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Comparative analysis of short-term and long-term prophylactic intravesical chemotherapy of superficial bladder cancer

Prospective, randomized, controlled studies of the Japanese Urological Cancer Research Group

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Summary. The Japanese Urological Cancer Research Group has conducted three randomized clinical studies on intravesical chemoprophylaxis of superficial bladder cancers. This paper presents a comparative analysis of the first and second of these. The protocol used in the first study was a so-called short-term schedule in which drugs (for group A, ADM 30 mg/30 ml; group B, ADM 20 mg/40 ml; group C, MMC 20 mg/40 ml; and group D, control) were administered twice a week for 4 weeks after transurethral resection (TUR), and in the second study a long-term schedule was used, in which drugs (for group E, ADM 30 mg/30 ml; group F, ADM 20 mg/40 ml; group G, MMC 20 mg/40 ml; and group H, control) were administered twice a week for 1 week, every 2 weeks for 7 weeks, monthly for 8 months, and finally once every 3 months for 1 year. In the first study 575 patients were evaluated and followed up for 5 years. The second study started 28 months later, and 607 patients were evaluated. A generally good prophylactic effect was obtained in the second study when the patients' backgrounds were adjusted in combination with the history and number of the tumors. The second study did not reveal any promoting or inhibitory effect on the progression of the recurrent tumors. There were no significant side effects in either study. The indications and the schedule for prophylactic intravesical chemotherapy should be more carefully studied.

Introduction

Intravesical chemoprophylaxis is considered to be an important tool in the prevention of recurrence of superficial bladder tumors. However, because of the empirical manner in which this treatment has been developed, there are many aspects that still need to be studied. The time schedule, including the interval and duration of the prophylactic treatment, is one of the most important problems [1, 14].

This paper presents a comparative analysis of the results of the first and second studies of the Japanese Urological Cancer Research Group with reference to the interval and duration of the prophylactic treatment. In these studies, adriamycin (ADM) and mitomycin C (MMC) were used because they have been found by many investigators to produce significant prophylactic effects with tolerable local toxicity [4, 5, 10, 11].

Materials and methods

The Japanese Urological Cancer Research Group (Table 1) has implemented collaborative studies on prophylactic intravesical chemotherapy for the treatment of superficial bladder tumors. The first study [11] was initiated in April 1980 and, as shown in Table 2, a short-term regimen entailing instillation therapy was followed for a postoperative period of 4 weeks (two instillations per week). The second study was conducted exclusively in patients with primary occurrence and was started in July 1982; as shown in Table 2, a long-term regimen was followed over a 2-year period (once a week for the first 2 weeks; once every other week for 14 weeks; once a month for 8 months; and once every 3 months for 1 year, giving a total of 21 instillations). The drugs and doses administered were 30 mg ADM in 30 ml saline, 20 mg ADM in 40 ml saline, and 20 mg MMC in 40 ml saline; these were administered respectively, to groups A, B, and C in the first study and to groups E, F, and G in the second study. The control groups, i. e., group D in the first study and group H in the second study, did not receive any drugs. Within 1 week after surgery, patients giving informed consent were each allocated to a group by the envelope method, and the treatment was started.

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Table 1. The Japanese Urological Cancer Research Group (Chairman: Tadao Niijima, MD)

Hokkaido University	(T. Koyanagi, MD)
Asahikawa Medical College	(S. Yachiku, MD)
Iwate Medical University	(T. Ōhori, MD)
Iwate Prefectural Central Hospital	(I. Yoshida, MD)
Tohoku University	(S. Orikasa, MD)
Sendai Municipal Hospital	(Y. Imai, MD)
Fukushima Medical College	(Y. Shiraiwa, MD)
Fukushima Rosai Hospital	(R. Chiba, MD)
Akita University	(S. Tsuchida, MD)
Niigata Cancer Center	(Y. Sakata, MD)
Niigata University	(S. Sato, MD)
Saitama Medical School	(K. Okada, MD)
Mito Kyodo Hospital	(Y. Koizumi, MD)
Mito Red Cross Hospital	(R. Suzuki, MD)
University of Tsukuba	(K. Koiso, MD)
Chiba University	(J. Shimazaki, MD)
Chiba Cancer Center	(T. Nagyama, MD)
Juntendo University	(R. Kitagawa, MD)
Tokyo Medical and Dental University	(H. Ohshima, MD)
Nippon Medical School	(S. Akimoto, MD)
Jikei University School of Medicine	(T. Machida, MD)
University of Tokyo	(T. Niijima, MD)[a]
Tokyo Medical College	(M. Miki, MD)
Cancer Research Hospital	(T. Kawai, MD)
Showa University, Fujigaoka Hospital	(Y. Kai, MD)
Yokohama City University	(M. Hosaka, MD)
Toho University, Ohmori Hospital	(K. Ando, MD)
Kanagawa Cancer Center	(I. Kondo, MD)
Kawakita Sogo Hospital	(K. Tannowa, MD)
Hamamatsu University School of Medicine	(Y. Aso, MD)
National Nagoya Hospital	(K. Yoshida, MD)
Nagoya City University	(K. Ohtaguro, MD)
Nagoya University	(H. Mitsuya, MD)
Japanese Red Cross Nagoya First Hospital	(T. Murase, MD)
Japanese Red Cross Nagoya Second Hospital	(K. Obata, MD)
Shakai Hoken Chukyo Hospital	(S. Ohshima, MD)
Aichi Medical University	(A. Segawa, MD)
Gifu University	(T. Nishiura, MD)
Kyoto Prefectural University of Medicine	(H. Watanabe, MD)
Nara Medical University	(E. Okajima, MD)
Wakayama Medical College	(T. Ohkawa, MD)
Osaka City University	(M. Maekawa, MD)
Osaka University	(T. Sonoda, MD)
Center for Adult Diseases, Osaka	(T. Kotake, MD)
Osaka Medical College	(S. Miyazaki, MD)
Kansai Denryoku Hospital	(H. Katamura, MD)
Kanazawa University	(H. Hisazumi, MD)
Kobe University	(S. Kamidono, MD)
Kobe City General Hospital	(M. Matsuo, MD)
Okayama University	(H. Ohmori, MD)
Kawasaki Medical School	(H. Tanaka, MD)
Tottori University	(H. Goto, MD)
Hiroshima University	(H. Nihira, MD)
Yamaguchi University	(J. Sakatoku, MD)
Kochi Medical School	(Y. Fujita, MD)
University of Tokushima	(K. Kurokawa, MD)
Shikoku Cancer Center	(T. Uyama, MD)
Matsuyama Red Cross Hospital	(T. Shiraishi, MD)
Kyushu University	(J. Kumazawa, MD)
Kurume University	(K. Eto, MD)
Kumamoto University	(K. Ikegami, MD)
Nagasaki University	(Y. Saito, MD)
Medical College of Oita	(J. Ogata, MD)
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Table 2. Regimens followed in the first and second studies

First study (Short-term regimen)			
Group	A	Adriamycin	30 mg/30 ml saline
	B	Adriamycin	20 mg/40 ml saline
	C	Mitomycin C	20 mg/40 ml saline
	D	Control	
			Twice weekly for 4 weeks, i.e., 8 doses in all
Second study (Long-term regimen)			
Group	E	Adriamycin	30 mg/30 ml saline
	F	Adriamycin	20 mg/40 ml saline
	G	Mitomycin C	20 mg/40 ml saline
	H	Control	
			Once weekly for 2 weeks, *then* Once every 2 weeks for 14 weeks, *then* Once monthly for 8 months, *then* Once every 3 months for 1 year, i.e., 21 doses in all, over 2 years

The criteria for eligibility were (1) histologically confirmed superficial bladder tumor (T_a or T_1) and (2) absence of tumor after TUC or TUR. The first study included subjects with primary tumors and patients with recurrences, while the second study was restricted exclusively to patients with primary tumors.

The following exclusion criteria were applied in both studies: (1) other therapies, such as chemotherapy, immunotherapy and/or radiotherapy, within 4 weeks before initiation of the study; (2) severe cardiovascular, renal, hepatic or hematopoietic disturbances; and (3) simultaneous presence of another active cancer.

For evaluation of the test treatment, cystoscopy and urinary cytology studies were repeated at 12-week intervals during the observation period. A diagnosis of recurrence was established by pathological examination of biopsy specimens. The results were evaluated according to the disease-free survival rates. The disease-free interval was defined as the time interval between the operation and the date of the first positive pathological findings. Statistical analyses were performed by the X^2-test and the generalized Wilcoxon test.

A preliminary report of the first study, based on the results of follow-up for 18 months, has been published elsewhere [11]. This paper includes the final results of the first study after 5 years of follow-up.

During the latter half of the second study, the stages and grades of recurrent tumors were assessed and compared with their pretreatment status. The second study is still in progress, and 226 cases (37%) have so far been observed for 3.5 years.

Results

In the first study, 707 patients were enrolled and 575 were evaluated, 389 with primary occurrences and 186 with recurrences. In the second study, 665 patients, all with primary tumors, were enrolled, and 607 were considered suitable for evaluation. Absolutely no intergroup differences were found in either of these studies in number of cases, histological grade, degree of infiltration, size, number, configuration or location of tumors, or treatment method.

Therefore, the patient groups in these studies are considered to have been extremely well matched.

The number of cases, average age, size of the largest tumor and number of tumors in each treatment group are summarized in Table 3. The curves for the non-recurrence rates of all groups in the first study are compared in Fig. 1, which makes it clear that tumor recurrence was significantly inhibited in groups B and C in comparison with group D (control).

The patients in the first study were divided into those with primary occurrence and those with recurrence, and the results were compared with the results of the second study.

Figure 2 shows the curve for the non-recurrence rate in patients with primary occurrence in the first study. Tumor recurrence was significantly inhibited in groups B and C. Compared with 70% in the control group, the non-recurrence rate during the 1st year was 73.1% in group A, 76.6% in group B, and 84.0% in group c. The non-recurrence rate during the 2nd year was 58.5% in group A, 64.2% in group B, and 64.3% in group C, as against 48.5% in the control group. The curve showing the results of the second study, with its long-term regimen, is shown in Fig. 3. Significant inhibition of recurrence was observed in all the drug-treated groups compared with the control group. The non-recurrence rate during the first year was 74.8% in group E, 75.0% in group F, and 76.3% in group G, compared with 66.7% in the control group. During the 2nd year, in comparison with 51.8% in the control group, the non-recurrence rate was 62.3% in group E, 59.1% in group F, and 62.3% in group G.

For correct assessment of the risk factors [9] relating to the recurrence of bladder tumors, factors relating to the therapeutic modalities administered during the assessment must obviously be carefully considered. Thus, the risk factors for tumor recurrence were first examined in the un-

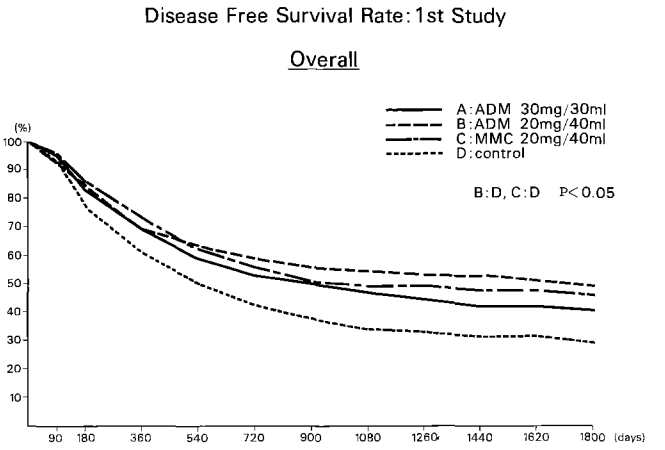

Fig. 1. Total disease-free survival rate in first study

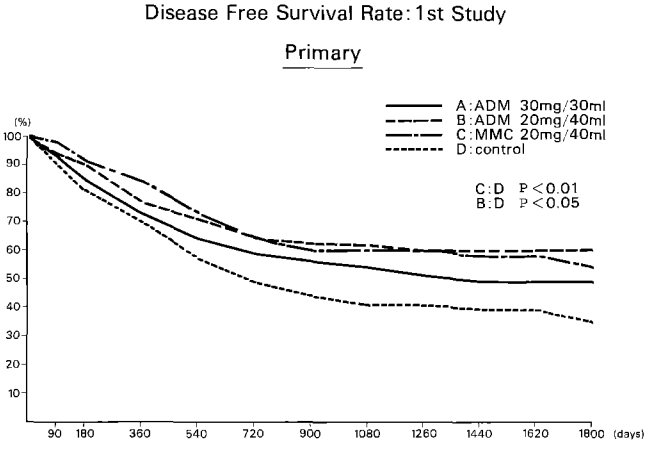

Fig. 2. Disease-free survival rate in first study among patients treated for primary tumor disease

Table 3. Patient characteristics in the first and second studies

	First study				Total	Second study				Total
	Regimen					Regimen				
	A	B	C	D		E	F	G	H	
No. registered	192	176	185	154	707	170	175	164	156	665
No. evaluated	149	148	139	139	575	151	158	150	148	607
Average age (years)	62.3	62.9	62.9	62.9		63.1	62.1	62.3	62.0	
Sex										
Male	123	112	104	103	442	121	130	123	120	494
Female	26	36	36	35	133	30	28	27	28	113
History										
Primary	105	102	92	90	389	151	158	150	148	607
Recurrent	44	46	47	49	186					
Size of largest tumor										
<1 cm	60	55	61	64	240	48	48	54	57	207
1–3 cm	64	78	54	67	263	77	84	66	73	300
3–5 cm	22	11	17	7	57	22	18	17	10	67
$\geqslant 5$ cm	1	2	2	1	6	4	7	10	7	28
Other	2	2	5	0	9	0	1	3	1	5
No. of tumors										
1	96	94	67	84	341	97	88	83	99	367
2–4	39	38	55	42	174	45	48	50	35	178
$\geqslant 5$	12	16	16	13	57	9	20	16	12	57
Other	2	0	1	0	3	0	2	1	2	5

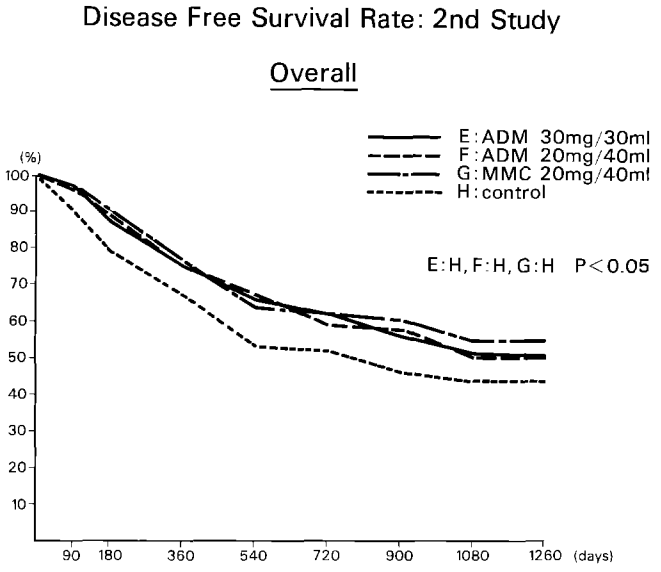

Fig. 3. Total disease-free survival rate in second study

Table 4. Non-recurrence rates of the control groups as function of history (%)

Control group						
First study						
Observation period (months)	6	12	24	36	60	(*n*)
Primary*	81.0	70.0	48.5	40.8	35.4	(90)
Recurrent*	69.8	44.7	31.5	20.9	16.7	(49)
Second study						
Observation period (months)	6	12	24	36		(*n*)
Primary	78.9	66.7	51.8	43.7		(148)

* $P < 0.05$ for difference between these patient groups

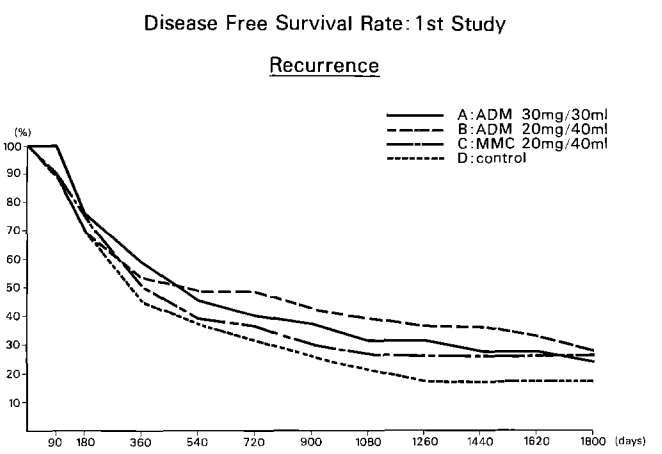

Fig. 4. Disease-free survival rate in first study among patients treated for tumor recurrence

Table 5. Non-recurrence rates in the control groups as function of number of tumors (%)

First study						
Observation period (months)	6	12	24	36	60	(*n*)
Single*	89.9	72.5	54.6	45.8	38.1	(84)
2–4*	55.9	44.7	30.8	22.2	–	(42)
⩾5*	58.5	41.8	8.4	–	–	(13)
Second study						
Observation period (months)	6	12	24	36		(*n*)
Single*	88.3	77.5	62.9	53.7		(99)
2–4*	61.7	44.7	31.3	23.5		(35)
⩾5*	49.9	38.8	25.9	–		(12)

* Significant difference ($P < 0.05$)

treated control groups in both studies, and then the efficacy of each intravesical instillation method was assessed.

The non-recurrence rate in the control group of the first study is summarized in Table 4, based on the presence or absence of a past history of a bladder tumor. The postoperative non-recurrence rate is significantly lower in the recurrence group than in the primary occurrence group.

Figure 4 presents the plots of the results for the recurrence cases in the first study. All treatment groups showed a higher non-recurrence curve; however, those differences were not statistically significant, compared with the control group. Thus, our short-term regimen did not exert a significant prophylactic effect on the cases of recurrence.

The non-recurrence rates according to the number of tumors in the control groups for both the first and second studies are summarized in Table 5. The multiple-tumor group displayed a significantly lower non-recurrence rate than the single-tumor group. Comparative analyses of the treatment groups revealed that both previous tumor history and number of tumors were proved significant determining factors in tumor recurrence (Table 6). Therefore, an efficacy was compared between the first and second studies on the combination of these factors. As shown in Table 7, there was no statistically significant difference between the combined treated groups and the appropriate control group in each study when the backgrounds were adjusted with reference to the history and number of the tumors in the first study. On the other hand, there was a significant difference between all treated groups and control groups in cases with primary and single tumor ($P=0.041$), and in cases with primary and two to four tumors ($P=0.001$) in the second study. Even in cases with primary and tumors of over 5, a considerable prophylactic effect was observed ($P=0.053$) in the second study. Thus, our long-term regimen was superior in preventing a subsequent tumor after eradication of superficial bladder tumors with no previous history.

The relationships between various other background factors and the recurrence-inhibiting effects in both studies are summarized in Table 6. With regard to the kinds of drugs used dosages good recurrence-inhibiting effects were observed in both the ADM 20 mg/40 ml saline group (group B) and the MMC 20 mg/40 ml saline group (group C) in the first study. In the second study, patients over 60 or patients with T_1 disease were found to have significant effects. Information on side effects are summarized in Table 8. Pollakiuria, pain on urination, hematuria and pyuria were the main local side effects.

In the first study, pain on urination, hematuria and pyuria were more prominent in group A than in group B [11], whereas in the second study there were no significant differences between the treatment groups. There were no

Table 6. Relationships between backgrounds and recurrence-inhibiting effects

Background	First study Short-term regimen			Second study Long-term regimen		
	Group A	B	C	E	F	G
Total cases	●	○	○	○	○	○
History of tumor						
Primary	●	○	○	○	○	○
Recurrent	●	●	●			
No. of tumors						
Single	○	○	○	●	○	●
2–4	○	○	○	○	○	○
⩾5	●	●	●	●	●	●
Histological grade						
G_1	●	●	●	○	●	●
G_2	●	●	●	●	●	●
Stage of tumor						
T_a	●	●	●	●	●	●
T_1	●	●	●	○	○	○
Size of largest tumor						
<1 cm	●	○	●	●	●	●
1–3 cm	●	●	○	●	●	●
3–5 cm	○	●	●	●	●	●
Sex						
Male	●	○	○	●	○	○
Female	●	●	●	●	●	●
Age						
<60	●	●	●	●	●	●
⩾60	●	●	●	○	○	○

Statistical analyses were done by application of the generalized Wilcoxon test to the complete non-recurrence curves
○, statistically significant effect compared with the control group; ●, effective, but no statistically significant difference from the control group

significant systemic side effects. Table 9 compares the stage and grade of tumors before the start of the prophylactic instillations and during the latter half of the second study. In the treatment groups, 8 of 43 cases (18.6%) had an increase in the grade and in 10 of 36 cases (27.8%) a more advanced stage was found.

In the control group, 3 of 20 cases (15%) had an increase in grade, and 3 of 17 cases (17.6%) had more advanced stage. No significant differences were observed between the treatment and control groups in regard to the disease progression.

Discussion

Few studies have involved comparative analysis to determine the optimal method for prophylactic intravesical chemotherapy [13–15]. Important factors include determination of the appropriate interval between drug administrations and the time required for a satisfactory prophylactic effect to appear.

It has so far been possible to analyze the results recorded in the second study over follow-up periods of 3.5 years: to date, good prophylactic effects have been observed in the second study with regard to the mode of appearance and degree of the recurrence-inhibiting effect in patients with primary occurrence.

However, further comparative studies on recurrence are still needed for the purpose of designing a method of prophylaxis that is both effective and economic [1, 6, 14]. In other words, we have to distinguish whether the prophylactic effect of the long-term instillation treatment outweighs the economic burden on the patient and the possibility of carcinogenic stimulations to the urothelium [2, 3, 8].

In animal experimentation, continuous infusion of MMC and *cis*-DDP often resulted in lesions that were morphologically indistinguishable from what is currently classified as carcinoma [3].

In the first study regimens B and C had more favorable effects than regimen A; the instillations scheduled in regimen B are lower in concentration (500 μg/ml) and larger in volume (40 ml) than those received as part of regimen A (1000 μg/ml, 30 ml). This fact may be useful in explaining not only the appropriate volume for maximum contact between the drug and the bladder surface but also the optimal concentration of the drug.

The benefits anticipated from the intravesical instillation method include such short-term effects as inhibition of recurrence and inhibition of stage advancement or upgrading of recurrent tumors and the long-term effect of improving the patient's prognosis.

Schulman et al [12], reported that 15.6% of cases showing tumor recurrence after prophylactic intravesical chemotherapy had progressed to a more highly invasive lesion than before treatment.

In the cases enrolled during the latter half of the second study, the stage and grade of recurrent tumors were assessed and compared with their pretreatment status. Although the number of patients cannot be called adequate, no notable difference has yet been observed from controls. In other words, the intravesical instillation method has not been found to promote or inhibit the disease progression of recurrent tumors.

Table 7. Statistical analysis by generalized Wilcoxon test of non-recurrence rates as functions of history and number of tumors (comparisons between all treatment groups and matched control groups)

	First study			Second study		
	No. treated	: Control	*P*-value	No. treated	: Control	*P*-value
Primary and solitary	113	: 41	$P = 0.135$	261	: 94	$P = 0.041$
Primary and 2–4	70	: 25	$P = 0.915$	139	: 35	$P = 0.001$
Primary and >5	–	–	–	47	: 13	$P = 0.053$
Recurrent and solitary	39	: 18	$P = 0.480$			
Recurrent and 2–4	59	: 19	$P = 0.081$			

Table 8. Summary of side effects of intravesical chemoprophylaxis

Incidence of side effects (%)	Pollakiuria	Pain on urination	Hematuria	Pyuria
First study				
A (ADM 30 mg/30 ml)	33.8	36.9	20.0	23.8
B (ADM 20 mg/40 ml)	28.3	27.5	11.6	19.6
C (MMC 20 mg/40 ml)	33.1	27.4	9.7	8.9
Total	31.6	30.6	13.8	17.6
Second study				
E (ADM 30 mg/30 ml)	16.0	25.6	13.6	10.4
F (ADM 20 mg/40 ml)	18.7	25.2	7.3	10.6
G (MMC 20 mg/40 ml)	23.8	27.0	11.1	19.8
Total	19.5	25.9	10.7	13.6

Table 9. Comparisons of stage and grade of tumors before and after prophylactic instillations

	Before treatment	Recurrence after prophylactic instillations				Before treatment	Recurrence without prophylactic instillations			
		Grade	1	2	3		Grade	1	2	3
Grade 1	19		13	6	0	10		7	2	1
2	24		5	17	2	10		3	7	0
		Stage (p)	T_{is}	T_a	T_1	T_2	Stage (p)	T_{is}	T_a	T_1	T_2
Stage (p) T_a	21		1	13	5	2	9	0	6	2	1
T_1	15		2	7	3	3	8	0	3	5	0

X^2 test: NS

Based on the results of the first and second studies, a third study was started by the Japanese Urological Cancer Research Group in 1985. This third study is concentrating on patients in whom no clear efficacy was observed during the previous studies: patients with recurrent tumors and/or those with multiple initial tumors. The recurrence indices (RI/m and RI/c), the recurrence rate (RR), the mean annual recurrence rate (MARR), and the mean time between recurrences (MTBR) [7] are taken into consideration in a more detailed analysis. It is hoped that the true status of intravesical instillation therapy for prophylaxis of recurrence of superficial bladder cancer will be clearly defined and elucidated.

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References

1. Akaza H (1986) Intravesical chemotherapy. [in Japanese] Medical View, Tokyo, p 34 (Bladder cancer, progress in cancer clinics, no. 4)
2. Akaza H, Koiso K, Niijima T, Oshi M, Nakamura F, Asano M (1982) Prophylactic intravesical chemotherapy: its unexpected course. Jpn J Clin Oncol 12: 315
3. Akaza H, Murphy WM, Soloway MS (1984) Bladder cancer induced by noncarcinogenic substances. J Urol 131: 152
4. Bracken RB, Swanson DA, Johnson DE, Furia D, Won Eschenbach, Crooke S (1980) Role of intravesical mitomycin C in management of superficial bladder tumors. Urology 16: 11
5. Edsmyr F, Berlin T, Boman J, Duchek M, Esposti PL, Gustafsson H, Wijkström H, Collste LG (1980) Intravesical therapy with adriamycin in patients with superficial bladder tumors. Eur Urol 6: 132
6. Farrow GM, Utz DC, Rife CC (1976) Morphological and clinical observations of patients with early bladder cancer treated with total cystectomy. Cancer Res 36: 2495
7. Jauhiainen K, Alfthan O (1984) Adriamycin instillations as recurrence prophylaxis in superficial urinary bladder cancer. Ann Chir Gynecol 73: 206
8. Koseki K, Akaza H, Niijima T (1986) Neoplastic promotion by instillation of mitomycin C and cauterization on rat bladder urothelium. Cancer 57: 774
9. Lutzeyer W, Rübben H, Dahm H (1982) Prognostic parameters in superficial bladder cancer: an analysis of 315 cases. J Urol 127: 250
10. Mishina T, Oda K, Murata S, Ohe H, Mori Y, Takahashi T (1975) Mitomycin C bladder instillation therapy for bladder tumors. J Urol 114: 217
11. Niijima T, Koiso K, Akaza H (1983) Randomized clinical trial on chemoprophylaxis of recurrence in cases of superficial bladder cancer. Cancer Chemother Pharmacol 11 [Suppl]: S 79
12. Schulman CC, Denis LJ, Oosterlinck W, De Sy W, Chantrie M, Bouffioux C, Van Changh PJ, Van Erps P (1983) Early adjuvant adriamycin in superficial bladder carcinoma. World J Urol 1: 86
13. Soloway MS (1982) Intravesical chemotherapy for superficial bladder cancer. In: Chemotherapy and urological malignancy. Springer, New York, p 50
14. Soloway MS, Tannock I, Heppner G (1985) Bladder cancer, intravesical chemotherapy of bladder cancer. Organ Systems Newslett 1: 1
15. Zincke H, Utz DC, Taylor WF, Myers RP, Leary FJ (1983) Influence of thiotepa and doxorubicin instillation at time of transurethral surgical treatment of bladder cancer on tumor recurrence: A prospective, randomized, doubleblind, controlled trial. J Urol 129: 505