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The value of EORTC risk tables in evaluating recurrent non–muscle–invasive bladder cancer in everyday practice

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Introduction. Due to the risk of recurrence and progression, patients with non–muscle–invasive bladder cancer have to be under observation. The aim of this study is the evaluation of early recurrence at the first control cystoscopy, as a prognostic factor for recurrence and progression based on EORTC risk tables.

Material and methods. This study analyzed 243 patients with non–muscle–invasive bladder cancer, with an average observation time of 46 months. Recurrence was observed in case of 99 patients. Among these patients, we selected 79 who had the first cystoscopy 3 months after the transurethral electroresection of the bladder tumor. Subsequently, 45 patients with early recurrence at the first control cystoscopy were compared with 34 patients whose cancer recurred at later control cystoscopies. The patients were compared with respect to the number of points assigned by EORTC tables.

Results. Those patients who had an early recurrence had a significantly higher score in the EORTC table in the progression scale (p = 0.017) but not in the recurrence scale (p = 0.11), as compared with patients who had a late recurrence.

Conclusions. Early recurrence that occurs within 3 months after TURBT indicates a higher risk of progression, as compared with a late recurrence. Patients who had an early recurrence had a significantly higher EORTC risk score for progression. Their EORTC risk score for recurrence was also higher, but the difference was not statistically significant. Every patient with an early recurrence has a worse prognosis and a higher risk of progression.

Key Words: non-muscle-invasive bladder cancer ‹› EORTC risk tables ‹› recurrence ‹› progression

INTRODUCTION

Bladder cancer is the second most common urinary tract cancer. Bladder cancer is the cause of 4.1% of male and 1.8% of female deaths from cancer. After prostate, lung and colorectal cancer, it is the fourth most commonly diagnosed cancer type in males [1]. In Poland, the mortality rate for bladder cancer is one of the highest in Europe; it is equal to 7 per 100.000 people [2].

Patients with non–muscle–invasive bladder cancer (NMIBC) have to be monitored due to the risk of recurrence and progression. The frequency of cystoscopy and medical imaging of the upper urinary tract should reflect the risk of recurrence and progression of each individual patient [3]. The result of the first cystoscopy 3 months after the trans–urethral electroresection of bladder tumor (TURBT) is a very important prognostic factor for recurrence and progression prediction [3, 4, 5] and should always be conducted. Subsequent schedule of control cystoscopies should be determined based on the European Organization for Research and Treatment of Cancer (EORTC) tables [6].

The aim of this study is the evaluation of early recurrence at the first control cystoscopy following TURBT as a prognostic factor for recurrence and progression based on EORTC risk tables.

MATERIALS AND METHODS

This study analyzed 243 patients with histopathologically confirmed non–muscle–invasive urothelial bladder cancer who underwent treatment and observation in our hospital from January 2005 till May 2012. Their average age was 69 and the majority of them were men – 209 cases (86%). The follow–up average was 49 months. The average tumor size was 20.2 millimeters. Pathological stage T1 was determined in 114 patients (47%). CIS was found in 9 patients (4%). Table 1 presents the characterization of patients and tumors.

Bimanual examination under anesthesia was routinely carried out before TURBT. Prior to treating the tumor, the pathological changes were characterized in regards to size, number and morphology (papillary / non–papillary). Samples from the tumor were sent to the histopathologist in separate containers. The patients were given all the necessary information concerning the requirement of further observation after the primary treatment. Medium and high–risk patients were qualified for chemo– or immunotherapy with maintenance therapy. High risk patients were monitored every 3 months for 2 years, and every six months in the following years. Low–risk patients had a cystoscopy after 3 months and if the result was negative, the next examination was scheduled in 9 months and subsequently once a year during five years [7, 8].

The study compared only those patients who had a recurrence and those who had the first cystoscopy 3 months after TURBT. The patients were compared with respect to the number of points assigned by EORTC risk tables. The distribution of variables was verified with Kolmogorov–Smirnov test for one sample ($p < 0.05\%$). The results indicated that the distribution of variables under analysis was not close to normal distribution. Further analysis was therefore conducted using nonparametric tests. The Mann–Whitney U test was applied in order to perform the analysis of differences between patients who had an early recurrence detected at the first cystoscopy after TURBT and those who were found to have a recurrence at later cystoscopic examinations.

Table 1. *Characterization of patients and tumors*

Number of patients	243	
Age – average	69 years (22–93)	
Age	≤60	60 (24%)
	61–70	68 (28%)
	71–80	70 (29%)
	>80	46 (19%)
Sex	Men	209 (86%)
	Women	34 (16%)
Pathological stage	Ta	129 (53%)
	T1	114 (47%)
Grading	G1	162 (66%)
	G2	54 (22%)
	G3	27 (11%)
CIS	Yes	9 (4%)
Number of tumors	1	127 (52%)
	2–7	87 (36%)
	≥8	29 (12%)
Tumor size (mm)	≤10	75 (31%)
	10–30	89 (37%)
	≥30	79 (32%)
Tumor morphology	Papillary	209 (86%)
	Non–papillary	34 (14%)
Follow–up – average	46 months (5–89)	
EORTC – recurrence risk	Low	51 (21%)
	Medium	167 (69%)
	High	25 (10%)
EORTC – progression risk	Low	52 (21%)
	Medium	89 (37%)
	High	102 (42%)
First control cystoscopy after 3 months	Yes	138 (57%)
	No	105 (43%)

RESULTS

In the course of the study, we monitored 243 patients under NMIBC treatment. Recurrence was observed in 99 cases (41%). Histopathological progression in non–muscle–invasive tumors (a change to a more advanced T or G stage) occurred in 45 (18%) patients. Within this group, 25 (10%) patients progressed to stage T2 (Table 2). The average number of points assigned to all patients according to EORTC tables was 4.5 in the recurrence scale and 5.4 in the progression scale. Ninety–nine (41%) patients with recurrent bladder tumor were analyzed in detail. Seventy–nine (32%) of them had their first control cystoscopy after 3 months and these patients were selected for fur-

Table 2. *Recurrence and progression in the group of treated patients*

Number of patients	243	
Recurrence	No	144 (59%)
	Yes (all cases)	99 (41%)
	Yes (≤1 x/year)	71 (29%)
	Yes (>1 x/year)	28 (11%)
Progression (all cases)	Yes	45 (18%)
Progression to muscle–invasive bladder cancer (MIBC)	Yes	25 (10%)

ther analysis in order to make sure that the observation of all patients was carried out properly. Next, we compared 45 (18%) patients with recurrence at the first control cystoscopy after 3 months with the group of 34 (14%) patients with recurrence at later control cystoscopies. The result in EORTC tables was on average higher in early relapse compared with late relapse, both for recurrence (7.4 *vs.* 6.1) and progression (8.4 *vs.* 6.4) (Table 3). The difference was statistically significant in the progression scale (p = 0.017), but not in the recurrence scale (p = 0.11).

DISCUSSION

The EORTC table model divides patients into four risk groups both for recurrence and for progression (Table 4). The evaluation of risk factors such as number of tumors, tumor size, recurrence frequency, stage, grade and CIS in patients with NMIBC is the basis for prognosis prediction and determination of control cystoscopy cycle. The probability of recurrence ranges from 31 to 78% and the probability of progression from less than 1% to 55% over the course of five years [3].

EORTC tables are prognostic tools recommended by the European Association of Urology (EAU) for clinical use [6]. The treatment following the first TURBT can be modified according to prognosis from these tables. Low–risk patients obtain solely a single immediate postoperative instillation of chemotherapy. The therapy of choice for high–risk patients consists of additional chemo– or BCG therapy carried out for at least one year [6]. The main advantage of EORTC tables is the possibility of their straightforward use in clinical practice. The knowledge of clinical and histopathological parameters permits initial and uncomplicated classification of the patient into one of the four group risk and enables planning of subsequent follow–up and adjuvant treatment. However, EORTC tables are not as exact as expected. More recent table series, adapted for patients treated with BCG for at least five to six months, present a scoring model determined by Club Urológico Español de Tratamiento Oncológico (CUETO, Spanish Oncology Group). In these tables, the probability of recurrence ranges from 0 to 60% and the probability of progression from 0 to 31% over the course of five years. Detailed analysis reveals that EORTC tables overestimate the recurrence risk in all groups and the progression risk in the high–risk group [9]. Among the Polish patients with NMIBC, the recurrence risk rates are overestimated and progression risk rates are underestimated in almost all risk groups [10]. We are still in the process of correcting EORTC tables. Although they are far from perfection, they provide useful information. An optimal system should provide the possibility of fluent calculation of short– and long–term recurrence and progression risk, based on clinical and pathological factors. None of the currently available tests (NMP22, UroVysion and ImmunoCyt) or imaging methods can substitute the follow–up based on cystoscopy [11].

The result of the first control cystoscopy 3 months after TURBT is a very important prognostic factor for recurrence and progression [3, 4, 5, 12]. Our statistics confirmed the results of previous studies indicating

Table 3. *Characterization and EORTC risk tables score in patients with recurrent NMIBC*

		Recurrence at the first control cystoscopy	Recurrence at later control cystoscopies
Number of patients		45	34
Pathological stage	Ta	11 (25%)	17 (50%)
	T1	34 (75%)	17 (50%)
Grading	G1	24 (53%)	24 (70%)
	G2	17 (38%)	8 (24%)
	G3	4 (9%)	2 (6%)
Number of tumors	1	17 (38%)	17 (50%)
	2–7	19 (42%)	13 (38%)
	≥8	9 (20%)	4 (12%)
Tumor size (mm)	<30	26 (58%)	24 (71%)
	≥30	19 (42%)	10 (29%)
Recurrence	<1/rok	31 (69%)	22 (65%)
	>1/rok	14 (31%)	12 (35%)
EORTC risk tables score	Recurrence score – average	7.4 (1–14)	6.1 (0–12)
	Progression score – average	8.4 (2–15)	6.4 (0–12)

Table 4. *Probability of recurrence and progression according to calculated scores*

Recurrence score	Prob recurrence 1 year	Prob recurrence 5 years
0	15%	31%
1–4	24%	46%
5–9	38%	62%
10–17	61%	78%
Progression score	**Prob progression 1 year**	**Prob progression 5 years**
0	0.2%	0.8%
2–6	1.0%	6%
7–13	5%	17%
14–23	17%	45%

an important prognostic value of the first cystoscopy after endoscopic treatment. Our analysis revealed a statistically significant increase of the EORTC progression score for early recurrence compared with late recurrence (p = 0.017). This indicates that a positive cystoscopy 3 months after TURBT is a negative prognostic factor for progression. We did not observe statistically significant changes in EORTC recurrence scores (p = 0.11), which was probably due to a low number of patients included in the study.

In our study, tumor recurrence occurred in 99 patients (41%). This is a result similar to EORTC (45%) and CUETO (33.5%) series (Table 5). Early relapse occurred in 45 patients (18%). In a pooled analysis of seven randomized EORTC studies, early tumor recurrence was observed in 13% (6.7–40%) of 2410 patients (13). In our study, early recurrence was characterized by a high score in EORTC tables. The recurrence risk was on average 7.4 (from 1 to 14) and the progression risk was on average 8.4 (from 2 to 15), which classifies most of the patients into the medium– and high–risk group. Each form of high–risk NMIBC recurrence is related to a higher progression risk and to disease–specific mortality (DSM) [14]. Fernandez–Gomez and coworkers reported results obtained based on 1062 patient treated with BCG in a randomized controlled sample. The cohort included both primary (66.5%) and recurrent (33.5%) tumors in medium– and high–risk groups. Multifactorial analysis showed that recurrent tumors had a significantly higher progression index than primary tumors. Moreover, it was reported that a recurrence after 3 months increased progression risk [15]. Other studies also showed that recurrent tumors indicate a higher progression risk [16]. It seems that a significant number of early relapses can be more probably attributed to a residual tumor resulting from an incomplete resection, than to a *bona fide* NMIBC relapse [17]. The influence of routinely performed re–TURBT and supplemental intravesical therapy on recurrence frequency has been confirmed by several studies [18–21]. Unfortunately, in our study, 105 (43%) patients did not undergo the first, prognostically important, cystoscopy 3 months after TURBT. The data from the US show that practice does not keep pace with guideline recommendations. Up to 42% physicians failed to perform a single cystoscopy or cytologic examination in case of patients with high–grade NMIBC during the first two years of observation [22]. The age of our patients differs significantly from CUETO (3.4%) and EORTC (4.5%) data. Forty–six (19%) of our patients are ≥80 years old. Moreover, the fact that most of our patients come from rural areas can be of significance in the context of control cystoscopies and adjuvant treatment.

Patients with an early NMIBC relapse after 3 months should be carefully observed, just like high–risk patients. It is however of primary importance to thoroughly inform patients about the high frequency of bladder tumor recurrence and the necessity of control cystoscopies.

Table 5. *Characterization of patients and tumors compared with EORTC and CUETO groups*

	Study Group	CUETO	EORTC
Age			
≤60	60 (24%)	331 (33.2%)	859 (33.1%)
61–70	68 (28%)	394 (37.1%)	890 (34.4%)
71–80	70 (29%)	301 (28.3%)	690 (26.6%)
≥80	46 (19%)	36 (3.4%)	118 (4.5%)
Sex			
Man	209 (86%	–	2044 (78.7%)
Woman	34 (16%)	–	561 (19.8%)
Number of tumors			
1	127 (52%)	535 (50.4%)	1465 (56.4%)
2–7	87 (36%)	438 (41.3%)	836 (32.2%)
≥8	29 (12%)	89 (8.4%)	255 (9.8%)
Tumor size (mm)			
≤10	75 (31%)	283 (26.6%)	920 (35.4%)
10–30	89 (37%)	298 (28.1%)	1167 (45%)
≥30	79 (32%)	481 (45.3%)	464 (17.9%)
Pathological stage (T)			
Ta	129 (53%)	214 (20.2%)	1451 (55.9%)
T1	114 (47%)	848 (79.8%)	1108 (42.1%)
Grading (G)			
G1	162 (66%)	167 (15.7%)	1121 (43.2%)
G2	54 (23%)	629 (59.2%)	1139 (43.9%)
G3	27 (11%)	266 (25%)	271 (10.4%)
CIS	9 (4%)	80 (7.5%)	113 (4.4%)
Tumor recurrence			
No	144 (59%)	706 (66.5%)	1405 (54.99%)
Yes	99 (41%)	356 (33.5%)	1150 (45.01%)
Tumor progression to MIBC	25 (10%)	142 (13.4%)	279 (11%)

CONCLUSIONS

An early recurrence 3 months after TURBT indicates a higher risk of progression as compared with a late recurrence. Probability of recurrence in case of patients with a positive first cystoscopy was higher, but the difference was not statistically significant. Every patient with an early recurrence has a worse prognosis and a higher risk of progression. These patients should be observed like patients with high–risk tumors. The EORTC risk tables that we have used as an evaluation tool are useful in everyday practice to identify high–risk patients. The steps undertaken by physicians can be decisive for the length and quality of life of these patients.

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