CROATIAN MEDICAL JOURNAL
CMJ

44(2):187-192,2003

CLINICAL SCIENCES

# Immunoprophylactic Intravesical Application of Bacillus Calmette-Guerin after Transurethral Resection of Superficial Bladder Cancer

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**Aim.** To evaluate the effect of intravesical instillation of Bacillus Calmette-Guerin (BCG) in the prevention of recurrence and progression of the superficial bladder cancer.

**Methods.** Between February 1989 and May 1994, 170 patients with histologically proven superficial transitional cell carcinoma of the bladder stage Ta and T1 were assessed as eligible for 6-week + 6-month protocol of intravesical BCG instillation at the Split University Hospital. All patients underwent complete transurethral resection of the tumor, which established tumor size, histology, stage, and absence of muscle invasion. Out of 170 patients offered to receive intravesical BCG instillations, 80 agreed to undergo the treatment (BCG group), and 90 refused it (control group). The median duration of follow-up was 64 months (range, 16-128).

**Results.** The BCG group had lower incidence rates of recurrence (12 vs 26 events per 100 patient-years in controls, $p < 0.001$) and progression (3.0 vs 6.6 events per 100 patient-years in controls, $p = 0.017$, large-sample one-sample binomial test in both cases) than the control group, but similar mean intervals to first recurrence or progression. The 5-year recurrence-free rates were 55% in BCG patients and 31% in controls, and in case of progression, 86% and 70%, respectively. Cox regression showed that the independent predictors of recurrence were tumor size ($p < 0.001$), absence of BCG treatment ($p = 0.002$), and patient age ($p = 0.05$). The single independent predictor of tumor progression was absence of BCG treatment, but only in case of tumor grade III (roughly doubling the relative risk of the event).

**Conclusion.** Our data suggest that BCG intravesical instillation, using 6 week + 6 month scheme, prevents against recurrence and progression of superficial bladder tumors. This treatment should be especially advocated in patients with advanced grade tumors, but the scheme remains to be evaluated against other BCG treatment schemes.

***Key words:*** *bladder; bladder neoplasms; carcinoma in situ; carcinoma, transitional cell; disease progression; Mycobacterium bovis; neoplasm recurrence, local*

According to the present TNM classification (1), superficial bladder tumor includes the tumors that invade mucosa (Ta), lamina propria (T1), and carcinoma in situ (CIS). It accounts for 70-80% of all transitional cell carcinomas of the bladder (2). Considering its malignancy and recurrence and progression potential, superficial bladder tumor represents a very heterogeneous group of tumors. Transurethral resection is a diagnostic and therapeutic standard in the initial phase of treating the superficial carcinoma of the bladder. For smaller tumors, as well as solitary tumors of lower grade, this method may be curative. However, in most cases, the tumor resection alone does not prevent subsequent recurrence and progression of the cancer. For this reason, different agents (chemotherapeutics, vitamins, or immunomodulators) are applied intravesically after the tumor resection to reduce the probability of recurrence and progression. For the last two decades, Bacillus Calmette-Guerin (BCG) vaccine, a non-specific immunostimulator, has been established in clinical practice as the most effective agent that can change the course of the disease. Numerous studies proved its efficacy and advantages over other agents (3-5). However, there are still unresolved issues, such as the optimal application scheme, patients' selection, and side effects. The aim of this study was to evaluate hitherto unknown efficiency of 6 week + 6 months protocol scheme in the prevention of recurrence and progression of the superficial stage Ta/T1 transitional cell carcinoma of the bladder.

## Patients and Methods

### *Patients*

Out of 270 patients with superficial bladder carcinoma admitted to the Split University Hospital between February 1989 and May 1994, 170 had histologically proved superficial transitional cell carcinoma stage Ta and T1 and were eligible for

intravesical BCG instillation treatment. The inclusion criteria for the therapy were presence of any of the following: recurring tumor, multiple tumors, involvement of lamina propria (T1 stage disease), or poorly differentiated tumor (grade III). All patients underwent complete transurethral resection of the tumor (in one or two acts), which established the tumor size, histological type, grade, stage, and absence of muscle invasion. Tumors were staged according to the TNM classification of The Union Internationale Contre le Cancer (1) and tumor grade by Mostofi system (6). Multiple random punch biopsies from other areas of the bladder were taken to document the presence or absence of carcinoma in situ. Intravesical BCG instillations were offered to all patients, of whom 80 agreed to undergo the treatment (BCG group), whereas the remaining 90 (control group) refused it and were only followed-up (Fig. 1). In the BCG group, there were 14 patients with recurrent tumors and 66 with primary tumor, whereas all patients in the control group had primary tumor.

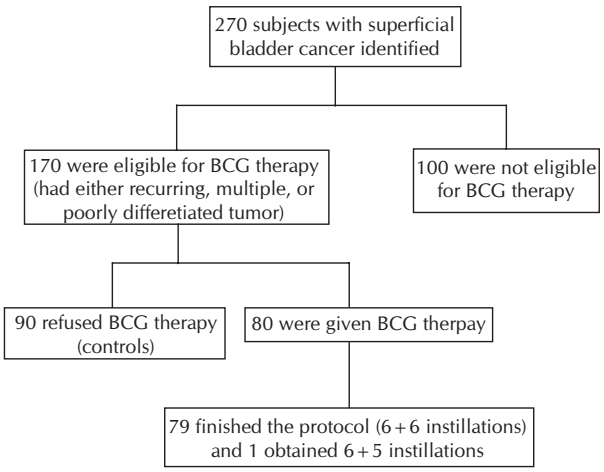


**Figure 1.** Flow-chart of admission, selection and compliance of patients in the study.

*Method*

The protocol of immunoprophylaxis with BCG consisted of 6 weekly instillations + 6 monthly instillations. Instillations began 2-3 weeks after transurethral resection and after obtaining histological documentation of papillary transitional cell carcinoma for each patient. Prophylaxis consisted of bladder instillations of 120 mg of Pasteur strain 1173 (Torlak, Belgrade, Yugoslavia) in the concentration of 75 mg/mL suspended in 50 mL of saline, in the first two years of the study. In the 1992-1994 period, 3 mL of the Stamm-Connaught strain "Imumcyst" (Connaught Laboratories Ltd, Ontario, Canada) was used in the concentration of 27 mg/mL suspended in 50 mL saline. These two different strains were compatible (7). Instillations were performed after the bladder was catheterized and completely drained. We ensured not to insert any air or cause trauma or bleeding during catheterization. The patients were instructed to lie down for 2 h and change position every 30 min to allow maximal contact of the suspension with the bladder mucosa. Follow-up consisted of cystoscopic examinations every 3 months, urine cytology, and mucosal biopsies of all overt or suspicious areas in the bladder in the first year and at the 6-month intervals in the second year and later. An excretory urogram was done once per year. The response evaluation criteria for recurrence and progression were recurrence rate (number of recurrences per 100 person-years of follow-up), mean recurrence interval (defined by total number of months of follow-up divided by the total number of recurrences), mean interval to first recurrence, stage progression rate (number of progressions per 100 person-years of follow-up), mean progression interval (defined by total number of months of follow-up divided by the total number of progressions), and mean interval to progression. The follow-up lasted until the end of the study, the death of a patient, tumor recurrence (when this event was analyzed), or tumor progression (when this event was analyzed). The median duration of follow-up was 64 months (range, 16-128), similar for both groups.

*Statistics*

SPSS 10.0 (SPSS Inc., Chicago, IL, USA) software package was used for statistical analyses. In case of non-censored data, the groups were compared with the chi-square test (categorical variables) and Student's t-test (metric variables). The recurrence and progression rates (events per person-years) were compared using large-sample one-sample binomial test for incidence rates (8). To avoid the constraints of the person-year concept (ie, the assumption that the risk of an event does not change in time), the data were further evaluated by survival-time methods. The Kaplan-Meier method was used to obtain the disease-free survival curves for the groups, which were compared by log-rank test. The relative risks of recurrence or progression were obtained from Cox regression. In case of categorical variables, the relative risk was defined as the instantaneous risk of an event (recurrence or progression) per unit time for an individual with the risk factor (e.g., absence of BCG treatment, or recurrent tumor at baseline), compared with an individual without the risk factor (e.g. presence of BCG treatment or primary tumor), provided that the event had not yet occurred in either of them (univariate estimates) and that they were well matched by all studied covariates (multivariate estimates). In case of continuous variables, the above definition refers to categories obtained by unit change of the variable in question (e.g., 10 years of age, or 10 $cm^3$ of tumor volume). In multivariate analyses, the outcome (dependent) variables were recurrence or progression of cancer, whereas possible predictors (independent variables, covariates, or risk factors) were BCG treatment, sex, age, and tumor characteristics (recurrence, stage, grade, size, and number of tumors). The highly associated variables (e.g., stage and grade) were never entered in the model simultaneously (in that case, the independent estimates of risk ratios would be meaningless). Instead, each of these two variables was tested separately and the regression model producing better overall fit was finally accepted. The possibility of interaction between independent variables was also considered, if suggested in univariate analyses (e.g., grade x treatment, in case of progression, and size x treatment, in case of recurrence). The particular method chosen was backward Wald step-wise regression in each case (with entry and removal p-values set at 0.05 and 0.1, respectively). To test the possibility that the protective effect of BCG on tumor recurrence or progression decreases in time, the BCG treatment was also considered the time-dependent covariate in Cox-regression. The particular model function tested was BCG × $e^{-\lambda t}$, where $\lambda$ was varied from 0 (representing constant) to 1 (representing relatively fast decreasing function) and t was time from BCG treatment in years.

## Results

*Comparisons of Groups and Their Strata*

The groups were similar with respect to their mean age; sex ratio; and tumor number, grade, stage, and size (Table 1). There were no cases of an associated transitional carcinoma in situ. BCG-treated patients had lower incidence of recurrence and progression, but similar mean interval to first recurrence and progression (Table 2). Response to therapy was also analyzed with respect to several tumor characteristics. The relative risk of recurrence was significantly lower in BCG-treated patients with stages Ta, grades II and III, single tumors, and small-size tumors than in the control group (Table 3). Relative risk of progression was significantly lower in BCG-treated than in control patients, but only in those with grade III tumor (Table 4). Since the treatment group included 14 (17.5%) patients with recurrent tumor at baseline, the analyses were also performed for the subgroups of patients with primary tumor (Tables 3 and 4). The analysis showed that patients with recurrent tumor at baseline who were given BCG treatment had greater inci-

**Table 1.** Characteristics of patients with superficial bladder tumor who received 6 week + 6 month intravesical instillations of Bacillus Calmette-Guerin (BCG) and in controls*

| Patient characteristics | No. (%) of patients | |
|---|---|---|
| | BCG group (n = 80) | controls (n = 90) |
| Age (years; median, range) | 63 (34-86) | 65 (40-85) |
| Sex: | | |
| men/women | 63/17 | 71/19 |
| Tumor characteristics: | | |
| single | 45 (56) | 57 (63) |
| multiple | 35 (44) | 33 (37) |
| Stage: | | |
| Ta | 60 (75) | 63 (70) |
| T1 | 20 (25) | 27 (30) |
| Grade: | | |
| I | 6 (7.5) | 8 (9) |
| II | 52 (65) | 56 (62) |
| III | 22 (27.5) | 26 (29) |
| Size ($cm^3$): | | |
| small (< 5) | 53 (66) | 57 (63) |
| medium (5-15) | 18 (23) | 15 (17) |
| large (> 15) | 9 (11) | 18 (20) |
| Recurrent tumor at baseline | 14 (18) | 0 |
| Associated transitional carcinoma in situ | 0 | 0 |
| Median follow-up (months; range) | 64 (16-128) | 64 (27-105) |

*No statistically significant difference between BCG treated patients and controls; Mann-Whitney test for metric and chi-square test for nominal data.

**Table 3.** Disease recurrence in patients with superficial bladder tumor according to the treatment and tumor characteristics (univariate analysis)

| Tumor characteristics | No. (% in stratum) of patients with recurrent tumor according to tumor characteristics | | | |
|---|---|---|---|---|
| | BCG* 36 (45) | controls† 68 (76) | Relative risk‡ (controls vs BCG) | p‡ |
| Tumor multiplicity | | | | |
| single | 20 (44) | 41 (72) | 2.1 | < 0.001 |
| multiple | 16 (46) | 27 (81) | 1.1 | 0.842 |
| Stage: | | | | |
| Ta | 24 (40) | 46 (73) | 1.5 | 0.040 |
| T1 | 12 (60) | 22 (82) | 1.6 | 0.141 |
| Grade: | | | | |
| I | 4 (67) | 7 (88) | 1.3 | 0.172 |
| II | 19 (37) | 40 (71) | 1.7 | 0.009 |
| III | 13 (59) | 21 (81) | 1.9 | 0.041 |
| Size ($cm^3$): | | | | |
| small (< 5) | 17 (32) | 37 (65) | 1.6 | 0.022 |
| medium (5-15) | 11 (61) | 14 (93) | 1.3 | 0.430 |
| large (> 15) | 8 (89) | 17 (94) | 1.9 | 0.164 |
| Primary tumor | 27 (41) | 68 (76) | 1.6 | 0.003 |

*6 week + 6 month intravesical instillations of Bacillus Calmette-Guerin (BCG) after tumor resection.
†Only tumor resection.
‡Cox-regression, stratified analysis.

**Table 4.** Disease progression in patients with superficial bladder tumor according to the treatment and tumor characteristics (univariate analysis)

| Tumor characteristics | No. (% in stratum) of patients with tumor progression according to the tumor characteristics | | | |
|---|---|---|---|---|
| | BCG* (n = 12; 15%) | Controls† (n = 28; 31%) | Relative risk‡ | p‡ |
| Tumor multiplicity: | | | | |
| single | 7 (16) | 18 (32) | 1.4 | 0.092 |
| multiple | 5 (14) | 10 (30) | 0.8 | 0.432 |
| Stage: | | | | |
| Ta | 5 (8) | 12 (19) | 1 | 0.960 |
| T1 | 7 (35) | 16 (59) | 1.6 | 0.162 |
| Grade: | | | | |
| I | 0 | 0 | / | / |
| II | 5 (10) | 12 (21) | 1.1 | 0.784 |
| III | 7 (32) | 16 (62) | 1.9 | 0.043 |
| Size (cm3) | | | | |
| small (< 5) | 6 (11) | 10 (18) | 0.79 | 0.241 |
| medium (5-15) | 4 (22) | 8 (53) | 2.0 | 0.074 |
| large (> 15) | 2 (22) | 10 (56) | 2.1 | 0.130 |
| Primary tumor | 8 (12) | 28 (31) | 2.7 | 0.011 |

*6 week + 6 month intravesical instillations of Bacillus Calmette-Guerin (BCG) after tumor resection.
†Only tumor resection.
‡Cox-regression, stratified analysis.

dences of both recurrence and progression than patients with primary tumor (64% vs 41% and 29% vs 12%, respectively). Thus, patients in BCG group with recurrent tumor at baseline had roughly similar outcome as control patients (not treated, but with primary tumor at baseline).

*Comparison of Survival Curves*

Recurrence and progression-free curves, obtained by Kaplan-Meier method, differed significantly between BCG treated and control patients (Figs. 2 and 3). Recurrence-free survival rates at 5 years were 55% in BCG patients and 31% in controls, whereas progression-free rates were 86% and 70%, respectively. The difference in the steepness of the two curves was relatively constant over time in case of both recurrence and progression.

*Independent Predictors of Recurrence and Progression*

In case of tumor recurrence, the independent predictors were the immunoprophylaxis treatment (negative association), tumor size, and patient's age (positive association) (Table 5). The apparent interaction between treatment and tumor size, suggested by univariate descriptive statistics (Table 3), was not confirmed by Cox regression. In case of tumor progres-

**Table 2.** Outcomes after resection of superficial bladder tumor in patients who received 6 week + 6 month intravesical instillations of BCG and their controls

| Outcomes | BCG (n = 80) | Controls (n = 90) | p |
|---|---|---|---|
| No. (%) of patients with recurrence | 36 (45) | 68 (76) | < 0.001* |
| Recurrence rate/100 patients-years | 12 | 26 | < 0.001† |
| Relative risk of recurrence | 0.64 | 1.56 | 0.005‡ |
| Mean ± SD interval to first recurrence (months) | 25 21 | 27 20 | 0.432§ |
| Mean ± SD recurrence interval (months) | 46 26 | 39 22 | 0.132§ |
| No. (%) of patients with stage progression | 12 (15) | 28 (31) | 0.013* |
| Progression rate/100 patients-years | 3.03 | 6.6 | 0.017† |
| Relative risk of progression | 0.46 | 2.18 | 0.023‡ |
| Mean ± SD interval to progression (months) | 36 25 | 37 23 | 0.781§ |

*Chi-square test.
†Large sample one sample binomial test.
‡Cox regression (univariate analysis).
§t-test for independent samples.

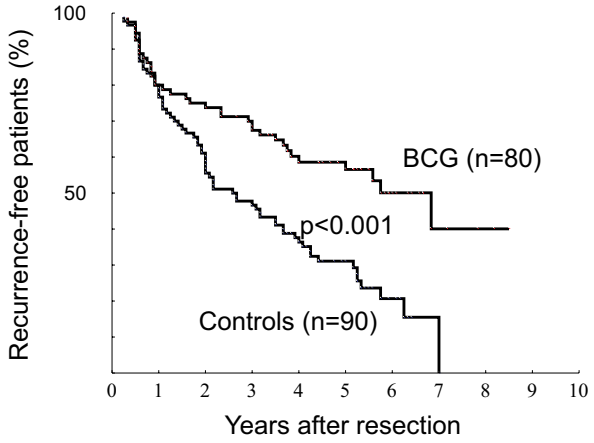


**Figure 2.** The rate of decrease in percentage of recurrence-free patients was slower in Bacillus Calmete-Guerin (BCG)-treated patients with superficial bladder cancer than in BCG-untreated controls (the "survival" curves were obtained by Kaplan-Meier method and compared by log rank test).

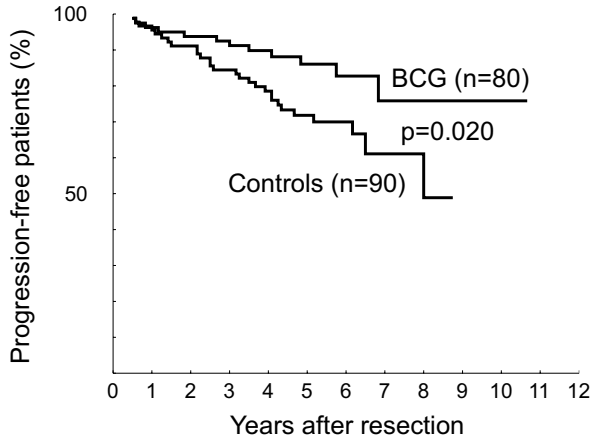


**Figure 3.** Percentage of progression-free patients decreased slower in Bacillus Calmete-Guerin (BCG)-treated patients with superficial bladder cancer than in BCG-untreated controls (the "survival" curves were obtained by Kaplan-Meier method and compared by log rank test).

**Table 5.** Predictors of superficial bladder tumor recurrence (multivariate analysis)*

| Predictors | p | Relative risk | 95% confidence interval |
|---|---|---|---|
| Age (in deciles) | 0.050 | 1.17 | 1-1.4 |
| BCG† treatment | 0.002 | 0.61 | 0.5-0.8 |
| Tumor size (per 10 cm3) | <0.001 | 1.34 | 1.2-1.6 |

*Cox regression (stepwise-backward Wald algorithm).
†Bacillus Calmette-Guerin.

**Table 6.** Treatment with Bacillus Calmette-Guerine (BCG) as a predictor of superficial bladder tumor regression (multivariate analysis)*

| BCG-treatment in | p | Relative risk | 95% confidence interval |
|---|---|---|---|
| grade I patients | 0.715 | 1.2 | 0.4-3.6 |
| grade II patients | 0.744 | 0.93 | 0.6-1.3 |
| grade III patients | 0.030 | 0.52 | 0.3-0.9 |

*Cox regression (stepwise-backward Wald algorithm).

sion, the only significant independent predictor was the variable BCG × grade. BCG treatment appeared to be protective only in case of grade III tumors, reducing the risk ratio of progression by about 50% (Table 6). The recurrent tumor did not appear as an independent predictor of either recurrence or progression. The model with BCG variable used as a constant ($\lambda = 0$) produced better overall fit than models in which the effect of BCG was allowed to decrease in time ($\lambda > 0$) in case of both tumor recurrence and progression (in concord with the overall appearances of the Kaplan -Meier curves, described above).

Out of the 12 patients with progression in the BCG group, 3 underwent radical cystectomy, 3 radiation therapy, and 6 symptomatic therapy. Out of 28 patients with progression in the control group, 9 underwent radical cystectomy, 7 radiation therapy, and the remaining 12 underwent a symptomatic therapy.

*Complications of BCG Therapy*

Mild hematuria, fever, and dysuria (minor side effects) were found in 90% of patients. Antituberculotic treatment was necessary in 4 patients, due to arthritis in 3 of them and BCG sepsis in one case. Patients with arthritis were given 300 mg of isoniazid and 600 mg of rifampin for 3 months. Patient with BCG sepsis was treated with 300 mg isoniazid, 600 mg rifampin, and 1 g pyrazimanide for 3 months, followed by another 3 months of 600 mg isoniazid and 900 mg rifampin. They all responded well to the therapy.

## Discussion

One of the standard schemes of prophylaxis after bladder cancer resection, the 6 weekly instillations of BCG vaccine, evokes positive response in 28-78% of patients followed-up for more than 4 years (9-11). However, the response of immune system to BCG vaccine stimulation decreases over time. The maximum response is reached after 6 weeks (12), and the lymphocyte infiltration of the bladder wall weakens after 6 months (13). To account for this, the "booster doses" were applied for prolonged periods of time. These booster doses, applied monthly or quarterly during 3 years, resulted in positive response in 49-75% of patients followed-up over 3 years (14,15).

In this study, 6 week + 6 month BCG intravesical instillations were associated with significantly lower recurrence and progression rates of superficial bladder cancer, compared with BCG-untreated controls. The study groups were not obtained by randomization, but were similar in possible predictors of outcome. The only difference was that there were 14 (17%) patients with recurrent tumor at baseline in the BCG-treated group, and none in the control group. The patients in BCG group with recurrent tumor at baseline had roughly similar outcome as control patients, which was in accordance with findings from other study (16). However, multivariate analysis showed that the recurrent tumor did not emerge as an independent predictor of either tumor recurrence or progression. Most patients were followed-up over 5 years or until tumor recurrence. Longer follow-up

would enable further insights in progression rates and survival.

Overall, such results were expected, but what we consider a valuable finding is that tumor characteristics affected the treatment outcome. It seemed that the given prophylaxis might be effective in all patients and all tumors where prevention of recidivism is concerned (reducing the risk ratio for about 40%), but only in grade III tumors for prevention of tumor progression (reducing the risk ratio for about 50%). The protective effects of the 6 week + 6 month BCG application scheme did not decrease in time, which suggests that prolonged applications of BCG vaccine may not be necessary.

It is not easy to compare our results with outcomes of other BCG application schemes. There are also differences in patient selection, BCG strains, duration of follow-up, and parameters reported. The risk ratio, as the parameter that theoretically does not change over time, allows us to compare various studies with different duration of follow-up. Additionally, the risk ratio can be controlled for confounding variables by multivariate techniques. However, some reports do not include the risk ratios or give only the univariate estimates.

The best long-term results in the high-risk patients were reported in the SWOG (Southwest Oncology Group) study (15). This study is the standard against which the effectiveness of other intravesical agents and different application protocols is compared (15). After the 6 induction doses in the SWOG Study (15), 3 week booster doses were started 3 months after the surgery, and then repeated every 6 months until the end of the third year. The results suggested superiority of that scheme in comparison with the 6 induction doses alone. After 7 years of follow-up, the recurrence appeared only in 25% of the patients. However, the SWOG study (15) included only patients that did not develop recurrence during the 3 months after resection, which means positive selection of patients for further 3-week booster instillations.

Most studies claim that the prolongation of the time period to first recurrence proves BCG vaccine effectiveness. According to published data, the average time to first recurrence is 18-22 months with immunoprophylaxis, and 10-11 months without it (17). We think that this time is greatly influenced by surgical approach to resection. Some authors define the true, or orthoptic recurrence as the recurrence at the site of resection, whereas the one at distal locations is called heterotopic recurrence (18,19). Orthoptic recurrence within the 3 months after resection is probably due to inadequate primary resection and may be considered a residual tumor. The importance of surgical skills is supported by the data on early recurrence rates (within the 3 months after resection) in patients who underwent the surgery in the 1970's (43%) vs those operated in late 1980's (4%) (20). In our study, the average time to first recurrence was 26 months in both groups of patients, which indicates that the surgical procedures were adequate and BCG treatment has no influence on this variable. Furthermore, the most significant predictor of recurrence in our patients was the tumor size, which was not observed (or analyzed) by others. The same was found for patient age. However, our hypothesis that the efficacy of BCG treatment declines with age was not supported by our results, since age turned out to be the independent predictor of recurrence, but not through the interaction with BCG treatment.

Generally, the published data suggest that BCG vaccine is less efficient in prevention of tumor progression than in the prevention of tumor recurrence. Only a few studies demonstrated statistically significant effectiveness of the BCG vaccine in prevention of disease progression or its delay (21-23). A thorough analysis of disease progression demands a long-term follow-up and is related to the calculations of survival rates. In the study of Herr et al (21) in high-risk patients, a 6-week scheme was used in 86 selected patients who were randomly assigned to either BCG treatment or follow-up only. Their results were successively published after 5 (21), 10 (22), and 15 years (24). After 5-year follow-up, the results strongly suggested that the BCG immunoprophylaxis was effective in prevention or delay of the disease progression (21). After 10 years, there was a slight, statistically non-significant difference in progression rates in favor of the BCG patients, whereas the time-to-progression was significantly longer than in control patients (22). After 15 years, the progression rates were 53% in both groups (24). Pagano et al (23) used the scheme of 6 weekly doses followed by monthly doses until the end of the first year, and 4 quarterly doses the next year. After 3 years of follow-up, the progression of the disease was found in 4% of patients in the BCG group and 17% of patients in the control group. Despite the statistically significant difference between the two groups, it is hard to come up with strong conclusions since the follow-up period was rather short (23). In our study, the progression-free curves in BCG-treated and control patients were significantly different and this difference did not decrease over the years of follow-up. However, the multivariate analysis revealed that this beneficial effect of BCG treatment was confined to grade III tumors only. Smaller grade tumors either did not progress (grade I) or progressed irrespectively of BCG treatment (grade II). This points to a possibility that poorly differentiated grade III bladder tumors are more susceptible to BCG treatment than better differentiated tumors of grade I and II. This was not observed in previous studies, possibly due to the lack of adequate data analysis.

The BCG application scheme used in this study was relatively simple, short, and allowed for good patients compliance. It should be advocated in all patients with superficial bladder cancer, since a significant number of them would be spared from reoperation or a recurrence would be delayed. BCG immunoprophylaxis would be especially usefull in patients with grade III tumors, preventing progression to muscle invasion. It could be used in clinical practice in combination with an individual approach to patient. The results should be analyzed again after longer follow-up, and this method should be directly evaluated against other application schemes.

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Received: July 19, 2002
Accepted: November 18, 2002

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