



## EFFECTIVENESS OF SINGLE DOSE INTRAVESICAL MITOMYCIN C THERAPY AS PROPHYLAXIS TO PREVENT RECURRENCE AND PROGRESSION OF SUPERFICIAL NON-MUSCLE INVASIVE BLADDER TUMOR.

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### INTRODUCTION

Bladder cancer is one the common malignancies of bladder cancer. An estimated 400,000 new cases of bladder cancer are reported annually<sup>1,2</sup> and more than 14,000 mortalities due to bladder cancer are reported every year.<sup>3</sup> Prevalence is 3 to 4 times higher among male population because of higher rate of smoking and exposure to toxins. Female population most offently in advanced age.<sup>4</sup> About 75% of all patients who present with bladder cancer are diagnosed of having non-muscle invasive bladder tumor (NMIBT). NMIBT patients have a good prognosis but with high recurrence rate of 30-80% and 1-45% of these recurrence cases develop muscle invasive bladder tumor.<sup>5,6</sup> Prognosis is poorer in female patients when compared with males.<sup>7</sup>

The ultimate goal of treatment of non-muscle invasive bladder cancer is to cure the disease, to prevent recurrence and to improve the prognosis

**ABSTRACT...** To determine the effectiveness of instillation of single dose of intravesical mitomycin C in patients with low grade non-muscle invasive bladder tumor (NMIBT). **Study Design:** Retrospective cross-sectional study. **Setting:** Tabba kidney institute Karachi. **Period:** 2016 to Jan-2018. **Materials and Methods:** A total of 76 patients with first time diagnosis of non-invasive bladder tumor were included. Data of patients of SNMIBT who underwent trans-urethral resection of bladder tumor (TURBT) and received single dose instillation of mitomycin C (MMC, 40 mg) within 24 hours after resection from 2016 to Jan-2018 were included in this analysis. All these patients were followed for 6 months after TURBT, cystoscopy was performed at 3 and 6 monthly to check and record any recurrence or progression. **Results:** Out of 76 cases, 43 (56.57%) had one lesion, 27 (35.52%) had two lesion and 6 (7.89%) cases had three lesion. Single dose intravesical mitomycin C was effective in 81.57% (62/76) cases, recurrence occurred in 6 (7.89 %) cases and progression of disease in 8 (10.52%) cases. **Conclusion:** The results of present study confirmed the positive effect of instillation of single immediate dose of MMC in patients with low risk superficial bladder tumor. 81.57% patients will not require any further treatment if MMC-40 is given immediately following TURBT.

**Key words:** Intravesical, Mitomycin C, Recurrence, Superficial Non-Muscle Invasive Bladder Tumor, TUR (BT).

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of patients. Recurrence may be due to new tumor development from the remnant tumor cells after inadequate tumor resection, or may be due to seeding of tumor cells in the spoiled mucosal portions.<sup>8,9</sup> Therefore, intravesical instillation after early period of resection may prove fruitful in preventing the reoccurrence by destroying the floating tumor or residual floating tumor cells. Literature has proven that for prophylaxis a single dose Mitomycin C (MMC) is effective for a unifocal superficial bladder tumor.<sup>10,11</sup> A study conducted by El- Ghobashy et al concluded that only 16% patients developed early recurrence after intravesical instillation of mitomycin C compared to 34.0% in control group.<sup>12</sup> Not enough recent data has been published locally regarding to outcomes of single dose intravesical instillation of mitomycin C in patients with low grade superficial bladder cancer. This study may give us recent information regarding the treatment of superficial bladder cancer in our population.

**METHODS**

This descriptive case series was conducted in Tabba Kidney Institute. A total number of 76 patients having age 35-80 years with the diagnosis of superficial non-invasive bladder cancer were included in this case series from 2016 to 2018. Diagnosis of cancer stage was made histopathologically after cystoscopic biopsy. Patients with invasive bladder tumors, or with High grade (G2 and higher) bladder tumors were excluded from analysis.

Trans-urethral resection of bladder tumors (TURBT) was done under spinal anesthesia in all patients. Within 24 hours of TURBT, 40 mg Mitomycin C (MMC) was instilled via per-urethral catheter and retained for 2 hours with change of posture supine, right lateral, prone and left lateral positions according to standard operating procedure. Patients was discharged next morning and followed up in OPD for final histopathological report. Follow up cystoscopy was performed at 3 and 6 monthly to check and record any recurrence or progression.

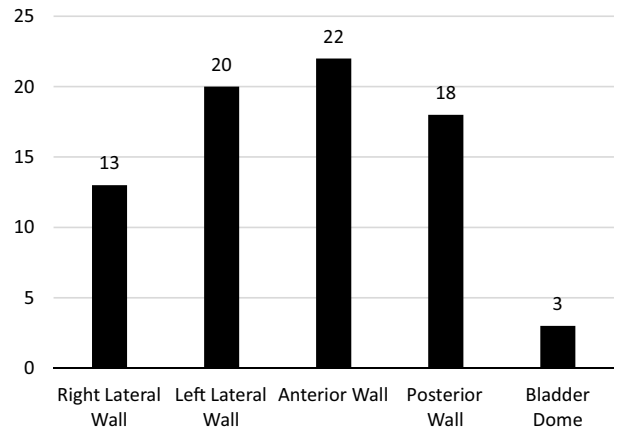
The data was entered and analyzed using Statistical Package for Social Sciences (SPSS Version 23). Mean and standard deviation was calculated for age. Frequency Percentage was calculated for gender, site of lesion, number of lesion/s and effectiveness.

**RESULTS**

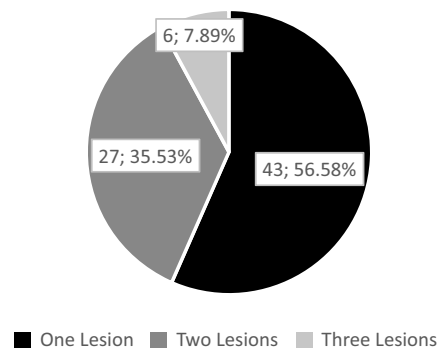
The Mean age of the patients was 60.05±6.71 years. There were 44 (57.89%) were male patients and 32 (42.10%) female patients. Anterior wall, left lateral and posterior wall was commonly observed in this study as presented in Figure-1.

Out of 76 cases, 43 (56.58%) had one lesion, 27 (35.53%) had two lesion and 6 (7.89%) cases had three lesion (Figure-2).

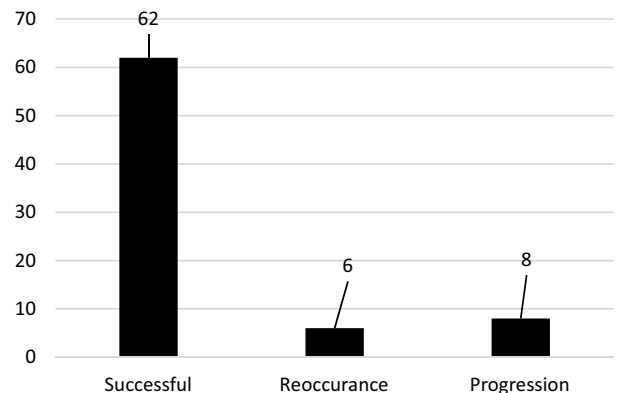
Single dose intravesical mitomycin C was effective in 81.57% (62/76) cases, recurrence occurred in 6 (7.89 %) cases and progression of disease in 8 (10.52%) cases (Figure-3).



**Figure-1. Site of bladder tumor.**



**Figure-2. Total number of Lesions.**



**Figure-3. Outcomes of single dose of mitomycin C injection after 6 months.**

**DISCUSSION**

Patients with non-muscle invasive bladder tumor (NMIBT) have been documented to have good prognosis after surgical excision of tumor cells.<sup>13</sup> Till date, TURBT have been the gold standard procedure for patients with NMIBT. After first reports of Oostelinck et al. and Tolley et al. on

the effectiveness of immediate instillation of chemotherapeutic agents into the intra-vesical sac,<sup>14,15</sup> this protocol has also gained worldwide acceptance. Both EUA and AUA guidelines have recommended the usage of instillation of chemotherapeutic agents immediately after TURBT.<sup>16,17</sup> However the choice the chemotherapy agent used for instillation varies from center to center. A meta-analysis compared the outcomes of different agents (e.g. BCG and MMC) and failed to demonstrate any difference in the effectiveness of different chemotherapeutic agents.<sup>18</sup> And up till now, no standard chemotherapy agent has been recommended. Moreover, the EORTC trial conducted by Bouffieux et al. concluded that there is no difference in immediate single dose administration of mitomycin C, monthly maintenance dose after every month for one year and monthly maintenance dose after every month for 6 months.<sup>8</sup> So in present study, we determined the effectiveness of intra-vesical instillation of single dose of MCC in patients of SNMIBT.

In present study, mean age of the patients was  $60.05 \pm 6.71$  years, with 57.89% male patients and 42.10% female. In the study of Ather et al. the mean age was  $55.5 \pm 13.7$  years. There were 90% male patients and 10% female patients.<sup>19</sup>

In present study effectiveness of single intravesical dose of mitomycin C was 81.57%, recurrence was observed in 7.89% cases and progression of disease in 10.52% cases at 6 months follow-up. Ather et al. reported reoccurrence in 15% cases after intra-vesical injection of MMC.<sup>19</sup> Another study conducted by conducted by El-Ghobashy et al reported early reoccurrence in 16% patients in MMC group as compared to 34% in control group.<sup>12</sup> Kaasinen et al. reported that the rate of reoccurrence is doubled if MMC is not given within 5 days after surgery.<sup>20</sup> A resent large scale RCT have found a significant difference in reoccurrence rate in patients receiving immediate instillation of MMC 27% versus 36% in patients receiving delayed instillation of MMC as single dose.<sup>21</sup> In present study, we gave mitomycin C instillation within 24 hours after surgery.

After instillation MMC produce alkylating agents in

the bladder and inhibits DNA synthesis.<sup>22</sup> However the exact mechanism is not clearly understood. Based on these alkylating properties of MMC, a recent study conducted by Hamit et al. done alkalization of bladder before instillation of MMC and compared these results with standard MMC therapy. These authors concluded that there is no additional benefit of additional alkalization before instillation of MMC in patients of NMIBT.<sup>23</sup>

## CONCLUSION

The results of present study confirmed the positive effect of instillation of single immediate dose of MMC in patients with low risk superficial bladder tumor. 81.57% patients will not require any further treatment if MMC-40 is given immediately following TURBT.



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**AUTHORSHIP AND CONTRIBUTION DECLARATION**

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Sherjeel Saulat	Conceived, designed the research methodology and supervision of research work, and is accountable for all aspects of the work in ensuring that question related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.	
2	Anees Ur Rehman Soomro	Did data collection, helped in drafting and review the manuscript.	
3	M. Murtaza Azad	Did data collection, helped in drafting and review the manuscript.	