

Prophylactic intravesical instillation therapy with adriamycin and mitomycin C in patients with superficial bladder cancer

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Summary. Intravesical instillation of adriamycin (ADM) or mitomycin C (MMC) was carried out for the purpose of preventing the recurrence of superficial bladder cancers (Ta and T1) after transurethral resection or transurethral coagulation. First, eligible patients were divided into two groups (solitary and multiple) and then they were randomized into the following three groups: (1) ADM group, intravesical instillation with 50 mg ADM dissolved in 100 ml physiological saline; (2) MMC group, intravesical instillation with 30 mg MMC dissolved in 100 ml physiological saline; (3) control, transurethral resection or transurethral coagulation alone. The drugs were given six times by instillation within 2 weeks after TUR or TUC; after 2 weeks the drugs were administered for 2 consecutive days every 4 weeks for 2 years. Of the 134 patients admitted to the study, 103 were evaluable and 31 were eliminated as non-evaluable patients. The cumulative nonrecurrence rates were 73.6% for ADM, 63.4% for MMC, and 22.5% for controls after a follow-up of 24 months. The cumulative non recurrence rates of the ADM and MMC groups were significantly higher than that of the control group. The incidence of side effects was low and the grade of these side effects mild. This instillation therapy with ADM and MMC was considered useful for preventing the recurrence of superficial bladder cancers.

Table 1. Members of Okayama Urological Cancer Collaborating Group (OUCC Group)

	Director	Vice Director
Okayama University	H. Ohmori	Y. Matsumura
Kawasaki Medical School	H. Tanaka	M. Amano
Kagawa Prefectural Central Hospital	K. Ohkita	T. Asahi
Okayama Red Cross Hospital	A. Kondo	K. Kondo
Okayama Citizen's Hospital	K. Namba	T. Tanahashi
Okayama Saiseikai Hospital	K. Shiraga	
Mitoyo General Hospital	T. Matsumoto	
Hiroshima Citizen's Hospital	T. Johsen	K. Aramaki
Kurashiki Adult Disease Hospital	T. Araki	
Tamano Citizen's Hospital	Y. Katayama	
Kure Kyosai Hospital	Y. Ozaki	N. Mitsuhashi
Kochi Prefectural Central Hospital	N. Ike	
Tsuyama Central Hospital	T. Akaeda	
Kasaoka Citizen's Hospital	H. Takamoto	
Ritsurin Hospital	M. Hirano	
Marugame Rosai Hospital	M. Nishi	
Kobe West Citizen's Hospital	H. Kamada	
National Iwakuni Hospital	B. Suyama	
Onomichi Citizen's Hospital	N. Akazawa	
Tottori Citizen's Hospital	T. Tsushima	

Introduction

Various drugs and schedules have been employed for the intravesical instillation of chemotherapeutic agents for prophylaxis of the recurrence of superficial bladder cancers, but no definite method has yet been universally accepted [2, 7, 10, 12].

Since December 1981, a randomized prospective study concerning the effects of prophylactic instillation therapy using adriamycin (ADM) and mitomycin C (MMC) has been carried out at the Department of Urology, Okayama University Medical School and Okayama Urological Cancer Collaborating Group (OUCCG) (Table 1). This protocol was characterized by a large amount (100 ml) of solution with relatively low concentration of the drug and

long-term instillation for 2 years. At present both ADM and MMC groups appear to provide better results for prevention of recurrence than the control group.

Materials and methods

Cases included in this study consisted of Ta and T1 superficial bladder tumors, but grade 3 cases or cases receiving preoperative intravesical chemotherapy were excluded. All cases were registered in the present study after visible lesions had been cleared from the bladder by transurethral resection (TUR) or transurethral coagulation (TUC). Eligible patients were divided into two groups (solitary and multiple) and then were randomized into three groups: ADM, MMC, and controls (Fig. 1). The ADM group received 50 mg ADM dissolved in 100 ml physiological saline, while the MMC group received 30 mg MMC dissolved in 100 ml physiological saline. Instillation was performed 6 times in the first 2 weeks after TUR and thereafter on 2 consecutive days, once every 4 weeks; this was

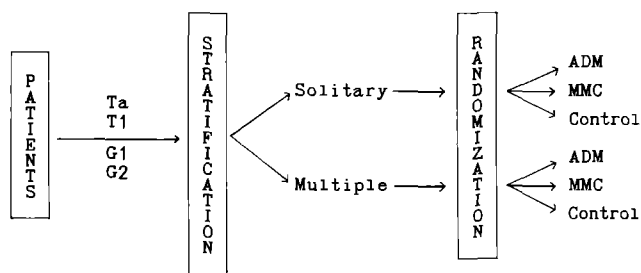
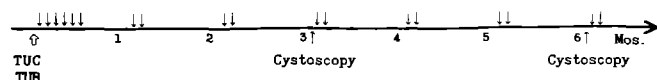


Fig. 1. Design of protocols



ADM group : ADM 50 mg / 100 ml of physiological saline
 MMC group : MMC 30 mg / 100 ml of physiological saline
 Control group : TUR or TUC only

Fig. 2. Treatment schedule

continued for 2 years. The drug was retained in the bladder for more than 1 h, but there was no specific change in the body position. On the other hand, the control group underwent surgery alone. All groups received a cystoscopic examination every 3 months to detect possible recurrence (Fig. 2). When recurrence was detected in either ADM or MMC group, TUR or TUC was performed; then the same drug was instilled for 2 consecutive days every 4 weeks for 2 years after the initial treatment. Controls were treated by TUR or TUC alone for the first two recurrence episodes, but as of the third episode they were removed from the protocol and treated by other modalities. Calculation of nonrecurrence was performed by the Kaplan-Meier method and statistical significance was evaluated by the generalized Wilcoxon test.

Results

A total of 134 cases were registered in the present study. However, only 103 cases were evaluable; the remaining 31

Table 2. Randomized patients and reasons for exclusion

No. of patients entered	134
No. of patients evaluable	103
No. of patients dropped	31
Ineligibility ^a	3
Lost to follow-up	20
Grade up at recurrence	3
Protocol violation	2
Insufficient drug retention	1
Microhematuria ^b	1
Renal dysfunction ^b	1

^a Invasive carcinoma, grade 3 etc.

^b Not related to instilled drugs

were eliminated. In the cases that were dropped, 3 were subsequently found to be unqualified candidates; in 20 cases the patients stopped coming for their regular follow-up. In 3 cases the grades went up at recurrence, and in 2 cases the conditions of the protocol were contravened (Table 2). The 103 evaluable cases consisted of 33 ADM cases, 37 MMC cases, and 33 control cases. Cases with single lesions were made up of 17 ADM cases, 20 MMC cases, and 15 control cases. Cases with multiple lesions comprised 16 ADM cases, 17 MMC cases, and 18 control cases. The number of patients were approximately the same in all three groups, and no significant difference was recognized in background factors, as evaluated by the χ^2 test, such as sex, primary or recurrent lesions, grade or shape of tumor growth (Table 3). Evaluable cases ranged in age from 28 to 89 years, with an average of 66.1. Side effects were evaluated in a total of 90 cases (48 ADM cases and 42 MMC cases).

In this study the rates of nonrecurrence at 1 year after treatment were 80.3% for ADM, 76.1% for MMC, and 30.0% for controls, while the rates at 2 years were 73.6%, 63.4%, and 22.5%, respectively (Fig. 3). The difference between the ADM group and controls was statistically significant ($P < 0.001$) and that between the MMC group and controls also significant ($P < 0.01$). Next the results were compared in terms of the single or multiple lesion category. In cases with a single lesion, the nonrecurrence rates at 1 year were 82.0% in ADM, 95.0% in MMC, and 58.3% in

Table 3. Characteristics of randomized patients

	ADM group		MMC group		Control group		Total	χ^2 test
	S (17)	M (16)	S (20)	M (17)	S (15)	M (18)	103	
Male	14	14	16	14	12	15	85	NS
Female	3	2	4	3	3	3	18	
Primary	11	9	19	12	13	9	73	NS
Recurrent	6	7	1	5	2	9	30	
Grade 1	3	6	6	7	5	4	31	NS
Grade 2	12	9	14	10	8	14	67	
Others	2	1	0	0	2	0	5	
Papillary	15	13	19	16	14	14	91	NS
Non-papillary	1	2	1	1	1	2	8	
Others	1	1	0	0	0	2	4	

S, Solitary; M, multiple

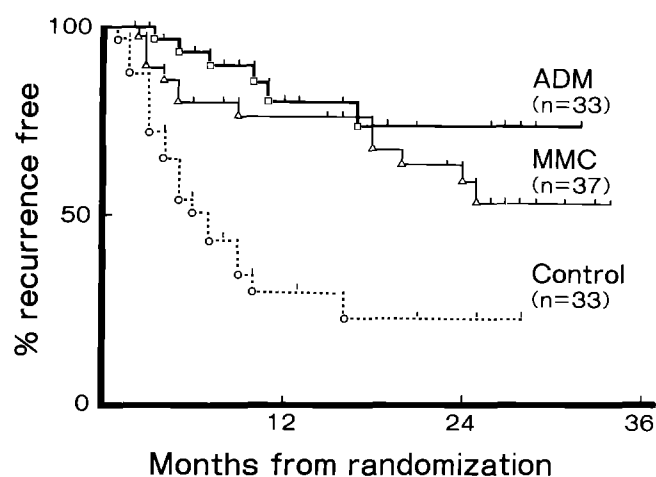


Fig. 3. Interval free from recurrence (all cases)

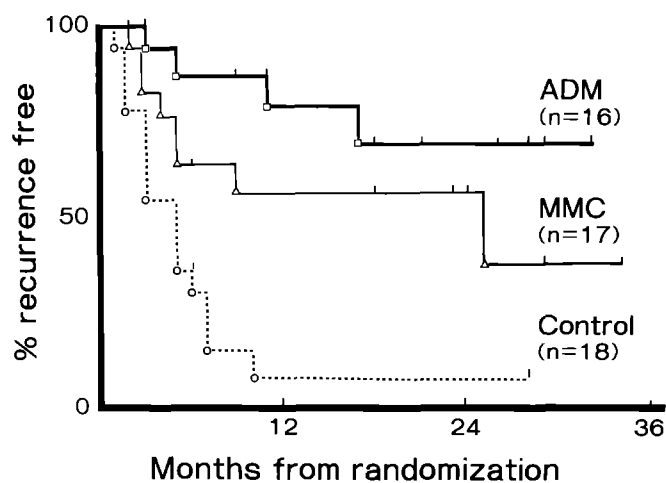


Fig. 5. Interval free from recurrence (multiple)

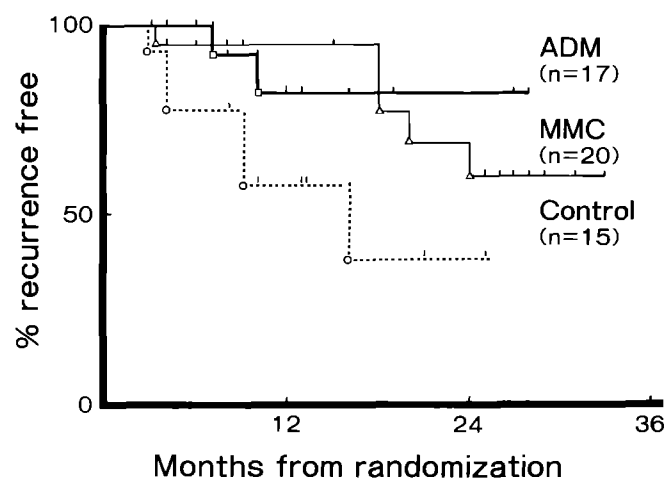


Fig. 4. Interval free from recurrence (solitary)

controls, while at 2 years the rates were 82.0%, 69.0%, and 38.8%, respectively (Fig. 4). Both ADM and MMC groups showed higher rates of nonrecurrence than the control group, but the results were not statistically significant. On the other hand, in cases with multiple lesions the nonrecurrence

rates at 1 year were 78.3% for ADM, 56.3% for MMC, and 7.4% for controls, while at 2 years the rates were 68.5%, 56.3%, and 7.4%, respectively (Fig. 5). Statistically significant differences were recognized between ADM and controls ($P < 0.001$) and between MMC and controls ($P < 0.05$). Also, the rate of nonrecurrence for ADM tended to be higher than that of MMC, but the difference was not statistically significant. Furthermore, the recurrence rates per patient-year were analyzed. In cases with solitary lesion, 17 patients in the ADM group were followed up from 3 to 28 months and had 3 recurrence episodes, showing a recurrence rate per patient-year of 0.17. The rate for MMC was also 0.17, while that for control was 0.66. In cases with multiple lesions, the recurrence rates per patient-year were 0.18, 0.42, and 1.34, respectively. The recurrence rates per patient-year for both ADM and MMC groups were lower than that for controls (Table 4).

Side effects were recognized in 5 of 42 cases (11.9%) of the ADM group. Three of these cases involved bladder irritation, and instillation had to be halted in 1 case because of the side effects. In 1 case, a slight transient increase in urea-N (from 18.4 to 25.0) and s-creatinine (from 1.36 to 1.55) was recognized following 6 instillations. The other

Table 4. Recurrence rates according to treatment group

	ADM group	MMC group	Control group
Solitary			
No. of patients	17	20	15
Median months follow-up (range)	10 (3–28)	19.5 (3–33)	13 (3–27)
Recurrences:			
No. of patients (%)	2 (11.8)	5 (25.0)	6 (40.0)
No. of recurrences	3	5	11
No. of recurrences/patient-year	0.17	0.17	0.66
Multiple			
No. of patients	16	17	18
Median months follow-up (range)	19.5 (2–32)	23 (3–34)	13 (2–29)
Recurrences:			
No. of patients (%)	4 (25.0)	8 (47.1)	15 (83.3)
No. of recurrences	4	11	27
No. of recurrences/patient-year	0.18	0.42	1.34

Table 5. Complications

	ADM (<i>n</i> = 42) No. (%)	MMC (<i>n</i> = 48) No. (%)
Bladder irritability	3	4
Renal dysfunction	1	0
Itching	1	1 ^a
Macrohematuria	0	1 ^a
Total	5 (11.9)	5 (10.4)

^a Same case

case developed itchiness of the soles of the feet and palms. In the MMC group, side effects developed in 5 of 48 cases (10.4%). Four of these involved bladder irritation and instillation had to be halted in 1 case. Also, in 1 case macrohematuria was recognized the day after MMC instillation; itching developed on the fingers and trunk of the body and administration had to be discontinued. The above side effects were mild and transient (Table 5).

Discussion

In cases with superficial bladder cancer (Ta and T1) treated by TUR or TUC, the rate of intravesical recurrence is high and prophylactic instillation therapy has been attempted in order to prevent this outcome. Various drugs such as ADM [7], MMC [7, 12], thio-TEPA [2], epipodophyllotoxin [10], cytosine arabinoside [9], carboquone [6] and bleomycin [3] have been employed for prophylactic instillation therapy. This study was performed using two drugs, ADM and MMC, which have been shown to have excellent antitumor effects in therapeutic intravesical chemotherapy [4, 5].

The characteristic features of our protocol consisted of frequent (6 times) instillations of the drug within 2 weeks after TUR, followed by subsequent instillation on 2 consecutive days at 4-week intervals. Furthermore, large quantities (100 ml) of instillation fluid containing relatively low concentrations (500 µg/ml of ADM or 300 µg/ml of MMC) were employed.

Various factors can be considered to be involved in the recurrence of bladder cancers and Hinman [1] has pointed out the following five features: (1) tumors missed at operation; (2) tumors already initiated at the time of surgery; (3) postoperative activity of carcinogens; (4) seeding into raw areas; (5) increased vulnerability of resected area to carcinogens. The role of our prophylactic instillation therapy in relation to these points is as follows. Concerning the question of repopulation of bladder tumors because of insufficient resection or cauterization, we do not think this is a real recurrence and exclude this point from consideration. Regarding the question of implantation, Soloway [11] has reported that transurethral electrical damage to the bladder mucosa plays an important role in tumor cell implantation; he has also reported that instillation of anticancer agents immediately after the procedure reduced the rate of implantation. In the present study, early and frequent instillations, 6 times within the first 2 weeks after TUR, were performed in order to prevent recurrences resulting from implantation of tumor cells. It is also considered that this method would have an effect on precancerous changes existing in the bladder before the surgical

procedure. Furthermore, long-term instillation was performed to eliminate precancerous cells existing preoperatively or developing postoperatively due to the continuous effects of carcinogenetic agents. On the other hand, in 265 cases with superficial bladder tumors treated at the Department of Urology, Okayama University Medical School, recurrences were detected in 100 cases, of which 72 were recognized within 2 years [8]. As there is the possibility of a secondary carcinogenetic effect caused by long-term instillations of anticancer drugs, it was decided that the instillations would be done for 2 years and discontinued thereafter.

The reason why two consecutive daily instillations were administered every 4 weeks was that this method of instillation was considered to obtain better results than one administration every 2 weeks, which is the same amount of drug. Furthermore, the 100 ml volume was selected because the large volume was believed to allow sufficient drug contact with the whole bladder mucosa. Sufficient contact would indicate a good prophylactic effect even with low drug concentrations. Also, because the concentrations were low, frequent instillations, 6 times within 2 weeks after the operation and 2 consecutive instillations every 4 weeks, were possible without causing a high incidence of side effects.

The study results to date indicate that the rates of non-recurrence in the two instillation groups were significantly higher than that in the control group. However, the period of follow-up is still too short, being only 3 years at present. Also, since the instillation therapy will be complete in 2 years, a follow-up for a further 2 years is considered important.

The incidence of side effects was low, 11.9% for ADM and 10.4% for MMC, and they were both mild and transient. The most common side effect was bladder irritation, and there was one case each in the ADM and MMC groups in which this side effect necessitated discontinuation of the drug. The frequency of side effects was lower than that reported by other investigators [7], and this probably reflects the advantage of the low drug concentrations in our instillation therapy.

Conclusions

1. The prophylactic effects of low-concentration, large-volume, long-term intravesical instillation of ADM and MMC were examined in a randomized study.
2. The nonrecurrence rates at 2 years in 103 evaluable cases were 73.6% for ADM, 63.4% for MMC, and 22.5% for controls, showing significantly higher rates of nonrecurrence in the ADM and MMC groups than in the control group.
3. Thirty-one cases (23%) were excluded or dropped. The incidence of side effects was 11.9% in ADM (5 of 42 cases) and 10.4% in MMC (5 of 48 cases), and the degree of the side effects was mild.

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