Acta Medica Okayama

Volume 34, *Issue* 1 1980 *Article* 6

FEBRUARY 1980

The effects of intravesical instillation of Thio-Tepa on the recurrence rate of bladder tumors.

Toshihiko Asahi[*] Yosuke Matsumura[†] Toyoko Tanahashi[‡]
Jun Yoshimoto[**] Tetsuzo Kaneshige[††]
Yukitoshi Fujita[‡‡] Hiroyuki Ohmori[§]

[*]Okayama University,
[†]Okayama University,
[‡]Okayama University,
[**]Okayama University,
[††]Okayama University,
[‡‡]Okayama University,
[§]Okayama University,

The effects of intravesical instillation of Thio-Tepa on the recurrence rate of bladder tumors.*

Toshihiko Asahi, Yosuke Matsumura, Toyoko Tanahashi, Jun Yoshimoto, Tetsuzo Kaneshige, Yukitoshi Fujita, and Hiroyuki Ohmori

Abstract

Seventy-eight patients were treated with intravesical instillation of Thio-Tepa in an attempt to prevent postoperative recurrences of bladder tumors. Fifty-six patients who were given no preventive treatment against recurrences were taken as the control group. The patients in this series presented at the Okayama University Hospital between 1961 and 1976 and only the first recurrence after the primary operation was taken into consideration. There was no significant difference in the recurrence rates of the control and instillation groups.

KEYWORDS: bladder tumor, intravesical instillation, thiotepa, recurrence rate.

---

*PMID: 6446839 [PubMed - indexed for MEDLINE]

Acta Med. Okayama **34**, (1), 43—49 (1980)

THE EFFECTS OF INTRAVESICAL INSTILLATION OF THIO-TEPA ON THE RECURRENCE RATE OF BLADDER TUMORS

Toshihiko ASAHI, Yosuke MATSUMURA, Toyoko TANAHASHI, Jun YOSHIMOTO, Tetsuzo KANESHIGE, Yukitoshi FUJITA and Hiroyuki OHMORI

Department of Urology, Okayama University Medical School, Okayama 700, Japan

Received September 22, 1979

Abstract. Seventy-eight patients were treated with intravesical instillation of Thio-Tepa in an attempt to prevent postoperative recurrences of bladder tumors. Fifty-six patients who were given no preventive treatment against recurrences were taken as the control group. The patients in this series presented at the Okayama University Hospital between 1961 and 1976 and only the first recurrence after the primary operation was taken into consideration. There was no significant difference in the recurrence rates of the control and instillation groups.

Key words: bladder tumor, intravesical instillation, thiotepa, recurrence rate.

The treatment and prognosis of bladder tumors differ completely depending on whether the tumor in question is high grade/high stage or low grade/low stage. The prognosis of superficial bladder tumors, for example, is said to be good. Operations which preserve the bladder, however, are followed by repeated rccurrences within the bladder remnant and, in some cases, advance in the grade of tumor also occurs. The treatment of such recurrences, in much the same way as effective treatment of advanced bladder tumors is still a problem, is unsatisfactory at present.

The alkyl chemical Thio-Tepa has been reported by Semple (1) and Jones *et al.* (2) as being effective against bladder tumors when given intravesically, and Thio-Tepa has come to be widely used since Westcott (3) and Veenema *et al.* (4) reported that suppression of recurrences was possible. However, all series published so far have been for only short periods of observation, the majority being from two to three years up to a maximum of five years. In the present study, 78 patients were treated with intravesical instillation of Thio-Tepa and followed for one to sixteen years in an attempt to prevent post-operative recurrences. The results are compared with those for 56 patients not given anti-recurrence therapy.

MATERIALS AND METHODS

The patients in this series presented at the Okayama University Hospital between January 1961 and December 1976 for primary treatment of bladder tumors (5, 6). The control group (Group C) comprised 56 patients not given anti-recurrence therapy. Thio-Tepa was given by intravesical instillation to 78 patients (Group T) and the results compared with those for the control group to see if there were any differences in the rates of recurrences. Patients were followed for 1 to 16 years in group C and group T.

Group C and Group T age group structure is shown in Fig. 1. Intravesical

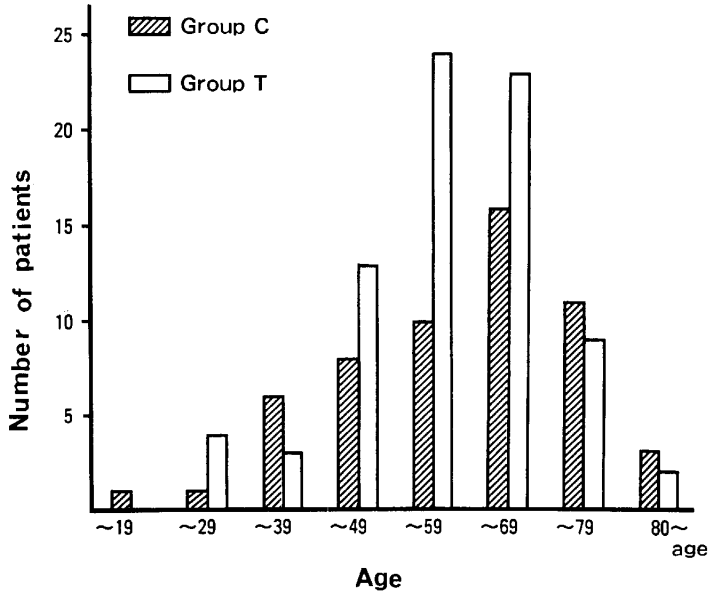

Fig. 1. Distribution according to age.

Thio-Tepa instillation was commenced from the end of the second week after operation at a concentration of 30–50 mg/30–50 ml. The bladder was preserved in these operations. Intravesical Thio-Tepa administration was continued twice a week for a total of seven times (a 3.5 week period). Anti-cancer drugs were not given into the bladder during the remainder of the follow-up period.

In the present paper, only the first recurrence after the primary operation was taken into consideration. The time which elapsed before the first recurrence was defined as the time from the day of operation to the day that recurrence was recognized at outpatient cystoscopy. The recurrence rate was defined as the number of cases with recurrences in each time period studied. The number of recurrences in each of these periods was totalled and taken as the intra-period recurrence number. The number of cases in each period was defined as the total of the number of cases with demonstrated recurrences during the period added to

the number of cases studied during that period but in which recurrences were not seen.

RESULTS

The initial treatments of bladder tumor in Group C and Group T are shown in Table 1. The recurrence rates in Group C and Group T are shown in Fig. 2 and Table 2. There was no significant difference between the rates in these two groups.

Next, Group C and Group T cases were compared in terms of cystoscopy and histopathological findings. Solitary tumors occurred in 38/56 (67.9%) of Group C and 49/78 (62.8%) of Group T. Recurrences were detected in 13/38 (34.2%) of Group C and 14/49 (28.6%) of Group T solitary tumors. Multiple tumors occurred in 18/56 (32.1%) of Group C and 29/78 (37.2%) of Group T at initial diagnosis. They recurred in 10/18 (55.6%) of Group C and 17/29 (58.6%) of Group T.

Tumors were divided into two groups on the basis of size: large (larger than the tip of the index finger) and small (smaller than the tip of the index finger). In Group C, 32/56 (57.1%) were small and 24/56 (42.9%) were large at the

TABLE 1. INITIAL TREATMENT OF BLADDER TUMORS

	Number of patients (Recurrences)	
	Group C	Group T
Transurethral resection and fulguration	26 (7)	47 (16)
Suprapubic resection and fulguration	14 (7)	22 (11)
Segmental resection	16 (9)	9 (4)
Total	56 (23)	78 (30)

TABLE 2. RECURRENCE RATES IN GROUP C AND GROUP T

Observation period (years)	Incidence of recurrence			
	Group C		Group T	
	Number	%	Number	%
1	10/55	18.2	12/76	15.8
2	17/53	32.1	17/70	24.3
3	20/53	37.7	22/66	33.3
4	21/51	41.2	25/63	39.7
5	21/48	43.8	26/56	46.4
7	22/39	56.4	28/43	65.1
10	23/32	71.9	30/39	76.9

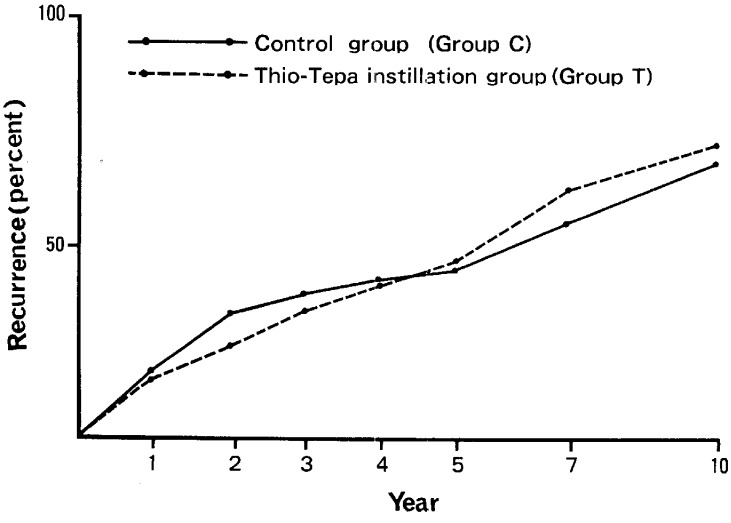

Fig. 2. Recurrence rates in group C and group T. Differences in the recurrence rates in group C and group T were not statistically significant during the observation period.

time of diagnosis. In Group T, 43/78 (55.1%) were small and 34/78 (43.6%) were large. Recurrence rates in relation to tumor size were: Group C, 11/32 (34.4%) for tumors that were initially small, and 12/24 (50.0%) for those that were initially large. In Group T, 17/43 (39.5%) recurred from small, and 14/35 (40.0%) from large, primary tumors.

Recurrence rates in terms of the grade of tumor were: Grade 0-I, Group C 4/13 (30.8%) and Group T 2/16 (12.5%); Grade II, Group C 5/18 (27.8%)

TABLE 3. INTERVAL BETWEEN THE TUMOR RESECTION AND THE FIRST RECURRENCE

Interval before recurrence (years)	Number of patients (%)	
	Group C	Group T
~0.5	6 (26)	4 (13)
~ 1	4 (17)	8 (26)
~ 2	7 (30)	5 (16)
~ 3	3 (13)	5 (16)
~ 4	1 (4)	3 (10)
~ 5	0	1 (3)
~ 7	1 (4)	2 (6)
~10	1 (4)	2 (6)
10~	0	1 (3)
	23(100)	13(100)

and Group T 14/35 (40.0%) ; and Grade III, Group C 6/10 (60.0%) and Group T 8/14 (57.1%).

Recurrence rates in terms of the stage of tumor were: Stage 0-A, Group C 5/19 (26.3%) and Group T 5/21 (23.8%) ; and Stage B, Group C 2/6 (33.3%) and Group T 4/8 (50.0%).

In Group T, recurrence rates for papillary, non-papillary, pedunculated, and broadbase tumors were 29/70 (41.4%), 2/8 (25.0%), 26/64 (40.6%), and 5/14 (35.7%) respectively. In Group C, these were 21/53 (39.6%), 2/3 (66.7%), 16/47 (34.0%), and 7/9 (77.8%).

The time elapsing until the first recurrence in each group was analysed (Table 3).

DISCUSSION

Numerous agents have been introduced into the bladder of patients with bladder cancer since Jones *et al.* (2) first reported the anti-tumor effectiveness of direct intravesical instillation. Reports of effective drugs such as MMC and Adriamycin are frequent and, recently, combinations of two and three drugs have been tried. Intravesical instillation of Thio-Tepa, however, is effective not only against the tumor but also against recurrences. According to Veenema (4), the frequency of recurrences is reduced with consequent improvement in the prognosis. After Veenema, numerous researchers (7) have studied the effect of drugs such as MMC and Thio-Tepa in suppressing recurrences. However, in conventional reports, there are weaknesses in the establishment of control groups ; moreover, almost all follow-up periods are for less than five years.

In contrast to this, our series took, as the study group, patients with bladder cancer who were being treated for the first time and concentrated on the details of their first recurrence. Fifty-six patients who, over the same period, were given no preventive treatment against recurrences were taken as the control. Seventy-eight patients given Thio-Tepa topically into the bladder post-operatively to prevent recurrences were compared with this control.

In our schedule, intravesical instillation of Thio-Tepa was only given a total of 7 times at the rate of twice a week. Other workers have, in general, worked with six month schemes involving approximately 10 bladder instillations. Our results for long-time follow-up where suppression of recurrence had been achieved over a short-term period indicate that, in effect, the number of cases with recurrences has been increasing. As other workers suggest (8), therefore, intravesical instillation over longer periods of time may result in adequate suppression of recurrences. Their periods of observation are too short, however, to enable any definitive statement to be made. Furthermore, instillation only once a month has been reported as ineffective in adequately suppressing recurrences (9).

Inoue *et al.* (10) reported good results with intravesical instillation of Thio-Tepa in preventing recurrences of low grade pedunculated papillary tumors of the bladder. Our results, however, were 29/70 (41.4%) cases of recurrence in patients with papillary tumors treated by topical Thio-Tepa. Recurrence occurred in only 2/8 (25.0%) of cases with non-papillary tumors. Pedunculated tumors recurred in 26/64 (40.6%) whereas broad-base tumors only occurred in 5/14 (35.7%) cases. The proportion of non-papillary and broad-base tumors was slightly greater in Group T and, in comparison with the control group, it was evident that non-papillary and broad-base tumors responded better to Thio-Tepa therapy.

The rate of small to large tumors (defined in relation to the tip of an index finger) at the time of diagnosis was approximately the same for Group C (57 : 43) and Group T (55 : 44). It was thought, however, that in comparison with Group C (50.0%) the recurrence of large tumors had been suppressed post-operatively in Group T (40.0%). There was no difference in recurrence rates for small tumors.

Tumors were more inclined to be multiple in Group T (multiple : solitary : : 59% : 29%) compared with Group C (56% : 34%). Thio-Tepa may have been more effective againt solitary tumors but the difference was not significant (Group T 28% recurrence rate compared with 34% for Group C).

Recurrence rates for grade 0–I tumors were 31% for Group C and 13% for Group T. Hence, Thio-Tepa was effective against grade 0–I tumors, but gave results no different from the control group for grade II and III tumors. There was no difference between the two groups in relation to the stage of tumor.

In regard to the time which elapsed until the first recurrence, 10 (43.5%) occurred within one year and 17 (74.9%) within two years in the control group of 23 patients. In contrast to this, the results for the 31 patients in Group T were only 12 (38.7%) within one year and 17 (54.8%) within two years. Even after five years, however, 5 (16%) cases of recurrence were diagnosed in Group T. This suggests that intravesical instillation of anti-cancer agents, although effective in suppressing early recurrences may, over a long period, have the adverse effect of promoting recurrences. As the National Bladder Cancer Collaborative Group A (11) has pointed out, therefore, further studies of the effectiveness of Thio-Tepa against both tumors and recurrences are necessary.

REFERENCES

1. Semple, J. E.: Papillomata of bladder treated with podophylin. *Br. Med. J.* **1**, 1235-1237. 1948.
2. Jones, H. C. and Swinney, J.: Thiotepa in the treatment of tumors of the bladder. *Lancet* **2**, 615-618, 1961.
3. Westcott, J. W.: The prophylactic use of thiotepa in transitional cell carcinoma of the bladder. *J. Urol.* **96**, 913-918, 1966.

4. Veenema, R. J., Dean, A. L. Jr., Uson, A. C., Roberts, M. and Longo, F.: Thiotepa bladder instillations: Therapy and prophylaxis superficial bladder tumors. *J. Urol.* **101**, 711-715, 1969.
5. Ohmori, H., Fujita, Y., Ike, N., Asahi, T., Ozaki, Y., Nishi, M., Tanahashi, T., Mannami, R., Suyama, B., Yoshimoto, J., Matsumura, Y., Shiraishi, T. and Katayama, Y.: Clinicostatistic study on recurrence of the bladder. Report I: Recurrence rate estimated by cystoscopic findings. *Acta Urol.* **24**, 469-474, 1978.
6. Asahi, T., Ike, N, Ozaki, Y., Nishi, M., Tanahashi, T., Mannami, R., Suyama, B., Yoshimoto, J., Fujita, Y., Ohmori, H., Matsumura, Y., Shiraishi, T. and Katayama, Y.: Clinicostatistic study on recurrence of tumor of the bladder. Report II: Recurrence rate according to the operation methods and the pathological findings. *Acta Urol.* **24**, 713-719, 1978.
7. Toyama. T.: Effects of intravesical instillation of antitumor agents on bladder cancer. *Jpn. J. Urol.* **63**, 497-518, 1972.
8. Gavrell, G. J., Lewis, R. W., Meehan, W. L. and Leblanc, G. A.: Intravesical Thio-Tepa in the immediate postoperative period in patients with recurrent transitional cell carcinoma of the bladder. *J. Urol.* **120**, 410-411, 1978.
9. Nieh, P. T., Daly, J. J., Heaney, J. A., Heney, N. M. and Prout, C. R. Jr.: The effect of intravesical Thio-Tepa on normal and tumor urothelium. *J. Urol.* **119**, 59-61, 1978.
10. Inoue, T., Hirano, A., Osada, T., Tanaka, K., Taguchi, A., Fukushima, S. and Iwamoto, T.: The effects of topical thiotepa on the recurrence rate of superficial bladder tumors. *Jpn. Clin. Urol.* **25**, 897-900, 1971.
11. National bladder cancer collaborative group A: The role of intravesical thio-TEPA in the management of superficial bladder cancer. *Cancer Res.* **37**, 2916-2917, 1977.