Intravesical 4'-Epi-Doxorubicin (Epirubicin) versus Bacillus Calmette–Guérin

A Controlled Prospective Study on the Prophylaxis of Superficial Bladder Cancer

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Background. **The selection of the most appropriate antineoplastic agent and optimal treatment schedule for the prophylaxis of superficial bladder cancer against tumor recurrences is the subject of continual investigations.**

Methods. **A controlled prospective trial involving 161 patients evaluated and compared the efficacy of intravesical epirubicin and bacillus Calmette–Guérin (BCG) administration as prophylaxis against recurrences after complete transurethral resection of superficial bladder cancer. The treatment schedule, consisting of one 6- or 8-week course of instillations (50 mg epirubicin or 150 mg BCG per instillation) followed by single maintenance doses to the responders at follow-up examinations, was modified for those of the initial responders who were at high risk for recurrence and who received an additional separate 4-week course of treatment 6 months after the start of therapy.**

Results. **Sixty percent of the patients treated with epirubicin, 68% of the patients treated with BCG, and 41% of the control subjects, who underwent resection only, remained free of recurrences for a mean follow-up of 32.9 months. The only significant difference was found between patients treated with BCG and control subjects, in favor of the former. Conversely, recurrence rate per 100 patient-months and mean interval to recurrence showed both drugs to be superior to resection alone regarding several tumor characteristics. However, a significant benefit in favor of BCG when compared with epirubicin was shown in those patients who had Stage T1 and Grade 3 tumors at presentation.**

Conclusions. **Intravesical epirubicin and BCG were superior to transurethral resection alone in the prophylaxis of superficial bladder cancer, but with respect to superficially invasive and high-grade tumors, BCG demonstrated a remarkable advantage. *Cancer* 1993; 72:1749–55.**

Key words: bladder neoplasms; carcinoma, transitional cell, superficial; bacillus Calmette–Guérin vaccine; epirubicin.

The selection of the most appropriate antineoplastic agent for the prophylaxis of superficial bladder cancer is a subject of continuous investigation. Intravesical bacillus Calmette-Guérin (BCG) is recognized as one of the most effective treatments available for superficial bladder cancer (Stages Ta and T1 and carcinoma in situ) in the treatment of existing disease and prevention of tumor recurrences.[1–19] Epirubicin is a new derivative of doxorubicin synthesized with the aim of finding anthracycline analogues with an improved spectrum of antitumor activity and lower toxicity. It yields at least similar antitumor effects to those of doxorubicin but with lower incidence of reactions and toxicity to the heart and other organs.[20–25]

Although the effectiveness of the standard 4-, 6-, or 8-week induction phases of intracavitary BCG or epirubicin treatment, with or without maintenance therapy, has been demonstrated repeatedly in numerous clinical trials, these treatment methods are insufficient for many patients. The optimal intravesical regimen, therefore, remains to be defined. In the current study, BCG and epirubicin were given in a modified treatment

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schedule and the results were compared with those of patients who underwent transurethral resection (TUR) alone. Because few clinical studies have compared subjects receiving prophylactic epirubicin therapy with control subjects and, to our knowledge, none with BCG and control subjects simultaneously, at least with our modified protocol, the experience gained here furnishes additional useful data in the prophylactic management of superficial bladder cancer.

Material and Methods

One hundred ninety consenting patients with histologically proven superficial transitional cell carcinoma of the bladder (Stages Ta and T1 and Grades 1 to 3 according to the recommendations of the World Health Organization[26]) were enrolled in a prospective randomized controlled trial. After bladder mapping with biopsies and complete removal of all visible tumors with TUR, which was repeated (with fulguration) for Stage T1 neoplasms and concomitant carcinoma in situ, patients were stratified according to tumor stage and history of previous tumor recurrences. They were then allocated randomly on a 2:2:1 basis within strata and according to date of birth, with the smaller number to undergo TUR alone (control subjects, Group C) and the two larger numbers to receive intravesically 50 mg epirubicin (Farmitalia Carlo-Erba, Milan, Italy) (Group A) or 150 mg Pasteur-F strain immune BCG (Pasteur Laboratories, Paris, France) (Group B) suspended in 50 ml sterile saline and retained in the bladder for 1½ hours after TUR of the cancer. The study included subjects with primary or recurrent neoplasms, most commonly within 1 year after previous TUR, and with single or multiple tumors. Patients with multifocal carcinoma in situ and another cancer or history of another cancer outside the bladder and who had had previous local or systemic chemotherapy or radiotherapy were excluded from the study.

Immunochemoprophylaxis started 2 weeks after the last resection and included an initial 6-week course of instillations and, for patients who remained free of recurrences, a single maintenance dose at every follow-up examination (with cystoscopy and urinary cytology every 3 months during the first 2 years and every 6 months thereafter). For 47% of the patients treated with epirubicin and BCG who were at high risk for recurrence (i.e., having Stage T1 and/or Grade 3 neoplasms, multiple tumors, a history of recurrences at presentation, and/or concomitant carcinoma in situ, excluding, however, those with Stage Ta, Grade 1 tumors, considering the low probability of recurrence and progression of that tumor), and who had initially responded to therapy, the treatment schedule was modified so that they received, in addition to the initial 6- or 8-week course of instillations (with BCG or epirubicin, respectively), one separate 4-week course at month 6 of follow-up. Patients in the epirubicin and BCG groups were monitored for toxicity and received oral antimicrobial agents after each instillation and for 2 days after instillation. Although failure did not exclude subjects from further therapy, we terminated study follow-up of the patients with recurrences at demonstration of the recurrent tumor. Of the initial 190 subjects, 161 were evaluated, the remainder being ineligible due to protocol violation, loss to follow-up, or other reasons. Clinical data of the comparable groups of patients are presented in Table 1.

Table 1. Patient and Tumor Characteristics

	Group A	Group B	Group C
No. men/no. women	56/11	51/11	27/5
Mean age (yr) (± 2 SD)	65.8 (8.1)	67.1 (12.5)	67.7 (5.5)
Primary tumor (no.)	47	44	23
Recurrent tumor (no.)	20	18	9
Solitary disease (no.)	44	40	19
Multiple tumors (no.)	23	22	13
Stage Ta tumors (no.)	42	41	21
Stage T1 tumors (no.)	25	21	11
Grade 1 tumors (no.)	31	27	13
Grade 2 tumors (no.)	25	27	14
Grade 3 tumors (no.)	11	8	5
Associated Tis (no.)	3	4	2

Group A: epirubicin group; Group B: bacillus Calmette–Guérin; Group C: control subjects; SD: standard deviation; Tis: carcinoma in situ.
P was not significant for Group A versus Group B, Group A versus Group C, and Group B versus Group C.

Comparisons of the simple recurrence rates, relative risks of recurrences (estimated by the life-table method[27]), recurrence rates per 100 patient-months (defined as the number of patients with positive tumor cystoscopies divided by the total number of follow-up months for all patients in each group and then multiplied by the factor 100 for simplicity), and disease-free intervals (defined as the interval from the last TUR to the first recurrence) were the objectives of the current cohort study. Cumulative rates of tumor progression by stage and muscle invasion were also compared. All visible recurrent lesions seen on cytoscopy were resected, with recurrence being established by histological examination of the biopsy material. Disease-free interval (disease-free survival) curves were estimated according to the Kaplan–Meier method and compared by the Mantel–Haensel test. The statistical value of differences revealed by the pair-wise comparisons among the three groups of patients was calculated using the chi-square test with the Yates correction (and Fisher exact test when dichotomous variable frequencies were less than five), Student *t* test, and Wilcoxon signed-rank test,

Table 2. Response to Therapy by Treatment Assignment

	Group A	Group B	Group C	*P*
Total no. of patients	67	62	32	
Total mo of follow-up	1745	1784	603	
Follow-up mo of patients with recurrences	438	363	210	
No. of patients with recurrences (%)	27 (40.3)	20 (32.2)	19 (59.4)	B versus A, $P > 0.1$ A versus C, $P > 0.1$ B versus C, $P < 0.05$
Relative risks for recurrences	0.79	0.69	1.88	B versus A, $P > 0.1$ A versus C, $P < 0.05$ B versus C, $P < 0.01$
Mean mo to tumor recurrences	16.2	18.15	11.05	B versus A, $P > 0.1$ A versus C, $P < 0.05$ B versus C, $P < 0.01$
Recurrence rate per 100 patient-months	1.55	1.12	3.15	B versus A, $P > 0.1$ A versus C, $P < 0.05$ B versus C, $P < 0.01$
No. of patients with tumor progression in stage (%)	6 (9)	4 (6.5)	7 (21.9)	B versus A, $P > 0.1$ A versus C, $P > 0.1$ B versus C, $P = 0.065$
No. of patients with muscle invasion (%)	3 (4.5)	2 (3.2)	4 (12.5)	B versus A, $P > 0.9$ A versus C, $P > 0.2$ B versus C, $P > 0.1$

whereas the relative risks of recurrences were compared using the log-rank test, including the Yates correction for continuity.

Results

The treatment results are summarized in Table 2. The percentage of patients treated with epirubicin who remained free of recurrences (60% for a total follow-up of 1307 months) did not differ significantly from that of patients treated with BCG (68% for a total of 1421 follow-up months) and control subjects (41% for a total follow-up of 393 months), as did the percentage of patients treated with BCG from that of control subjects. However, pair-wise comparisons of the relative risks of recurrences, recurrence rates per 100 patient-months, and mean intervals to recurrences revealed significant differences in favor of epirubicin and BCG. Among patients with recurrences, six (9%) in Group A, four (6.5%) in Group B, and seven (22%) in Group C had progressive disease by stage. Local urothelial spread (spreading carcinoma in situ, involvement of the prostatic urethra, and/or lamina propria invasion) occurred in three patients treated with epirubicin, two patients treated with BCG, and three control subjects, and muscle infiltration (with or without concomitant local urothelial spread) occurred in three patients treated with epirubicin, two patients treated with BCG, and four control subjects. These differences were not statistically significant, except the difference demonstrated between Groups B and C, which approached statistical significance (Fisher exact test, $P = 0.065$). Comparisons of the muscle invasion rates did not yield any significant difference.

Response to therapy was analyzed by several tumor characteristics. Concerning relative risk of recurrence, global comparisons of the three groups of patients showed significant differences regarding multifocal and recurrent disease and Stages Ta and T1 and Grades 2 and 3 neoplasms (Table 3). Pair-wise comparisons among the three groups revealed that epirubicin and BCG significantly lowered the incidence of recurrences in patients with the aforementioned tumors, except in those with Stage T1 and Grade 3 disease, in which BCG but not epirubicin was significantly superior when compared with the control subjects. Furthermore, comparison between BCG and epirubicin indicated the superiority of the former, although statistical significance was approached but not reached. These results are presented graphically using the Kaplan–Meier method (Figures 1–3). Similar results were obtained for recurrence rate per 100 patient-months, although for Stage T1 and Grade 3 tumors, comparisons between BCG and epirubicin groups revealed a significant benefit in favor of the former (Table 4).

The complications of both drug regimens were acceptable. In most cases, these were mild and brief and limited usually to drug-induced cystitis, the rate of which was notably higher with BCG than with epirubicin (79% versus 34%, respectively), as were the rates of

Table 3. Global and Pair-wise Comparisons of the Relative Risks of Recurrences Among the Three Groups of Patients With Respect to Tumor Factors

	Relative risks for recurrences				
Tumor	*Group A*	*Group B*	*Group C*	*P**	*P†*
Primary	1.04	0.73	1.57	NS	NS
Recurrent	0.82	0.66	3.31	< 0.01	A or B versus C, $P < 0.02$ B versus A, $P > 0.1$
Solitary	1.13	0.76	1.33	NS	NS
Multiple	0.76	0.65	2.89	< 0.01	A or B versus C, $P < 0.01$ B versus A, $P > 0.5$
Stage Ta	0.76	0.89	1.96	< 0.05	A or B versus C, $P < 0.05$ A versus B, $P > 0.5$
Stage T1	1.19	0.51	2.16	< 0.05	B versus A, $P = 0.07$ A versus C, $P > 0.1$ B versus C, $P < 0.05$
Grade 1	0.99	0.92	1.24	NS	NS
Grade 2	0.78	0.74	2.27	< 0.01	A or B versus C, $P < 0.05$ B versus A, $P > 0.5$
Grade 3	1.17	0.39	3.37	< 0.01	B versus A, $P = 0.09$ A versus C, $P > 0.1$ B versus C, $P < 0.01$

NS: not significant.
* Global comparisons.
† Pair-wise comparisons.

fever with or without chills (27.4% versus 3%), influenza-like syndrome (13% versus 0%), and macroscopic hematuria (22.6% versus 15%). In cases of more severe or prolonged local or systemic side effects, symptoms diminished with administration of spasmoanalgesics and antihistamines and rarely with nonsteroidal antiinflammatory agents. Treatment was delayed in 7.5% and 5% of the patients treated with epirubicin and

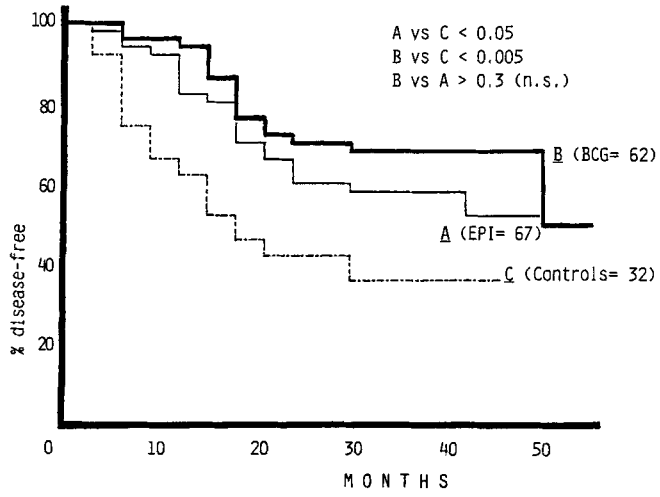

Figure 1. Overall disease-free survival curves. The number of patients at risk at the corresponding times are as follows. Group A: 67 at 0 mo; 61, 10 mo; 42, 20 mo; 25, 30 mo; 14, 40 mo; 2, 50 mo (27 failed). Group B: 62 at 0 mo; 60, 10 mo; 45, 20 mo; 28, 30 mo; 15, 40 mo; 2, 50 mo (20 failed). Group C: 32 at 0 mo; 21, 10 mo; 13, 20 mo; 7, 30 mo; 2, 40 mo; 0, 50 mo (19 failed).

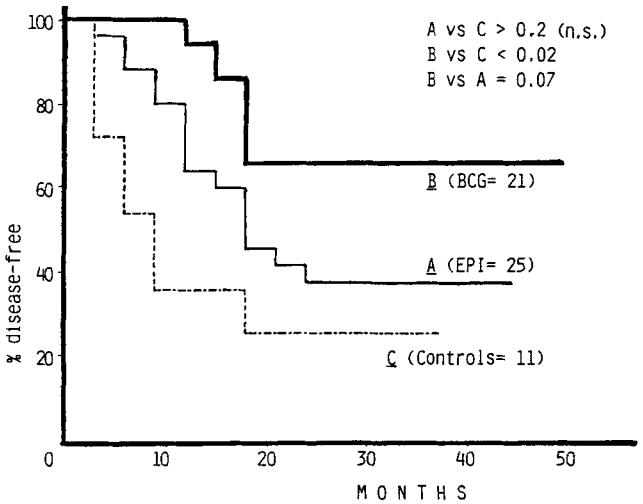

Figure 2. Disease-free survival curves of patients with Stage T1 neoplasms. The number of patients at risk at the corresponding times are as follows. Group A: 25 at 0 mo; 20, 10 mo; 10, 20 mo; 6, 30 mo; 2, 40 mo; 0, 50 mo (15 failed). Group B: 21 at 0 mo; 21, 10 mo; 14, 20 mo; 9, 30 mo; 6, 40 mo; 0, 50 mo (7 failed). Group C: 11 at 0 mo; 4, 10 mo; 3, 20 mo; 1, 30 mo; 0, 40 mo; 0, 50 mo (8 failed). Group C: 11 at 0 mo; 4, 10 mo; 3, 20 mo; 1, 30 mo; 0, 40 mo; 0, 50 mo (8 failed).

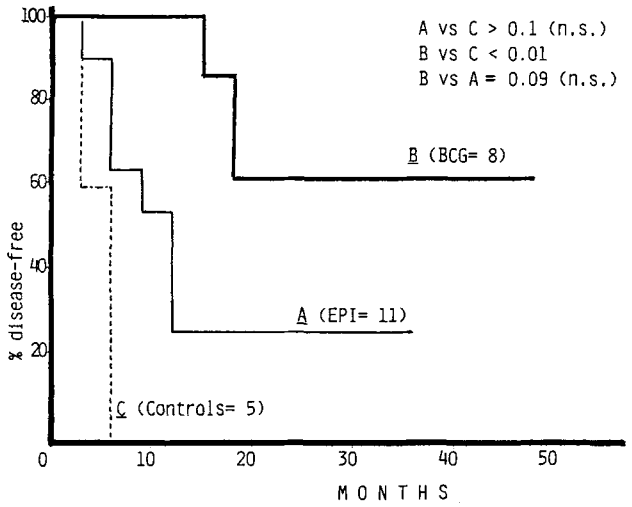

Figure 3. Disease-free survival curves of patients with Grade 3 tumors. The number of patients at risk at the corresponding times are as follows. Group A: 11 at 0 mo; 6, 10 mo; 3, 20 mo; 2, 30 mo; 0, 40 mo; 0, 50 mo (8 failed). Group B: 8 at 0 mo, 8, 10 mo, 5, 20 mo, 4, 30 mo, 3, 40 mo; 0, 50 mo(3 failed). Group C: 5 at 0 mo; 0, 10 mo; 0, 20 mo; 0, 30 mo; 0, 40 mo; 0, 50 mo (5 failed).

BCG, respectively, but was completed in all cases. One patient in the epirubicin group suffered a reduced bladder volume.

Discussion

Although the total patient population evaluated in this prospective trial was at low risk for recurrence (70% of the subjects were treated after their first tumor diagnosis; approximately 69% of those with Stage Ta disease presented with a single tumor, whereas 44% of all patients had Grade 1 neoplasms), observation of the control group (comparable to the other two treatment groups) confirmed the high recurrence rate of superficial bladder tumors with recurrences most likely to occur within 1 year postoperatively and with at least 20% chance of progression of the recurrent cancer.[1,12,28,29] The current study also confirmed previous reports indicating that intravesical epirubicin and BCG alter favorably the pattern of tumor recurrence.[1-9,22-25] Overall, 40% and 32% of the patients treated with epirubicin and BCG, respectively, suffered recurrences, compared with 59% of the control subjects. Pair-wise comparisons among the three groups revealed only one significant difference, which occurred between the patients treated with BCG and control subjects and favored BCG treatment. Comparison of the overall relative risks of recurrences, recurrence rates per 100 patient-months, and mean intervals to recurrences revealed significant differences in favor of both drugs. If the aim of the adjuvant prophylactic intracavitary immunochemotherapy is to prevent recurrences, then these three last objective parameters may be considered among the most important end points.

Further comparisons of the treatment outcome regarding several tumor prognostic factors (considering their different pattern of recurrences)[7,12,28,29] revealed a significant benefit with intravesical epirubicin and BCG in terms of relative risk of recurrence and recurrence

Table 4. Recurrent Rate per 100 Patient-Months by Treatment Assignment

	Recurrence rate per 100 patient-months			
Tumor	*Group A*	*Group B*	*Group C*	*P*
Primary	1.42	1.00	2.11	NS
Recurrent	1.87	1.46	9.88	A or B versus C, $P < 0.002$ B versus A, $P > 0.5$
Solitary	1.53	1.02	1.69	NS
Multiple	1.58	1.31	8.53	A or B versus C, $P < 0.002$ B versus A, $P > 0.6$
Stage Ta	0.97	1.11	2.39	A or B versus C, $P < 0.05$ A versus B, $P > 0.6$
Stage T1	2.98	1.14	5.63	B versus A, $P < 0.03$ A versus C, $P > 0.1$ B versus C, $P < 0.002$
Grade 1	1.26	1.18	1.50	NS
Grade 2	1.12	1.02	3.67	A or B versus C, $P < 0.01$ B versus A, $P < 0.8$
Grade 3	5.03	1.26	20.83	B versus A, $P < 0.03$ A versus C, $P < 0.02$ B versus C, $P < 0.002$

NS: not significant.

rate per 100 patient-months, not only in patients with Stage Ta neoplasms but also in those having Grade 2 multiple and recurrent tumors at presentation. These differences were also depicted by comparing the Kaplan–Meier disease-free survival curves. The incidence of hospitalization for TUR of a recurrent tumor decreased significantly by adjuvant immunoprophylaxis or chemoprophylaxis when applied in subjects with the aforementioned tumor characteristics at entry. Moreover, BCG was shown to be remarkably superior than TUR alone and epirubicin in patients with Stage T1 and Grade 3 disease. The observed effectiveness of our BCG regimen in preventing recurrences of Stage T1 cancer is of particular importance, because it opposes previous reports suggesting a decreased response rate of Stage T1 tumor to intravesical BCG[9,13] but confirms the favorable results of other recent trials in which more than one courses of this agent has been used.[15,16]

Although tumor recurrence is worrisome to patients, it is less important than tumor progression, which involves either local urothelial progression resistant to TUR and intravesical therapy or muscle invasion and/or metastasis. Without prophylaxis, subsequent tumors are usually of the same stage and grade, but the chance of a tumor recurring and then invading muscle ranges from 4% to approximately 30%, a figure surpassed by Stage T1 and Grade 3 neoplasms.[7,12,13,28,29] In the current study, the rate of tumor progression into a higher stage did not differ between patients receiving BCG and patients receiving epirubicin nor between patients receiving epirubicin and control subjects. However, tumor stage increase (including local urothelial spread) occurred at a lower rate in patients receiving BCG compared with control subjects, thus suggesting strongly the efficacy of our BCG regimen in retarding this event. In contrast, pair-wise comparisons of the muscle invasion rates among the three groups did not reveal any significant difference, thus the survival benefit in patients who received the agents is uncertain. Only a few reports on superficial bladder cancer and its management with antineoplastic agents (namely, with BCG) have indicated a statistically significant improvement in occurrence of the disease progressing to a higher stage[10,18] in the need for cystectomy,[10] or in increasing the interval to cystectomy and survival.[10]

Various intravesical treatment protocols with several antineoplastic drugs have been used empirically, but it is unknown which regimen is optimal. There is agreement that an initial or induction phase is necessary for effective therapy. Most patients achieve an antitumor response with 4–8 weekly instillations, yet this single course is suboptimal for others. More favorable results have been obtained with prolonged, intensive regimens.[2] Unfortunately, intensive therapy has been associated with greater toxicity and delay in instituting alternative therapy in patients who do not respond. The purpose of maintenance therapy at variable intervals (monthly or quarterly) is based on benefit that may occur after beneficial effects of the primary treatment have waned. However, the benefit of intermittent maintenance therapy or even long-term administration of intravesical therapy over short schedules has been questioned.[5,8] Conversely, increasing evidence suggests that a second separate weekly course of intravesical therapy with the same drug at the time of tumor recurrence enhances the overall long-term tumor-free response rate of patients failing the initial course of treatment.[3,4,6,11,12,14,15,17–19,24,30] For BCG in particular, timing of additional weekly courses seems to be important. Treatment results from two separated 6-week courses of BCG, if needed, are higher than those achieved by 12 continuous weekly treatments with which, apart from the increasing toxicity, an associated depression in immunologic responsiveness has been noted.[6,19,31] The protocol used in the current study, therefore, which consisted of an additional 4-week course of instillations to the initial responders who are at high risk for recurrence, seems reasonable, considering also that patients with a durable response to the initial therapy are likely to benefit from additional intravesical courses.[6,14]

In the current study, the response rates obtained compared favorably with the initial average responses demonstrated in previous clinical trials, in which a single 4- or 6-week or more course of epirubicin and BCG (with or without maintenance therapy) was used, with rates ranging from 27–77% for epirubicin,[12,32,33] and 34–80% for BCG.[2–4,6,9,11,15,17] However, the observed differences in response rates among these studies, including our own, may also be accounted for by the different response definitions, entrance criteria, length of follow-up, treatment protocols, and dose levels (or strains for BCG) used in patients at different levels of risk for tumor recurrence and progression.

The toxicity of the intravesical treatment in our study was acceptable, with a higher rate of side effects in the BCG group. The rate of complications seen with our BCG regimen compares favorably with that reported previously.[1,11,34] Similarly, the epirubicin-induced toxicity rate was lower compared with that observed with doxorubicin,[22,30,33] whereas all of our patients were able to complete the planned courses of intravesical treatment.

In conclusion, the current study suggests that BCG and epirubicin, administered intravesically according to our treatment protocol, are superior to TUR alone in the prophylaxis of superficial bladder cancer, and of the available chemotherapeutic agents, epirubicin may be one of optimal efficacy with lesser toxicity as compared

with other chemotherapeutic intravesical agents, particularly doxorubicin. Thus, epirubicin could be regarded as one of the treatments of choice after BCG failure, but it would not be considered as a substitute for BCG, especially in patients with superficially invasive and high-grade bladder cancer.

References

1. Brorman SA. BCG in the management of superficial bladder cancer. *Urology* 1984; 23(Suppl 4): 82–7.
2. Morales A. Long-term results and complications of intracavitary BCG therapy for bladder cancer. *J Urol* 1984; 132:457–9.
3. Lamm DL. Bacillus Calmette-Guérin immunotherapy for bladder cancer. *J Urol* 1985; 134:40–7.
4. Haaff EO, Dresner SM, Ratliff TL, Catalona WJ. Two courses of intravesical bacillus Calmette-Guérin for transitional cell carcinoma of the bladder. *J Urol* 1986; 136:820–4.
5. Badalament RA, Herr HW, Wong GY, Gnecco C, Pinsky CM, Whitmore WF Jr., et al. A prospective randomized trial of maintenance versus nonmaintenance intravesical bacillus Calmette-Guérin therapy of superficial bladder cancer. *J Clin Oncol* 1987; 5:441–9.
6. Catalona WJ, Hudson MA, Gillen DP, Andriole GL, Ratliff TL. Risks and benefits of repeated courses of intravesical bacillus Calmette-Guérin therapy for superficial bladder cancer. *J Urol* 1987; 137:220–4.
7. Herr HW, Laudone VP, Whitmore WF Jr. An overview of intravesical therapy for superficial bladder tumors. *J Urol* 1987; 138:1361–8.
8. Hudson MA, Ratliff TL, Gillen DP, Haaff EO, Dresner SM, Catalona WJ. Single course versus maintenance bacillus Calmette-Guérin therapy for superficial bladder tumors: a prospective randomized trial. *J Urol* 1987; 138:295–8.
9. Soloway MS, Perry A. Bacillus Calmette-Guérin for the treatment of superficial transitional cell carcinoma of the bladder in patients who have failed thiotepa and/or mitomycin-C. *J Urol* 1987; 137:871–3.
10. Herr HW, Laudone VP, Badalament RA, Oettgen HF, Sogani PL, Freeman BD, et al. Bacillus Calmette-Guérin therapy alters the progression of superficial bladder cancer. *J Clin Oncol* 1988; 6:1450–5.
11. Kavoussi LR, Torrence RJ, Gillen DP, Hudson MA, Haaff EO, Dresner SM, et al. Results of 6 weekly intravesical bacillus Calmette-Guérin instillations on the treatment of superficial bladder tumors. *J Urol* 1988; 139:935–40.
12. Soloway MS. Introduction and overview of intravesical therapy for superficial bladder cancer. *Urology* 1988; 31(Suppl 3):5–16.
13. Herr HW, Badalament RA, Amato DA, Laudone VP, Fair WR, Whitmore WF Jr. Superficial bladder cancer treated with bacillus Calmette-Guérin: a multivariable analysis of factors affecting tumor progression. *J Urol* 1989; 141:22–9.
14. Bretton PR, Herr HW, Kimmel M, Whitmore WF Jr., Laudone VP, Oettgen HF, et al. The response of patients with superficial bladder cancer to a second course of intravesical bacillus Calmette-Guérin. *J Urol* 1990; 143:710–3.
15. Coplen DE, Marcus MD, Myers JA, Ratliff TL, Catalona WJ. Long-term follow-up of patients treated with 1 or 2, 6-week courses of intravesical bacillus Calmette-Guérin: analysis of possible predictions of response free of tumor. *J Urol* 1990; 144:652–7.
16. Martinez-Pineiro JA, Leon JJ, Martinez-Pineiro L Jr., Fiter L, Mosteiro JA, Navarro J, et al. Bacillus Calmette-Guérin versus doxorubicin versus thiotepa: a randomized prospective study in 202 patients with superficial bladder cancer. *J Urol* 1990; 143:502–6.
17. Melekos MD, Pantazakos A, Markou S, Athanassopoulos A, Barbalias G. Intravesical bacillus Calmette-Guérin administration in the prophylaxis of superficial bladder cancer. *Int Urol Nephrol* 1990; 22:433–40.
18. Lamm DL. Prophylaxis for recurrent transitional cell carcinoma. *Urology* 1991; 37(Suppl 5):21–3.
19. Lamm DL. Optimal treatment for carcinoma in situ. *Curr Opin Urol* 1991; 1:62–4.
20. Bonfante V, Villani F, Bonadonna G. Toxic and therapeutic activity of 4-epi-doxorubicin. *Tumori* 1982; 68:105–11.
21. Ganzina F. 4-epi-doxorubicin, a new analogue of doxorubicin: a preliminary overview of preclinical and clinical data. *Cancer Treat Rev* 1983; 10:1–22.
22. Matsumura Y, Tsushima T, Ozaki Y, Yoshimoto J, Akagi T, Obama T, et al. Intravesical chemotherapy with 4-epi-adriamycin in patients with superficial bladder tumors. *Cancer Chemother Pharmacol* 1986; 16:176–7.
23. Calais de Silva F, Gomes C, Brandao T, Santos A. 4-epi-doxorubicin versus mitomycin-C in intravesical chemoprophylaxis of superficial bladder cancer [abstract 134]. *Eur Urol* 1990; 18(Suppl 1): 70.
24. Kurth K, Vijgh WJV, ten Kate F, Bogdanowicz JF, Carpentier PJ, van Reyswoud I. Phase ½ study of intravesical epirubicin in patients with carcinoma in situ of the bladder. *J Urol* 1991; 146:1508–13.
25. Melekos MD, Dauaher H, Fokaefs E, Barbalias G. Intravesical instillations of 4-epi-doxorubicin (epirubicin) in the prophylactic treatment of superficial bladder cancer: results of a controlled prospective study. *J Urol* 1992; 147:371–5.
26. Mostofi FK, Sobin HL, Torlini H. Histological typing of urinary bladder tumors. International Histological Classification of Tumors, Monograph Series No 10. Geneva: World Health Organization, 1973.
27. Cutler SJ, Ederer F. Maximum utilization of the life table method in analysing survival. *J Chron Dis* 1958; 8:699–702.
28. Lutzeyer W, Rübben H, Dahm H. Prognostic parameters in superficial bladder cancer: An analysis of 315 cases. *J Urol* 1982; 127:250–3.
29. Heney NM, Ahmed S, Flanagan MJ, Frable W, Corder MP, Hafermann MD, et al. for the National Bladder Cancer Collaborative Group A. Superficial bladder cancer: progression and recurrence. *J Urol* 1983; 130:1083–6.
30. Mukamel E, de Kernion JB. Conservative treatment of diffuse carcinoma in situ of the bladder with repeated courses of intravesical therapy. *Br J Urol* 1989; 64:143–6.
31. Ratliff TL, Catalona WJ. Depressed proliferative responses in patients treated with 12 weeks of intravesical BCG [abstract 244]. *J Urol* 1989, part 2; 144:230 A.
32. Fossâ SD, Urnes T, Ous S. Short-term effect of prophylactic treatment of superficial bladder cancer with intravesical adriamycin. *Eur Urol* 1985; 11:382–5.
33. Khanna OP, Son DL, Son K, Mazer H, Read J, Nugent D, et al. Multicenter study of superficial bladder cancer treated with intravesical bacillus Calmette-Guérin or adriamycin: results of long-term follow-up. *Urology* 1991; 38:271–9.
34. Lamm DL, van der Meigden APM, 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; 147:596–600.