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17-YEAR FOLLOW-UP OF A RANDOMIZED PROSPECTIVE CONTROLLED TRIAL OF ADJUVANT INTRAVESICAL DOXORUBICIN IN THE TREATMENT OF SUPERFICIAL BLADDER CANCER

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ABSTRACT

Purpose: To evaluate the efficacy of adjuvant intravesical doxorubicin in superficial transitional cell carcinoma of the urinary bladder on long-term follow-up.

Materials and Methods: Between July 1986 and November 1991, all patients harboring superficial bladder cancers (Ta or T1) with one or more of these criteria (stage > a, grade > 1, size > 1 cm, multiple or recurrent tumors) were randomized to receive either 50 mg doxorubicin or no adjuvant therapy. Patients with recurrences were allowed to receive doxorubicin or other intravesical agents. Recurrence, progression and survival were analyzed.

Results: There were 82 patients included (64 males and 18 females). The mean age was 64 years. Forty-six patients were randomized to the doxorubicin group and 36 to the control group. Final analysis was made at median follow-up of 45, 128 and 131.5 months for recurrence, progression and survival, respectively. Recurrence free, progression free and disease specific survival did not differ significantly between groups. The 10-year Kaplan-Meier estimates for recurrence free, progression free and disease specific survival were 67%, 84% and 92%, respectively for the doxorubicin group, and were 50%, 89% and 97%, respectively for the control group. Tumor size predicted recurrence ($p = 0.013$) and grade predicted progression ($p = 0.004$) with multivariate analysis.

Conclusions: Adjuvant intravesical doxorubicin could not be shown to improve recurrence, progression and survival of superficial bladder cancer, compared with control on long-term follow-up. Tumor size and grade were shown to be prognostic factors for recurrence and progression, respectively.

Key words:bladder neoplasms; transitional cell; intravesical instillations; doxorubicin
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INTRODUCTION

The usefulness of intravesical doxorubicin in decreasing the likelihood of recurrence in superficial bladder cancer had been shown in several studies (1-3). Occasional studies also reported improved progression rate (4,5). The current report explores its efficacy in the long run and identifies those prognostic factors that influence recurrence and progression on long-term follow-up. The role of intravesical doxorubicin in the treatment of superficial bladder cancer is discussed.

MATERIALS AND METHODS

Between July 1986 and November 1991, all patients in the Prince of Wales Hospital harboring superficial (Ta or T1) bladder transitional cell

carcinoma (TCC) with one or more of the following criteria were entered into the trial: stage > a, grade > 1, size > 1 cm, multiple or recurrent tumors. In cases of mixed stages or grades, the highest stage or grade was documented. Those with carcinoma in situ or previous intravesical treatment were excluded. All patients gave informed consent.

After complete resection of all visible tumors, patients were randomly assigned to receive either intravesical adjuvant doxorubicin or no adjuvant therapy. For the doxorubicin group, the first instillation was administered 2 weeks after the transurethral resection (TURBT). Fifty mg doxorubicin diluted with 50 mL saline was administered intravesically and retained for 2 hours. The treatment was given weekly for 4 weeks, monthly for 5 months and then 3-monthly for 6 months.

Patients were evaluated with cystoscopy every 3 months for 2 years and then urine cytology every 6 months. Cystoscopy, biopsy and TURBT were carried out if necessary. Patients with recurrences in either treatment group, again after complete TURBT, were allowed to receive doxorubicin or other forms of intravesical therapy, such as epirubicin or bacillus Calmette-Guerin (BCG), even repeatedly, until muscle invasiveness occurred.

At the time of final evaluation, follow-up information was obtained from case notes, patient or family telephone contact or electronic medical records. Moreover, patients were called back for cystoscopy at the time of final evaluation, if none had been done in the past 1 year.

The time to first recurrence, the time to progression and the survival were analyzed. Recurrence was defined as histologically proven recurrence. Definitions of progression differ among studies in the literature. Some studies (2,3,5) classified progression as an increase in the grade and/or the stage. On the other hand, only T2 disease or worse were categorized as progression in other studies (1,4). In our study, progression was considered as stage T2 disease or above, positive lymph node or distant metastasis. Disease specific death was defined as death due to TCC. Recurrence-free interval, progression-free interval and patient survival were defined as the time from TURBT to the end point (recurrence, progression, death or censored). In the analysis of disease-specific survival, patients who died of any urothelial cancer (including those in the upper urinary tract) were classified as deaths. Toxicity was not recorded in this study.

Patient characteristics were compared to the chi-square test and the Student's t test between the 2 treatment groups. The Kaplan-Meier method was used to calculate the survival curves. The log-rank test and the Cox proportional hazards model were used for univariate and multivariate analyses respectively, to assess the influence of several variables (initial adjuvant treatment, patient and tumor characteristics) on the survival curves.

RESULTS

Eighty-two consecutive patients were randomized during the 64 months retrieval period. Sixty-four of them were males and 18 were females. Forty-six belonged to the doxorubicin group and 36 were in the control group. The study ended prematurely with the commencement of a new protocol in the hospital utilizing BCG and epirubicin for superficial bladder cancer. The number of patients recruited was hence less than planned in the protocol. This might account for the asymmetrical distribution of the 2 groups in the study. The mean age was 64 years (range 35 to 87). See Table-1 for distributions of patient and tumor characteristics including sex, age, stage, grade, size and multiplicity. There were no significant differences in these characteristics between the two treatment groups, except that there were more solitary tumors in the control group ($p = 0.01$).

Final analysis of treatment results was made at a median follow-up of 45 months (range 0 to 190) pertime of first recurrence, 128 months (range 0 to 193) per time to progression and 131.5 months (range 1 to 193) per duration of survival. One patient lost to follow-up one month after entry into the trial without any cystoscopy surveillance performed. Out of the 31 patients being called back for cystoscopy at the time of final evaluation, three were found to have harboring asymptomatic tumors. One of them belonged to the doxorubicin group (which was a new occurrence occurring 130 months after the initial

Table 1 – *Distributions of patient and tumor characteristics.*

	Doxorubicin Group	Control Group	Significance Level
Patient Characteristics			
Sex	M = 33, F = 13	M = 31, F = 5	0.12
Age (years)	65.5 (SEM 1.7)	62.1 (SEM 2.3)	0.22
Tumor Characteristics			
Stage	Ta = 31 T1 = 10	Ta = 23 T1 = 5	0.52
Grade	G1 = 16 G2 = 15 G3 = 11	G1 = 15 G2 = 7 G3 = 6	0.43
Size (cm)	0.1 to 1 = 10 1.1 to 3 = 20 3.1 to 10 = 11	0.1 to 1 = 9 1.1 to 3 = 10 3.1 to 10 = 8	0.60
Multiplicity	Single = 23 Multiple = 20	Single = 26 Multiple = 3	0.01

SEM, standard error of mean.

TURBT) and the other 2 were in the control group (one was a new occurrence occurring 150 months after the initial TURBT and the other had history of previous recurrence). All of these three incidental recurrences were small tumors approximately 1 cm.

Recurrence

Figure-1 shows the recurrence free survival curves of the doxorubicin group and the control group (log rank test, p = 0.12).

Of the 46 patients in the doxorubicin group, 17 (37%) had one or more recurrences. The median recurrence free survival was 190 months. The 10-year Kaplan-Meier estimate for recurrence free survival was 67%. The median time to the first recurrence was 13 months (range 1 to 190). Recurrences were not treated by any additional intravesical therapy in eight patients and were treated by one additional course in 6 patients and by 2 additional courses in 3 patients.

Of the 36 patients in the control group, 19 (53%) had one or more recurrences. The median recurrence free survival was 89 months. The 10-year Kaplan-Meier estimate for recurrence free survival was 50%. The median time to the first recurrence was 8 months (range 1 to 175). Recurrences were not treated by any additional intravesical therapy in 4 patients, and were treated by one additional course in 7 patients, 2 additional courses in 4, 3 additional courses in one and 4 additional courses in one patient. Data concerning treatment for recurrence was missing in 2 patients.

Progression

Figure-2 shows the progression free survival curves of the 2 groups (log rank test, p = 0.44). As a matter of fact, we are comparing early adjuvant doxorubicin with delayed intravesical therapy, as patients with recurrences were allowed to receive doxorubicin or other intravesical agents.

In the doxorubicin group, progression was first detected as muscle invasion in 2 patients and as metastasis in 4 (regional lymph node, liver, bone and malignant pleural effusion, respectively). The 10-year Kaplan-Meier estimate for progression free survival

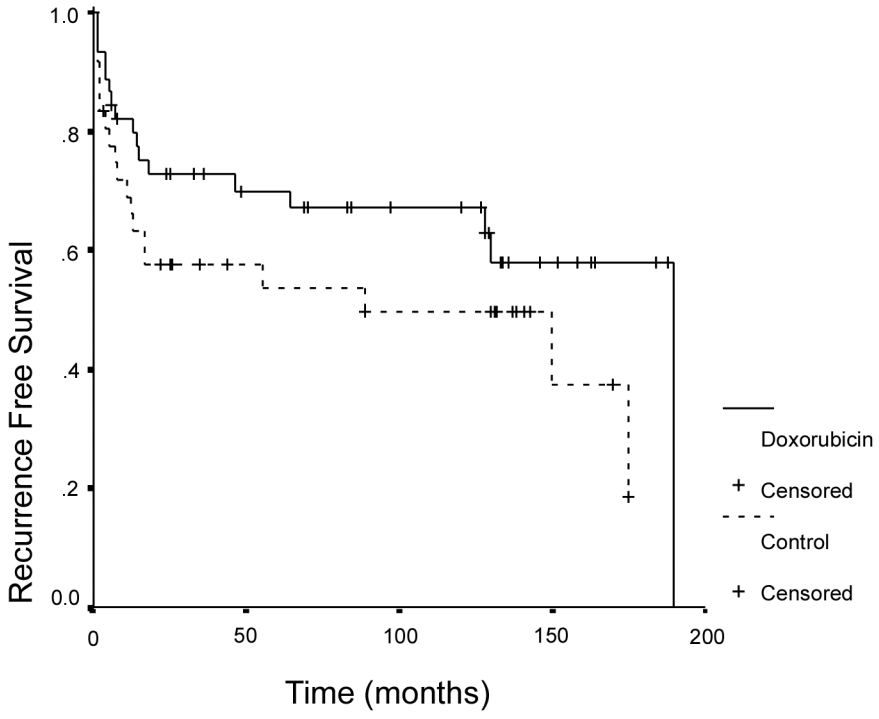

Figure 1 – *Recurrence free survival curves of doxorubicin group (solid line) and control group (dotted line). Log rank test, p = 0.12.*

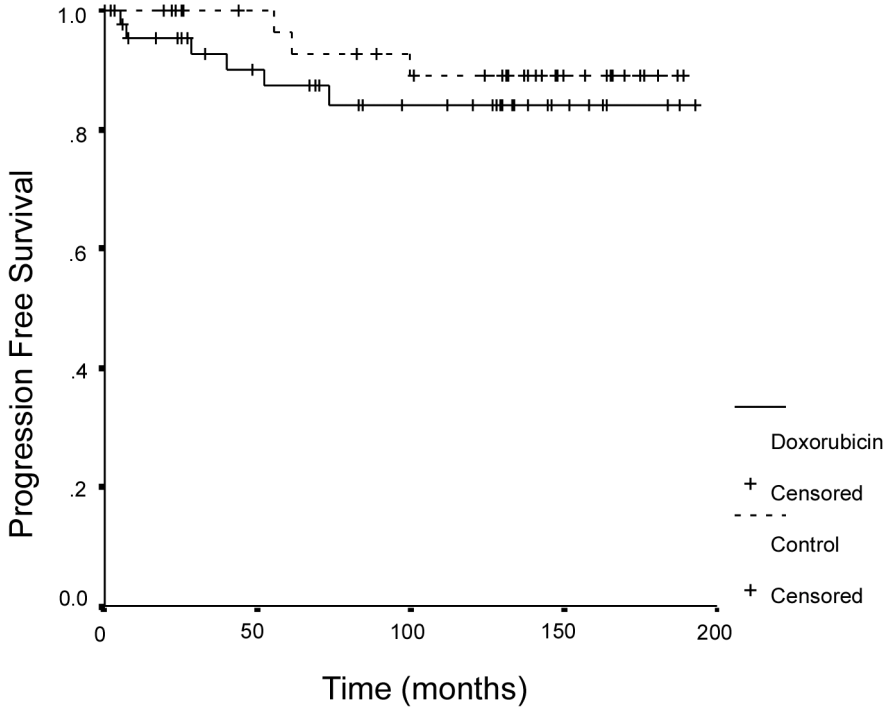

Figure 2 – *Progression free survival curves of doxorubicin group (solid line) and control group (dotted line). Log rank test, p = 0.44.*

was 84%. The median time to progression was 34 months. Of the 2 patients who progressed into muscle invasive disease, one underwent radiotherapy and one died of an unrelated condition.

In the control group, progression was first detected as muscle invasion in 2 patients and as metastasis in one (liver). The 10-year Kaplan-Meier estimate for progression free survival was 89%. The median time to progression was 61 months. Of the 2 patients who progressed into muscle invasive disease, one underwent radiotherapy and one had cystectomy.

Survival

Figures-3 and 4 show the disease specific survival curves (log rank test, p = 0.40) and overall survival curves (log rank test, p = 0.13), respectively, of the 2 groups. Essentially, we were again comparing early adjuvant doxorubicin with delayed intravesical therapy, as patients with recurrences were allowed to receive doxorubicin or other intravesical agents.

For the 46 patients in the doxorubicin group, 3 patients died of TCC and 14 died of unrelated conditions. The 10-year Kaplan-Meier estimate for disease specific survival and overall survival were 95% and 68% respectively. Those died of TCC did so at a median time of 73 months.

For the 36 patients in the control group, one patient died of TCC and 6 died of unrelated conditions. The 10-year Kaplan-Meier estimate for disease specific survival and overall survival were 97% and 83% respectively. The one who died of TCC did so at 55 months.

Other Prognostic Factors

The Cox proportional hazards model was used for multivariate analysis to assess the influence of patient and tumor characteristics (sex, age, stage, grade, size and multiplicity) on the survival curves (recurrence free, progression free and disease specific). The risk of recurrence was significantly increased with larger tumor size (p = 0.013) and the

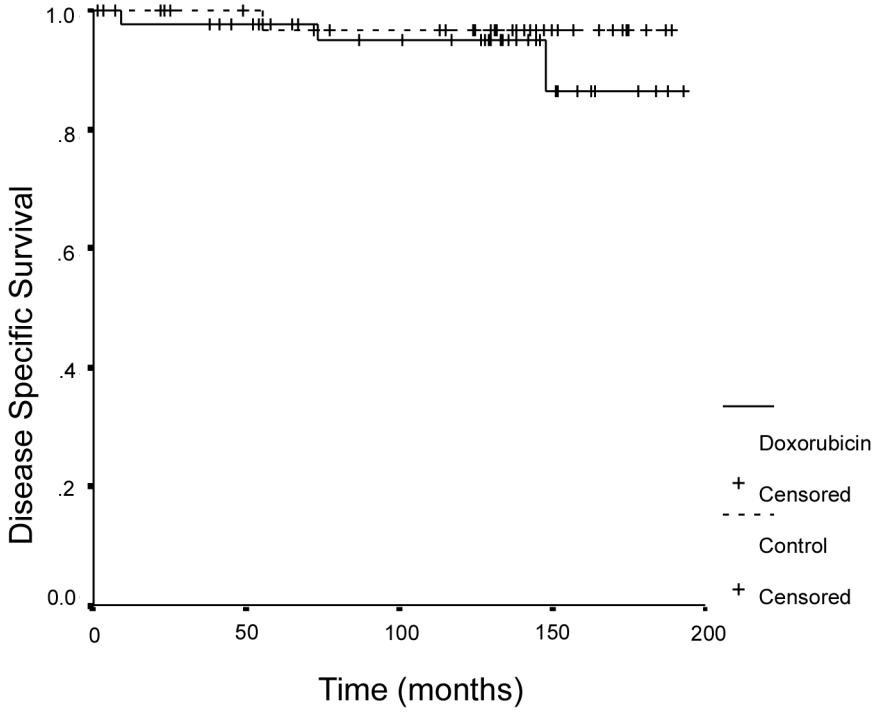

Figure 3 – *Disease specific survival curves of doxorubicin group (solid line) and control group (dotted line). Log rank test, p = 0.40.*

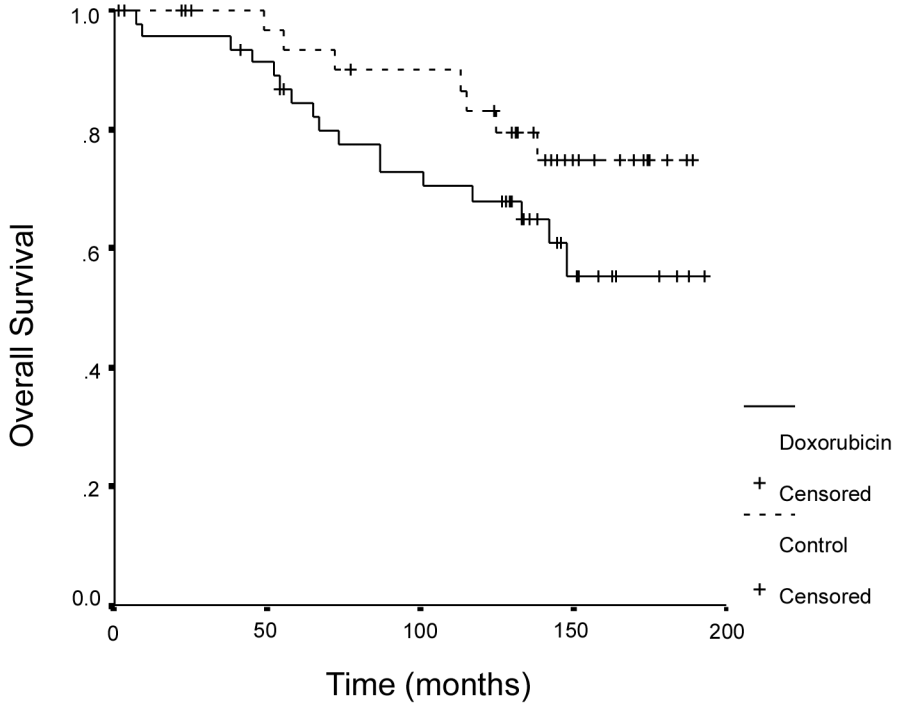

Figure 4 *– Overall survival curves of doxorubicin group (solid line) and control group (dotted line). Log rank test, p = 0.13.*

risk of progression was significantly raised with higher grade (p = 0.004). Tumor stage and number were not shown to affect prognosis in this study.

COMMENTS

The long follow-up of our study allows us to observe the treated natural history of superficial bladder TCC. Regarding recurrence, our follow-up actually covers the whole period until all or nearly all patients had either recurred or been censored (as the Kaplan-Meier estimate approaches zero). As shown in Figure-1, most of the recurrences occurred within 1 year, and almost all had recurred or been censored by 15 years.

For the treated natural history regarding progression and survival, essentially we are observing the long-term effects of repeated courses of intravesical therapy, as patients with recurrences in either treatment group were allowed to receive doxorubicin or other intravesical agents. As can be seen in Figures-2 and 3, progression and cancer death were uncommon occurrences even on long-term follow-up and this had made a meaningful comparison between the treatment groups difficult. However, looking at these 2 groups as a whole, there are 2 observations. Firstly, repeated courses of intravesical therapy on repeated recurrences may not be detrimental to the progression free survival as our treatment policy results in a reasonable 10-year Kaplan-Meier estimate of 84-89%. Secondly, our patients died of other causes far more common than TCC, with a 10-year Kaplan-Meier estimate for overall survival of 68-83%, compared to a 10-year Kaplan-Meier estimate for disease specific survival of 95-97%. This high overall to cancer death ratio may imply that even a statistically significant difference in disease specific survival (not in our study) may not translate into a clinically significant difference when the overall survival is put into consideration. Our figures are comparable with those reported in the literature. Kurth et al. (1) reported a

randomized controlled trial involving 443 patients with superficial bladder cancer. With adjuvant doxorubicin, they reported a progression free survival at a median follow-up of 5 years of 86%, while the overall and disease specific survivals at a median follow-up of 10 years were 46% and 82% respectively.

Several studies had showed that doxorubicin was useful in preventing recurrence but did not affect progression or survival (1-3), though occasional studies concluded that it even improved progression (4,5). Our studies cannot even identify a significant difference between the recurrence free survival curves of the treatment and control groups. Of course, this may result because the effect of doxorubicin in delaying the time to recurrence actually disappears in the long run. However, this may also be due to our small sample size. Moreover, the fact that our intravesical therapy started two weeks after the TURBT may jeopardize its efficacy. Early instillation of doxorubicin had been shown to lower recurrence rate (6). Lastly, the higher frequency of solitary tumors in the control group may actually favor the control group as far as recurrence is concerned. Regarding progression, as mentioned above, the number of our patients with progression is too small to make a meaningful comparison between the treatment groups.

On the other hand, prospective randomized trials had showed the superiority of BCG compared with doxorubicin for reduction of recurrence and delay in progression (7-9). Together with our finding that doxorubicin did not improve recurrence, progression and survival on long-term follow-up, this seems to make doxorubicin obsolete in the adjuvant therapy of superficial bladder cancer. However, the recurrence free survival curve of our doxorubicin group is always above the corresponding curve of the control group, only that the difference does not reach statistical significance. As mentioned above, the lack of statistical significance can be the result of our small sample size. The median time to recurrence is actually extended from eight months to 13 months with doxorubicin compared to control. The 10-year Kaplan-Meier estimate for recurrence free survival is also improved from 50% to 67% with doxorubicin. Moreover, in the real clinical situation, for many patients with superficial recurrences after intravesical BCG, cystectomy may not be the best option and an intravesical chemotherapeutic agent is then a solution, provided that there is a stringent surveillance protocol.

In our study, the risk of recurrence is significantly increased with larger tumor size and the risk of progression is significantly raised with higher grade. Tumor prognostic factors had been mentioned by other studies on adjuvant doxorubicin. Shinohara (3) suggested that solitary tumor scored better with respect to recurrence. Gustafson et al. (10,11) showed that recurrence was linked to grade, multiplicity and ploidy while progression was also linked to ploidy. Isaka (12) showed that in terms of recurrence, doxorubicin was more effective with multiple, big, higher stage and higher grade tumors. In our study, tumor stage and number were not shown to affect prognosis.

CONCLUSIONS

According to our data, adjuvant intravesical doxorubicin did not improve recurrence, progression and survival of superficial bladder cancer, compared with control on long-term follow-up, although it still has a role in recurrent superficial tumors, in case cystectomy is not the treatment of choice. Tumor size and grade were shown to be prognostic factors for recurrence and progression, respectively.

The Lithotripsy and Urodynamics Center of the Prince of Wales Hospital assisted in patient contact and arrangement of cystoscopy surveillance.

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EDITORIAL COMMENT

The authors performed a small randomized trial, which compared delayed but relatively long term intravesical doxorubicin to no intravesical therapy following a TUR of a Ta or T1 urothelial tumor of the bladder. The authors interpret this as a negative study as indicated by their statement "this seems to make doxorubicin obsolete in the adjuvant therapy of superficial bladder cancer". I do not share their conclusion. Their result was predictable. The patients who were randomized to doxorubicin received their first dose two weeks following the TUR and then followed the indicated schedule. Although the difference between the two groups did not reach statistical significance, there was a lower "recurrence" rate for those who received chemotherapy (Figure-1). Kaasinen et al. (1) have shown us that where adjuvant intravesical therapy is not initiated within hours of the resection, the efficacy declines. The procedure of endoscopic resection establishes a scenario in which residual tumor cells may implant on the urothelial surface as indicated by animal (2,3) and clinical studies (4) or growth factors may be upregulated thus enhancing the growth of preneoplastic urothelium. In either case, "immediate" intravesical mitomycin C or epirubicin (even a simple dose) decreases the chance that a patient will have a subsequent tumor. As indicated in this study, the benefit is manifested by a reduction in early "recurrences". If subsequent tumors are not due to implantation (most are probably not) then given sufficient time the patient will develop another tumor.

The current guidelines state that adjuvant chemotherapy is indicated following resection of a Ta or T1 urothelial cancer unless there is a contraindication such as bladder perforation (5).

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REPLY BY THE AUTHORS

The manuscript mentioned that although the results seem to make doxorubicin obsolete in the adjuvant therapy of superficial bladder cancer, actually it is not the case. Doxorubicin extended the median time of recurrence and may be useful for superficial recurrences after intravesical BCG.

There is no dispute in that evidence showed the effectiveness of immediate mitomycin C and epirubicin. However, cases of extravasation after immediate mitomycin C (1,2) and epirubicin (3) had also been reported. Actually, it was suggested that immediate instillation should be avoided when there was even suspected bladder wall perforation. This risk can be eliminated by our delayed regimen.

While reducing the chance the complications, our regimen did not compromise efficacy. Sylvester et al. (4) in their meta-analysis showed a recurrence free rate of 63.3% at a median follow-up of 3.4 years, after single immediate instillation of epirubicin, mitomycin C, thiotepa or pirarubicin. This compares to our 10-year Kaplan-Meier estimates for recurrence free survival of 67% at a median follow-up of 45 months, after delayed but continuous instillation of doxorubin.

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Respectfully,

The Authors