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Adjuvant single-dose upper urinary tract instillation of mitomycin C after therapeutic ureteroscopy for upper tract urothelial carcinoma: a single-centre prospective non-randomized trial

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Keywords

Upper tract urothelial carcinoma; Mitomycin C; Topical chemotherapy; Kidney-sparing surgery; Recurrence

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Introduction

Upper tract urothelial carcinoma (UTUC) accounts for 5%–10% of urothelial carcinomas, with a rising incidence in recent decades[1]. Radical nephroureterectomy is considered the gold standard for treatment of UTUC. However, endoscopic management of non-invasive UTUC is increasingly considered a valuable option for selected patients, given that it reduces morbidity and the risk of dialysis and that it has been proven that survival outcomes are not adversely affected. Currently, the European Association of Urology (EAU) Guidelines recommend kidney-sparing surgery in elective cases of low-risk UTUC, such as non-invasive and unifocal disease, tumours less than 2 cm and low-grade tumours, and imperative cases[1].

Nevertheless, a recurrence may occur in up to 60% of these patients[2]. The implantation of floating neoplastic cells after endoscopic resection may explain the high risk of early recurrence, either in the bladder or in the upper urinary tract[3]. In this setting, the search for adjuvant treatments to reduce recurrences is of the utmost importance. Few studies have reported on the use of mitomycin C for UTUC, with variations in the forms of application and the timing of the procedure, and its utility remains controversial. Therefore, the aims of this study were: (a) to address the safety and feasibility of upper urinary tract instillation of a single dose of mitomycin (ASDM) immediately after therapeutic ureteroscopy and (b) to assess urothelial recurrence rates, i.e. ipsilateral local or bladder recurrences, in the ASDM group compared with a population treated conventionally.

Materials and Methods

Between 1 April 2015 and 31 August 2018, 52 patients affected by UTUC were treated by therapeutic ureteroscopy with laser ablation. Although postoperative instillation of mitomycin has been proven to reduce the risk of recurrence in non-muscle invasive bladder cancer, the Institutional Committee did not consider randomization ethical given the lack of phase 2 trials in upper urinary tract; however, it validated the use of mitomycin in upper tract based on proof of efficacy and tolerance in bladder [4,5,6]. Patients with (a) concomitant multifocal or sessile/flat or >3 cm bladder lesion or (b) incomplete upper tract

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ablation were excluded from this prospective phase 2a trial. ASDM was offered to patients with a preoperative CT scan showing a clear diagnosis of papillary UTUCs with no signs of ≥T2 and in whom complete endoscopic ablation appeared technically feasible based on the shape, size and number of lesions.

The controls were patients submitted to complete tumour ablation who (a) had no diagnosis of papillary lesions on CT, a suspicious imaging that required a URS or no recent (within 3 months) CT scan, (b) were intolerant to mitomycin or (c) declined ASDM. The study was conducted in accordance with the Declaration of Helsinki (1964) and its later amendments. All patients signed an informed consent at the time of hospitalization. Ethical approval was obtained from the Institutional Board Committee of Fundació Puigvert (2014/17). To evaluate oncological outcomes, patients submitted to induction upper tract/intravesical instillations following ureteroscopy were excluded from group comparison.

Technique

Second-generation cephalosporins or targeted antibiotics on the basis of urine culture were administered 30 minutes before the surgery.

An initial cystoscopy was conducted. If a vesical lesion was observed, a transurethral resection (TURB) was performed after ureteroscopy.

The distal ureter was explored with semirigid ureteroscope while flexible ureteroscope (Storz Flex XC) was used in all cases for mid/upper ureter, renal pelvis and calyx inspection. Ureteroscopy was usually performed according to the "no-touch technique" to increase the detection of erythematous lesions[7]. The urinary tract was explored with white light and Clara + Chroma/Spectra B technology (IMAGE1 S, Karl Storz, Tuttlingen, GE) to increase the diagnostic accuracy of the procedure[8]. Selective urine samples were collected for cytology. For each tumour, biopsies were carried out using a 2.2-French Nitinol basket, 3-French reusable biopsy forceps and/or BIGopsy forceps (Cook, Bloomington, IN, USA)[9]. In cases of ablation with a flexible ureteroscope, a 12/14 Flexor Parallel (Cook, Bloomington, IN, USA) access sheath was inserted. The lesions were ablated with a holmium (10–12 Hz x 0.8–1.2 J) and/or thulium laser (setting: 18–22 W). At the end of the ablation, a retrograde

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pyelography was performed. Drainage consisted in an open-ended 6-French ureteral catheter left in the pelvicalyceal system if no sign of ureteral damage was found; otherwise, at the surgeon's choice, a double-J stent (7 French, 26/28 cm) was placed.

Immediate postoperative upper urinary tract instillation of mitomycin

A single-dose upper urinary tract instillation of 40 mg/40 ml mitomycin C diluted in 20 ml saline solution was administered in 1 h through a single-J catheter. In cases of instillation via a bladder catheter and double-J stent, 40 mg/40 ml mitomycin C diluted in 100 ml saline solution was administered in 1 hour. All the instillations were performed within 6 h after the surgery. The ureteral catheter was removed on postoperative day 2 while the double-J stent was removed after 7–14 days. Patients were usually discharged on postoperative day 2.

Endpoints

Clinical and perioperative data and 30-day complications (according to the Clavien-Dindo scale) were prospectively collected[10]. The primary endpoint was the safety and feasibility of ASDM. The secondary endpoint was urothelial recurrence, defined as a recurrence in the ipsilateral upper urinary tract and/or bladder. Follow-up consisted in a second-look ureteroscopy within 3 months and CT scan/ureteroscopy every six months for two years. Cystoscopies were scheduled according to the risk category of the patients[1]. Tumour grading was assessed according to the 2004 World Health Organization classification system.

Statistics

Absolute frequencies and percentages were used to describe the qualitative variables. Quantitative variables were described as mean, standard deviation (SD), median and quartiles. Student's t-test (Mann-Whitney U-test if normality was not assumed) was used for comparison of quantitative variables. The chi-square test (Fisher test for frequencies <5) was employed for the comparison of categorical variables. A Kaplan-Meier curve was generated for cancer-specific survival outcomes.

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Backward stepwise Cox regression analysis was performed for urothelial recurrence-free survival. *P* values <0.05 were considered statistically significant. The statistical packages R Studio V 3.1 and SPSS V 25 were used for the statistical analyses.

Results

Fifty-two patients met the inclusion criteria, 26 of whom were selected for ASDM. One (4%) patient was excluded from the study owing to urinary leakage at final pyelography, which contraindicated ASDM.

Overall, the mean age was 72.1 years, with a male-to-female ratio of 3:1. ASA score was I–II, III, IV in 26 (51%), 20 (39%) and 5 (10%) patients, respectively. ASDM and controls did not differ in terms of clinical characteristics (Table 1).

The mean UTUC size was 15.1 mm (SD 11.3 mm). UTUCs were located in the calyx, pelvis and ureter in 15 (29%), 19 (37%), and 25 (49%) cases, respectively; multifocality was present in 33%. For postoperative drainage, a single-J stent was used in 19 cases (76%) and a double-J stent in six (24%), comprising four patients in whom UTUC was located in the ureter and two in whom a grade I/II ureteral injury was observed after removal of the ureteral sheath.

Safety and tolerability

All patients allocated to ASDM received the entire dose of mitomycin and no side effects were reported during the instillation. No systemic side-effects were observed. The overall complication rate in ASDM and controls was 40% and 30.7%, respectively (p>0.7; Table 1). Complications with a Clavien grade ≤II comprised self-limiting haematuria (total/ASDM/controls: 16%/16%/15%), lumbar discomfort (8%/12%/4%) and infection (8%/8%/8%) (all p>0.9). Two (4%) Clavien grade III complications were reported in the ASDM group. One patient with a functional solitary kidney and moderate chronic kidney disease experienced obstructive renal failure due to blood clots on postoperative day 2, which required substitution of the single-J and a dialysis session. The second patient experienced postoperative severe heamaturia as a complication of a concomitant TURB.

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Infectious complications were not related to a positive preoperative urine culture (7/52; 13.4%). During follow-up, one patient per group (4.7%) developed a ureteral stenosis.

Oncological outcomes

Postoperative follow-up is summarized in Figure 1. In the ASDM group, two patients (8%) were assigned to nephroureterectomy for high-grade or recurrent neoplasia. The overall survival rate was 90.6% (39/43), and the cancer-specific survival rate was 97.6% (42/43). Eight patients (18.6%) had maintenance treatment consisting in weekly upper tract instillations (mitomycin in five and BCG in three).

The oncological outcomes of ASDM were evaluated by comparing 17 ASDM patients (group A) with the 18 patients who did not receive any other adjuvant treatment after therapeutic ureteroscopy (group B) (Figure 1). Tumour characteristics are reported in Supplementary Table 1 (all p>0.4). Median follow-up was 18 months (IQR 10–29). Urothelial recurrence occurred in 23.5% of patients in group A vs 55.5% in group B (p=0.086) (Figure 1).

In groups A and B respectively, urothelial recurrence consisted in upper tract recurrence in 17.6% (3/17) vs 33.3% (6/18) and bladder recurrence in 21.4% (3/14) vs 31.3% (5/16). Bladder and local recurrence were metachronous in two patients (11.8%) of group A and synchronous in one patient (5.5%) of group B.

Mean URFS was 28.8 months in group A and 18.8 months in group B (log-rank p=0.067; Figure 2). Multivariate Cox regression included age, tumour grade, dimensions, multifocality, history of UTUC, UTUC risk stratification and primary/synchronous bladder tumour; the best model selected the variables age, tumour grade, ASDM and primary/synchronous bladder tumour (-2log likelihood=42.15; Hosmer-Lemeshow p=0.25). The risk of urothelial recurrence was significantly higher in patients with high-grade UTUC (95% CI 2.19–127.67; HR=16.7; p=0.07) or previous or concomitant bladder tumour (95% CI 1.13–32.74; HR=6.07; p=0.036). ASDM reduced the risk of recurrence 7.7-fold (95% CI 0.03–0.65; HR=0.13; p=0.013) (Table 2).

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Discussion

In this study assessing immediate postoperative upper urinary tract instillation of mitomycin after endoscopic treatment of UTUC, it was found that ASDM had been feasible in >95% of the selected patients and resulted in a significant 50% relative reduction in urothelial recurrence. Adjuvant topical instillations may have a role in reducing UTUC recurrence, ultimately minimizing the need for nephroureterectomy and the number of endoscopic treatments per patient.

To the best of our knowledge, this is the first prospective non-randomized trial on adjuvant prophylactic upper tract topical chemotherapy after endoscopic management of UTUC. The EAU recommendations, which state that upper urinary tract instillations are feasible, rely on non-comparative studies of induction protocols at least 14 days following ureteroscopy[1,11].

The tolerability of upper tract induction and maintenance instillation of mitomycin C has been assessed in a non-comparative cohort[12]. Martínez-Piñeiro et al. reported a case of death due to mitomycin extravasation during upper tract instillations[13]. Based on this experience, we strongly recommend performing a pyelography at the end of ureteroscopy and to exclude patients with contrast extravasation from ASDM. All of our patients completed the instillation without any related urinary symptoms or adverse events. The complication rate was 40% (10/25 patients), which may be considered relatively high. However, 8/10 patients experienced minor complications requiring analgesia/observation in 50% of cases and antibiotics in the remainder. No major complication was directly related to ASDM.

Two retrospective series have reported on the use of mitomycin after endoscopic management of UTUC, but timing, complications and oncological outcomes were not specified[2,14]. Eastham and Keeley described no systemic side effects related to adjuvant treatment with mitomycin on postoperative days 1-3[15,16]. Aboumarzouk et al. reported that one of 19 patients (5%) did not tolerate an immediate postoperative instillation and that three (15.7%) had ureteral strictures[17]. In our series, one patient per group (2/43; 4.7%) developed a ureteral stenosis. Considering that a single dose of mitomycin was

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administered, we speculate that ureteral strictures are more likely related to the endoscopic procedure than to the endocavitary instillation.

The oncological outcomes of adjuvant mitomycin C after ureteroscopy are controversial. Martínez-Piñeiro et al. reported a UTUC recurrence rate of 14% with mitomycin compared with 25% in unmatched controls who were characterized only by grade 1–2 tumours and a lower rate of T1 UTUC[13]. Keeley et al. found a higher rate of local recurrence in the mitomycin group (42% vs 18%) but the unequal pathological grade (grade 3: 52% vs 33%) and number of multifocal tumours (63% vs 33%) between the groups rendered the comparison heavily biased[16]. Cutress et al., in a retrospective case-control series, showed that adjuvant mitomycin did not modify the recurrence rate of UTUC. However, the dosage and timing of administration were not described and the number of instillations per patient was not clear (29 instillations for 18 patients)[18].

In our study, bladder recurrence rates in the ASDM and non-ASDM groups were, respectively, 21.4% vs 31.3% (p=0.7). ASDM was associated with an absolute reduction in local recurrence of 15% [3/17 (17.6%) in group A vs 6/18 (33.3%) in group B; p=0.4]. In group A, two high-grade UTUC recurred and one low-grade tumour progressed to become high grade. In group B, all six local recurrences occurred within the control visit at 1 year, and four (66.6%) were low-grade UTUC. Timing of recurrence differed between the groups, with a mean delay of 10 months in group A (28.8 months vs 18.8 months in group B). On multivariate analysis, the risk of urothelial recurrence was reduced 7.7-fold with ASDM (HR =0.13; p=0.013). This result suggested that early instillation of mitomycin C after therapeutic ureteroscopy reduces the risk of urothelial recurrence in patients affected by low-grade UTUC without primary/synchronous bladder tumour.

This study has some limitations. No randomization was performed. The two populations compared are relatively small. ASDM was delivered via either a single-J or a double-J stent. As described in Table 3, the type of delivery, timing and dosage of mitomycin C differ widely among studies reporting upper tract mitomycin instillations for UTUC. Upper urinary tract topical chemotherapy using a double-J stent is not recommended[15]. We considered not to modify the indication of urinary diversion after ureteroscopy in order to

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give a treatment which beneficial was yet to be established. Moreover, when using a double-J, mitomycin was diluted in 140 ml to guarantee a proper vesicoureteral reflux in ureters which were just dilated, assuming the risk of an excessive dilution of Mytomicin[19]. However, it must be highlighted that in group A, 2/3 (66.6%) patients in whom a double-J was used suffered a local recurrence compared with only 1/13 (7.7%) when using a single-J. As the implantation of neoplastic floating cells has been shown to take place early after endoscopic resection, we believe that ASDM should be performed as soon as possible after surgery[3,20]. Regarding the formulation of mitomycin C, no studies have succeeded in establishing a standard dose; a phase 3 trial analyzing an induction plus maintenance protocol for the administration of MitoGel™ is ongoing (NCT02793128). Another limitation is represented by the low number of events, which increases the risk of overfitting in the multivariate Cox regression analysis. In this respect, however, it is to be noted that the 1-to-10 rule (minimum of ten outcome events per predictor variable) has been proven to be too conservative[21]. Basing on the results of the present study, a randomized controlled trial is starting.

Conclusions

Adjuvant single-dose upper urinary tract instillation of mitomycin C within 6 h after therapeutic ureteroscopy was well tolerated. It appeared to reduce the risk of urothelial recurrence in patients affected by low-grade UTUC without bladder tumour. Therefore, its use should be tested on a randomized controlled trial.

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Abbreviations and Acronyms

ASDM = adjuvant single-dose Mitomycin C

EAU = European Association of Urology

SD = standard deviation

TURB = transurethral resection of bladder

URS = ureteroscopy

UTUC = upper tract urothelial carcinoma

Table 1. Demographic and perioperative data and tumour characteristics [mean (SD) or n (%)]

	Total n=51	**ASDM** n=25	**Controls** n=26	**p value**
Age (yrs)	72.1 (11.8)	73.6 (12.1)	70.7 (11.7)	0.4
Gender				
Male	38 (75)	17 (68)	21 (81)	0.3
Female	13 (25)	8 (32)	5 (19)	
ASA score				
I–II	26 (51)	12 (48)	14 (54)	0.8
III	20 (39)	11 (44)	9 (35)	
IV	5 (10)	2 (8)	3 (11)	
Smoking history				
Yes	13 (25)	7 (28)	6 (23)	0.8
No	14 (27)	6 (24)	8 (31)	
Previous	24 (47)	12 (48)	12 (46)	
Solitary kidney				
Yes	8 (16)	4 (16)	4 (15)	0.9
No	43 (84)	21 (84)	22 (85)	
Previous bladder tumour				
Yes	27 (53)	12 (48)	15 (58)	0.6

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No	24 (47)	13 (52)	11 (42)	
Previous UTUC				
Yes	20 (39)	11 (44)	9 (35)	0.6
No	31 (61)	14 (56)	17 (65)	
Synchronous bladder tumour				
Yes	7 (14)	5 (20)	2 (8)	0.2
No	44 (86)	20 (80)	24 (92)	
Tumour grade				
High	12 (24)	9 (36)	3 (11)	0.1
Low	29 (57)	13 (52)	16 (62)	
Not evaluable	9 (18)	3 (12)	6 (23)	
Benign	1 (2)	0	1 (4)	
Tumour size	15.3 (11.3)	15.1 (10.2)	15.5 (12.5)	0.9
<2 cm	36 (71)	18 (72)	18 (69)	1
≥2 cm	15 (29)	7 (28)	8 (31)	
Multifocal disease				
Yes	17 (33)	5 (20)	12 (38)	0.07
No	34 (67)	20 (80)	14 (62)	
UTUC location (including multifocal)				

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Calyx	15 (29)	9 (33)	6 (19)	0.4
Pelvis	19 (37)	8 (30)	11 (34)	
Ureter	25 (49)	10 (37)	15 (47)	
eGFR (ml/min/1.73 m^2)				
Preoperative	59.6 (22.3)	57.7 (25.8)	61.9 (17.9)	0.5
Postoperative	56.0 (23.6)	55.3 (27.2)	56.8 (1.8)	0.8
Haemoglobin (g/dl)				
Preoperative	13.2 (2.2)	12.9 (2.2)	13.6 (2.2)	0.3
Postoperative	12.5 (6.3)	12.7 (1.7)	12.4 (1.9)	0.6
Preoperative urine culture				
Positive	15 (29)	7 (28)	8 (31)	1
Negative	36 (71)	18 (72)	18 (69)	
Length of hospital stay (days)	3.4 (3.5)	4.3 (4.6)	2.5 (1.8)	0.07
Postoperative complications				
None	33 (65)	15 (60)	18 (69)	0.7
Clavien-Dindo scale I–II	16 (31)	8 (32)	8 (31)	
Clavien-Dindo scale III	2 (4)	2 (8)	0	

Table 2. Univariate and stepwise backward multivariate Cox regression for urothelial recurrence

	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
Age	0.97	(0.93–1.02)	0.26	0.94	(0.89–0.99)	0.04
ASDM	0.36	(0.11–1.15)	0.08	0.13	(0.03–0.65)	0.013
Tumour grade	4.34	(0.99–19.0)	0.05	16.7	(2.19–127.67)	0.007
Dimensions	0.59	(0.18–1.9)	0.3			
Multifocality	1.85	(0.58–5.96)	0.3			
Risk stratification	1.37	(0.46–4.08)	0.6			
Primary/concomitant bladder tumour	2.5	(0.69–8.96)	0.16	6.07	(1.12–32.74)	0.036
Previous UTUC	1.67	(0.58–4.84)	0.34			

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Table 3. Comparison of studies reporting upper tract mitomycin instillations for UTUC

				MITOMYCIN INSTILLATION				TUMOUR GRADE			FOLLOW-UP		
STUDY	**Year**	**Type of study**	**N. (renal units)**	**Type of delivery**	**Dose**	**Bladder Catheter clamp (min)**	**Timing**	**Low**	**High**	**CIS**	**Local recurrence (%)**	**Bladder recurrence (%)**	**Follow-up (months)**
EASTHAM	1993	Case series	7 (7)	Single-J Nephrostomy	5 mg / 20 ml 40 mg / 1000 ml in 24 h	30 /	POD 1 and 2	G2: 3	G3: 3	1	28.5	N/A	7.4
MARTINEZ-	199	Case	14 (14)	SJ or	40 mg	/	3 to 6	G1-	G3:		14.2	N/A	31

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PINEIRO	6	series		Nephrosto my Double-J	/ 100 ml		times 15 times	2: 10 (3 N/A)	1				
KEELEY	199 7	Case series	19 (21)	Single-J	40 mg / 30 ml saline divide d in 3 doses	10	POD 1-3	G1 or G1/ 2: 7 G2:8	G3: 4	0	54	50	30
ABOUMARZO UK	201 2	Prospectiv e single-arm	19 (20)	Single-J Nephrosto my	40 mg / 40 ml saline in 1 h	60	Within 6 hours	16	4	1	35	N/A	24
METCALFE	201 7	Case series	27 (28)	Single-J	40 mg/ 60 ml	/	Induction (x 6) Maintenan	21	7	0	39	29	19 (media

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					saline in 2 h		ce (x 3)							23 n)
PRESENT SERIES	2019	Prospective non-randomized	24 (24) Vs 24 controls	Single-J Double-J	40 mg/ 60 ml saline in 1 h 40 mg/ 140 ml saline in 1 h	60	Within hours	6	9 (2 N/A) Vs 12 (3 N/A)	4 Vs 2	0	20 Vs 35.3	23 Vs 26.7	20.7

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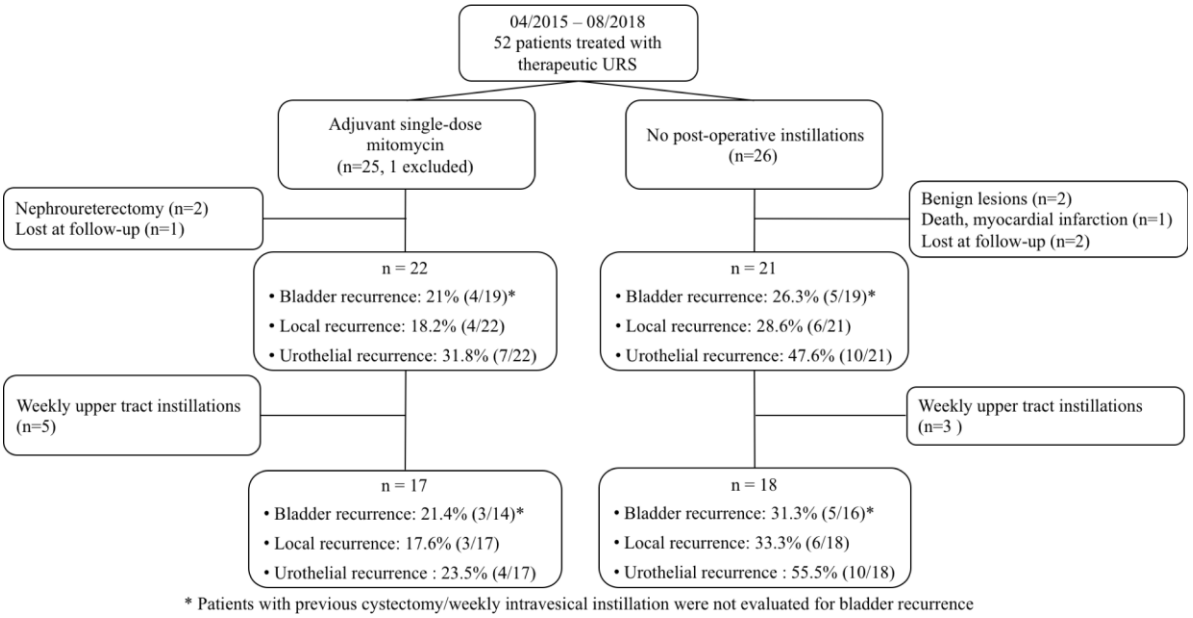

Figure 1. Flowchart for comparison of oncological outcomes between patients treated with and without ASDM

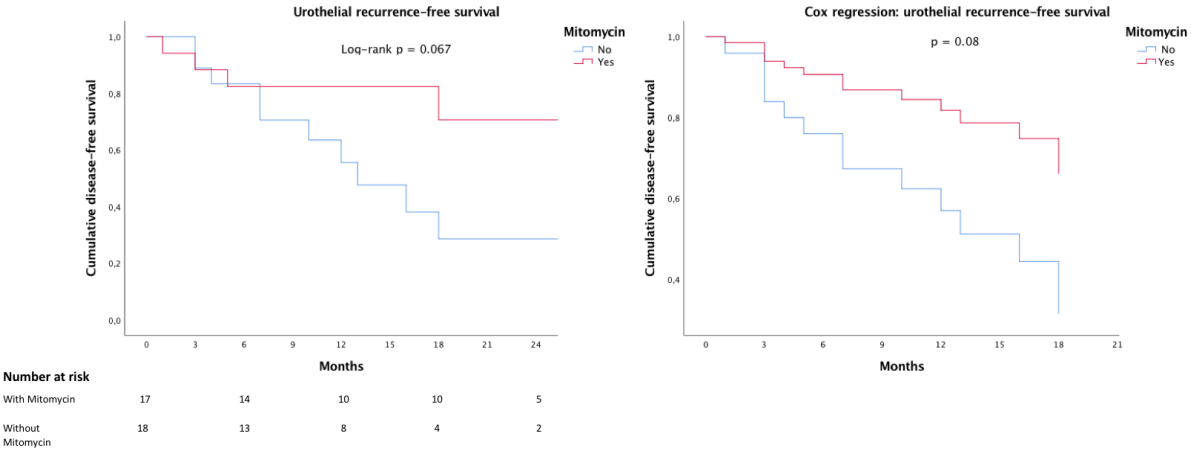

Figure 2. Urothelial recurrence-free survival (Kaplan-Meier and univariate Cox regression model) for patients submitted to mitomycin (group A) or treated conventionally (group B)

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Supplementary Table 1. Group comparison in respect of tumour characteristics in the patients included in the evaluation of oncological outcomes (group A, patients treated with ASDM; group B, patients treated conventionally, without any other adjuvant treatment after histology)

Mean (SD) or n (%)	**Group A n= 17**	**Group B n= 18**	**p value**
Age (yrs)	73.9 (11.6)	73.5 (11.6)	0.9
Primary/concomitant bladder tumour			
Yes	10 (59)	11 (61)	0.9
No	7 (41)	7 (39)	
Previous UTUC			
Yes	7 (41)	4 (22)	0.3
No	10 (69)	14 (78)	
Tumour grade			
High	4 (24)	2 (11)	0.5
Low	11 (65)	12 (67)	
Not applicable	2 (11)	4 (22)	
Size	14.9 (12.2)	14.7 (9.6)	0.9
<2 cm	12 (71)	12 (67)	0.9
≥2 cm	5 (29)	6 (33)	
Multifocal disease			

Yes	3 (18)	5 (28)	0.7
No	14 (82)	13 (72)	
Risk stratification			
High risk	10 (59)	10 (56)	0.9
Low risk	7 (41)	8 (44)	
Median follow-up (IQR)	18 (10.5–30)	17 (10–29.3)	0.6

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