

Role of Mitomycin C as an Adjuvant to Endoscopic Resection of Superficial Bladder Tumours

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An experience in 171 cases of superficial urinary bladder tumors treated with transurethral resection (TUR) at the Mayo Hospital Lahore between 1985 to 1990 is reported. In 160 cases out of 171, the tumors were resected endoscopically followed by intravesical instillation of Mitomycin-C 20mg. This resulted in significant reduction in the number of recurrences. In the remaining 11 cases, the tumors were too numerous for endoscopic resection. In these cases the intravesical Mitomycin-C 20mg twice weekly for 4 weeks resulted in marked improvement and the tumors were either rendered resectable or disappeared completely.

Key words: Mitomycin-C, superficial bladder tumors

Treatment of superficial bladder tumors with chemotherapeutic and immunotherapeutic agents has evolved successfully over the last 3-4 decades. The primary treatment starts with TUR (transurethral resection of the tumor) after which 60-70% will recur¹. In 10-20% of cases, superficial tumors progress to muscle invasion or metastatic disease². Therefore early diagnosis and treatment of tumors likely to recur, with minimum number of follow-up cystoscopies causing less inconvenience and anxiety to the patient is the goal of management of superficial bladder tumors.

It has been shown in a number of studies that chemotherapeutic agents can be used as an adjunct to transurethral resection^{3,4}. This study highlights the role of intravesical Mitomycin-C as an adjunct to the transurethral resection of bladder tumors (TUR).

Patients and Methods

Between January 1985 to December, 1990, 171 cases of superficial urinary bladder tumors were treated in the Second Surgical Unit of Mayo Hospital, Lahore.

Patients presenting with urinary symptoms were thoroughly examined. A detailed history was taken and a thorough physical examination including per rectal examination was carried out in all patients.

The upper urinary tract was investigated by performing intravenous urography (IVU) in almost all patients and /or plain abdominal radiography combined with ultrasonography. Urinary cytology was also done in selected patients.

All patients underwent cystoscopy and the site, size, number of fronds and resectability of the tumors were noted. The specimens were subjected to histological examination and tumor was properly graded. Tumors beyond T₂ on histological examination were excluded from the study.

After confirmation of diagnosis Mitomycin-C 20mg was instilled intravesically either before resection of tumor or after resection. In 160 cases out of 171, the tumor was resected first and then intravesical Mitomycin-C 20mg was instilled. First check cystoscopy was carried out at 6 weeks interval. If no recurrence was found, 20mg

Mitomycin-C was instilled & catheter clamped for 2 hours or for a maximum time, the patient could tolerate it. Then the bladder was washed and catheter removed.

If there was recurrence at the first follow up cystoscopy, the tumor was resected and patient advised to come back in 6 weeks time. Subsequent check cystoscopies were done at three monthly intervals for 1 year and then six-monthly intervals for another year and finally yearly

Results

A total number of 171 cases of superficial bladder tumors were included in this study. Their ages ranged between 24 years and 90 years with an average of 55 years. Male to female ratio was 4:1 (137 males versus 34 females). Patients presented with various symptoms listed in table-1.

Table-1

Presentation	
1.	Majority presented after catheterisation
2.	Average duration of symptoms 2 years.
3.	Nocturnal frequency.
4.	Inability to interrupt stream.
5.	Poor stream.
6.	Hesitancy.
7.	Painless haematuria.
8.	Retention or retention with overflow.

On first cystoscopy, 11 patients (6.4%) were diagnosed to have irresectable tumors (having numerous fronds). In these patients Mitomycin-C 20 mg was instilled intravesically twice weekly for 4 weeks. These patients were then rescoped. Six out of these 11 patients (54.5%) had complete disappearance of tumor. In 3 cases (27%) majority of the tumors had disappeared leaving only one or two fronds which were resected.

One patient (9%) had moderate response and had to undergo another 4 weeks instillation of Mitomycin-C 20 mg twice weekly. Good response was seen at 8 weeks cystoscopy in this patient.

Another patient (9%) did not respond at all and the dose of Mitomycin-C was increased to 40mg twice. But this patient started to bleed profusely and the treatment

Role of Mitomycin

was abandoned. This patient was offered total cystectomy but the patient refused and was lost to follow-up.

In the remaining 160 patients (93.6%), the bladder tumors were resectable at first cystoscopy. Various sites of tumor presentation, are shown in Fig:1 & Table 2. Check cystoscopy was carried out at 6 weeks. None of these patients had any recurrence as shown in Table-3

After cystoscopy all cases were treated with Mitomycin-C 20mg intravesically for 2 hours. At 3 months, only one group of patients (7 patients) having tumours at the fundus of bladder did not have recurrence. Others had recurrences as shown in Table 3. However at the second three monthly cystoscopy the rate of recurrence was reduced considerably as shown in Table. 3

Only a few cases presented with recurrence at the 6 monthly cystoscopies after that this clearly indicates reduction in the rate of recurrence of these tumors.

Out of 160 patients, 79(49%) came regularly for follow up for 2 years. 36 of these are still alive and well without any symptom for the last 5 years. Out of 79, 16 patients developed prostatic symptoms and had their TURP carried out successfully.

Table 2

Tumour Site		No. of cases	%age
Single Frond	Ruo	55	32.2
	Luo	45	26.4
Bilateral	UO	11	6.4
	-	7	4.1
Fundus		12	7.1
Anterior	BN	11	6.4
Multiple	-	30	17.4
Base	-	171	100
Total			

Discussion

A variety of topical agents have been used for the treatment of superficial bladder cancers. These are of two types.

1. Chemotherapeutic agents

Thiotepa, Mitomycin-C Doxorubicine (Adriamycin) & Epirubicin^{3,4}.

2. Immunotherapeutic agents.

BCG(Bacillus calmette guerin^{5,6,7}).

Interferon⁸

Keyhole limpet haemocyanin

Among chemotherapeutic agents, Mitomycin-C & Doxorubicin & epirubicin have least chances of systemic toxicity which is directly related to the molecular weight. The greater the molecular weight, the less likely it is to be absorbed and the less the risk of systemic toxicity. Haematological side effects like leucopenia and thrombocytopenia are less commonly seen with Mitomycin-C (Mol-wt-329) as compared to thiotepa (Mol.wt. 189)^{9,10,11,12}

As seen in our study, two prognostic factors have been delineated¹³:

- Whether the tumor is solitary or multifocal
- Whether there was any recurrence at the first follow-up cystoscopy at 3 months.

We found 160/171 patients with solitary or resectable tumors. These were the patients who had a relatively long disease free interval as shown by the recurrence rates at first 3 months cystoscopy.

The dose of Mitomycin-C used in other studies^{3,4,9,10,12,14} was 30mg as a single instillation immediately after TURT which decreased the rate of recurrence by upto 80% in low risk patients.

Tolley et al¹⁴ compared TURT alone with TURT combined with post operative Mitomycin-C and further instillation at each 3 monthly follow-up visits during the first year.

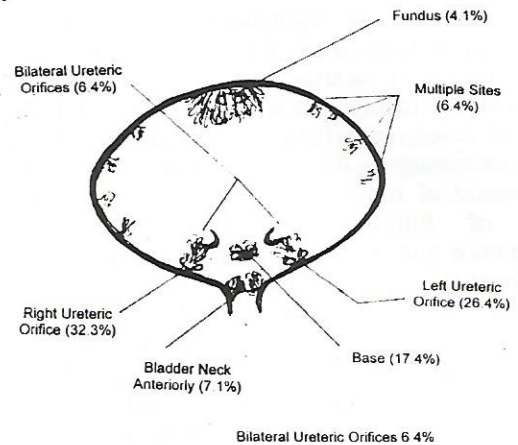


Fig. 1. Various sites of superficial bladder tumours at presentation

The dose of Mitomycin-C used in our study was 20 mg single dose post TURT instillation. In patients with irresectable tumors, Mitomycin-C 20mg twice weekly for 4 weeks was given and then the tumor was resected. Mitomycin-C 20mg single instillation was carried out at each follow-up cystoscopy every 3 months. In our patients with recurrence in our study, patients with fundal tumors showed good response (Table-3)

In patients with single frond, 18% showed recurrence at 6 weeks follow-up cystoscopies whereas in those with bilateral fronds, 27% showed recurrence at 1 year follow-up. The recurrence rate in our study fell to 0.04% at the end of first year and further reduced to 0.02% at the end of 2nd year.

Mitomycin-C as compared to BCG immunotherapy has less systemic side effects^{15,16}

We can safely conclude that Mitomycin-C has proved to be a useful adjuvant to TURT in patients with superficial bladder tumors.

Table 3

	6/52		3/12		3/12		3/12		6/12		6/12		12/12
	No.	%age	No.	%age	No.	%age	No.	%age	No.	%age	No.	%age	No.
Single Frond													
Right R.U.	Nil	10/55	18.18	2/55	3.63	5/55	9.9	1/45	2.22	-	-	-	-
Left R.U.		6/45	13.33	1/45	2.22	7/45	15.55						
Bil. Frond	Nil	2/11	18.18	Nil		3/11	27.27%	-	-	-	-	-	-
Ant. BN	Nil	2/12	16.66	Nil	Nil	Nil	Nil	Nil	Nil	1/12	8.33		
Base	Nil	4/30	13.33	2/30	6.66	1/30	3.33%	-	-	2/30	6.66%		
Fundus	Nil	Nil		1/7	14.20	Nil	-	-	-	-	-		

References

- Greene LF, Hanash KA, Farrow GM: Benign papilloma or papillary cancer of the bladder. *J Urol* 1973; 110: 205-207.
- Lutzeyer W, Rubben H, Dahm H: Prognostic parameter of superficial bladder cancer: an analysis of 315 cases. *J Urol*, 1982; 127: 250-252.
- Lum BL, Torti FM: Adjuvant intravesical pharmacotherapy for superficial bladder cancer. *J Natl Cancer* 1991; 83: 683-695.
- Franklin J, Benson MC: New techniques in management and treatment of superficial in management and treatment of superficial bladder cancer. In: Neal DE ed. *Tumors in Urology*, Springer Verlag, London, 1994; ;. 65-75.
- Morales A, Epidinger D, Bruce AW: Intracavitary bacillus calmette genurin in the treatment of superficial bladder tumours. *J Urol* 1976; 116: 180-183.
- Herr HW: Progression of stage T₁ bladder tumours after intravesical bacillus. Calmette Guerin. *J. Urol* 1991; 145: 40-44.
- H Roudy, G.H. Muir et al: The role of immunotherapy for urological tumours. *B.J. of Urol* 1997; 79: 307-316.
- William Den Otter, Z Dobrowski et al: Intravesical interleukin T₁ papillary bladder carcinoma: Regression of marker lesion in 8 our of 10 patients. *J Urol* 1998; 159: 1183-1186.
- Mishina T, H Walanabo et al: Prophylactic use of mitomycin C bladder instillation for preventing recurrence of bladder tumours. 19th international congress of Society Internationale d'Urologic, San Francisco 1982; abs. 169: 27.
- Danis L, Keuppens F et al: Mitomycin therapy in superficial bladder cancer. *Prog Clin Biol Res.* 1985; ;185: 113-122.
- Pavone M, Macaluso M et al: Intravesical adriamycin. *Prog. Clin Biol Res.* 1985; 185B: 123-133.
- Keel Fx Jr et al: Adjuvant mitomycin C following endoscopic treatment of upper tract transitional cell carcinoma. *J. Urol* 1997; 158(6): 2074-7.
- Parmar MKB, Freedman LS et al: Prognostic factors for recurrence and follow up policies in the treatment of superficial bladder cancer. *J. Urol* 1989; 142: 284-288.
- Tolley DA, Hargreave TB et al: Effect of intravesical mitomycin C on recurrence of newly diagnosed superficial bladder cancer. Interim Report from the MRC Subgroup on supervicial bladder cancer. (Urological Cancer working Party) *BMJ*, 1988; 296: 1759-1761.
- Debruyne F, Vonder Meyder A et al: BCG RIVM intravesical immunoprophylaxis for superficial bladder cancer. Progress and controversies in oncological urology II, EORTC Monograph. V. Alan R Liss, New York. 1988, p.511.
- Lamm DL et al: Incidence and treatment of complications of bacillus calmette guerin intravesical therapy in superficial bladder cancer. *J. Urol.* 1992a. 147: 596-200.