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Difference in recurrence frequencies of non-muscle-invasive-bladder tumors depending on optimal usage of intravesical immunotherapy of bacillus Calmette-Guérin

Razlika u učestalosti recidiviranja mišićno-neinvazivnih tumora mokraćne bešike zavisno od optimalne primene intravezikalne imunoterapije bacilom *Calmette-Guérin*

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Abstract

Background/Aim. The therapy with intravesical instillation of bacillus Calmette-Guérin (BCG) after transurethral resection (TUR) of the tumor is the gold standard of treatment of non-muscle invasive bladder cancer (NMIBC). The aim of this study was to compare the frequencies of reccurence between a group of patients submitted to TUR + BCG therapy (group I) and a group of patients submitted only to TUR (group II). **Methods.** The patients with NMIBC, a total of 899, treated in our Institution from January 1, 2007 to March, 2013, were included in this study and divided into two groups: group I and group II. These two groups were divided into three subgroups: solitary first diagnosed tumor ≤ 3 cm (SFDGT), solitary first diagnosed tumor > 3 cm and multiple first diagnosed tumors (MFDGT), and recedive tumors (RCT). Statistical analysis was performed by using χ^2-test and Kolmogorov-Smirnov test. **Results:** In the group I a total of 133 cases had reccurence contrary to 75 in the group II, making a statistically highly significant difference. Analysis of recurrences through the subgroups revealed: in the group I SFDGT recurrence occured in 27 of the cases *vs* 9 cases in the group II; in the group I MFDGT recurrence occured in 49 of the cases *vs* 31 in the group II ($p < 0.001$), and finally, in the group I RCT recurrence occured in 57 cases *vs* 35 cases in the group II ($p < 0.001$). **Conclusion.** The obtained results indicate no difference in the frequency of reccurence between the group I and group II regarding SFDGT, but a very high significant difference regarding those with MFDGT and RCT. These results should be taken into consideration in everyday clinical practise.

Key words:
urinary bladder, neoplasms; carcinoma in situ; immunotherapy; mycobacterium bovis; recurrence.

Apstrakt

Uvod/Cilj. Intravezikalna imunoterapija bacilom Calmette-Guérin (BCG) smatra se zlatnim standardom u lečenju mišićnoneinvazivnih tumora mokraćne bešike (NIMBC) nakon transuretralne resekcije (TUR) tumora. Cilj istraživanja bio je uporediti učestalost recidiviranja tumora između bolesnika podvrgnutih terapiji TUR + BCG (grupa I) i samo terapiji TUR (grupa II). **Metode.** Bolesnici sa NIMBC lečeni u našoj instituciji od 1. 1. 2007. do 3. 3. 2013. (n = 899), bili su uključeni u istraživanje. Dve grupe bolesnika podeljene su u tri podgrupe: bolesnike sa solitarnim novootkrivenim tumorima ≤ 3 cm (SFDGT), bolesnike sa solitarnim novootkrivenim tumorima > 3 cm i multiplim novootkrivenim tumorima (MFDGT), i bolesnike sa recidivnim tumorima (RCT). Statistička analiza obavljena je primenom χ^2-testa i Kolmogorov-Smirnov testa. **Rezultati.** U grupi I došlo je do recidiva kod 133 bolesnika, nasuprot 75 u grupi II, što je statistički visokoznačajna razlika. Ako se analizira učestalost recidiviranja uzimajući u obzir formirane podgrupe nađeno je da se u grupi I SFDGT recidiv javio kod 27 bolesnika, nasuprot 9 bolesnika u grupi II ($p > 0,05$) u grupi I MFDGT recidiv se desio kod 49 bolesnika nasuprot 31 u grupi II ($p < 0,001$) kao i da se u grupi I RCT recidiv javio kod 57 bolesnika nasuprot 35 u grupi II ($p < 0,001$). **Zaključak.** Dobijeni rezultati ukazuju da ne postoji statistički značajna razlika u učestalosti recidiviranja kod podgrupe SFDGT, ali je prisutna kod podgrupa MFDGT i RCT. Ovo može biti od značaja za svakodnevnu kliničku praksu.

Ključne reči:
mokraćna bešika, neoplazme; karcinom in situ; imunoterapija; bacillus calmetteguerin; recidiv.

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Introduction

Urinary bladder cancer, transitional cell carcinoma (TCC) is one of the most common malignancies in the USA and Europe. Most bladder tumors are non-muscle invasive tumors (NMIBC) at the moment when they were diagnosed (75–85%) [1, 2]. After more than 30 years of research, intravesical instillation of bacillus Calmette-Guérin (BCG) after transurethral resection of bladder tumor (TUR BT) remains the most effective intravesical treatment in NMIBC, but there steal exists a room for improvement [3]. The key element of BCG antitumor activity resides in its ability to switch on a robust cellular immune response, although the precise mechanism of action is not yet fully understood. The complex immunologic cascade starts with the initial adherence of mycobacteria to the urothelial lining and proceeds through the secretion of cytokines from urothelial cells, a process that attracts a large array of inflammatory cells (neutrophils, monocytes). BCG immunotherapy requires robust immune system [4, 5]. BCG has currently become the most commonly used intravesical agent and is known to be superior to other intravesical agents for prevention of tumor recurrence [2, 6]. Standard BCG induction treatment consists of six weekly bladder instillations. Many institutions give three to twenty one additional instillations during the first three years to improve results [7]. Although this therapy has been proven to reduce significantly the incidence of stage progression and recurrence in NMIBC [8, 9] there was also registered that it has minor side effects occurring in 35–71% of patients and significant morbidity in 5–23% of patients due to systematic sepsis [10]. In our institution in compliance with international standards this therapy was applied. Regarding recurrence within one year of monitoring, frequency was consistent with published data, namely 15–20%, depending on the period of follow-up. The frequency and severity of adverse effects of the treatment were also in line with literature data. According to our experience, the most common side effects were chills, fever, micro and macrohematuria. Significantly less common were severe complications such as the development of tuberculosis (TBC) of urinary tract, miliary TBC of lung, bladder contracture, reduced bladder capacity, urethral stenosis. Most rare were complications such as TBC encephalitis and hepatitis. This therapy was applied in our institution regularly until the start of 2012 and after that due to the discontinuance of production of this medication (ImmuCyst®, Sanofi-Aventis) and as no similar product has been registered so far for the Serbian market, TUR BT was the only treatment for patients suffering from NMIBC. Current situation, including side effects and costs of this therapy has imposed an idea to investigate is the usage of this therapy necessary in all cases of this stadium of the illness. The aim of our investigation was to compare the frequency of recurrence between a group of patients submitted to therapy TUR + BCG (group I) and a group of patients submitted only to TUR (group II).

Methods

The study included patients with NMIBC treated and controlled in our institution in the period January, 2007 – March 3, 2013. The study included 899 participants of both sexes [male 660 (73,4%), female 239 (26.6%)], of various ages, average 61.05 ± 10.52 years and different occupations. Whether respondents belonged to a risk group of developing bladder cancer and recurrence of the disease did not affect the possibility to be included in the study. The respondents, depending on the applied treatment, were divided into two groups: patients who underwent BCG intravesical therapy after TUR (TUR + BCG), the group I, 674 subjects, and a group in which TUR was the only treatment, the group II, 225 subjects. The patients with intravesical BCG therapy, received a single dose *per* week following the therapy, a total of six weeks. These two groups were divided into three subgroups: the solitary first diagnosed tumor ≤ 3 cm (SFDGT), the low risk of recurrence group according to the recommendations of the Guidelines of the European Association of Urologists (EAU) [2]; solitary first diagnosed tumor > 3 cm and multiple first diagnosed tumors (MFDGT) subgroups; the recidive tumours (RCT) subgroups. The group I subgroup SFDGT included 363 subjects, the group I subgroup MFDGT 152 subjects, and the group I subgroup RCT 159 subjects. The group II subgroup SFDGT included 128 subjects, the group II subgroup MFDGT 51 subjects, and the group II subgroup RCT 46 subjects. All the formed groups and subgroups were homogeneous in terms of age and gender. After the therapy was conducted, all of the respondents were in regular quarterly controls that involved basic laboratory tests, ultrasonic examination and uretrocystoscopy. If and when there was a recurrence of the disease, progresion in the grade and stage of the disease was estimated. The disease progress in terms of grade and stage was determined after the new TUR.

All the results in the text, tables and graphs are presented as the mean value ± standard deviation (SD). The significance of the differences in frequency distributions of individual parameters was checked using $\chi 2$-test or the Kolmogorov-Smirnov test. The correlation of various parameters was investigated using parametric or nonparametric correlation analysis (Pearson). The three levels of statistical significance were determined: $p < 0.05$; $p < 0.01$ and $p < 0.001$. Data processing was performed using a commercial statistical software for PCs (Stat for Windows, R.4.5, Stat Soft, Inc., USA, 1993).

Results

The results obtained in this study suggest a highly statistically significant difference in incidence of recurrence between the groups I and II. Table 1 shows the incidence of the disease recurrence in the groups I and II.

Table 1

The incidence of recurrence in relation to the therapy

Therapy	Patients (n)	Recurrences n (%)
TUR + BCG	674	133 (19.73)
TUR	225	75 (33.33)*
Total	899	208 (23.14)

TUR – transurethal resection; BCG – Bacillus Calmette-Guérin *$\chi^2 = 16.78$, $p < 0.001$ (χ^2 test).

The results shown in Table 1 clearly indicate the difference in the frequency of recurrence between the groups I and II confirming the importance of the application of intravesical BCG therapy in treatment of patients suffering from NMIBC.

Between the subgroups SFDGT in the group I and the group II, there was no statistically significant difference in the incidence of recurrence within one year of follow-up, while there was a statistically significant difference in the frequency of recurrence between the subgroups RCT and subgroups MFDGT.

Table 2 shows the frequency of the desease recurrence depending on the forms of cancer and the applied therapy.

As it is shown in Table 2, it is clear that in addition to the applied therapy a significant role in the incidence of recurrence is played by the shape of the tumor. So in the SFDGT subgroup which according to the Guidelines of EAU included low-risk tumors, no statistically significant differences in the frequency of recurrence was observed, while this significance was present in patients with high risk NIMBC.

Between the subgroups SFDGT there was no statistically significant difference during the period of the disease relapse.

Table 3 shows the period of the disease relapse in the SFDGT subgroups of both groups.

As shown in Table 3 in the patients with low-risk NIMBC there was no statistically significant difference in the relapse period depending on the applied therapy, while in all other shapes of NMIBC there was a statistically significant difference in relapse period due to the applied therapy (Tables 4 and 5). Kolmogorov - Smirnov test was used for statistical analysis of the results.

Between the MFDGT subgroups there was a statistically significant difference in the incidence of recurrence after 9 and 12 months of follow-up and between the subgroups RCT a statistical significance was present after 6 and 9 months of follow-up. Tables 4 and 5 show the period of relapse for these two subgroups of patients.

Disease progression in grade between the SFDGT subgroups was not present in a statistically significant extent,

Table 2

Frequency of recurrence depending on the forms of cancer and the applied therapy

Applied therapy	SFDGT		MFDGT		RCT	
	Number of patients	Number (%) of recurrences	Number (%) of patients	Number (%) of recurrences	Number (%) of patients	Number (%) of recurrences
TUR + BCG	363	27 (7.4)	152	49 (32.2)	159	57 (35.8)
TUR	128	9 (7.0)	51	31 (60.8)	46	35 (76.1)
χ^2 test		n.s.		$p < 0.001$		$p < 0.001$

SFDGT – solitary first diagnosed tumors; MFDGT – multiple first diagnosed tumors;RCT – recedive tumors;TUR – transurethal resection; BCG – Bacillus Calmette-Guérin.

Table 3

Period of disease relapse in the subgroups of solitary first diagnosed tumors (SFDGT) of both groups of patients

Applied therapy	Number of patients	Number (%) of recurrences			
		months			
		3	6	9	12
TUR + BCG	363	1 (0.3)	11 (3.0)	2 (0.5)	13 (3.6)
TUR	128	1 (0.8)	3 (2.3)	1 (0.8)	4 (3.1)
Kolmogorov-Smirnov test		n.s.	n.s.	n.s.	n.s.

TUR – transurethal resection; BCG – Bacillus Calmette-Guérin.

Table 4

Period of disease relapse in the solitary first diagnosed tumors > 3 cm and multiple first diagnosed tumors (MFDGT) subgroups of both groups of patients

Applied therapy	Number of patients	Number (%) of recurrences			
		months			
		3	6	9	12
TUR + BCG	152	7 (4.6)	11 (7.2)	13 (8.6)	18 (11.8)
TUR	51	2 (3.9)	5 (9.8)	11 (21.6)	13 (25.5)
		n.s.*	n.s.†	$p < 0.05^{\dagger}$	$p < 0.05^{\dagger}$

TUR – transurethal resection; BCG – Bacillus Calmette-Guérin.
*** Kolmogorov-Smirnov test; $^{\dagger}\chi^2$ test**

Table 5

Period of disease relapse in RCT subgroups of both groups of patients

Applied therapy	Number of patients	Number (%) of recurrences			
		months			
		3	6	9	12
TUR + BCG	159	1 (0.6)	12 (7.5)	17 (10.7)	27 (17.0)
TUR	46	2 (4.3)	9 (19.6)	12 (26.1)	12 (26.1)
		n.s.*	$p < 0.05^{\dagger}$	$p < 0.05^{\dagger}$	n.s. †

RCT – recedive tumors; TUR – transurethal resection; BCG – Bacillus Calmette-Guérin;
*** Kolmogorov-Smirnov test was performed; $^{\dagger}\chi^2$ test.**

whereas the difference in grade progression between the MFDGT and RCT subgroups was at the level of statistical significance, as shown in Table 6.

The results in this Table indicate that BCG therapy, in the patients belonging to the low-risk group did not affect the progression of grade, whereas a significant difference in the progression of grade was present in the MFDGT and RCT subgroups, depending on the application of BCG therapy.

There was no significant statistical differences in the frequency of progression of the stadium of the disease between the SFDGT subgroups, while a statistically significant difference in the frequency of the stadium progression was present between the MFDGT and RCT subgroups, as shown in Table 7.

The most important parameter in monitoring and treating NIMBC is certainly the progression of NIMBC in infiltrative

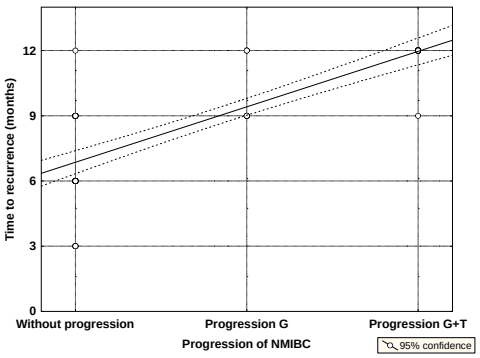

Fig. 1 – Correlation of time to recurrence and disease progression

G – grade of the disease
T – stadium of the disease
NMIBC – non-muscle invasive bladder cancer.

Table 6

Tumor progression from the grade 2 to the grade 3 in both groups of patients

Applied therapy	SFDGT		MFDGT		RCT	
	Number of patients	Number (%) of recurrences with grade progression	Number of patients	Number (%) of recurrences with grade progression	Number of patients	Number (%) of recurrences with grade progression
TUR + BCG	363	7 (1.9)	152	18 (11.8)	159	25 (15.7)
TUR	128	3 (2.3)	51	19 (37.2)	46	16 (34.8)
χ^2 test		n.s.*		$p < 0.001^{\dagger}$		$p < 0.01^{\dagger}$

TUR – transurethal resection; BCG – Bacillus Calmette-Guérin;
SFDGT – solitary first diagnosed tumors ≤ 3 cm; MFDGT – solitary first diagnosed tumors > 3 cm and multiple first diagnosed tumors; RCT – recidive tumors;
*** Kolmogorov-Smirnov test; $^{\dagger}\chi^2$ test.**

Table 7

Progression from the stadium 1 to a higher stadium of the disease in both groups of patients

Applied therapy	SFDGT		MFDGT		RCT	
	Number of patients	Number (%) of recurrences with stadium progression	Number of patients	Number (%) of recurrences with stadium progression	Number of patients	Number (%) of recurrences with stadium progression
TUR + BCG	363	6 (1.6)	152	16 (10.5)	159	22 (13.8)
TUR	128	2 (1.6)	51	12 (23.5)	46	13 (28.3)
		n.s.*		$^{\dagger}p < 0.05$		$^{\dagger}p < 0.05$

TUR – transurethal resection; BCG – Bacillus Calmette-Guérin; SFDGT – solitary first diagnosed tumors ≤ 3 cm; MFDGT – solitary first diagnosed tumors > 3 cm and multiple first diagnosed tumors; RCT – recidive tumors;
*** Kolmogorov-Smirnov test; $^{\dagger}\chi^2$ test.**

tumor of the bladder. The results of this study, shown in Table 7, suggest that in the low-risk of NIMBC recurrence there is no significant difference in the progression of the disease, depending on the application of BCG therapy.

Table 8 shows the correlation of NIMBC progression and the time of recurrence according to the applied therapy.

A statistically highly significant correlation between NIMBC progression and the time of recurrence was present in the patients of the group II treated with TUR, as opposed to the group I in which no statistically significant correlation was established. This correlation is graphically shown in Figure 1.

Discussion

The role and significance of intravesical BCG immunotherapy after TUR BT in reducing the rate of recurrence was confirmed by numerous publications. In the study of Gontero et al. [9] it was concluded that intravesical BCG therapy should be considered as the most effective form of intravesical therapy, but the role of this therapy in the progression of the disease in papillary tumors remains to be elucidated. Morales et al. [11] in their work from 1976, which initially included 10 patients, later reduced to 7 patients (1 died of other disease and

Table 8

Correlation of NIMBC progression and the time of recurrence according to the applied therapy

Applied therapy	Coefficient of correlation (r)	*t*-value	*p*
TUR + BCG	-0,1419	1.64	0.10
TUR	0.8131	11,93	0.001

TUR – transurethal resection; BCG – Bacillus Calmette-Guérin.

two had inadequate follow-up), announced that in 7 of these patients, in whom the intravesical BCG therapy was conducted, during 47 months of follow-up, no recurrence observed. Lamm et al. [12] published in 1980 results of a randomized prospective study on comparison, as in our study, the effects of two types of therapy: TUR and TUR + BCG. Their study included 37 patients, the follow-up period was, as with us, a year after completion of the therapy. Out of 19 patients treated with only TUR therapy in 8 (42%) recurrence developed within the follow-up period, and out of 18 patients treated with TUR + BCG therapy, patients, recurrence was registered in 3 (17%) patients. This difference is more pronounced than in our study, but our study included a much larger number of patients. Brandau et al. [3] showed the effectiveness of this therapy based on 30 years of experience, and pointed out that there is still room for improvement in the application of this therapy, indicating thereby that although numerous studies have confirmed the superiority of BCG as adjuvant therapy yet are always possible improvements in the mode of application of this therapy. Vázquez-Lavista et al. [4] showed the importance of this therapy and emphasized the role of BCG as an immunomodulator in patients with NMIBC. A history of the application of this therapy was described by Herr and Morales [8]. About treatment strategy of high risk NMIBC wrote Sharma et al. [5]. Tne incidence and the treatment of complications of BCG therapy were described by Lamm et al. [10] in their research in 1992. Ríos et al. [13] in their work amounts to conclusion that BCG is the most effective adjuvant for patients with NMIBC, especially in high risk patients. Our research verified the importance of this therapy in the same group of patients, MFDGT and RCT. The extent to which medicine has advanced in the application of this therapy, in patients with NMIBC was described by Jacobs et al. [14]. Shelley et al. [15] published a systematic overview of randomized trials and meta-analyzes that confirm the importance and place of this therapy in treatment of patients with NMIBC. An affirmative answer to the question of whether intravesical BCG instillation may reduce the rate of NMIBC recurrence, provided Han and Pan [16] in their study. Recommendations for the treatment of patients with NMBIC in clinical practice were given by Lamm et al. [17]. In spite the fact that BCG has become the most widespread and widely applied intravesical therapy in treating NMIBC [2], recommended by the guidelines of the European Association of Urologists, due to the side effects of this therapy, the critiques and questions whether this therapy is really necessary for all cases with NMBIC are inevitable.

On attempts to modify BCG therapy using a reduced dose of BCG reported Ojea et al. [18] and Martinez-Piñeiro et al. [19]. The results of our research showed that recurrence 3 months after the therapy, depending on the form of the tumor and the applied therapy, occurred in 1–7 of the patients. Such an early occurance of recurrence may open the question of whether it really is a recurrence of illnes or possibly overlooked tumor during the TUR. Brausi et al. [20] in 2002 published the analysis that included 2,410 patients from seven European Organisation for Research and Treatment af Cancer (EORTC) studies that were in the third phase of testing, in which they dealt with the phenomenon of recurrence at the first control cystoscopy. They emphasized that the rate of recurrence depended very much on the institutions, and ranged, in patients with solitary tumor in patients who did not receive adjuvant intravesical therapy, from 3.4% to 20.6%, while for patients with adjuvant intravesical treatment this percentage was from 0% to 15.4%. When it came to patients with multiple tumors with adjuvant intravesical therapy, this percentage ranged from 7.4% to 45.8%.

In our study we found no statistically significant difference in the incidence of recurrence in the patients with low risk NIMBC. Also, when it comes to this subgroup of patients there was no statistically significant difference between any of recurrences, as well as in the incidence of the disease grade progression or the stage of the disease progression. In patients with MFDGT or RCT (patients with high-risk NIMBC) there were significant differences, depending on the applied therapy (BCG + TUR or TUR the only therapy) in terms of the frequency of recurrence, as well as the progression of the disease.

Conclusion

This study indicates the importance of applying BCG intravesical immune therapy after transurethal resection of the tumor, that was also confirmed by the other authors.

However, our research indicates that it is necessary to be selective in the intravesical instillation of Bracillus Calmette-Guérin after transurethal resection of the tumor, because each non-muscle invasive tumor does not require the application of this therapy, which was confirmed by comparing the frequency of recurrence of solitary first diagnosed tumors ≤ 3. We believe that this fact, in addition to the side effects of this therapy, as well as high costs of this treatment, leaves a question whether the use of this therapy is really necessary for each patient with non-muscle invasive tumor.

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