



## Recurrence rate of superficial bladder cancer with intravesical BCG and mitomycin.

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**ABSTRACT... Objective:** To compare the recurrence rate of superficial transitional cell carcinoma of urinary bladder using intravesical BCG and Mitomycin-C. **Study Design:** Randomized Controlled Trial. **Setting:** Urology Department, Teaching DHQ Hospital, Gujranwala. **Period:** November 2018, to Sep, 2019. **Material & Methods:** Was carried out on total 270 patients, admitted with suspicion of urothelial tumors. They were grouped in Group A and B, comprising 135 in each group. Group A received BCG and Group B received Mitomycin-C intravesically following TUR-BT. **Results:** Out of 270 patients male to female ratio was 3:1. Age range of patients was between 30 to 70 years with mean of  $50.0 \pm 13.1$  and  $55.2.3 \pm 12.9$  years in Group A and B respectively. Recurrence was noted in 05.38% and 15.38% patients in Group A and B respectively. Regarding side effects pyrexia was associated with BCG in 27.40% patients which were self-limited in 26.66% cases however required anti-tuberculosis therapy for six months in 0.74%. Whereas only 06.67% patients receiving Mitomycin had pyrexia. Dysuria occurred in 74% and frequency in 68% patients who received BCG. Whereas Dysuria occurred in 20% and frequency in 36.29% patients who received Mitomycin-C. However genital skin rash was more common (08.14%) in Mitomycin group than BCG. **Conclusion:** Keeping in mind less recurrence rate and bearable toxicity, it is concluded that BCG is superior to Mitomycin. This study suggests long term follow up is required to establish recurrence in the management of superficial bladder cancer.

**Key words:** Intravesical BCG, Mitomycin-C, Superficial Transitional Cell Carcinoma of Urinary Bladder.

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## INTRODUCTION

In the world, bladder cancer is the second commonest occurring urological growth. Several patients of bladder tumor present with superficial transitional cell carcinoma.<sup>1</sup> The patients with bladder cancer are diagnosed mostly in the age of 65 years and at the moment of diagnosis about 75% of bladder tumors are localized and 25% of patients have presentation with regional lymph nodes involvement or distant metastasis. Approximately 90% are transitional cell carcinoma, adenocarcinoma <2% (may be preceded by cystitis) and squamous cell carcinoma constitutes 5-10%.<sup>2</sup>

The problem in superficial bladder tumor is its trend to reappear, about 50 to 80%, following

surgical ablation alone. Superficial bladder tumor may progress to muscle of urinary bladder in 20 to 25% cases<sup>3</sup> and recurrence rate remains high in the first year after transurethral resection of bladder tumor (TUR).<sup>4</sup> Superficial bladder tumor after transurethral resection (TUR) is known to reappear repeatedly, even in patient who receives intravesical instillation of chemotherapy or immunotherapy. If superficial bladder cancer left untreated after TUR, it will recur within 03 years in 70 % of cases.<sup>5</sup>

The high recurrence rate in non-muscle invasive bladder tumor (>70%) is caused by the bond of free floating cancer cells during transurethral resection, by partial resections, by unnoticed and new tumors. Regular follow-ups and resections

are required.<sup>6</sup> Superficial bladder tumor is usually managed by transurethral resection along with adjuvant intravesical instillations of chemotherapy or immunotherapy. Adjuvant instillation therapy with chemo or immunotherapeutic agents is an essential element in the management of patient with superficial bladder tumor.<sup>7</sup>

Different chemotherapeutic drugs are available for intravesical instillation; one of them is Mitomycin-C, which is antibiotic alkylating agent. It reduces recurrence and prevents tumor cell implantation on the site of resection and eliminates any residual disease.<sup>8</sup> After TURBT, a single immediate intravesical instillation of chemotherapy is helpful in reducing recurrence rates as much as 4.5% at one year as compared to 38.1% in patients with TUR-BT alone.<sup>9</sup> Efficacy of mitomycin-C is optimum within 6 hours of resection. The usual optimal contact time of the drug is one hour.<sup>8,10</sup>

Another possibility is the use of intravesical bacillus Calmette Guerin BCG instillation which is considered to be the most useful therapy and prophylaxis for transitional cell carcinoma Ta, T1, and CIS and reduces tumors recurrences, disease progression and mortality. At the beginning of 20<sup>th</sup> century, tuberculosis was noted to have anti-tumors effect. Pearl performed a series of autopsy at John Hopkins Hospital in 1929 and published a lesser incidence rate of cancer in patients with tuberculosis. Novard isolated Mycobacterium Bovis from a cow with tuberculous mastitis in 1904. During the passage through laboratory the Mycobacterium culture showed strong affinity to cluster.<sup>11</sup>

## OBJECTIVE

To compare the recurrence rate in superficial transitional cell carcinoma of urinary bladder using intravesical instillation of BCG and Mitomycin-C.

## MATERIAL & METHODS

This randomized trial was carried out on total 270 patients, admitted with suspicion of urothelial tumors. They were grouped in Group A and B, comprising 135 in each group. Group A received BCG and Group B received Mitomycin-C

intravesically following TUR-BT.

Recurrence was defined as reappearance of tumor (confirmed on check cystoscopy and histopathology of biopsy). The inclusion criteria was; all patients of any age, both gender with superficial bladder tumor Ta (noninvasive papillary carcinoma and T1 (tumor invades sub epithelial connective tissue the lamina propria), Low grade superficial bladder carcinoma and Biopsy confirmed recurrent superficial bladder tumor. Exclusion criteria was; patients with active tuberculosis, Immunocompromised patients (known impaired immune response, positive HIV serology, patients getting steroids/ immunosuppressive therapy, leukocytes count <3500/mm<sup>3</sup>, Patients not willing for intravesical therapy and Patients with positive mantoux negative test.

The patients were clinically evaluated with respect to history, physical examination, cytology, ultrasonography, and intravenous urography. We did trans-urethral resection of bladder tumor (TUR-BT) and deep biopsy was preserved in formalin in separate containers, marked them and sent for histopathology. Diagnosis was confirmed with histopathology. Tumours were graded according to the WHO classification system TNM. The patients age ranged from 30-70 years, regardless of sex with superficial bladder tumour Ta (non-invasive papillary carcinoma and T1 (Tumour invades sub-epithelial connective tissue the lamina propria), Low grade superficial bladder carcinoma, biopsy confirmed recurrent superficial bladder tumour were included in the study.

Patients after staging and grading the tumor and fulfilling the inclusion criteria were randomly allocated into two groups (Group A & B) by using Open Epi-version software. Group-A was comprised 135 patients randomly allocated for intravesical Onco Tice BCG and advised the patients to come without drinking water from last 6 hours. I put the face mask and wore the hand disposable gloves. Before instillation urinary bladder emptied, BCG 50 mg, (OnCo-Tice), diluted with 50 ml of saline in bladder wash

syringe.

Group-B was comprised 135 patients randomly allocated for intravesical Mitomycin-C 40mg. Patients were advised to come without drinking water 6 hours before instillation and explained the procedure and its side effects to patients. I put the face mask and wore the hand disposable gloves. Mitomycin C 40 mg, mixed with 50 ml of sterile water in bladder wash syringe.

Cleaned glans penis and OnCo-Tice BCG was administered intravesically after passage per urethral nelton catheter No.14 Fr and patient was instructed to hold the urine for two hours in different positions (supine, prone, right and left lateral). After two hours, according to advice patients emptied bladder in wash room and washed the perineal area also. During Intravesical therapy was given weekly for six consecutive weeks.

Patients came for check cystoscopy every 3 month for 1 year. They were advised to come earlier if they suffered from haematuria, lower urinary tract symptoms or fever. TUR-BT biopsy was carried out if necessary. Recurrence was defined as histological proven recurrence. Side effects were recorded based on patient's complaint, physical examination, mantoux test, blood and urine analysis. OnCo-Tice BCG instillations were stopped in patients with BCG sepsis and anti-tuberculous treatments were started for six months. The patients were followed for one year for recurrence and side effects. The patients were advised to follow up for cystoscopy every 3 months for a period of 2 years, every 4 months in the third year, and every 6 months thereafter until 5 years, and yearly thereafter.

## RESULTS

The study is divided into two groups, Group A and Group B. Each group comprised 135 patients. The mean age of patients in group-A and group-B was  $50.0 \pm 13.1$  years and  $52.3 \pm 12.9$  years respectively. There were 100(74%) male and 35(26%) female patients in Group-A, while 102(75%) male and 33 (25%) female patients in Group-B. The number of patients involved in different professions showing

that maximum numbers of patients are factory workers 60(22.2%). In the history of smoking, it was found that smoker male patients were 79 and 70 in both groups A and Group B respectively, while less percentage of female were smoker in both groups.

Painless haematuria was seen in 247 patients and clot retention was observed in 152 patients. 20 patients were presented with the symptoms of urgency and dysuria. Only 3 patients were presented with microscopic haematuria. On cystoscopy, most common site of growth was right lateral wall, 130(48.14%) patients had tumour on this site. Only in six patients tumor was positioned on Vault. Twenty seven patients presented with multiple tumor on right lateral wall, left lateral wall, posterior wall and bladder neck.

Cystoscopy helped in the size of tumour. One hundred patients showed less than 1 cm size of tumour. One to two cm size of growth found in one hundred and twenty nine patients. Only 30.36% patients showed two to three cm growth on cystoscopy. In group A, the cystoscopic findings during TUR-BT revealed that 87(64.44%) of patients has single tumour and 48(35.55%) has multiple tumours while in Group B, patients with single tumour are 81(60%) and with multiple 54 (40%) respectively. Regarding the Tumor appearance on cystoscopy it was 121(89.62%) papillary and 14(10.38%) solid appearing tumors in Group A and 108(80%) papillary and 27(20%) solid appearing tumours in Group B.

On histopathology some tumors turned out to be low grade i.e. 81(60%) after first presentation and 54(40%) low grade with recurrence in Group-A, while in Group-B, 73(54.07%) were low grade tumors on first presentation and 62(45.93%) were low grade tumors with recurrence. Regarding the TNM staging, the tumors with Ta stage were 108(80%) and T1 were 27(20%) in group-A. Stage Ta tumors were 99(73.33%) and stage T1 were 36(26.67%) in Group-B.

In case of local side effects of BCG, dysuria was observed in 74 patients. Low grade fever was noted in 37 patients. Dysuria and fever settle

within 48 hours and do not need any particular management apart from standard painkillers and anti-spasmodic. Patients with persistent fever were treated with anti-tuberculous therapy for six months.

Only 5 patients developed rigors after BCG instillation and those were treated with anti-histamine. Frequency was observed in 68 patients. Urgency and nacturia were seen in 13 and 21 patients respectively. Irritative bladder adverse effects associated with Onco TICE administration were managed with anti-cholinergic and anti-inflammatory.

Three patients developed macroscopic haematuria. Sixty three patients did complaint of malaise/fatigue and only 05 patients were observed with skin rash which reflected hypersensitivity reaction and were treated with anti-histamine. Flu like symptoms was noted in 39 patients and treated them symptomatically.

One patient developed BCG sepsis on the 3<sup>rd</sup> day of BCG instillation and was treated with isoniazid and rifampicin.

There were 27 patients who developed frequency and dysuria after Mitomycin instillation which was resolved after a few days antibiotics. Haematuria were noted in 2 patients. Nine patients developed low grade fever which was treated with tablet Paracetamol. Palmer and genital rash was noticed in 11 patients and four patients developed itching sensation and advised them to cautious with the first urination so as to minimize splashing.

There were only 7(5.38%) in Group-A showing recurrence on follow up cystoscopy after intravesical BCG instillation as compared to 20(15.38%) with recurrence in Group-B, who received intravesical Mitomycin-C. The Recurrence at first year follow-up in both groups showed a significant difference ( $p < 0.05$ ).

Symptoms	Group A		Group B	
	No. of Patients	%	No. of Patients	%
Painless Haematuria	120	88.89	127	94.07
Clot Retention	82	60.74	70	51.85
Urgency, Dysuria, Frequency	08	05.92	12	0.89
Microscopic haematuria	02	01.48	01	0.74

Table-I. Percentage of patients according to symptoms in both groups

Site of the Growth	Group A		Group B	
	No. of Patients	%	No. of Patients	%
Right lateral wall	81	60.00	49	36.29
Left lateral wall	28	20.74	47	34.81
Posterior wall	09	06.67	14	10.37
Bladder Neck	03	02.22	06	04.44
Vault	03	02.22	03	02.22
Multiple sites	11	08.14	16	11.85

Table-II. Site of the growth in group A and group B

	Recurrence (+ve)		Recurrence (-ve)		P-Value	Significance
Group A	07	5.38%	123	94.61%		
Group B	20	15.38%	110	84.62%		

Table-III. Recurrence in Group A and Group B during one year follow up on cystoscopy

## DISCUSSION

Bladder tumor is a common illness presenting to urological discipline across the globe. It is associated with significant mortality as well as morbidity. Although there has been tremendous research in early detection of TCC bladder and break through has been established in controlling the clinical risk factors in terms of preventing the recurrences resulting in improvement in quality of life, lesser hospital stay and better cost effectiveness. However there has been no major success regarding the intravesical therapy in term of recurrence.

The strength of our study is that it is first study in present set up that is addressing complete spectrum of disease. The weakness of our study is that we could only follow the patients for one year; while such patients need long term follow up. The mean age of the patients in our study for group A and group B was  $50.0 \pm 13.1$  and  $52.3 \pm 12.9$  years respectively. This observation is also consistent with other international studies that have evidence that this tumor is commonly present in 5<sup>th</sup> and 6<sup>th</sup> decade of life.<sup>12</sup> In another study by Blaszyk H, et al, the average age of the patients was 70 years.<sup>13</sup>

Bladder cancer is more common in male than female, with a worldwide man/woman ratio of 10:3.<sup>14</sup> In our study, the male to female ratio was 3:1 which shows that this tumour is more common in males than in females. In the study by Blaszyk H, et al, the male to female ratio was 3:1.<sup>13</sup> Result of our study is same to international studies. This ratio was somewhat closer to that of American<sup>15</sup>, British<sup>16</sup> and Australian studies.<sup>17</sup>

The comparatively high incidence in males may be due to the more exposure to different carcinogens in relation to smoking and occupational exposure because in our set up females are restricted to home and it is the male who earns the living. Smoking in female is also uncommon in our part of world. Women also come to doctor late in their stage of the disease mainly due to social taboos while men seek treatment earlier.<sup>18</sup>

Patients treated with short-term BCG instillations

had a 25.1% recurrence rate at 1 yr, compared with 25.7% in the short-term MMC group and 10.4% in those receiving long-term MMC. Recurrence-free rates in the second and third year were, respectively, 70.5% and 68.6% for short-term MMC, 68.5% and 65.5% for short-term BCG, and 88.3% and 86.1% for long-term MMC.<sup>19</sup>

In our research, the recurrence rate, In Mitomycin group after one year is 15.38% and in BCG group recurrence is 05.38 % which is quite different from international data. The possible reason for this discrepancy could be complete resection, good intravesical instillation, proper stay time of therapy and follow up the patients.

Our study is implicated on the urologists who are involved in initial management of bladder tumors. More over as TCC is occupational hazard it is also implicated on public health authorities and legislative bodies for implementation of rules regarding compensation for the workers in different industries. We have observed that our patients present very late as compared western hemisphere. In our country, patient's presentation and diagnosis of disease is delayed more importantly due to ignorance of the early symptoms by patients, poverty, lack of health education and poor diagnostic facilities.

## CONCLUSION

Bladder tumor is quite common in this part of world. Occupation may play a role, but the exact etiological factors are still to be determined. However smoking has definitive association with CA bladder. The patients are usually male in the 5<sup>th</sup> decade of life painless haematuria is the commonest presenting symptom of the bladder growth. Intravesical instillation of On Co Tice BCG significantly decreases the risk of recurrence in patients with stage Ta, T1, single to multiple papillary bladder cancer, in low grade (G<sub>1</sub>, G<sub>2</sub>) tumours. So intravesical instillation of OnCo Tice BCG is recommended in all low grade tumor patients to reduce the recurrence rate and progression.






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