# INTRAVESICAL CHEMOTHERAPY FOR SUPERFICIAL CARCINOMA OF THE BLADDER

K T Foo, E C Tan, K H Tung, E P C Tock

*ABSTRACT*

***Intravesical chemotherapy has been shown to be of value in the treatment of superficial transitional cell carcinoma of the bladder, not only in the prevention of recurrence but possibly progression of the disease to higher stage as well.***

***At the Department of Surgery, National University of Singapore from 1980 to 1986 we had used intravesical chemotherapy for multiple or recurrent superficial carcinoma of bladder in 45 patients. Of these, 21 patients had associated carcinoma in situ.***

***Initially, thiotepa was used as the main intravesical chemotherapeutic agent. Since 1984, mitomycin C was introduced. The schedule used is 30 mg in 30 ml of water, and left in the bladder for 2 hours weekly for 4 weeks. Intermittent courses were given when deemed necessary on follow -up cystoscopy at 3 to 6 months. Patients were deemed to have good response if there was no evidence of tumour on cytology and biopsy at follow-up cystoscopy.***

***Eleven patients had thiotepa only, of these 4 had good response, 4 were stable and 3 had progression of disease to higher stage. Thirty-four patients had mitomycin therapy. Thirteen of them following thiotepa treatment. Twenty-one patients (64%) had good response to therapy. Three patients (9%) had progression of disease, requiring cystectomy.***

***Of those who responded to therapy, none had developed muscle invasive disease so far with mean follow -up of 43 months. Of the group of patients treated with mitomycin, no patient developed myelosuppresion. Two patients had generalised rashes, 1 had severe calcified concretions in the bladder and 1 developed reduction in bladder capacity.***

***Seventy-four percent of patients with carcinoma in situ showed good response to intravesical mitomycin therapy. Patients with multiple or recurrent superficial tumours did not respond as well, the rate being 50%.***

*Keywords : Carcinoma bladder, superficial, mitomycin C, intravesical*

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## INTRODUCTION

Intravesical chemotherapy has been shown to be of value not only in the treatment of superficial transitional cell carcinoma of the bladder[1,2] but possibly in preventing progression of the disease to higher stage as well[3]. The drug of choice and the exact schedule use for this modality of treatment had not been fully agreed upon. The aim of this paper is to review our results and to work out a schedule of intravesical chemotherapy, best suited to our local population in Singapore.

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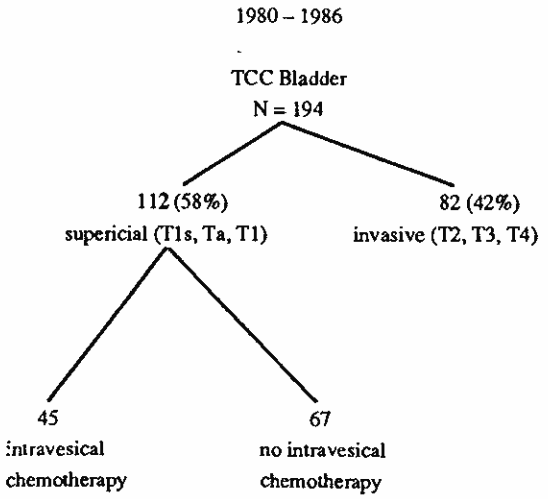
## MATERIAL AND METHOD

Over a 7-year-period from 1980 to 1986, 194 patients with transitional cell carcinoma of the urinary bladder were diagnosed histologically. Of these 112 (58%) were staged as superficial carcinoma ($T_a$,$T_1$,$T_{is}$) while 82 (42%) were found to have muscle invasive disease ($T_2$ - $_4$ ). Forty-five patients with superficial disease who had associated carcinoma in situ or multiple or recurrent disease were treated with intravesical chemotherapy. This formed about 40% of our patients with superficial disease. The other 60% of patients with superficial carcinoma was treated with transurethral resection only. (See Fig 1)

**Fig 1 – Staging of TCC Bladder**
**University Dept of Surgery, SGH**




Initially, thiotepa was used for intravesical chemotherapy. This was gradually changed to mitomycin C in 1984 as this

drug became more easily available. The schedule used was 30 mg of either thiotepa or mitomycin weekly for 4 weeks. This was instilled into the bladder for 2 hours. Follow-up cystocopy is done at 3 months after the course of intravesical chemotherapy and thereafter at 3 to 6 months interval. Repeat courses were given if there was recurrent disease not controlled by transurethral resection. Cystectomy or Deep X-ray therapy was advised for patients with progressive disease invading the muscle layer.

Forty-five patients were treated. There were 35 males and 10 females and their age ranged from 29 to 84 years with a mean of 60.5 years. The majority was in 50 to 69 years age group. Twenty-one of the 45 patients had superficial bladder tumours associated with carcinoma in situ.

Patients were deemed to have good response if there is no evidence of recurrent disease on cytology and bladder biopsy at follow-up cystoscopy after the first or second course of intravesical chemotherapy.

## RESULTS

To assess results of treatment, patients were divided into 2 groups, according to the drugs used.

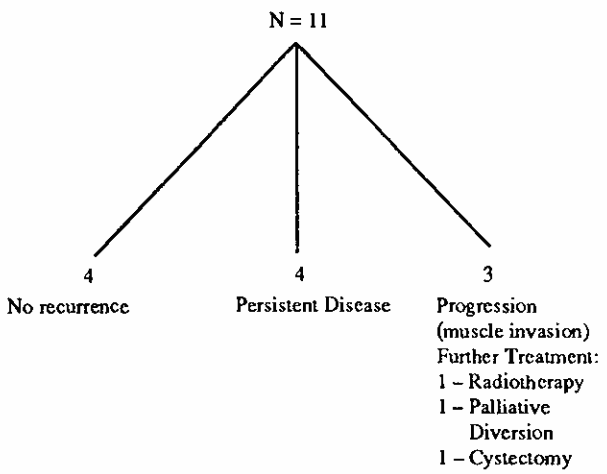
1. 11 patients had thiotepa only.
2. 34 patients received thiotepa and mitomycin or mitomycin only.

### Thiotepa Group (See Fig 2)

Thiotepa only, was used early in the series from 1980 to 1984. Follow-up had not been ideal as our urological services had not been properly organised then. Of the 11 patients, 9 had multiple or recurrent superficial tumours while 2 had associated carcinoma in situ.

Four patients showed no recurrent tumours at initial evaluation but 2 subsequently recurred which was controlled with transurethral resection. One of these 2 patients died of unrelated cause 2 years later. Four patients showed persistent tumour recurrences and one responded after a repeat course of thiotepa. Three patients developed progression of the disease to muscle invasion. All these 3 patients responded to thiotepa initially but were not followed up regularly. One patient had DXT and is still being followed up. The other 2 patients with associated carcinoma in situ developed invasive disease 2 and 6 years later, one had palliative urinary diversion only because disease was too advanced. The other patient had total cystectomy and urethrectomy, but died of metabolic complication and bronchopneumonia a month after surgery.

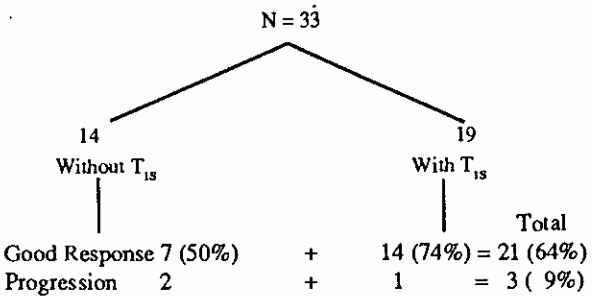
**Fig 2 - Intravesical Thiotepa for Superficial Bladder Carcinoma**




### Mitomycin C therapy (See Fig 3)

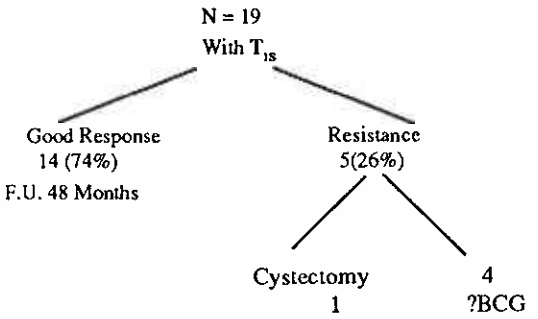
Thirty-four patients received mitomycin C therapy. One was lost to follow-up and not available for evaluation. Of the 33 patients, 13 had previous intravesical thiotepa. Seven of these were thiotepa failures and 4 responded to mitomycin C.

**Fig 3 - Intravesical Mitomycin C for Superficial TCC Bladder**



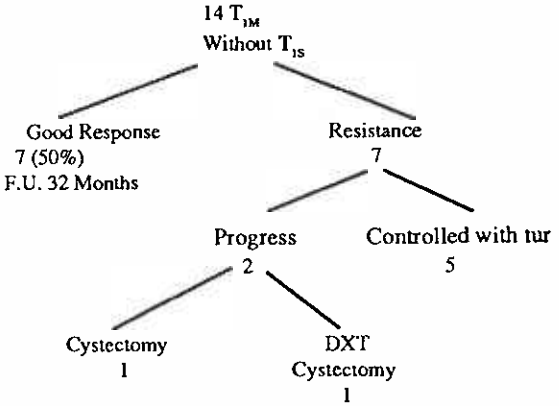

There were 19 patients with carcinoma in situ treated with mitomycin C (See Fig 4). Fourteen (74%) showed good response to treatment with a follow-up of 48 months. Good response is defined as no evidence of tumour on cytology and bladder biopsy at time of follow-up cystoscopy 3-6 months after treatment. Five (26%) showed poor response and one patient had a total cystectomy because of involvement of the ureteric orifice. The 4 patients who do not respond well to mitomycin C and continue to have superficial disease may be good candidates for intravesical BCG therapy[6].

**Fig 4 - Intravesical Mitomycin C for Superficial TCC Bladder**




Fourteen patients had no evidence of associated carcinoma in situ (See Fig 5). Of these 7(50%) showed good response with a mean follow-up of 32 months. Five had recurrences which were controlled with transurethral resection, while 2 patients had progression of disease on evaluation at 3 months. One had papillomatosis grade 2 disease and total cystectomy was done. She died of metastatic disease a year later. The other patient had rapidly progressive disease. Radical radiotherapy was given with no response and total cystectomy was done, and he subsequently died also within a year.

**Fig 5 - Intravesical Mitomycin C for Superficial TCC Bladder**



**Complications**

FBC was done before and after completion of an intermittent course of mitomycin therapy. No myelosuppression was found. Two patients developed generalised rashes and the couse of mitomycin had to be terminated. One patient developed severe calcified concretions on the resected areas and these were passed out as 'stones' and caused difficulty in micturition. One patient who had DXT previously for multiple tumours, developed further bladder contracture after the course of mitomycin. His bladder capacity was 150 ml 4 years after DXT and this was reduced to 50 ml after 2 courses of mitomycin a year later.

## DISCUSSION

The main objective of intravesical chemotherapy for superficial bladder carcinoma is to prevent the progression of disease, without having to resort to cystectomy.

In this series, intravesical chemotherapy was given only to patients with multiple or recurrent superficial tumours and those patients with associated carcinoma in situ. These are patients who are in the high risk group of developing muscle invasive disease. They form about 40% of our patients with superficial bladder carcinoma. The other 60% can probably be controlled with transurethral resection alone.

Short intermittent courses of intravesical chemotherapy is used and this will probably help to determine further management of this disease. If there is progression of disease a more radical form of treatment such as cystectomy or radiotherapy is indicated as in 2 of our patients. If there is no response, a second course of intravesical chemotherapy could be given. Two of our 8 patients with carcinoma in situ treated with mitomycin responded after the second course of treatment.

If there is no response after the second course, another intravesical chemotherapeutic agent should be used if indicated. Four of 7 patients who failed to respond to thiotepa treatment, responded to mitomycin C therapy. This has also been reported by other authors[4].

For those patients who responded well to the intravesical agent but recurred at regular intervals, they would probably benefit from regular maintenance therapy.

In patients with carcinoma in situ, urine cytology is useful in monitoring and serves as a guide as to the timing of follow-up cystoscopies and the need for another course of intravesical chemotherapy.

Comparative studies had been made as to the effectiveness of thiotepa and mitomycin C, and no significant difference had been found by Zincke et al at Mayo Clinic[5].

At present, in Singapore, mitomycin C is more readily available and it is our first drug of choice for intravesical treatment of multiple, recurrent superficial bladder carcinoma or carcinoma in situ. In this series it is 74% effective in the treatment of carcinoma in situ and 50% showed good response in the prevention of recurrent superficial tumours.

For those patients who do not respond and there is no evidence of progression of disease, intravesical BCG can be used. BCG vaccines had been shown to be effective for treatment of carcinoma in situ of the bladder as well as the multiple and or recurrent superficial disease [6,7].

Thus far, it is significant that none of the patients with carcinoma in situ who responded to treatment, had developed muscle invasive disease with a follow-up of 48 months. Intermittent courses of mitomycin C probably has a role in its prevention, though our follow-up of patients is still not been long enough to come to a definite conclusion.

With the availability of intravesical chemotherapy, the need for total cystectomy has probably been reduced to give patients a better quality of life. However, one needs to be vigilant in our follow-up of patients and advise early cystectomy if the disease is deemed to progress so as to achieve better survival.

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