

Survival Analysis of Patients with Bladder Cancer after Radical Cystectomy

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Abstract: One of the most commonly used surgical operations among patients with bladder cancer (BC) is radical cystectomy (RC), which includes the removal of the entire bladder along with the surrounding lymph nodes and other nearby organs that are affected by malignant neoplasms. During this operation, the most important stage that has a direct impact on the further quality of life of the patient is the choice of the method of uroderivation (UD).

Patients and Methods: Have been reviewed retrospectively the clinical records of 586 patients who had BC RC at the Oncourological Department of the Sverdlovsk Regional Oncological Dispensary (SROD) between December 2001 and May 2021 after RC with three methods of UD: external urine removal, internal urine removal, intestinal reservoir.

Results: The direct dependence of the presence and severity of some complications after RC on the method of urine removal chosen by the oncologist surgeon were determined. The analysis of survival curves was carried out, as well as the 5- and 10-year survival rate of patients of the SROD after RC. According to the results of the analysis, it was found that the worst survival was observed in patients with external urine diversion, the best survival was found in patients with internal urine diversion ($p < 0.05$).

Conclusions: Urinary diversion is definitely an important stage in the performance of such a surgical intervention as RC. The study revealed statistically significant differences between patient survival curves ($p < 0.05$) plotted for different groups of urinary diversion and differences between the medians of several types of survival for the groups considered ($p < 0.05$).

Keywords: Bladder cancer, Radical cystectomy, Uroderivation, Survival.

Background

According to the World Health Organization (WHO) data for 2020, BC is during the ten most widespread localizations of malignant neoplasms ¹. In men, BC is the seventh most widespread type of cancer ²⁻⁴. Although the yearly BC incidence rate is approximately 4 times higher in men than in women, the 5-year general survival rate is higher in men compared with women (66% against 60%) ^{5,6}.

In a number of cases, BC takes a particularly aggressive course. One of the main problems is that some of these tumors do not respond to conservative medication treatment and radiotherapy. In these cases, RC may be a good treatment option even for locally spread tumors ^{7,8}.

RC is one of the principal treatments for muscle-invasive and non-muscle-invasive BC with a high risk of progression ⁹. In terms of complexity, RC involving various types of urinary diversion is considered one of the most difficult interventions in cancer treatment.

In the literature, one may often come across patient survival estimates for various combinations of preoperative characteristics in BC patients ^{2,9-12}. However, it is often overlooked that one of the most important stages in this surgical intervention is the application of one of the possible methods of UD ¹³.

The purpose of this study is to analyze the survival of patients after RC with the use of three methods of urinary diversion.

Patients and methods

The study reported was carried out at the SROD. We reviewed retrospectively the clinical records of 586 patients who had BC RC at the Oncourological Department of the SROD (Ekaterinburg, Sverdlovsk region, Russia) between December 2001 and May 2021.

The study involved 523 men (89.3%) and 63 women (10.7%) aged 28 to 81 years. The average age of the subjects was 59.8 ± 8.6 years.

The patient data were divided into the following categories: demographic, preoperative, operative, postoperative, pathological, and clinical.

Surgical Procedures. The retrospective analysis included only patients with BC and excluded patients subjected to salvage or palliative cystectomy. RC and lymph node dissection were performed by the standard techniques. The extent of lymph node dissection needed was determined by the surgeon and varied from standard intervention including distal common ileac, external and internal ileac, hypogastric, obturator and paravesical lymph nodes to extended lymphadenectomy which included these lymph nodes and the lymph nodes along the proximal segment of the common ileac artery and the distal segments of the aorta and the inferior vena cava. The lymph nodes removed from each anatomic zone were presented in the form of a separate package. Urinary diversion was performed by ureterocutaneostomy or transuretero-ureterocutaneostomy, formation of an ileal conduit, and orthotopic replacement of the bladder by a segment of the small or large intestine.

In terms of UD type, the patients were divided by a specialist into three groups:

Group 1 – patients with external urinary diversion (ureterocutaneostomy (UCC) or transuretero-ureterocutaneostomy (TUUCC));

Group 2 – patients with urinary diversion into an isolated segment of the ileal intestine (patients with Bricker ileoconduit or Turnbull stoma);

Group 3 – patients with orthotopic intestinal reservoirs (Camey I, Melchior, Hautmann, Studer, J-type neobladder, and a large intestine reservoir).

Fig. 1 shows that 82 patients (14%) had had UCC and TUUCC; 373 (64%) patients had had a Bricker or Turnbull urinary diversion intervention, and 131 patients (22%) had been provided with an intestinal neobladder.

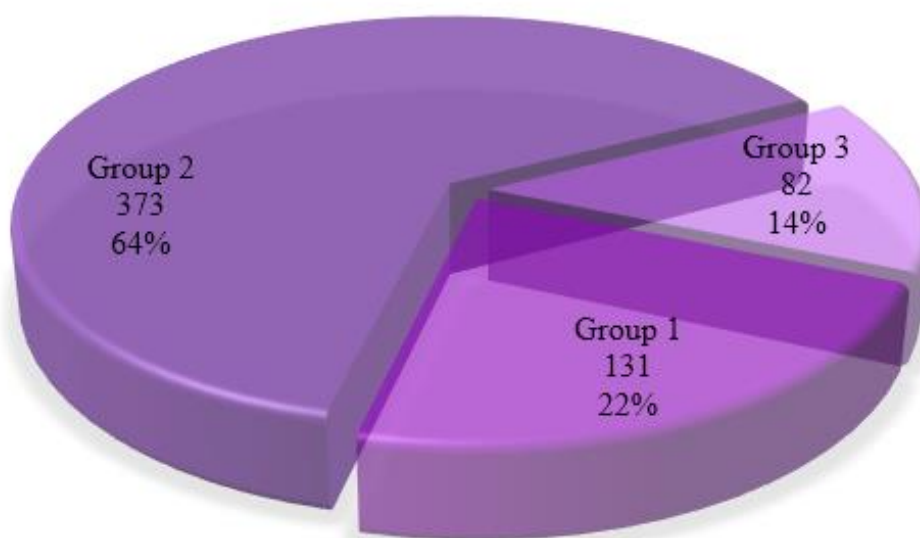


Figure 1. Distribution of patients by urinary diversion group

Pathological Assessment. All surgical samples were processed in accordance with standard pathological techniques. The tumors were classified according to the 2010 TNM staging system of the Union for International Cancer Control (UICC).

Follow Up. After the RC, patients had a follow-up every three months during the first year, and every 6 months during the next 2-6 years, then once annually. Follow-up included: history taking, physical examination, general blood and urine tests, and biochemical blood analysis. Imaging included thorax X-raying, ultrasonic examination, and abdominal and pelvic computer tomography every 6 and 12 month after the surgery and then annually. Considering indications, we performed osteo- and nephro-scintigraphy, pelvic MRT, and 18-FDG PET-CT. Loco-regional relapse was defined as a recurrence in the pelvic cavity. Remote metastases were confirmed by imaging and, in some cases, by cylindrical biopsy. A malignant tumor of the ureter was considered a secondary primary tumor, while a tumor occurring in the urethra was referred to local relapses.

The follow-up duration median was 46 months (range: 1–230 months).

Statistical Analysis. The causes of death were established from medical records and cancer register data.

The patient groups were compared according to the type of urinary diversion (UD).

The descriptive statistics included calculation of mean values and their standard deviations for normally distributed variables, and medians for quantities that did not follow the normal distribution law. To analyze differences in 5-year and 10-year survival rates between the groups, we used the comparison of proportions test ¹⁴.

The relapse-free survival rate was calculated as the time from the radical surgical intervention to the first recorded relapse. Kaplan-Meier curves were used for assessing the overall survival rate and the relapse-free and progression-free survival rates in each group of UD technique, and these were used to draw comparisons using the log-rank test. Differences between the medians were analyzed by the Kruskal-Wallis median test.

Comparisons between the 5-year and 10-year survival rates were visualized by heat mapping ¹⁵⁻¹⁷. All statistical tests were two-sided, and the statistical significance of differences was estimated at $\alpha = 0.05$.

Data analysis throughout the study was performed by means of Statistica for Windows 10 version. Heat mapping was done in MatLAB2021b.

Results

The clinical and pathological characteristics of the 586 patients studied are presented in Table 1. Of these, 523 (89.2%) were men and 63 (10.8%) were women. The mean age of the patients was 59.8 ± 8.6 years.

Table 1. Clinical and pathological characteristics of the SROD patients

Characteristics	First Group (n=82) Number of Patients (%)	Second Group (n=373) Number of Patients (%)	Third Group (n=131) Number of Patients (%)
Gender			
Males	77 (93.9)	318 (85.3)	128 (97.7)
Females	5 (6.1)	55 (14.2)	3 (2.3)
Age, $\mu \pm \sigma$	63.4 $\pm$ 8.3	60.9 $\pm$ 7.9	54.4 $\pm$ 8.5
CACI, Me	4	3	2
90-day lethality	2 (2.4)	3 (0.8)	1 (0.8)
Category pT			
pT0	1 (1.2)	5 (1.3)	0
pT1	6 (7.3)*	85 (22.8)**	47 (35.8)***
pT2a	6 (7.3)*	47 (12.6)**	28 (21.4)***
pT2b	17 (20.7)	66 (17.7)	17 (13.0)
pT3a	9 (11.0)*	15 (4.0)	2 (1.5)***
pT3b	13 (15.9)	52 (13.9)**	8 (6.1)***
pT4a	11 (13.4)	28 (7.5)**	5 (3.8)***
pT4b	0	1 (0.3)	0
Non-muscle invasive relapse of BC	6 (7.3)	33 (8.9)	16 (12.2)
Muscle invasive relapse of BC	13 (15.9)	41 (11.0)	8 (6.1)
Category pN			
pN0	65 (79.3)	285 (76.4)**	121 (92.4)***
pN1	6 (7.3)	31 (8.3)	6 (4.6)
pN2	6 (7.3)	42 (11.3)**	3 (2.3)***
pN3	5 (6.1)	15 (4.0)	1 (0.8)

*Statistically significant differences between the 1st and 2nd groups of patients ($\alpha = 0.05$);

**Statistically significant differences between the 2nd and 3rd groups of patients ($\alpha = 0.05$);

***Statistically significant differences between the 1st and 3rd groups of patients ($\alpha = 0.05$).

Pathological staging confirmed that among the 563 (96.8%) subjects with lymph node dissection, there were metastases only in 114 (20.2%) patients. The average number of lymph nodes removed from one patient was 20 (range: 1–63), and the mean number of positive lymph nodes was 1 (range: 0–37). More detailed characteristics of the patients are presented in Table 1.

Analysis of Survival Curves for Patients with Three Different Techniques of UD. One of the principal methods for the evaluation of a treatment and identification of regularities in expected event occurrence in clinical practice is survival curve plotting. The survival curve defines the probability of surviving any time-point after the onset of a certain initial event.

The estimates of SROD patient survival rates after an RC with different methods of urinary diversion were used to plot survival curves shown in Figures 2-4.

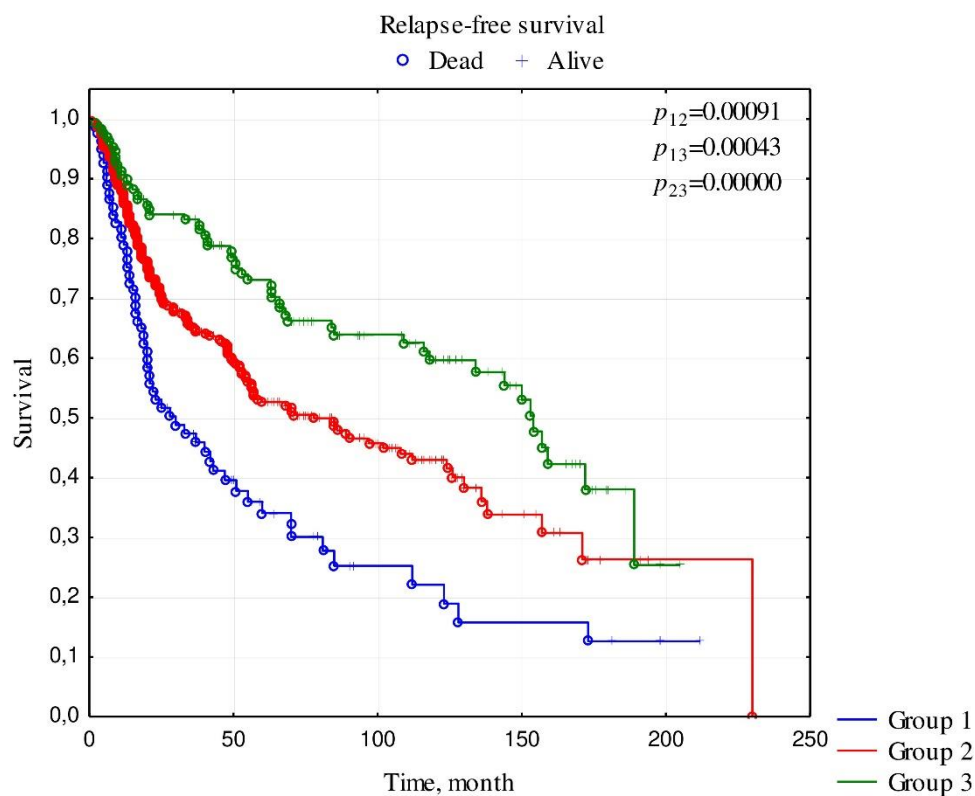


Figure 2. Relapse-free survival curves for SROD patients after RC with different methods of urinary diversion

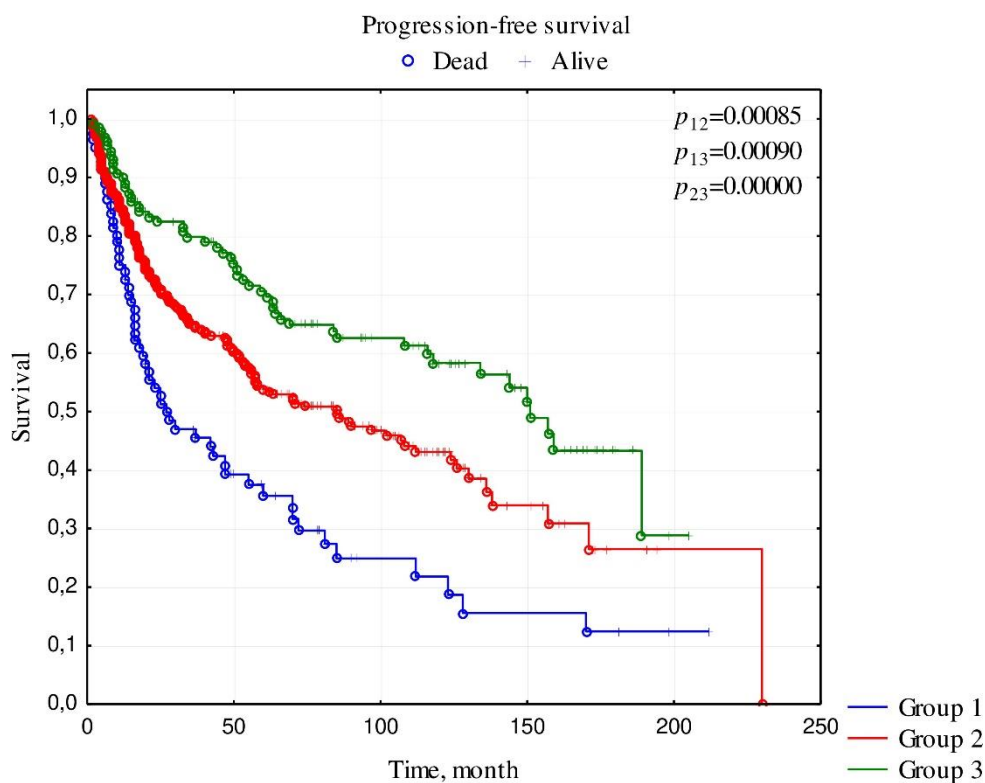


Figure 3. Progression-free survival curves for SROD patients after RC with different methods of urinary diversion

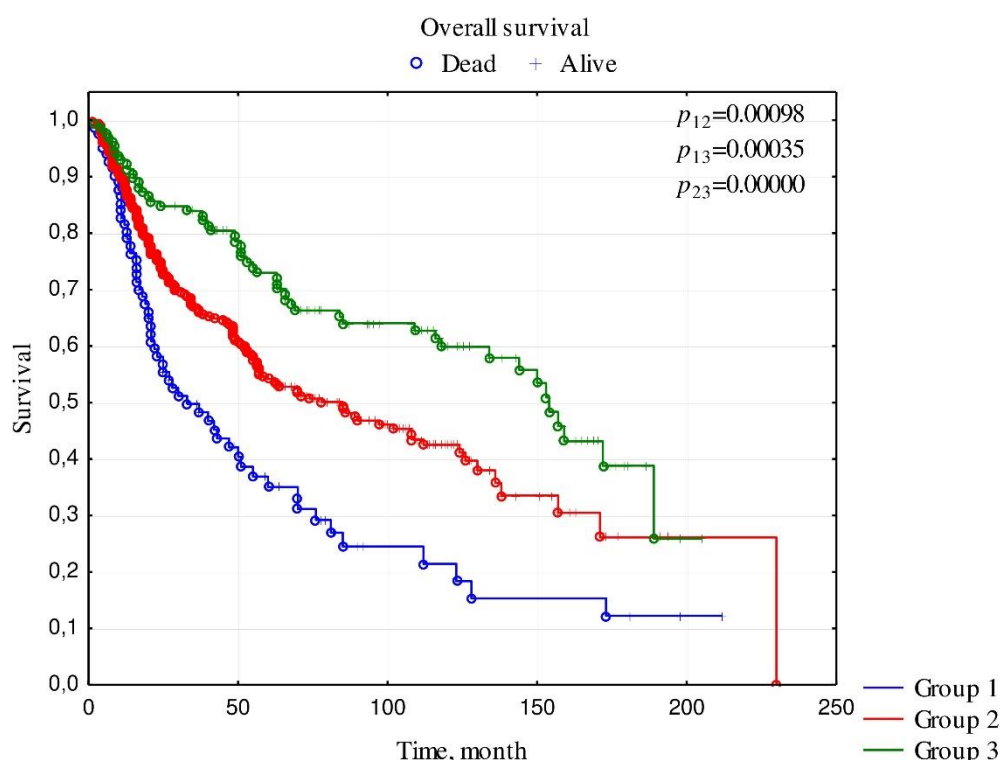


Figure 4. Overall survival curves for SROD patients after RC with different methods of urinary diversion

Analysis of Survival Medians in the Groups with Different Techniques of UD. Medians for each type of survival were computed for all groups studied (Table 2). The Kruskal-Wallis median test was applied and revealed statistically significant differences between the medians of all types of patient survival in the three groups at a significance level of $\alpha = 0.05$.

Table 2. Median survival rates of SROD patients with different methods of UD

Median, months	First Group (n=82)	Second Group (n=373)	Third Group (n=128)
Relapse-free survival median	30	75	154
Progression-free survival median	28	85	151
Overall survival rate	37	78	154

Analysis of 5-year and 10-year Survival of Patients with Three Different Techniques of UD. One of the key indicators in cancer statistics is 5-year and 10-year patient survival rates.

Cancer-specific survival reflects patient lethality attributed exclusively to cancer. Overall survival is associated with patient lethality due both to malignant neoplasms and non-cancer causes in aggregate. Relapse-free survival reflects lethality associated with recorded clinical relapses. Progression-free survival characterizes lethality connected with the progression of a malignant tumor.

The 5-year and 10-year cancer-specific survival rates for the entire cohort of patients was 70.1% and 66.3%, respectively, while the 5-year and 10-year levels of overall survival were

61.7% and 55.6%, respectively. The 5-year and 10-year relapse-free survival rates were 60.9% and 55.6%, respectively. For progression-free survival, the 5-year and 10-year survival indicators were 60.9% and 55.3%, respectively.

The results of the analysis were used to construct heat maps, shown in Figure 5. The significance of the differences between the survival rates were estimated by the comparison of proportions test. In our study, we used a color scale that is more convenient for perception: from black color, meaning the lowest rate of survival, to white, i.e. the highest percentage of surviving patients.

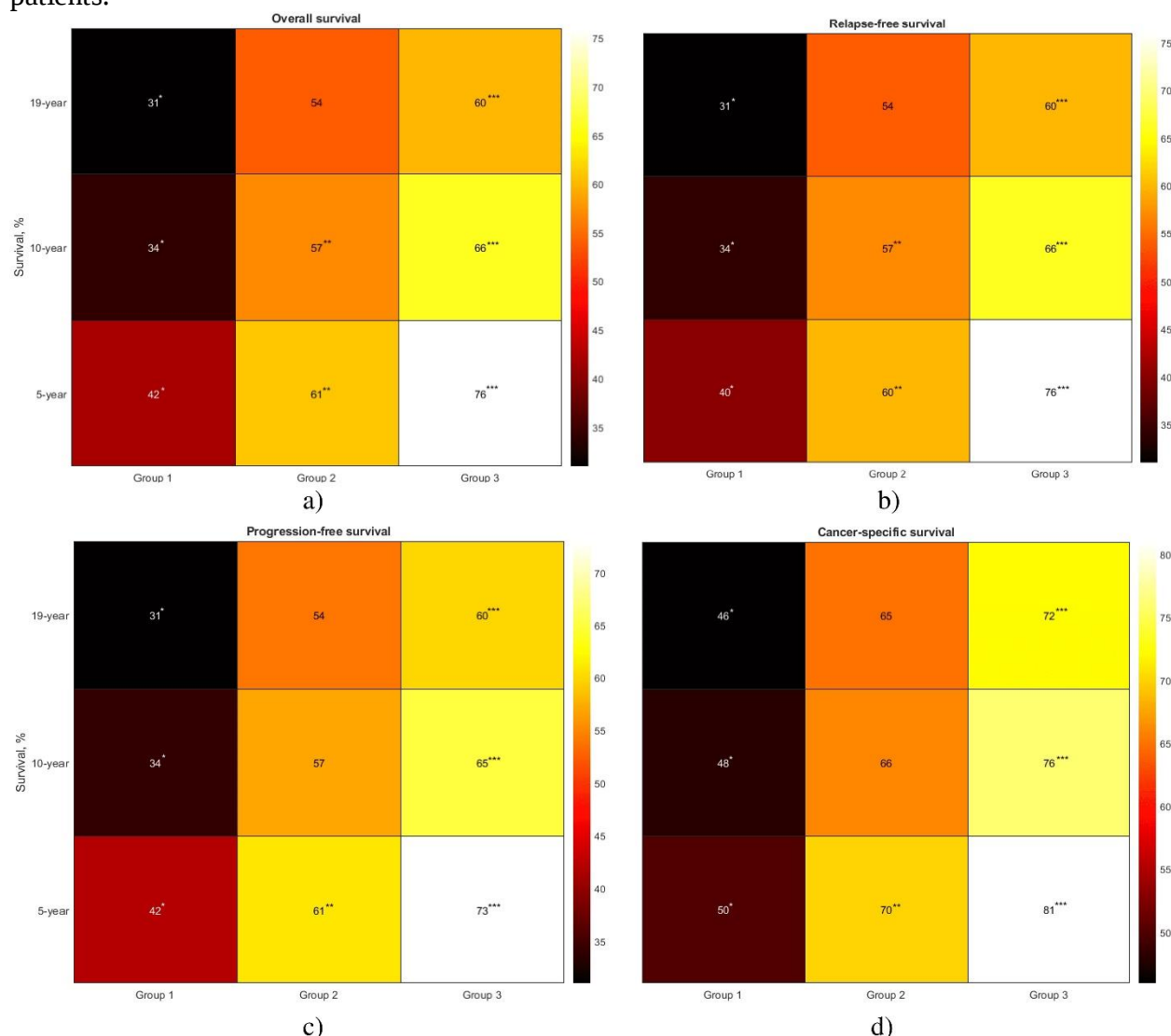


Figure 5. The heat maps of overall (a), relapse-free (b), progression-free (c) and cancer-specific (d) survival rates in the three groups of SROD patients with different techniques of urinary diversion in different urinary diversion time intervals

*Statistically significant differences between the 1st and 2nd groups of patients ($\alpha=0.05$);

**Statistically significant differences between the 2nd and 3rd groups of patients ($\alpha=0.05$);

***Statistically significant differences between the 1st and 3rd groups of patients ($\alpha=0.05$).

Discussion

Table 1 demonstrates that the patients of the first group in terms of UD technique were the most advanced in age, and it is this group that showed the highest value of the comorbidity

index. An analysis of the BC incidence rate in our sample revealed the same gender differences as in previous studies: in men, BC occurs more than 4 times more often than in women ^{5,6}.

Indicators such as annual mortality and mortality are the most significant for assessing the timeliness of breast cancer treatment. The results of our study are consistent with the data obtained in the study by Chemakina A.A. et. al., according to which in the Russian Federation the rates of one-year and total mortality were 22.4% and 14.4%, respectively ¹⁹. No statistically significant differences in 90-day lethality were discovered between the three groups of patients.

The results of the analysis of 90-day mortality in the uroderivation groups are close to the results of the study by Faba O.R. et al., where mortality does not exceed 3% ⁹.

For all types of survival considered, we found statistically significant differences between the survival curves for patients with three UD techniques. The differences between the curves were estimated by means of the Log-Rank Test at a significance level of $\alpha = 0.05$. The lowest survival rate among all the types considered was demonstrated by patients from the first group (with external urinary diversion). The same group was the most advanced in age and had a high Charlson Comorbidity index. The highest survival rate (of all types) was observed in the third group of patients (with orthotopic intestinal neobladder). This group had a lower middle age and comorbidity index. The results obtained by us are consistent with the results of previous studies ^{13,18,19}.

Like in the analysis of survival curves, the highest survival rate was found in Group 3 (with orthotopic intestinal neobladder), and the lowest, in the first group (with external urinary diversion).

Heat map analysis revealed identical trends in the behavior of cancer-specific, overall, relapse-free and progression-free survival in the groups under consideration: the lowest survival rate was found in the first group of patients in all time intervals (the left column); the survival rates of patients in the second and third groups practically did not differ, but the highest survival rate was demonstrated by the patients of the third group over the entire period of the study (19 years).

We compared our results with the data of previous studies involving a similar sample in terms of gender and age structure ². In our sample, the 5-year cancer-specific survival rate is slightly lower than the similar indicator of international colleagues (70.1% for the patients included in our study, and 70.8% for patients in Korea).

Also comparison of the 10-year cancer-specific survival data for patients after RC showed insignificant differences between the results of the two studies (66.3% for the patients included in our study, and 65.1% for patients in Korea). A similar trend is seen also for relapse-free survival: a slightly lower 5-year survival rate in comparison with the results of the international colleagues (60.9% and 61.8%, respectively). The 10-year relapse-free survival indicators in our sample are lower than those of the colleagues abroad (55.6% for the patients included in our study, and 57.7% for patients in Korea).

In general, the clinical results obtained in our study demonstrate that RC ensures good outcomes in terms of bladder-cancer patient survival. These results provide a reference standard against which other methods of BC treatment could be compared.

Conclusions

The results obtained in our study are consistent with the results of other studies that have found that radical cystectomy provides good survival outcomes for patients with bladder cancer. Urinary diversion is definitely an important stage in the performance of such a surgical intervention as RC.

The study revealed statistically significant differences between patient survival curves ($p < 0.05$) plotted for different groups of urinary diversion and differences between the medians of several types of survival for the groups considered ($p < 0.05$).

An analysis of the 5-year and 10-year survival rates showed statistically significant differences in all time intervals between the first and second groups ($p < 0.05$). The first and third groups differed in all time intervals of overall survival ($p < 0.05$). The second and third groups differed only on the 5- and 10-year time interval of overall survival ($p=0.0034$ and $p=0.0446$). The lowest overall survival rate was found in the first group of patients (with external urinary diversion) in all time intervals – less 41.5%. The highest overall survival rate was discovered in the third group of patients (with orthotopic intestinal neobladder) in the 5-year period – 75.6%.

Heat maps have proven themselves to be a transparent algorithm with highly visible analysis results as well as easily interpretable graphical images. Based on two approaches to visualizing a large volume of medical and biological data, a comprehensive analysis of the influence of risk factors on the survival of bladder cancer patients was carried out. The possibility of identifying relationships between numerical data based on visual analysis using several methods simultaneously has been demonstrated, which allows high-quality conclusions to be obtained.

References

1. World Health Organization [Internet]. Cancer 2020 [updated 2021 Mar 3]. Available from: <https://www.who.int/ru/news-room/fact-sheets/detail/cancer>. Accessed: 9/09/2022.
2. Kwon T, Jeong IG, You D, Hong B, Hong JH, Ahn H, Kim CS. Long-term oncologic outcomes after radical cystectomy for bladder cancer at a single institution. *Journal of Korean Medical Science* 2014; 29: 669-675.
3. Mohammadian M, Safari A, Allah Bakeshel K, Allah Bakeshel F, Asti A, Mohammedian-Hafshejani A, Salehiniya H, Emamiyan M, Khakpour H. Recent patterns of bladder cancer incidence and mortality: A global overview. *World Cancer Res Journal* 2020; 7: e1464.
4. Hassanipour S, Delam H, Fathalipour M, Sharifi M, Abdzadeh E, Fouladseresht H, Arab-Zozani M. The incidence of bladder cancer in Iran: a systematic review and meta-analysis. *World Cancer Research Journal* 2019; 6: 1-10.
5. Richters A, Leliveld AM, Goossens-Laan CA, Aben KK, Özdemir BC. Sex differences in treatment patterns for non-advanced muscle-invasive bladder cancer: a descriptive analysis of 3484 patients of the Netherlands Cancer Registry. *World journal of urology* 2022; 1: 1-7.
6. Lynch CF, Cohen MB. Urinary system. *Cancer* 1995; 75: 316-329.
7. Russell B, Liedberg F, Khan MS, Nair R, Thuraija R, Malde S, Van Hemelrijck M. A systematic review and meta-analysis of delay in radical cystectomy and the effect on survival in bladder cancer patients. *European Urology Oncology* 2020; 3: 239-249.
8. Cavaliere C, D'Aniello C, Cecere SC, Di Napoli M, Berretta M, Franco R, Pisano C, Perdonà S, Setola S, Fisichella R, Spartà D, Tambaro R, Pignata S, Facchini G. Non muscle invasive bladder cancer treatment. *World Cancer Res Journal* 2014; 1: e126.
9. Faba O.R., Tyson M.D., Artibani W., Bochner B.H., Burkhard F., Gilbert S.M., Kälble T., Madersbacher S., Seiler R., Skinner E.C., Thalmann G., Thüroff J., Wiklund P., Hautmann R., Palou J. Update of the ICUD–SIU International Consultation on Bladder Cancer 2018: urinary diversion. *World J Urol* 2019; 37: 85-93.
10. Karyakin OB. Bladder cancer: what's new in 2020-2021. *Oncourology* 2021; 17: 115-123.
11. Ginkel N, Hermans TJ, Meijer D, Boormans JL, Voortman J, Mertens L, Vis AN. Survival outcomes of patients with muscle-invasive bladder cancer according to pathological

- response at radical cystectomy with or without neo-adjuvant chemotherapy: a case-control matching study. *International Urology and Nephrology* 2022; 1: 1-8.
12. Kotov SV, Khachatryan AL, Kotova DP, Zhuravleva AK, Sargsyan SM, Magomedov DM. Analysis of the patients' quality of life after radical cystectomy with the orthotopic neobladder or ileal conduit formation. *Vestnik Urologii* 2021; 9: 47-55.
 13. Dursun F, Elshabrawy A, Wang H, Wu S, Liss MA, Kaushik D, Mansour AM. Histological variants of non-muscle invasive bladder cancer: Survival outcomes of radical cystectomy vs bladder preservation therapy. In *Urologic Oncology: Seminars and Original Investigations* 2022; 40: 275-e1.
 14. Musaev TN. Early complications of radical cystectomy with various types of urine diversion: analysis of prognostic factors. *Oncourology* 2020; 1: 78-89.
 15. Borovikov VP. *Statistica: The art of data analysis on a computer*. Peter: St. Petersburg; 2001; 1: 656.
 16. Wilkinson L, Friendly M. The history of the cluster heat map. *The American Statistician* 2009; 63: 179-184.
 17. Romanova IK. Modern methods of multidimensional data visualization: Analysis, classification, implementation and applications in technical systems. *Science and Education: Scientific Publication of BMSTU* 2016; 1: 133-167.
 18. The Wall Street Journal [Internet]. Battling Infectious Diseases in the 20th Century: The Impact of Vaccines [cited 2015 Feb 11]. Accessed: 10/08/2022
 19. Chemakina A.A., Keln A.A. Epidemiology of bladder cancer in the Tyumen region for the period 2008-2018. *Academic Journal of Western Siberia* 2020; 16(2): 39-42.
 20. Kotov SV, Khachatryan AL, Kotova DP, Zhuravleva AK, Sargsyan SM, Magomedov DM. Analysis of the quality of life of patients after radical cystectomy with the formation of orthotopic neobladder or ileoconduit. *Bulletin of Urology* 2021; 9: 47-55.
 21. Petrosyan GS, Shkolnik MI, Keln AA, Lykov AV, Kupchin AV, Ivanov DA. 8 years of experience in performing "V" shaped heterotopic ileocystoplasty in the Tyumen region. *Palliative Medicine and Rehabilitation* 2021; 1: 37-42.