

Staging and modern approaches to bladder cancer treatment

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Summary

The treatment tactics for patients with superficial urothelial carcinoma and muscle-invasive bladder cancer differ significantly; therefore, diagnosis, staging and prescription of appropriate therapy remain relevant. Over a period of 5 years, follow-up data were collected on 61 cases of papillary urothelial carcinoma, 26 primary and 7 secondary muscle-invasive bladder cancer. The median recurrence-free survival in patients with transitional cell carcinoma was 4.1 years, with the greatest impact on this indicator observed for the sum of recurrence risk scores, which included tumor stage, malignancy, size, and number. Neoadjuvant polychemotherapy resulted in partial regression of malignancy according to RECIST in only 48% of patients with muscle-invasive cancer who then underwent organ-preserving surgery. The tumor regression score correlated with the degree of malignancy and had a statistically significant effect on progression-free survival. In the remaining 52% of cases with muscle-invasive cancer, after neoadjuvant polychemotherapy, tumor growth was diagnosed as stabilised, which gave grounds for radical cystectomy. After the operation, patients reported improvement in their mental and physical condition, but the median overall survival was 3.3 years. The results obtained demonstrate the impact of tumor assessment, tumor stage and appropriate treatment on overall and recurrence-free survival in bladder cancer.

KEYWORDS: *urothelial carcinoma, muscle-invasive cancer, overall survival, chemotherapy*

INTRODUCTION

Bladder cancer (BC) in men is one of the leading cancers in the structure of oncological diseases. According to the National Cancer Registry of Ukraine, just over 4,400 cases were registered in 2022, accounting for almost 6% of all malignant tumors(1). Urothelial carcinoma (transitional cell carcinoma) is most detected (70-80%) in men of working age. This type of tumor is rare in women. A serious problem for treatment is the high frequency of disease recurrence (30-85%) and a significant prevalence of cases of progression to muscle-invasive form (10-25%). The remaining (20-30%) bladder tumors are characterised by infiltrative growth at the stage of initial diagnosis.

The clinical diagnosis includes the stage of cancer, general assessment of the tumor, its loca-

tion and size, and the degree of anaplasia. Patients with haematuria and dysuria undergo cystoscopy and an ultrasound of the entire urinary system. When visualising the tumor, additional computed tomography is performed to assess its size, shape, and location, and to detect metastases in neighbouring lymph nodes(2). Visual methods cannot be used to determine the degree of malignancy of the tumor, so urine cytology is mandatory(3).

In the treatment of superficial tumors, it is necessary not only to remove the tumor but also to prevent recurrence and prevent the development

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of invasive forms. Therefore, it is essential to determine the stage of breast cancer correctly and the degree of malignancy based on histological findings. To obtain biopsy material in the papillary form of bladder cancer, a transurethral resection (TUR) is performed. In the presence of a locally advanced form, the procedure is cystoscopy with biopsy(4).

Postoperative histology results determined the risk of tumor recurrence and progression and guided treatment decisions. In many cases of urothelial carcinoma, repeated TUR or *Bacillus Calmette-Guérin* (BCG) therapy is required to improve overall and disease-free survival(5,6). In some cases, histological results after repeated TUR may differ from previous ones, suggesting errors in staging and tumor assessment based on clinical data, or errors after the first resection. Such errors necessitate a fundamental change in treatment tactics, which negatively affects the patient's morale and the economic justification for the provision of medical services.

The treatment regimen for invasive carcinomas depends directly on accurate staging and assessment of the tumor. Two treatment tactics can be used in BC. Organ-preserving Trimodal therapy (TMT) is indicated for highly differentiated single tumors; in other cases, radical cystectomy (RC) with lymphadenectomy is performed(7,8).

The advantages of organ-preserving surgery include maintaining working capacity, a satisfactory quality of life, and psychological health for patients. The complexity and duration of radical cystectomy with bilateral lymphadenectomy increase the risk of postoperative complications. Profuse haematuria, which is a characteristic feature of BC, leads to severe anaemia and cardiovascular disorders. Complex and prolonged surgeries in patients with this condition increase the risk of urosepsis, pulmonary embolism, and other life-threatening complications(9).

Data from several randomised controlled trials have convincingly demonstrated the key role of neoadjuvant polychemotherapy (NAC) in the selection of trimodal organ-preserving therapy(10). Such a strategy significantly prolongs relapse-free and overall survival (OS) in patients and enables satisfactory long-term treatment outcomes.

Correct and timely assessment of a malignant neoplasm and an adequate choice of Surgical tac-

tics can delay the occurrence of recurrent tumors, reduce the risk of progression, and improve the quality of life of patients. The study aimed to assess the overall and recurrence-free survival of patients with bladder cancer using modern approaches to tumor staging and treatment.

MATERIALS AND METHODS

A prospective, uncontrolled, non-randomised empirical study was conducted in the Department of Oncology and the outpatient clinic of the regional clinical oncological dispensary for 5 years. At the preparatory stage, clear criteria for patient inclusion and exclusion in the study were defined. The inclusion criterion was primary bladder cancer without distant metastases in patients who first visited a urologist between January 2019 and November 2023, with a minimum follow-up period of 4 months (120 days). Patients with tumor recurrence who were registered before this period were excluded. Other exclusion criteria were severe comorbidity and complete or partial absence of medical records that would reliably track the patient's medical history.

The stage of material collection and observation lasted 5 years (1,800 days). The International Classification of Tumor, Nodes, and Metastasis (TNM) was used for staging and assessment of the extent of tumor spread, and the histological classification of the degree of differentiation was used for the level of anaplasia. The algorithm of diagnosis measures corresponded to the protocol of medical care approved by the Ministry of Health of Ukraine, including laboratory data, ultrasound diagnostics (ultrasound) of the abdominal cavity, pelvis, retroperitoneal space, magnetic resonance imaging (MRI) of the pelvis with intravenous contrast, and cystoscopy with biopsy.

The sample included 87 patients aged 43-72 years with bladder cancer of varying degrees. Patients with superficial cancer at stages Ta, T1 and Tis underwent TUR of the tumor with biopsy and mandatory single intravesical instillation of epirubicin or mitomycin C. Based on the histological examination of the biopsy material, the postoperative stage of the tumor process was clarified, after which repeated TUR, BCG therapy or further observation was prescribed. The appointment of repeat TUR in the period of 4-10 weeks after the first

resection due to incomplete or low-quality initial TUR, as well as in low-differentiated and/or T1 neoplasms, was not considered a recurrence. Based on cystoscopy and postoperative biopsy, the patient was classified as low, intermediate, or high risk to start adjuvant intravesical chemotherapy with epirubicin or mitomycin C; in the intermediate- and high-risk groups, immunotherapy with the BCG vaccine was included in the regimen unless there were absolute contraindications.

In patients with muscle-invasive tumors at stages T2-T4, treatment began with 3-4 courses of neoadjuvant polychemotherapy using the GC (gemcitabine + cisplatin) regimen. In patients with a highly differentiated single tumor at stage T2, bladder resection was performed to preserve the organ. The remaining patients with low-grade and/or locally advanced muscle-invasive BC underwent radical cystectomy with regional lymphadenectomy to form an orthotopic bladder or internal urinary diversion.

General methods of descriptive statistics were used. To detect a statistically significant difference between the indicators, the χ^2 criterion was used, with a hazard ratio (HR) and confidence interval (CI) of 95% at a significance level of $p < 0.05$. Overall recurrence-free survival was analysed using Cox proportional hazards regression. The Kaplan-Meier method was used to construct survival curves. STATISTICA 10.0 software was used to process the data.

Thus, it is important to adopt a modern approach to the staging and treatment of bladder cancer to improve overall and disease-free survival for patients. For statistical analysis of the data, the Cox proportional hazards regression model and the Kaplan-Meier method are used to estimate hazard ratios (HRs) and median survival in patients with breast cancer, depending on tumor stage, degree of anaplasia, and treatment method(11).

RESULTS

Bladder cancer is often diagnosed through a combination of clinical symptoms and diagnostic tests. Early detection plays a crucial role in determining the appropriate treatment strategy, especially in cases of non-muscle-invasive bladder cancer (NMIBC), where intervention can significantly reduce the risk of progression. Diagnostic

imaging, such as ultrasound and computed tomography, along with cystoscopy, is commonly employed to visualise the tumor and assess its size and location. However, these methods alone cannot fully determine the degree of malignancy or predict the risk of recurrence. Therefore, additional tests, such as urine cytology, are essential for providing a more accurate assessment of the tumor's characteristics. The main complaints of bladder cancer are haematuria, dysuria, and urgency to urinate. One of the mandatory examinations for such complaints is a cytological examination of the urine sediment after bladder flushing, which allows for the detection of cancer cells and their initial assessment (Figure 1).

The methods used included 87 patients with confirmed bladder cancer in the study. Based on the results of laboratory and instrumental examinations, the first staging of the tumor was performed using clinical data (Table 1).

Thus, 61 patients with transitional cell BC at tumour stages pTisN0M0, pTaN0M0 and pT1N0M0, and 26 patients with the muscle-invasive form at stages pT2N0M0, pT3N1M0, pT4N1M0 were included in the study.

All patients with a superficial neoplasm underwent TUR surgery with a single intravesical injection of a chemotherapeutic agent within a day after surgery.

Also, based on clinical data, the risk of recurrence and progression was calculated, and patients were divided into groups accordingly. The low-risk group (0 points) included 9 patients (15%), all of whom were scheduled for a control cystoscopy in 3 months after a single instillation. The intermediate-risk group (1-9 points) included 49 patients (80%) who received adjuvant chemotherapy with epirubicin on days 7-10 after surgery and BCG on day 21, unless there were indications for repeat TUR. The high-risk group included 3 patients (5%), all of whom received BCG therapy starting on day 21 unless a second TUR was required.

Repeated THR within 4-10 weeks after the first operation was performed in the following cases:

- when, for anatomical or other reasons, it was not possible to remove the tumour bed during TUR;
- in the absence of the detrusor muscle in the surgical specimens;
- for low-grade and/or T1 tumours.

According to these criteria, repeated TUR was indicated in 49 (80%) patients. After surgery, the tumour was re-staged and evaluated. The histological examination showed that pT0 was determined in 25

patients (51%), pTa in 13 (26%), pT1 in 10 (20%), and pT2 in 1 (2%). Thus, in half of the patients, no residual malignancy was detected, and healthy tissues were removed during repeated TUR.

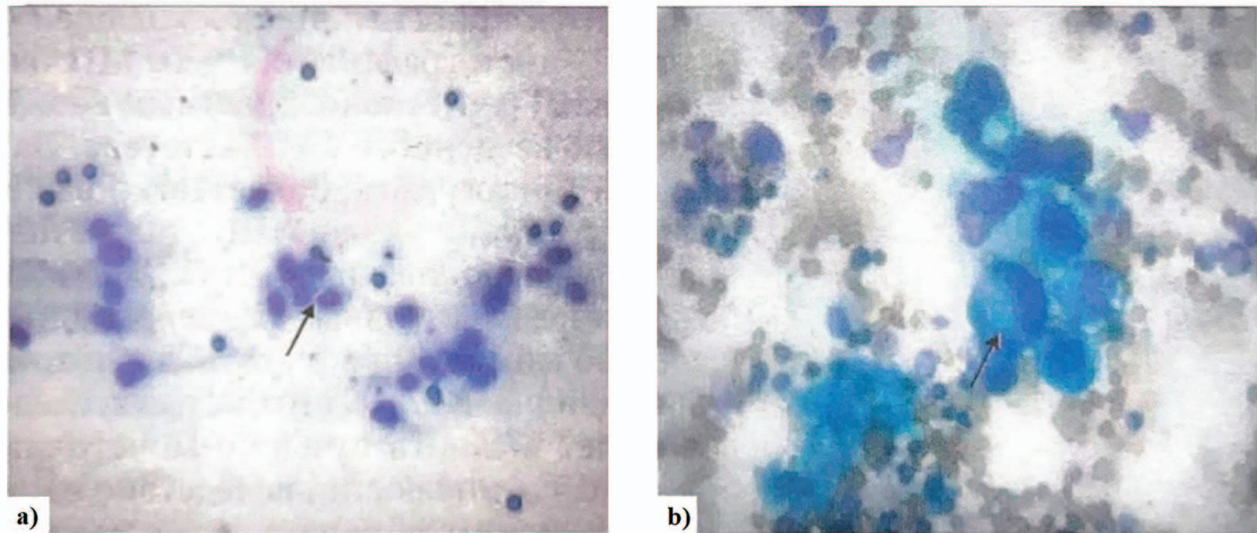


Figure 1. Cytological examination of urine sediment (Pappenheim staining, objective x40): a) highly differentiated transitional cell carcinoma (G 1); b) low-grade transitional cell carcinoma (G 3).

Table 1.

Clinical and demographic characteristics of patients before treatment

Name	Description	Absolute (%) number
Gender	male	75 (86)
	female	12 (14)
Age	40-49	15 (17)
	50-59	45 (51)
	60-69	23 (27)
	70<	4 (5)
Stage, category T	Tis	1 (1)
	Ta	18 (20)
	T1	42 (48)
	T2	6 (7)
	T3	17 (20)
	T4	3 (3)
Regional lymph nodes, category N	N0	79 (91)
	N+	8 (9)
Malignancy	G1	48 (55)
	G2	30 (34)
	G3	9 (10)
Number of tumours	1	26 (30)
	2-7	43 (49)
	8≤	18 (20)
Average diameter	≤3	67 (77)
	3<	20 (23)

Table 2.

Evaluation of the influence of factor features on the recurrence-free survival of patients with superficial BC using the Cox proportional hazards regression model

Factor	Chi-square test	e	Risk ratio, HR (95% CI)
Gender	0.0089	0.925	1.11 (0.14-5.90)
Age	2.99	0.084	5.49 (1.62-9.40)
Assessment of the state after the 1st TUR	0.47	0.486	1.57 (0.44-3.96)
The sum of relapse risk scores	5.81	0.016	3.63 (1.24-10.35)
BCG therapy	3.70	0.054	2.38 (0.96-7.24)

Evaluation of the surgical material obtained from the remaining patients confirmed the presence of a tumour. In 10 patients (20%), a highly differentiated tumour (anaplasia grade G1) was diagnosed; in 11 cases, a moderately differentiated tumour (G2); and in 1 patient, a low-differentiated tumour (G3).

To select an adjuvant chemotherapy regimen, the sum of the risk and progression scores was calculated, based on the number of tumours removed during repeated TUR. In 5 (10%) patients, a single malignant tumour was resected; in 17 patients (34%), the number of tumours was 2-7; only 2 patients (4%) who underwent repeated transurethral resection had more than 7 tumours removed at the same time. The average tumour size was also determined. In most patients (16, 33%), the affected tissue was less than 3 cm; in 8 patients (16%), it was more than 3 cm. The intermediate risk group, according to a certain number of points (1-9), included all patients in whom repeated TUR revealed a residual tumour. Thus, intravesical BCG therapy was indicated for all patients. Within 3-6 months after the start of BCG vaccine administration, 17% (4 patients) had immunotherapy toxicity, such as urosepsis and allergy, and 1 patient developed BCG resistance and relapse, after which a long-term valrubicin chemotherapy regimen was chosen. All patients underwent a control cystoscopy 3 months after the end of treatment, and if no tumour recurrence was detected, observation was recommended.

In one case, muscle-invasive breast cancer with a grade of anaplasia G3 was recognised. The interval between the first and second TUR was 9-10 weeks, so in this case, both an error in the preliminary assessment of the neoplasm and the progression of tumour cell remnants in the interval between resections, leading to the development of a secondary invasive neoplasm, cannot be excluded.

When observing patients in the intermediate-risk group, the fact that, with a relapse risk score of 1-4, the probability of recurrence within a year is 24%, and with a score of 5-9, it is 38%, was accounted for. Therefore, at the end of the observation and data collection phase, the patients in this sample were divided into two groups at the next stage of statistical analysis: an intermediate risk group of 24% (*intermediate-24*) and an intermediate risk group of 38% (*intermediate-38*). A scale of 3 parameters was used to assess the effectiveness of 1 TUR:

- *high efficiency*, if there was no need for a second tour;
- *medium efficacy* when a low-differentiated tumour was confirmed after 1 TUR and/or at the T1 stage;
- *low effectiveness* if the tumour bed was not removed or the detrusor muscle was not present in the surgical material.

A Cox proportional hazards regression model was used to assess the impact of independent factors on progression-free survival in patients with transitional cell carcinoma after TUR or repeated TUR and intravesical therapy (Table 2).

The regression model showed that only the total number of recurrence risk scores, which considers the stage and degree of anaplasia, as well as the number of detected tumours and their size, has a significant effect on disease-free survival in patients with non-invasive breast cancer. In this regard, recurrence-free survival was plotted as a function of the number of risk scores using the Breslow survival function (Figure 2). The risk of recurrence in 1 year in the low-risk group was 1%, in 3 years 4%, and in 5 years 15%. In the intermediate-risk group with a score of 1-4 (*intermediate-24*), the risk of recurrence at 1 year was 10%, at 3 years 25%, and at 5 years 45%. In the intermediate-risk group with a score of 5-9 (*intermedi-*

ate-38), the mortality rate was 15% at 1 year, 38% at 3 years, and 80% at 5 years.

The Kaplan-Meier method was used to make an overall estimate of the progression-free survival of patients with non-invasive breast cancer (Figure 3).

Each case of recurrence was designated as *complete*, and if no recurrence was recorded during the follow-up, such data were designated as *censored*. During the 5 years of data collection, 11 cases of recurrence (18%) were recorded, 10 in patients with transitional cell carcinomas and 1 in a

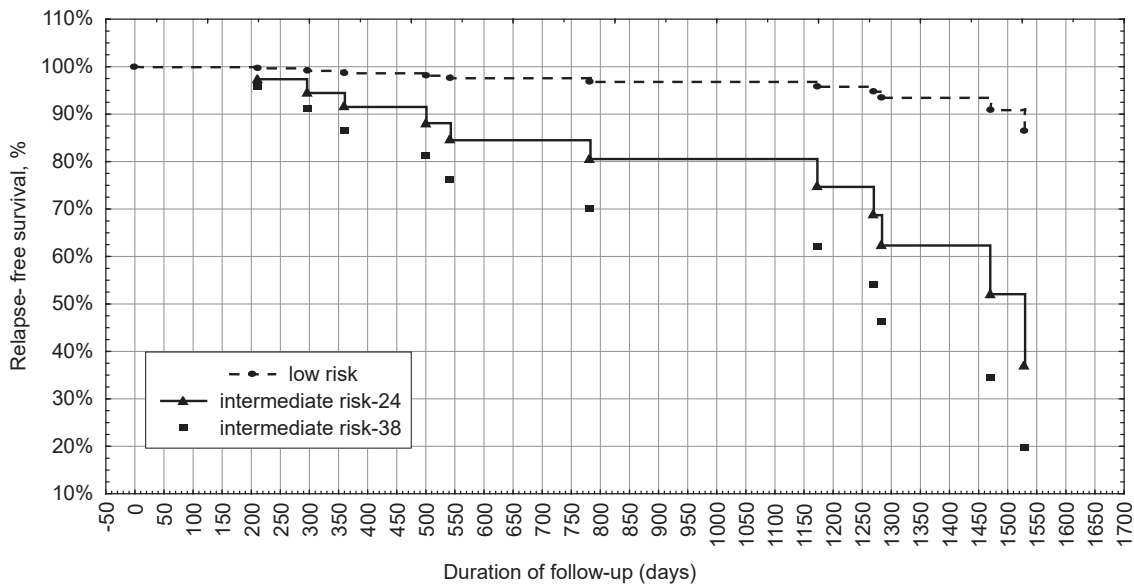


Figure 2. Comparison of recurrence-free survival of patients with superficial breast cancer depending on the number of risk scores

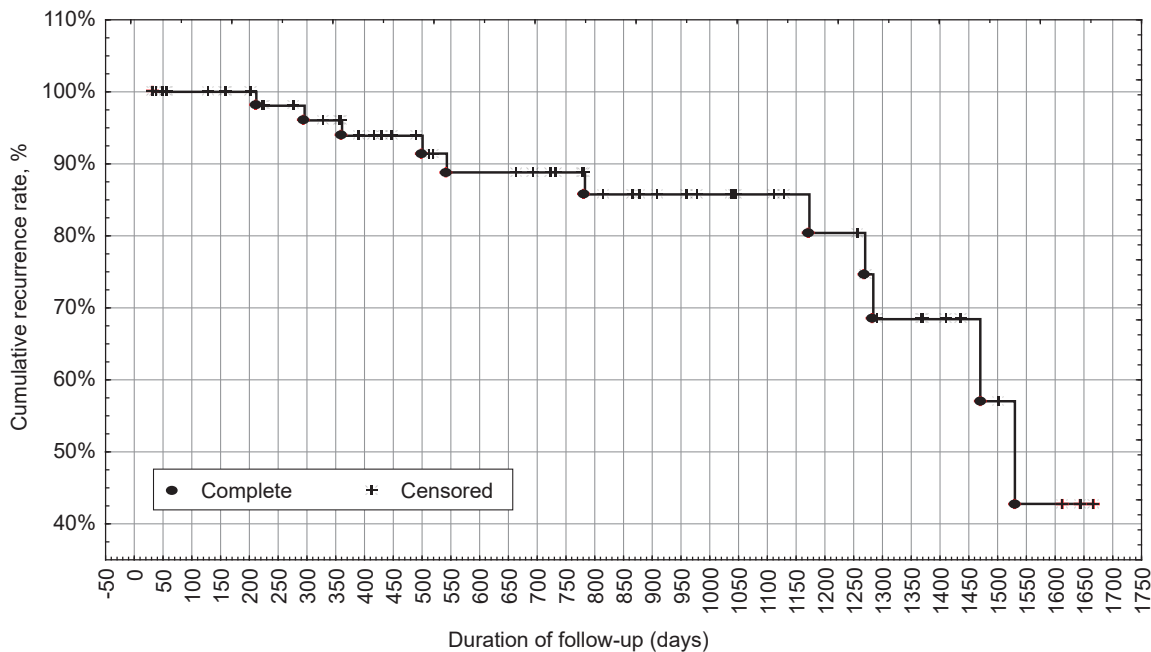


Figure 3. Kaplan-Meier progression-free cumulative survival in patients with superficial BC.

patient with carcinoma in situ. The median progression-free survival (50%) was 1,500 days (4.1 years), the lower quartile (25%) was 1,264 days (almost 3.5 years), and the upper quartile (75%) was not recorded for five years, which roughly coincides with official statistics for this category of cancer patients. In 6 patients, recurrence was accompanied by the progression of the superficial tumor to an invasive form. Thus, during the entire five-year period of material collection, 33 patients with muscle-invasive breast cancer were identified, including 26 with primary tumors and 7 with secondary tumors.

Among patients with primary muscle-invasive BC, 7 had indications for organ-preserving therapy. There were 6 men and 1 woman aged 45-61 years. All of them had a single tumor localised at the bottom or lateral wall of the bladder, no bilateral ureterohydronephrosis and no metastases. In 2 patients (29%), the average tumor diameter was ≤ 3 cm, and in the remaining 3-6 cm. Highly differentiated neoplasm was diagnosed in 4 patients (57%), and 3 (43%) had G2 anaplasia. Tumor staging based on the results of clinical examination confirmed the stage cT2N0M0 in 5 patients (71%) and the stage cT3N0M0 in 2 patients.

All patients with muscle-invasive tumors, regardless of initial tumor assessment or prior treatment, received 3-4 courses of neoadjuvant polychemotherapy with the gemcitabine + cisplatin regimen. After that, pelvic and abdominal ultrasound, computed tomography of the urinary system (CT urography), cystoscopy and cytological examination of urine sediment after bladder flushing were performed to monitor the effectiveness of NAC. Depending on the degree of tumor regression according to the Response Evaluation Criteria in Solid Tumors (RECIST), organ-preserving surgery or radical cystectomy with bilateral lymphadenectomy was recommended (Table 3).

The relationship between tumor anaplasia and treatment response was statistically confirmed using a multiple linear regression model. As a result of the calculations, the multiple correlation coefficient R of 0.416, the adjusted coefficient of determination R^2 -adjusted of 0.147, Fisher's F -criterion of 6.49, and the linear scatter plot showed an inverse relationship between the points.

No patients had a complete regression of the malignancy. There were also no cases of tumor progression or NAC intolerance, which made it possible to avoid treatment adjustments and did not require patients to be transferred to the 2nd line of NAC.

Another advantage of administering neoadjuvant NAC to all patients with muscle-invasive BC was a doubling of the number of patients with indications for organ-preserving surgery. Before NAC, there were 7 such patients, and after treatment, 9 more patients were added. All patients reported improvement in their condition, reduction of pain and dysuria.

Accordingly, they underwent TUR and bladder wall resection.

In 17 patients, the level of regression was insignificant, as defined by RECIST criteria as stabilisation. Objectively, the condition of these patients remained severe due to dysuria and pain during urination, continued micro- and macrohaematuria, which led to moderate to severe anaemia. All patients with a poor response to NAC underwent radical cystectomy with bilateral lymphadenectomy. Transurethral urinary diversion surgery with the formation of an orthotopic bladder using the Double-U technique was performed in 6 patients (35%), and in 11 (65%) cases, cystectomy operations with internal urinary diversion were performed: among them, 8 direct ureterosigmoid anastomoses, 1 case of ureteroile-

Table 3.

Surgical intervention depending on the effectiveness of neoadjuvant NAC

Evaluation of tumour regression by RECIST	Number of patients, n (%)	Average % regression, (95% CI)	Surgical intervention		
			TUR	Resection of the bladder wall	Radical cystectomy
Full regression	0				
Partial regression	16 (48)	48.7 (42.4-57.5)	6	10	
Stabilisation	17 (52)	10.3 (6.4-15.1)			17
Progression	0				

Table 4.

Evaluation of the influence of factor characteristics on the recurrence-free survival of patients with muscle-invasive BC using the Cox proportional hazards regression model

Factor	Chi-square test	e	Risk ratio, HR (95% CI)
Gender	0.69	0.41	0.43 (0.056-2.21)
Age	0.34	0.56	0.55 (0.07-3.14)
Stage	2.95	0.086	0.22 (0.04-1.24)
Malignancy degree	5.71	0.017	2.53 (0.70-6.75)
Evaluation of tumour regression by RECIST	6.26	0.012	5.15 (1.39-14.32)

osigmoid anastomosis and 2 cases of transrectal urinary derivation using Mainz-pouch II.

The long-term results of surgical treatment were monitored for 4 months to 4 years. Control cystoscopy, ultrasound of the abdominal cavity, pelvis, retroperitoneal space, and CT urography were performed 3 months after surgery, and then every six months. As a result, 2 cases of malignant tumor recurrence were recorded in patients after organ-preserving surgery and 13 cases in patients after radical cystectomy. Among the recurrences after RC, there was 1 pelvic recurrence, 1 case of lymph node metastasis in lymph node dissection and 11 distant metastases. In 1 patient, deterioration was detected due to progressive chronic renal failure (CRF). Using the Cox proportional

hazards regression model, the influence of several factor attributes on the disease-free survival function in patients with muscle-invasive BC was studied (Table 4).

As expected, the assessment of the degree of tumor regression by RECIST demonstrated the most statistically significant contribution to the recurrence-free survival of patients with invasive BC according to the chi-square, p-value and HR hazard ratio. Moreover, a significant effect was observed in the dependence of recurrence on tumor malignancy. Relapse-free survival curves were constructed depending on the efficacy of neoadjuvant NAC (Figure 4).

The curve of patients who experienced stabilisation of tumor growth after neoadjuvant NAC

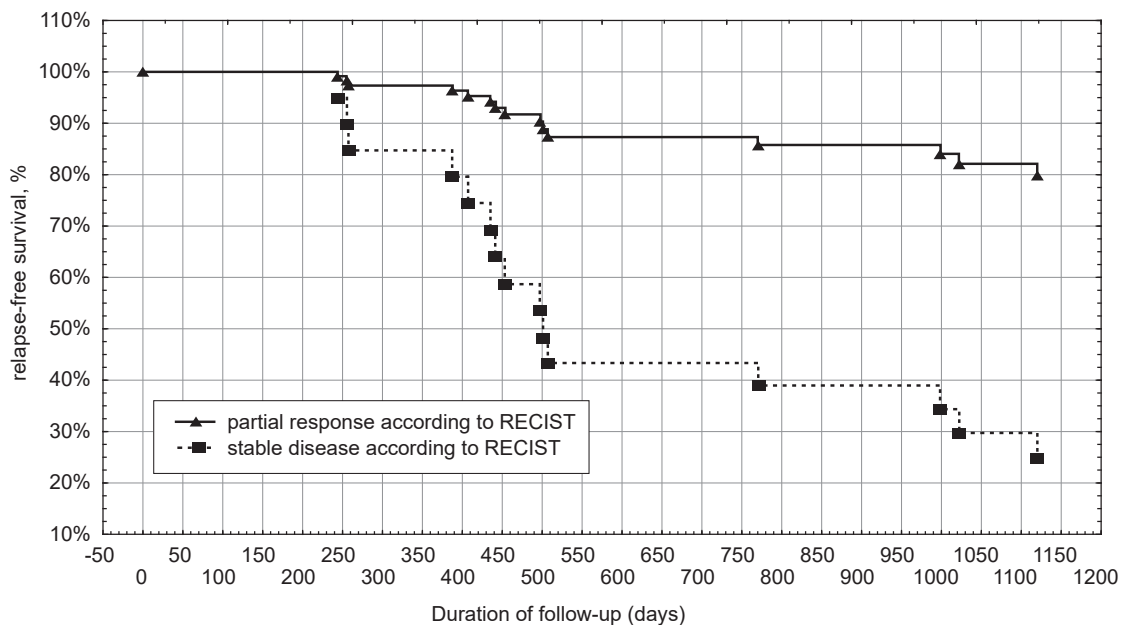


Figure 4. Comparison of progression-free survival in patients with in situ BC by tumor regression score according to RECIST.

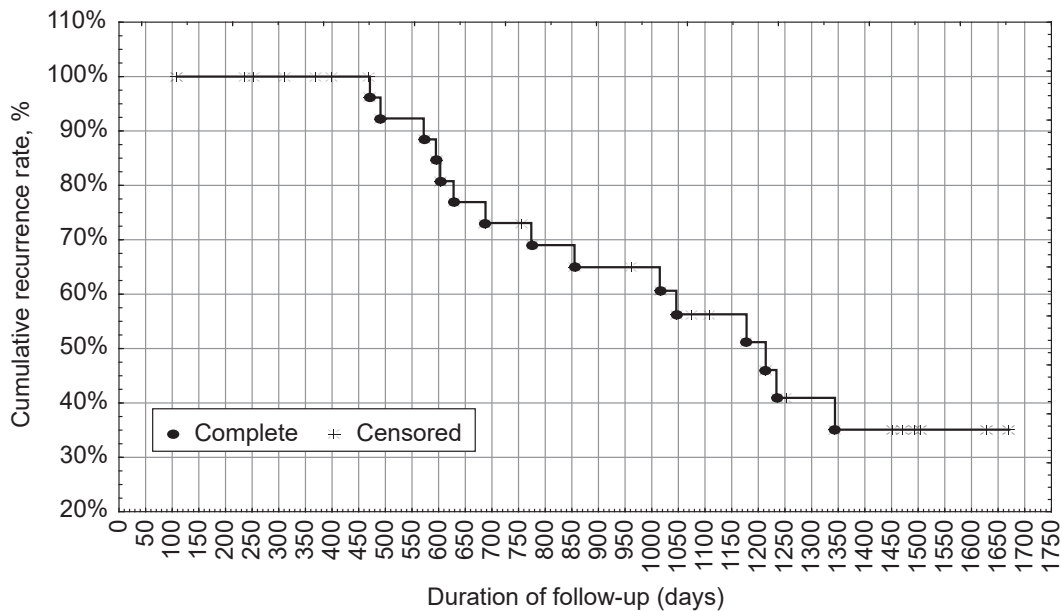


Figure 5. Overall cumulative Kaplan-Meier survival in patients with muscle-invasive BC.

showed that, at 1 year of follow-up (360 days), approximately 15% of patients had a relapse; at 2 years (730 days), 55%; and at 3 years (1,100 days), 70%. In the group of patients with partial tumor regression, recurrence occurred in only 2% of cases at 1 year of follow-up, 12% at 2 years, and only 18% of patients had recurrent BC at 3 years of follow-up (1,100 days).

To estimate overall survival in patients with invasive BC, we used the Kaplan-Meier method (Figure 5).

Each case of death during the follow-up period was designated as *complete*; the opposite cases were designated as *censored*. The median overall survival (50%) was 1,186 days (3.3 years), the lower quartile (25%) was 658 days (1.8 years), and the upper quartile (75%) was not recorded during follow-up.

Treatment for bladder cancer, especially with neoadjuvant chemotherapy and organ-preserving surgeries, is associated with several side effects and complications, which can significantly impact patients' overall health and quality of life. Chemotherapy regimens like gemcitabine and cisplatin, commonly used in muscle-invasive bladder cancer, are known to cause systemic side effects, including nephrotoxicity, ototoxicity, myelosuppression, and gastrointestinal disturbances. These

effects are dose-dependent and can lead to hospitalisation, dose modification, or discontinuation of therapy in severe cases. Additionally, intravesical treatments, such as BCG therapy, while effective in preventing recurrence in non-muscle-invasive bladder cancer, can cause local side effects like cystitis, hematuria, dysuria, and pain. Systemic side effects may also occur, including fever, chills, and fatigue, due to BCG's immune-modulatory effects. These side effects can be particularly concerning for patients with comorbidities or those undergoing multiple cycles of treatment.

Surgical interventions, such as radical cystectomy, also come with inherent risks, including infections, urinary tract complications, bleeding, and delayed wound healing. Long-term complications from cystectomy can involve the development of chronic kidney disease or metabolic imbalances, particularly when the patient undergoes urinary diversion or orthotopic bladder reconstruction.

The variability in patient response to treatment can be attributed to a range of factors, including tumor molecular characteristics, host-related factors, and the specific treatment approach. One key factor influencing treatment response is the tumor's genetic makeup, including mutations in genes such as TP53, FGFR3, and PIK3CA, which

can affect sensitivity to chemotherapy or immunotherapy. For example, tumors those with FGFR3 mutations may respond better to BCG therapy, whereas those with TP53 mutations are often more resistant to conventional chemotherapies. Another critical factor is the degree of tumor regression following neoadjuvant chemotherapy. Patients whose tumors exhibit significant regression, as measured by RECIST criteria, tend to have better long-term survival. Maybe due to the greater chemosensitivity of these tumors, which are more susceptible to the cytotoxic effects of chemotherapy. Additionally, the host immune response plays a crucial role in treatment efficacy. A robust immune response can enhance the effectiveness of immunotherapies, such as BCG, whereas patients with compromised immune systems or underlying conditions like diabetes may experience less favourable outcomes. The presence of comorbidities and overall patient health can also impact recovery and the ability to tolerate aggressive treatments, influencing both short-term and long-term survival. Understanding these mechanisms is essential for optimising treatment regimens and personalising patient care, ensuring that the most appropriate therapies are used for each individual based on their specific tumor characteristics and health status.

In conclusion, the results of this study highlight the significant impact of tumor staging, risk stratification, and tailored treatment approaches on the overall and recurrence-free survival of bladder cancer patients. The data show that tumor characteristics, including stage, degree of malignancy, and tumor size, play a crucial role in predicting patient outcomes. Neoadjuvant chemotherapy, particularly with gemcitabine and cisplatin, demonstrated varying degrees of tumor regression, with partial regression correlating with better survival and a higher likelihood of organ-preserving surgery. Additionally, intravesical BCG therapy showed effectiveness in preventing recurrence in non-muscle-invasive bladder cancer, although side effects and complications, including immunotherapy toxicity and cystitis, were noted. The variability in treatment responses underscores the importance of individualised patient management, accounting for molecular features, comorbidities, and treatment-related factors to optimise therapeutic outcomes.

DISCUSSION

Bladder cancer remains a serious challenge in modern urology, affecting mainly men of working age(1). The study included 75 men, which was 86% of the total sample. More than half of them (42 men, 51%) were aged 50-59 years. The first manifestations of the disease are highly characteristic, so most patients are diagnosed with BC at stage T1; in the present study, this stage was observed in 42 patients (48%).

The primary method of treatment for superficial forms of urothelial carcinoma is minimally invasive transurethral resection. There are several circumstances in which a second TUR is recommended after 2-6 weeks, but in 30-75% of cases, residual tumor is not detected(12,13). After the second TUR, the pT0 stage was determined in 51% of the operated patients. Thus, unnecessary redundant surgery was performed in half of the patients, which significantly increased the trauma and cost of treatment. It is worth noting that in one patient, histological examination of material samples after repeated TUR did not match the previous results, and instead of non-invasive BC, a muscle-invasive form of BC was diagnosed. In some cases, repeated resection improves the quality of tumor staging and assessment, but the criteria for the second TUR require further clarification.

The high efficacy of first-line intravesical immunoadjuvant therapy for papillary BC of medium and high risk has been proven(14). Induction and maintenance regimens of BCG vaccine instillation for 3 years significantly reduced the incidence of malignant progression and increased the duration of the disease-free period by 30-70%(15). However, clinical trials of the vaccine in Europe and the United States showed that 27% (USA) to 80% (Europe) of patients completed the three-year course, while the rest preferred chemotherapy due to BCG resistance or severe side effects after administration of mycobacterial antigens(16). In the present study, 5 patients (21%) were identified as such, which is consistent with data from the European Organisation for Research and Treatment of Cancer (EORTC).

To assess recurrence-free survival in patients with superficial BC, censored initial data were used to fit a Cox proportional hazards model. Logically, the statistical significance of Chi-square 5.81 at $p=0.016$ showed that there is a dependence

of the risk (probability) of an event, in the current case, relapse, on the factor attribute *sum of relapse risk scores*. The hazard ratio HR was also calculated and was equal to 3.63. Meaning that all patients with a higher total number of recurrence risk scores in the selected period have a 3.63 times higher risk of recurrence compared to others.

The Kaplan-Meier survival function for this group of patients revealed a median survival rate (MSR) of 1,500 days (4.1 years). Half of the patients in the study lived for 1,500 days without a recurrence of the disease. The lower quartile (25% percentile) of 1,264 days showed that 75% of patients with papillary BC were not diagnosed with recurrence during this period, consistent with other authors' data(17). According to EORTS data, the average 5-year recurrence rate in patients with urothelial carcinoma at stages T1 and T2 ranges from 31-78%, i.e., it may not reach the upper quartile (75% percentile), which, in the study, exceeds the time limits of the observation phase(18).

A systematic review of prospective and retrospective studies on the effectiveness of trimodal organ-preserving therapy in patients with muscle-invasive BC without metastases and severe comorbidity has demonstrated the advantages of this treatment compared to radical cystectomy(19). Probably due to a significant improvement in the moral state and quality of life of patients(20). However, there is still no single approach to TMT. Positive results were obtained with the administration of adjuvant chemotherapy with gemcitabine/cisplatin or gemcitabine/carboplatin after radical endoscopic removal of the tumor with bladder preservation(21). Another treatment regimen included a combination of postoperative NAC with GC, followed by parallel cisplatin infusions and radiotherapy sessions(22). Based on the successful results of clinical trials of this regimen, a decision was made in favour of neoadjuvant GC therapy before TUR surgery(23). According to the RECIST criteria, 46% of patients showed partial regression of malignancy, which made it possible to increase the number of patients with a successful prognosis for organ-preserving surgery by more than twice as much as before neoadjuvant NAC.

Removal of the affected bladder remains the standard of care for muscle-invasive urothelial carcinoma despite the serious functional consequences associated with urinary derivation prob-

lems(24). Over the past 30 years, several types of surgical interventions have been introduced that allow these problems to be addressed depending on the patient's condition and the anatomical and functional features of the urinary tract and intestines(25). The formation of an orthotopic bladder is considered the most promising method due to its improved quality of life for patients(26). A contraindication to this type of surgery is the unsatisfactory functional state of the kidneys and liver. Prolonged contact of urine with the intestinal area can lead to hyperchloremic metabolic acidosis, which can be threatening in the event of decreased renal filtration function. Orthotopic bladder formation is allowed only in patients with a creatinine clearance of more than 60 ml/min(27). In the study, only 6 patients (35%) met all the criteria for this operation.

The Cox proportional hazards model was used to evaluate multivariate regression of censored data on recurrence-free survival in patients with muscle-invasive BC. As expected, the HR values showed that the risk of recurrence was 2.53 times higher in patients with low-grade malignancies. However, in patients with partial tumor regression according to RECIST criteria after neoadjuvant NAC, the risk of recurrence was 5.15 times lower, as indicated by p , HR, and χ^2 values, compared with patients who only had stabilisation of the malignant process in response to therapy. These results reflected the progression-free survival curves. Although at 1 year after radical cystectomy all patients noted significant improvement in their physical and mental condition, by 3 years of follow-up, 70% had recurred, consistent with other authors' data(28). Organ-preserving tactics significantly reduced the risk of recurrence; after 3 years, recurrent BC was recorded in only 18% of cases, i.e., in almost 4 times fewer people, due to the selection criteria used for TMT. According to these criteria, organ-preserving surgery was performed only in patients with partially regressed tumors who had undergone effective neoadjuvant NAC. In the selected cohort of patients, there was a correlation between the degree of tumor regression and anaplasia, which directly affects the recurrence rate.

OS data in patients with muscle-invasive BC are consistent with those of the European Association of Urology(29). Notably, overall survival in

BC is affected, among other factors, by the development of CRF, the risk of which increases after radical cystectomy(30). Among the selected cohort of patients, there was also a case of severe CRF in a patient after RC, which led to death.

The study aimed not to compare the effectiveness of different treatment methods or surgical interventions; therefore, the data on progression-free survival after TMT differ from those of clinical randomised trials. Studying the problem in a healthcare facility imposed specific responsibilities on the implementers: first and foremost, providing each patient with quality medical care. Nevertheless, convincing results on the impact of accurate and timely staging and the introduction of modern treatment approaches on the overall and recurrence-free survival of patients with bladder cancer were obtained.

CONCLUSIONS

This study points out the importance of accurate tumor staging, risk stratification, and the implementation of modern treatment protocols in the management of bladder cancer.

The analysis of superficial urothelial carcinoma patients highlighted the importance of repeated transurethral resection for ensuring correct tumor staging and detecting possible progression to muscle-invasive disease. The findings confirm that the recurrence-free survival of patients with superficial bladder cancer is in correlation with the total number of recurrence risk scores, incorporating factors such as tumor stage, degree of malignancy, and tumor size.

The study underscored the impact of neoadjuvant chemotherapy (NAC) on improved outcomes for patients with muscle-invasive bladder cancer. Although only a portion of patients showed significant tumor regression, the majority of patients treated with NAC experienced stabilisation or partial regression, which increased the feasibility of organ-preserving surgeries. Furthermore, the degree of tumor regression, as assessed by RECIST played a key role in predicting long-term survival, with a substantial correlation to progression-free survival.

The work performed in a healthcare facility did not allow randomisation in selecting patients for trimodal organ-preserving therapy, which im-

posed limitations and led to an underestimation of disease-free survival in this group. The results obtained indicate the prospects for improving the criteria for prescribing repeated transurethral bladder resection in patients with superficial urothelial carcinoma. As for patients with muscle-invasive BC, the need for further study of predictors of neoadjuvant NAC's success with the prospect of their mandatory use in the clinic is recorded.

The study confirms the relevance of modern diagnostic and therapeutic approaches in improving both disease-free and overall survival in bladder cancer patients. For patients with muscle-invasive BC, the findings support the continued exploration of predictive markers for NAC response, which could guide more personalised treatment strategies and improve clinical outcomes. The data also highlight the necessity for regular follow-up and monitoring to detect recurrences and manage treatment effectively, thereby enhancing patient prognosis and quality of life.

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Sažetak

Stadij i suvremeni pristupi liječenju raka mokraćnog mjehura

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Taktike liječenja pacijenata s površinskim urotelijalnim karcinomom i mišićno-invazivnim karcinomom mokraćnog mjehura značajno se razlikuju, stoga dijagnoza, stadij i propisivanje odgovarajuće terapije ostaju relevantni. Tijekom razdoblja od 5 godina prikupljeni su podaci praćenja 61 slučaja papilarnog urotelijalnog karcinoma, 26 primarnih i 7 sekundarnih mišićno-invazivnih karcinoma mokraćnog mjehura. Medijan preživljavanja bez recidiva kod pacijenata s prijelaznostaničnim karcinomom bio je 4,1 godina, s najvećim utjecajem na ovaj pokazatelj u zbroju bodova rizika od recidiva, koji su uključivali stadij tumora, malignost, veličinu i broj. Neoadjuvantna polikemoterapija rezultirala je djelomičnom regresijom malignosti prema RECIST-u samo u 48% pacijenata s mišićno-invazivnim karcinomom koji su zatim podvrgnuti operaciji očuvanja organa. Bodovi regresije tumora korelirali su sa stupnjem malignosti i imali su statistički značajan učinak na funkciju preživljavanja bez progresije bolesti. U preostalih 52% slučajeva s mišićno-invazivnim karcinomom, nakon neoadjuvantne polikemoterapije, rast tumora dijagnosticiran je kao stabiliziran, što je dalo osnovu za radikalnu cistektomiju. Nakon operacije, pacijenti su izvijestili o poboljšanju moralnog i fizičkog stanja, ali je medijan ukupnog preživljavanja za ove pacijente bio 3,3 godine. Dobiveni rezultati pokazuju utjecaj procjene tumora, stadija tumora i odgovarajućeg liječenja na ukupno preživljavanje i preživljavanje bez recidiva kod raka mokraćnog mjehura.

KLJUČNE RIJEČI: *urotelijalni karcinom, mišićno-invazivni karcinom, ukupno preživljenje, preživljenje bez recidiva*