

## Predictors and prognostic implications of clinical decisions in patients with primary high-risk non-muscle-invasive bladder cancer – results of a cross country retrospective study

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Adjuvant diagnostic and therapeutic procedures are available to reduce the risk of recurrence or progression in patients with high-risk non-muscle-invasive bladder cancer (NMIBC). However, their indications and efficacy remain a matter of debate. The aim of this study was to analyze therapeutic decisions in patients with primary high-risk NMIBC and to analyze the adherence to clinical guidelines in this field.

545 consecutive patients, aged a median of 70.3 years, diagnosed with primary high-risk NMIBC in thirteen urological institutions, were enrolled into this retrospective study. Diagnostic and therapeutic decisions after transurethral resection (TUR) were recorded, and predictive factors were analyzed.

Restaging TUR was offered to 260 patients (47.7%), up-front intravesical Bacillus Calmette-Guerin (BCG) therapy to 74 patients (13.6%), immediate radical cystectomy to 38 patients (7.0%), and intravesical chemotherapy with the maintenance therapy to 12 patients (2.2%). No additional procedure was performed in 161 patients (29.5%). The strongest predictive factor for restaging TUR was G3 or high-grade cancer (RR 1.68,  $p < 0.01$ ), for upfront BCG therapy it was carcinoma *in situ* (RR 3.20,  $p = 0.01$ ), for immediate cystectomy it was stage T1 tumor (RR 3.71,  $p < 0.01$ ), for no additional procedures it was G2 or low-grade cancer (RR 2.18,  $p < 0.01$ ).

Clinical management of patients with high-risk NMIBC is suboptimal and not standardized. As this can directly influence patients' survival, urgent improvement of urological care in this field should be considered.

*Key words: bladder cancer, clinical decision-making, multicenter study, survival*

In patients with non-muscle-invasive bladder cancer (NMIBC), transurethral resection of the bladder tumor (TUR) remains the critical step in disease management [1]. However, there is a subgroup of patients, in whom the probability of disease recurrence and progression during the follow-up is particularly high, reaching 78% and 45% at five years, respectively [2]. Experts of the European Association of Urology define this high-risk group as patients with stage T1 tumors, G3 tumors, high-grade tumors or carcinoma *in situ* (Cis) [3].

The primary goals of TUR are complete removal of the tumor and proper pathological staging [3]. They both may require second or restaging TUR, especially in high-risk patients. Once proper pathological staging is completed, various therapeutic procedures are believed to reduce the risk of disease recurrence, including intravesical chemotherapy, intravesical Bacillus Calmette-Guerin (BCG) immunotherapy, and immediate radical cystectomy. To date, in patients with high-risk NMIBC, there are controversies regarding indications for restaging TUR, indications and

safety of BCG therapy, as well as qualification for immediate radical cystectomy.

The aim of the study was to describe therapeutic decisions in patients with primary high-risk NMIBC and to analyze the adherence to clinical guidelines in this field.

## Patients and methods

**Patients.** 545 consecutive patients, diagnosed with primary high-risk non-muscle-invasive urothelial bladder carcinoma in thirteen Central European urological institutions, were enrolled into this study. All patients underwent TUR. The definition of high-risk cancer was adopted from the Expert Panel of the European Association of Urology [3], and covered stage T1 cancer according to 2009 TNM staging classification [4], grade G3 cancer according to 1973 WHO grading classification [5], high-grade cancer according to 2004 WHO/ISUP grading classification [6], or Cis. The exclusion criteria were as follows: muscle-invasive disease, pathological stage Tx disease (primary tumor cannot be assessed), recurrent urothelial cancer, age <18 years.

**Medical records** of all patients were retrospectively analyzed with special attention paid to the further diagnostic and therapeutic procedures and their predictive factors. The primary end-point of the study was the first clinical decision after the diagnosis of high-risk NMIBC, including restaging TURBT, intravesical chemotherapy with the maintenance, intravesical BCG immunotherapy with or without the maintenance, immediate radical cystectomy, or observation only. Moreover, an attempt to identify factors predicting the management decisions was undertaken.

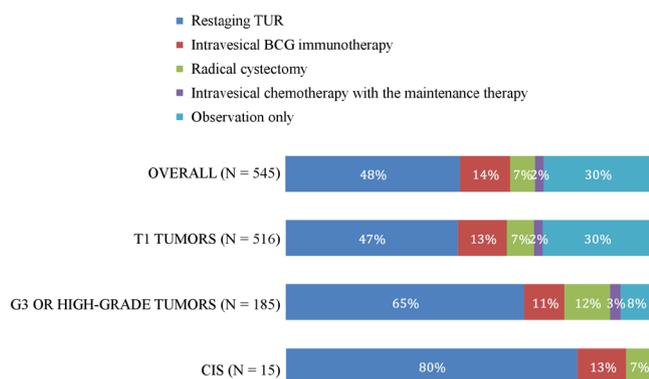


Figure 1. Clinical decisions after the diagnosis of high-risk NMIBC.

This was a retrospective non-interventional study; the Ethical Board approval was waived according to institutional regulations. Simultaneously, the study conformed to the provisions of the Declaration of Helsinki.

## Results

**A basic characteristic** of the study group is presented within Table 1. Among patients with G3 or high-grade tumors, there were 26 cases of stage Ta tumors and 159 cases of stage T1 tumors. Among 15 patients with Cis, only 2 patients had isolated primary Cis, while in the remaining cases Cis was concomitant to papillary high-risk tumors.

**Restaging TUR** was performed in 260 patients (47.7%), including 47.3% of stage T1 cases, 65.4% of G3 or high-grade cases and 80% of Cis cases. Simultaneously, BCG therapy was initiated in 74 patients (13.6%), 38 patients (7.0%) were qualified for radical cystectomy, while 12 patients (2.2%) received intravesical chemotherapy with the maintenance therapy. No additional staging or therapeutic procedure was offered to 161 patients (29.5%). This group was included into a follow-up with regular cystoscopies. Figure 1 presents the first clinical decision after the diagnosis.

**The analysis of potential predictors** of clinical decisions revealed that restaging TUR was offered mainly for G3 or high-grade cancer patients (RR 1.68,  $p < 0.01$ ); upfront BCG therapy for patients with Cis (RR 3.20,  $p = 0.01$ ); immediate cystectomy for patients with T1 tumors (RR 3.71,  $p < 0.01$ ), with the exception of those aged >70 years (RR 0.47,  $p = 0.02$ ); while the risk of no additional treatment was the highest among patients with T1 G2 or T1 low-grade cancer (RR 2.18,  $p < 0.01$ ) and the lowest among patients with G3 or high-grade cancer (RR 0.45,  $p < 0.01$ ). Detailed data regarding the predictors of qualification to staging and therapeutic procedures or observation only depending on clinical settings is presented in Table 2.

## Discussion

Bladder cancer is the most common neoplasm of the urinary system. In Europe, the highest age-standardized death rates are reported for Poland and Spain [7]. A recent Polish analysis revealed that one of the underlying reasons could be a particularly high incidence of high-risk NMIBC [8]. Being aware of the significant risk of disease recurrence and progression in this group of patients, we decided to

Table 1. Basic characteristics of the study group.

	Overall	T1 tumors	G3 or HG tumors	Cis
Number of patients	545	516	185	15
Mean age of patients	70.3	70.1	71.8	72.7
Male to female ratio	3.7:1	3.6:1	4.4:1	2.8:1
Number (percentage) of patients receiving immediate single postoperative intravesical instillation of chemotherapy	74 (13.6%)	65 (12.6%)	38 (20.5%)	2 (13.3%)

**Table 2. Relative risk values for qualification to staging and therapeutic procedures or observation only depending on clinical settings.**

Procedures \ Potential predic- tive factors	Restaging TUR			Intravesical BCG immunotherapy			Immediate radical cystectomy			Observation only		
	% of patients*	RR	p-value	% of patients*	RR	p-value	% of patients*	RR	p-value	% of patients*	RR	p-value
TaG3 or Ta high-grade tumor	57.7%	1.20	0.00	20.0%	1.22	0.91	4.2%	0.55	0.16	34.6%	0.98	0.94
T1G2 or T1 low-grade tumor	39.4%	0.60	0.00	15.9%	1.42	0.13	4.4%	0.34	0.00	43.5%	2.18	0.00
T1G3 or T1 high-grade tumor	67.5%	1.65	0.00	10.4%	0.65	0.08	15.0%	3.71	0.00	17.2%	0.40	0.00
Any T1 tumor	48.1%	0.85	0.00	13.9%	0.75	0.78	7.6%	2.05	0.13	35.4%	1.06	0.81
Any G3 or high-grade tumor	66.3%	1.68	0.00	11.1%	0.71	0.15	12.9%	2.97	0.00	19.6%	0.45	0.00
Cis	81.3%	1.70	0.03	42.9%	3.20	0.01	7.1%	0.99	0.99	12.5%	0.35	0.05
Female sex	48.2%	0.99	0.87	11.6%	0.78	0.59	7.2%	1.00	0.99	34.8%	0.98	0.90
Male sex	48.8%	1.01	0.91	14.9%	1.28	0.37	7.2%	1.00	0.99	35.5%	1.02	0.90
Age >70 years	51.1%	1.11	0.32	12.6%	0.80	0.36	4.6%	0.47	0.02	36.1%	1.04	0.72
Abnormal BMI (<18 or >25 kg/m <sup>2</sup> )	42.9%	1.14	0.16	17.5%	1.29	0.23	5.1%	0.40	0.04	38.9%	1.20	0.18
Anaemia (haemo- globin concentra- tion <12mg%)	43.5%	0.87	0.45	9.7%	0.63	0.27	11.6%	1.93	0.04	42.1%	1.25	0.09

\*The percentage of patients with predictive factor present who underwent the procedure. BMI – body mass index; RR – relative risk.

perform a multi-institutional analysis of clinical decisions made in patients with primary high-risk NMIBC with the special attention paid to their predictors. Our study showed that clinical management in this group of patients is suboptimal, with restaging TUR performed in less than 50% of patients and almost 30% of patients with no adjuvant procedures offered. To our knowledge, this is first such analysis in the region of Central Europe. It identifies potential reasons for unsatisfactory treatment outcomes in bladder cancer patients and indicates the need for urgent improvement in everyday clinical practice.

Almost one third of patients in the present cohort was treated out of clinical guidelines. They were either qualified for intravesical chemotherapy, which is not recommended in high-risk patients, or they were included into an observational protocol only after initial TUR with no adjuvant treatment. In the study by Witjes et al., the percentage of high-risk patients who received intravesical chemotherapy as the sole treatment mode or who had not received any additional procedure after TURBT were 12.5% and 9%, respectively [9]. While all these numbers are clinically very relevant, they are particularly alarming in the present study. Among Polish patients with primary high-risk NMIBC, 30% undergo TUR followed by observation only. Even in the subgroup of patients with the high-grade T1 disease, this percentage is still as high as 17%. As stated previously, in high-risk patients the five-year risk of progression reaches 45% and this scenario seems probable especially in patients who are staged incorrectly or who do not receive any further treatment [2]. On the other hand, there were many cases of T1 low-grade

or T1 G2 cancers in our cohort. These diagnoses were the most important predictors of the decision of performing no additional procedure after the initial TUR. The histological diagnosis of low grade T1 disease is controversial, while the data concerning prognosis and optimal treatment are lacking. Even though the indications for restaging TUR are a matter of debate and the availability of BCG treatment was limited in previous years, it seems incomprehensible that 30% of patients did not receive any further treatment. The underestimation of malignant potential of high-risk NMIBC can be one of the triggers for shorter survival among Polish patients as compared to other European countries [7].

In patients with high-risk NMIBC, restaging TUR allows to diagnose residual disease in up to 55% of stage T1 cases and 41% of stage Ta cases [3]. Furthermore, it ensures the proper staging and improves oncological outcomes [10]. According to the 2016 clinical guidelines of the European Association of Urology, restaging TUR is indicated in all patients with stage T1 tumors, poorly differentiated tumors (high-grade or G3), incomplete resection or when no detrusor muscle tissue is sampled [3]. However, in our study, we noticed that restaging TUR was offered only to 48% of patients. Our results are in concordance with data previously published by Gontero et al. In their study, presenting real-life patterns of care in Italian patients with high-risk NMIBC, the authors found that restaging TUR was performed in 49.2% of cases [11]. This represents a high level of non-adherence to clinical guidelines. Potentially low rate of restaging TUR can result from doubts among clinical practitioners regarding the indications for the procedure. Gontero et al. recently showed that

restaging TUR can be omitted in T1 patients if the muscle is present in the specimen with no influence on patients' survival [12]. Consequently, a consensus document reviewed and endorsed by Bladder Cancer Canada, Canadian Urologic Oncology Group, and Canadian Urological Association does not recommend routine restaging TUR in patients staged TaHG and states that it can be omitted in selected patients staged T1 when muscle is sampled [13]. However, a recent retrospective analysis by Gotto et al. showed that restaging TUR in patients with high-grade T1 tumors has positive impact on five-year overall survival and is underused in Canada [14]. Finally, it is under the debate who should undergo restaging TUR and who can safely avoid this procedure. Unfortunately, the number of randomized controlled studies presenting the clinical value of restaging TUR is very limited and the available evidence is based mainly on retrospective observational studies.

Intravesical BCG immunotherapy is regarded as a standard adjuvant treatment in patients with high-risk NMIBC that improves the recurrence-free survival [3]. In our cohort, BCG therapy was the first therapeutic decision in almost 14% of patients. The probability of receiving BCG therapy was the highest among patients with Cis. Moreover, one can suspect that the majority of patients undergoing restaging TUR was also eventually qualified for BCG immunotherapy, increasing the final rate of BCG therapy up to about 60% of the studied patients. At this point, our results are again comparable to these presented by Gontero et al., who noticed the use of BCG therapy in 60.5% of high-risk cases [11]. On the other hand, Nielsen et al. presented a 91% rate of BCG therapy in patients with high-grade NMIBC. However, this was a survey study with a very low response-rate, limiting its reliability [15]. The problem of underuse of BCG therapy is a well-known phenomenon in urology. There are several possible reasons, however, that were never objectively assessed. The most important two issues are probably the risk of BCG-related toxicity and the reduced availability of BCG strains in recent years. The EORTC study revealed that almost 70% of patients receiving BCG therapy experience at least one side effect related to the treatment. On the other hand, in the same study, toxicity was the rarest reason for treatment discontinuation [16]. To date, the influence of safety profile on decision of patients and urologists regarding BCG therapy was not assessed.

Apart from qualification, also the schedule of the BCG therapy is of great clinical importance. While this was not assessed within the present study, a recent international analysis by Witjes et al. showed that only 50% of patients with high-risk NMIBC in Europe, Canada and United States received BCG therapy with maintenance [9]. Moreover, an analysis of the SEER database indicated that 99% of all patients with bladder cancer do not receive more than 6 instillations [17].

The decision of performing radical cystectomy in patients with high-risk NMIBC is difficult to undertake. There is no fully reliable predictive tool of progression to muscle-invasive

disease, so the risk of overtreatment cannot be ignored in any case. Additionally, there are studies showing a long-term survival of patients operated at the time of progression comparable to that in patients undergoing immediate surgery [18, 19]. In our study, 7% of patients were qualified for radical cystectomy, with the extensive T1 high-grade or G3 histopathology being the most common indication. The most important factors for disqualification from the surgery were abnormal body mass index (BMI) value and elder age defined as the age >70 years. Both of these conditions are considered risk factors of post-radical cystectomy complications [20–23]. Surprisingly, low haemoglobin concentration was found to be predictor of radical cystectomy in the current cohort, despite elsewhere demonstrated negative impact on postoperative survival [24, 25]. An analysis of the SEER database by Canter et al. revealed that less than 5% of patients with high-grade T1 disease underwent immediate cystectomy. Moreover, early radical surgery had no effect on cancer-specific survival [26]. Witjes et al. in their international individual patient data survey noticed that immediate radical cystectomy was performed in 9% of patients with high-risk NMIBC, and this was more common in academic centers [9]. Based on these data, it seems that early radical cystectomy performed at the time of BCG failure is definitively more common than immediate radical cystectomy performed directly after initial diagnosis of NMIBC. However, exact data regarding this issue are lacking.

Our study is not free of limitations. As the study's end-point was the first clinical decision, we did not consider the results of restaging TUR or cystectomy and their clinical sequelae. Hence, it is possible that there are under staged patients with muscle-invasive bladder cancer in our cohort. At the same time, patients who underwent restaging TUR followed by intravesical BCG immunotherapy are not recorded with the second intervention. Furthermore, due to the retrospective nature of our analysis, we were not able to incorporate patients individual risk of recurrence and progression into our considerations, while this data could significantly influence the clinical decisions. Simultaneously, we present a representative homogenous cohort of consecutive patients with primary high-risk NMIBC. While there were thirteen urological institutions involved, the risk of bias related to regional trends of care is assessed as minimal.

In conclusion: clinical management in patients with high-risk NMIBC is not uniform. The decisions taken after the diagnosis seem suboptimal in many cases, what can directly influence patient survival. Clinical practice in Europe seems unified in terms of the use of restaging TUR and radical cystectomy. However, in Central Europe significantly more patients receive no additional treatment after initial TUR, what can lead to understating and lower survival rates in the region. While the adherence to clinical guidelines should improve, the urological community is in need of high-level evidence on the indications for restaging TURBT and radical cystectomy in NMIBC patients.

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