# Effectiveness of Immediate Mitomycin C Instillation in Patients with Low Risk Non-Muscle Invasive Bladder Cancer

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## ABSTRACT:

**BACKGROUND:**

We determined if immediate instillation chemotherapy after transurethral resection (TUR) decrease the risk of recurrence and\or progression in patient with stage Ta T1 bladder cancer.

**OBJECTIVES:**

This study has been designed to analyze the impact of a single immediate mitomycin C instillation after transurethral resection of bladder cancer on recurrence and progression rates in patients with low risk superficial bladder cancer.

**METHODS:**

A total of 50 patients with low risk superficial bladder cancer were included in a prospective randomized controlled trial. All patients had a 3 cm. or less single, papillary bladder tumer. The tumor was completely resected before patients were randomized into 2 arms of no further treatment (control group) and a single immediate instillation (usually within 6 hours) of 40 mg. mitomycin c (mitomycin c group). Median follow up was 24 months .The events studied were the recurrence free rate, the recurrence rate/year, and the number of new tumors developing /year.

**RESULTS:**

At 24-month follow-up the recurrence-free rate was significantly increased (84.7% VS 54.2%). Recurrence (15.3% VS 45.8%), and recurrence per year rate (7% VS 20%) and tumor per year rate(11% VS 33%) were significantly decreased in the mitomycin c compared to the control group.

**CONCLUSION:**

This study confirms the positive effect of a single immediate mitomycin C instillation in patients with low risk superficial bladder cancer. Thus, this approach is an alternative to observation. This study also suggests cell implantation as a mechanism of early recurrence can be controlled with a single immediate mitomycin c instillation.


***KEY WORDS:*** transurethral resection, mitomycin c, non-muscle invasive bladder cancer.

## INTRODUCTION:

Bladder cancer is the second most common urological malignancy[1], and it is the fourth most common cancer in men accounting for 6.6% of all cancer cases. In women, it is the ninth most common cancer, accounting for 2.4% of all cancers[2]. Bladder cancer is nearly three times more common in men than in women [2.] Approximately 90% of the bladder neoplasm's are transitional cell carcinoma (TCC) and almost two thirds will present as superficial bladder cancer which includes all non muscle invasive TCCs[2]. The initial step in the management of superficial bladder cancer is complete transurethral resection (TUR) of the tumor, despite the initial complete visual ablation of the primary tumor, the recurrence rate is generally high and 40% to 80% of patients will develop tumor recurrences within five years[3].By analyzing the hazard curve of recurrences after TUR, Akaza et al.[4] demonstrated a biphasic recurrence curve with an initial peak within 3- 6 months and a second peak between 1.5 and 2.5 years (Fig.1). These new tumors arise from areas of dysplastic urothelium, from inadequate resection[5], or from implanted tumor cells[6-7].

The natural course of bladder carcinogenesis after TUR is probably mixture of all these events. The early recurrences are explained mainly by the inadequate resection or implanted tumor cells, while late recurrence related mainly to tumors that arise from areas of dysplastic urothelium that's apparently normal at time of first TUR[7-8]. The risk of recurrence and progression represent an uncomfortable psychological problem for patients as well as dilemma for urologists[9].

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Several cytotoxic and immune modifying agents have been used intravesically for therapeutic and prophylactic purposes. On the other hand, many trials have demonstrated lower recurrence rates with early instillation of endovesical chemotherapy, suggesting that tumor cells floating free within the bladder can be controlled early with chemotherapy agents.[10-11] Moreover, the concept of cell implantation at transurethral resection of superficial bladder cancer as a recurrence mechanism has been supported in animal models and clinical trials.[12, 13, 14, and15].

This study has been designed to confirm this concept and to evaluate whether a single early instillation of a mitomycin c influences recurrence and progression of low risk non muscle invasive bladder cancer or not.

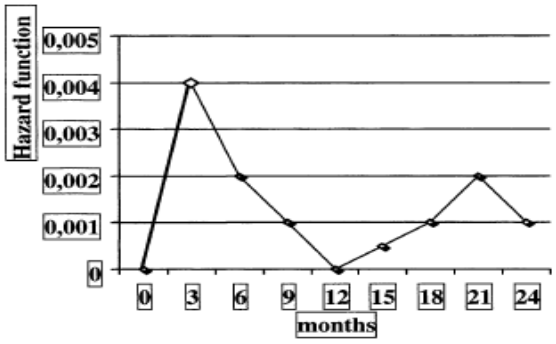


**Fig 1: Time of recurrence-after TUR only (adapted from Akaza etal, Urol Oncol 1998; 4:121-9).**

## PATIENTS AND METHODS:

Prospective randomized controlled study of patients with newly diagnosed Ta or T1 transitional cell carcinoma of the bladder with a *3* cm. or less ,single, papillary, primary tumor ,65 patients were entered into the study from Al-Khadmyia teaching center between May 2005 and December 2007 .

In all patients the upper urinary tract was normal on excretory urography. Patients with muscle invasive or G3 tumors or bladder carcinoma in situ on pathological examination, age older than 80 years were excluded. Bladder tumors were staged and graded in accordance with TNM and WHO reference center classifications, respectively. To make a uniform diagnosis of T category and grade all histological examinations were done by the same reference pathologist .After complete transurethral resection of bladder tumor were performed, Patients were randomly allocated to observation only (control group) or to receive a single dose of 40 mg. mitomycin C diluted in 50 ml. saline (mitomycin C group), which was instilled when hematuria ceased, usually was within 6 hours of transurethral resection and side effects were noted. The instillation was retained for 2 hour with catheter clamping and then the bladder was irrigated with saline. Patients were evaluated with urinary cytology, ultrasound and cystoscopy at 3, 6, 9, 12, 18 and 24 months.

At each cystoscopy any tumor or abnormal looking urothelium was resected and tissue sent to reference pathologist to confirm recurrence. The first end point of the study was recurrence-free interval which is the period between initial transurethral resection and first recurrence. Statistically recurrence represent the percentage of patients with recurrence during the follow up period, recurrence per year represent the number of positive cystoscopies divided by the total years of follow-up where both numerator and denominator are totaled over all patients in the group . Tumor per year represent the total number of tumors observed during all positive cystoscopies divided by the total years of followup where both numerator and denominator are totaled over all patients in the group .Recurrence free rate were calculated according to the Kaplan-Meier method and compared by the log-rank test [16] .

A second end point of the study was progression, which was the percentage of cases of invasive bladder tumor or metastases. Complete blood count, serum creatinine, urinalysis and urine culture were performed before and 1 week after transurethral resection. Allergic reactions, urinary disturbances, catheter duration, and hospitalization period were recorded. Standard chi-square and Student's t tests were used to compare groups. Values were considered statistically significant at $p < 0.05$.

## RESULTS:

Out of the 65 patients initially included in the study 15 were excluded because pathological examination revealed muscle invasive tumor in 4, G3 tumor in 3 , bladder CIS in 1, no histological evidence of tumor in 1, and 6 were lost during followup.

Therefore, 26 patients in the mitomycin c and 24 in the control group were eligible for study. Out of the 50 patients who entered the study 5 were women and 45 were men, with an average age plus or minus standard deviation of 60.2 ± 9.4 years. Both groups were comparable in regard to clinical and pathological characteristics Table (1). Mean follow-up was 25 months. Of the 24 patients in the control group 11 experienced at least 1 recurrent tumor compared to 4 of 26 given mitomycin c. A significantly lower recurrence rate was observed in the mitomycin c compared to the control group (table 2) .Only 2 patients (4%, 1 in each group) had progression (table 2). The recurrence free rates are shown in the figure (2) and at two years were 54.2% and 84.7% for the control group and mitomycin c group, respectively.A significantly longer recurrence-free interval was observed in the mitomycin C compared to the control group, log-rank test (p=0.012) A significantly lower recurrence and tumor per year rates were noted in the mitomycin c compared to control group (Table3).There is 1out of 4 (25%) patients in mitomycin c group present with multiple tumors recurrence, 8 out of 11(72%) patients in control group presented with multiple tumors recurrence. Recurrence timing was considered using different cutoff points when determining the possible impact of single early instillation of mitomycin c on cell implantation as a mechanism of early recurrence. Early recurrence developed during the first 12 months in 72% of the control but only 25% of the mitomycin c group (p=0.005), no significant differences were observed in the second year, figure (3). Side effects were not a severe problem.

In the mitomycin c group 3patients (11.5%) had chemical cystitis and slight allergic skin reactions. No hematological changes were recorded.

**Table1: Patient characteristics.**

| Mitomycin group | | Control group | Over all |
|---|---|---|---|
| Patients no. | 26 | 24 | 50 |
| Mean age | 59.2 | 60.3 | 60.2 |
| No. men / No. women | 8/1 | 9/1 | 8.5/1 |
| Mean tumor size (cm) | 2 | 2.2 | 2.1 |
| No. pathological stage (%) | | | |
| Ta | 10(38.6) | 9(37.5) | 19(38) |
| T1 | 16(61.5) | 15(62.5) | 31(62) |
| G1 | 14(53.8) | 13(54.1) | 27(54) |
| G2 | 12(46.1) | 11(45.8) | 23(46) |
| Median follow-up(mos.) | 26 | 24 | 25 |

**Table 2: Recurranc and Progression No.(%)**

| | Control group | Mitomycin c group | p value |
|---|---|---|---|
| total | 24 | 26 | |
| recurrence | 11(45.8) | 4(15.3) | 0.018 |
| progression | 1(4.1) | 1(3.8) | 0.951 |


| GROUPS | 3MOS. | 6MOS. | 9MOS. | 12MOS. | 18MOS | 24MOS. |
|---|---|---|---|---|---|---|
| CONTROL | 91.7% | 83.3% | 79.1% | 74.9% | 62.4% | 54.2% |
| MITOMYCIN C | 100% | 100% | 100% | 96.2% | 87.8% | 84.7% |

**Figure 2 : Recurrence –free interval for 24 months follow-up**

**Table 3: Recurrence and tumor per Year rates** .

| | Control Group | Mitomycin C Group | P Value |
|---|---|---|---|
| Recurrence | 0.20 | 0.10 | 0.046 |
| Tumor | 0.33 | 0.11 | 0.037 |

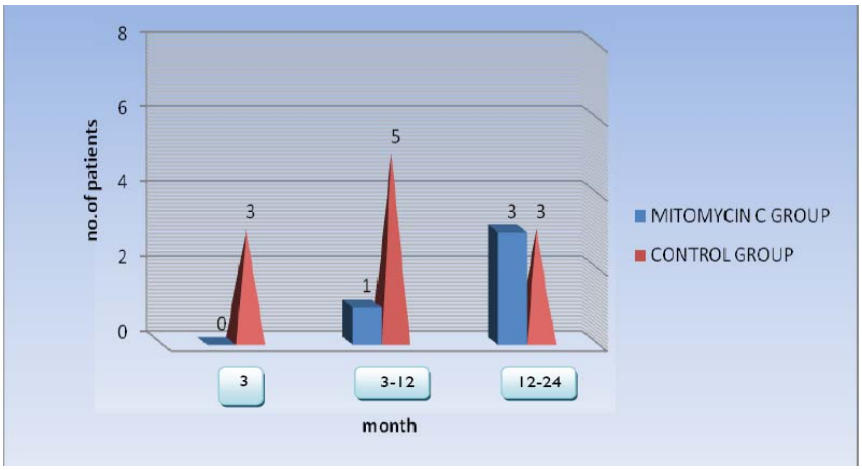


**Figure3: Time of Recurrence.**

## DISCUSSION:

Many regimes of intravesical therapy have been tried in attempt to reduce the recurrence rates of superficial bladder cancer, these generally require frequent attendance for instillation [17]. Mitomycin c has been shown to be active in treating superficial bladder cancer and when given in multiple Instillations it is clearly effective, producing response rate of 40% to 50% [17]. Multiple instillation of mitomycin c however, are associated with an increased incidence of side effects [18]. For this reason and in view of the cost incurred by frequent hospital attendance single instillation at the time of cystoscopies would be preferable if shown to be effective . Several studies have demonstrated that tumor size, multifocality, morphology, disease-free interval, grade, stage and bladder carcinoma in situ are reliable prognostic factors for recurrence and progression in patients with superficial bladder cancer[19-20]. Considering these clinical factors patients with a 3 cm. or less single, papillary, primary or

recurrent tumor, who are disease-free for more than 1 year can be defined as at low risk for progression .Inclusion criteria in this study were based on these findings, and the low risk status of this group was corroborated since with a median followup of 24 months only 3.9% had progression. On the other hand, a single Mitomycin c instillation did not impact progression (P value 0.271). In this study during 24 months of followup recurrence, and recurrence and tumor per year rates were significantly decreased, and the recurrence-free interval was significantly increased in the mitomycin c compared to the control group. These results are comparable to those obtained in controlled trials of a single instillation of epirubicin or mitomycin c with short-term followup[7,21] . Clinically, this outcome indicated a significant reduction in transurethral resection for patients treated with Mitomycin c.

The benefit of immediate intravesical instillation in lowering recurrence rates must be balanced against toxicity .The incidence of side effect in this study was extremely low. One immediate instillation of mitomycin c after TUR is an adjuvant treatment that adds hardly any morbidity to the operation itself. Nearly all patients already have a catheter after TUR and if local regional anesthesia is used, patients will not suffer from any additional discomfort .However in case of a perforated bladder or extended TUR an immediate instillation should not be given.

This approach also provided an important psychological benefit since many patients were preoccupied with early recurrence, despite being previously informed that they were at low risk. The significant reduction in early recurrence with a single instillation of mitomycin c strongly supports the hypothesis of cell implantation as a recurrence mechanism. Moreover, recurrences were concentrated during the first 12 months in 72% of the control compared to only 25% of the mitomycin c group. Furthermore, among the 3 patients in the control group with recurrence at 3-month evaluation all present with more than 1 tumor, at least 1 tumor was in the same place as it was initially, while none in the mitomycin c group had recurrence during this period. This finding suggests that in controls early recurrences mostly correspond to a cell implantation process, which would not be related to the natural history of the tumors. In patients with papillary disease, hyperplasia, atypia or dysplasia may be discovered in apparently normal areas of the bladder and recurrences are more frequent in these cases than in those without urothelial abnormalities[22,23].

This may explain the recurrences occurs in mitomycin c group. which proves that a single mitomycin c instillation does not have any impact on the biology of low risk bladder cancer .

## CONCLUSIONS:

In patients with low risk superficial bladder cancer a single mitomycin c instillation significantly increased the disease free interval and significantly decreased recurrence, and recurrence and tumor per year rates ,the study suggests that cell implantation as a mechanism of early recurrence can be controlled with a single immediate mitomycin c instillation.

This inexpensive and safe approach spares a significant number of transurethral resections in these patients .Consequently; this approach can be considered an alternative for observation only in patients with low risk superficial bladder cancer.

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