approximately evenly divided between epithelial and mesenchymal phenotypes. Muscle-invasive tumors show a mixed population of epithelial and mesenchymal phenotypes, in contrast to low-grade lesions that are formed entirely of an epithelial phenotype.

At the molecular level these tumors exhibit epithelial to mesenchymal transition changes [35]. Such clinically aggressive tumors are also characterized by pronounced aneuploidy and complex chromosomal abnormalities [35]. Muscle-invasive tumors generally show more complex chromosomal changes as compared to low grade tumors with frequent *TP53* mutation and rare *FGFR3* mutation. Loss of heterozygosity of the PTEN locus on chromosome 10 appears to be very common in muscle-invasive as compared to superficial tumors [36]. The lower prevalence of *PIK3CA* mutations in muscle-invasive tumors further strengthens the notion that papillary non-invasive and muscle-invasive tumors are two different molecular entities [37].

The clinical spectrum of bladder cancer can be divided into 3 categories that differ in prognosis, management, and therapeutic aims. The first category consists of non-muscle-invasive bladder cancer, for which treatment is directed at reducing recurrences and preventing disease progression. The second group encompasses muscle-invasive disease, for which the approach to treatment uses definitive local therapy with curative intent. Systemic therapy, including neoadjuvant chemotherapy, is frequently integrated with local therapy for these patients. The third category includes locally advanced and metastatic lesions. Concern in this group is how to prolong quantity and maintain quality of life [4].

We observed that the biological behavior of the tumors belonging to low- and high-grade subtypes differ, which coincides with literature data [28, 30, 31], in particular, the low-grade bladder cancer tumors are more prone to local recurrence, whereas high-grade tumor are more prone to distant progression and metastases. This implies that preserving the bladder in HGBC patients whenever technically feasible should be attempted for the purpose of improving quality of patient's life, considering low rate of local recurrence in HGBC.

Another finding which prompts us to consider the bladder sparing approach in surgical treatment of HGBC is the character of growth of high-grade tumor in the bladder. Based on our observations reported earlier [38], 90% of high-grade tumors grew as solitary deep muscle-invasive lesions without multifocality and with negative random mucous layer biopsies elsewhere in the bladder. The remaining 10% of lesions grew along with tumors of other grades and featured multifocality of diverse depth of invasion of bladder wall. This finding can be considered as an indication for bladder sparing technique as feasible and justified treatment approach in selected bladder cancer patients.

High-grade muscle-invasive bladder cancer has relatively poor 5-year overall survival, 68% for stage II and 15% for non-organ-confined disease (i.e., pT3 and pT4) [39]. In 2017 in USA statistics changed insignificantly: 5-year overall survival for bladder cancer patients with stages I–II was 70%, for locally advanced disease 30%, for metastatic process — 5% [39, 40].

In our study 5-year overall survival for stage I HGBC patients was 83%, for stage II — 58%, for stage IIIA — 42%, and for stage IIIB–IV — 40%. From this data we can conclude that our results of managing organ-confined muscle-invasive disease is worse than reported in the literature, whereas in stage III and IV we demonstrated better outcomes.

RCE is a treatment, which carries high burden of perioperative morbidity and mortality [5, 7, 9], which urges the search for additional treatment approaches, including bladder sparing, which would not compromise the oncological results of treatment.

PCE, on the other hand, is better tolerated, but is recommended in selected patients with cT2 (and not cT3) muscle-invasive bladder cancer with solitary lesion in locations suitable for segmental resection with adequate margins, without concomitant Tis as determined by random biopsies [3, 4]. Bilateral pelvic lymphadenectomy should be performed and include common, external, internal iliac, and obturator nodes. PCE is recommended to be performed with neoadjuvant cisplatin-based combination chemotherapy [4]. Current literature data demonstrates low pattern of use of neoadjuvant chemotherapy globally [25]. It is indicated that only less than 5% of high-grade muscle-invasive tumors could be treated with PCE [4]. Out data points at higher share of partial cystectomies performed, 25.6%.

The utilization of perioperative chemotherapy and radiotherapy turned out to be low, with adjuvant radiotherapy being administered in only 12.7% of treated patients, and postoperative chemotherapy administered in 4% of patients with palliative purpose. No patient in our retrospective series was treated with tri-modal bladder sparing approach (bladder sparing surgery with perioperative chemoradiotherapy).

The results of the statistical analysis of the survival data after three surgical approaches (TURB, PCE and RCE) demonstrate that in patients with HGBC of any stage (I, II, III or IV) the statistically significant differences between survival curves have not been observed, which means that bladder sparing approach is not inferior to RCE in treating selected HGBC patients. Hypothesis about inferiority of TURB to RCE in stage III HGBC patient has not been validated, also it contradicts with indications for the organ-preserving surgery in muscle-invasive bladder cancer published in the guidelines [1, 3]. Nevertheless, in stage III patients the survival curve after TURB lies lower than curves after RCE and PCE, but the small number of the patients in the analysis group (102 patients) does not allow to draw a conclusion about statistically significant differences. As all survival curves (after TURB, PCE and RCE) are considered statistically identical, there is no need to run paired analysis of the curves. The survival is identical in our data set.

CONCLUSIONS

PCE with adequate safety margins and TURB in selected patients are not inferior to RCE in terms of cancer-specific survival when treating patients with HGBC of all stages. The PCE in managing HGBC has been performed in 25.6% of patients, which is higher than 5% reported in the literature. The TURB in our setting turned out to be the most widely used surgical modality (39.1% of cases). The extirpative technique was never applied to patients in stage I. The overall 5-year survival of HGBC patients after radical treatment was 83%, 58%, 42%, and 40% for patients in stage I, II, III and IV. The utilization of perioperative chemotherapy (4%) and radiotherapy (12.7%) was low in our patients set, and mostly was provided with palliative purpose.

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