

Treatment of Large Non-Muscle-Invasive Bladder Cancer: The Potential Role of Neoadjuvant Intravesical Chemotherapy

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Keywords

Bladder cancer · Non-muscle-invasive · Intravesical chemotherapy · Mitomycin.

Abstract

Introduction: The endoscopic resection of large and bulky bladder cancers represents a challenge. To reduce the tumor and make it more easy to resect, we used neoadjuvant short and intensive intravesical mitomycin (MMC) therapy. **Methods:** Patients with large bladder tumors were evaluated for this study. At cystoscopy, the surgeon evaluated the feasibility of complete resection. In patients where this was not possible, biopsies from the tumor, bladder mucosa, and prostatic urethra were taken. These patients then underwent a short and intensive cytoreductive schedule of intravesical MMC. This was then followed by TUR-BT. **Results:** Fifteen patients were included in our study. The mean age was 74 years (range: 56–82; SD ±6 years). Mean tumor size was 51 mm (range: 35–65; SD ±8 mm). After neoadjuvant treatment, complete resection was then feasible in all patients. The mean tumor volume after the chemo-resection had reduced to 34 mm (range: 10–50; SD ±13 mm). No adverse effects

were reported. **Conclusion:** Intravesical cytoreductive neoadjuvant MMC as an initial treatment of large NMIBC can be considered safe, effective, and feasible.

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Introduction

When first diagnosed, bladder tumors are non-muscle invasive (NMIBC) in approximately 75% of cases [1]. Sometimes symptoms are mild or delayed, and the tumor can grow unnoticed into a large intra-luminal, multicentric, polymorphic branching bulky mass.

Most of these large bladder cancers pose a significant risk for tumor recurrence and progression. Immediate radical cystectomy is an option which, when done before progression in high-risk NMIBC cases, has a better sur-

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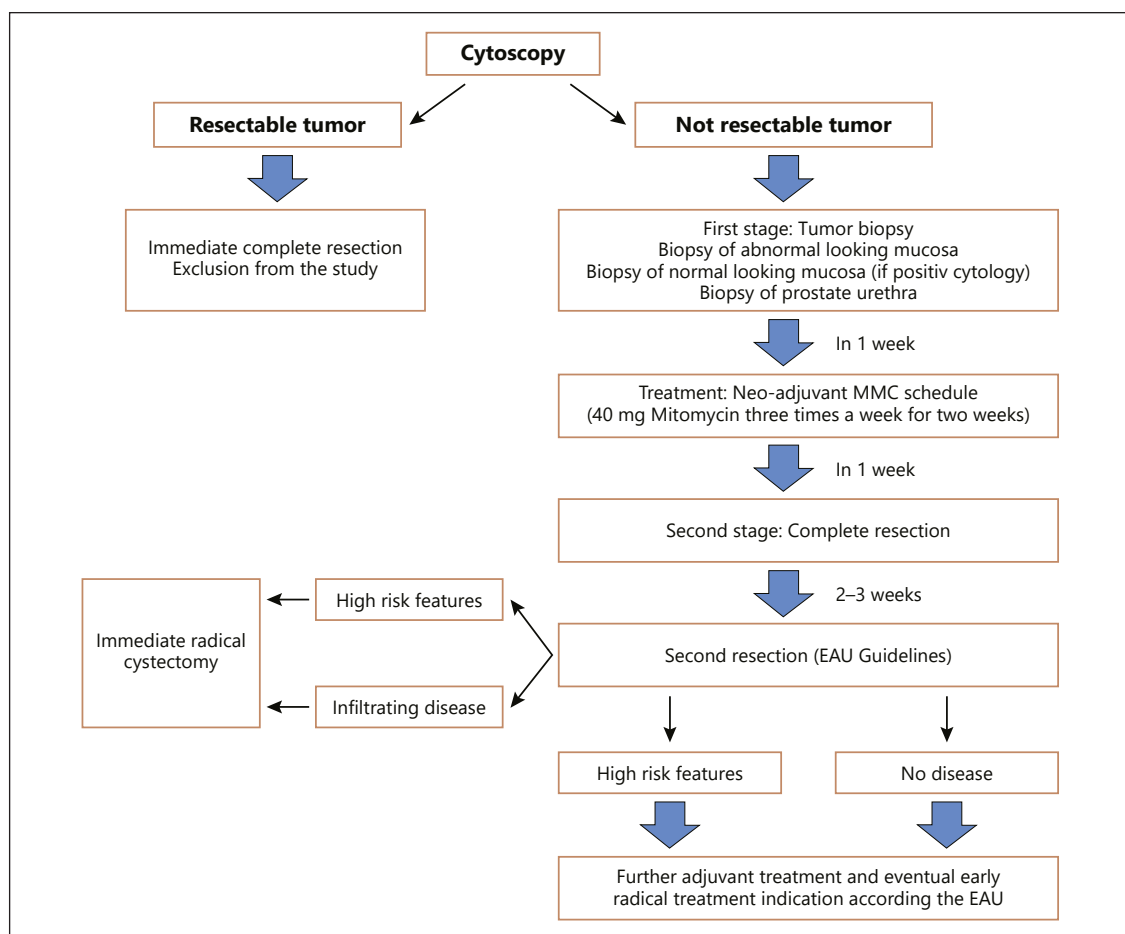


Fig. 1. Study design.

vival rate [2–7]. It is however impossible to predict which patient will progress and which one will not. In the latter, radical cystectomy might result in a significant overtreatment with its well-known associated morbidities. In patients unfit for major surgery, or patients who are reluctant to undergo cystectomy unless a definite bladder wall infiltration has been proven, bladder-sparing treatment in the form of a transurethral resection (TUR-BT) remains the only option. Complete resection of these large tumors can be difficult or impossible in one session, with a significant associated morbidity, that is severe bleeding, bladder perforation, etc.

Intravesical chemotherapy can reduce tumor size before TUR-BT [8, 9]. Thus, these unresectable tumors could be reduced in size and become easily amenable to complete resection. The aim of this study was to assess whether a short intensive course of mitomycin (MMC) can indeed reduce the tumor bulk of large NMIBC and make them easier resectable.

Methods

Study Design

Patients with large exophytic bladder tumors were identified. All patients underwent the following diagnostic steps:

- urine cytology;
- CT staging with measurement of the tumor diameter;
- cystoscopy with the patients prepared for eventual complete resection if possible;
- during cystoscopy, the surgeon would assess the feasibility of complete resection (tumor volume, complexity of morphology, presence of numerous papillary tumor branches, and bleeding risk);
- tumor resection or, in cases of non-feasible resection:
 - biopsies from tumor and abnormal-looking urothelium;
 - biopsies from normal-looking urothelium when cytology positive;
 - biopsies from prostatic urethra.

In cases of non-resectable tumors, we defined the above steps as “stage 1.” Seven days post-cystoscopy, these patients underwent neoadjuvant cytoreductive bladder instillations with 40 mg MMC in normal saline, 3 times a week for 2 weeks.

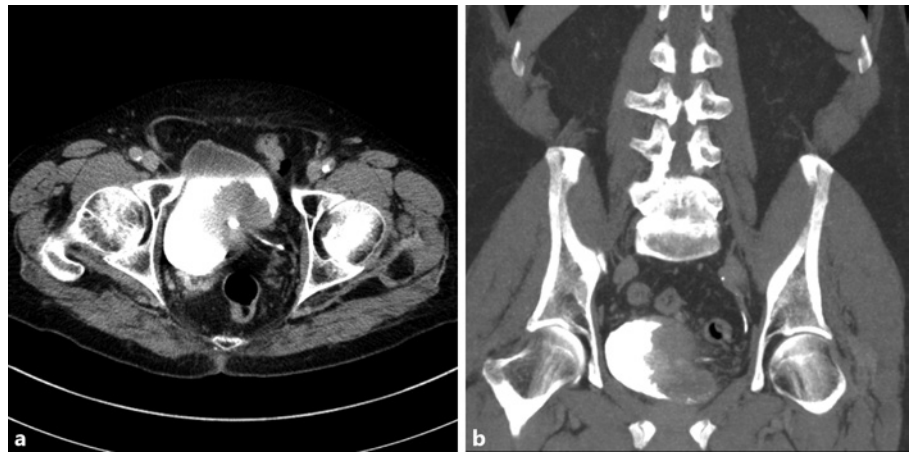


Fig. 2. a, b Large-volume intravesical tumor filling more than 50% of the bladder volume. No peri-vesical invasion visible.

Seven days after completion of this MMC schedule, patients underwent transurethral complete resection of the bladder tumor. We defined this step as “stage 2.” After secondary complete tumor resection, further treatment and follow-up was according to EAU guidelines [10].

Histological examination was performed according to the WHO/ISUP classification of tumors of the urinary tract [11, 12] and revised according to the recently introduced WHO 2016 classification [13, 14] (Fig. 1).

Patient Population

A sub-group of 15 patients with large non-resectable bladder tumors but not suitable for cystectomy because of either individual preference and/or comorbidities was included in this study. Patients were informed and consented about the technical difficulties in transurethral resection of such large bladder tumors and the potential for uncontrolled bleeding that might necessitate an open procedure or even an emergency cystectomy. They were also made aware about the high likelihood of a staged procedure in order to reduce the tumor volume and to increase the chance to complete the resection and staging. Patients were informed about the high risk of having an infiltrating or progressive disease, and about an early radical cystectomy being a viable option. A specific informed written consent was obtained from all patients in our study.

Follow-Up

The first follow-up was at 3 months postoperatively with cystoscopy and urinary cytology. If negative, subsequent cystoscopies and cytologies were repeated every 3 months for a period of 2 years, and every 6 months thereafter for the next 3 years, and then yearly. In addition, a CT-IVU was done yearly.

Therapy failure was defined according to the EAU guidelines [10] as follows:

- progression to muscle-invasive bladder cancer;
- BCG refractory tumor;
- high-grade recurrence after BCG;
- BCG relapsing tumor;
- BCG unresponsive tumor.

Data Collection and Statistical Analysis

Data were recorded in an Excel worksheet (Microsoft Corporation, Redmond, WA, USA). We collected baseline patient charac-

teristics at diagnosis and after the initial cystoscopy/first attempt of resection (stage 1). In detail, we recorded the patient age, the tumor size (main diameter), urine cytology, and the biopsy results of the tumor biopsy, abnormal-looking urothelium, and normal-looking mucosa when cytology was positive.

In the same way, we collected the post-treatment results and we recorded the residual tumor size (main diameter), T stage and grade, the results after the “2nd look” resection [10], the following adjuvant treatment, and follow-up. The variations of the tumor volumes after treatment, as a continuous variable, were statistically compared with *t*-test and were considered significantly different when $p < 0.05$.

Results

Between November 2012 and July 2016, 15 patients were treated for large exophytic bladder tumors. Eleven of them (73%) were male. After initial cystoscopy, a complete resection was found technically impossible in all 15 patients. Mean patient age was 74 years (range: 56–82; SD ± 6 yr). Mean tumor size was 51 mm (range: 35–65; SD ± 8 mm). In these cases, CT-IVU scan showed a normal upper urinary tract and no peri-vesical invasion (Fig. 2a, b). Urinary cytology was positive in 5 (33%) patients.

The tumor biopsy showed high grade in 8 (53%) and low-grade transitional cell carcinoma in 7 (47%), respectively. Concomitant carcinoma in situ was found in 3 (20%) of patients, thereof in 2 (13%) in the prostatic urethra.

Patients were then treated with an MMC schedule as described above. No adverse effects were reported. Patient compliance was good, and there were no dropouts. After this cytoreductive treatment, the complete resection was then feasible in all patients. The mean tumor volume after the chemo-resection was reduced to 34 mm (range: 10–50; SD ± 13 mm). This 33% reduction in size was statistically significant ($p < 0.0001$).

Table 1. Study's results

Age	Pre-MMC treatment					Post-MMC treatment			2nd look	Adjuvant treatment	Follow-up	Results at follow-up
	Characteristics at initial cystoscopy and resection attempt (stage 1)					Characteristics at cystoscopy and TUR-BT (stage 2)						
	size	cytol	tumor grade	CisB	CisPU	size	tumor grade	tumor stage	tumor stage			
72	62	Pos	High	-	-	48	High	Ta	Free	BCG	72	Ta low-grade rec
80	51	Neg	High	-	-	34	High	T1	Free	BCG	48	Ta low-grade rec
65	58	Neg	Low	-	-	48	Low	Ta	Free	BCG	60	Ta low-grade rec
68	65	Pos	High	Cis	Cis	52	High	T1	T1	RC	0	
78	55	Pos	High	-	-	40	High	T1	Free	BCG	48	CR
82	60	Pos	High	Cis	-	50	High	ND	T1	BCG	3	Early RC
67	45	Neg	Low	-	-	20	Low	Ta	Free	BCG	60	CR
56	40	Neg	Low	-	-	20	Low	Ta	Free	BCG	60	CR
67	36	Neg	Low	-	-	15	Low	Ta	Free	BCG	48	CR
72	48	Neg	Low	-	-	25	Low	Ta	Free	BCG	60	CR
75	60	Pos	High	Cis	Cis	50	High	T2		RC	0	
80	50	Neg	High	-	-	35	High	T1	Free	BCG	60	Ta low-grade rec
81	45	Neg	Low	-	-	20	Low	Ta	Free	BCG	60	CR
82	60	Neg	High	-	-	45	High	T1	Free	BCG	48	Ta low-grade rec
79	35	Neg	Low	-	-	10	Low	Ta	Free	BCG	60	CR

Pre-MMC treatment baseline characteristics and the results of initial 1st stage resection. In the post-MMC treatment section, the final staging results are shown. CisPU, cis in biopsies of prostate urethra; CisB, cis in biopsies of abnormal-looking urothelium and biopsies from normal-looking mucosa when cytology was positive; CR, complete response; RC, radical cystectomy; BCG, induction and maintenance schedule; MMC, mitomycin; TUR, transurethral resection.

Staging showed Ta in 8 (53%), T1 in 5 (33%), and T2 in 1 (7%) of patients, respectively. One patient (7%) had no muscular layer in the biopsies and therefore remained unstaged. The T2 patient underwent immediate radical cystectomy. The remaining fourteen went for a second resection according to the EAU guidelines [10].

Twelve of these (86%) were disease-free, whereas 2 (14%) still were stage T1 in their re-resection histology. One of the T1 patients underwent immediate radical cystectomy because of a high progression risk.

Postoperatively, all remaining patients underwent BCG induction and maintenance treatment. One patient had a T1 recurrence 1 month after BCG induction and underwent early cystectomy. Twelve patients (80%) thus preserved their bladder within a mean follow-up of 55 months (range: 36–72; SD \pm 9 months) (Table 1).

Discussion

In our study, neoadjuvant treatment of large unresectable bladder tumors did lead to a significant volume reduction of 33%. Still, in about 50% of patients, this reduc-

tion resulted in a tumor volume that could be considered as too large for a primary TUR-BT before neoadjuvant chemotherapy. However, for a same given volume, resection before and after treatment is quite different in terms of difficulty. In our experience, even large tumors became resectable because of the loss of their diffuse papillary branches as a result of cytoreduction (Fig. 3a, b). In fact, the resection after MMC treatment became easier, faster, without significant bleeding and complete with a good sampling at the tumor base. In 1 patient (7%) only, staging was still not possible because of the lack of muscle layer in the biopsy.

The sensitivity of urinary cytology in our study was 62.5% which is quite lower than expected. In fact, a recent review and meta-analysis on the topic estimates the sensitivity as 83% in high grade cancers [15]. However, sensitivity is usually reported in literature as the examination of morning urine on 3 consecutive days. In our study, all the patients were hospitalized, and we did not have the chance to do a complete set of 3 cytologies. Another reason of underestimation is the low number of patients. A little change in false and true positives and negatives can reflect in a high variation of sensitivity.

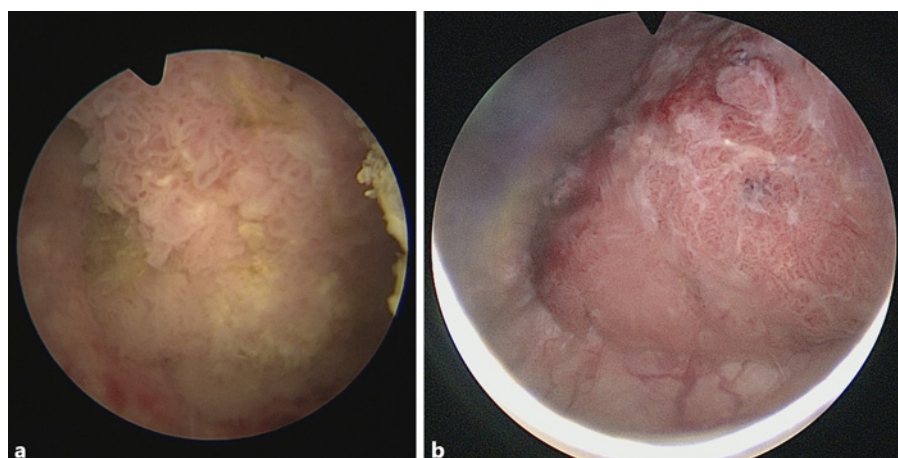


Fig. 3. a, b Large bladder tumor with diffuse papillary branches on initial cystoscopic assessment (**a**) and after cytoreductive MMC treatment (**b**). MMC, mitomycin.

Of all our patients with large bladder tumors that would potentially have been treated with immediate radical cystectomy, at the end, only 1 (7%) had proven infiltrating disease. One might speculate that in the natural history of some non-symptomatic NMIBC, infiltration is a late phenomenon and the need for radical treatment may therefore be less than expected. However, we must of course not ignore that large volume bladder cancers are at high risk of infiltration and progression and immediate radical cystectomy should be carefully discussed with the patient [2–7]. Patients reported here either were not good candidates for radical cystectomy because of significant comorbidities, or they refused radical cystectomy having no proof of invasive cancer.

Intravesical MMC is empirically administered traditionally on a weekly basis. The short-term intensive MMC schedule was based on previous *in vitro* studies that took into consideration the observed biology of the tumor growth [16]. However, 3 instillations a week for 2 weeks are expected to increase the side effects and the tolerability of this treatment. Colombo et al. [17] presented their preliminary results of a randomized phase 2 study of neoadjuvant short-term intensive intravesical MMC compared with a weekly schedule of MMC for the treatment of low-grade recurrent NMIBC before TUR-BT. There were no significant differences in local or systemic toxicity between the groups although 2 patients on the intensive schedule discontinued treatment after the fourth instillation because of severe cystitis symptoms. In our experience, the safety profile was similar, without any side effects. Moreover, we did not experience any dropouts in our patient series.

Earlier, the same group studied the effect of neoadjuvant cytoreductive microwave hyperthermia with the SB-

TS 101 system (Synergo® Medical Enterprises, Amsterdam, The Netherlands) combined with intra-vesical MMC. This showed an increased cytoreductive effect on large bladder tumors with both treatments combined [18]. Although we used a different and more intense neoadjuvant schedule without hyperthermia, our results were similar in terms of resection being made feasible in all cases. In the absence of a microwave machine, our approach seems to be more cost-effective and immediately available.

In our series, 2 (13%) patients received immediate radical cystectomy after TUR-BT, and 1 (7%) underwent early cystectomy after BCG failure. Admittedly, in these patients, the schedule delayed the radical treatment by 4 weeks. Whether this delay could affect the patient survival is questionable. Gore et al. [19] reported that delaying cystectomy for patients with muscle-invasive bladder cancer over and above 12 weeks confers worse disease-specific and overall survival. This can be considered a potential limitation of our study. Another limitation is the low number of patients.

Intravesical cytoreductive neoadjuvant MMC regimen as an initial treatment for large non-resectable NMIBC can be considered safe, effective, and feasible and, if carefully done, it does not delay significantly a potentially curative treatment. Through significant reduction of tumor volume, it will facilitate the complete resection with less bleeding and a good access to the tumor base which is a prerequisite for accurate staging. Moreover, the outcome of this approach may help us to determine further management either conservatively or with radical cystectomy. Multicenter prospective randomized studies are needed to verify the use of intensive neoadjuvant intravesical MMC.

Statement of Ethics

Most of the applied study protocol is part of the official guidelines of European Association of Urology [10]. The feasibility of the bladder cancer resection was evaluated by the surgeon at the time of cystoscopy and included a risk assessment according to the rules of good medical practice. The study was approved by the internal medical board of the Istituto Clinico Citta' Studi, Milan/Italy.

Patients were informed and consented about the technical difficulties and risks in attempting a complete transurethral resection and the potential of severe bleeding that could necessitate an emergency cystectomy. They were consented for the possibility of an incomplete or no resection of their bulky bladder cancer and the need for later cystectomy if indicated by histology.

Conflict of Interest Statement

All authors have no conflicts of interest to declare.

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Author Contributions

All the authors had active part in the following:

- the conception and design of the work or the acquisition and interpretations of data
- drafting the work or revising it critically for important intellectual content
- final approval of the version to be published
- agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.