

# Comparison of sterile water irrigation versus intravesical mitomycin C in preventing recurrence of nonmuscle invasive bladder cancer after transurethral resection

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## ABSTRACT

**Introduction:** Early recurrence of nonmuscle invasive bladder cancer (NMIBC) following transurethral resection (TUR) remains relatively high. An immediate single instillation of mitomycin C (MMC) reduces the recurrence rates in the first 2 years but has not shown benefits in tumor progression or overall survival. Distilled water irrigation has shown to delay tumor recurrence by osmolysis of tumor cells. There are only limited clinical studies comparing the efficacy of MMC with continuous sterile water irrigation (CSWI) in preventing the recurrence of NMIBC after TUR in clinical setting.

**Materials and Methods:** A prospective, randomized, open-label, two-arm, single-center, pilot study was conducted between December 2013 and September 2015 at a tertiary-care center in South India. Patients were randomized into CSWI group ( $n = 19$ ) or single dose intravesical MMC group ( $n = 17$ ) following TUR for NMIBC and analyzed. All patients were followed up with flexible cystoscopy and urine cytology at 3 months interval for 1 year. Recurrence-free rate was estimated as the primary criterion for outcome analysis.


**Results:** At the end of 12 months, recurrence-free rates for MMC and CSWI groups were 47.1% and 52.6%, respectively. The mean recurrence-free interval for MMC and CSWI groups were 10.9 months and 9.8 months, respectively. The difference in recurrence-free rate or recurrence-free interval between two groups was statistically nonsignificant. Further, the complications in MMC group were significantly higher than that in CSWI group ( $P = 0.047$ ).

**Conclusions:** Continuous bladder irrigation with sterile water after TUR may be comparable to immediate single dose intravesical MMC in preventing tumor recurrence in NMIBC.

## INTRODUCTION

Bladder cancer comprises a heterogeneous group of tumors. Of them, approximately 70% are diagnosed as nonmuscle invasive bladder cancer (NMIBC) at presentation.<sup>[1]</sup> Transurethral resection (TUR) remains the gold standard for NMIBC treatment. Although state-of-the-art TUR by itself can eradicate Ta, T1 tumors completely, these tumors frequently recur and/or progress to muscle-invasive bladder cancer in up to 40% of cases within a year<sup>[2]</sup> mainly due to

persistence or re-growth of residual tumor after incomplete TUR.<sup>[3]</sup> Therefore, a single perioperative dose of intravesical chemotherapy is recommended immediately after initial TUR in low-risk disease patients.<sup>[4,5]</sup> A single instillation of mitomycin C (MMC), which acts by chemoresection of tumor or by destruction of circulating tumors, at the time of TUR reduces the rate of recurrence in the first 2 years. However, it does not reduce the risk of tumor progression or overall survival. Further, the clinical benefits of MMC are weak in treating recurrent, large (>5 cm), high-grade tumors, or high-risk patients.<sup>[4-7]</sup> Recently, sterile water

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has emerged as a valuable alternative.<sup>[8-13]</sup> The majority of these studies have shown significant efficacy of sterile water in lysing tumor cells, where the cytotoxic effects are mainly caused by osmotic cytolysis. Initially, Price indicated that sterile water can be used for the irrigation of peritoneal cavity to destroy released cancer cells after surgery for several types of cancers.<sup>[14]</sup> An *in-vitro* study has also demonstrated that sterile water causes significant tumor cell death within 10 min in all cell lines.<sup>[8]</sup> Another study demonstrated that postoperative irrigation with saline for 18 h post-TUR significantly prolonged the time to the first recurrence, with about 17% reduction in relative risk of recurrence.<sup>[15]</sup> In another study, the osmotic tumor cytolysis by overnight irrigation with sterile water has shown to reduce the recurrence rate by 19%.<sup>[16]</sup> Since there are no trials comparing the efficacy of MMC and sterile water, we designed a randomized study to compare the recurrence-free rate and recurrence-free interval in NMIBC patients receiving continuous sterile water irrigation (CSWI) versus single dose intravesical MMC following TUR.

## MATERIALS AND METHODS

### *Study design and patient population*

We conducted a prospective, randomized, open-label, two-arm, single-center, pilot study between December 2013 and September 2015 at a tertiary-care center in South India. Patients undergoing TUR with cystoscopic findings (visual impression) suggestive of NMIBC were considered for enrolment. Of them, patients with previous history of intravesical therapy, synchronous upper tract tumor, bladder perforation during TUR, significant hematuria after TUR, tumor size >3 cm, prostatic involvement on cystoscopy, or incomplete resection of bladder tumor were excluded from the study. Signed informed consent was obtained from each patient. The institutional ethics review board approved the study protocol.

### *Treatment allocations*

Enrolled patients were assigned to receive either single dose intravesical MMC or CSWI following TUR for NMIBC. For patients randomized to MMC group, TUR was performed with glycine as irrigant (for those undergoing bipolar TUR, normal saline was used). A three-way catheter was placed into the bladder and the inflow port was attached to a saline infusion bag while still in the operating room. A single dose of intravesical MMC (40 mg in 20 mL saline) was instilled within 6 h of TUR through the outflow port in the recovery room and the outflow tubing was clamped with a hemostat. After 1 h, the outflow tubing was released and saline was run through the irrigation port. All intervention was done using strict aseptic precautions. For patients randomized to CSWI group, TUR was performed with sterile water as irrigant. Thorough bladder wash was performed on table with 1 L sterile water following TUR. CSWI was continued for

next 24 h, that is, 2000 mL/h for first hour, 1000 mL/h for next 3 h, and 250 mL/h for 14–18 h: a total of 8.5–9.5 L.

### *Data collection*

An expert pathologist reviewed all hematoxylin and eosin stained slides of surgical specimens of tumor collected from each patient. Bladder tumors were classified according to seventh edition American Joint Committee on Cancer tumor-nodes-metastasis staging system.<sup>[17]</sup> Tumors were graded using the World Health Organization/International Society of Urological Pathology classification of noninvasive urothelial tumors.<sup>[18]</sup> The European Organization for Research and Treatment of Cancer (EORTC) criteria were used for tumor risk stratification.<sup>[19]</sup> Accordingly, patients diagnosed to have intermediate and high-risk disease continued to receive further treatment as per European Association of Urology (EAU) guidelines.<sup>[20]</sup> Those with muscle-invasive bladder cancer were excluded from the analysis and received further treatment as per EAU guidelines.<sup>[20]</sup> All enrolled patients were followed up with white light cystoscopy and urine cytology at 3-monthly interval for 1 year. Urologists blinded to the form of postoperative intravesical therapy performed cystoscopy. All enrolled patients were followed up with check cystoscopy and urine cytology at 3-monthly interval for 1 year. Tumor recurrence was defined as identification of tumor at cystoscopy and/or positive urine cytology.

### *Outcome measures*

The primary outcome measure was recurrence-free rate at 1 year, whereas recurrence-free interval was estimated as secondary outcome measure. In addition, postoperative complications of local toxicities such as macrohematuria, irritative bladder symptoms, micturition pain, frequency of urination, and systemic toxicities were examined. Tumor progression was also monitored.

### *Statistical analysis*

Continuous variables were expressed as mean  $\pm$  standard deviation, whereas categorical variables were expressed as frequency and percentages. Fisher's exact test was used to determine association between categorical variables. The independent Student's *t*-test was used to compare continuous variables. The Kaplan–Meier method with log-rank test was used to evaluate a statistically significant difference between two groups. The value of  $P < 0.05$  was considered statistically significant. Data were analyzed using the Statistical Package for Social Sciences (SPSS for Windows, version 20.0; IBM Corp., New York, USA).

## RESULTS

### *Demographic details*

A total 39 patients were included in the study. Of them, 19 and 20 patients were assigned to the MMC and CSWI

groups, respectively. Subsequently, two patients with T2 tumor stage and one patient with neuroendocrine tumor were excluded from the analysis after histopathological findings. Therefore, the final analysis included 17 patients in the MMC group and 19 patients in the CSWI group. Demographic characteristic of these patients are given in Table 1. No significant differences were observed between two groups in terms of age, sex, stage, grade, and number of tumors, tumor size, or risk group.

#### Analysis of primary and secondary outcomes

At 1 year, recurrence-free rates for MMC and CSWI groups were 47.1% and 52.6% respectively. Mean recurrence-free intervals for MMC and CSWI groups were 10.9 (range: 10.0–11.8) months and 9.8 (range: 8.4–11.2) months, respectively [Figure 1]. No significant difference in recurrence-free rate or recurrence-free interval was noted between two groups. Detailed findings are described in Table 2.

#### Analysis of outcomes in risk-stratified patients

After stratifying patients as per the EORTC risk criteria, the recurrence-free rate at 1 year was 60%, 60%, and 28.6% in the low-risk, intermediate-risk, and high-risk MMC group of patients respectively, and 80%, 40%, and 44.4%, in the low-risk, intermediate-risk, and high-risk CSWI group of patients, respectively. Conversely, the mean recurrence-free interval was 10 (range: 8.1–12.3), 11.4 (range: 9.9–12.8), and 11.1 (range: 10.0–12.3) months for low-risk, intermediate-risk, and high-risk MMC group of patients, respectively, and 12, 7.8 (range: 4.6–10.9), and 9.6 (range: 8.1–11.2) months for low-risk, intermediate-risk, and high-risk CSWI group of patients, respectively. The difference in recurrence-free rates or recurrence-free intervals between two arms was statistically nonsignificant in all risk categories. Detailed findings are described in Table 2.

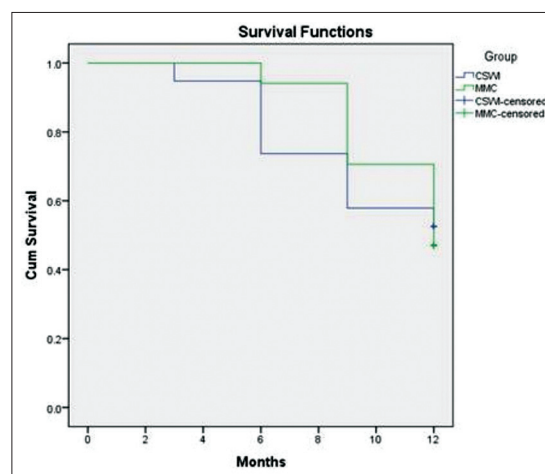
#### Analysis of outcomes in patients stratified according to tumor stage and tumor grade

For patients with Ta tumor stage, the recurrence-free rate at 1 year was 63.6% in the MMC group and 58.3% in the CSWI group, whereas the mean recurrence-free interval was 10.9 (range: 9.5–12.2) months for the MMC group and 9.7 (range: 7.6–11.8) months for the CSWI group. For patients with low-grade tumors, the recurrence-free rate at 1 year was 46.7% in the MMC group and 54.5% in the CSWI group, whereas the mean recurrence-free interval was 10.8 (18–11.8) months for the MMC group and 9.8 (range: 7.7–11.9) months for the CSWI group. The difference in recurrence-free rates or recurrence-free intervals between the two arms was statistically nonsignificant among patients stratified according to tumor stage or tumor grade. Detailed findings are described in Table 2.

**Table 1: Mitomycin C versus continuous sterile water irrigation groups: Patient characteristics**

Patient characteristic	MMC (n=17)	CSWI (n=19)	P
Mean age	64.42±14.7	65.25±10	0.840
Sex (%)			
Male	94.7	90	0.999
Female	5.3	10	
Tumour stage (%)			
Ta	63.2	64.7	1.00
T1	36.8	35.3	
Tumor grade (%)			
High	88.2	63.2	0.128
Low	11.8	36.8	
EORTC risk stratification (%)			
Low	29.4	26.3	0.93
Intermediate	29.4	26.3	
High	41.2	47.4	
Tumor type (%)			
Primary	73.7	80	0.999
Recurrent	26.3	20	

CSWI=Continuous sterile water irrigation, EORTC=European Organization for Research and Treatment of Cancer, MMC=Mitomycin C



**Figure 1:** Efficacy of mitomycin C versus continuous sterile water irrigation: Kaplan-Meier curve for recurrence-free survival during 12-month follow-up period for overall patients

#### Analysis of postoperative complications and tumor progression

Of 19 patients who had received intravesical MMC, 7 (36.8%) patients exhibited local complications of irritative voiding symptoms (i.e., micturition pain, urgency or frequency of urination) requiring anticholinergic medication (Clavein Dindo II). On the other hand, of 20 patients who had received CSWI, 2 (10%) patients displayed self-limiting hyperkalemia in the postoperative period (Clavien Dindo I). No other complications were noted. Although the complication seen in the MMC group were minor irritative symptoms, the difference between two groups was statistically significant ( $P = 0.047$ ). All complications were managed conservatively. In addition, 2 (10.5%) patients from the CSWI group and 1 (5.8%) patient from the MMC group showed evidences of progression in tumor stage (from Ta to T1) or tumor grade (from low

**Table 2: Efficacy of mitomycin C versus continuous sterile water irrigation: Recurrence-free rates during 12-month follow-up period in overall patients, in risk-stratified patients, and in patients stratified according to tumor stage/grade**

Risk stratification	Randomization group	Recurrence-free rate (%)				P (log-rank test)
		At 3 months	At 6 months	At 9 months	At 12 months	
Overall patients	MMC (n=17)	100	94.1	70.6	47.1	0.900
	CSWI (n=19)	94.7	73.7	57.9	52.6	
Low risk patients (n=10)	MMC (n=5)	100	80	60	60	0.460
	CSWI (n=5)	100	100	100	80	
Intermediate risk patients (n=10)	MMC (n=5)	100	100	80	60	0.346
	CSWI (n=5)	80	40	40	40	
High risk patients (n=16)	MMC (n=7)	100	100	71.4	28.6	0.976
	CSWI (n=9)	100	77.8	44.4	44.4	
Ta stage (n=23)	MMC (n=11)	100	90.9	72.7	63.6	0.680
	CSWI (n=12)	91.7	66.7	66.7	58.3	
T1 stage (n=13)	MMC (n=6)	100	100	66.7	16.7	0.794
	CSWI (n=7)	100	85.7	42.9	42.9	
Low grade (n=27)	MMC (n=15)	100	93.3	66.7	46.7	0.957
	CSWI (n=12)	90.9	72.7	63.6	54.5	
High grade (n=9)	MMC (n=2)	100	100	100	50.0	0.658
	CSWI (n=7)	100	71.4	42.9	42.9	

CSWI=Continuous sterile water irrigation, MMC=Mitomycin C

grade to high grade). The difference in progression was not significant ( $P = 0.999$ ).

## DISCUSSION

We present the outcome of a randomized study that compared the 1-year recurrence-free rate in patients receiving CSWI versus single dose intravesical MMC following TUR in NMIBC patients. The sex-wise distribution of NMIBC showed a clear male preponderance with a male to female ratio of 12:1. This is much higher compared to western literature, which can be due to the decreased exposure to industrial carcinogens as fewer number of women work outside the home. In the present study, we randomized 39 patients with bladder tumor following cystoscopy, with visual impression of NMIBC. Of them, 36 were found to have NMIBC on final biopsy. This is in concordance with other studies,<sup>[21]</sup> indicating that combination of negative urine cytology and cystoscopic expertise accurately identifies histologically confirmed low-grade and low-stage tumors in >90% cases.

In the present study, the overall recurrence-free rate at 12 months was 47% for the MMC group and 52.6% for the CSWI group. Further, the mean recurrence-free interval was 10.9 (range: 10.05–11.8) months and 9.78 (range 8.4–11.17) months for MMC and CSWI group, respectively. These observations may imply that continuous postoperative intravesical instillation of sterile water in NMIBC could have similar or even better efficacy compared to a single intravesical cytostatic factor administration. A retrospective study by Grivas *et al.* have also shown that single and multiple bladder tumors receiving sterile water irrigation had a recurrence-free rate similar to those receiving immediate single dose of MMC.<sup>[9]</sup> In another study by Onishi *et al.*, the recurrence-free rate at the end of 1 year with

continuous saline bladder irrigation ( $n = 123$ ) and intravesical instillation of MMC ( $n = 115$ ) after TUR were 76.7% and 81%, respectively, for patients with intermediate-risk NMIBC. They found no significant difference in the recurrence-free rate, the period to first recurrence and frequency of recurrence between the two groups.<sup>[13]</sup> In a recent publication, Onishi *et al.* showed similar 5-year recurrence-free rates for continuous saline bladder irrigation and MMC group (62 vs. 70.4%  $P_{\text{LogRank}} = 0.53$ ), where median time to recurrence was 8 months in saline irrigation group and 8.5 months in MMC group.<sup>[22]</sup>

In our study, the recurrence-free rate for intermediate-risk tumors was 40% in the CSWI group and 60% in the MMC group. The low recurrence-free rate in our study can be attributed to less number of patients in each subgroup. We also observed that the recurrence-free rate was low for both MMC and CSWI groups in high-risk tumors. Analysis of outcomes according to Tumor staging revealed that recurrence-free rates in MMC and CSWI groups were distinctly better for Ta tumors than for T1 tumors. On the other hand, analysis of outcomes according to tumor grading revealed that recurrence-free rates in MMC and CSWI groups were comparable for low-grade and high-grade tumors. Further, the efficacy of CSWI for low-grade tumors in the present study was comparable to that with Grivas *et al.* study in terms of recurrence-free rates (55% and 61%, respectively) and recurrence-free interval (11 months and 15 months respectively).<sup>[9]</sup> In the present study, the number of patients with high-grade tumors was very small. Further, the complication rates in our study are similar to a study by Onishi *et al.*<sup>[13]</sup>

### Study limitations

The major limitation of the present study is its small sample size and short follow-up period. Another drawback of our

study is that three patients were excluded from the analysis after randomization, as histopathology was not compatible with the inclusion criteria of our study.

## CONCLUSIONS

Findings of the present randomized pilot study indicate that continuous bladder irrigation with sterile water after TUR may be comparable to immediate intravesical MMC in preventing tumor recurrence in NMIBC with significantly lower adverse effects. Further studies of similar design with a large population and longer follow-up are warranted.

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