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The 4th study of prophylactic intravesical chemotherapy with Adriamycin in the treatment of superficial bladder cancer: the experience of the Japanese Urological Cancer Research Group for Adriamycin

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Summary. A multicentric randomised trial was conducted for the purpose of investigating the efficacy of intravesical chemoprophylaxis of superficial bladder cancers. A total of 443 patients (number of evaluable patients, 284) were registered from July 1987 to December 1989 and randomised into 3 groups. Group A received 21 intravesical instillations of Adriamycin (ADM) at 20 mg/40 ml physiological saline for 2 years after undergoing transurethral resection (TUR); group B was given the same dose as group A but received 6 intravesical instillations for 2 weeks before undergoing TUR; and group C served as a control and underwent TUR only. Better prophylactic effects were obtained in group A. The overall non-recurrence rates calculated for groups A and B differed significantly ($P < 0.05$) on day 240, and those determined for groups A and C were also significantly different ($P < 0.01$) on day 480. No benefit was obtained using intravesical instillation prior to TUR (group B). The major side effects encountered were pollakisuria and miction pain, which occurred in 32% of the patients in group A and in 52% of those in group B.

Introduction

Our group has carried out intravesical instillation therapy since 1980 for the purpose of preventing the recurrence of superficial bladder tumors. The first cooperative study was conducted between 1980 and 1982 as a randomised trial with four arms (A, B, C and D arms). The non-recurrence rate was monitored in 599 patients, and group B, which received Adriamycin (ADM) at 20 mg/40 ml physiological saline, achieved the best results [2]. The second cooperative study, conducted between 1982 and 1984, was based on the findings of the first trial. Drug concentrations were the same as those used in the first study, but the instillation schedule was changed. The results were analysed for 607 patients, and the best non-recurrence rate was obtained in the group that received ADM at 20 mg/40 ml physiological saline [1]. The third cooperative study was conducted to investigate the efficacy of adding 5-fluorouracil (5-FU) to treatment with 20 mg ADM/40 ml physiological saline. Analysis of the results obtained in 331 patients revealed that the addition of 5-FU failed to improve the efficacy of ADM therapy.

The present investigation, which represents the fourth cooperative study, was conducted to investigate the usefulness of pre-operative intravesical instillation of ADM at 20 mg/40 ml physiological saline in the prevention of superficial bladder-tumor recurrence.

Table 1. Number of patients: fourth study

Arm	Number of patients entered	Evaluable	Incomplete patient's card	Drop-out, ineligible
A	182	126	16	40
B	126	75	13	38
C	135	83	13	39
Totals	443	284	42	117

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Table 2. Breakdown of drop-out, ineligible patients

Drop out	26
Ineligible	91
Double cancers	3
Stage T2	2
Not primary	2
Primary and solitary	82
Others	2

Table 3. Patients' characteristics

Characteristics	Arm	A	B	C	Totals	Test χ^2
Sex	M	103	59	70	232	N. S.
	F	23	16	13	52	
Age (years)	≤49	9	3	10	22	
	50–59	19	15	11	45	N. S.
	60–69	43	24	26	93	
	≥70	54	33	35	122	
History	Primary	51	29	41	121	N. S.
	Recurrent	75	46	42	163	
Prior treatment	None	67	52	53	172	
	Unknown	15	7	8	30	
	Chemotherapy					
	Systemic (+ADR)	2	4	1	7	N. S.
	Systemic (–ADR)	5	2	6	13	
	i. v. Inst. (+ADR)	19	6	8	33	
	i. v. Inst. (–ADR)	16	4	5	25	

N. S., Not significant; i. v. Inst., intravesical instillation

Patients and methods

The eligibility criteria included the presence of (a) transitional-cell carcinoma categorised as Tis, Ta or Tl; (b) primary tumor with multiple lesions; or (c) recurrent tumors. In other words, patients with a high risk of recurrence were selected and a randomised trial was conducted. A total of 443 patients were enrolled in this study between July 1987 and December 1989 (Table 1). The number of drop-out and ineligible patients was 26 and 91, respectively, and most of these individuals had a primary and solitary tumor (Table 2). No significant difference in sex, age, past disease history or previous treatment was observed among the three groups (Table 3). Moreover, no significant difference in tumor characteristics was found between these groups (Tables 4, 5).

The intravesical instillation schedule used in the present trial was the same as that tested in the second cooperative study. After undergoing transurethral resection (TUR), group A received instillations once a week ×2, then every 2 weeks ×7, once a month ×8, and once every 3 months ×4 (total, 21 courses over 2 years). Group B received 6 instillations of ADM at 20 mg/40 ml physiological saline for a 2-week period before undergoing TUR. Group C underwent TUR only.

Results

Overall non-recurrence rate

A significant difference in the non-recurrence rate (P <0.05) was observed between groups A and B on day 240 and between groups A and C on day 480 (P <0.01). No significant difference was found between groups B and C.

Table 4. Tumor size, number, sites, grade, and stage

Characteristics	Arm	A	B	C	Totals	Test χ^2
Size of tumor	~1 cm	66	37	46	149	
	~3 cm	43	32	28	103	
	~5 cm	9	5	6	20	N. S.
	>5 cm	1	1	1	3	
	Unknown	2	0	2	4	
	Lack of data	5	0	0	5	
Number of tumors	Single	33	17	20	70	
	2–4	74	35	45	154	
	≥5	15	19	15	49	N. S.
	All over surface	1	2	1	4	
	Unknown	2	1	1	4	
	Lack of data	1	1	1	3	
Sites (double count)	Urethra	1	0	1	2	
	Bladder neck	29	13	16	58	
	Trigone	30	14	18	62	
	Posterior wall	54	39	40	133	
	Lateral wall	57	46	36	139	
	Dome	13	10	10	33	
	Anterior wall	3	2	3	8	
	Unknown	0	0	0	0	
Grade	G0	3	6	2	11	
	G1	42	26	27	95	
	G2	46	23	30	99	N. S.
	G3	5	3	0	8	
	Unknown	25	14	23	62	
	Lack of data	5	3	1	9	
Stage	pTis	1	2	3	6	
	pTa	41	26	27	94	
	pTI	54	26	30	110	N. S.
	Unknown	25	18	21	64	
	Other	0	0	1	1	
	Lack of data	5	3	1	9	

N. S., Not significant

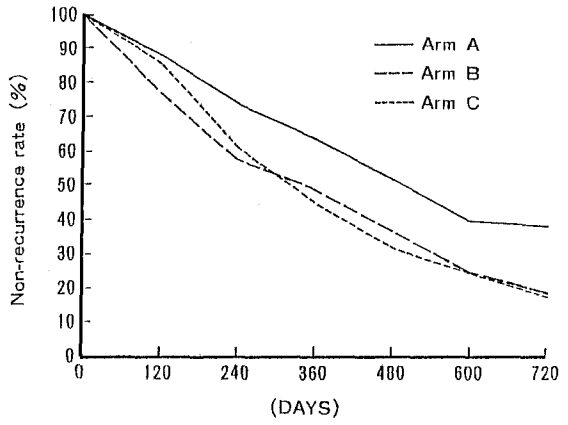
Table 5. Morphological features of the tumors

Characteristics	Arm	A	B	C	Total	Test χ^2
Shapes of bladder neoplasms (double count)	Papillary, narrow stalk	76	48	56	180	
	Papillary, broad base sessile	41	25	24	90	
	Non-papillary, broad base sessile	3	1	1	5	
	Non-papillary, narrow stalk	0	0	1	1	N. S.
	Velvet-like, granular, ulcerative	2	6	4	12	
	Unknown	1	0	0	1	
	Other	0	0	0	0	

N. S., Not significant

The curves shown in Fig. 1 represent interim results rather than final results because the observation period for about 50% of the patients was 240 days.

The non-recurrence rates determined up to day 240 (Fig. 2) revealed a significant difference (P <0.05) be-



Overall

Arm \ day	120	240	360	480	600	720	N
A	88.0	73.8△	63.8△	52.0▲	40.0△	38.2▲△	126
B	77.0	57.8△	49.0	37.0	25.1	18.8△	75
C	85.2	61.2	45.2△	32.0▲	24.5△	17.8▲	83

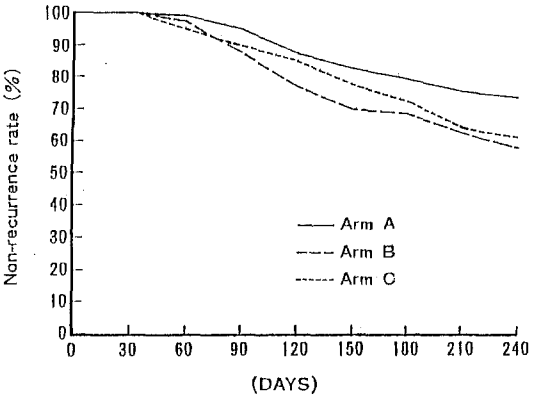
▲ : P<0.01 △ : P<0.05 (%)

No. of Patients

Arm \ day	1	121	241	361	481	601
A	126	108	86	66	42	42
B	75	56	35	26	17	9
C	83	67	43	30	17	13

(N)

Fig. 1. Overall non-recurrence rates



≦240 days

Arm \ day	60	120	180	240	N
A	99.2	87.9	79.7	73.8△	126
B	97.3	76.9	68.5	57.8△	75
C	95.1	85.2	72.2	61.3	83

△ : P<0.05 (%)

No. of Patients

Arm \ day	1	61	121	181
A	126	124	108	96
B	75	72	56	47
C	83	78	67	54

(N)

Fig. 2. Non-recurrence rates as determined during the first 240 days of the study

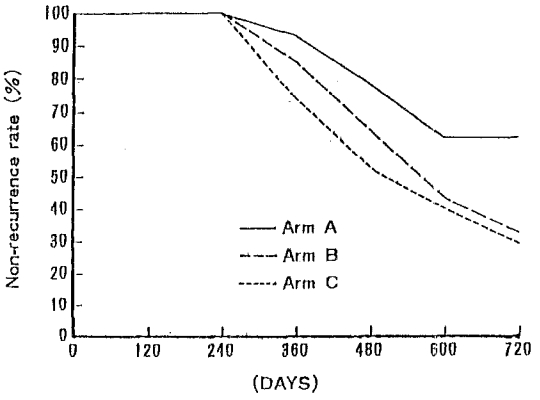
Table 6. Incidence of side effects

Arm	Grade	Pollakiuria		Pain on urination		Dysuria		Hematuria		Pyuria		Contracted bladder	
A	+	11		12		4		4		5		0	
(n = 126)			13		13		4		5		5		0
	++	2		1		0		1		0		0	
			(10.3%)		(10.3%)		(3.2%)		(4.0%)		(4.0%)		(0)
	+++	0		0		0		0		0		0	
B	+	11		7		3		5		6		1	
(n = 75)			13		9		3		6		7		1
	++	1		1		0		0		1		0	
			(17.3%)		(12.0%)		(4.0%)		(8.0%)		(9.3%)		(1.3%)
	+++	1		1		0		1		0		0	

tween groups A and B. Figure 3 shows the non-recurrence rates determined after day 240 for patients who displayed no sign of recurrence up to that point. Accordingly, the number of patients involved in this analysis was smaller than the initial total. The results demonstrate a significant difference between groups A and B on day 720 (P <0.05) and between groups A and C on days 360 and 600 (P <0.05) as well as on days 480 and 720 (P <0.01). No significant difference was observed between groups B and C. Group A achieved the best results.

Side effects

The frequency of side effects was nearly the same in groups A and B, and pollakisuria and miction pain were observed in approximately 10% of the patients in both groups (Table 6).



240 days<

Arm \ day	120	240	360	480	600	720	N
A	100.0	100.0	92.7△	78.3▲	61.7△	61.7▲△	58
B	100.0	100.0	84.8	64.1	43.4	32.6△	45
C	100.0	100.0	76.1△	56.3▲	41.1△	29.9▲	53

▲ : P<0.01 △ : P<0.05 (%)

No. of patients

Arm \ day	1	121	241	361	481	601
A	58	58	58	48	35	24
B	45	43	35	26	17	9
C	53	49	43	30	17	13

(N)

Fig. 3. Non-recurrence rates as determined after day 240 of the study

Discussion

Non-recurrence rate in control groups

Figure 4 shows the non-recurrence rates recorded for control groups in previous studies. The curves calculated from the rates obtained during the first and second studies were similar, while those determined for the third and fourth studies were similar. The similarity might be related to the type of patients involved in each study; i.e., the first and second studies included patients at low risk for recurrence, whereas the third and fourth studies excluded these patients and evaluated only those at high risk for recurrence. This indicates that control groups are not necessary when only high-risk patients are studied; in addition, the establishment of a control group for such a study might pose ethical problems.

Study results

This investigation compared the efficacy of ADM given on two intravesical instillation schedules in preventing bladder tumor recurrence. Group A received ADM after undergoing TUR, according to the most successful schedule used in our previous studies 1–3, and group B received the same doses prior to TUR. ADM is used worldwide in instillation therapy designed to cure or reduce the size of tumors, yielding a response rate of 60%–70%. Thus far, no report has addressed the effect of this therapy on the prevention of tumor recurrence.

Conclusions

The intravesical instillation of ADM given at 20 mg/40 ml physiological saline six times within a 2-week period prior to TUR did not show any usefulness in preventing recurrence. The major side effects encountered in this study were pollakisuria and miction pain, which occurred in 32% of the patients in group A and 52% of those in group B. In our next study, we will investigate the efficacy of short-term ADM instillation immediately after TUR. Further studies on the intravesical chemoprophylaxis of superficial bladder tumors are needed.

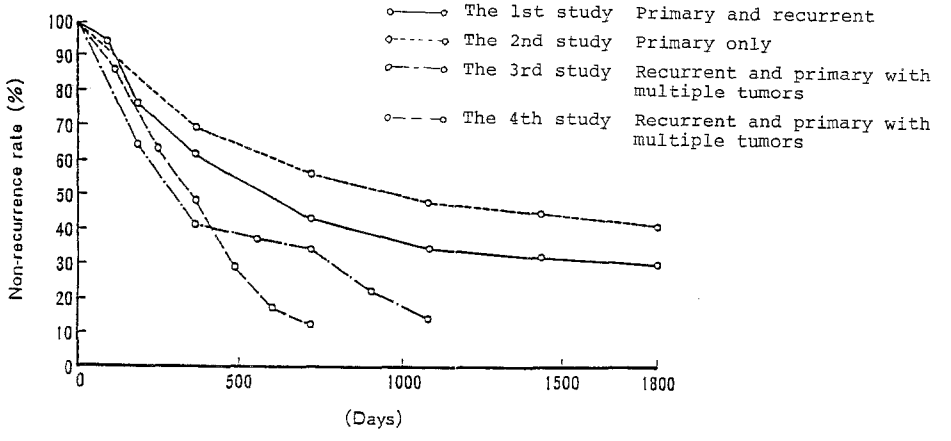


Fig. 4. Non-recurrence rates obtained in the control group for studies 1–4

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Appendix 1

The Japanese Urological Cancer Research Group for Adriamycin (Chairman, T. Niijima)

Hokkaido University	(T. Koyanagi)
Hachinohe Municipal Hospital	(H. Majima)
Iwate Medical University	(T. Kubo)
Iwate Prefectural Central Hospital	(I. Yoshida)
Iwaki Kyoritsu Hospital	(M. Takeuchi)
Iwaki Municipal Joban Hospital	(K. Katayose)
Matsumura General Hospital	(H. Kiuchi)
Tohoku University	(S. Orikasa)
Sendai Municipal Hospital	(Y. Imai)
Fukushima Medical College	(Y. Shiraiwa)
Fukushima Rosai Hospital	(R. Chiba)
Ohta General Hospital	(H. Ishiwata)
Mito Red Cross Hospital	(R. Suzuki)
University of Tsukuba	(K. Koiso)
Niigata Cancer Center	(Y. Sakata)
Niigata University	(S. Sato)
Juntendo University	(R. Kitagawa)
Tokyo Medical and Dental University	(H. Oshima)
Nippon Medical School	(M. Akimoto)
Jikei University School of Medicine	(T. Machida)
University of Tokyo	(Y. Aso)
Tokyo Medical College	(M. Miki)
Cancer Institute Hospital	(T. Kawai)
Omori Hospital, Toho University	(M. Shirai)
Kawakita General Hospital	(Y. Fujioka)
National Nishi-Saitama Central Hospital	(A. Kido)
Chiba University	(J. Shimazaki)
Asahi Central Hospital	(S. Murakami)
Kimitsu Central Hospital	(S. Kataumi)
National Konodai Hospital	(A. Kitamura)
National Chiba Hospital	(T. Ishikawa)
Kameda General Hospital	(T. Hara)
Urayasu Hospital, Juntendo University	(Y. Kawaji)
Fujigaoka Hospital, Showa University	(Y. Kai)
Yokohama City University	(M. Hosaka)
Hamamatsu University School of Medicine	(K. Kawabe)
Yaizu Municipal Hospital	(K. Suzuki)
Seirei Hamamatsu Hospital	(A. Ashiki)
National Tosei Hospital	(S. Ohba)
National Nagoya Hospital	(K. Yoshida)
Nagoya City University	(K. Ohtaguro)
Nagoya University	(K. Miyake)
Japanese Red Cross Nagoya First Hospital	(T. Murase)
Japanese Red Cross Nagoya Second Hospital	(K. Obata)
Shakai Hoken Chukyo Hospital	(S. Ohshima)
Aichi Medical University	(A. Segawa)
Gifu University	(Y. Kawada)
Narita Kinen Hospital	(S. Hirabayashi)
Okazaki Municipal Hospital	(T. Kinukawa)
Komaki City Hospital	(Y. Ono)
Kanazawa University	(H. Hisazumi)
Fukui Medical School	(K. Okada)
Toyama Medical & Pharmaceutical University Faculty of Medicine	(T. Katayama)
Kyoto Prefectural University of Medicine	(H. Watanabe)
Nara Medical University	(E. Okajima)
Wakayama Medical College	(T. Ohkawa)
Osaka City University	(M. Maekawa)
Osaka University	(T. Sonoda)
Center for Adult Diseases, Osaka	(T. Kotake)
Osaka Prefectural Hospital	(S. Sagawa)
Osaka Tetsudo Hospital	(A. Horii)
Kansai Rosai Hospital	(K. Hirooka)
Toyonaka Municipal Hospital	(T. Nishijima)
Yao Municipal Hospital	(T. Yamaguchi)
Kobe University	(S. Kamidono)
Kobe West City Hospital	(Y. Matsumura)
Hyogo Prefectural Amagasaki Hospital	(M. Hamami)
Nishiwaki Municipal Hospital	(N. Kataoka)
Himeji Red Cross Hospital	(O. Tomioka)
Okayama University	(H. Omori)
Kawasaki Medical School	(H. Tanaka)
Tottori University	(I. Miyagawa)
Hiroshima University	(T. Usui)
Yamaguchi University	(N. Yamamoto)
Kochi Medical School	(Y. Fujita)
University of Tokushima	(S. Kagawa)
Shikoku Cancer Center Hospital	(Y. Sumiyoshi)
Ehime University	(M. Takeuchi)
Matsuyama Red Cross Hospital	(T. Shiraishi)
Kyushu University	(J. Kumazawa)
Kurume University	(K. Eto)*
Kumamoto University	(S. Ueda)
Nagasaki University	(Y. Saito)
Medical College of Oita	(J. Ogata)
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