The Turkish Journal of Pediatrics
Volume 26, Nos 1 - 4, 1984

THE VALUE OF THIOTEPA IN THE TREATMENT OF SUPERFICIAL BLADDER TUMORS*

*Atıf Akdaş MD**, *Ziya Kırkalı MD****, *Feridun Şengör MD****, *Yalçın İlker MD****, *Çelik Taşar MD***

Key words: histopathological grading, intracavitary chemotherapy, recurrence

Bladder tumors are common in Turkey. While solid and invasive tumors require other therapeutic modalities such as radiotherapy and systemic chemotherapy, the current mode of treatment of superficial tumors is by TUR. After the introduction of intravesical chemotherapy in the 1960s, this has been a form of therapy widely used after the transurethral management of superficial tumors[1-3]. Many chemotherapeutic agents such as thiotepa (triethylenethiophosphoramide), Epodyl® (ethoglucid-triethyleneglycol diglycidyl ether), Adriamycin®, Mitomycin C®, and VM 26® are being used for this purpose[1,4-6]. Thiotepa, one of the most popular intracavitary chemotherapeutic agents is reported to be effective in the prevention of recurrences and in reducing tumor progression[7-9]. Here we present our experience in the treatment of recurrent superficial bladder tumors with thiotepa.

Material and Methods

Fifty-nine patients (49 male, 10 female) with histologically confirmed superficial bladder tumors (TCC, Stage T1) were treated in the Hacettepe University Department of Urology between January 1979 and December 1983. Our policy in cases of primary superficial tumors, is to perform TUR and follow up; whereas in cases of recurrent tumors intracavitary chemotherapy (ICC) with thiotepa adjuvant to TUR is given. Without randomizing, 30 of these patients who had primary tumors with a mean age of 54 (ranging from 20 to 76) were treated with TUR alone, and 29 patients who had recurrent tumors with a mean age of 55 (ranging from 23 to 70) received intracavitary thiotepa adjunct to TUR.

Patients underwent cystoscopies at 3 monthly intervals in the first year and at 6 monthly intervals in the second year and afterwards yearly for 5 years. All of the

* From the Department of Urology, Hacettepe University Faculty of Medicine, Ankara.
** Associate Professor of Urology, Hacettepe University Faculty of Medicine.
*** Research Asslstant in Urology, Hacettepe University Faculty of Medicine.

patients treated with thiotepa and 22 patients who had TUR only were regularly followed up. Eight patients with insufficient follow-up were excluded from the study (Table I). The mean duration of follow-up in the thiotepa group was 26 months, and for surgically treated primary patients it was 24 months.

TABLE I

Follow-up of Patients with Superficial Bladder Tumors ($p<0.05$)

	Primary tumors treated by TUR	Recurrent tumors treated by TUR + ICC (thiotepa)	Total number of patients
Regular follow-up	22	29	51
Insufficient follow-up	8	—	8
Total	30	29	59

TABLE II

Size of Tumor at First Assessment ($p>0.05$)

	Tumor Size			
Treatment	0 - 1 cm	1.1 - 3 cm	3.1 cm	Total number of patients
TUR	4	18	8	30
TUR + ICC (thiotepa)	10	11	8	29
Total	14	29	16	59

TABLE III

Number of Tumors at First Assessment ($p>0.05$)

	Number of tumors		
Treatment	1 or 2	More than 2	Total number of patients
TUR	27	3	30
TUR + ICC (thiotepa)	21	8	29
Total	48	11	59

The size, number and grade of the tumors in both groups showed no statistical difference (Tables II, III, IV).

Dosage and administration. Intracavitary thiotepa instillations were started 3 weeks after TUR. Sixty mg of thiotepa in 60 ml of sterile water was given intravesically and retained for one hour, changing the position of the patient every 15 minutes. The

TABLE IV

Grade of Tumor at First Assessment (p>0.05)

Treatment	Grade of tumor 1	Grade of tumor 11	Total number of patients
TUR	15	15	30
TUR + ICC (thiotepa)	20	9	29
Total	35	24	59

instillations were given at weekly intervals for 4 weeks followed by monthly intervals for 11 months, for a total of 15 instillations over a period of one year. A urinalysis was made and the WBC count taken before each instillation and the presence of infection or a WBC count of less than 3000/cu.mm. delayed the therapy.

Statistical analysis. Fisher's exact chi Square test is used for statistical analysis in Tables, I, II, III, IV, VI, VII and significance test between two proportions (t test) is used for Tables VIII and IX.

TABLE V

The Results of treatment of Patients with Superficial Bladder Tumors

	Treatment TUR	Treatment TUR + ICC (thiotepa)	Total
Number of patients	30	29	59
Number of patients with regular follow-ups	22	29	51
Number of patients with recurrences	5	10	15
Total number of recurrences	10	18	28
Number of months of follow-up	523	766	1289
Recurrence rate of tumors (%)	22.7	34.5	29.4
Mean time between recurrences (months)	52.3	42.6	46.0
The recurrence rate per 100 patient month of follow-up	1.91	2.34	2.17

TABLE VI

The Relationship Between the Initiation of Intracavitary Thiotepa Treatment and Recurrent Tumors (p>0.05)

		Out come	
	Number of patients	No recurrence	Recurrence
After the first recurrence	14	11	3
After the second recurrence	8	3	5
After the third and fourth recurrences	7	5	2
Total	29	19	10

TABLE VII

The Relationship Between the Tumor Grade and Patients with Recurrence (p>0.05)

	Tumor Grade	
Patients	I	II
Total	35	24
With regular follow-up	31	20
With recurrences	8	7

TABLE VIII

Ratio of Recurrences in Respect to the Size of the Tumor at First Assessment

	Size of primary tumor			
Treatment	0 - 1 cm	1.1 - 3 cm	3.1 cm	Total
TUR	0/4	4/18	1/8	5/30
TUR + ICC (thiotepa)	0/10	6/11	4/8	10/29
Total	0/14	10/29	5/16	15/59

Results

The results are summarized in Table V. Ten recurrences in 5 patients were detected out of 22 patients with primary tumor who were regularly cystoscoped and controlled for a mean duration of 24 months. Similarly ten out of 29 patients with recurrent tumor who received intracavitary thiotepa had recurrences during a mean period of 26 months. The recurrence rate of tumors in the first group was 22.7% and it was 34.5% in the latter. The recurrence rate per hundred patient-months of follow-up was 1.91 and 2.34 respectively.

The relationship between the initiation of intracavitary thiotepa treatment and recurrent tumors is shown in Table VI. No significant relation was found between the initiation of intracavitary thiotepa treatment and recurrences ($p > 0.05$).

For the patients evaluated with regular follow-ups, the grade of the tumor did not affect the recurrence rate (Table VII). Among those receiving thiotepa there was recurrence in 6 patients with G_1 tumors and 4 patients with G_2 tumors. The size of the tumor was checked for significance in recurrences (Table VIII). In the thiotepa group recurrence was significantly less for tumors of 1 cm or less, than it was for larger ones ($p < 0.05$). The ratio of recurrences in respect to the number of tumors in the first assessment is shown in Table IX. In neither group was the recurrence rate found to be dependent on the number of tumors ($p > 0.05$). The appearance of the first recurrence in both groups is shown in Table X.

TABLE IX

Ratio of Recurrences in Respect to the Number of Tumors at First Assessment ($p>0.05$)

Treatment	Number of tumors		Total number of patients
	1 or 2	More than 2	
TUR	4/27	1/3	5/30
TUR + ICC (thiotepa)	6/21	4/8	10/29
Total	10/48	5/11	15/59

TABLE X

The Timing of the First Recurrence in the two Groups

Treatment	During treatment	At 0 - 1 years	At 1.1 - 2 years	At 2.1 - 3 years	Total number of patients
TUR	—	2	3	—	5
TUR + ICC (thiotepa)	7	2	—	1	10
Total number of patients	7	4	3	1	15

There were no serious complications arising out of the intracavitary thiotepa treatment and there were no deaths in either group.

Discussion

Among many other intravesical chemotherapeutic agents thiotepa is widely used to prevent recurrences and deter tumor progression[4,7-9]. In an EORTC randomized study thiotepa was found to be effective in comparison with the controls and VM 26[5]. England, Blandy and Paris[10] reported an 81% success rate with adjuvant intravesical thiotepa treatment. According to Byar[11], in a randomized study of placebo, thiotepa and pyridoxine thiotepa treatment was found to decrease the recurrence rate of stage I bladder tumors. Koontz et al[8] stressed the efficacy of thiotepa treatment when used prophylactically after ablation of the whole tumor by TUR.

Zincke et al[12] did a comparative study on doxorubicin, thiotepa and controls and 3 to 4 months post-operatively, found a recurrence rate of 32%, 30% and 71% respectively. Nocks et al[13], noted a benefit from weekly instillations of thiotepa in terms of fewer patient recurrences, longer tumor-free intervals and the formation of fewer tumors.

Recently, Prout et al[14] reported the long-term results of intravesical thiotepa treatment in a randomized study with controls. There was recurrence in 29 out of the 45 in the prophylactic group and in 34 out of the 45 controls and a significant prolongation of intervals free of tumor was noted. In the present study, the recurrence rate per hundred month of follow-up was 1.91 for primary tumors treated with TUR alone and 2.34 for recurrent tumors treated with intracavitary thiotepa adjuvant to TUR. These figures may be low because the series were small. It is obvious from these figures that among patients who received thiotepa in addition to TUR, the tendency for tumors to recur was greater than among patients with transurethrally resected primary tumors. The reason for this inconsistency with the literature may be due to the fact that selection of the patients was not randomized. Patients who received thiotepa all had recurrent tumors while in the other group all patients had primary tumors. The tendency to recur in the first group may have been stronger than in the latter where all patients had primary tumors.

There is a place for ICC in the treatment of supercifial bladder tumors in order to prevent recurrences. Today, various drugs are still being tested to find the most effective treatment. In our experience ICC with thiotepa in patients with recurrent tumors has not been found to be effective in reducing recurrences.

Summary

Fifty-nine patients with superificial bladder tumors were treated between 1979-1983. Twenty-nine of these patients, those with recurrent tumors, were treated with intra-

cavitary thiotepa adjuvant to transurethral resection (TUR) and the other 30 patients, who had primary tumors, were given only TUR. The size, number and grade of the tumors in both groups showed no statistical difference. The recurrence rate per hundred patient-months of follow-up in the primary tumors was 1.91 and in the recurrent tumors, treated with thiotepa, it was 2.34.

As a conclusion, intracavitary thiotepa treatment as an adjuvant to TUR in patients with superficial bladder tumors has not been found to be effective in controlling recurrences.

REFERENCES

1. Jones HC, Swinney J. Thiotepa in the treatment of tumours of the bladder. *Lancet* 2:615, 1961.
2. Veenema RJ, Dean AL Jr, Roberts M, et al. Bladder carcinoma treated by direct instillation of thio-TEPA. *J Urol* 88:60, 1962.
3. Jones HC, Swinney J. The treatment of tumours of the bladder by transurethral resection. *Br J Urol* 34:215, 1962.
4. Abbasian A, Wallace DM. Intracavitary chemotherapy of diffuse and non-infiltrating papillaary carcinoma of the bladder. *J Urol* 96:461, 1966.
5. Schulman CC, Sylvester R, Robinson M, et al. Preliminary results from EORTC (European Organisation for Research and Treatment of Cancer) studies on chemotherapy for superficial bladder tumours. In Oliver RT, Hendry WF, Bloom HJG (eds). *Bladder Cancer: Principles of Combination Therapy.* London: Butterworths, 1981, p 75.
6. Edsmyr F. Intravesical chemotherapy with doxorubicin in patients with, superficial bladder tumours. In Oliver RT, Hendry WF, Bloom HJG (eds). *Bladder Cancer: Principles of Combination Therapy.* London: Butterworths, 1981, p 107.
7. England HR, Paris AMI, Blandy JP. Intravesical thio-tepa as adjuvant to cystodiathermy in multiple recurrent superficial bladder tumours. In Oliver RT, Hendry WF, Bloom HJG (eds). *Bladder Cancer: Principles of Combination Therapy.* London: Butterworths 1981, p 67.
8. Koontz WW Jr, Prout GR Jr, Smith W, et al. The use of intravesical thio-tepa in the management of non-invasive carcinoma of the bladder. *J Urol* 125:307, 1981.
9. Green DF, Robinson MR, Glashan R, et al. Does intravesical chemotherapy prevent invasive bladder cancer? *J Urol* 131:33, 1984.
10. England HR, Blandy JP, Paris AMI. The treatment of single and multiple papillary tumours of the bladder. In Pavone-Macaluso M, Smith PH, Edsmyr F (eds). *Bladder Tumours and Other Topics in Urological Oncology.* New York: Plenum Press, 1980, p 343.
11. Byar DP. The Veterans Administration study of chemoprophylaxis for recurrent stage I bladder tumours: Comparison of placebo, pyridoxine and topical thio-tepa. In Pavone-Macoluso M, Smith PH, Edsmyr F (eds). *Bladder Tumours and Other Topics in Urological Oncology.* New York: Plenum Press, 1980, p 363.
12. Zincke H, Utz DC, Taylor WF, et al. Influence of thio-tepa and doxorubicin instilation at time of transurethral surgical treatment of bladder cancer on tumour recurrence: a prospective, randomized, double-blind, controlled trial. *J Urol* 129:505, 1983.
13. Nocks BN, Nieh PT, Prout GR. A longitudinal study of patients with superficial bladder carcinoma successfully treated with weekly intravesical thio-tepa. *J Urol* 122:27, 1979.
14. Prout GR Jr, Koontz WW Jr, Coombs LJ, et al. Long-term fate of 90 patients with superficial bladder cancer randomly assigned to receive or not to receive thio-tepa. *J Urol* 130:677, 1983.

DISCUSSION

Smith: Will you accept that there are 3 groups of patients, the ones with primary tumors that may or may not recur, those with a recurrent tumor that is easy to deal with, and those with a recurrent tumor where there is a major problem, like difficulty in controlling the bladder. Now what would be your clinical message for the place of chemotherapy, intravesically, at the moment? When would you use it, on every recurrent patient? Or only on those where there was difficulty?

Akdaş: Coming back to the morning session, I think we have to work with the pathologist very closely, and we have to know the cause of the changes as well. It seems to me that the red-cell antigens are also giving a message that we have to accept. As for the recurrent tumors, as a whole I mean, we have to do something, we can't just follow them. We have to give intravesical chemotherapy for the whole group.

Smith: Even for the man who has one recurrence in a year?

Wickham: Could I put it to you, what advantages does chemotherapy have over a bit of judicious diathermy in recurrent tumors?

Akdaş: According to the information we have, in 70% of the patients with superficial tumors, there is recurrence during the first year but after intercavitary chemotherapy the interval between recurrences is longer.

Wickham: But is that better than you'd achieve if you used cystodiathermy?

Akdaş: No statistical difference, according to Mr. Smith and his co-workers who, in 1975 started to give thiotepa to one group and VM26 to a control group. Am I correct?

Smith: You are.

Hussien: I have an English patient in Abu Dhabi. He's been coming to me every 3 months since 1976, with a recurrent tumor in his bladder. I fulgurate it for him, and after 3 months he comes back for review and again there is a recurrence; sometimes when he has delayed his check-up for 5 or 6 months I find more than one tumor.He seems satisfied with the treatment. What should I do for him? Should I just carry on fulgurating? This has been going on for 8 or 9 years. He's satisfied, the upper urinary tract is normal; there seems to be no problem. What shall I do now?

Smith: Now that is the absolutely perfect introduction to the talk that I have to give. For the question is, is repeated fulguration adequate therapy for bladder cancer which is known to be non-invasive? We're talking about TA, T1 bladder cancer. The short answer is, I think, to continue as you are, if your patient is happy.

The Turkish Journal of Pediatrics
Volume 26, Nos 1-4, 1984

CLINICAL TRIALS IN SUPERFICIAL AND INVASIVE BLADDER CANCER*

*Philip H. Smith MB, FRCS***

Key words: clinical staging, invasive, superficial, transitional cell carcinoma

Bladder cancer is associated with certain occupations, cigarette smoking, infestation with schistosomiasis and perhaps with metabolic abnormalities of tryptophan metabolism. It is generally believed that the tumor develops over a period of 10 - 20 years and one may expect associated changes of hyperplasia and dysplasia. In general the patients with superficial lesions survive longer than those with invasive tumors. As a rough approximation one may expect 75%, 50%, 25% and 0% survival for categories T1, T2, T3 and T4 tumors respectively. Recently Anderström and Nilsson[1] and Pocock et al[2] have shown a distinct difference between the category Ta tumor which does not involve the lamina propria and the T1 lesion which does (Table I).

TABLE I

5 Year Survival of Ta and T1 Tumors

	5 Year Survival	
	Ta	T1
Anderström and Nilsson (1980)	98%	75%
Pocock et al 1982*	90%	40%

* most Ta lesions are G1.

Seventy percent of all tumors recur and 10% of patients develop lesions of a higher stage or grade[3]. For this reason there has been interest in developing therapy additional to biopsy, fulguration or transurethral resection and intravesical chemotherapy has been investigated extensively in recent years.

Intravesical chemotherapy may be used for the treatment or prevention of carcinoma *in situ* or non-invasive bladder tumors. The 4 commonly used agents are

* From the Department of Urology, St. James's University Hospital, Leeds, United Kingdom.
** Consultant in Urology, St. James's University Hospital, Leeds.

Adriamycin®, Epodyl, Mitomycin C and Thiotepa and the effect of these is briefly summarized in Table II[4]. Each of these agents is slightly different and their molecular weights, tendency to cystitis, absorption and likelihood of systemic effects are shown in Table III.

TABLE II

Some Results of Intravesical Chemoprophylaxis

	Prophylaxis		Therapy	
	No.	Recurrence Free	No.	Response CR + PR
Adriamycin	179	124 (69%)	411	239 (58%)
Epodyl	9	9•	183	147 (80%)
Mitomycin C	101	86	281	213 (76%)
Thiotepa	325	177 (54%)	406	243 (60%)

• patients given prophylaxis after successful therapy.

TABLE III

Intravesical Chemotherapy: Characteristics of the Commonly Used Agents

	Mol. Wt.	Cystitis	Absorption	Systemic
Thiotepa	189	+	+ +	+ +
Epodyl	256	+ +	+	+
Mitomycin C	334	+	±	—
Adriamycin	578	+	—	—

Although intravesical chemotherapy is expensive, inconvenient for the patient and may produce both chemical cystitis and systemic toxicity, there is little doubt that it has some effect in reducing the number of recurrences.

EORTC and MRC Trials in Superficial Bladder Cancer

In 1975 the EORTC Urological Group was formed, initially as a "bladder club" which decided to investigate the effect of VM26, and thiotepa, as prophylactic agents following complete transurethral resection of superficial bladder tumors. The patients randomized to these agents were compared with patients receiving TUR

but no additional therapy. Following recruitment of this study, two other intravesical studies have been completed and a third has now been launched. In addition, work has been undertaken to investigate the incidence of abnormal tryptophan metabolites and the effect, if any, of pyridoxine upon this potentially carcinogenic situation.

The trials which have been carried out are summarized in Table IV and the results of these studies, some of which are preliminary, are shown in Table V.

TABLE IV

Outline of EORTC Protocols for Patients with Superficial Bladder Cancer

Protocol	Trial					Patients entered
30751 *	Thiotepa 30 mg	vs	VM26 50 mg	vs	Control	340
30782 *	Thiotepa 50 mg	vs	DDP 50 mg	vs	ADM 50 mg	224
30791 *	Control	vs	Epodyl 1.19 mg	vs	ADM 50 mg	356
30831 30832	MMC 30 mg ADM 50 mg	Immediate or delayed therapy for 6 or 12 months				Recruiting

* weekly x 4, then monthly x 11.

TABLE V

Current Results of EORTC Studies in Invasive Bladder Cancer

Protocol	Drug	Recurrence rate (per 100 patient months)
30751 Primary + Recurrent Ta/T1	Thiotepa VM26 Control	6.58 10.12 9.97
30782 Recurrent Ta/T1	Thiotepa ADM DDP	5.1 4.5 5.2
30791 Primary + Recurrent Ta/T1	Epodyl ADM Control	2.85 3.71 7.03

The reduction in recurrence rate is a definite finding, but merely means that the patient is likely to have perhaps 4 - 6 recurrences in 100 months of observation (8 ½ years) rather than 10 - 18 recurrences over such a period. This in itself is not adequate justification for the inconvenience and cost of this treatment.

Its benefit will lie in:-

1. The ability of the agents to reduce the bulk of tumor, thereby rendering transurethral resection in the difficult case more simple, and

2. The demonstration that there is a reduction in the incidence of invasive bladder cancer and of death from this cause as a result of therapy. As yet, there is no firm indication to prove or disprove this aim.

The Urological Working Party of the Medical Research Council (MRC) has adopted a slightly different approach, having chosen to investigate the capacity of thiotepa initially, and latterly mitomycin C to reduce tumor recurrence when given only at the time of TUR and at subsequent check cystoscopies. This study has been undertaken to add further information to the concept introduced by Burnand et al (1976) that cytotoxic chemotherapy given in this way would be adequate. So far 377 patients have been entered to the first MRC Study, but the data have not yet been analyzed.

Invasive Bladder Cancer

The results of the management of invasive bladder cancer by cystectomy, radiotherapy, or combination therapy can hardly be considered acceptable since survival at 5 years does not exceed 40%. Some results of these techniques are shown in Table VI. Forty percent of these patients die within a year and 40% develop metastases, usually within the first 12 months[5].

TABLE VI

Some Results of the Conventional Management of Invasive Bladder Cancer[9]

a) Five-year Survival after Cystectomy

Author and reference	T Category - numbers of patients (and % survival)			
	T1	T2	T3	T4
Whitmore & Marshall (radical)	75 (47)		76 (14)	74 (3)
Cordonnier (simple)	54 (54)	19 (53)	42 (25)	11 (0)
Poole-Wilson and Barnard	66 (35)	32 (25)	8 (12)	1 (100)
Bracken *et al.*	*53 (82)	—	—	—
Osborn *et al.*	16 (37)	6 (33)	10 (10)	5 (40)

* Includes stage O.

b) Five-year Survival Following Radical Radiotherapy

Author and reference	Number of patients	Percentage survival by stage T1	T2	T3	T4
External beam therapy					
van der Werf-Messing	326	12	12	5	1
Franks	90	80	57	31	10
Goffine *et al.*	218	—	—	28	—
Morrison	540	41		28	7
Miller	348	40	24	20	8
Edsmyr *et al.*	598	—	32	22	10
Reddy *et al.*	53	—	—	17	—
Backhouse	124	—	—	19	—
Bloom (Institute of Urology)	85	—	—	31	—
Implantation					
van der Werf-Messing					
radium with or without external irradiation	606	75	55	25	—
radium with 3×350 rad preoperative external irradiation	245	—	55	35	—
Pedersen and Herting					
radium alone	32	25	0	9	—
radium + previous surgery	63	55	47	45	—
Williams	147	69	41	21	—

* Age-adjusted rates excluding the theoretically expected deaths from diseases other than cancer of the bladder.

c) Five-year Survival after Pre-operative Irradiation and Cystectomy

Author and reference	T Category - numbers of patients (and % survival) T1	T2	T3	T4
Miller	1 (0)	3 (0)	69 (30)	13 (0)
van der Werf-Messing (simple cystectomy)	—	—	141 (45)	—
Bracken *et al.*	56 (68)	—	—	—
Whitmore				
4000 rad (40 Gy) + radical cystectomy	13 (62)	36 (50)	50 (33)	11 (0)
2000 rad (20 Gy) + radical cystectomy	6 (66)	22 (45)	52 (40)	5 (0)
Bloom *et al.*	—	—	98 (38)	—

The challenge facing the urologist and the oncologist is to develop effective systemic therapy which may be administered in addition to standard treatment thereby controlling micro metastases and increasing survival.

There is some evidence from the work of Socquet[6] that high dose methotrexate may have some benefit on survival when used in association with partial or total cystectomy. There have also been other studies of adjuvant chemotherapy but none has been shown to be of benefit (Table VII).

The Yorkshire Urological Cancer Research Group has carried out one such study using 5 FU and Adriamycin following radiotherapy. In an analysis of 105 evaluable patients no increase in survival was demonstrated[7].

The London and Oxford Group are currently engaged in a study in which the patient receives standard therapy with or without methotrexate given as shown in Table VIII. As yet no information is available from this study.

TABLE VII

Some Studies of Adjuvant Chemotherapy in Invasive Bladder Cancer

Author	No. of patients	Radiotherapy	Surgery	Chemotherapy	Immunotherapy
Martinez Pinelro	10	4000 - 6000 r	Nil/TUR Diversion	ADM 50 mg/m^2 + 5FU 500 mg/m^2 q 21	BCG 150 mg qW×4 + q4W
Martinez Pineiro	10	4000	Radical cystectomy	ADM 50 mg/m^2 + 5FU 500 mg/m^2 q 21	BCG 150 mg qW×4 + q4W
Merrin and Beckley	25	Nil	Radical cystectomy	ADM 40 mg/m^2 + CTX 200 mg/m^2 qD×4 q 21	Nil
Merrin	21	Nil	Radical cystectomy	DDP 50 mg/m^2 qW×6 then q3W	Nil
Socquet	33	Nil	Partial (25) or total (8) cystectomy	MTX 1000 mg + CF then MTX 2000 mg q3W for 6 months at least	Nil
Yucrg	18	4500 - 6000 r	Nil	ADM 50 mg/m^2 + 5FU 500 mg/m^2 minimum 4 cycles q3W	Nil

The National Bladder Cancer Cooperative Group A (NBCCGA) has adopted a slightly different approach (Table IX) in which patients are given radiotherapy followed by radical cystectomy, reassessed and then randomized to receive cisplatin or no additional treatment. Interestingly, of 429 patients evaluated between 1978 and 1982,

TABLE VIII

Role of Adjuvant Methotrexate in Patients with T3NXM0 Bladder Cancer (Outline of Current Study of the London and Oxford Group)

Outline

Age ⩽65 YRS—44GY + RADICAL CYST[Y]
>65 YRS—64GY ± SALVAGE CYST[Y]

RANDOMIZE

MTX - 100 mg/m^2
+ 3L fluid/24 hrs
$NaHCO_3$ 1 g bd
FOLINIC ACID
15 mg IM at 24 hrs

NO ADDITIONAL THERAPY

Regimen

PRELIMINARY MTX
— DAY 0, 7, 14 - 100 mg/m^2

DAY 21 - HER
— 44GY (22 × 2GY) to whole pelvis
DAY 52 - 20GY to bladder
or DAY 72 - Radical cystectomy

MAINTENANCE MTX
— DAY 100 — 100 mg q2W × 6

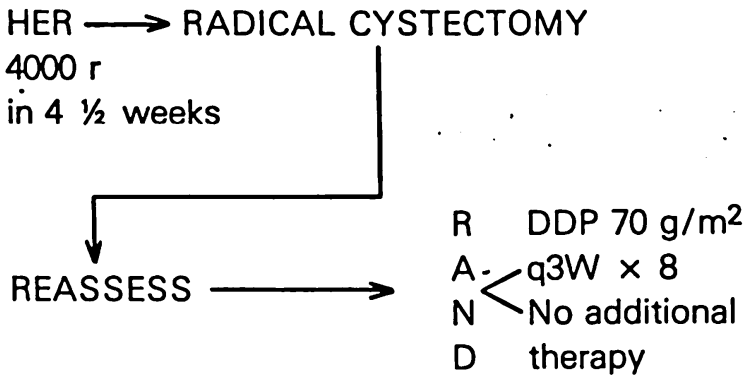
only 189 were entered and of these 84 were randomized, 4 to receive cisplatin and 41 to control (Table IX) [8].

It seems perfectly clear that the general use of chemotherapy in patients with invasive bladder cancer is not likely to be of immediate benefit, in part because the drugs and combinations so far developed produce inadequate numbers of complete responses, and in part because in these elderly patients it is difficult to give effective chemotherapy. It seems unlikely however that conventional treatment will improve survival and one must hope that better agents soon become available.

TABLE IX

Outline of NBCCGA Study for Patients with Invasive Bladder Cancer

Patients Entered 1978 - 1982



423 patients were evaluated between 1978 - 1982.
Of these, 199 were entered but only 84 randomized,
43 to DDP and 41 to control.

REFERENCES

1. Anderström C, Johansson S, Nilsson S. The significance of lamina propria invasion on the prognosis of patients with bladder tumors. *J Urol* 124:23, 1980.
2. Pocock RD, Ponder BA, O'Sullivan JP, et al. Prognostic factors in non-infiltrating carcinoma of the bladder: a preliminary report. *Br J Urol* 54:711, 1982.
3. England HR, Blandy JP, Paris AMI. The treatment of single and multiple papillary tumours of the bladder Ta/Ti NX MO. In Pavone-Macaluso M, Smith PH, Edsmyr F (eds). *Bladder Tumors and Other Topics in Urological Oncology.* New York, London: Plenum Press, 1980, p 343.
4. Smith PH. Superficial tumours of the bladder - treatment. In Hall RR (ed). *A Comprehensive Guide to the Therapeutic Use of Methotrexate in Bladder Cancer.* Short Hills NJ: Pharmalibra, 1983, p 1.
5. Prout GR Jr, Griffin PP, Shipley WU. Bladder carcinoma as a systemic disease. *Cancer* 43:2532, 1979.
6. Socquet Y. Surgery and adjuvant chemotherapy with high-dose methotrexate and folinic acid rescue for infiltrating tumors of the bladder. *Cancer Treat Rep* 65:187, 1981.
7. Richards B, Bastable JR, Freedman L, et al. Adjuvant chemotherapy with doxorubicin (Adriamycin) and 5-fluorouracil in T3, NX, MO bladder cancer treated with radiotherapy. *Br J Urol* 55:386, 1983.
8. Prout GR Jr, Kopp J. Evaluation and management of patients with primary bladder carcinoma. Protocols of the National Bladder Cancer Collaborative Group A. In Denis L, Murphy GP, Prout GR, Schröder F (eds). *Controlled Clinical Trials in Urologic Oncology.* (European Organization for Research on Treatment of Cancer (EORTC) Monograph: Vol 13). New York: Raven Press, 1984, p 221.
9. Smith PH. Invasive bladder cancer - a lethal enigma. In Smith PH, Prout GR Jr (eds). *Bladder Cancer.* Woburn: Butterworths, 1983, p 223.

DISCUSSION

Wickham: I understand that when you treated the controls with cystodiathermy they came out worse than the ones that were treated with the chemotherapy, for that period of time.

Smith: That's right.

Wickham: But do I also understand the continentals were giving the controls chemotherapy, and wasn't this the aim of the trial?

Smith: No, the end point of the trial was something quite different let me explain. Over lunch I was talking to someone. I said, "Well really, you need chaps with ideas to invent things, and then you need somebody else, the cart-horse, who will go along and ask if an idea is of general use." If one runs one of these trials, one is usually either trying to prove a negative, that drug B, which is 400 times as expensive, is no better than drug A. And that's the sort of trial that I've been doing in prostatic cancer. Or you are trying to prove that there is some benefit, which is the sort of trial that they were doing here, but the end point of the initial study was the first recurrence to occur after the end of the period of study. And the whole of the analysis of the first study was centred round the question: "does it affect the recurrence rate?" So these chaps were perfectly entitled to give Adriamycin® or anything else they wanted, because in 1975, we had not realized that we would want to keep these people under continuing surveillance. We'd raised the matter and we had been told by the statisticians that this would be quite impracticable.

Wickham: So during the control period you were cystodiathermizing all these people?

Smith: Yes, and in Yorkshire we got our control group and gave them thiotepa rather automatically, and they never got anything else, and the same with the ones on VM26. We'd all had very strong feelings on this, though we hadn't discussed it. We had all, by chance, done the same thing. We had not given them anything else.

Hussien: And they'd done worse?

Smith: The ones with chemotherapy had done very much better. But it wasn't statistically significant.

Tellaloğlu: We have been using thiotepa for nearly 20 years now, after an article came out about it in a urology journal in the beginning of the sixties. I'm sorry to say we didn't put it on a scientific basis; but from the clinical experience, I can say that recurrences have been quite satisfactorily controlled by it. We have followed up cases for eighteen years which prior to the initiation of this particular treatment, had shown recurrences every three months on cystoscopy.

Smith: Have you treated them for 18 years with thiotepa? Or how long have you treated them?

Tellaloğlu: No, for about two years. The patient comes weekly for the first four weeks and is given 60 mg. After that he comes at 3 monthly intervals for cystoscopy and at that time he is given 30 mg.

Erözenci: Mr. Smith have you had any experience of immunotherapy with BCG?

Smith: No, I don't have any personal experience. Some papers strongly suggest that this is also of potential benefit, but we did one study in Yorkshire where two of the patients got symptoms of what we call BCG'osis and had to have antituberculose chemotherapy. But it does offer some benefit.

Tellaloğlu: I must say we've found thiotepa more effective than Epodyl.

Chisholm: Can I comment on that BCG thing? Recently, a colleague visiting Edinburgh was amused at our discussions on intravesical chemotherapy, and he said that the goal standard. the basis of comparison, should be intravesical BCG. However, he agreed that there seems to be something odd about the different results from different centers, and suggested that it's the particular BCG strain that makes the difference. They use BCG Pasteur; I don't know what you use.

Smith: Oh, over that we've had big arguments. The whole continent uses Pasteur BCG. We use Glaxo BCG, and it has been recognized as being much less effective.

Chisholm: Yes. Well at any rate, that's the comment from one center, that believes that the value of BCG exceeds any of these other chemotherapeutic agents.

Smith: Intravesically alone?

Chisholm: Yes.

Erözenci: One report favors intravesically and intradermally.

Kırkalı: What do people feel about excavating the whole bladder wall, doing a radical TUR?

Smith: This has been done in association with a high dose of methotrexate. In one such study 75% of the patients were alive at 2 years. But when you're doing something like this, one has to take into account the difference between T3A and T3B and the patients, and in this study they were mostly T3A. One would expect a much better result then, than with a large number of people with an obviously palpable tumor.

Sade: How reliable is cytology for such patients?

Smith: Cytology is not invariably reliable, but it has its uses. If we have patients with superficial tumors we just see them once a year and do a cytology. Incidentally, we have a regional cytology service but it's not available to everybody.

Wickham: About the trial you described. There was a follow-up on deaths; you say. Was there also a follow-up on tumor recurrence?

Smith: The information I gave you was a follow-up which related to death from bladder cancer. The findings were unexpected and so we wanted to publish it.

Wickham: I wouldn't think it is statistically significant is it?

Smith: No it isn't. But it was just that we wanted to draw people's attention to the fact that it was important, if you were doing something like that, to follow it up and see what happened over a long period of time.

Wickham: It's the same with stones. I don't think it's particularly meaningful to look at anything in the way of stones or tumors for a period of less than 10 years.

Smith: I would agree with you.

Akdaş: We have patients who have recurrences in the urethra. TI bladder-tumor recurrence in the urethra. What is your approach to this particular group of patients? The bladder is clear, but in the urethra we have the TI, GI transitional cell bladder tumor.

Smith: Well, I have never seen that.

Wickham: I'd treat them with a little gentle cystodiathermy, taking care not to go right through the mucosa.

Akdaş: But recurrence continued. So I wonder whether we should give something in the way of chemotherapy.

Chisholm: You really can't give chemotherapy.

Smith: Someone was telling me quite recently that the thing to do was intravesical chemotherapy, not with a catheter but with a syringe and you squeezed it up the urethra. That was the way to control any problem within the lower urinary tract, he said.

Wickham: Not very satisfactory. I've got one chap, I've done a number of times with just a little cystodiathermy.

Türkyılmaz: While doing a TUR prostate, what would you do if you came upon a bladder tumor?

Smith: See to it at the same time.

Türkyılmaz: How about recurrences?

Smith: Well, I haven't run into any trouble. If I'm doing a prostate and I find a bladder tumor, I do the bladder tumor first, if I can get at it, and then I do the prostate.

Tellaloğlu: Which is sometimes very difficult if you've got a big prostate.

Smith: Well, sometimes you've got to take middle lobe, or take most of the prostate and then do the bladder tumor. Do you do them both together?

Wickham: Yes.

Chisholm: I always have.

Türkyılmaz: I usually do them at the same time, too. My practice is, before I remove the catheter, to put a high dose of thiotepa inside the bladder; then I remove the catheter, make the patient turn around and then ask him to void.

Şimşek: May I ask a question at this point? Doesn't it maximize the risk of intoxication since you are resecting a huge area?

Türkyılmaz: Nothing has ever happened to my patients.

Smith: How much thiotepa do you use?

Türkyılmaz: 120 mg.

Smith: Do you check the white count at all ten days later?

Türkyılmaz: I see these patients again after two weeks. I rarely come up against toxic effects.

Vatandaşlar: Mr. Smith, what are your views on intraarterial chemotherapy for the patient with an invasive tumor?

Smith: Well, I have no experience of it myself, but people working on it have been able to show a significant decrease in size of tumor; I don't know that it produces cure.

Wickham: Would you like to comment on implantation radiotherapy?

Smith: We used to use it at Leeds, but I haven't used it for years. Do you still use it?

Wickham: No, I don't. I don't treat bladder carcinoma. At St Peter's they did a back check on bladder carcinomas treated over a period of about twenty years, by ten different surgeons each using their favorite techniques such as radium needles or gold grains. The results were pretty much the same whatever the variety of treatment used, and a survival of five to ten years was more or less standard.

Smith: Would you accept that as an argument against cystectomy?

Wickham: Yes, I would. One ought to draw a graph of surgeon's age against cystectomy rate. I think you'll find that it'll drop fairly sharply.

Chisholm: Can I comment on this? There have been two or three very aggressively phrased papers in the last two or three years from North America, stating that a proper radical cystectomy, achieves far better results than any of these other combinations of radiotherapy and so forth and the figures that are being put around, are

50% in five years. All I would say is, that when you look at those reports you have to be very careful in interpreting them because they come from referral centers where the patients are very carefully selected all the way along; to start with, only certain patients get to certain cancer centers. The operations are being done by good surgeons, and further the advances in surgery and anesthesia over the last 25 years, really mean that surgery is now a good choice. But I still want to say that these are such selected patients that they do not represent the biological range that you have in any group of patients in a normal hospital.