

## Prophylaxis of superficial bladder cancer with instillation of adriamycin or mitomycin C

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**Summary.** A multicenter trial for postoperative prophylaxis of superficial Ta-T<sub>1</sub>, G<sub>1</sub>-G<sub>2</sub> bladder cancer was performed. Intravesical instillation using either 20–30 mg adriamycin or 20 mg mitomycin C per dose was carried out for 4 weeks or 2 years. Patients without instillation served as controls. A total of 259 patients was considered eligible for the evaluation. The instillation group showed a better disease free survival rate than the control group. Better prophylactic effects of instillation therapy were observed when one of following factors was present: multiple tumors, large tumors, T<sub>1</sub> and G<sub>2</sub> bladder cancer. The total dose of drug instilled seemed to correlate with the effects, but there were no differences between adriamycin and mitomycin C. The side effects were minimal and temporary.

### Introduction

The high incidence of local recurrence after initial management of a superficial bladder cancer (Ta-T<sub>1</sub>, G<sub>1</sub>-G<sub>2</sub>) is one of the important therapeutic problems. Prophylactic instillation with some anticancer drugs after surgery has been used to reduce local recurrence; however, there is still controversy concerning the effects of such treatment [13]. Moreover, the relationship between method and response is still not clearly established.

To evaluate intravesical instillation with anticancer drugs for the prophylaxis of recurrence in Ta-T<sub>1</sub> bladder cancer, the present study was undertaken for comparison with various modalities of instillations using adriamycin (ADM) and mitomycin C (MMC).

### Patients and methods

**Patients.** For the trial, 259 patients with primary, untreated, superficial (Ta-T<sub>1</sub>), low-grade (G<sub>1</sub>-G<sub>2</sub>) transitional cell carcinoma of the urinary bladder were used who had been treated between January 1980 and December 1985. All of the tumors were examined histologically to confirm stage and grade according to the UICC TNM classification. After surgery the patients were considered to be free of tumors.

**Intravesical instillation of ADM and MMC.** One of following solutions was used: 20 mg ADM/40 ml or 30 mg ADM/30 ml physiological saline, or 20 mg MMC/40 ml distilled water. Patients retained the drugs for at least 2 h. Intravesical instillation was started 1–2 weeks after surgery. Two courses concerning the duration of the instillation period were established. The short-term course consisted of treatment twice a week for 4 weeks, which was then halted. The long-term course consisted of 2 year schedule, beginning with instillation twice a week for 1 month, followed by instillation once a month for 1 year and 11 months. Some cases in the long-term group were changed to different treatment because of recurrence, etc., but all cases completed a minimum of 3 months on the above regimen. In both courses, randomly selected cases without instillation were chosen as control. Cystoscopy and urinary cytology were performed every 3 months during the observation period. When recurrence appeared, the patients were excluded from the trial.

**Evaluation of instillation therapy.** The disease-free survival rate calculated by the Kaplan-Meire method was used for evaluation of effect. Except when indicated separately, the effectiveness of instillation was examined by evaluating the overall effects in both the short- and long-term instillation groups. Statistical analyses were obtained according to the generalized Wilcoxon test.

### Results

#### Patients' characteristics

One hundred sixty-one patients were treated with prophylactic intravesical instillation with ADM or MMC, and 98 patients served as controls (Table 1). Comparison of patient characteristics in the instillation and control groups showed no significant differences in sex, age, tumor number, size, grade, stage, or operation methods. Mean follow-up periods were different between the two groups, as more frequent recurrences occurred in the control group.

#### Disease-free survival rate

The disease-free survival rate of the instillation group was compared with that of the control group (Fig. 1). These two curves revealed significant differences; therefore, intravesical instillation was showed to be effective in the prevention of recurrence of bladder cancer.

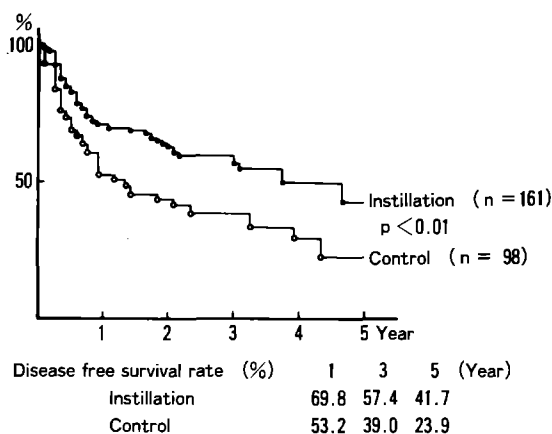


Fig. 1. Disease-free survival curve

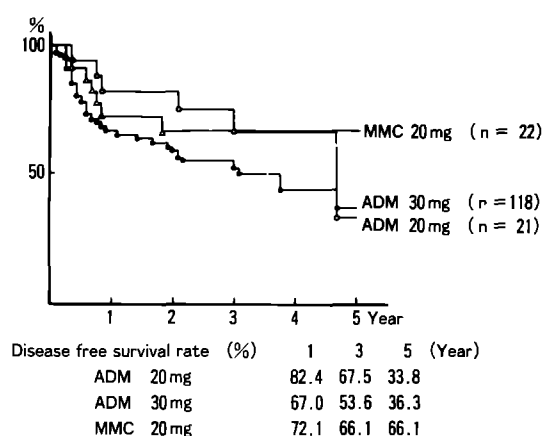


Fig. 2. Influences of drugs on disease-free survival curve

Table 1. Patient characteristics

	Instillation	Control
Total number	161	98
Sex: male/female (%)	89/11	86/14
Age (M ± SD, years)	63 ± 12	65 ± 15
Tumor number:		
Single/multiple (%)	54/46	62/38
Tumor size:		
< 3 cm/> 3 cm/unknown (%)	81/15/4	83/14/3
Stage: Ta/T <sub>1</sub> /unknown (%)	58/38/4	58/33/9
Grade: G <sub>1</sub> /G <sub>2</sub> /unknown (%)	58/40/2	57/40/3
Operation methods:		
TUR/partial cystectomy/ Tumor resection/others (%)	95/4/1/0	88/6/4/2
Mean follow-up (months)	23	15

Table 2. Influence of tumor properties on effects of instillation

	Instillation (%)	Control (%)
Tumor number: Single	81	68
Multiple**	57	30
Tumor size:		
< 1 cm	77	69
1-3 cm	67	49
> 3 cm*	71	43
Stage:		
Ta	72	61
T <sub>1</sub> **	65	41
Grade:		
G <sub>1</sub>	74	64
G <sub>2</sub> **	64	37

Data are expressed as disease-free survival rate (%) 1 year after surgery

Statistical differences between instillation and control groups:

\* $P < 0.05$ ; \*\* $P < 0.01$

#### Influences of tumor properties of effects of instillation

The disease-free survival rate 1 year postoperatively was compared with regard to multiplicity, size, stage, and grade between the instillation and control groups (Table 2). In terms of recurrence prevention, intravesical

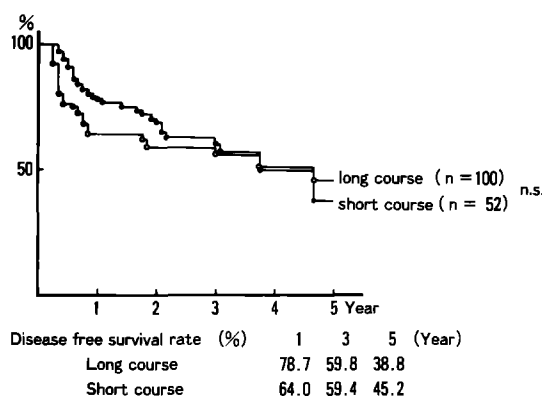


Fig. 3. Influences of instillation duration on disease-free survival curve. Cases of recurrence within 3 months after surgery are excluded

instillation was seen to be more effective in multiple tumors than solitary tumors, in tumors greater than 3 cm in size than those less than 3 cm, in T<sub>1</sub> rather than Ta, and in G<sub>2</sub> rather than G<sub>1</sub>. Therefore, tumors showing one of above properties showed more prophylactic effectiveness as a result of instillation with ADM and MMC.

#### Drugs and duration of instillation

Although three kinds of instillation methods were used, no differences in disease-free survival rate were revealed. The effects were similar irrespective of the drugs (Fig. 2).

When the disease-free survival rate of the short-term instillation group was compared with that of the long-term group, a tendency towards better effect was observed with long-term instillation for up to 2 years postoperatively, but there were no statistical differences between the two courses (Fig. 3). When effectiveness was evaluated in terms of the total overall dosage administered (small, intermediate, large), the prophylactic effect was seen to increase with dosage, but there was no statistically significant difference (Fig. 4).

#### Side effects

Bladder irritability was a prominent side effect. Systemic side effects such as skin eruption, palpitation, nausea, and

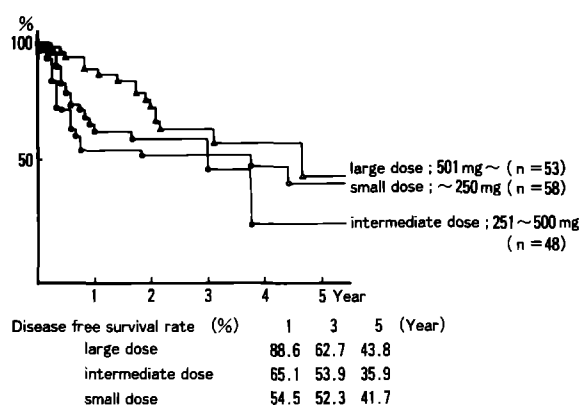


Fig. 4. Effects of total instillation dosages of either adriamycin or mitomycin C

Table 3. Side effects

	Adriamycin	Mitomycin C
Total number	139	22
Bladder irritability	19 (14) <sup>a</sup>	3 (14)
Skin eruption	3 (2)	0
Palpitation	2 (1)	0
Nausea	1 (1)	0
Sensory disturbance	1 (1)	0
Number of cases with side effects	23 (17)	3 (14)

<sup>a</sup> Number in parentheses is percent of total cases

sensory disturbance were noticed in a few cases of ADM group. All side effects, however, were temporary and tolerable (Table 3).

## Discussion

A high recurrence rate of superficial bladder tumors (40%–70%) has been reported within 6–12 months [15], and this has prompted many prophylactic forms of treatment after surgery. Among them, adjuvant local chemotherapy is one of the strategies commonly used. Since many factors such as the continuous exposure of the bladder epithelium to carcinogens, multicentric growth of bladder cancer, implantation of cancer cells during surgery and inadequate resection of tumors may be related to recurrence, intravesical instillation of anticancer drugs for prevention appears to be a reasonable method.

There have been many reports of prophylactic instillation using thio-TEPA [8, 16], ADM [1, 4, 14], MMC [3], and Epodyl [12]. However, there has been little discussion about the relationship between the effect of instillation and tumor type. It has been reported by Zincke et al. [17] that instillation prophylaxis is more effective on low-grade, papillary, multiple, and recurrent tumors than in tumors with opposite features. The present study confirmed good prophylaxis in cases of multiple tumors, but a better effect was obtained in T<sub>1</sub> and G<sub>2</sub> tumors compared to T<sub>a</sub> and G<sub>1</sub>. Concerning recurrent tumors, contradictory observations have been made: some consider that a greater effect is obtained in newly diagnosed cases [2]; others feel just the opposite [4].

After prophylactic instillation, the disease-free survival rate has been reported by the Japanese Urological Cancer Research Group for ADM to be approximately 55% at 18

months postoperatively, in contrast to 38% in controls, with ADM showing a better effect than MMC [11]. A tendency towards increased prevention of recurrence in relation to overall dosage and period of administration has been suggested. Instillation of ADM and MMC has been used to treat superficial bladder cancer [9, 10], and prolonged instillation may treat any tiny recurrent tumors developing during the observation period, which would yield better results in long-term instillation. The ideal duration of instillation for prophylaxis is an important problem [7].

There are other methods for prophylaxis of recurrence in bladder cancer. Pyridoxine [2] and  $\beta$ -glucuronidase inhibitor [6] administered orally prevented recurrence to a slight degree. Other orally administered anticancer drugs have been reported to reduce recurrence [5], but the effectiveness of such treatment is now under discussion. Instillation prophylaxis appears to be an easy and reliable method for the reduction of recurrence in bladder cancer.

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