The value of EORTC risk tables in evaluating the results of patients treated for non-muscle invasive bladder cancer with TUR

Jarosław Bobiński, Marek Lipiński
II Clinic of Urology, Medical University of Łódź, Poland

KEY WORDS

EORTC risk tables ◗ nomogram ◗ non-muscle invasive bladder cancer ◗ progression ◗ recurrence

ABSTRACT

Introduction. EORTC risk tables are a new nomogram constructed by EORTC to predict the probability of recurrence and progression in patients treated for non-muscle invasive bladder cancer. Scoring system used in this nomogram is based on the six clinical and pathological factors such as: number of tumors, tumor size, recurrence rate within one year, T category, grade and the presence of carcinoma *in situ* (CIS). The aim of the study was the assessment of the EORTC risk tables usefulness in daily urological practice.

Materials and methods. Ninety-six patients aged 43 to 86 treated for non-muscle invasive bladder cancer with TUR were analyzed. Based on EORTC risk tables they were divided into four groups separately for probability of recurrence and progression. During follow-up a cystoscopy in white light was carried out.

Results. Forty-five patients developed recurrent bladder tumor in 12 months of follow-up. Statistical analysis showed statistically essential relationship between the occurrence of recurrence after one year and recurrence risk groups. The risk of bladder tumor recurrence was statistically more frequent in higher group. The recurrence rate was 13.33%, 43.9%, 64.86% and 33.33% in I, II, III and IV recurrence risk group, respectively. The progression of bladder cancer in the analyzed group within one year occurred in 19 patients out of 45 (42.22%) who developed recurrence in this time, and in the entire examined group (96 patients) the rate of progression was 19.7%. The risk of bladder tumor progression was statistically more frequent in the higher group. In group I there was no progression at all. In group II, III and IV the progression rate was 11.11%, 66.67% and 100%, respectively.

Conclusions. EORTC risk tables enable us to predict outcomes of treatment in patients with non-muscle invasive bladder cancer with great accuracy in recurrence risk groups as well as in progression risk groups. Using EORTC nomograms it is possible to separately estimate the risk of recurrence and progression for patients treated with TUR for primary or recurrent non-muscle invasive bladder cancer.

INTRODUCTION

Urinary bladder cancer is the fourth most common cancer in male adults and 16th in female adults in Poland. As a reason of cancer-related deaths in adult males, bladder cancer takes fifth place [1].

Approximately 90% of bladder tumors are carcinomas derived from bladder epithelial surface (the urothelium). In most regions of the world, transitional cell carcinoma is the most common histological type of bladder cancer [2].

Many of the etiological factors are known. Habitual exposures to chemical carcinogens, either environmental or industrial, are well-established major risk factors for development of bladder cancer [3]. Aromatic amines were the first to be recognized [4]. At-risk groups include workers in the following industries: printing, iron and aluminum processing, industrial painting, and gas and tar manufacturing. The most important risk factor is cigarette smoking, which triples the risk of developing bladder cancer [5].

The main criterion used to evaluate progression of bladder cancer is the depth of the bladder wall's infiltration. Basing on these principles Jewett and Strong in 1946 developed an original clinical classification of bladder cancer. This classification generally divides bladder tumors into superficial and invasive [6]. The TNM classification commonly used in Europe is based on the same principles. According to the TNM system, non-muscle invasive bladder cancers are tumors confined to the mucosa (Ta, Cis) and tumors that have invaded the lamina propria (T1) [7].

A very important risk factor for bladder cancer is histological classification. The 1973 WHO grade classifies bladder tumors as: well differentiated (G1), moderately differentiated (G2), and poorly differentiated (G3) papillary urothelial carcinoma [8]. The new WHO/ISUP grading classifies the tumors as papillary urothelial neoplasm of low malignant potential (PUNLMP) and urothelial carcinoma into low grade or high grade [9].

The classic way to categorize patients with non-muscle invasive bladder cancer into risk categories is to use prognostic factors. In such a way, it should be possible to divide patients into low-risk (50%), intermediate-risk (35%), and high-risk (15%) [10]. The aim of such categorization is to use the optimal method for further treatment and follow-up after TUR. When using these groups, however, no separation is made between the risk of recurrence and progression. Although prognostic factors may indicate a high risk for recurrence, the risk of progression may still be low and other tumors may have high risk for both recurrence and progression.

In order to separately predict the short-term and long-term risk of both recurrence and progression in individual patients, the EORTC developed a scoring system and risk tables [11]. Scoring system used in EORTC risk tables (nomogram) is based on six routinely assessed clinical and pathological factors that are: number of tumors, tumor size, prior recurrence rate, T category, presence of carcinoma *in situ* (Cis), and grade (Table 1). This nomogram is constructed to easily

calculate a non-muscle invasive bladder cancer patient's probability of recurrence and progression after TUR (Table 2).

There is lack of issues in recent literature that would evaluate the practical application of EORTC risk tables. Authors of few international publications refer to EORTC risk tables. On the one hand they present disadvantages and some shortcomings on the other hand they show the potential benefits that may emerge from application of these tables [12, 13, 14].

The aim of the study was the assessment of the EORTC risk tables usefulness in daily urological practice and in particular obtaining an answer for the following questions:

1. To what degree do EORTC risk tables enable prediction of outcomes in treated patients with primary or recurrent non-muscle invasive bladder cancer?

2. Do EORTC nomograms enable to estimate the real, independent risk of recurrence and progression in patients treated for primary or recurrent non-muscle invasive bladder cancer?

MATERIALS AND METHODS

A group of 96 patients treated from 2005 to 2008 with transurethral resection for primary or recurrent non-muscle invasive bladder cancer was analyzed. Patients age at treatment ranged from 43 to 86 years (mean age 67 years, standard deviation 10.3 years). There were 27 females and 69 males, 84 patients were treated for primary and 12 for recurrent non-muscle invasive bladder cancer.

Number of tumors found in bladder and their size were evaluated during each transurethral resection. The tumor size was measured in a subjective way by comparing it with the diameter of the resectoscope's loop. A single tumor was found in 50 patients, 44 patients with number of tumors between 2 and 7, and 4 of them with 8 and more tumors. The tumor size was 3 cm or less in 62 patients and 34 patients had tumors with diameter greater than 3 cm.

The obtained specimen of tumor after performed TUR was assessed by pathologist to determine staging (T), grading (G) and coexistence of *carcinoma in situ* (CIS).

In the analyzed group there were 34 – Ta stage tumors and 60 – T1 stage. The distribution of tumor grade was G1 – 63 tumors, G2 – 24, and G3 – 9. Coexisting CIS was found in 6 cases.

After performed TUR, separately for each patient, 6 risk factors were assessed: tumor size (in cm), number of tumors located in bladder, recurrence rate within one year, staging (T), grading (G), and the presence of CIS. Then, basing on mentioned factors and using the EORTC scoring system (Table 1), the total score for recurrence and progression for each patient was calculated separately. According to the total score, patients were divided into 4 recurrence and progression risk groups. Patients with total recurrence score 0 were classified to group I, 1-4 points to group II, 5-9 to group III, and 10-17 to group IV risk of recurrence.

Analogical group division was done for progression: patients with 0 points – group I, 2-6 group II, 7-13 group III, and 14-23

Table 1. Weights used to calculate the recurrence and progression scores.

Factor	Recurrence	Progression
Number of tumors		
Single	0	0
2 to 7	3	3
>7	6	3
Tumor size		
<3 cm	0	0
>3 cm	3	3
Priori recurrence rate		
Primary	0	0
< 1 rec/yr	2	2
>1 rec/yr	4	2
T category		
Ta	0	0
T1	1	4
Cis		
Yes	0	0
No	1	6
Grade		
G1	0	0
G2	1	0
G3	2	5
Total score	0-17	0-23

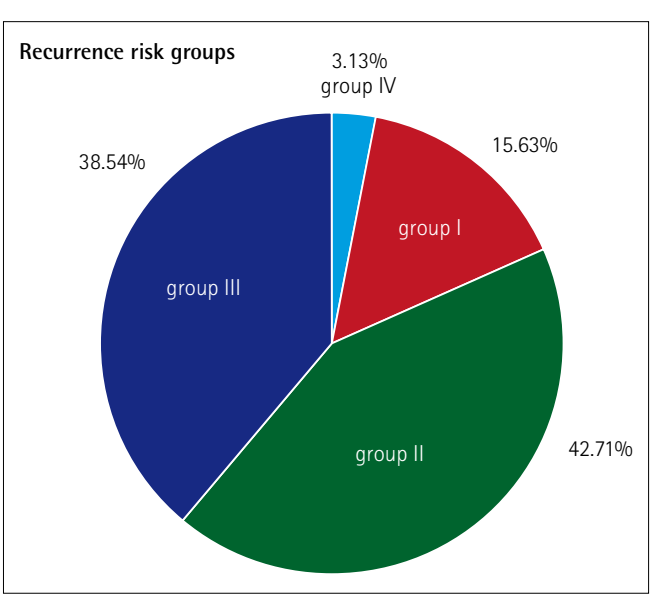

Fig. 1. Distribution on recurrence risk groups in analyzed material.

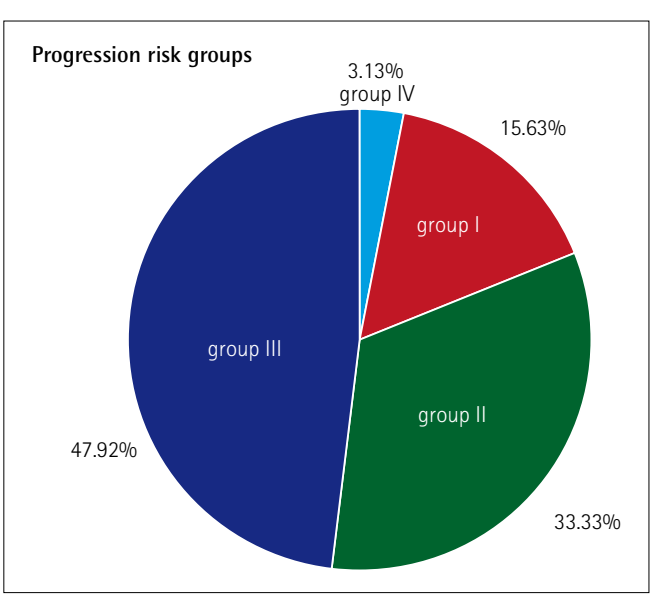

Fig. 2. Distribution on progression risk groups in analyzed material.

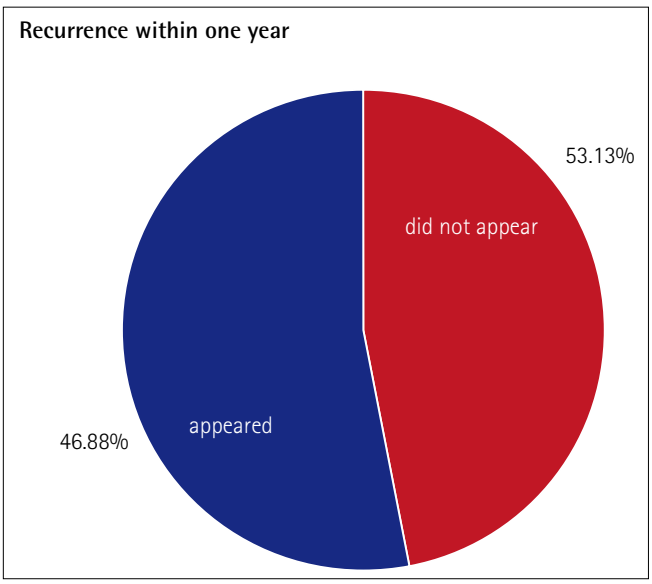

Fig. 3. Recurrence rate within one year in examined group.

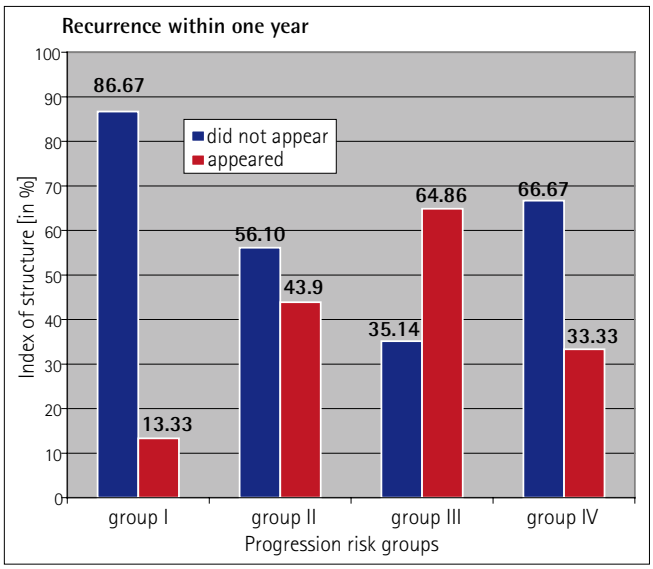

Fig. 4. Recurrence rate within one year in recurrence risk groups in examined group.

group IV risk of progression. Distribution on risk group shows Table 3 and Fig. 1 and Fig. 2.

Follow-up a cystoscopy in white light was carried out. The first examination was performed 3 months after TUR and the next in the 6th, 9th, 12th, 15th, 18th, 21st, and 24th month after TUR. Patients with recurrent non-muscle invasive bladder cancer were treated with TUR again.

The observation period of enrolled patients was various because patients were constantly incorporated into follow-up. Part of them was observed only 12 months and few were followed-up 36 months. Owing to that fact, the statistical analysis was computed for one year of follow-up, for 96 patients.

RESULTS

Forty-five patients developed recurrent bladder tumor in 12 months of follow-up (Fig. 3).

Statistical analysis showed a statistically essential relationship between the occurrence of recurrence after one year and recurrence risk groups. The rate of recurrence in group III compared to group II and I was greater, and in group II was greater comparing to group I. In group IV only 1 patient developed recurrent tumor. Detailed data are presented in Table 4 and on Fig. 4.

From among 45 patients, who were treated with TUR for recurrent bladder tumor, progression occurred in 19 of them – Fig. 5.

Table 2. Probability of recurrence and progression according to total score.

Recurrence score	Prob. recurrence 1 year (95% CI)	Prob. recurrence 5 years (95% CI)
0	15% (10%, 19%)	31% (24%, 37%)
1-4	24% (21%, 26%)	46% (42%, 49%)
5-9	38% (35%, 41%)	62% (58%, 65%)
10-17	61% (55%, 67%)	78% (73%, 84%)
Progression score	Prob. progression 1 year (95% CI)	Prob. progression 5 years (95% CI)
0	0.2% (0%, 0.7%)	0.8% (0%, 1.7%)
2-6	1.0% (0.4%, 1.6%)	6% (5%, 8%)
7-13	5% (4%, 7%)	17% (14%, 20%)
14-23	17% (10%, 24%)	45% (35%, 55%)

Computed statistical analysis revealed statistically essential relationship progression's occurrence within one year depending on progression risk group. In group III the rate of progression was significantly higher than in group I and II. In group I there was no progression observed and in group IV the only one patient developed progression. Detailed data are presented in Table 5 and on Fig. 6.

DISCUSSION

In analyzed research material the incidence of bladder tumor recurrence within one year was 46.87%. The above-mentioned outcome does not differ in principle from outcomes presented by other, authors. Allard et al. [15] evaluated that the probability of bladder tumor recurrence within one year oscillates from 15% up to 70%. Millan-Rodriguez et al., in a study evaluating the prognostic factors of recurrence, progression and mortality in non-muscle invasive bladder cancers, claimed that the recurrence rate in their cohort was 48% [16].

Computed statistical analyses revealed statistical significance between the occurrence of bladder tumor recurrence and recurrence risk groups. The risk of bladder tumor recurrence was statistically more frequent in the higher group. The recurrence rate was 13.33%, 43.9%, 64.86%, and 33.33% in I, II, III, and IV recurrence risk group, respectively. The low rate of recurrence in group IV is due to the fact that only 3 patients were included in this group, and statistical analysis was computed for the first 3 groups.

Results presenting the incidence of recurrence within one year in particular risk groups differ to a certain extent from the probability of recurrence calculated on the basis of EORTC risk tables. The calculated risk of recurrence within one year is 15% (10-19%), 24% (21-26%), 38% (35-41%), and 61% (55-67%) in group I, II, III, and IV, respectively [11].

Table 3. Distribution in risk groups.

Risk group of recurrence	Number of patients	Risk group of progression	Number of patients
I	21	I	21
II	42	II	32
III	29	III	39
IV	2	IV	2

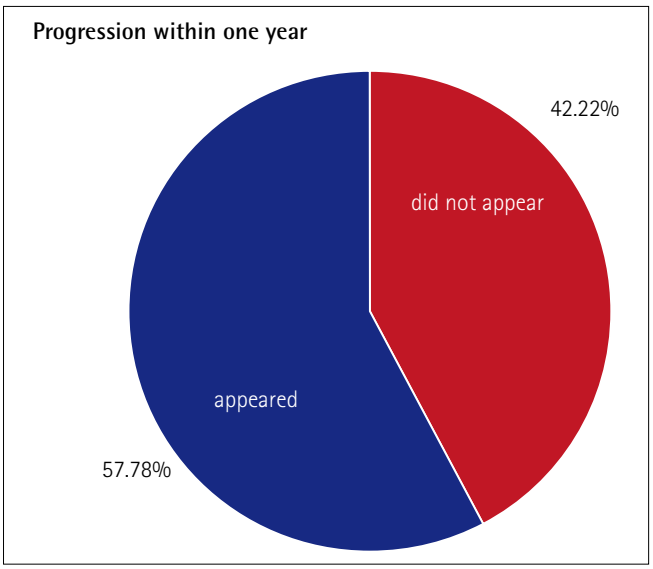

Fig. 5. Progression rate in patients who developed recurrence within one year in examined group.

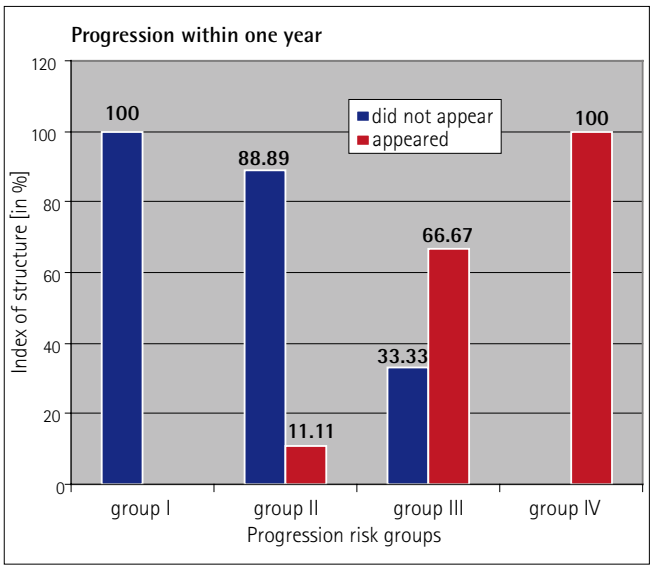

Fig. 6. Progression rate within one year after second TUR in progression risk groups in examined group.

There is lack of issues in recent literature that would evaluate the practical application of EORTC risk tables. Authors of several papers that evaluate risk factors in non-muscle invasive bladder carcinomas used to usually isolate 3 risk groups (low, intermediate, high). In mentioned above paper of Millan-Rodriguez the recurrence rate was 37%, 45%, and 54% in the low, intermediate and high risk, respectively. Parmar et al. in two years observation found that the recurrence in their risk groups occurred in 26%, 56%, and 79% patients from low, intermediate, and high risk, respectively [17]. Also Fradet et al. evaluated the risk of recurrence in particular risk groups, they showed that in low, intermediate, and high group the recurrence was 21%, 36%, and 66%, respectively [18]. If we take for granted that patients from group III and IV risk of recurrence together constitute the high risk group, from group II constitute the intermediate risk group and those from group I – the low risk group, the outcomes presented in this paper do not vary from the results of the above mentioned authors.

On the other hand, almost twofold higher incidence of bladder tumor recurrence in group II and III compared to EORTC risk tables requires us to find the reason of such a condition. The main reason might be the wrong classification of patients to particular groups. It should be assumed that part of patients from group II should be in fact classified into group III and analogically part from group III into group IV. The reason of incorrect classification patients into recurrence risk group may result from a fact that some of risk factors were assessed wrongly. That aspect as a principal weak point of EORTC risk tables was presented in detail by two researchers from Bolzano in Italy [12]. They discuss all 6 risk factors from EORTC risk tables pointing at week points and possible faults that may fundamentally affect risk stratification. It is difficult for them to understand why a diameter of 2.9 cm of papillary tumor is weighted with 0 points and the same tumor with 1 mm more is quoted with 3 points or 7 papillary lesions have the value of 3 points but 1 lesion more counts double. They also discuss the low rate of reproducibility in staging (T) as well as in grading (G).

The progression of bladder cancer in the analyzed group occurred within one year in 19 patients out of 45 (42.22%) who developed recurrence in this time, and in entire examined group (96 patients) the rate of progression was 19.7%.

Various authors, who were analyzing the influence of risk factors in the natural history of non-muscle invasive bladder tumors, assessed that probability of bladder cancer progression varies from 10% to 35% [19, 20, 21]. Millan-Rodriguez et al. evaluated the rate of progression to be only 7.5% in their cohort [16].

Computed statistical analyses revealed statistical significance between the occurrence of bladder tumor progression and progression risk groups. The risk of bladder tumor progression was statistically more frequent in the higher group. In group I there was no progression at all. In group II, III, and IV the progression rate was 11.11%, 66.67%, and 100%, respectively. These outcomes need to be explained because of the fact that such high values of progression are not presented in any available papers.

Table 4. The statistical analysis of recurrence's occurrence within one year after primary TUR depending on recurrence risk group in analyzed group.

Recurrence within one year	Recurrence risk groups								Total	
	Group I		Group II		Group III		Group IV			
	Number of examined	Index of structure [In%]	Number of examined	Index of structure [In%]	Number of examined	Index of structure [In%]	Number of examined	Index of structure [In%]	Number of examined	Index of structure [In%]
Did not appear	13	86.67	23	56.10	13	35.14	2	66.67	51	53.13
Appeared	2	13.33	18	43.90	24	64.86	1	33.33	45	46.87
Total	15	100	41	100.00	37	100.00	3	100.00	96	100.00
Statistical analysis	Test Chi^2 Person = 11.77 p <0.01 ; Test Chi^2 NW = 12.67 p <0.01 V_{Cramer} Factor = 0.35; $C_{Pearson}$ Factor = 0.35									

Statistical analysis with regard to statistical assumptions was computed for group I, II, and III (only a few patients in group IV).

Table 5. The statistical analysis of progression's occurrence within one year after second TUR depending on progression risk group in analyzed group.

Progression within one year	Progression risk groups								Total	
	Group I		Group II		Group III		Group IV			
	Number of examined	Index of structure [In%]	Number of examined	Index of structure [In%]	Number of examined	Index of structure [In%]	Number of examined	Index of structure [In%]	Number of examined	Index of structure [In %]
Did not appear	2	100.00	16	88.89	8	33.33	0	0.00	26	57.78
Appeared	0	0.00	2	11.11	16	66.67	1	100.00	19	42.22
Total	2	100.00	18	100.00	24	100.00	1	100.00	45	100.00
Statistical analysis	Accurate Fisher test p <0.05									

Statistical analysis with regard to statistical assumptions was computed for group II and III (only few patients in group I and IV).

In this study, the progression rate was calculated in an individual risk group for those patients from a particular progression risk group who developed recurrence within one year.

The rate of progression with reference to the whole observed group (96 patients) was 0%, 2%, 16.6%, and 1% in group I, II, III, and IV risk of progression, respectively. Presented results vary in group III and IV from probability of progression assessed based on EORTC risk tables. EORTC risk tables indicate that progression within one year may affect 0.2%, 1%, 5%, and 17% patients from group I, II, III, and IV risk of progression, respectively. Differences in group III and IV may result from two main reasons. First of all, there were only 3 patients enrolled into group IV and secondly, patients were wrongly classified into particular risk groups. The problem of wrong classification was mentioned above in this paper, and presented arguments refer to progression as well.

Very few authors evaluated the influence of various risk factors on bladder cancer progression. In the already cited division for 3 risk groups, proposed by Fradet et al., occurrence of progression within one year was 0%,1%, and 9% in low, intermediate, and high risk groups, respectively [18]. Similar results were presented by Millan-Rodriguez et al., in their study progression occurred in low, intermediate, and high risk groups with an incidence of 0%, 1.8, and 15%, respectively [16]. If it take for granted, as it was done for recurrence, that patients from group I risk of progression are in low, those from group II are intermediate, and the patients from III and IV together are in the high risk group, the outcomes presented in this paper do not vary from the results of the above mentioned authors.

CONCLUSIONS

1. EORTC scoring system and risk tables allow predicting outcomes of treatment in patients with non-muscle invasive bladder cancer with great accuracy in recurrence risk groups as well as in progression risk groups.

2. Using EORTC nomograms it is possible to separately estimate the risk of recurrence and progression for patients treated with TUR for primary or recurrent non-muscle invasive bladder cancer.

3. The division for 4 independent risk groups of recurrence and progression will soon allow development of new strategies for further follow-up and complementary treatment. On the basis of obtained findings the conclusion may be formulated that patients who need watchful follow-up are those from group III and IV risk of recurrence and progression. On the other hand patients from group I risk both recurrence and progression might be followed-up in cystoscopy not so frequently.

REFERENCES

1. Wojciechowska U, Didkowska J, Tarkowski W, Zatoński W.: *Nowotwory złośliwe w Polsce w 2002 roku, Centrum Onkologii – Instytut im. Marii Skłodowskiej-Curie (Cancer in Poland in 2002, The Maria Skłodowska-Curie Memorial Cancer Center and Institue of Oncology),* Warszawa 2004, pp. 15-16.
2. Adi F, Gazdar P, Czerniak B: *Filling the void: urinary markers for bladder cancer risk and diagnosis.* J Natl Cancer Inst 2001; 93 (6): 89-90.
3. Scher H, Shipley W, Herr H: *Cancer of the bladder.* In: DeVita V Jr, Hellman S, Rosenber S eds, Cancer principles and practice of oncology. 5th ed. Philadelfia (PA): Lippincott; 1997, pp. 1300-1322.
4. Oosterlinck W, Van der Meijden A, Sylwester R et al: *Guidlines on TaT1 (Non-muscle invasive) Bladder Cancer,* European Association of Urology 2006, pp. 5
5. Zeegers MP, Tan FE, Dorant E, van den Brandt PA: *The impact of characteristics of cigarette smoking on urinary tract cancer risk: a meta-analysis of epidemiologic studies.* Cancer 2000; 89: 630-639.
6. Chłosta P: *Leczenie powierzchownego raka pęcherza moczowego (The treatment of superficial bladder cancer),* In: Borówka A (ed), Wykłady z urologii, Warszawa 2003, vol. II, pp. 126-143.
7. Sobin DH, Wittekind Ch: TNM classification of malignant tumors. 6th edn. NewYork, Wiley-Liss, 2002, pp 199-202.
8. Sauter G, Algaba F, Amin M et al: *Tumors of the urinary system: non-invasive urothelial neoplasm.* In: Eble JN, Sauter G, Epstein JL, Sesterhenn I eds, WHO classification of tumors of the urinary system and male genital organs. Lyon, IARCC Press, 2004, pp. 20-25.
9. Epstein JI, Amin MB, Reuter VR, Mostofi FK: *The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder.* Am J Surg Pathol 1998; 22: 1435-1448.
10. Oosterlinck W, Lobel B, Jakse G et al: *Guidelines on bladder cancer.* EUA Guidelines, 2001, pp. 8-9.
11. Sylvester RJ, van der Meijden AP, Oosterlinck W et al: *Predicting recurrence and progression in individual patients with stage TaT1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials.* Eur Urol 2006; 49: 466-477.
12. Mian Ch, Pycha A: *Risk stratification in superficial bladder cancer: fact or fiction.* Eur Urol 2007; Update series 5: 63-69.
13. Shariat SF, Margulis V, Lotan Y: *Nomograms for bladder cancer.* Eur Urol 2008; 54: 41-53.
14. Kattan MW: *Nomograms are difficult to beat.* Eur Urol 2008; 53: 671-672.
15. Allard P, Bernard P, Fradet Y, Tetu B: *The early clinical course of primary Ta and T1 bladder cancer: a proposed prognostic index.* Br J Urol 1998; 81: 692-698.
16. Millan-Rodriguez F, Chechile-Toniolo G, Salvador-Bayarri J et al: *Primary superficial bladder cancer risk groups according to progression, mortality and recurrence.* J Urol 2000; 164: 680-684.

17. Parmar MKB, Freedman LS, Hargreave TB et al: *Prognostic factors for recurrence and follow-up policies in the treatment of superficial bladder cancer: report from the British Medical Research Council Subgroup on Superficial Bladder Cancer.* J Urol 1989; 142: 284.
18. Fradet Y: *Prognostic factors: Back to the future.* In: Pagano F, Fair WR eds, Superficial Bladder Cancer, Oxford: ISIS Medical Media, 1997; Chapt 5, pp. 57-70.
19. Heney NM, Amned S, Flangan M J et al: *Superficial bladder cancer. Progression and recurrence.* J Urol 1983; 130: 1083-1086.
20. Kołodziej A, Zdrojowy R, Woźniak SP et al: *Znacznie kliniczne nowej klasyfikacji histopatologicznej WHO/SIUP 2004 w zakresie raków Ta/T1 pęcherza moczowego (The clinical significance of the new WHO/ISUP 2004 classification in pTa/pT1 bladder cancer carcinoma).* Urol Pol 2007; 60 (3): 221-226.
21. Solsona E, Iborra I, Dumont R et al: *The 3-month clinical response to intravesical therapy as a predictive factor for progression in patients with high risk superficial bladder cancer.* J Urol 2000; 164: 685-689.

Correspondence
Jarosław Bobiński
II Clinic of Urology
62, Pabianicka Street
93-513 Łódź, Poland
phone: +48 42 689 52 11
encefalit@wp.pl