The clinical course of non-muscle invasive bladder cancer after transurethral resection of the tumor with or without subsequent intravesical application of bacillus Calmette-Guérin: The influence of patients gender and age

Klinički tok karcinoma mokraćne bešike bez zahvatanja mišićnog sloja njenog zida posle transuretralne resekcije tumora sa ili bez naknadne intravezikalne aplikacije bacila *Calmette-Guérin*: uticaj pola i godina života bolesnika

Radovan Milošević*[†], Novak Milović*[†], Predrag Aleksić*[†], Miodrag Lazić[‡], Snežana Cerović[§†], Rade Prelević*, Aleksandar Spasić*, Dejan Simić*, Božidar Kovačević[§]

*Clinic of Urology, [§]Institute for Pathology, Military Medical Academy, Belgrade, Serbia; [†]Faculty of Medicine of the Military Medical Academy, University of Defence, Belgrade, Serbia; [‡]Department of Urology, Clinical Hospital Center "Dr Dragiša Mišović", Faculty of Medicine, University of Belgrade, Belgrade, Serbia

Abstract

Bacground/Aim. The therapy with intravesical instillation of bacillus Calmette-Guérin (BCG) after transurethral resection (TUR) of tumor is the gold standard of treatment of non-muscle invasive bladder cancer (NMIBC). The role and importance of BCG intravesical therapy in various shape of tumors, were confirmed by our previous investigation. The aim of this study was to examine whether incidence of recurrence and tumor regression differs depending on sex and age of patients. **Methods.** This study included a total of 899 patients suffering from NIMBC, treated at our institution from January 1, 2007 to March 1, 2013. Two groups of patients were formed: patients underwent TUR + BCG therapy (the group I) and the group II with patients in whom TUR was performed as only therapy. These two groups of patients were divided into subgroups of respondents male and female, age 60 years or younger and older than 60 years. Statistical analysis was performed using χ^2 test and the Kolmogorov-Smirnov test. **Results.** This research suggests that if the frequency of recurrence is seen as the only parameter, considering all the subjects, the lowest recurrence rate was determined in the male subjects, aged 60 years and younger who had received BCG after TUR. A high statistical significance was found in the incidence of recurrence in patients younger than 60 years, depending on the response to the therapy, while in those older than 60 years, the difference was at the level of statistical significance. This can be attributed to a certain degree of infravesical obstruction in older men. **Conclusions.** Sex and age of patients may have a significant influence on the course and outcome of NMIBC. The disease has the most malignant and most aggressive behavior when present in males older than 60 years.

Key words:
urinary bladder neoplasms; recurrence; sex; age factors; risk factors; immunotherapy; urological surgical procedures.

Apstrakt

Uvod/Cilj. Intravezikalna imunoterapija bacilom Calmette-Guérin (BCG) smatra se zlatnim standardom u lečenju tumora mokraćne bešike bez zahvatanja mišićnog sloja [*non-muscle invasive bladder cancer* (NMIBC)] nakon transuretralne resekcije (TUR) tumora. Uloga i značaj BCG intravezikalne terapije za ishod lečenja, zavisno od oblika i veličine NMIBC, utvrđeni su našim prethodnim istraživanjem. Cilj ovog rada bio je da se utvrdi incidencija recidiviranja i progresije bolesti u zavisnosti od pola i životnog doba bolesnika. **Metode.** Ispitivanjem je obuhvaćeno 899 bolesnika sa NIMBC, lečenih u našoj instituciji od 1.1.2007 do 1.3.2013. Formirane su dve grupe bolesnika: bolesnici lečeni kombinacijom terapija TUR i BCG (grupa I) i bolesnici podvrgnuti samo terapiji TUR (grupa II). Ove dve grupe bolesnika podeljene su, zatim, u podgrupe: ispitanici muškog i ženskog pola, stari 60 godina ili mlađi, i stariji od 60 godina. Statistička analiza obavljena je primenom χ^2 testa i Kolmogorov-Smirnov testa. **Rezultati.** Posmatrajući učestalost recidiviranja kao jedini parametar, uzevši u obzir sve ispitanike, najniža stopa recidiva nađena je kod ispitanika muškog pola, starih 60 godina ili mlađih, koji su primali BCG nakon TUR-a. Visoka statistička značajnost u učestalosti recidiviranja nađena je kod mlađih od 60 godina, zavisno od primenjene terapije, dok je kod starijih od 60 godina ova razlika bila na nivou statističke značajnosti. Ovo se može pripisati određenom stepenu infravezikalne opstrukcije kod starijih muškaraca. **Zaključak.** Pol i starost bolesnika mogu imati značajan uticaj na tok i ishod NMIBC. Bolest se najmalignije i najagresivnije ponaša kada je prisutna kod osoba muškog pola, starijih od 60 godina.

Ključne reči:
mokraćna bešika, neoplazme; recidiv; pol; životno doba, faktori; faktori rizika; imunoterapija; hirurgija, urološka, procedure.

Correspondence to: Radovan Milošević, Clinic of Urology, Military Medical Academy, Crnotravska 17, 11 000 Belgrade, Serbia.
E-mail: milosevic9@gmail.com

Introduction

Urinary bladder cancer, transitional cell carcinoma (TCC) is one of the most common malignancies in the USA and Europe. Most bladder tumors (75–85%) are non-muscle invasive tumors (NMIBC) at the moment when they were diagnosed [1, 2]. After more than 30 years of research, intravesical instillation of bacillus Calmette-Guérin (BCG) after the transurethral resection (TUR) of bladder tumor (TUR BT) remains the most effective intravesical treatment in NMIBC, but there is still room for improvement [3–5]. 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, 6–9]. The standard BCG induction treatment consists of six weekly bladder instillations. Many institutions give 3–21 additional instillations during the first three years to improve results [10]. Although this therapy has been proven to significantly reduce the incidence of stage progression and recurrence in NMIBC [11, 12] it 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 systemic sepsis [13].

TCC is the fourth most frequent malignancy diagnosed in men and the eighth most frequent among women in the USA. The influence of factors such as gender and age on the incidence, prognosis and survival has not yet been elucidated sufficiently [14]. It is believed that the binding of BCG to the surface of urothelium is the most important step in the BCG anti-tumor activity and studies have shown that the hormonal milieu in the organism of patient may have a significant role in the establishment of this link [15]. Previous studies, which have dealt with the evaluation of the impact of gender on the outcome of BCG therapy, showed different results starting from the fact that there is no connection between sex and treatment outcomes [1, 16, 17] up to, data that the shorter period without disease recurrence in women was found after BCG therapy [18]. A literature review that talked about the influence of gender and age on treatment outcome of TCC was published by Shariat et al. [19] in their work during 2009. Marsit et al. [20] in their study on 331 patients with TCC described the importance of male sex and age in the prediction of outcome of disease in patients suffering from NIMBC with a high grade of disease. In our institution in compliance with international standards this therapy was applied. Regarding recurrence within one year of monitoring, the frequency was consistent with published data – 15% to 20%, depending on the period of follow-up. The frequency and severity of adverse effects of 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 the 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 year 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 has been the only treatment for patients suffering from NMIBC. By our previous investigation [21], the role and importance of BCG intravesical therapy at various shape of tumors, has been confirmed. The aim of this study was to examine whether the incidence of recurrence and tumor progression differ depending on sex and age of patients.

Methods

The study included patients with NMIBC, treated and controlled in our Institution in the period from January 1, 2007 to March 1, 2013. The study included a total of 899 respondents of both sexes, [male 660 (73.4%), female 239 (26.6%)], various ages (average 61.05 ± 10.52 years), and different occupations. Whether respondents belong to the risk group of developing bladder cancer and recurrence of the disease did not affect the possibility that respondents were included in the study. Respondents, depending on the applied treatment, were divided into two groups: patients who underwent BCG intravesical therapy after TUR of the tumor (TUR + BCG) – the group I, 674 subjects, and the group in which TUR of the tumor 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. Given that our goal was to determine whether the frequency of recurrence varies depending on sex and age of patients, the two groups of patients were further divided according to sex and age – the male up to 60 years of age and older, and the women up to 60 years of age and older. Out of 660 male subjects, 487 belonged to the group I, and 173 to the group II. The group I included 222 patients to 60 years of age and 265 subjects older than 60 years, and the group II 77 patients up up to 60 years of age and 96 patients older than 60 years. Of 239 female subjects in the group I were 187 respondents, and in the group II 52 subjects. In the group I there were 89 patients up to 60 years of age and 98 patients older than 60 years, and in the group II, 28 patients up to 60 years of age and 24 patients older than 60 years.

After the therapy had been conducted, all of the respondents were in regular quarterly controls that involved basic laboratory tests, ultrasonic examination and uretrocystoscopy. Based on the results obtained in the controls, it was established if and when there was a recurrence of the disease, depending on the applied therapy, whether patients with the developed recurrence, progressed in the grade and stage of the disease.

All the results in the text and tables are presented as the mean value ± standard deviation (SD). The significance in the differences in frequencies distributions of individual parameters was checked using the χ^2 test or Kolmogorov-Smirnov test in cases when the frequencies were less than 5. 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 the commercial statistical software for PCs (Stat for Windows, R.4.5, Stat Soft, Inc., USA, 1993).

Results

The frequency of recurrence of NMIBC depending on the age group and response to the therapy concerning all the subjects, is shown in Table 1.

The frequency of recurrence of NMIBC depending on age and the applied therapy in the females is shown in Table 3 it is shown that there was no statistically significant difference in the incidence of recurrence in female subjects nor in relation to the applied therapy and age, despite the fact that

Table 1

Frequency of non-muscle invasive bladder cancer recurrence depending on the age group and response to the therapy concerning all the subjects

| Therapy | Age groups (years) | | | | p |
| | ≤ 60 | | > 60 | | ($\leq 60: > 60$) |
	Patients (n)	Recurrences, [n (%)]	Patients (n)	Recurrences, [n (%)]	
TUR + BCG	311	37 (11.9)	363	96 (26.4)	$\chi^2 = 21.47; p < 0.001$
TUR	105	32 (30.5)	120	43 (35.8)	n.s.
p (TUR + BCG : TUR)	$\chi^2 = 18.26; p < 0.001$		$\chi^2 = 3.43; p = 0.064$		

TUR – transurethral resection; BCG – bacillus Calmette-Guérin.

The results in Table 1, show that in the patients up to 60 years of age there was a statistically significant difference in the frequency of recurrence between the group I and the group II, whereas this difference was not present in the patients over 60 years. At the same time, in the group I there was a highly statistically significant difference in the frequency of recurrence depending on age, with a statistically higher incidence of recurrence in the patients older than 60 years. In the group II this significance was not noticed.

Results presented in Table 2 show that regarding males there was a statistically significant difference in the

the percentage of recurrence between the groups I and II, in the patients up to 60 years of age, differsed by as much as 15%. It raises the question of the relevance of comparison of the small absolute numbers of recurrences.

The incidence of disease progression concerning grade (G) and stage of disease (T) at recurrences, registered in all the male respondents, depending on the applied therapy is shown in Table 4.

The results shown in Table 4 indicate that there was a statistically significant difference in the incidence of disease progression in recurrences, so the progression of the disease

Table 2

Frequency of recurrence of non-muscle invasive bladder cancer depending on the age group and the applied therapy observed only in the males

| Therapy | Age groups (years) | | | | p |
| | ≤ 60 | | > 60 | | ($\leq 60: > 60$) |
	Patients (n)	Recurrences [n (%)]	Patients (n)	Recurrences [n (%)]	
TUR + BCG	222	25 (11.3)	265	80 (30.2)	$\chi^2 = 24.48; p < 0.001$
TUR	77	24 (31.2)	96	41 (42.7)	n.s.
p – TUR + BCG : TUR	$\chi^2 = 15.11; p < 0.001$		$\chi^2 = 4.41; p < 0.05$		

For abbreviations, see under Table 1.

Table 3

Frequency of recurrence of non-muscle invasive bladder cancer depending on age and the applied therapy observed only in the females

| Therapy | Age groups (years) | | | | p |
| | ≤ 60 years | | > 60 years | | ($\leq 60: > 60$) |
	Patients (n)	Recurrences [n (%)]	Patients (n)	Recurrences [n (%)]	
TUR + BCG	89	12 (13.5)	98	16 (16.3)	n.s.
TUR	28	8 (28.6)	24	3 (12.5)	n.s.
p – TUR + BCG : TUR	n.s.		n.s.		

For abbreviations, see under Table 1.

frequency of recurrence between the groups I and II, and in those up to 60 years this difference was even highly statistically significant. It is also shown that in the group I there was a highly statistically significant difference according to age, while it was not registered in the group II, although the recurrence rate was the highest among those older than 60 years who did not receive BCG therapy after TUR (Table 2).

was significantly more frequent in males, who did not receive BCG therapy after TUR.

The incidence of the disease progression to grades (G) and stage of the disease (T) in recurrences, registered in all the female subjects, depending on the applied therapy is shown in Table 5.

The results in Table 5 shows that there was no significant difference in the incidence of the disease progression at

Table 4

Incidence of disease progression concerning grade (G) and stage of disease (T) at recurrences, registered in all the male respondents, depending on the applied therapy.

Therapy	Treated patients (n)	Recurrences with progression [n (%)]	
		Progression G	Progression G + T
TUR + BCG	487	47 (9.6)	41 (8.4)
TUR	173	34 (19.6)	25 (14.4)
p (TUR + BCG : TUR)		$\chi^2 = 10.95; p < 0.001$	$\chi^2 = 4.51; p < 0.05$

For abbreviations, see under Table 1.

Table 5

Incidence of disease progression to grades (G) and stage of the disease (T) in recurrences, registered in all the female subjects, depending on the applied therapy

Therapy	Treated patients (n)	Recurrences with progression [n (%)]	
		Progression G	Progression G + T
TUR + BCG	187	3 (1.6)	3 (1.6)
TUR	52	4 (7.7)	3 (5.8)
p (TUR + BCG : TUR)		n.s.	n.s.

For abbreviations, see under Table 1.

recurrences registered in the females, depending on the applied therapy, although it remains an open question whether these findings can be considered relevant, given the low absolute number of relapses with progression.

The frequency of disease progression to grades (G) and stage of the disease (T) in recurrences, depending on the applied therapy registered in the male respondents aged 60 years or younger, is shown in Table 6.

The results in Table 6 indicates that there was a statistically highly significant difference in the incidence of disease progression at recurrences in the males aged 60 years and younger, according to the applied therapy.

The frequency of disease progression to grades (G) and stage of the disease (T) in recurrences, registered in the male subjects, older than 60 years, depending on the applied therapy is shown in Table 7.

The results in Table 7 show that there was no statistically significant difference in the incidence of progression of the disease in recurrences, registered in the male subjects older than 60 years, depending on the applied therapy.

Discussion

The role and significance of intravesical BCG immunotherapy after TUR BT in reducing the rate of recurrence was confirmed by numerous publications, e.g. by Gontero et al. [12]. In their survey, they 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.

Our research, clearly shows that the frequency of recurrence in patients with no BCG therapy after TUR was statistically significantly higher than among patients in whom the therapy was applied, which is in line with the results obtained by Brandau and Suttmann [3] and Herr and Morales [11].

In addition to this, based on the established knowledge our aim was also to determine a possible impact, of age and sex of patients subjected to different forms of treatment on the frequency of recurrence and progression of the disease.

Table 6

Frequency of disease progression to grades (G) and stage of the disease (T) in recurrences, registered in the male respondents aged 60 years or younger, depending on the applied therapy

Therapy	Treated patients (n)	Recurrences with progression [n (%)]	
		Progression G	Progression G + T
TUR + BCG	222	8 (3.6)	6 (2.7)
TUR	77	13 (16.9)	11 (14.3)
p (TUR + BCG : TUR)		$\chi^2 = 13.47; p < 0.001$	$\chi^2 = 12.22; p < 0.001$

For abbreviations, see under Table 1.

Table 7

Frequency of disease progression to grades (G) and stage of the disease (T) in recurrences, registered in the male subjects, older than 60 years, depending on the applied therapy

Therapy	Treated patients (n)	Recurrences with progression [n (%)]	
		Progression G	Progression G + T
TUR + BCG	265	39 (14.7)	35 (13.2)
TUR	96	21 (21.9)	14 (14.6)
p (TUR + BCG : TUR)		n.s.	n.s.

For abbreviations, see under Table 1.

There are still present controversies on this topics, even in studies that included a representative number of respondents, as that of Madeb and Messing [14] in 2004.

Our results showed that in the patients up to 60 years of age there was a statistically significant difference in the frequency of recurrence between the group of patients with BCG after TUR and the group of patients with TUR as the only treatment, whereas this difference was not present in the patients above 60 years of age. At the same time, in the group of patients with BCG after TUR there was a statistically significant difference in the frequency of recurrence depending on age, with the incidence of recurrence statistically higher in the patients older than 60 years, while in the group of patients with TUR as the only treatment this significance was not noticed. Thus, it follows that if the frequency of recurrence is seen as the only parameter, considering all the subjects, the lowest recurrence rate was in the patients with BCG after TUR, up to 60 years, that is partly consistent with the results published by Sylvester et al. [1], Babjukand et al. [2] and Brandau and Suttmann [3].

Considering only male subjects, there was a high statistical significance of the difference in the frequency of recurrence in younger than 60 years, depending on the applied therapy, and in those older than 60 years this difference was on the level of statistical significance. This difference can be attributed to a certain degree of infravesical obstruction, that is present in older men. In patients with no BCG there was no statistically significant difference in frequency of recurrence.

Further, in the females there was no statistically significant difference in the incidence of recurrence, although in the women younger than 60 years, the incidence of recurrence if they did not receive BCG increased by as much as 15%. However, it should be considered that, regarding only females, when the population is divided into groups and subgroups, the absolute number of recurrences was small, so the representativeness of the results remains an open question. These results suggest that in addition to the forms of the therapy, sex and age may have an impact on the incidence of recurrence rate of NMIBC. These results are partly in line with the results published by Madeb and Messing [14], Chen et al. [15] and Shariat et al. [19].

If we look at the progression of the disease from the point of our results it can be seen that in the men with no BCG treatment the incidence of disease progression is statistically more frequent, while this significance was not registered in the females. As we already mentioned, the fact of a small absolute number of recurrences with disease progression in women should not be overlooked. Our results are not consistent with the results published by Takenaka et al. [16] and Lerner et al. [17]. Our findings, however, show a considerable degree of agreement with the results published by Chen et al. [15].

Further analysis of the obtained results show to what extent could age of men, in addition to forms of the applied therapy impact the incidence of disease progression at recurrences. In the males aged 60 years and younger, the incidence of disease progression was statistically more frequent depending on whether they received BCG therapy or not, while this significance was not observed in the subjects older than 60 years, which is consistent with the results published by Chen et al. [15], and partly in compliance with the results published by Marsit et al. [20].

The results of our study indicate that the use of BCG therapy in patients with NMIBC has a definite significance, as confirmed also by the results of other authors. In our research, however, there are the results that are not fully in accordence with the results of other researchers, pertaining to the influence of gender and age of the respondents on the frequency of recurrence and progression of the grade and stage of the disease.

Conclusion

Sex and age of a patient may have a significant influence on the course and outcome of non-muscle invasive bladder cancer. Also, non-muscle invasive bladder cancer has the most malignant and most aggressive behavior when present in males older than 60 years.

R E F E R E N C E S

1. Sylvester RJ, van der Meijden AP, Oosterlinck W, Witjes J, Bouffioux C, Denis L, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol 2006; 49(3): 466−77.

2. Babjuk M, Oosterlinck W, Sylvester R, Kaasinen E, Böhle A, Palou-Redorta J. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder. Eur Urol 2008; 54(2): 303−14.

3. Brandau S, Suttmann H. Thirty years of BCG immunotherapy for non-muscle invasive bladder cancer: a success story with room for improvement. Biomed Pharmacother 2007; 61(6): 299−305.

4. Jacobs BL, Lee CT, Montie JE. Bladder cancer in 2010: how far have we come. CA Cancer J Clin 2010; 60(4): 244−72.

5. Shelley MD, Mason MD, Kynaston H. Intravesical therapy for superficial bladder cancer: a systematic review of randomised trials and meta-analyses. Cancer Treat Rev 2010; 36(3): 195−205.

6. Böhle A, Jocham D, Bock PR. Intravesical bacillus Calmette-Guerin versus mitomycin C for superficial bladder cancer: a formal meta-analysis of comparative studies on recurrence and toxicity. J Urol 2003; 169(1): 90−5.

7. Han RF, Pan JG. Can intravesical bacillus Calmette-Guérin reduce recurrence in patients with superficial bladder cancer? A meta-analysis of randomized trials. Urology 2006; 67(6): 1216−23.

8. Lamm DL, Colombel M, Persad R, Soloway M, Bohle A, Palou J, et al. Clinical practise recommendations for the management of non-muscle invasive bladder cancer. Eur Urol 2008; 7(1): 651−66.

9. Ojea A, Nogueira JL, Solsona E, Flores N, Gómez JM, Molina JR, et al. A multicentre, randomized prospective trial comparing three intravesical adjuvant therapies for intermediate-risk superficial bladder cancer: low-dose bacillus Calmette-Guerin (27 mg) versus very low-dose bacillus Calmette-Guerin (13. 5 mg) versus mitomycin C. Eur Urol 2007; 52(5): 1398−406.

10. *Ströck V, Dotevall L, Sandberg T, Gustafsson CK, Holmäng S.* Late bacille Calmette-Guérin infection with a large focal urinary bladder ulceration as a complication of bladder cancer treatment. BJU Int 2011; 107(10): 1592−7.

11. *Herr HW, Morales A.* Hystory of bacillus Calmette-Guérin and bladder cancer: an immunotherapy succes story. J Urol 2008; 179(1): 53−6.

12. *Gontero P, Bohle A, Malmstrom PU, O'Donnell MA, Oderda M, Sylvester R,* et al. The role of bacillus Calmette-Guérin in the treatment of non-muscle-invasive bladder cancer. Eur Urol 2010; 57(3): 410−29.

13. *Lamm DL, van der Meijden PM, Morales A, Brosman SA, Catalona WJ, Herr HW,* et al. Incidence and treatment of complications of bacillus Calmette-Guérin intravesical therapy in superficial bladder cancer. J Urol 1992; 147(3): 596−600.

14. *Madeb R, Messing EM.* Gender, racial and age differences in bladder cancer incidence and mortality. Urol Oncol 2004; 22(2): 86−92.

15. *Chen F, Langenstroer P, Zhang G, Iwamoto Y, See WA.* Androgen dependent regulation of bacillus Calmette-Guerin induced interleukin-6 expression in human transitional carcinoma cell lines. J Urol 2003; 170(5): 2009−13.

16. *Takenaka A, Yamada Y, Miyake H, Hara I, Fujisawa M.* Clinical outcomes of bacillus Calmette-Guérin instillation therapy for carcinoma in situ of urinary bladder. Int J Urol 2008; 15(4): 309−13.

17. *Lerner SP, Tangen CM, Sucharew H, Wood D, Crawford ED.* Failure to achieve a complete response to induction BCG therapy is associated with increased risk of disease worsening and death in patients with high risk non-muscle invasive bladder cancer. Urol Oncol 2009; 27(2): 155−9.

18. *Fernandez-Gomez J, Solsona E, Unda M, Martinez-Piñeiro L, Gonzalez M, Hernandez R,* et al. Prognostic factors in patients with non-muscle-invasive bladder cancer treated with bacillus Calmette-Guérin: multivariate analysis of data from four randomized CUETO trials. Eur Urol 2008; 53(5): 992−1001.

19. *Shariat SF, Sfakianos JP, Droller MJ, Karakiewicz PI, Meryn S, Bochner BH.* The effect of age and gender on bladder cancer: a critical review of the literature. BJU 2010; 105(3): 300−8.

20. *Marsit CJ, Houseman EA, Schned AR, Karagas MR, Kelsey KT.* Promoter hypermethylation is associated with current smoking, age, gender and survival in bladder cancer. Carcinogenesis 2007; 28(8): 1745−51.

21. *Milošević R, Milović N, Aleksić P, Lazić M, Cerović S, Bančević V,* et al. Difference in recurrence frequencies of non-muscle-invasive-bladder tumors depending on optimal usage of intravesical immunotherapy of bacillus Calmette-Guérin. Vojnosanit Pregl 2014; OnLine-First (00): 72−72.