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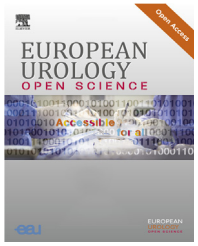

European Association of Urology

Urothelial Cancer

Intraoperative Mitomycin C Bladder Instillation During Radical Nephroureterectomy Is Feasible and Safe

Naomi Nadler[a,b,*], *Kimie Oedorf*[a], *Jørgen Bjerggaard Jensen*[c,d], *Nessn Azawi*[a,b]

[a] *Department of Urology, Zealand University Hospital, Roskilde, Denmark;* [b] *Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark;* [c] *Department of Urology, Aarhus University Hospital, Aarhus, Denmark;* [d] *Department of Clinical Medicine, Aarhus University, Aarhus, Denmark*

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Abstract

Background: Bladder recurrence after radical treatment of upper urinary tract urothelial cancer (UTUC) is frequent, and patients are required to undergo surveillance cystoscopies following surgery. The use of intravesical adjuvant chemotherapy is an accepted method to prevent bladder recurrence, but the timing of this method is not standardized and the concept of intraoperative use is unexplored.
Objective: The objective of the study is to examine the feasibility and safety of intraoperative intravesical mitomycin C (MMC) instillation using a closed-circuit system following bladder cuff excision and bladder closure.
Design, setting, and participants: All patients who underwent radical nephroureterectomy (RNU) for UTUC at the Department of Urology of Zealand University Hospital, Roskilde, Denmark from 2017 to 2020 were identified. Patient complications within 30 d and data regarding oncological outcome were registered.
Outcome measurements and statistical ana lysis: Clavien-Dindo grade for complications and descriptive statistics were used.
Results: During the study period, 64 patients underwent RNU. Of these patients, 49 received bladder instillation of MMC during RNU. Complications were observed in 11 patients (21.4%), where four patients (8.2%) had Clavien-Dindo complication grade (CD) I, four patients (8.2%) had CD II, one patient (2%) had CD III, and one patient (2%) had CD IIIa. None of the complications were suspected to be related to MMC. Five of the 15 patients (33%) who did not receive MMC experienced complications. There were no significant differences in complication rates between patients who received MMC and those who did not. Study limitations include a small sample size and a single-center study.
Conclusions: Intraoperative vesical instillation of MMC is feasible and was, in the present study, not associated with an increased complication rate.
Patient summary: Bladder recurrence after radical treatment of upper urinary tract cancer is frequent. The present study findings indicate that intraoperative bladder irrigation with the chemotherapeutic mitomycin C during surgery does not lead to excessive complications and could be a method to reduce the risk of bladder recurrence.

* Corresponding author. Department of Urology, Zealand University Hospital, Sygehusvej 10, 4000 Roskilde, Denmark.
E-mail address: naon@regionsjaelland.dk (N. Nadler).

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1. Introduction

Most urothelial tumors arise in the bladder, whereas upper urinary tract urothelial carcinoma (UTUC) is less frequent. Thus, UTUC accounts for 5–10% of all urothelial tumors, with an estimated annual incidence of one to two cases per 100 000 people globally [1].

The standard surgical treatment for high-risk UTUC or low-grade tumors unsuitable for local endoscopic treatment is radical nephroureterectomy (RNU) with bladder cuff excision. After radical treatment of UTUC, intravesical recurrence occurs in 22–47% of cases [2,3]. In a large Danish cohort, the incidence of intravesical recurrence was 21%, and 85% of recurrences occurred within the first 2 yr after operation [4].

The use of intravesical chemotherapy is a well-established method to reduce intravesical recurrence [5]; however, the time of instillation is debated because of the adverse effects that can occur as a result of extravasation of the instilled chemotherapeutic in the peri- or postoperative period. The present study examines the feasibility and safety of intraoperative intravesical instillation of mitomycin C (MMC) using a closed-circuit system after securing a watertight closure of the bladder following bladder cuff excision.

2. Patients and methods

The study sample included patients who were offered RNU as treatment for UTUC and who were scheduled for perioperative bladder installation of mitomycin (Medac GmbH, Wedel, Germany), according to standard procedure, at the Department of Urology, Zealand University Hospital, Roskilde, Denmark, during the period from 2017 to 2020. All patient data were prospectively stored in a secure database. The General Data Protection Regulation was met accordingly [6].

2.1. Surgical procedure

All patients were operated upon using the da Vinci Xi robot-assisted platform (Intuitive Surgical Inc., Sunnyvale, CA, USA) at an insufflation pressure of 15 mmHg using an AirSeal iFS device. The procedure was performed minimally invasively without redocking the robot. The procedure began with ureter dissection toward the bladder cuff, after which the ureter was ligated with a Hem-o-lok clip distal to the tumor. If the tumor was close to the bladder and ureteral orifice, the bladder was dissected, an incision to the bladder was made, and the ureteral orifice was identified and closed with a 2-0 Vicryl suture. Subsequently, the ureteral orifice was excised and backward dissection of the ureter was performed. The cystotomy was closed using an absorbable 2-0 V-Loc suture in one layer.

A bladder leak test was carried out using 300 ml saline to ensure a watertight closure. If the bladder was tight, a surgical nurse performed MMC instillation according to department procedure, while the surgeon continued with the proximal surgical procedure of RNU. The patients did not receive MMC postoperatively if the cystostomy was leaking during the bladder leak test. At the end of the operation, the entire specimen was placed in an EndoCatch bag and was removed through a 6–8 cm inguinal incision.

2.2. MMC instillation procedure

A closed-circuit system was developed: a two-way output connector was inserted into the bladder catheter, with one end connected to the urine output bladder catheter bag with a 2.0 m tube and extended outside the sterile field of the patient (output tube) and the other end connected to a 3.0 m long standard intravenous fluid tube with 3 mm internal diameter and extended outside the sterile field of the patient (input tube). The input tube was connected to a three-way stopcock. The opposite end had a suitable female connector to the MMC instillation kit (Medac GmbH), and the middle outlet was connected to a 10 ml syringe of sterile water (Fig. 1).

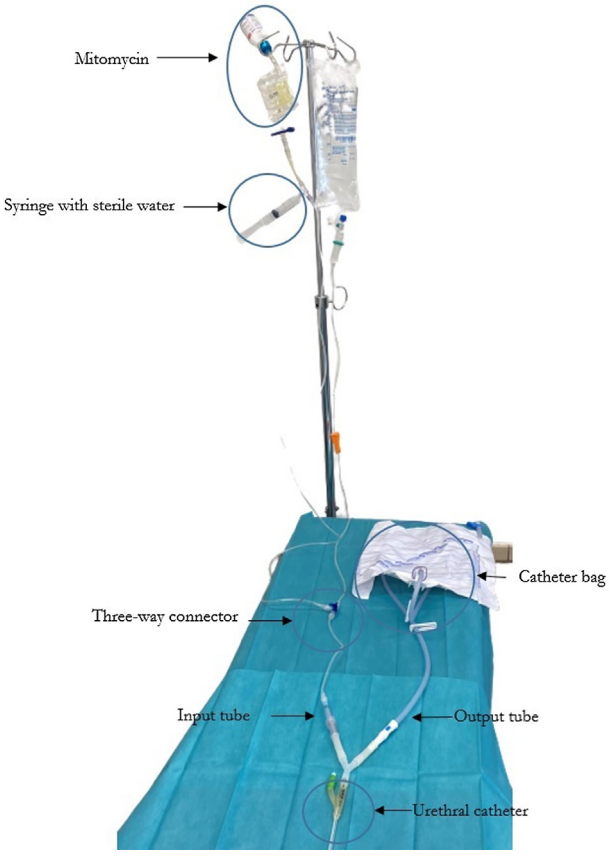

Fig. 1 – MMC instillation setup.
MMC = mitomycin C.

The system was initially tested using a bladder phantom. MMC was mixed with methylene blue–colored material. The urine output was interrupted by closing the output tube outside the sterile field tightly. Subsequently, MMC was instilled in the bladder through the input tube, and the tube was washed with 10 ml sterile water to ensure that no residual MMC remained in the input tube. No leak of blue-colored fluid was observed outside the bladder catheter, and there was no blue-colored fluid in the input tube.

MMC (40 mg) diluted in 40 ml of 0.9% standard saline was instilled. The system remained closed for 1 h. At the end of surgery, the closed-circuit system, including the bladder catheter, was removed and disposed of according to standard procedure. If the surgery lasted for >1 h, the output tube was unlocked, and the spillage of urine and MMC drained into the bladder catheter bag and was disposed of according to standard procedure. A new bladder catheter was then inserted and connected to a catheter bag for 5 d after operation to ensure healing of the cystotomy.

2.3. Follow-up

After RNU, patients were enrolled in a standardized surveillance cystoscopy schedule according to national guidelines. Surveillance cystoscopy was performed at 4, 8, and 12 mo and subsequently once a

year until 5 yr postoperatively. Cytology was performed concurrently with cystoscopies in patients with high-grade tumors. Patients with invasive tumors had additional computed tomography (CT) scans of the thorax and abdomen according to national guidelines for 3 yr following the same intervals as the surveillance cystoscopies.

2.4. Statistical analysis

All tests were two sided, and the significance level was set at $p < 0.05$. Statistical analysis was performed with R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria). The chi-square test was used to compare proportions. Categorical variables were reported as counts and percentages, and medians were used to report numeric variables.

3. Results

During the 3-yr period from December 2017 through July 2020, 64 patients underwent RNU. Fifty-six patients underwent diagnostic nephroureteroscopy prior to RNU. In total, 49 patients received bladder instillation of MMC during RNU immediately after bladder cuff closure. Fifteen patients did not receive MMC due to various reasons. Eight patients did not receive MMC due to uncertainty with the procedure within the medical staff, and seven patients did not receive MMC due to bladder leakage after suturing of the cystotomy. In the study sample, 16 patients had bladder cancer prior to UTUC (Fig. 2).

3.1. Demographics

The median age of the patients in the study sample who underwent RNU and final histological examination–confirmed UTUC, and received an intravesical instillation of MMC (47 patients) was 71.8 yr. In this group, 31 patients were male and 16 were female. The median follow-up time was 16 mo (interquartile range [IQR]: 9–27 mo).

A total of 27 patients (59.5%) were diagnosed with a pTa tumor, seven patients (14.9%) with pT1, six patients (12.8%) with pT2, and six patients with pT3 (12.8%). Twenty-three patients (48.9%) were diagnosed with a high-grade tumor. Malignancy was located in the renal pelvis in 29 patients (61.7%), whereas 12 patients (25.5%) had a tumor in the ureter. Five patients (12.8%) had multifocal tumors.

The median operation time was 195 min (IQR: 155–229 min). The median postoperative hospital stay was 4 d (IQR: 1–5 d). Patient characteristics are presented in Table 1.

3.2. Complications

Ten out of 47 (27.0%) patients who received an intravesical MMC instillation experienced complications. Five patients (13.5%) had Clavien-Dindo complication grade (CD) I, three patients (8.1%) had CD II, one patient (2.7%) had CD IIIa, and one patient (2.7%) had CD IIIb. None of the complications were suspected to be related to MMC instillation, and no instillation failures were reported. Details regarding complications are listed in Table 2.

Of the 15 patients who did not receive MMC, five (33%) experienced complications. Two patients developed pneumonia, one patient developed ileus, one patient developed acute nephropathy, and one patient developed gastrointestinal symptoms.

The complication rates in the two groups, either receiving or not receiving MMC instillation, were not significantly

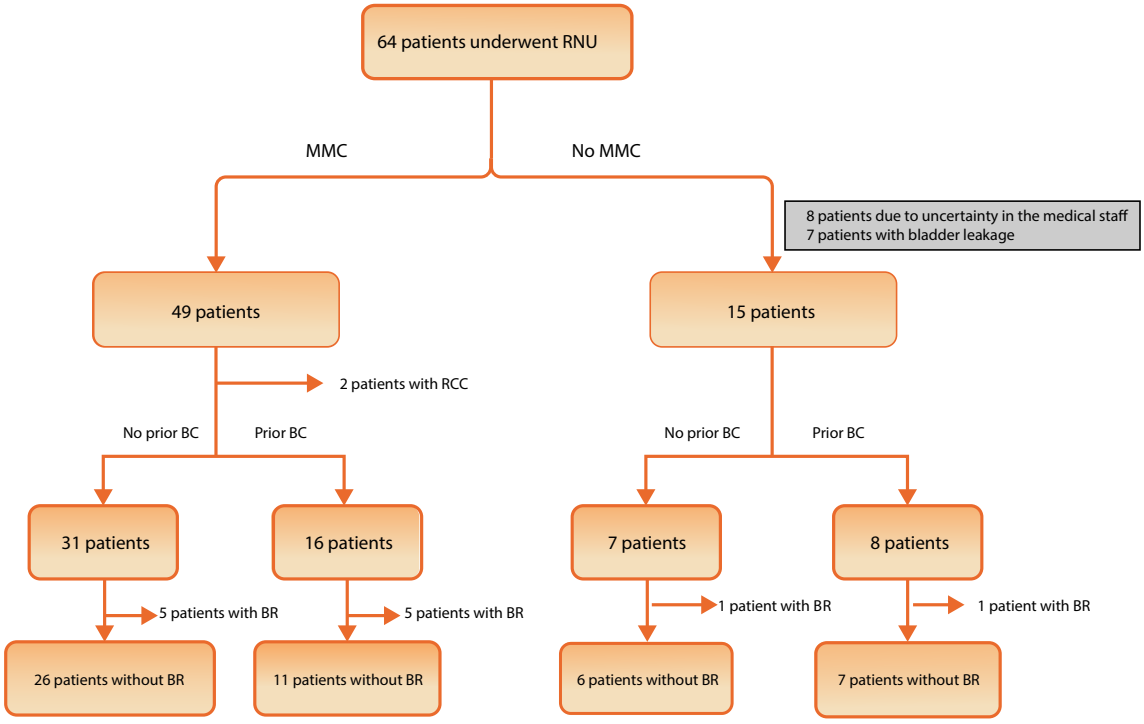

Fig. 2 – Flow chart of patients who underwent RNU.
RCC = renal cell carcinoma. BC = bladder cancer; BR = bladder recurrence; MMC = mitomycin C; RCC = renal cell carcinoma; RNU = radical nephroureterectomy.

Table 1 – Patient characteristics[a]

Patient characteristics	No mitomycin instillation (*N* = 15)	Mitomycin instillation (*N* = 47)	*p* value
Gender, *n* (%)			
Female	8 (53.3)	16 (34.0)	0.303
Male	7 (46.7)	31 (66.0)	
Age (yr), median (IQR)	75.7 (5.34)	71.6 (11.2)	0.159
Prior BC, *n* (%)			
No	8 (53.3)	31 (66.0)	0.566
Yes	7 (46.7)	16 (34.0)	
Diagnostic nephroureteroscopy, *n* (%)			
No	2 (13.3)	5 (10.6)	1
Yes	13 (86.7)	42 (89.4)	
Diagnostic biopsy, *n* (%)			
No	4 (26.7)	10 (21.3)	0.936
Yes	11 (73.3)	37 (78.7)	
Tumor grade (diagnostic biopsy), *n* (%)			
High grade	2 (18)	9 (24)	0.879
Low grade	6 (55)	20 (54)	
Unknown	3 (27)	8 (22)	
Tumor side, *n* (%)			
Left	7 (46.7)	16 (34.0)	0.566
Right	8 (53.3)	31 (66.0)	
Tumor location, *n* (%)			
Pelvis	7 (46.7)	29 (61.7)	0.525
Ureter	3 (20.0)	12 (25.5)	
Multifocal	3 (20.0)	5 (10.6)	
Missing	2 (13.3)	1 (2.1)	
Tumor size (mm)			
Median (IQR)	34.0 (27.5)	34.0 (25.0)	0.661
Missing, *n* (%)	4 (26.7)	1 (2.1)	
Tumor stage (nephroureterectomy), *n* (%)			
pT0	3 (20.0)	1 (2.1)	0.0206
pTa	6 (40.0)	27 (57.4)	
pT1	0 (0)	7 (14.9)	
pT2	1 (6.7)	6 (12.8)	
pT3	5 (33.3)	6 (12.8)	
Tumor grade (nephroureterectomy), *n* (%)			
High grade	7 (47)	23 (49)	0.0438
Low grade	5 (33)	23 (49)	
Unknown	3 (20)	1 (2)	
Concomitant CIS, *n* (%)			
No	13 (86.7)	45 (95.7)	0.521
Yes	2 (13.3)	2 (4.3)	
Nodal status, *n* (%)			
N0	15 (100)	46 (97.9)	1
N+	0 (0)	1 (2.1)	

BC = bladder cancer, CIS = carcinoma in situ; IQR = interquartile range.
[a] Two-sample *t* test was performed for numeric variables (tumor size and age) and χ^2 test for categorical variables (gender, prior BC, diagnostic nephroureteroscopy, diagnostic biopsy, tumor side, tumor stage, and concomitant CIS).

different, as estimated using Fisher's exact test (p = 0.50, 95% confidence interval or CI [0.14–2.65]).

3.3. Recurrences

Two patients were excluded from the study sample due to the presence of renal cell carcinoma in their final histological examination; thus, a total of 47 patients were included in the analysis. Among patients with histologically confirmed UTUC, the median follow-up time was 16 mo (IQR: 9–27 mo). Ten patients (21.3%) had a bladder recurrence within a median time of 27 mo (IQR: 22–31 mo).

Excluding patients with a previous history of bladder cancer (16 patients), the median follow-up time was 16 mo (IQR: 9–27 mo). Out of 31 patients without a history of bladder cancer, five (16.1%) had a bladder recurrence within a median time of 28 mo (IQR: 23–31 mo). Among this group, the bladder recurrence rate (BRR) within the 1st year following the operation was zero (0%). The first recurrence occurred 15 mo after RNU.

One bladder recurrence occurred in seven patients who did not receive MMC and had no history of bladder cancer (14.3%). The median follow-up time in this group was 9 mo and the bladder recurrence occurred after 13 mo.

4. Discussion

Bladder recurrence after radical treatment of UTUC is frequent [5,7] and patients are enrolled in a cystoscopy surveillance program following surgery. Two hypotheses have been suggested for the high rate of intravesical recurrence. The first potential explanation is that the urothelium of the urinary tract is predisposed for tumorigenesis due to its exposure to carcinogens that drive genetically independent alterations at different locations throughout the urothelium. These alterations may lead to the development of multifocal tumors. The second theory suggests the possibility of tumor seeding of proliferating tumor cells of monoclonal origin that implant in the urothelium [8]. Similar

Table 2 – Different complications that patients experienced within 30 days after radical nephroureterectomy

Type of complication	Tumor side	Treatment	T stage	Tumor grade	Localization	Operation time (min)	LOS	Mitomycin	Gender	Clavien-Dindo
Acute nephropathy	Right	Furosemide	pTa	LG	Pelvis	208	3.9	Yes	Male	CD I
Acute nephropathy	Left	Furosemide	pTa	LG	Ureter	207	1.9	Yes	Male	CD I
Postoperative bleeding	Left	Conservative treatment	pTa	LG	Ureter	193	0.9	Yes	Male	CD I
Postoperative bleeding	Left	Conservative treatment	pTa	LG	Pelvis	185	4.9	Yes	Male	CD I
Superficial wound infection	Left	Oral antibiotic	pTa	LG	Pelvis	238	4.9	Yes	Male	CD II
Epididymitis	Left	Oral antibiotic	pTa	LG	Ureter	157	0.9	Yes	Male	CD II
Walking difficulty	Left	Physiotherapy	pTa	HG	Pelvis	124	4.9	Yes	Male	CD I
Postoperative urinary tract infection	Right	Oral antibiotic	pT1	HG	Pelvis	149	0.9	Yes	Female	CD II
Localized abscess at renal site	Right	Radiological drain	pTa	LG	Pelvis	150	4.9	Yes	Female	CD IIIa
Small intestinal lesion	Right	Reoperation	pT2	HG	Pelvis	131	3.9	Yes	Female	CD IIIb
Acute nephropathy	Left	Furosemide	pTa	LG	Pelvis	190	4.9	No	Female	CD I
Ileus	Right	Operation and ICU stay	pTa	LG	Ureter	128	3	No	Male	CD IV
Pneumonia	Right	Intravenous antibiotic	pT3	HG	Pelvis	113	4.9	No	Female	CD II
Pneumonia	Right	Oral antibiotic	pTa	LG	Pelvis	206	4.9	No	Female	CD II
Diarrhea and vomiting	Right	Conservative treatment	pTa	LG	Pelvis	241	4.9	No	Female	CD 1

CD = Clavien-Dindo grade; HG = high grade; ICU = intensive care unit; LG = low grade; LOS = length of stay.

DNA mutations in tumor tissue from the primary UTUC lesion support this theory, as do subsequent lesions in the bladder [9,10].

The timing of intravesical chemotherapy in relation to radical treatment of UTUC is therefore of great interest to researchers and practitioners. Administration of single-dose MMC within 24 h of transurethral resection of non–muscle-invasive bladder cancer to prevent recurrence has been proved to be more effective than deferred intravesical instillation within 2 wk postoperatively [11]. In contrast, the European Association of Urology UTUC guideline recommends intravesical instillation of a single dose of chemotherapy but does not specify the time interval from RNU [12]. This recommendation is based on the possible risk of spillage of the chemotherapeutic agent into the abdomen after excision and closure of the ureteral orifice. Serious adverse effects, such as chemical necrosis after intravesical instillation, have been reported after deep transurethral bladder resection or undetected bladder perforation [13].

Two meta-analyses have reported lower BRRs in patients receiving intravesical chemotherapy after RNU, and early instillation seems to be of importance as well as single-dose instillation is comparable with multiple instillations [14,15].

In the present study, intravesical instillation of MMC was administered during the operation, after securing a watertight closure of the excised bladder cuff. Complication rates experienced were comparable with those of another study that investigated perioperative outcomes and postoperative complications after RNU [16]. None of the observed complications in the present study were suspected to be caused by intravesical instillation of MCC.

In 2018, Noennig et al [17] compared intraoperative intravesical instillation of MMC (before bladder cuff excision) with postoperative intravesical instillation of MMC and noted a significantly lower 1-yr BRR in the intraoperative group (16%) than in patients who received postoperative MMC, who had a BRR of 33%. Notably, this study did not exclude patients with prior bladder tumors. This finding suggests that the timing of intravesical therapy after radical treatment of UTUC may have an impact on the risk of bladder recurrence.

In the present study, we found an overall BRR of 21% in the study population. Strikingly, in the present study, only 16% of the bladder tumor–naïve patients (five out of 31) had a bladder recurrence during the median follow-up time of 16 mo. The first bladder recurrence in the present study occurred 15 mo after RNU.

These findings are comparable with those of a prospective, randomized controlled trial by O'Brien et al [18]—the ODMIT-C study. The ODMIT-C study reported a BRR of 17% in the MMC arm and 27% in the standard treatment arm ($p = 0.055$; 16), as well as a 40% relative risk reduction in bladder recurrence with a single dose of postoperative MMC. In this study, intravesical instillation of MMC was performed just before the removal of the transurethral catheter 7–10 d postoperatively.

Ito et al [19] reported on bladder recurrence in a randomized trial comparing early bladder instillation with pirarubicin versus saline within 48 h after RNU. The results from this study are comparable with those of the ODMIT-C study, with a recurrence of 16.9% at 1 yr and 16.9% at 2 yr in the pirarubicin group compared with 31.8% at 1 yr and 42.2% at 2 yr in the control group ($p = 0.025$).

To our knowledge, no studies have reported on the safety and feasibility of intraoperative MMC instillation subsequent to cystotomy closure.

It is likely that robot-assisted surgery may lead to a tighter cystostomy and therefore fewer complications than open or standard laparoscopic surgical techniques. To our knowledge, there are no studies comparing bladder leakage after cystostomy closure between open, laparoscopic, and robot-assisted RNU. All surgeries performed in our study

were robot-assisted ones, and theoretically this might be the reason why we did not experience a higher complication rate. Prospective studies including laparoscopic, open, and robot-assisted RNU are needed in order to compare cystostomy closures and subsequent complication rates.

The present study demonstrates promising results with regard to the safety of intraoperative instillation of MMC; however, possible study limitations must be addressed. The small sample size in the single-center study is a notable limitation, and 16 patients were not included in the final recurrence analysis due to prior bladder cancer, which bladder recurrences can be attributed to and not UTUC; therefore, the recurrence analysis is hypothesis generating and not comparable with the aforementioned prospective ODMIT-C trial. Furthermore, there were significant differences in tumor stage and grade between the two groups, which can influence the BRRs, and the median follow-up time of 16 mo causes the possibility of missed bladder recurrences, as we know from prior studies that 85% of recurrences occur in the first 3 yr postoperatively [4]. Future studies calls for prospective, well-powered, multicenter randomized controlled trials with standardized timing of intravesical instillation of MMC in order to demonstrate a significant decrease in BRR.

5. Conclusions

This study reports that intraoperative intravesical MMC instillation immediately after bladder cuff excision is feasible and safe. This method may reduce the incidence of bladder recurrence following RNU.

***Author contributions*:** Naomi Nadler had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Azawi, Jensen, Nadler, Oedorf.
Acquisition of data: Nadler, Oedorf.
Analysis and interpretation of data: Azawi, Jensen, Nadler, Oedorf.
Drafting of the manuscript: Nadler.
Critical revision of the manuscript for important intellectual content: Azawi, Jensen, Nadler, Oedorf.
Statistical analysis: Azawi, Nadler.
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References

[1] Soria F, Shariat SF, Lerner SP, et al. Epidemiology, diagnosis, preoperative evaluation and prognostic assessment of upper-tract urothelial carcinoma (UTUC). World J Urol 2017;35:379–87.
[2] Xylinas E, Kluth L, Passoni N, et al. Prediction of intravesical recurrence after radical nephroureterectomy: development of a clinical decision-making tool. Eur Urol 2014;65:650–8.
[3] Seisen T, Colin P, Rouprêt M. Risk-adapted strategy for the kidney-sparing management of upper tract tumours. Nat Rev Urol 2015;12:155–66.
[4] Azawi NH, Næraa SH, Subhi Y, et al. Oncological outcomes of radical nephroureterectomy for upper urinary tract urothelial neoplasia in Denmark. Scand J Urol 2020;54:58–64.
[5] Seisen T, Granger B, Colin P, et al. A systematic review and meta-analysis of clinicopathologic factors linked to intravesical recurrence after radical nephroureterectomy to treat upper tract urothelial carcinoma. Eur Urol 2015;67:1122–33.
[6] The Danish Data Protection Agency. http://www.datatilsynet.dk/databeskyttelse/lovgivning.
[7] Peyronnet B, Seisen T, Dominguez-Escrig J-L, et al. Oncological outcomes of laparoscopic nephroureterectomy versus open radical nephroureterectomy for upper tract urothelial carcinoma: an European Association of Urology guidelines systematic review. Eur Urol Focus 2019;5:205–23.
[8] Jones TD, Wang M, Eble JN, et al. Molecular evidence supporting field effect in urothelial carcinogenesis. Clin Cancer Res 2005;11:6512–9.
[9] Sidransky D, Frost P, Von Eschenbach A, Oyasu R, Preisinger AC, Vogelstein B. Clonal origin of bladder cancer. N Engl J Med 1992;326:737–40.
[10] Ito A, Shintaku I, Satoh M, et al. Intravesical seeding of upper urinary tract urothelial carcinoma cells during nephroureterectomy: an exploratory analysis from the THPMG trial. Jpn J Clin Oncol 2013;43:1139–44.
[11] Sylvester RJ, Oosterlinck W, van der Meijden APM. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. J Urol 2004;171:2186–90.
[12] Rouprêt M, Babjuk M, Compérat E, et al. European Association of Urology guidelines on upper urinary tract urothelial carcinoma: 2017 update. Eur Urol 2018;73:111–22.
[13] Filson CP, Montgomery JS, Dailey SM, et al. Complications associated with single-dose, perioperative mitomycin-C for patients undergoing bladder tumor resection. Urol Oncol 2014;32:40.e1–8.
[14] Hwang EC, Sathianathen NJ, Jung JH, Kim MH, Dahm P, Risk MC. Single-dose intravesical chemotherapy after nephroureterectomy for upper tract urothelial carcinoma. Cochrane Database Syst Rev 2019;5:CD013160.
[15] Wu P, Zhu G, Wei D, et al. Prophylactic intravesical chemotherapy decreases bladder tumor recurrence after nephroureterectomy for primary upper tract urothelial carcinoma: a systematic review and meta-analysis. J BUON 2015;20:1229–38.
[16] Lee H, Kim HJ, Lee SE, Hong SK, Byun S-S. Comparison of oncological and perioperative outcomes of open, laparoscopic, and robotic nephroureterectomy approaches in patients with non-metastatic upper-tract urothelial carcinoma. PLoS One 2019;14:e0210401.
[17] Noennig B, Bozorgmehri S, Terry R, Otto B, Su L-M, Crispen PL. Evaluation of intraoperative versus postoperative adjuvant mitomycin c with nephroureterectomy for urothelial carcinoma of the upper urinary tract. Bladder Cancer 2018;4:389–94.
[18] O'Brien T, Ray E, Singh R, Coker B, Beard R. British Association of Urological Surgeons Section of Oncology. Prevention of bladder tumours after nephroureterectomy for primary upper urinary tract urothelial carcinoma: a prospective, multicentre, randomised clinical trial of a single postoperative intravesical dose of mitomycin C (the ODMIT-C Trial). Eur Urol 2011;60:703–10.
[19] Ito A, Shintaku I, Satoh M, et al. Prospective randomized phase II trial of a single early intravesical instillation of pirarubicin (THP) in the prevention of bladder recurrence after nephroureterectomy for upper urinary tract urothelial carcinoma: the THP Monotherapy Study Group trial. J Clin Oncol 2013;31:1422–7.