

Predicting recurrence of non-muscle-invasive bladder cancer after transurethral resection

Haris Đug¹, Samed Jagodić¹, Jasmina Ahmetović-Đug², Zijad Selimović¹, Alemdar Sulejmanović¹

¹Department of Urology, Clinic of Surgery, ²Clinic of Anesthesiology and Reanimation, University Clinical Centre of Tuzla; Tuzla, Bosnia and Herzegovina

ABSTRACT

Aim To determine clinical prognostic factors and their impact on the risk of recurrence of newly discovered non-muscle-invasive bladder cancer.

Methods The study included 120 patients of both sexes aged 45-80 years with newly discovered non-muscle-invasive bladder cancer. All the patients were treated surgically by transurethral electro resection (TUER). The outcome of patients with and without recurrence was followed at intervals of three months after surgery, the total of two years. For monitoring the probability of early recurrence the criteria of the European Organization for Research and Treatment of Cancer (EORTC) were used.

Results The average age of the patients was 65.9 years, 79 (79.2%) males and 21 (20.8%) females. The total of 67 (55.8%) patients had a recurrence during the period of monitoring. The average time to the first and fourth recurrence was 15.4 and 23.9 months, respectively. Numbers of tumors and a degree of invasion had a significant prognostic impact on the risk of recurrence. The EORTC score was a highly significant predictor of recurrence (OR=1.237; p<0.001).

Conclusion Based on available clinical and pathological prognostic factors and by stratification of patients into three disease risk groups it is possible to predict the possibility of disease. Individual approach and recommendations for the treatment using EORTC risk tables should improve the quality of treatment.

Key words: immunotherapy, probability, treatment

Corresponding author:

Haris Đug
Department of Urology, Clinic of Surgery,
University Clinical Centre of Tuzla
Golubrijeg45, 75000 Tuzla
Phone: +387 35 303 720;
Fax: +387 35 303 285;
E-mail: haris.djug@gmail.com

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INTRODUCTION

Urothelial bladder cancer is the 7th most common cancer in men and the 17th most common in women worldwide. The incidence varies between regions and countries; in Europe, the highest age standardized incidence rate has been reported in Spain (41.5 in men and 4.8 in women) and the lowest in Finland (18.1 in men and 4.3 in women) (1). The incidence of bladder cancer has decreased in some registries possibly reflecting decreased impact of causative agents mainly smoking and occupational exposure (2). The mortality of bladder cancer has also decreased possibly reflecting increased standard of care (3).

Approximately 75% of newly diagnosed urothelial bladder cancer are noninvasive and have a high rate of recurrence and progression despite local therapy (4). Genetic predisposition has a significant influence on bladder cancer especially via its impact on susceptibility to other risk factors. Tobacco smoking is the most important risk factor for bladder cancer accounting for approximately 50% of cases (5). Medical conditions may predispose individuals to bladder tumor genesis through direct causation or as a side effect of treatment. Examples of direct causative include chronic urinary retention and upper tract dilation increasing urothelial exposure to carcinogens and carcinogenesis associated with chronic inflammation or schistosomiasis (6).

Non-muscle-invasive bladder cancer has a high prevalence due to low progression rates and long-term survival in many cases; patients with muscle-invasive bladder cancer are at higher risk of cancer-specific mortality (5). Patients with Ta, T1 tumors can be divided into risk groups based on prognostic factors (7). To predict separately the short and long-term risk of both recurrence and progression in individual patients a scoring system was developed by the EORTC (7).

Depending on the characteristics of the patients, after transurethral electro resection (TUER) the possibility of recurrence within one year ranges from 15-70% and the possibility of progression over five years ranges between 7-40% (6). Prognostic factors in patients with non-muscle-invasive bladder cancer have a major impact on the future course of the disease and appropriate adjuvant treatment after TUER (chemotherapy or immunotherapy) (8).

The guidelines panel recommends stratification of patients into three risk groups that will facilitate treatment recommendations. The recommendation is similar to that provided by the International Bladder Cancer Group (9).

The treatment of patients with non-muscle-invasive bladder cancer requires high costs. The reasons are: the disease is common, many patients survive and require lifelong monitoring, and more than half of the cancers recur and require repeated surgical treatment. The aim is to reduce the number of recurrences thereby reducing the cost of treatment (10). In Bosnia and Herzegovina in major clinical centers records of registration of malignant diseases are kept, but there is no official data on the incidence, prevalence and mortality from bladder cancer.

The aim of the study was to determine the clinical prognostic factors and their impact on the risk of recurrence in the patients with newly discovered non-muscle-invasive bladder cancer attending Department of Urology, Clinic of Surgery of the University Clinical Center Tuzla. The purpose of the study was to compare the number and frequency of recurrences in our patients who do not receive any form of adjuvant intravesical therapy compared to other centers that provide protocol intravesical chemotherapy or immunotherapy. The results will be used to revise our treatment protocols and lead to expanding the indications for the use of adjuvant therapy in order to reduce the number of recurrences, better treatment and reducing treatment costs.

PATIENTS AND METHODS

Study design and patients

Retrospective-prospective clinical study was conducted in the period 2004-2008 at the Department of Urology, Clinic of Surgery of the University Clinical Center Tuzla. The retrospective part of the study was performed in the period from 2004-2006 and included 70 patients, and prospective part of the study was done from 2006 to 2008 and included 50 patients.

The study included 120 patients of both sexes aged 45-80 years with newly discovered non-muscle-invasive bladder cancer. All patients were treated surgically by transurethral electro resection (TUER). All pathohistological analyses were performed by

standard methods at the Clinic of Pathology, University Clinical Center Tuzla. The Ethical Committee of Public Health Institution University Clinical Center Tuzla approved this investigation.

Methods

The outcome of the patients with and without recurrence (frequency and number) was followed.

Patients were categorized according to pathological findings of the type of cancer and a degree of malignancy: Ta, T1 bladder cancer according to the depth of invasion, and G1, G2, and G3 degree of malignancy (11, 12). The patients were divided into 3 groups with low, low intermediate and high intermediate risk of recurrence and progression (no patients with carcinoma in situ, CIS) and the research was carried out in relation to newly discovered non-muscle-invasive cancers.

For monitoring of the probability of early recurrence, the criteria (risk tables) of the European Organization for Research and Treatment of Cancer (EORTC) were used (7).

We performed univariate and multivariate Cox’s regression analysis of impact of the number of tumors (tumor may occur as solitary or can be presented in the form of multiple tumors of the urinary bladder), the size, degree and the degree of invasion on the risk of recurrence. Each prognostic factor is scored so that for example a recurrence with more than one tumor is awarded more points and carries a higher risk of recurrence.

In the EORTC research the ranking data were obtained from 2596 patients with non-muscle-invasive bladder cancer, and the patients with only CIS were not included ; 78% of patients received intravesical therapy mostly chemotherapy, while the secondary TUR was not done nor was the BCG therapy administered according to the schedule.

Statistical methods

The basic tests of descriptive statistics were made and quantitative variables were compared by t-test with correction for unequal variances where they are distributed by the same normal distribution. For quantitative variables, which have not been distributed by the normal distribution, the Mann-Whitney U test was used. Categorical variables were analyzed by X² test or Fisher’s exact

test for cell values below 5. Univariate binomial logistic regression was used to test the level of predictive influence of each individual parameter for the presence of cancer. The performance of predictive scores and comparison of individual performance was analyzed by receiver operating characteristic (ROC) analysis. The value of p < 0.05 was considered significant for all analyses.

RESULTS

During the observation period 120 patients with newly discovered non-muscle-invasive bladder cancer were found. Mean age of patients was 65.9 years (45-80); males were represented more frequently than female patients, 79 (79.2%) and 21 (20.8%), respectively (p < 0.05).

A total of 53 (out of 120, 44.2%) patients were without recurrence, and 67 (55.8%) patients had a recurrence of newly discovered non-muscle-invasive bladder cancer. The average number of tumors was 1 (p < 0.05). The most common malignant grade was G1, and the rarest one was G3 (p < 0.05). The T1 stage of the disease was prevalent over the stage Ta (p < 0.05) (Table 1).

Table 1. Distribution and risk factors of patients with recurrence of newly discovered non-muscle-invasive bladder cancer

Variable	Value
Age (year)	65.9±10.6
Sex (m/f, %)	79.2 / 20.8
Median of tumor number %95	1 CI 1.07-1.37
Grade (G1/G2/G3; %)	41/35; 24
T stadium (Ta/T1; %)	27 / 73

Univariate Cox’s regression analysis of impact of the number, size, degree and the degree of invasion on the risk of recurrence has shown that the number and the degree of invasion of the tumor had significant prognostic impact (Table 2).

Table 2. Risk factors for recurrence of the disease

Risk factor		Univariate analysis	Multivariate analysis
Number of tumors	OR	1.21	1.19
	(%95 CI)	(1.07-1.37)	(1.05-1.34)
	p-value	0.002	0.006
Size of tumor	OR	1.16	
	(%95 CI)	(0.86-1.58)	
	p-value	0.33	
Grade	OR	1.45	
	(%95 CI)	(0.79-2.68)	
	p-value	0.23	
Degree of invasion	OR	2.05	1.87
	(%95 CI)	(1.10-3.84)	(1.00-3.53)
	p-value	0.025	0.05

The total of 67 (55.8%) patients had a recurrence during the observation period: one recurrence was noted in 28 (23.3%) patients, with an average time without recurrence of 15.49 months (%95 CI=13.96 to 17.02). The two recurrences were observed in 27 (22.5%) of patients, with average time to the appearance of second recurrence of 21.58 months (%95 CI=20.70 to 22.46). Six (5%) patients had three and four recurrences each with the average time to the appearance of recurrence of 23.74 months (%95 CI=23.49 to 23.99) and 23.93 months (%95 CI=23.83 to 24.02), respectively.

The analysis of EORTC score has shown highly significant recurrence prediction of (OR=1.237; %95 CI=1.115-1.374) ($p<0.001$): for every extra point of EORTC score for the recurrence, the risk of the recurrence has risen by an average of 1.237 times (Figure 1).

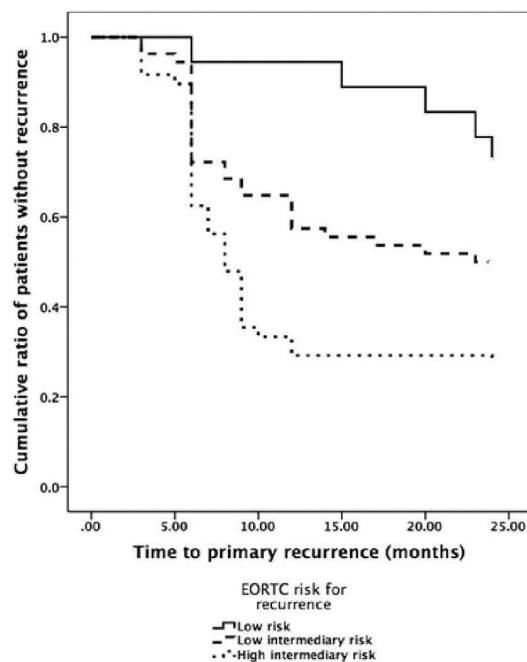


Figure 1. The European Organization for Research and Treatment of Cancer (EORTC) recurrence risk

By stratification of patients into risk groups the smallest number of recurrences was in the group with a low risk of recurrence, five (7.5%), following the group with low intermediate risk, 27 (40.3%), and the largest number of recurrences was recorded in the high intermediate risk group, 35 (52.2%).

The statistical analysis in our study did not include patients with CIS because of the small number of patients diagnosed with CIS (two patients).

DISCUSSION

This research has shown that the degree of invasion and number of tumors are the most important prognostic factors for recurrence of non-muscle-invasive bladder cancer. Sylvester et al. (2006) have shown that the number of tumors, tumor size, and the previous recurrence are the most important prognostic factors for disease recurrence (7).

More than half of the patients had a recurrence during the monitoring period of two years. The average time to the first recurrence was 15 months and 23 months to the fourth one. Using the EORTC risk tables and assessing individual risk of recurrence, planning frequency of control cystoscopies, the disease is diagnosed at an early stage of development which facilitates surgical treatment and reduces treatment costs. Statistical analysis showed a significant association of disease recurrence with risk groups: patients with a low risk of recurrence had the smallest percentage of recurrence and those with the highest risk had the highest percentage of recurrence.

In his study, which dealt with the treatment and monitoring of recurrence and disease progression in patients after TUER urinary bladder tumor and adjuvant intravesical immunotherapy, Seo (2010) has shown that the recurrence occurred to a lesser extent than in the EORTC study, explaining this as a consequence of a larger number of the patients receiving adjuvant intravesical immunotherapy (in the EORTC study only 5.9% of patients received adjuvant BCG therapy, while others have received intravesical chemotherapy after TUER) (13). Comparing with other studies in which recurrence rate of 41% was noticed (9,13), recurrence in the present study occurred in 56% of cases, and average time to recurrence was similar in both studies, 13.6 (13) and 15.4 months, respectively. During of median follow-up of 74 months 44% patients had a recurrence in patients from Spain, Netherlands and Denmark (14).

In a multi-centric study, Malmstrom et al. (2009) have shown that the risk of recurrence is reduced by 32% in patients with intermediate risk who were treated with adjuvant intravesical immunotherapy in comparison with those that were treated with adjuvant intravesical chemotherapy (15).

Bobinski and Lipinski (2009) in their study found that recurrence occurred in 46.87% patients, and

a significant association of the risk of recurrence with risk groups after one year has been found (stratification of patients into risk groups for risk of recurrence based on the total number of scores obtained by scoring clinical and pathological characteristics of the tumor). Their research is most similar to our study because the patients were also treated only surgically by TUEr and did not receive adjuvant intravesical chemotherapy or immunotherapy (16) suggesting that the risk of recurrence is being increased in patients from the group with a higher risk of recurrence and that the EORTC scoring system and risk tables allow prediction of disease progression after the treatment, and stratify patients according to the risk of recurrence. Fernandez-Gomez et al. (2011) demonstrated a lower risk of recurrence in all risk groups in relation to the EORTC study and showed that the EORTC risk tables overestimated the risk of recurrence in patients treated with adjuvant intravesical immunotherapy suggesting the need for its recalibration (17).

The results of our study have shown that EORCT score was a significant predictor of the disease recurrence. Comparing the results with the EORCT research, slightly higher percentage of recurrences was observed in our study probably because the patients were not receiving intravesical che-

motherapy immediately after TUEr nor did the examined group receive intravesical BCG immunotherapy. The EORCT study is a multi-centric with a large number of patients. The results show that the EORCT scoring system is an important aid in predicting the disease recurrence as well as in making treatment decisions (7).

In conclusion, a comparison of the results of our study with the results of EORTC research studies as well as the results of other authors ultimately led to the revision of our adjuvant therapy protocol with the goal of improving treatment outcomes of patients.

Based on available clinical and pathological prognostic factors and by stratification of patients into three disease risk groups it is possible to predict the possibility of disease recurrence. Individual approach and recommendations for the treatment using these tables should improve the quality of treatment.

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TRANSPARENCY DECLARATION

Competing interests: none to declare.

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Predviđanje rizika recidiva mišićnih neinvazivnih karcinoma mokraćnog mjehura nakon transuretralne resekcije

Haris Đug¹, Samed Jagodić¹, Jasmina Ahmetović-Đug², Zijad Selimović¹, Alemdar Sulejmanović¹

¹Odjel za urologiju, Klinika za hirurģiju, ²Klinika za anesteziologiju i reanimatologiju; Univerziteti klinički centar Tuzla; Tuzla, Bosna i Hercegovina

SAŽETAK

Cilj Utvrditi kliničke prognostičke faktore i odrediti njihov utjecaj na rizik od recidiva novootkrivenih mišićnih neinvazivnih karcinoma mokraćnog mjehura.

Metode Studijom je obuhvaćeno 120 pacijenata oba spola, starosti od 45 do 80 godina s novootkrivenim mišićnim neinvazivnim karcinomom mokraćnog mjehura. Svi ispitanici su tretirani operativnim zahvatom transuretralne elektroresekcije (TUER). Tokom istraživanja praćen je ishod sa i bez recidiva. Za praćenje vjerovatnoće ranog recidiva korištene su tablice rizika Europske organizacije za istraživanje i tretman karcinoma (EORTC).

Rezultati Prosječna dob ispitanika iznosila je 65,9 godina. U uzorku je detektirano 79 (79,2%) muških i 21 (20,8%) ženski ispitanik. Ukupno 67 (55,8%) ispitanika imalo je recidiv tokom perioda praćenja. Prosječno vrijeme do pojave prvog recidiva iznosilo je 15,4 mjeseci, a do četvrtog 23,9 mjeseca. Broj tumorâ i stepen invazije imali su signifikantan prognostički utjecaj na rizik od recidiva. Ustanovljen je EORTC-ov skor kao visokosignifikantan prediktor recidiva (OR=1,237; p<0,001).

Zaključak Na osnovu dostupnih kliničkih i patoloških faktora, te stratifikacijom pacijenata na tri grupe rizika od oboljenja, moguće je predvidjeti izgled recidiva oboljenja. Individualni pristup i preporuke u liječenju, koristeći EORTC-ove tablice rizika, trebalo bi da poboljšaju kvalitet liječenja.

Ključne riječi: imunoterapija, vjerovatnoća, tretman