

Efficacy of continuous bladder irrigation with saline after transurethral resection of nonmuscle-invasive bladder cancer stage Ta T1 to prevent cancer recurrence and progression in comparison with a single immediate instillation of mitomycin C chemotherapeutic

Mohamed Wishahi, Hani Nour, Khaled Elesaily, Ahmed Mehena

Department of Urology, Theodor Bilharz Research Institute, Cairo, Egypt

Correspondence to Mohamed Wishahi, MD, Department of Urology, Theodor Bilharz Research Institute, Embaba, Cairo, 12411, Egypt. Tel: +2 012 222 47437; e-mail: wishahi@gmx.net

Received: 12 November 2020

Revised: 10 November 2020

Accepted: 15 November 2020

Published: 18 May 2021

The Egyptian Journal of Surgery 2021, 40:278–283

Background

Continuous bladder irrigation (CBI) following transurethral resection of bladder tumor is a common practice, which usually continues in the early postoperative period. This irrigation may help to prevent tumor cell seeding, which is one of the precursors of tumor recurrence.

Aim

In our study, we investigated the efficacy and safety of CBI against the standard single post-tumor-resection installation of mitomycin C (MMC).

Patients and methods

An observational study was conducted for evaluation of patients admitted with bladder mass to our Urology Department. A total of 63 patients had single MMC instillation, whereas 73 had CBI with saline. Only patients with longer than 24 months of follow-up were analyzed.

Results

Overall complications were comparable in both arms except the need to administrate anticholinergic drugs for persistent irritative urinary symptoms in the MMC arm. Time to recurrence was shorter in CBI with saline arm, yet with no effect on recurrence incidence rate, nor the time to progression.

Conclusion

CBI with saline shows noninferior results to single postoperative adjuvant installation of MMC in terms of recurrence and progression with better tolerability.

Keywords:

intravesical instillation, mitomycin C, outcome assessment, recurrence, therapeutic irrigation, urinary bladder neoplasms

Egyptian J Surgery 40:278–283

© 2021 The Egyptian Journal of Surgery

1110-1121

Introduction

Carcinoma of the bladder represents a worldwide health problem ranked ninth in cancer incidence [1]. In Egypt, it represents a major health problem, with an estimated rate of 37.1 per 100 000 males [2].

At diagnosis, most of these cancers are nonmuscle-invasive lesions, yet they do show a high incidence of recurrence and progression. The main goal of treatment is tumor resection with preventing recurrence and/or progression [3].

Transurethral resection of bladder tumor (TURBT) is the first step in the diagnosis and management of bladder mass. It identifies cell type, grading, as well as the depth of muscle invasion. TURBT aims to resect all visible lesions, usually followed by an immediate intravesical instillation of single-dose chemotherapy as a standard procedure in nonmuscle-invasive bladder cancer (NMIBC). There is an accumulation of data

presuming that the instillation of a single dose of chemotherapy for low-grade NMIBC would have an effect on the reduction and/or prevention of tumor recurrence and progression [3], yet conflicting results are still emerging on its clinical benefit. The lifelong risk of recurrence and repeated interventions contributes to a poor physician and patient compliance, and it significantly burdens the health care system [4,5].

Intravesical chemotherapy decreases recurrence in up to 11% [3] of the cases, yet it can potentially cause several significant adverse effects, including severe lower urinary tract symptoms, persistent chronic bladder pain, and even bladder necrosis in case

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

reports [6,7]. Furthermore, chemotherapy is contraindicated when there is a concern for bladder perforation, and when there is significant postoperative gross hematuria and/or urinary tract infection. Considering these limitations, there is an urgent need for alternative strategies to prevent the reimplantation of tumor cells following TURBT, to reduce recurrence and minimize the morbidity of the disease.

One of the mechanisms for early recurrence of NMIBC after TURBT might be seeding of tumor cells during resection [8]. Several studies have been demonstrating the potential benefits of postoperative prolonged continuous saline irrigation of the bladder to cause cytolysis of these tumor cells and prevent this seeding, with up to 17% reduction in relative risk of recurrence compared with immediate single postoperative chemotherapy installation [3,4].

In our observational study, we reviewed the results of continuous bladder irrigation (CBI) using normal saline after TURBT in terms of recurrence and progression in patients with low-risk and intermediate-risk NMIBC with up to 20 years of follow-up, comparing it with patients who received mitomycin C (MMC) as a single postoperative adjuvant intravesical instillation.

A point of consideration is the cost of chemotherapy, availability of medicine, and the status of COVID-19 pandemic in low-middle income countries and developing countries.

Patients and method

An observation study was conducted following the tenets of Helsinki declaration. Files of 2153 patients admitted to the Urology Department of Theodor Bilharz Research Institute with bladder mass were reviewed and analyzed (Fig. 1). Ethics approval and consent to participate: Written consents were obtained from all patients. The study design was approved by the Research Ethical Committee of Theodor Bilharz Research Institute; and it was designed to be in accordance with the Helsinki Declaration of 1975. The procedures were part of standard treatment in the hospital.

Diagnosis of NMIBC was achieved by abdominal ultrasonography and computed tomography-urography, followed by urethrocystoscopy to establish the diagnosis of papillary NMIBC, which is distinct from other bladder lesions such as flat

exophytic muscle invasive bladder cancer, bilharzial granuloma, and leukoplakia.

All visual tumors are resected completely, with an additional random biopsy from suspected areas to exclude carcinoma *in situ*. A second-look cystoscopy was done in selected cases where there was doubt of incomplete tumor resection. Diagnosis of bladder perforation during the procedure was excluded or confirmed by performing cystogram while the patient on the operation table using a mobile imaging machine.

Inclusion criteria were classified into the following.

Patient criteria:

- (1) Age more than 18 years.
- (2) Naive cases with no history of bladder cancer.
- (3) Complete resection of the primary tumor.
- (4) Single immediate installation of 40 mg MMC as a single postoperative adjuvant therapy within less than 24 h of the resection (arm 1).
- (5) CBI with normal saline for more than 18 h postoperatively (arm 2).
- (6) Regular follow-up more than 24 months.

Tumor criteria:

- (1) NMIBC (Ta, T1).
- (2) Tumor grade (I and II) according to the 1973 WHO grading system.
- (3) Single tumor less than 3 cm in maximum diameter, or multiple tumors with the sum of their sizes being less than 3 cm.

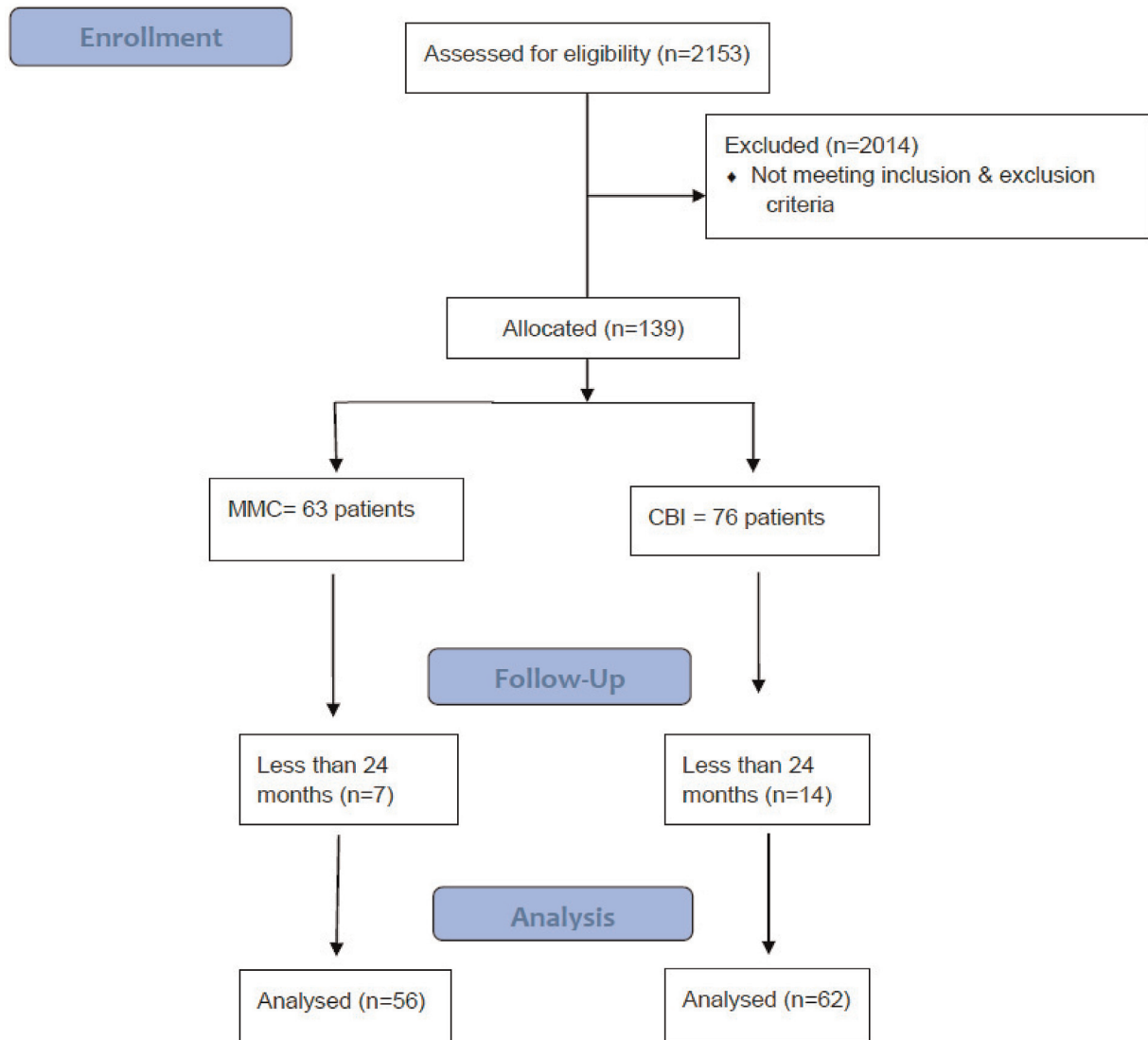
Exclusion criteria were as follows:

- (1) Muscle-invasive bladder cancer.
- (2) High-grade tumor GIII and/or carcinoma *in situ*.
- (3) Identified bladder perforation during TURBT.
- (4) Tumor at the posterior urethra.
- (5) Concomitant upper urinary tract tumors on imaging and ureterorenoscopy.
- (6) Incomplete files or lost to follow-up.

All patients underwent cystoscopy with TURBT followed either by a single instillation of 40 mg of MMC diluted in 20 ml of saline within 24 h postoperatively (63 patients) or CBI using normal saline for more than 18 h after TURBT (76 patients).

Follow-up protocol consisted of regular check cystoscopy every 3 months for the first 2 years, every

Figure 1



Patient enrollment.

6 months for 2 years, and then annually, with this in parallel to urine cytology twice yearly and imaging of the upper tract annually.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS), version 14; SPSS Inc., IBM Corp., Armonk, New York, USA), was used for statistical analysis. Using the Student's *t* test (independent sample *t* test) descriptive statistics for continuous variables were expressed as median (minimum–maximum).

The qualitative (categorical) data of the two arms were given as number of cases and percentages and were compared using χ^2 and Fisher's exact test. Differences were considered significant at a *P* value less than 0.05.

Results

The study was designed to evaluate CBI with saline in terms of efficacy and safety and compare it with single installation of MMC as adjuvant therapy. The length of follow-up was defined as the time from the first TURBT to the last cystoscopy control. Recurrence was determined by lesions that were detected at cystoscopy and confirmed pathologically during the follow-up. Progression was defined as an upstage in either tumor stage and/or grade.

At the time of analysis, only 118 patients completed at least 24 months of follow-up and were divided into two arms. There was a male predominance, with an incidence of male : female of around 2 : 1, with no statistically significant difference in other demographic data nor tumor characteristic (Table 1).

Table 1 Demographic data and tumor characteristics

	MMC (56)	CBI (62)	P
Age (median-range)	59 (42–72)	61 (41–76)	0.725
Sex [n (%)]			
Male	37 (66)	43 (69)	<0.05
Female	19 (34)	19 (31)	
Tumor stage [n (%)]			
Ta	22 (39.2)	24 (38.7)	0.635
T1	34 (60.8)	38 (62.3)	0.325
Tumor grade [n (%)]			
G1	18 (32.1)	19 (30.6)	0.428
G2	38 (67.9)	43 (69.4)	0.691

CBI, continuous bladder irrigation; MMC, mitomycin C.
P value=0.05.

Table 2 Complications

	MMC (56)	CBI (62)	P
Gross hematuria	2	3	0.591
Clot retention	1	1	0.524
Transfusion	–	–	–
Fever	3	2	0.539
Anticholinergic drugs	12	3	<0.05
Total	18 (32.1)	9 (14.5)	<0.05
Clavien-Dindo grade II complication	12	3	<0.05

CBI, continuous bladder irrigation; MMC, mitomycin C.
P value=0.05.

Postoperative complications were evaluated subjectively during the patient hospital stay in terms of presence of gross hematuria, clot retention, need for transfusion, reoperation, development of fever, and persistent irritative urinary symptoms necessitating administration of anticholinergic drugs. The results were objectively assessed using the modified Clavien-Dindo classification for urological complications (Table 2). Overall complications occurred in 18 and nine patients in MMC and CBI arms, respectively. There was no significant difference in all complications, except the need for administration of anticholinergic drugs in 12 patients in the MMC arm (grade II complication).

The median follow-up was 65 and 68 months for MMC and CBI arms, respectively. During follow-up, recurrences developed in 22 (18.6%) of the 118 patients. Overall, 10 recurrences occurred in the MMC arm, whereas 12 occurred in the CBI one. The median time to recurrence was significantly longer in cases with immediate MMC installation in comparison with CBI (Table 3).

Overall tumor progression occurred in 5.1% (6/118) of the patients, with three patients in each arm. In all patients, progression was an upstaging of tumor grade, with no change in tumor stage. The median time to

Table 3 Recurrence and progression

	MMC (56)	CBI (62)	P
Follow up (median-range)	65 (26–93)	68 (24–89)	0.527
Tumor recurrence [n (%)]	10 (17)	12 (19.3)	0.654
Time to recurrence (median-range)	33.5 (29–75)	29.5 (24–50)	<0.05
Tumor progression [n (%)]	3 (5.3)	3 (4.8)	0.631
Time to progression (median-range)	31 (31–38)	30 (30–39)	0.634

CBI, continuous bladder irrigation; MMC, mitomycin C.
P value=0.05.

progression was 30 and 31 months for MMC and CBI arms, respectively, with no significant difference between both arms.

Discussion

NMIBC accounts for ~70% of new cases of urothelial bladder cancer, with a high incidence of recurrence and progression [3,5,9]; thus, it was considered as a chronic disease owing to its high risk of future complications, which necessitates frequent monitoring and surveillance [9].

Recurrence of bladder tumor was postulated to result from incomplete resection of primary tumors, invisible mucosal changes, or tumor seedling during TURBT [10].

The effect of intravesical instillation chemotherapy may be explained either by its destroying circulating tumor cells or as having an ablative effect (chemo-resection) of residual tumor cells at the resection site [10,11].

Several chemotherapeutic agents have been used, yet MMC is the standard molecule used for immediate post-TURBT installation as adjuvant treatment in NMIBC with an objective reduction in the risk of recurrence in low-risk and intermediate-risk NMIBC, yet with reported serious morbidities [11].

The concept of surgical site irrigation using saline or distilled water to prevent local recurrence in oncological surgery was always a common practice among surgeons [12]. It is a safe procedure, with documented benefits. In 1987, Moskovitz and Levin [13] first postulated that intravesical distilled water irrigation following TURBT is associated with a lower risk of tumor recurrence. This was followed by other studies with conflicting results [14].

In our study, we retrospectively evaluated our 20 years of experience in the management of bladder cancer,

and we extracted results of CBI and single MMC intravesical administration in 118 patients with low-risk and intermediate-risk NMIBC.

Both CBI and MMC showed a low risk of recurrence and progression with more than 5 years of median follow-up. This was in accordance with all large series. There was no statistically significant difference in terms of recurrence rate and/or progression between the two arms. In 2011, Onishi *et al.* [4] performed a nonrandomized study comparing 18–22 h of postoperative CBI with saline to a full year of induction and maintenance MMC in patients with intermediate-risk NMIBC and showed no difference in several outcomes, including recurrence-free rates, time to first recurrence, and frequency of recurrences. This was confirmed in a prospective randomized study including 250 patients with a median follow-up of 37 months [14].

In our results, we had a statistically significant shorter time to recurrence in patients undergoing CBI; this shorter time of recurrence was in discordance with other studies [4,15]. However, Kuroda *et al.* [11] in 2020 have demonstrated that CBI shows shorter time to recurrence in relation to intravesical post-TURBT single installation of chemotherapy, yet in our study this relatively early time to recurrence did not affect the rate of recurrence nor the incidence and time to progression.

Single post-TURBT installation of MMC was demonstrated to be superior to continuous CBI in a retrospective analysis of 205 patients with NMIBC [16] in terms of recurrence-free survival (RFS) and incidence of progression, yet in this study, median follow-up was short (16 months), it included patients with high-grade tumors and even carcinoma *in situ*, and CBI with saline was done for only 2 h. In a systemic review of more than 1000 patients [17] with NMIBC receiving either single post-TURBT chemotherapy installation, CBI with saline, and distilled water irrigation in terms of RFS, there was no significant difference among all arms regarding the median RFS at 1 year, with saline irrigation showed the highest median RFS among the groups.

Although there are reported cases of devastating complications following intravesical single instillation of chemotherapeutic agents including bladder necrosis [6,7], both CBI with saline and MMC administration are safe procedures, and in our results, both arms had comparable safety profile, except for the development of irritative urinary symptoms necessitating

administration of bladder sedative drugs in the MMC arm.

Our study showed some points of strength yet not without limitations. We have the longest median follow-up between similar studies, yet we are a retrospective nonrandomized one with a relatively low sample size.

Conclusion

CBI following TURBT for low-risk and intermediate-risk patients with NMIBC is a valid option, with comparable efficacy and better safety profile to single post-TURBT installation to MMC. This option has to be considered especially in circumstances when the availability of drugs and access to medical care is restricted or hindered by the economic or global crisis.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

- 1 Antoni S, Ferlay J, Soerjomataram I, Znaor A, Jemal A, Bray F. Bladder cancer incidence and mortality: a global overview and recent trends. *Eur Urol* 2017; 71:96–108.
- 2 Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Pineros M, Znaor A, Bray F. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer* 2019; 144:1941–1953.
- 3 Babjuk M, Burger M, Compérat EM, Gontero P, Mostafid AH, Palou J, *et al.* European Association of Urology Guidelines on non-muscle-invasive bladder cancer (TaT1 and carcinoma in situ) – 2019 update. *Eur Urol* 2019; 76:639–657.
- 4 Onishi T, Sasaki T, Hoshina A, Yabana T. Continuous saline bladder irrigation after transurethral resection is a prophylactic treatment choice for non-muscle invasive bladder tumor. *Anticancer Res* 2011; 31:1471–1474.
- 5 Ersoy H, Yaytokgil M, Karakoyunlu AN, Topaloglu H, Sagnak L, Ozok HU. Single early instillation of mitomycin C and urinary alkalization in low-risk non-muscle-invasive bladder cancer: a preliminary study. *Drug Des Devel Ther* 2013; 7:1–6.
- 6 Lim D, Izawa JI, Middlebrook P, Chin JL. Bladder perforation after immediate postoperative intravesical instillation of mitomycin C. *Can Urol Assoc J* 2010; 4:E1–E3.
- 7 Hatem H, Leifeld J. A rare complication of intravesical early instillation of mitomycin C after TURBT. *Urol Case Rep* 2019; 26:100955.
- 8 Wang Z, Gao W, Li J, Wang T. Development and validation of a novel recurrence risk stratification for initial non-muscle invasive bladder cancer in the han Chinese population. *J Cancer* 2020; 11:1668–1678.
- 9 Burger M, Catto JW, Dalbagni G, Barton Grossman H, Herr H, Karakiewicz P, *et al.* Epidemiology and risk factors of urothelial bladder cancer. *Eur Urol* 2013; 63:234–241.
- 10 Narayan VM, Dinney CPN. Intravesical gene therapy. *Urol Clin North Am* 2020; 47:93–101.
- 11 Kuroda K, Tasaki S, Sato A, Asakuma J, Horiguchi A, Ito K. Effect of continuous saline bladder irrigation with concomitant single instillation of chemotherapy after transurethral resection on intravesical recurrence in patients with non-muscle-invasive bladder cancer. *Mol Clin Oncol* 2020; 13:6.
- 12 Ito F, Camoriano M, Seshadri M, Evans SS, Kane JM, Skitzki JJ. Water: a simple solution for tumor spillage. *Ann Surg Oncol* 2011; 18:2357–2363.

- 13 Moskovitz B, Levin DR. Intravesical irrigation with distilled water during and immediately after transurethral resection and later for superficial bladder cancer. *Eur Urol* 1987; 13:7–9.
- 14 Amos S, Gofrit ON. Prevention of bladder tumor recurrence. In: Kommu SS, editor. *Evolving trends in urology*. 1st ed. Rijeka, Croatia: InTech; 2012. pp. 69–76.
- 15 Onishi T, Sugino Y, Shibahara T, Masui S, Yabana T, Sasaki T. Randomized controlled study of the efficacy and safety of continuous saline bladder irrigation after transurethral resection for the treatment of non-muscle-invasive bladder cancer. *BJU Int* 2017; 119:276–282.
- 16 Lenis AT, Asanad K, Blaibel M, Donin NM, Chamie K. Continuous saline bladder irrigation for two hours following transurethral resection of bladder tumors in patients with non-muscle invasive bladder cancer does not prevent recurrence or progression compared with intravesical Mitomycin-C. *BMC Urol* 2018; 18:93.
- 17 Mahran A, Bukavina L, Mishra K, Buzzy C, Fish ML, Bobrow A, Ponsky L. Bladder irrigation after transurethral resection of superficial bladder cancer: a systematic review of the literature. *Can J Urol* 2018; 25:9579.