Original Article

Immediate gemcitabine bladder instillation following bladder closure during robotic-assisted radical nephroureterectomy: a multi-institutional report of feasibility and initial outcomes

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Background: Bladder recurrence after radical nephroureterectomy (RNU) is common and randomized data supports utilization of prophylactic intravesical mitomycin to reduce recurrence. Recently, gemcitabine has been shown to be safe and effective at reducing recurrence following transurethral resection of bladder tumors. We sought to evaluate the safety and efficacy of a single, intraoperative gemcitabine instillation immediately following bladder cuff closure during RNU, and to compare outcomes with non-gemcitabine intravesical chemotherapy agents.

Methods: We retrospectively reviewed all patients from two high volume centers who underwent robotic-assisted RNU between 2016–2020 and received either 2 g intravesical gemcitabine immediately following bladder cuff closure or non-gemcitabine intravesical chemotherapies [40 mg mitomycin C (MMC) or 50 mg doxorubicin] at the beginning of the procedure. Clinicopathologic factors were compared between cohorts. Bladder recurrence rates were evaluated using the Kaplan-Meier method and log-rank test.

Results: During RNU, 24 patients received gemcitabine and 31 patients received non-gemcitabine chemotherapy. In total, 35% (19/55) of patients experienced a bladder cancer recurrence. There was no significant difference in estimated bladder recurrence-free survival (bRFS) between gemcitabine and non-gemcitabine patient cohorts (P=0.64). By 12 months post-surgery, 25% of patients had experienced bladder recurrence. The estimated 1-year bladder RFS survival was 73% for gemcitabine and 76% for non-gemcitabine chemotherapy. Overall survival and cancer-specific survival did not differ between cohorts. No adverse events potentially attributable to the use of gemcitabine were noted within 30 days postoperatively.

Conclusions: Gemcitabine instilled immediately following bladder cuff closure during RNU has similar bRFS rates compared to established chemotherapy agents instilled at the start of surgery.

Keywords: Nephroureterectomy; intravesical gemcitabine; upper tract urothelial carcinoma; perioperative intravesical chemotherapy; bladder cuff closure

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Introduction

Radical nephroureterectomy (RNU) is the standard treatment for high-risk upper tract urothelial carcinoma (UTUC) (1,2). Recurrence within the bladder after RNU is common, with rates ranging from 22% to 47% (3-5). While the mechanism of bladder recurrence following RNU is likely multifactorial, genomic characterization of UTUC and subsequent bladder recurrence suggests a common clonal origin, lending credence to the theory of downstream seeding (6).

Multiple strategies exist to reduce bladder recurrence after RNU, including avoiding entry into the urinary tract, removal of the kidney and ureter en bloc with a bladder cuff, and early clipping of the ureter to avoid tumor seeding into the bladder (7,8). Perioperative instillation of intravesical chemotherapy has proven to be an effective strategy to reduce bladder recurrence. Based on two prospective trials demonstrating a reduction in bladder recurrence, the National Comprehensive Cancer Network and European Association of Urology UTUC guidelines recommend the use of a single dose of intravesical chemotherapy after RNU to reduce bladder recurrence, with the favored regimens being Mitomycin C (MMC) or pirarubicin at the time of catheter removal (1,2).

Despite the proven efficacy of MMC and other chemotherapeutic agents in reducing bladder recurrence following RNU, utilization is only 51% (9). This may be partly due cost and limited availability of MMC, but primarily due to concerns about the irritative effects of MMC instilled following a recent cystorrhaphy. In 2018, a large randomized controlled trial demonstrated intravesical gemcitabine to reduce bladder recurrence in patients with non-muscle-invasive bladder cancer (NMIBC) following transurethral resection of bladder tumors (TURBT) (10). Given these findings, we evaluated the use of single intraoperative gemcitabine instillation immediately following bladder cuff closure during RNU. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-23-112/rc).

Highlight box

Key findings

- Of patients undergoing radical nephroureterectomy (RNU) who received 2 g intravesical gemcitabine immediately following bladder cuff closure or non-gemcitabine intravesical chemotherapies at the beginning of the procedure, there was no difference in bladder recurrence-free survival (bRFS).
- No adverse events attributable to the use of gemcitabine occured within 30 days postoperatively.

What is known and what is new?

- Use of intravesical MMC reduces bladder recurrence after RNU. Intravesical gemcitabine reduces recurrence following transurethral resection of bladder tumors, but its efficacy in reducing bladder recurrence after RNU is unknown.
- This study shows that gemcitabine instilled immediately following bladder cuff during RNU closure is safe and has comparable bRFS compared to established chemotherapy agents.

What is the implication, and what should change now?

- Intravesical gemcitabine immediately after bladder neck closure is safe and effective.
- This lower-cost streamlined approach to perioperative intravesical chemotherapy could increase adherence among urologists performing RNU.

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). And Individual consent for this retrospective analysis was waived. After approval from the institutional review boards of University of Iowa Hospitals & Clinics and Hackensack University Medical Center, we retrospectively reviewed the records of patients at two tertiary referral centers (University of Iowa Hospitals & Clinics and Hackensack University Medical Center) from 2016 to 2020 who underwent robotic-assisted RNU and received perioperative intravesical gemcitabine (2 g immediately after bladder cuff closure for one hour) or non-gemcitabine chemotherapies [40 mg mitomycin C (MMC) or 50 mg doxorubicin for one hour following foley catheter placement at the beginning of the procedure and drained before bladder opening]. Informed consent was obtained on all patients prior to surgery and included consent for intravesical chemotherapy. Prior to RNU, 92% (22/24) of patients in the gemcitabine and 84% (26/31) of patients in the non-gemcitabine cohorts underwent diagnostic ureteroscopy and biopsy of suspicious lesions. Ureteroscopy and/or biopsies were omitted if preoperative imaging or retrograde pyelograms were concerning for UTUC, with either a positive cytology or poorly to non-functional kidney. No patients underwent percutaneous biopsy, and all patients underwent cystoscopy prior to RNU and were confirmed to be free of any bladder tumors. Only patients with pure UC were included. Patients who did not receive

intravesical chemotherapy or had no surveillance cystoscopy following RNU were excluded. Routine follow-up after RNU included physical examination, routine labs, selective use of urine cytology, cystoscopy, and imaging studies. Patients were typically evaluated at 3, 6, and 12 months following RNU, and every 6–12 months. Complications were graded according to the Clavien-Dindo classification.

All patients underwent transperitoneal RNU as previously described with the use of the da Vinci Xi platform (Intuitive Surgical Inc., Sunnyvale, CA) (11). RNU in the gemcitabine and non-gemcitabine cohorts were performed by one of two surgeons or one of three surgeons, respectively. During renal mobilization, the ureter was ligated immediately with a Hem-o-lok clip (Teleflex, Morrisville, NC) to reduce tumor seeding. Additional clips if there was known tumor distal to the initial clip. The ureterectomy was performed with an extravesical bladder cuff excision, noting to remove the entire intramural ureter and ureteral orifice. The cystotomy was closed in two layers with absorbable barbed suture in a running fashion. A leak test was performed with a minimum of 180 mL of saline to ensure a watertight cystorrhaphy. All patients were deemed to have a watertight closure and received gemcitabine. Using standard precautions and sterile technique, 2 g of gemcitabine in 100 cc normal saline was instilled via sterile IV extension tubing connected to the foley catheter. The catheter was then clamped for one hour. In the non-gemcitabine group, either MMC (40 mg in 40 mL sterile water) or doxorubicin (50 mg in 50 mL saline) was instilled for one hour at the beginning of the case and drained before bladder opening. This method has been previously reported (12). Outpatient cystogram was not routinely performed prior to catheter removal.

Statistical analysis

Chi-squared or Fisher's exact tests were used to compare categorical variables, whereas *t*-tests were used to compare continuous variables between gemcitabine and non-gemcitabine cohorts. The primary end point was bladder recurrence-free survival (bRFS) and was estimated using the Kaplan-Meier method. A log-rank test was used to evaluate differences in survival between cohorts. All tests were two-sided and assessed for significance at the 5% level using R v4.0.2 (http://www.r-project.org).

Results

We identified 55 patients with UTUC who received intraoperative intravesical chemotherapy while undergoing RNU, of whom 24 received gemcitabine and 31 received non-gemcitabine chemotherapies. Demographics, clinical information, and tumor characteristics are presented in *Table 1*. Median age at time of RNU was 74.0 (IQR 68–80.3) years old. Forty percent (22/55) of patients had prior or concurrent bladder cancer. Of patients receiving non-gemcitabine chemotherapy, 71% (22/31) received MMC and 29% (9/31) received doxorubicin. A similar proportion of patients in each cohort had high grade disease on final pathology, 76% versus 74% (P=1.0). Overall, 36% (20/55) of patients were found to have pathologic ≥ pT2 disease. Among the entire cohort, rates of ≥ pT2 disease after RNU were not statistically different between patients who received neoadjuvant chemotherapy (47%) versus those who did not (34%, P=0.34). While more patients (42%) in the non-gemcitabine cohort were ≥ pT2 compared the gemcitabine cohort (29%), this was not statistically different. Concomitant carcinoma *in situ* was not routinely reported by pathology and therefore was unable to be measured.

Median follow-up in the gemcitabine and non-gemcitabine cohorts was 11.9 (IQR 6.4–20.0) and 19.6 (IQR 12.2–30.5) months, respectively. Thirty-five percent (19/55) of patients experienced a bladder cancer recurrence which was diagnosed by surveillance cystoscopy and subsequent TURBT (Table S1). There was no difference in bRFS between the two cohorts (P=0.64) (*Figure 1*). By 12 months post-surgery, 25% of patients had experienced bladder recurrence. The 12-month bRFS survival was 73% for gemcitabine, 76% for non-gemcitabine, and 76% overall. Overall survival also did not differ between patient cohorts (P=0.71) (*Figure 2*). By 12 months after surgery, 9% of patients had died. Median survival time was 35.3 months overall, 35.3 months for the non-gemcitabine group, and 32.9 for the gemcitabine group. The estimated 12-month overall survival rate was 93% for gemcitabine, 90% for non-gemcitabine, and 91% overall. Cancer-specific survival did not differ between gemcitabine patient cohorts (P=0.21) (*Figure 3*). By 12 months after surgery, 4% of patients had died due to cancer. Median cancer-specific survival time was 35.3 months for the non-gemcitabine group but was

Table 1 Baseline demographic, clinical, and pathologic upper tract urothelial carcinoma characteristics of patients undergoing radical nephroureterectomy and receiving gemcitabine or non-gemcitabine chemotherapy

Covariate	Gemcitabine (N=24)	Non-gemcitabine (N=31)	P value
Age (years), median [IQR]	75 [70–80]	74 [68–80]	0.89
Gender			
Female	6 (25%)	13 (42%)	0.26
Male	18 (75%)	18 (58%)	
Race			
Black	1 (4.2%)	0 (0%)	0.72
Asian	0 (0%)	1 (3.2%)	
Hispanic	1 (4.2%)	0 (0%)	
White	22 (92%)	30 (97%)	
Type 2 diabetes			
No	17 (71%)	25 (81%)	0.53
Yes	7 (29%)	6 (19%)	
Smoking history			
Current	1 (4.2%)	6 (21%)	0.2
Former	14 (58%)	16 (55%)	
Never	9 (38%)	7 (24%)	
Missing	0	2	
History of bladder cancer			
No	14 (58%)	19 (61%)	1.00
Yes	10 (42%)	12 (39%)	
Neoadjuvant chemotherapy			
No	16 (67%)	24 (77%)	0.54
Yes	8 (33%)	7 (23%)	
Adjuvant chemotherapy			
No	23 (96%)	23 (74%)	0.02*
Yes	1 (4%)	8 (26%)	
Side			
R	11 (46%)	12 (39%)	0.77
L	13 (54%)	19 (61%)	
Preoperative grade			
HG	18 (82%)	15 (58%)	0.12
LG	4 (18%)	11 (42%)	
No biopsy	2	5	
Hydronephrosis			
Non-mild	17 (71%)	28 (90%)	0.08
Mod-severe	7 (29%)	3 (10%)	
Location			
Renal	12 (57%)	16 (52%)	0.79
Ureter/both	9 (43%)	15 (48%)	
Not reported	3	0	
Focality			
Unifocal	14 (67%)	22 (71%)	0.76
Multifocal	7 (33%)	9 (29%)	
Not reported	3	0	
Pathologic T stage			
<T2	17 (71%)	18 (58%)	0.42
≥T2	7 (29%)	13 (42%)	
Pathologic grade			
HG	16 (76%)	23 (74%)	1.00
LG	5 (24%)	8 (26%)	
Not reported	3	0	
Nodal status			
N0	12 (50%)	15 (48%)	0.46
N1	2 (8.3%)	0 (0%)	
N2	1 (4.2%)	2 (6.5%)	
Nx	9 (38%)	14 (45%)	
BMI (kg/m^{2}), median [IQR]	27.7 [26.2–31.4]	29.2 [24.4–34.8]	0.92
Tumor size (cm), median [IQR]	2.6 [1.6–4.3]	3.0 [1.9–5.3]	0.17
Follow-up (months), median [IQR]	12 [6.4–20.0]	20 [12.2–30.5]	#

*, values are statistically significant (P<0.05). #, P values are not provided for length of follow up. The significance of the difference in survival between cohorts is performed in the *Figures 1-3*. These numbers are for descriptive purposes. HG, high grade; LG, low grade; BMI, body mass index; IQR, interquartile range.

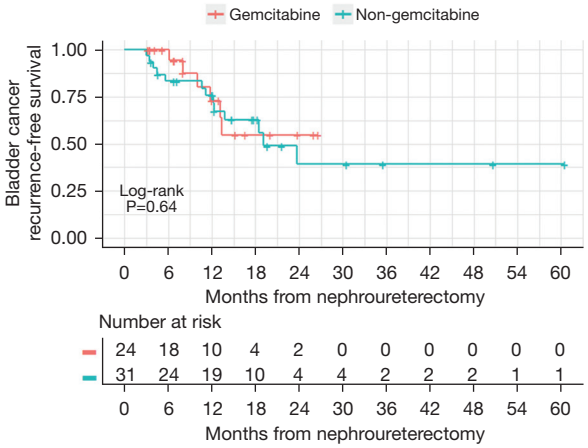

Figure 1 Bladder cancer recurrence-free survival for patients receiving gemcitabine *vs.* non-gemcitabine intravesical chemotherapy.

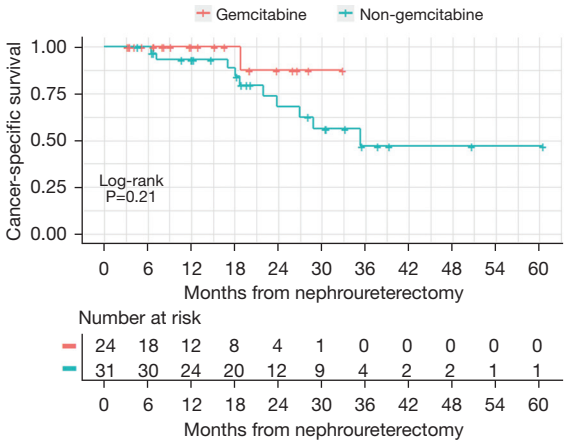

Figure 3 Cancer-specific survival for patients receiving gemcitabine *vs.* non-gemcitabine intravesical chemotherapy.

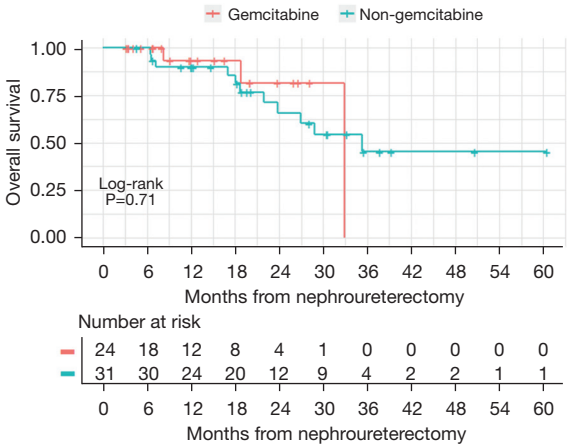

Figure 2 Overall survival for patients receiving gemcitabine *vs.* non-gemcitabine intravesical chemotherapy.

inestimable for the overall and gemcitabine curves. The estimated 12-month cancer-specific survival rate was 100% for gemcitabine, 93% for non-gemcitabine, and 96% overall.

The median length of stay was 2 days (IQR 2–4) and no patients were readmitted within 30 days of surgery in the gemcitabine cohort. The median length of stay was 3 days (IQR 2–4) and three patients (8%) were readmitted within 30 days of surgery in the non-gemcitabine cohort. Median foley catheter duration was 10 days (IQR 10–35) in the gemcitabine group with one patient requiring prolonged catheterization (35 days) due to a history of urinary retention and 12 days (IQR 10–40) in the non-gemcitabine group, with one prolonged catheterization (40 days) due to a bladder leak noted on cystogram. Complications are noted in *Table 2*. The gemcitabine group had an overall complication rate of 4/24 (17%) compared to 4/31 (13%) in the non-gemcitabine group. Half (2 of 4) of the complications in each group were high grade. No adverse events specifically attributable to gemcitabine chemotherapy were noted.

Discussion

Guidelines recommend a single dose of intravesical chemotherapy after RNU for UTUC to reduce the risk of bladder recurrence (1,2). The ODMIT-C trial utilized a single dose of MMC at the time of catheter removal and found an 11% absolute risk reduction and relative reduction of 40% for bladder recurrence, with a number needed to treat of nine in order to prevent one bladder tumor (13). The THP Monotherapy study group trial used pirarubicin instilled 48 hours postoperatively and found a reduction of 25% (14). A subsequent meta-analysis also demonstrated a benefit of postoperative intravesical chemotherapy, with an HR of 0.51 for bladder recurrence (95% CI: 0.32–0.82). After 12 months follow-up, this would result in 127 fewer bladder cancer recurrences (95% CI: 44–182) per 1,000 participants (15). Despite the efficacy of perioperative instillation of intravesical chemotherapy based on level one evidence, routine utilization of these agents has not been embraced by the majority of urologists (9). Common concerns include uncertainty regarding the risk of adverse events of these intravesical agents, high cost, and office infrastructure required during instillation at the time of catheter removal

Table 2 Postoperative complications by intravesical chemotherapy

Patient	Chemotherapy	Complication	Clavien-Dindo grade	LOS (days)
1	Gemcitabine	Delirium	1	4
2	Gemcitabine	UTI	1	2
3	Gemcitabine	PE	4	10
4	Gemcitabine	Chyle leak	3	8
5	Mitomycin C	SBO	3	1
6	Doxorubicin	Chyle leak	3	2
7	Mitomycin C	Bladder leak	1	1
8	Mitomycin C	Ileus	1	4

LOS, length of stay; UTI, urinary tract infection; PE, pulmonary embolism; SBO, small bowel obstruction.

(9,15). Consequently, only 51% of urological oncologists in the United States reported administering peri-operative intravesical chemotherapy (9). We assessed the safety and efficacy of immediate intraoperative intravesical gemcitabine instillation after cystotomy closure, as this approach may mitigate typical concerns associated with perioperative intravesical chemotherapy following RNU.

Messing *et al*. reported the use of intravesical gemcitabine for reduction of bladder recurrence following TURBT in the setting of NMIBC (10). Participants were randomized to receive intravesical instillation of gemcitabine or saline for 1 hour immediately following TURBT. Gemcitabine demonstrated decreased 4-year estimated disease recurrence rate compared to placebo (35% versus 47%, P<0.001). While hypotonic water or saline irrigation may flush out circulating tumor cells and cause cell osmolysis, it is likely that the direct cytotoxic effect of intravesical chemotherapy is more efficacious. Freifeld *et al*. (16) reported on the intraoperative use of gemcitabine in a retrospective study analyzing the impact of installation timing on bladder recurrence following RNU. In this study, patients received either intraoperative intravesical MMC or gemcitabine which was either drained before managing the bladder cuff, or postoperative MMC. Of the patients who received intraoperative intravesical chemotherapy, 68% received MMC and 32% received gemcitabine. There was no difference in 12-month bRFS between the those who received intraoperative chemotherapy 82% and postoperative chemotherapy (72%). Though trending toward a benefit of utilizing MMC over gemcitabine, there was no statistically significant difference in bRFS between gemcitabine and MMC at 12 months, with a HR of 2.67 (95% CI: 0.853–8.357; P=0.092) (16). Although the timing of bladder instillation was not immediately after closure, this study supports our finding of similar efficacy between gemcitabine and non-gemcitabine intravesical chemotherapy. In our cohort, estimated 12 months bRFS rates was 73% for gemcitabine and 76% for the non-gemcitabine group (P=0.64). This demonstrated that gemcitabine efficacy was similar to established chemotherapy mitomycin C (MMC) and doxorubicin with short-term (12 months) follow-up. Tumor-specific factors which increase the risk for bladder recurrence after nephroureterectomy include multifocality, ureteral tumor location, and ≥ pT2 disease (4). While there was no significant difference in pathologic stage between cohorts in this study, more patients were pT2 in the non-gemcitabine group, and this could possibly impact results in a larger cohort. We were unable to compare outcomes directly to patients who underwent RNU without any intravesical chemotherapy during this timeframe as the use of intravesical therapy is our standard practice, however the rates of bladder recurrence in the first year after RNU in patients who didn't receive intravesical therapy were 27% and 32% in the ODMIT-C and THP trials, respectively (13,14). There are currently two Phase II trials accruing patients to assess intravesical gemcitabine versus placebo for UTUC bladder recurrence NCT03062059 and GEMINI (NCT04398368).

Similar to intravesical chemotherapy use following TURBT for NMIBC, MMC is the primary perioperative intravesical chemotherapy utilized in the United States following RNU (9,17). Reported toxicities of MMC range from low grade (dysuria, transient hematuria) to high grade (prolonged chemical cystitis, dystrophic bladder

calcifications, perivesical inflammation and fibrosis) (18,19). Major complications have been reported to occur in 5.2% of patients after TURBT with MMC instillation compared to 0.9% after TURBT alone (18). The safety profile of intravesical gemcitabine has been demonstrated in several trials in the setting of TURBT. In the Messing trial, there was no significant difference in Clavien-Dindo 1–3 complications between Gemcitabine and saline groups and no Clavien-Dindo 4–5 events were demonstrated during the study (10). Similarly, in a prospective trial of 120 patients with BCG unresponsive NMIBC randomized to salvage intravesical regimens of monthly maintenance treatments of gemcitabine or MMC, gemcitabine demonstrated better tolerability than MMC with regards to chemical cystitis (21.1% in MMC and 5.5% in gemcitabine arm, P=0.013) and dysuria/frequency (20.0% in MMC and 9.2% in gemcitabine arm, P=0.023) (20). This improved safety profile was demonstrated in our gemcitabine cohort, reflected by low median length of stay of 2 days, no readmissions within 30 days, and overall complication rate of 17%, none of which were related to intravesical gemcitabine.

There is currently no consensus regarding the optimal timing of instillation of postoperative chemotherapy. The ODMIT-C trial required instillation of MMC at time of foley catheter removal, at least one week following RNU (13). In the pirarubicin trial instillation was performed within 48 hours of RNU (14). Based on the tumor seeding theory and TURBT studies, the earliest possible instillation of intravesical chemotherapy could result in the greatest reduction of recurrences since tumor cells implantation may occur within 24 hours (21). Immediate post-TURBT intravesical chemotherapy prevents tumor cell implantation secondary to the traumatic agitation of the TURBT (22). Noennig *et al.* compared MMC instilled intraoperatively to postoperatively on post-operative day 1 or later and found that patients who received intraoperative MMC had a lower 1-year rate of bladder recurrence (HR =0.113, 95% CI: 0.28–0.63, P=0.01), supporting the practice of intraoperative instillation to avoid tumor seeding (23). Freifeld *et al.* found no difference in recurrence rates between intraoperative and postoperative intravesical chemotherapy groups [12-month bRFS rates were 82% and 72% respectively (log rank P=0.365)]; however, the intraoperative group in their study had higher rates of high-grade and muscle invasive disease (16).

The lower cost of gemcitabine compared to MMC and the simplified logistics of intraoperative instillation of gemcitabine compared to outpatient intravesical chemotherapy administration at the time of catheter removal may also increase perioperative intravesical chemotherapy utilization. Compared with MMC, gemcitabine is considerably less expensive (average sales price for 2 g of gemcitabine is $55.70 and for 40 mg of MMC is $1,062.72) (10). As up to 10% of primary urothelial cell cancers are considered UTUC, 75% of which are considered high risk, the preferable use of gemcitabine over MMC during RNU could result in considerable cost savings. There have also been recent concerns of MMC shortage stemming from production hurdles. The additional obstacles of dedicating time during a post-operative visit, need for specialized nursing or healthcare provider for administration, varying discomfort experienced by a conscious patient during intravesical chemotherapy administration, and coordination with pharmacy can be overcome with intraoperative administration of gemcitabine immediately after bladder cuff closure.

Our study has several notable limitations. The retrospective nature of the study may have introduced unmeasured bias into patient selection and follow-up. Additionally, due to the retrospective study, heterogenous patient population, and low recurrence rates, the study may have been underpowered to detect a difference in bladder recurrence rates. Patients were not prospectively assigned to high or low risk categories per EAU guidelines. This was addressed to a degree, however, by comparing the proportion of patients with high grade UTUC on biopsy or cytology and preoperative hydronephrosis. There was heterogeneity in the non-gemcitabine group. Two different intravesical chemotherapy were used, as doxorubicin was utilized when MMC was in national short supply. However, use of doxorubicin, an analogue of the anthracycline pirarubicin, for the prevention of bladder recurrence has previously been utilized (12). Additionally, non-gemcitabine chemotherapy agents were instilled at the beginning of the case whereas gemcitabine was instilled after bladder cuff closure, and such differences could confound the results. Five different surgeons were included at two different centers, and while the nephroureterectomy technique described did not differ significantly between groups, un-captured differences could have confounded the recurrence risk. Post-operative complication data may not have been completely captured if patients presented to an outside facility, and retrospective assessment of complications could have resulted in measurement bias with systematic underreporting of low-grade complications. Lastly, the data

is limited by the small sample size with only 19 recurrences between groups, thus compromising an assessment of comparative effectiveness. Nevertheless, our aim was to report the safety and feasibility of a more affordable chemotherapy option, with a more streamlined workflow, in an effort to improve surgeon adherence to instillation of intravesical chemotherapy during RNU.

Conclusions

In patients undergoing RNU, intravesical gemcitabine instilled immediately following bladder cuff closure has similar rates of bRFS compared to non-gemcitabine chemotherapy. This lower-cost, more streamlined approach to perioperative intravesical chemotherapy could increase adherence among urologists performing RNU for UTUC.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-23-112/rc

Data Sharing Statement: Available at https://tau.amegroups.com/article/view/10.21037/tau-23-112/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-23-112/coif). Michael Stifelman is on the surgical advisory board for Intuitive Surgery and receives educational grants from Ethicon. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional review boards of University of Iowa Hospitals & Clinics and Hackensack University Medical Center and individual consent for this retrospective analysis was waived.

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Supplementary

Table S1 Patients with bladder recurrence after nephroureterectomy

Patient	Intravesical agent during RNU	History of bladder cancer	Time to recurrence (months)	Recurrence grade	Recurrence stage	Subsequent local therapy	Systemic treatments
1	Adriamycin	No	4	HG	Ta	BCG/IFN	
2	Mitomycin	No	12	HG	Ta	BCG	
3	Adriamycin	No	12	HG	Ta		AVETAZ clinical trial (avelumab and docetaxel) for metastatic disease time of RNU
4	Mitomycin	No	3	HG	Ta	BCG	
5	Adriamycin	Yes	23	HG	CIS	Valrubicin/docetaxel	
6	Adriamycin	Yes	3	LG	Ta		Pembrolizumab for metastatic disease
7	Mitomycin	Yes	13	HG	T1		Pembrolizumab for metastatic disease
8	Mitomycin	Yes	11	LG	Ta	Gemcitabine/docetaxel	
9	Adriamycin	No	18	HG	Ta	Gemcitabine/docetaxel	
10	Adriamycin	No	5	HG	Ta	Gemcitabine/docetaxel	Avelumab and docetaxel for metastatic disease after recurrence
11	Mitomycin	Yes	3	HG	T1	BCG	
12	Mitomycin	No	10	HG	T1	BCG	
13	Mitomycin	No	10	HG	T1	BCG	
14	Gemcitabine	No	10	LG	Ta	Gemcitabine/docetaxel	
15	Gemcitabine	Yes	8	LG	Ta	Gemcitabine/docetaxel	
16	Gemcitabine	Yes	6	HG	T1	Gemcitabine/docetaxel, then valrubacin/docetaxel, then cystectomy (end-stage bladder)	
17	Gemcitabine	Yes	13	HG	Ta	gemcitabine/docetaxel, then valrubacin/docetaxel	
18	Gemcitabine	Yes	13	HG	Ta	Contralateral RNU with concurrent cystectomy	
19	Gemcitabine	No	11	LG	Ta	BCG	PGV-001 (personalized genome vaccine), atezolizumab

RNU, radical nephroureterectomy; mo, months; HG, high grade; LG, low grade; BCG, bacillus Calmette-Guerin; IFN, interferon; CIS, carcinoma in situ.

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