

Availability and Patterns of Intravesical BCG Instillations

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Purpose: Intravesical BCG instillations improve recurrence free survival in patients with non-muscle-invasive bladder cancer (NMIBC).

Methods: This is a national survey study, covering 223 urological centres, aimed at reliable identification of BCG availability and implemented treatment patterns.

Results: Response rate was 93.7%. BCG was used in 56.5% of urological departments. Another 22.7% referred patients to other hospitals for instillations, while 20.8% did not recommend BCG at all. The most common indications for BCG instillations were as follows: T1 tumours (88.5%), carcinoma in situ (83.6%) and high grade tumours (73.8%). Maintenance therapy was routinely abandoned in 16.4% of centres or was scheduled for <1 year, 1 year, 3 years and 1-3 years in 6.6%, 19.7%, 21.3% and 31.2% of centres, respectively. Continuation of BCG despite treatment failure in carcinoma in situ cases was considered in 21.3% of departments.

Conclusion: Our findings indicate that BCG is underused, while patterns of maintenance and follow-up are sub-optimal.

Keywords: Bacillus Calmette-Guerin; Bladder cancer; Intravesical instillation; Physician survey; Recurrence.

INTRODUCTION

Intravesical Bacillus Calmette-Guerin therapy (BCG) improves recurrence-free, as well as may prolong progression-free survival in patients with high- and intermediate-risk non-muscle-invasive bladder cancer (NMIBC) after transurethral resection of bladder tumour (TURBT). However, BCG is associated with important limitations. First, half of patients does not complete full BCG course due to toxicity, discomfort, deterioration in quality of social life or disease recurrence.⁽¹⁾ Second, urological community has to face reduced availability of BCG strains. Finally, adherence to EAU guidelines on BCG therapy and monitoring of NMIBC patients vary between institutions and countries in Europe.⁽²⁾ These factors can lead to underuse of intravesical immunotherapy. Despite clear clinical significance, reliable real-life data on usage of BCG in Europe is limited. This data would be of special attention in the region of Central Europe, where survival of patients with bladder cancer was reported to be significantly lower than in Western Europe^(3,4) and where the incidence of high-risk NMIBC is relatively high.⁽⁵⁾ In this context, we decided to perform a national analysis of availability and patterns of BCG therapy in Poland.

METHODS

Based on National Health Fund registry, we identified 223 urological centres in Poland. Afterwards, we contacted these departments electronically and/or by

telephone in the period from December 2015 to March 2016. Urologists working in these centres were asked to complete a unified survey. It consisted of 23 questions in five blocks, concerning availability of BCG, indications for therapy, technique of instillations, duration and scheme of treatment, and follow-up protocols. Questions applied to hospital policy regarding BCG instillations and did not incorporate any patient clinical data. Before answering the questions, all responders were informed about the character of the study and were ensured about anonymous publication of data.

RESULTS

Response rate was 93.7% (n=209/223). Among the responders, there were 55 highly specialized or one-day surgery centres, which did not take care of patients with bladder cancer. They were excluded from further analysis, limiting the study group to 154 urological departments routinely performing TURBTs. BCG was available in 56.5% of these departments (n=87/154). In 22.7% of cases urologists declared to routinely refer patients to other centres for BCG (n=35/154). In 20.8% of departments BCG was not recommended irrespectively of oncological characteristics of individual patient (n=32/154) (**Figure 1**).

Full data regarding indications, preparation of patient, BCG strains and follow-up was available for 70.1% of centres (n=61/87; **Table 1**). In patients with high-risk NMIBC, follow-up cystoscopy was scheduled 3 and 6 months after TURBT in 95.1% and 78.7% of cases,

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Table 1. Adopted indications, patient preparation and BCG strains in Polish departments applying BCG treatment.

Indications	T1 tumours	88.5%	
	High grade or G3 tumours	73.8%	
	Carcinoma in situ	83.6%	
	Intermediate-risk NMIBC	44.3%	
Patient preparation	Urine alkalinisation before instillation	4.9%	
	Changing position after instillation	73.8%	
	Limitation of fluid intake before instillation	None	29.5%
		For 2-3 hours	50.8%
		For > 3 hours	14.8%
		Unspecified time	4.9%
	Limitation of fluid intake after instillation	None	59.0%
		For 1-2 hours	26.2%
For 2-3 hours		14.8%	
BCG strain used	RIVM	60.7%	
	Moreau	26.2%	
	Tice	3.3%	
	Different / unspecified	9.8%	
Duration of maintenance therapy	None (only induction course)	16.4%	
	< 1 year	6.6%	
	1 year	19.7%	
	1-2 years	4.9%	
	3 years	21.3%	
	1-3 years, depending on patient individual risk	31.2%	

Abbreviations: NMIBC – non muscle-invasive bladder cancer.

respectively. In patients with history of carcinoma in situ (Cis), 19.7% of departments routinely performed random bladder biopsy during follow-up. In case of presence of Cis at 3 and 6 months after TURBT, BCG

therapy was continued in 59.0% and 21.3% of departments, respectively. Urinary cytology complemented endoscopic assessment only in 32.8% of departments.

DISCUSSION

This is a unique national survey study, presenting real pattern of BCG treatment in Poland. As the study covered 94% of urological centres in the country, it presents fully reliable data. The importance of our findings are highlighted by the fact that mortality rate from bladder cancer in Europe is the highest among Latvian and Polish patients.⁽⁴⁾ Our survey study indicated significant shortcomings in the adjuvant treatment of patients with NMIBC. The most important findings can be summarized as a “triple one-fifth rule”. One fifth of patients has no access to BCG therapy, thus it is advocated to state this therapy is underused. One fifth of patients are not considered for maintenance therapy or its duration is inadequate, thus BCG therapy is suboptimal. Finally, in patients with Cis, in one fifth of cases the therapy is continued despite BCG failure.

Our data allowed us to formulate several possible reasons for unsatisfactory survival of bladder cancer patients in Poland. It can be assumed that both limited use of BCG and suboptimal follow-up, as well as delaying the decision for radical treatment could be the contributing factors. However, it is of utmost importance to establish whether these findings are a kind of regional phenomenon or they rather present global trend. This question is particularly relevant if one considers high toxicity related to the treatment, BCG shortage, data on decreased effectiveness in elderly and limited compliance of bladder cancer patients.^(1,6,7) However, none of these facts eventually advocate intentional underuse of BCG therapy.

The use of BCG in patients with high-risk NMIBC varies between institutions. Recent study by Witjes et

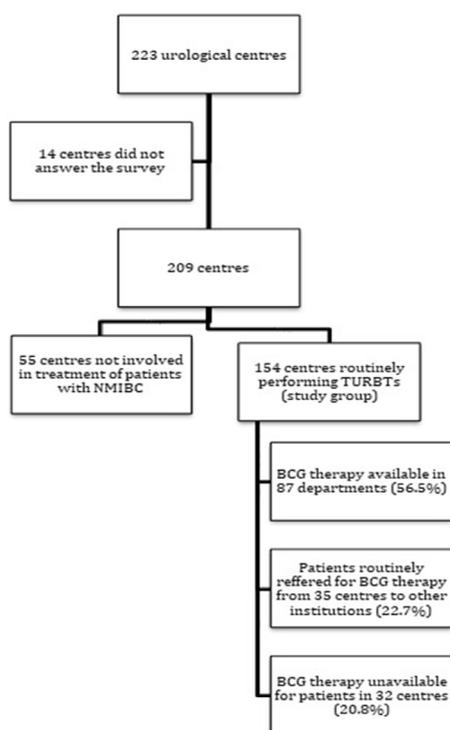


Figure 1. Flowchart presenting constitution of study group and availability of BCG in Polish urological centres. NMIBC – non muscle-invasive bladder cancer; TURBT – transurethral resection of the bladder tumour.

al. demonstrated significant non-adherence to clinical guideline recommendations for BCG use in North America and Europe. In their study only 29% of intermediate-risk patients received intravesical therapy, while in the group of high-risk patients BCG induction and maintenance was offered to 50% of patients.⁽⁸⁾ In contrast, based on survey study among American urologists, Nielsen et al. reported routine use of BCG induction and maintenance therapy in over 80% of patients with high-grade NMIBC. However, despite high number of responders included, the response rate in the study was only 6.9%.⁽⁹⁾ Gontero et al. showed that 22% of high-risk NMIBC patients receive no further treatment after TURBT in referral Italian centres, while BCG maintenance is implemented in 57% of cases.⁽¹⁰⁾ Historical analysis of SEER database by Chamie et al. presented the rate of implementation of maintenance BCG therapy in 26% of high-risk patients.⁽¹¹⁾ All papers cited above analysed individual patient data from selected urological centres or presented clinical practice of individual urologists. None of them present fully reliable regional schemes of BCG treatment. Our study presents strategies of bladder cancer treatment adopted in all Polish centres. It avoids individual preferences of urologists, as majority of centres usually have unified policy of BCG therapy. The most important limitation of our survey is the lack of questions on further treatment in departments that routinely do not recommend BCG therapy.

CONCLUSIONS

To conclude, BCG therapy in Poland is underused and treatment schemes are frequently suboptimal. There are significant differences in the policy of intravesical treatment of NMIBC patients between institutions. Improvement of adherence to guideline recommendations should become a priority for urologists treating patients with bladder cancer.

REFERENCES

1. Serretta V, Scalici Gesolfo C, Alonge V, Cicero G, Moschini M, Colombo R. Does the Compliance to Intravesical BCG Differ between Common Clinical Practice and International Multicentric Trials? *Urol Int.* 2016;96:20-4.
2. Aziz A. BP, Chun FK, Dobruch J, et al. Discrepancy between guidelines and daily practice in the management of non-muscle-invasive bladder cancer (NMIBC): Results of a European survey. *Eur Urol Suppl.* 2016;15:e216.
3. Dybowski B, Ossolinski K, Ossolinska A, Peller M, Bres-Niewada E, Radziszewski P. Impact of stage and comorbidities on five-year survival after radical cystectomy in Poland: single centre experience. *Cent European J Urol.* 2015;68:278-83.
4. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin.* 2015;65:87-108.
5. Poletajew S, Biernacki R, Buraczynski P, et al. Stage of bladder cancer in Central Europe - Polish perspective. *Neoplasma.* 2016;63:642-7.
6. Brausi M, Oddens J, Sylvester R, et al. Side effects of Bacillus Calmette-Guerin (BCG) in the treatment of intermediate- and high-risk Ta, T1 papillary carcinoma of the bladder: results of the EORTC genito-urinary cancers group randomised phase 3 study comparing one-third dose with full dose and 1 year with 3 years of maintenance BCG. *Eur Urol.* 2014;65:69-76.
7. Oddens JR, Sylvester RJ, Brausi MA, et al. The effect of age on the efficacy of maintenance bacillus Calmette-Guerin relative to maintenance epirubicin in patients with stage Ta T1 urothelial bladder cancer: results from EORTC genito-urinary group study 30911. *Eur Urol.* 2014;66:694-701.
8. Witjes JA, Palou J, Soloway M, et al. Current clinical practice gaps in the treatment of intermediate- and high-risk non-muscle-invasive bladder cancer (NMIBC) with emphasis on the use of bacillus Calmette-Guerin (BCG): results of an international individual patient data survey (IPDS). *BJU Int.* 2013;112:742-50.
9. Nielsen ME, Smith AB, Pruthi RS, et al. Reported use of intravesical therapy for non-muscle-invasive bladder cancer (NMIBC): results from the Bladder Cancer Advocacy Network (BCAN) survey. *BJU Int.* 2012;110:967-72.
10. Gontero P, Oderda M, Altieri V, et al. Are referral centers for non-muscle-invasive bladder cancer compliant to EAU guidelines? A report from the vesical antitubercular therapy Italian study. *Urol Int.* 2011;86:19-24.
11. Chamie K, Saigal CS, Lai J, et al. Compliance with guidelines for patients with bladder cancer: variation in the delivery of care. *Cancer.* 2011;117:5392-401.