

Induction and Maintenance Adjuvant Mitomycin C Topical Therapy for Upper Tract Urothelial Carcinoma: Tolerability and Intermediate Term Outcomes

Michael Metcalfe, MD,¹ Gavin Wagenheim, MD,^{1,2} Lianchun Xiao, MS,³ John Papadopoulos, MD,¹ Neema Navai, MD,¹ John W. Davis, MD,¹ Jose A. Karam, MD,¹ Ashish M. Kamat, MD,¹ Christopher G. Wood, MD,¹ Colin P. Dinney, MD,¹ and Surena F. Matin, MD¹

Abstract

Purpose: Endoscopic management of upper tract urothelial carcinoma (UTUC) is associated with higher recurrences, which could be reduced by application of topical therapy. Adjuvant induction Bacillus Calmette–Guerin has shown inferior outcomes for UTUC compared to bladder cancer, and maintenance regimens for UTUC are unexplored. We report on the efficacy, safety, and tolerability of Mitomycin C (MMC) induction and maintenance adjuvant topical therapy for UTUC.

Materials and Methods: Patients with UTUC who received adjuvant topical therapy after complete endoscopic control of Ta/T1 tumors were retrospectively reviewed. Patients were treated using percutaneous nephrostomy tube (NT) or cystoscopically placed weekly ureteral catheters, per patient preference, and all patients were offered induction and maintenance. Standardized follow-up of every 3 months in the first year, then at a minimum every 6 months, with ureteroscopy and at least annual CT, was performed. Primary outcomes were recurrence-free, progression-free, nephroureterectomy-free rate and cancer-specific and overall survival. Secondary outcomes were safety and treatment tolerability.

Results: Twenty-seven patients with 28 renal units received adjuvant topical therapy from January 2008 to March 2015. Median follow-up was 19 months (range 7–92). Three year recurrence-free, progression-free, and nephroureterectomy-free survival rates were 60% [confidence interval (95% CI): 42, 86%], 80% [95% CI: 64, 100%], and 76% [95% CI: 60, 97%]. Cancer-specific mortality rate was 0%, and 3-year overall survival was 92.9%. Nine patients experienced adverse outcomes, all related to interventions and none related to systemic toxicity.

Conclusions: Induction and maintenance adjuvant topical MMC for endoscopically resected UTUC is feasible, well tolerated and shows promising intermediate term data on recurrence, progression, and nephroureterectomy-free survival.

Keywords: ureteral cancer, renal pelvis cancer, chemotherapy, urothelial cancer, outcomes

Introduction

ALTHOUGH THE STANDARD OF CARE for upper tract urothelial carcinoma (UTUC) is considered to be radical nephroureterectomy with bladder cuff excision,^{1,2} there are indications for kidney-preserving approaches. These include patients with bilateral tumors, tumors in a solitary kidney, chronic renal failure, and more electively, those with select small low-grade tumors. Kidney-preserving treatments may be delivered surgically or endoscopically, through either antegrade or retrograde access, and are well described.^{1,2}

Unfortunately, reported recurrence rates after endoscopic treatment of UTUC have been high, from 30% to 90% (Table 1).^{3–12} Based on the effectiveness of adjuvant intravesical instillation therapy for UC of the bladder,^{13,14} the role of topical therapy for properly selected cases of UTUC has been described. Several agents have been proposed for topical treatment.^{15–20} But due to the rarity of the disease the sample sizes are small, and the optimal route and true benefit of adjuvant instillation therapy for UTUC remain unknown.

Published data show a recurrence-free survival (RFS) of 41% and progression free-survival (PFS) of 59% in patients with

¹Department of Urology, MD Anderson Cancer Center, The University of Texas, Houston, Texas.

²Department of Urology, The University of Texas Health Science Center at Houston, Houston, Texas.

³Department of Biostatistics, MD Anderson Cancer Center, The University of Texas, Houston, Texas.

TABLE 1. RECURRENCE RATES DEMONSTRATED IN STUDIES FOR PATIENTS UNDERGOING ENDOSCOPIC ABLATION ALONE OR WITH EITHER ADJUVANT MITOMYCIN C OR BACILLUS CALMETTE–GUERIN

<i>Intervention</i>	<i>Author (reference)</i>	<i>Date of publication</i>	<i>Number of patients</i>	<i>Recurrence rate, %</i>
Endoscopic ablation				
	Daneshmand et al. ⁵	2003	30	90
	Chen and Bagley ⁶	2000	23	65
	Raymundo et al. ¹⁰	2011	22	48
	Grasso et al. ⁷	1999	14	50
	Cutress et al. ³	2012	73	69
	Roupret et al. ⁸	2006	27	22
	Thompson et al. ⁹	2008	83	55
	Gadzinski et al. ¹¹	2010	34	84
	Pak et al. ¹²	2009	57	90
Endoscopic ablation with adjuvant BCG				
	Patel and Fuchs ²⁰	1998	12	13
	Rastinehad et al. ¹⁶	2009	89	36
	Giannarini et al. ¹⁵	2011	22	59
Endoscopic ablation with single dose adjuvant MMC				
	Aboumarzouk et al. ¹⁹	2013	19	35
	Keeley and Bagley ¹⁸	1997	19	54
	Cutress et al. ³	2012	17	68

BCG=Bacillus Calmette–Guerin; MMC=Mitomycin C.

Ta or T1 UTUC treated with antegrade perfusion of bacillus Calmette–Guerin (BCG) as an induction regimen.¹⁵ In that series, 23% of the treated units underwent subsequent nephroureterectomy.¹⁵ These results are inferior to what is seen in adjuvant treatment of bladder cancer,¹³ possibly due to higher rates of residual disease, greater difficulty in definitive delivery to the upper tract, and the absence of a reservoir allowing long dwell times. The results of BCG for treatment of upper tract carcinoma *in situ* (CIS) appear to be more promising.^{4,15}

The results of adjuvant Mitomycin C (MMC) as induction have also been reported in several small series.^{3,18,19,21} These results demonstrate the safety of upper tract instillation of MMC. However, neither the agent nor its method of delivery has been standardized. To our knowledge the feasibility, tolerability, and efficacy of induction and maintenance therapy have not been systematically assessed. Given the inferior outcomes of BCG as adjuvant treatment of endoscopically treated UTUC, we made a clinical decision in 2008 to offer MMC adjuvant therapy as induction, as well as maintenance therapy, in the hopes of achieving more optimal outcomes. We now report intermediate term data on the efficacy, safety, and tolerability of MMC topical adjuvant therapy given as an induction and maintenance regimen.

Materials and Methods

Patients

After Institutional Review Board approval, the charts of patients with UTUC who received adjuvant topical therapy after complete endoscopic control of Ta/T1 tumors were retrospectively reviewed. Patients with CIS were excluded as it has been a practice at our center to offer initial BCG to those patients given the more effective published data.¹⁵ Patients were classified as being treated on an elective, imperative, or palliative basis. Elective patients were treated with curative intent and had a normal contralateral upper tract and normal renal function. Imperative patients were treated with curative intent and had bilateral tumors, tumor in a solitary kidney, or chronic kidney

disease, defined as estimated GFR (eGFR) <60. Palliative patients were treated with the goal of local control for maintenance of renal function.

Additional variables collected included demographic data, smoking history, family history, cytology results, complications, renal function, and follow-up data. Lynch syndrome was considered positive based on Amsterdam criteria II, tissue, or genetic testing.²²

Diagnostic methods

Diagnoses were made with ureteroscopic or percutaneous guided biopsy. All pathologic results were reviewed at our institution by genitourinary fellowship trained pathologists.

Treatments

Endoscopic control consisted first of biopsy, then of either ureteroscopic or percutaneous resection, and/or laser ablation of all visible disease burdens. This was done either primarily or in a staged manner, but completed before the initiation of topical therapy. Ureteroscopic management included using a variety of tools to obtain adequate tissue for diagnosis, including use of access sheaths, and a variety of biopsy tools such as a 3F biopsy forceps, steel-wire basket, and 1.7F Nitinol stone extractor basket (Piranha[®], Atlas Wire Stone Basket[®], and N-Gage[®], respectively; Cook Medical, Bloomington, IN). Endoscopic ablation was performed with a holmium laser (200 micron fiber, 10 Hz, 100 mJ initial settings then adjusted as necessary). If staged procedures were necessary due to high volume of disease, or presence of hematuria, they were performed on average 2 weeks apart with a stent left in between the two procedures.

Patients were treated either through a 10F percutaneous nephrostomy tube (NT) or by weekly cystoscopic placement of 5F ureteral catheters (Fig. 1). The method of treatment was per patient preference after being informed of the pros and cons of either modality. Patients with NTs were given 2 weeks to have the tract mature before initiating infusion, with the NT changed every 3 months. Patients treated with a ureteral catheter

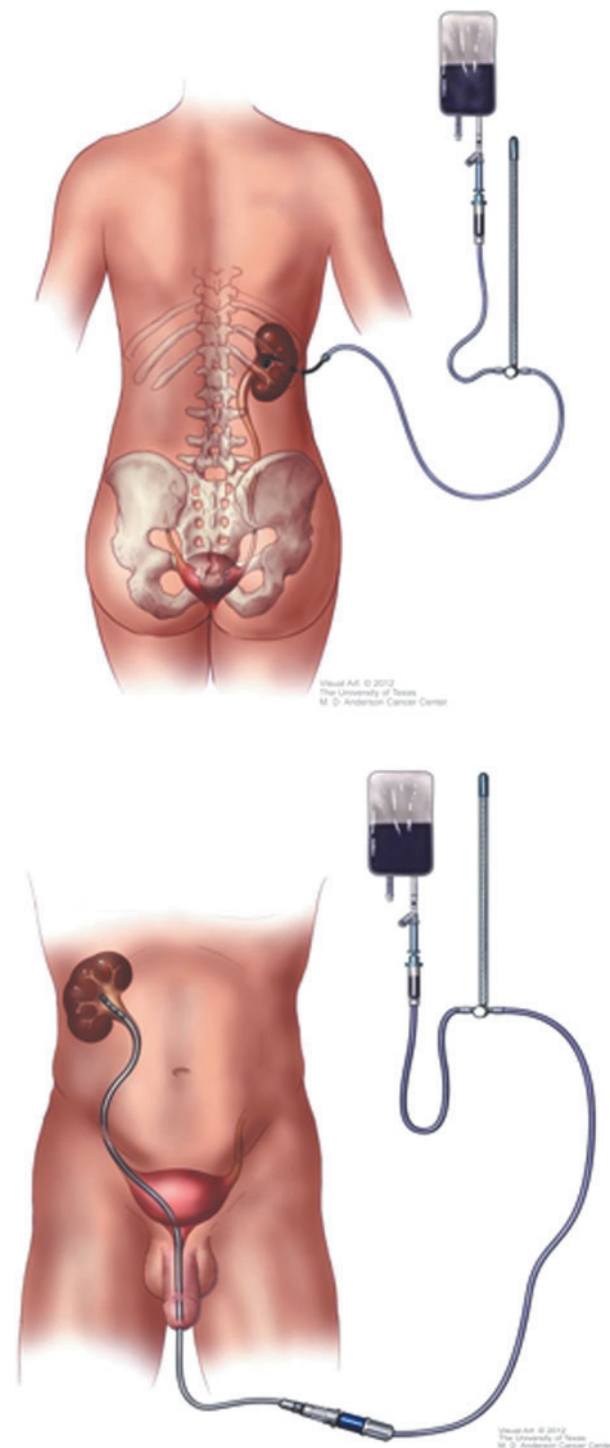


FIG. 1. Schema showing how patients received upper tract topical therapy with Mitomycin C either through percutaneous nephrostomy (*top*) or ureteral catheter (*bottom*).

had office flexible cystoscopy with placement of a ureteral catheter (Beacon[®] tip; Cook Medical) performed under fluoroscopic guidance using only intraurethral 2% lidocaine jelly for analgesia. A Foley catheter was placed to secure the Beacon tip with a silk tie.

Patients were treated by nurses in the urology ambulatory office setting with 40 mg of MMC mixed in 20 mL of physiologic saline, with slow drip infusion over 2 hours and controlled

by manometry pressures at or below 20 to 30 mmHg. Patients were asked to assume different positions (left side, right side, prone, and supine) every 15 to 20 minutes to ensure adequate contact with the entire upper tract system. After completion, the Beacon tip catheter and Foley catheter were removed. Patients with NTs had the tube capped. Urinary cultures were performed at the initial visit and subsequently only in the presence of symptoms or signs of infection. Prophylactic oral antibiotics were prescribed for one to two doses at the time of each treatment. Induction courses consisted of once weekly instillations for 6 weeks. Maintenance course consisted of either once monthly for at least 3 months or once weekly instillations for 3 weeks, following previously the protocol for BCG therapy¹³ depending on availability and convenience of the patient.

Follow-up

Patients were followed up every 3 months in the first year and then every 6 months for at least 2 years. Evaluations consisted of ureteroscopy, urine cytology, chemistry panel, complete blood count, and triple-phase CT. In patients with contraindication to contrasted scan, magnetic resonance urogram or retrograde studies were substituted for CT.

Outcome measures and statistical analyses

Primary outcomes measured were RFS, PFS, and nephroureterectomy-free survival (NUxFS) on a per renal unit (RU) basis and cancer-specific and overall survival on a per patient basis. Recurrence was defined as an ipsilateral UTUC tumor of higher stage and/or grade. Subanalyses were performed to evaluate RFS, PFS, and NUxFS rate based on delivery method and presence or absence of Lynch Syndrome. A secondary outcome measure was treatment tolerability. Adverse events (AEs) were recorded and classified based on the Clavien-Dindo scale.

Statistical analysis

Continuous variables are reported as median values with interquartile range. Comparison was made using Student's *t*-test for continuous variables and Fisher's exact test for nominal variables. The Kaplan-Meier method was used to estimate probability of RFS, PFS, and NUxFS. The log rank test was applied to compare these survival outcomes between subgroups of patients.

Results

Between January 2008 and January 2015, 140 patients underwent ureteroscopic biopsy for UTUC at our center. Forty-nine patients (35%) were identified for potential topical therapy after complete endoscopic assessment. Of these, 22 (45%) received BCG for CIS. Twenty-seven (55%) patients received MMC for endoscopically-managed papillary Ta/T1 tumors, one of whom had bilateral disease, resulting in 28 total RUs. These 27 patients and 28 RUs comprise the population of this study. Twenty-one RUs had low-grade UTUC (75%) and 7 RUs high-grade UTUC (25%) (Table 2). Median follow-up was 19 months with a median number of three ureteroscopies performed post initial diagnosis.

Most patients received all 6 doses of induction MMC (24/28, 85.7%), 1 (3.7%) RU received 5 doses, and 4 (14.8%) patients received 3 doses. One maintenance course was completed by 60.7% (17/28), 35.7% (10/28) completed 2 maintenance

TABLE 2. BASELINE DEMOGRAPHIC INFORMATION FOR PATIENTS UNDERGOING ADJUVANT MITOMYCIN C

Demographics	N = 27
Gender, n (%)	
Female	12 (42.9)
Male	16 (57.1)
Age (year)	
Median (IQR)	74 (64–79)
Race, n (%)	
Asian	1 (3.6)
African American	3 (10.7)
Hispanic	1 (3.6)
Caucasian	23 (82.1)
ASA classification, n (%)	
0–1	11 (40.1)
2–3	16 (59.3)
Biopsy grade, n (%)	
High	7 (25)
Low	21 (75)
Tumor focality, n (%)	
Solitary	19 (67.9)
Multifocal	9 (32.1)
Renal function at diagnosis, n (%)	
Normal	16 (57.1)
Insufficiency	12 (42.9)
Solitary Kidney, n (%)	
Solitary	6 (22.2)
Bilateral	21 (77.8)
Treatment indication, n (%)	
Elective	13 (46.4)
Imperative	13 (46.4)
Palliative	2 (7.1)
Delivery method, n (%)	
Nephrostomy	9 (32.1)
Ureteral catheter	19 (67.9)
Smoking history, n (%)	
Smoker	12 (42.9)
Nonsmoker	16 (57.1)
Lynch syndrome, n (%)	
Positive	5 (18.5)
Negative	22 (81.5)
Number of ureteroscopies postdiagnosis	
Median (IQR)	3 (2–4)

ASA = American Society of Anesthesiology; IQR = interquartile range.

courses 17.8% (5/28) completed courses 3, 4, and 5, and 7.1% (2/28) patients completed 6 courses. Two of the patients that received three doses of induction therapy went on to receive monthly maintenance. The other three patients who stopped induction early did not have any further instillation due to recurrent urinary tract infections¹; one patient did not want to continue traveling to our center and one patient had bothersome bladder spasms.

Upper tract recurrence occurred in 11 (39%) patients, with a 3-year recurrence-free survival of 60% [confidence interval (95% CI): 42, 86%]. Of these recurrences, 8 (38%) patients had low-grade disease and 3 (43%) had high-grade disease. Bladder recurrence was seen in 8 (29%) patients, 7 (33%) low grade and 1 (14%) high grade. The 3-year RFS rate was 62% [95% CI: 42, 91%] for low-grade patients and 60% [95% CI: 29, 100%] for high-grade patients (Table 3). Fifty-three percent (9/17) of patients had no evidence of recurrence on maintenance.

Local progression was seen in 5 (18%) patients

The 3-year progression-free survival rate was 80% [95% CI: 64, 100%], 87% [95% CI: 72, 100%] for low-grade patients and 67% [95% CI: 38, 100%] for high grade (Table 4).

Five (18%) of the 28 RUs proceeded to nephroureterectomy with a 3-year nephroureterectomy-free rate of 76% [95% CI: 60, 97%], 82% [95% CI: 65, 100%] for low-grade patients and 67% [95% CI: 38, 100%] for high grade (Table 5). Four patients who had a nephroureterectomy had tumor progression, two of whom were volume progression and two of whom were grade progression. One patient had multiple low-grade recurrences on MMC and elected for nephroureterectomy. Cancer-specific mortality rate was 0%, and overall 3-year survival rate was 92.9% (5% CI: 0.803, 1). Figure 2 shows Kaplan–Meir estimates for cumulative RFS, PFS, and NUxFS.

Ten AEs were seen in nine patients of which four (14%) were detected after induction and six (12%) after maintenance (Table 6). No events related to MMC absorption such as bone marrow depression, anemia, or leukopenia were identified. Four patients had ureteral strictures, all treated with ureteral catheter, three had ureteral tumors treated with strictures occurring at the site of endoscopic resection, and one patient had a past history of prostate radiation therapy.

Discussion

Adjuvant topical MMC as induction and maintenance for UTUC appears to be a well-tolerated, feasible, and possibly beneficial approach to conservative management of Ta/T1 tumors after complete endoscopic control. Our 3-year RFS and PFS rates of 60% and 80%, respectively, support further consideration of upper tract topical MMC as a reasonable initial therapeutic agent for UTUC when given with a maintenance regimen. This compares favorably to treatment with BCG with RFS and PFS of 41% and 59%, although NUxFS rates were similar.¹⁵ The treatment was well tolerated without evidence of systemic absorption, but with potential for local AEs.

Adjuvant topical therapy for UTUC was first described by Herr in 1985 for a patient with positive margins after resection for muscle invasive disease.²³ After this, several institutions reported on the use of upper tract BCG perfusion for both primary treatment of CIS and adjuvant therapy of papillary tumors. In a systematic review by Cutress and colleagues, the rate of recurrence of endoscopic resection ranges between 10% and 90%.⁴ Table 1 provides an outline of the recurrence rates of the larger and more contemporary studies. Adjuvant therapy of BCG and MMC has both been investigated. BCG demonstrated recurrence rates of 13% to 36% in the upper tract.^{4,16,19,24–26} These data do not mirror the success of intravesical BCG for UC of the bladder that has been extensively published.¹³ Use of MMC in the upper tract has been performed at times through endoscopic resection.^{3,18,19,21} And although in small series it is safe, it has demonstrated a recurrence rate of 24% to 68%. Our recurrence-free survival of 62% at 3 years represents one of the more favorable results in the literature. Most recently, much attention has been gained with the potential applicability of MMC using a thermo-sensitive polymer to increase the dwell time; however, no clinical data have been released.²⁷ We postulated that by utilizing a chemotherapeutic agent that does not rely on prolonged dwell times to incite an immunologic and cytokine response in a maintenance regimen, results could be improved.

TABLE 3. RECURRENCE-FREE SURVIVAL FOR PATIENTS UNDERGOING ADJUVANT MITOMYCIN C

<i>Variable</i>	<i>N</i>	<i>Recurrence</i>	<i>RFS rate at 3 years (95% CI)</i>	<i>RFS rate at 5 years(95% CI)</i>
Overall	28	11	0.6 (0.42, 0.86)	0.36 (0.16, 0.80)
Tumor grade				
Low	21	9	0.62 (0.42, 0.91)	0.31 (0.11, 0.89)
High	7	2	0.6 (0.29, 1)	
Focality				
Solitary	9	6	0.73 (0.52, 1)	
Multifocal	9	5	0.4 (0.17, 0.94)	0.4 (0.17, 0.94)
Renal function at diagnosis				
eGFR ≥60	15	4	0.67 (0.43, 1)	0.67 (0.43, 1)
eGFR <60	13	7	0.53 (0.30, 0.95)	
Treatment indication				
Elective	13	3		
Imperative	13	7	0.50 (0.27, 0.89)	0.37 (0.16, 0.84)
Palliative	2	1	1 (1, 1)	
Tobacco history				
Nonsmoker	12	5	0.509 (0.27, 0.95)	
Smoker	16	6	0.69 (0.44, 1)	0.33 (0.12, 0.97)
Delivery method				
Ureteral catheter	19	9	50% (0.25,1)	0.26 (0.08, 0.76)
Nephrostomy tube	9	2	63% (0.410, 0.99)	0.40 (0.23, 0.90)
Lynch syndrome				
Negative	23	8	0.62 (0.42, 0.93)	0.45 (0.09, 0.91)
Positive	5	3	0.56 (0.28, 1)	0.2 (0.10, 0.78)

CI=confidence interval; eGFR=estimated GFR; RFS=recurrence-free survival.

Our study shows a noticeable difference in recurrence, progression, and nephroureterectomy rates for patients depending on whether they were treated through NT or ureteral catheter. However, there were more patients with low-grade tumors treated with ureteral catheter (71%) compared to NT (29%). Previous animal studies have shown superior contact with a ureteral catheter than with a NT, suggesting that delivery

through a retrograde ureteral catheter may be optimal.²⁸ Our data tend to support that theory, but we cannot discount the possibility of bias given the nature of this retrospective study.

The effect of topical therapy on patients with Lynch Syndrome is still yet to be determined, and our small sample size was not adequately powered to show a difference. The hypermutational status of tumors in patients with Lynch

TABLE 4. PROGRESSION-FREE SURVIVAL FOR PATIENTS UNDERGOING ADJUVANT MITOMYCIN C

<i>Variable</i>	<i>n</i>	<i>Progression</i>	<i>PFS rate at 3 years (95% CI)</i>	<i>PFS rate at 5 years (95% CI)</i>
Overall	28	5	0.80 (0.64, 1)	0.64 (0.39, 1)
Tumor grade				
Low	21	3	0.87 (0.72, 1)	0.65 (0.36, 1)
High	7	2	0.67 (0.38, 1)	
Focality				
Solitary	19	4	0.8 (0.62, 1)	0.53 (0.23, 1)
Multifocal	9	1	0.83 (0.58, 1)	0.83 (0.58, 1)
Renal function at diagnosis				
eGFR ≥60	16	2	0.83 (0.63, 1)	0.83 (0.63, 1)
eGFR <60	12	3	0.79 (0.56, 1)	0.39 (0.10, 1)
Treatment indication				
Elective	13	2		
Imperative	13	3	0.78 (0.55, 1)	0.58 (0.3, 1)
Palliative	2	0	1 (1, 1)	1 (1, 1)
Tobacco history				
Nonsmoker	12	2	0.78 (0.549, 1)	
Smoker	16	3	0.8 (0.611, 1)	0.61 (0.32, 1)
Delivery method				
Ureteral Catheter	19	4	0.86 (0.69, 1)	0.56 (0.32, 0.1)
Nephrostomy tube	9	1	0.71 (0.45, 1)	0.83 (0.583,1)
Lynch syndrome				
Negative	23	4	0.77 (0.57, 1)	0.56 (0.32, 1)
Positive	5	1	0.86 (0.63, 1)	0.67 (0.41, 1)

PFS=progression-free survival.

TABLE 5. NEPHROURETERECTOMY-FREE SURVIVAL FOR PATIENTS UNDERGOING ADJUVANT MITOMYCIN C

Variable	n	Nephroureterectomy	NUxFS rate at 3 years (95% CI)	NUxFS rate at 5 years (95% CI)
Overall	28	5	0.76 (0.60, 0.97)	0.76 (0.60, 0.97)
Tumor grade				
Low	21	3	0.82 (0.65, 1)	0.82 (0.65, 1)
High	7	2	0.67 (0.38, 1)	
Focality				
Solitary	9	3	0.8 (0.62, 1)	0.8 (0.62, 1)
Multifocal	9	2	0.71 (0.45, 1)	0.71 (0.45, 1)
Renal function at diagnosis				
eGFR \geq 60	15	3	0.76 (0.55, 1)	0.76 (0.55, 1)
eGFR <60	13	2	0.79 (0.56, 1)	0.79 (0.56, 1)
Treatment indication				
Elective	13	2		
Imperative	13	3	0.7 (0.47, 1)	0.7 (0.467, 1)
Palliative	2	0	1 (1, 1)	1 (1, 1)
Tobacco history				
Nonsmoker	12	3	0.7 (0.47, 1)	
Smoker	16	2	0.82 (0.61, 1)	0.82 (0.61, 1)
Delivery method				
Ureteral catheter	19	4	0.86 (0.69, 1)	0.56 (0.32, 0.1)
Nephrostomy tube	9	1	0.63 (0.37, 1)	0.833 (0.58,1)
Lynch syndrome				
Negative	23	4	0.72 (0.52, 1)	0.56 (0.32, 1)
Positive	5	1	0.86 (0.63,1)	0.67 (0.41, 1)

NUxFS=nephroureterectomy-free survival.

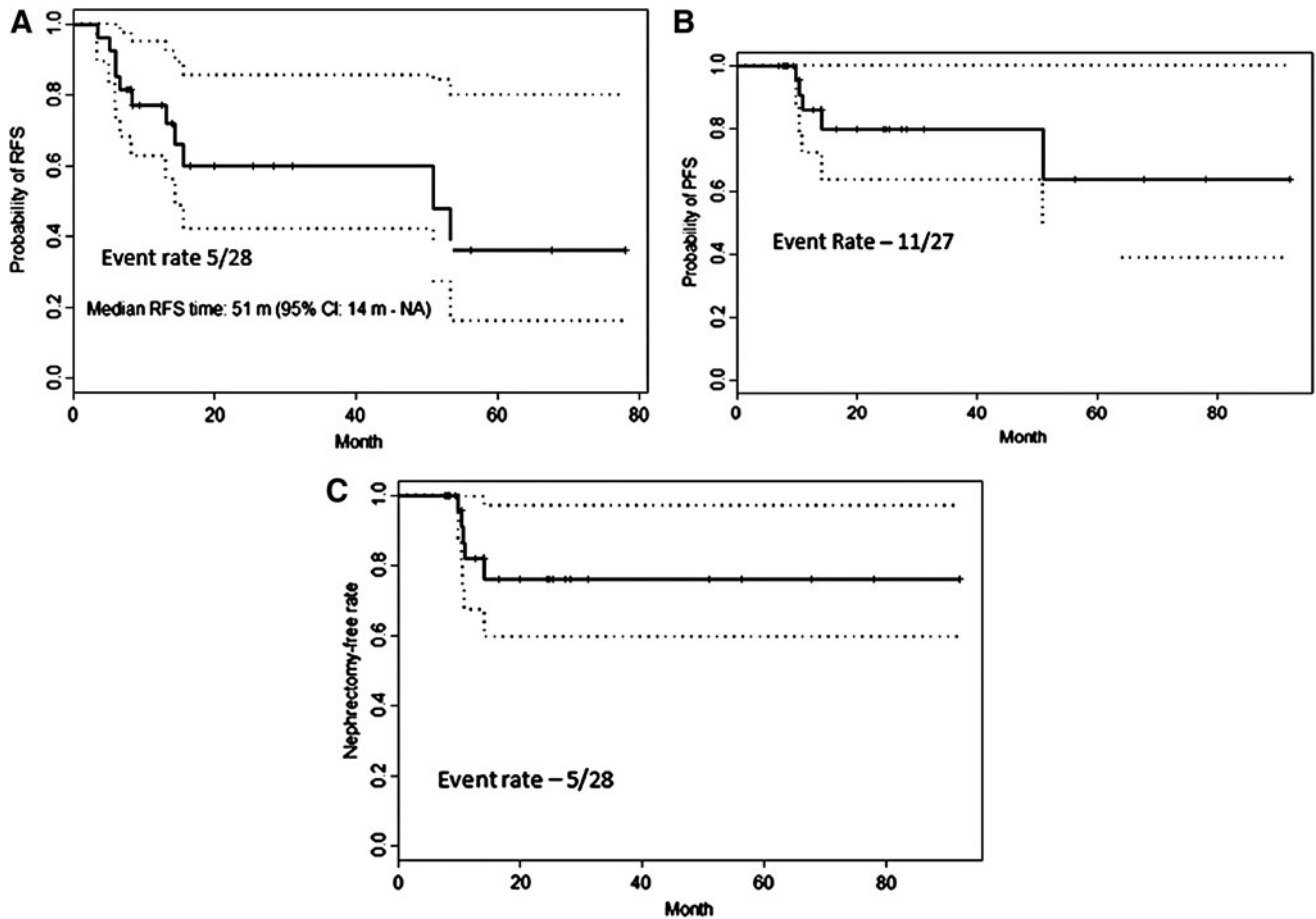


FIG. 2. Kaplan-Meier estimates for cumulative recurrence-free (A), progression-free (B), and nephroureterectomy-free (C) survival.

TABLE 6. ADVERSE EVENTS FOR PATIENTS UNDERGOING ADJUVANT MITOMYCIN C

Adverse event	n	Grade	Delivery
After induction	4		
Recurrent UTI	1	1	Ureteral catheter
Severe bladder spasm	1	1	Ureteral catheter
Ureteral stricture	1	2	Ureteral catheter
Pyelonephritis	1	2	Nephrostomy tube
After maintenance	5		
Hematuria	1	1	Nephrostomy tube
Ureteral stricture	3	1,2	Ureteral catheter
Infundibular stenosis	1	3	Ureteral catheter

Grade of complication as per Clavien-Dindo Classification.
UTI=urinary tract infection.

Syndrome is thought to make them more chemosensitive, as is seen with systemic therapy of colorectal cancers.²⁹ Whether this makes Lynch Syndrome patients with noninvasive UTUC more optimally suited to treatment with adjuvant topical chemotherapy is unknown and requires further exploration.

In our study, nine patients experienced AEs. Four of these events occurred during induction therapy, representing an AE rate of 14% as detailed in Table 6. No patients discontinued maintenance therapy due to AEs. The cause of the ureteral strictures is unknown. It could be related to endoscopic resection, multiple ureteroscopies, MMC, delivery method, or the additive effect of all these factors. Our findings are comparable to prior studies such as Aboumarzouk and colleagues who showed that 3/20 (15%) RUs in their cohort developed a ureteral stricture. Again, in their series the cause was unable to be attributed to any single factor.^{12,19} Other concurrent procedures and treatments such as the initial and subsequent multiple surveillance ureteroscopies may have contributed to the presence of these AEs. For example, the patient with infundibular stenosis had laser ablation of a circumferentially carpeting low-grade papillary tumor around the infundibulum. Regardless of the definitive cause of the ureteral stricture, it is recognized that the ureteral stricture rate in patients receiving upper tract instillation of MMC is high, and observation for onset of hydronephrosis and renal failure is recommended to prevent irreversible renal deterioration. New paradigms that decrease manipulations and improve outcomes are clearly needed.

A criticism of adjuvant and maintenance MMC for UTUC is the potential cost and insurance reimbursement of both weekly cystoscopic procedures and drug costs. We have not had any denials of payment to our knowledge. This may be because we are applying similar principles as for treatment of bladder cancer, the most common organ site for urothelial cancer, which has well accepted protocols.

While this series represents the largest published study on the use of adjuvant topical MMC for UTUC, it is not without significant limitations. It is a retrospective review of a relatively small sample size and there is no available control for this select group of patients. Retrospective bias and clinical heterogeneity may have affected some of the results. Clinical heterogeneity in this series is largely due to patient-focused and shared decision making, such as with the decision for MMC instillation through a ureteral catheter or NT. Given lack of data over the efficacy of either, and the significant impact that the decision may have on the patient's quality of life, we left this decision to the patient. A larger study is needed,

preferably prospective and with longer follow-up, to validate these findings. After this study was completed, a phase 3 open label multicenter trial of MitoGel™ (<https://clinicaltrials.gov/ct2/show/NCT02793128>, accessed May 31, 2017) opened in 2017 for chemoablative and adjuvant treatment of low-grade UTUC. The study design, in fact, emulates our approach of induction and maintenance therapy, but results are likely not forthcoming for a few years. Thus, in the meantime our data may help provide guidance to urologists and their patients. In addition, only after updating clinic processes recently have we systematically treated patients under optimized conditions with relative dehydration and urinary alkalization.³⁰ Thus, these results may be improved in this optimized setting.

Conclusions

We assess intermediate term data on the safety, efficacy, and tolerability of induction and maintenance adjuvant MMC for adjuvant topical therapy of endoscopically resected UTUC. The high degree of tolerability coupled with our intermediate term data showing promising recurrence, progression, and NUxFS is encouraging. While nephroureterectomy clearly remains the most definitive management for UTUC, this study provides support for further investigation of chemotherapeutic agents for topical adjuvant treatment of UTUC. Future research can be directed at testing induction and maintenance therapy in a prospective manner and ideally with methods that not only can improve oncologic outcomes but also minimize instrumentation and risk for AEs.

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Author Disclosure Statement

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Address correspondence to:
Surena F. Matin, MD
Department of Urology
MD Anderson Cancer Center
The University of Texas
1515 Holcombe Boulevard, Unit 1373
Houston, TX 77030

E-mail: surmatin@mdanderson.org

Abbreviations Used

AEs = adverse events
 BCG = Bacillus Calmette-Guerin
 CT = computed tomography
 CI = confidence interval
 IQR = interquartile range
 MMC = mitomycin C
 NT = nephrostomy tube
 NUxFS = nephroureterectomy-free survival
 PFS = progression-free survival
 RFS = recurrence-free survival
 RU = renal unit
 UTUC = upper tract urothelial carcinoma
 U = ureteral catheter