# Safety and feasibility of early single dose mitomycin-C bladder instillation post robot-assisted radical nephroureterectomy

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## Abstract

Objectives

To assess the safety and feasibility of early single dose mitomycin-C (MMC) bladder instillation following robot-assisted radical nephroureterectomy (RANU) at a tertiary kidney cancer centre.

Radical nephroureterectomy with bladder cuff excision and subsequent mitomycin-C (MMC) bladder instillation to reduce recurrence risk is the gold standard for high risk upper urinary tract urothelial carcinoma (UUTUC). We adapted a robot-assisted nephroureterectomy technique with precise distal ureteric dissection, bladder cuff excision and watertight bladder closure.

Materials and methods

We retrospectively reviewed all patients undergoing RANU for UUTUC at our centre performed as a standardised transperitoneal procedure comprising of: bladder cuff excision, 2-layer watertight closure and intra-operative bladder leak test; without re-docking/repositioning of the robotic surgical system. Patient demographics, the timing of MMC instillation, adverse events (surgical and potentially MMC-related) and

length of stay (LOS) were assessed according to the Clavien-Dindo (CD) classification.

Results

Sixty-nine patients underwent a RANU with instillation of MMC. The median age was 70 (interquartile range [IQR] 62-78) years. Median day of MMC instillation was 2 (IQR 1-3) days and median LOS was 2 (IQR 2-4) days, with urethral catheter removal on day of discharge in all cases. Only CD complications Grade 1 occurred (7 patients, 10%). Five patients had ileus, 1 wound infection and 1 self-limiting delirium; all managed conservatively. No adverse events potentially related to MMC instillation were noted within 30 days postoperatively.

Conclusion

The use of intravesical MMC instillation given in the immediate post-operative period appears feasible and safe in patients undergoing RANU with intraoperative confirmation of a water-tight closure ensuring early catheter free discharge, with no significant adverse events. The potential reduction in intravesical recurrence in patients receiving early MMC needs to be assessed with longitudinal follow up studies.

**Key words:** Robot-assisted, radical nephroureterectomy, mitomycin-C, upper urinary tract urothelial carcinoma, robotic nephroureterectomy

## Introduction

The gold standard surgical treatment for high risk upper urinary tract urothelial carcinoma (UUTUC) is a radical nephroureterectomy with a bladder cuff excision in the majority of patients (1). The risk of urothelial carcinoma recurrence in the bladder post radical surgery is considerable, within 22-47% (2). Although this may be a field effect, it is also suspected to be secondary to seeding of tumour cells. Avoidance of tumour spillage intra-operatively by careful tissue handling and clipping the ureter distal to the tumour early are key to reducing the risk of seeding and consequent extravesical recurrence (3).

The use of a single dose intravesical chemotherapy to reduce the intravesical recurrence rate is well described and has been shown to be efficacious (4-7). There remains concern and uncertainty however, regarding the risk of adverse events from extravasation of these intravesical agents (5). As a consequence, there is reluctance to administer intravesical chemotherapy early in the immediate postoperative period or before a cystogram is performed confirming a water-tight bladder closure. Whether this delay is likely to have a detrimental effect on its efficacy in reducing bladder recurrence is uncertain, because in the only prospective trial of single-dose postoperative mitomycin C (MMC) for UUTUC no predefined time point of planned instillation was reported (5). However, in superficial bladder cancer, a prospective

trial of 2243 patients demonstrated that immediate MMC within 24 hours after transurethral resection was superior to 2-weeks deferred MMC (8). For UUTUC, a retrospective study has reported that intraoperative instillation of MMC is superior to postoperative MMC as early as 1 day following nephroureterectomy (9). These data, although limited, suggest that early instillation after nephroureterectomy may be beneficial.

There is also varied opinion on the best surgical approach in the management of UUTUC, with surgeon preference likely to be the main contributory factor. There is evidence to show that a laparoscopic approach is at least equivalent to an open excision in terms of oncological outcomes (10). Accepted practice include combined endoscopic detachment of the bladder cuff (‘pluck’ technique), open excision of the distal ureter, or complete laparoscopic excision of the distal ureter.

With the increasing adoption of robot-assisted surgery particularly with the new platforms, performing the entire procedure minimally invasively is possible. We have adapted a transperitoneal minimally-invasive robot-assisted approach without redocking in which a bladder cuff is excised, followed by a watertight closure of the bladder (11). Here, we retrospectively assessed the safety and feasibility of early single dose MMC bladder instillation in the immediate postoperative period after using this standardised robot-assisted nephroureterectomy technique at a tertiary kidney cancer centre.

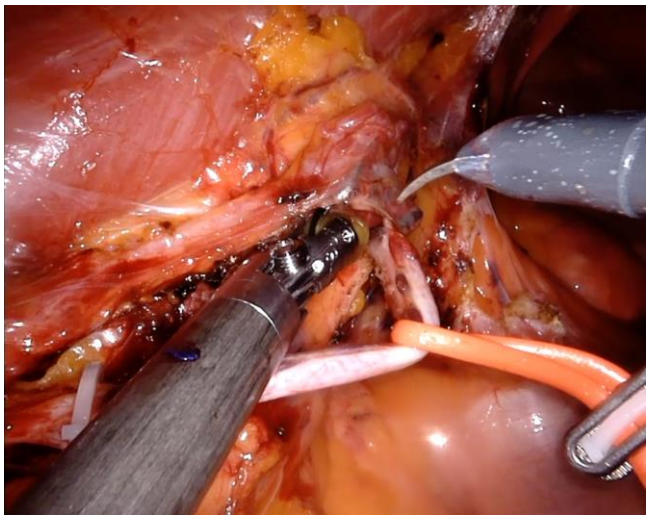
## Methods

We retrospectively reviewed all patients undergoing RANU for UUTUC at a tertiary referral centre over a two-year period between 2017 and 2019. All patients were operated on with the use of the Da-Vinci Xi robot-assisted platform at an insufflation pressure of 15 mm Hg and a standard insufflation device, with the entire procedure performed minimally invasively without redocking the robot. A standardised step-wise transperitoneal approach is used with an extravesical excision of a bladder cuff with the ureter ligated with a clip distal to the tumour. The excised distal ureter and bladder cuff including the ureteral orifice is then placed in a drop-in bag to avoid any potential tumour spillage (figure 1a-c). The cystotomy is subsequently closed intracorporeally with a barbed suture (absorbable V-loc 2-0) in two layers (figure 2a/b). A bladder leak test was carried out intraoperatively with 200-250mls saline to ensure a watertight closure. At completion the entire specimen is placed within an endocatch bag and is removed through an extension of the assistant port. MMC instillation (local protocol: 40 mg of MMC is diluted in 40 ml of 0.9% saline) is administered on the ward within 48 hours postoperatively through the indwelling catheter. If tolerated, the MMC instillation is allowed contact with the bladder for 60 minutes after which the bladder is drained and the catheter removed. The patient is then monitored to ensure voiding with adequate bladder emptying confirmed by ultrasound before discharge.

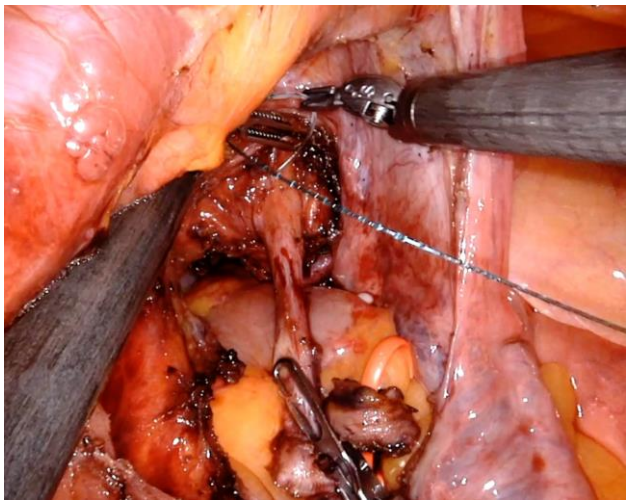
Patient demographics, the timing of MMC instillation, length of stay, catheter removal and adverse events according to Clavien-Dindo were reviewed. For patients with available cystoscopy follow-up the 1-year bladder recurrence rate (BRR) was assessed.

figure 1

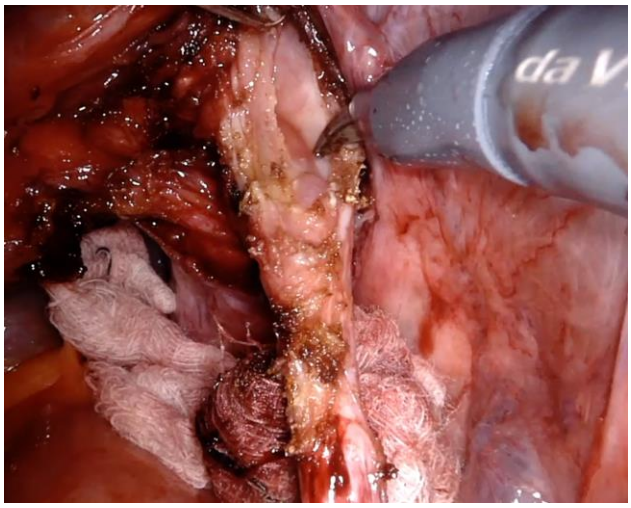
a) hem-o-lok clip on ureter and ureter slooped to aid retraction



b) stay suture prior to cystotomy



c) cystotomy performed with cold dissection



d) distal ureter placed in drop-in bag

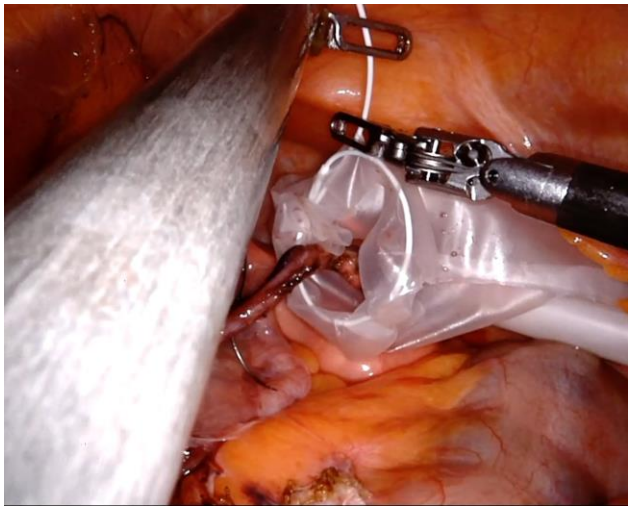
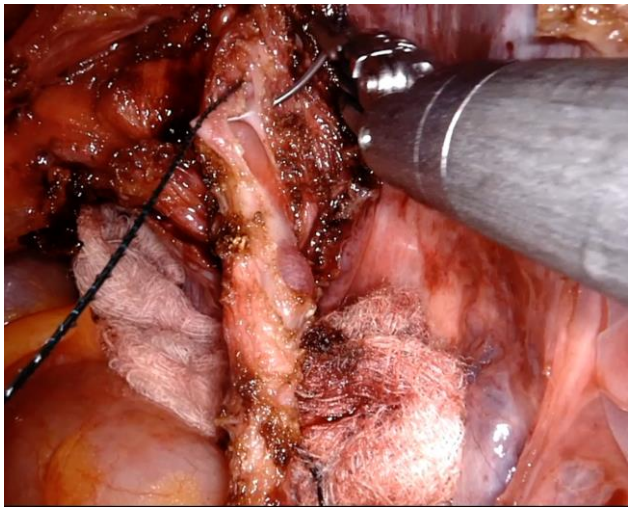
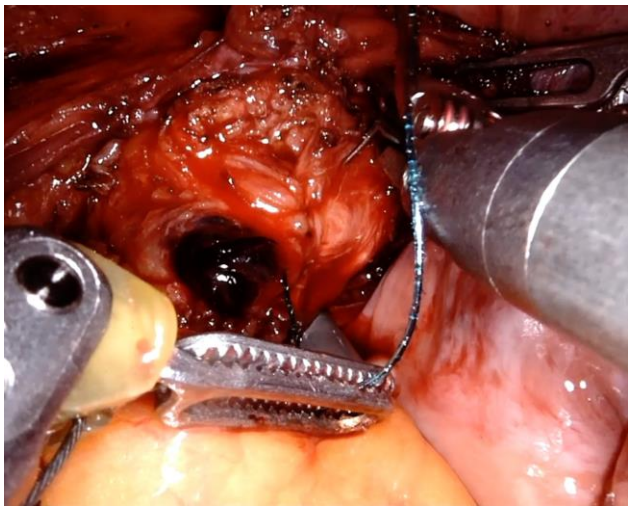


figure 2

a) closure of bladder mucosa



b) closure of second layer, checking for any bladder leak



## Results

Of 83 patients undergoing surgery for UUTUC, we identified 69 patients who underwent a RANU with a subsequent instillation of MMC. The reasons for the 14 patients who did not receive MMC are listed in figure 3. The median age was 70 (interquartile range [IQR] 62-78) years. Forty (58%) were male and 29 (42%) female (Table 1). Laterality was similar with 37 (54%) on the right and 32 (46%) on the left. Median day of MMC instillation was 2 (IQR 1-3, range 1-8) days after surgery. Twenty-six patients (37.7%) received MMC in the first 24 hours. Median LOS was also 2 (IQR 2-4) days, all patients were catheter free on discharge. There were 7 Clavien-Dindo classification grade 1 postoperative complications noted, including 5 patients with ileus, 1 wound infection and 1 patient with self-limiting delirium, all managed conservatively (Table 2). Ileus led to a prolonged stay with a median of 6 (range 4-11) days. No grade 3-4 adverse events potentially related to MMC instillation were noted both during the inpatient stay and at first follow up clinic 2-3 weeks post-operatively.

Of the patients with postoperative confirmed UUTUC (n=62), 47 patients (75.8%) had cystoscopy follow-up date available with a median follow-up of 13 months (range 2-30 months). Overall, 19 patients had a bladder recurrence (40.4%; 95% Confidence Interval (CI) 0.28-0.55) after a median of 6 months (2-19). The overall 1-year BRR was 34% (95% CI 0.22-0.48, n=16 patients). Excluding patients with a previous history of bladder cancer, the 1-year BRR was 26.8% (95% CI 0.16-0.41, n=11 of 41 patients)

Figure 3: Patients undergoing RANU

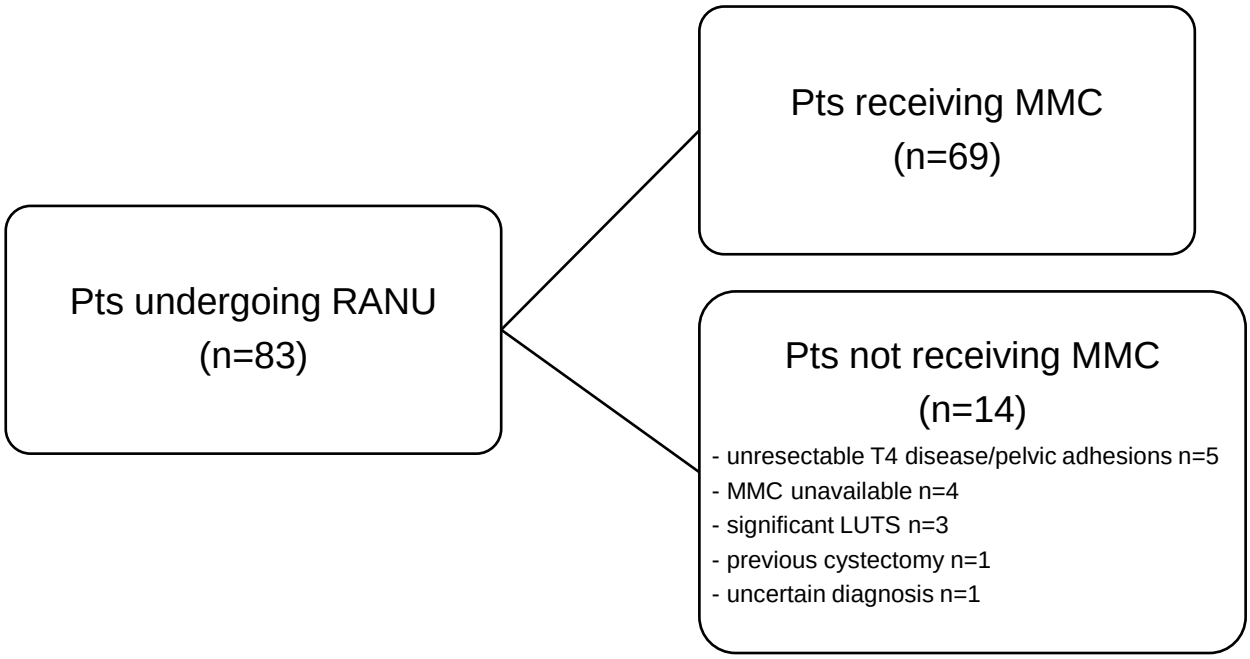



Table 1: Patient demographics and surgical outcomes

| | |
|---|---|
| number receiving MMC post RANU | 69/83 patients |

| | |
|---|---|
| median age | 70 (interquartile range [IQR] 62-78) years |
| male: female ratio | 40 (58%):29 (42%) |
| laterality | Right 37 (54%), Left 32 (46%) |
| median postoperative day of MMC instillation | 2 (IQR 1-3) days |
| median length of stay | 2 (IQR 2-4) days |
| definite histology | pT1-4 G3:38,<br>pTa G1-2: 24,<br>RCC: 5,<br>Benign: 2 |

Table 2: Postoperative complications

| Pt | Age (years) | Gender | BMI | Laterality | Tumour location | Console time (min) | Op Time (min) | EBL (ml) | POD MMC given (days) | Postoperative complications (Clavien-Dindo) | LOS (days) | Histology |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 69 | female | 34 | right | distal ureter | 121 | 157 | 100 | 2 | delirium (CD1) | 2 | pT2 G3 |
| | | | | | | | | | | | | |
| 2 | 65 | female | 28 | right | distal ureter | 116 | 172 | 50 | 2 | ileus (CD1) | 4 | pTa G2 |
| | | | | | | | | | | | | |
| 3 | 80 | male | 33 | right | renal pelvis | 210 | 240 | 400 | 2 | ileus (CD1) | 11 | pTa G2 |
| | | | | | | | | | | | | |
| 4 | 77 | female | 26 | left | renal pelvis | 156 | 195 | 50 | 2 | ileus (CD1) | 5 | pT1 G3 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 5 | 84 | male | 27 | left | mid ureter | 210 | 245 | 300 | 1 | ileus (CD1) | 9 | pTa G2 |
| 6 | 52 | male | 26 | left | renal pelvis | 110 | 140 | 30 | 1 | ileus (CD1) | 6 | RCC |
| 7 | 85 | female | 32 | left | mid ureter | 200 | 240 | 150 | 2 | wound infection (CD1) | 6 | pTa G3 |

## Discussion

Serious adverse events after early MMC instillation have been reported in the literature and are a concern. In a retrospective series comparing MMC after transurethral resection of bladder tumours (TURBT) in 116 patients to TURBT alone in an equal number of controls, major complications after MMC bladder instillation were reported in 5.2% versus 0.9% in the control group, with one patient suffering bladder perforation with necrotizing fasciitis in the instillation group (12). Chemical necrosis, which may be extensive, can occur after deep resection or occult bladder perforation requiring surgical debridement, cystectomy and/or intensive care admission (13, 14).

An oncologically sound nephroureterectomy requires resection of the ureteric orifice together with a bladder cuff and closure of the bladder wall. Based on the risk of potential extravasation of MMC it is therefore not surprising that the EAU UUTUC guideline recommendation to instil a single dose of MMC after the procedure is not associated with a specific time interval (1). This is in striking contrast to superficial bladder cancer where a large prospective trial confirmed that immediate MMC instillation within the first 24 hours is more effective than deferred instillation after 2 weeks or prolonged adjuvant MMC (8). In fact, the only prospective trial of postoperative single-dose MMC instillation after nephroureterectomy did not report the time points at which the instillation was performed (6). It is plausible, given the underlying biological similarities, that analogous to non-muscle invasive bladder cancer following transurethral resection, patients would benefit from early MMC

instillation following nephroureterectomy. The evidence, however, is not as robust as in non-muscle invasive bladder cancer and would require prospective evaluation.
It is therefore important that safety data are available for routine early instillation of MMC after nephroureterectomy with a bladder cuff removal. Our retrospective series demonstrates that following a postoperative protocol of instillation of MMC within the first 48 hours after a transperitoneal minimally-invasive robot-assisted approach in which a bladder cuff is excised with an intraoperatively tested watertight closure is safe. The observed CD grade 1 complications were mild and not specifically related to MMC instillation although it cannot be excluded that minor leakage of MMC with chemical irritation provoked the observed ileus. In the literature, however, extravesical leakage of MMC was associated with local pelvic tissue necrosis and the mild course of the surgical adverse events do not suggest an association with the MMC instillation. There is currently no consensus regarding the best approach to excising the bladder cuff and various approaches have been described in the literature, including hand-assisted bladder-cuff excisions during laparoscopic nephroureterectomy, transurethral excision of the orifice, hybrid laparoscopic approaches with open extravesical or transvesical bladder cuff excisions and our robotic approach (15-17). None of these approaches has been tested in a prospective randomised trial for oncological or surgical safety. A recent systematic review of retrospective studies suggests that laparoscopic nephroureterectomy may have poorer oncological outcomes than open nephroureterectomy, particularly when bladder cuff resection was required, and in pT3-pT4 disease (18), but the literature search did not identify a RANU series that was compared to the open approach. Nevertheless, the described robotic approach in our series allows for early recovery and discharge, and is performed adhering to oncological principles by using a hem-

o-lok clip to occlude the distal ureter and placing the resected distal ureter with bladder cuff in a laparoscopic bag immediately upon excision (11, 19). Animal studies have shown that the barbed suture we use to close the bladder lead to faster and simpler watertight bladder closures and similar leak pressures compared to monofilament (20, 21). Reported intermediate oncological outcome data with this approach were satisfactory (22). Regarding surgical safety, a very recent systematic review compared various nephroureterectomy techniques including resection of a bladder cuff (23). The series included more than 80,000 patients of which more than 10,000 underwent RANU. The authors concluded that RANU had a lower intraoperative complication rate but evidence remains sparse and of low quality. Clavien-Dindo complication rates after RANU appear to be low. In a recent multi-institutional series of 81 patients undergoing RANU or segmental ureterectomy only 6 (7.4%) had postoperative adverse events CD>2 (24).

This study is limited by retrospective evaluation. Although a protocol of immediate postoperative MMC instillation was followed, the median time of MMC instillation was 2 days with an upper range of 8 days. The outlier at 8 days had delayed instillation and removal of catheter due to significant benign prostatic obstruction and risk of urinary retention.

Data on the 1-year BRR was only available for 2/3 of the patients. The 1-year BRR was higher than in the ODMIT-C trial which reported a 17% 1-year BRR in the MMC arm versus a 27% 1-year BRR in the standard treatment arm (p=0.055) (6). Also, our data compare unfavourably to a small retrospective study which showed a 1-year BRR in the intra-operative MMC group of 16% versus 33% in the post-operative

group (p=0.09) (9). These outcomes should however be interpreted with caution given the small numbers and broad 95% CI. In addition, the ODMIT-C trial only included patients without a previous history of bladder cancer whereas our retrospective study of intra-operative MMC included 40% of patients with a history of bladder cancer prior to nephroureterectomy.

In summary, we describe the safety profile of a protocolised early MMC instillation strategy following an established and standardised robot-assisted laparoscopic approach to nephroureterectomy with bladder cuff. In the absence of a randomised controlled trial, this large retrospective cohort provides compelling evidence that this approach is feasible and safe.

This data may provide the necessary methodology to design a prospective randomized trial to test the potential improved reduction in intravesical recurrence in patients receiving MMC in the immediate post-operative period.

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