Review Article

Single instillation intravesical chemotherapy after radical nephroureterectomy for upper tract urothelial carcinoma: current evidence and future directions

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Abstract: Upper urinary tract urothelial carcinoma (UTUC) accounts for 5% to 10% of urothelial carcinomas and two-thirds are high-grade at the time of diagnosis. The gold standard management of high-grade UTUC is radical nephroureterectomy (RNU). Despite primary treatment, disease recurrence involves the bladder in 22% to 47% of cases. Single dose, postoperative intravesical chemotherapy (pIVC) is an adjunct to RNU to decrease bladder recurrences that is currently recommended in guidelines from the European Association of Urology, National Cancer Center Network, and American Urological Association. Two clinical trials, using single dose, postoperative intravesical mitomycin C or pirarubicin, have provided level 1 evidence to support the formation of these guidelines. Despite this evidence, pIVC utilization is reportedly low among urologists, ranging from 12% to 55% among three studies, with non-utilizers citing lack of supporting evidence, safety concerns, and clinical infrastructure as leading rationale. In the past 10 years, no additional trials on single dose pIVC have been completed and validated in systematic reviews or meta-analyses. Utilization of pIVC still has room for improvement and further studies on this subject are warranted to overcome the barriers to implementation. Herein, we describe the critical literature that supports guideline recommendations for single dose pIVC after RNU to understand efficacy, safety, practice patterns, and discuss the future directions of this treatment adjunct.

Keywords: Intravesical chemotherapy (IVC); nephroureterectomy; upper urinary tract urothelial carcinoma (UTUC)

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Introduction

Background

Upper urinary tract urothelial carcinomas (UTUCs) originate from urothelial cells lining the pelvicalyceal system and ureter that underwent malignant transformation. While urothelial carcinomas are relatively common, UTUCs are a rare subtype that accounts for 5% to 10% of urothelial tumors (1,2). As diagnostic methods continue to improve, the incidence of UTUCs has been slowly rising with an estimated annual incidence of two cases per 100,000 inhabitants in Western countries (3). The peak incidence of UTUC is seen in individuals aged 70 to 90 years and cases are twice as common in men (4). At the time of UTUC

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diagnosis, 64% of tumors occur in the pelvicalyceal system at nearly twice the rate as in the ureter, 60% are high-grade, and 7% have metastasized at the time of diagnosis. Additionally, the bladder is involved with concomitant UCC in 17% of UTUC cases at initial diagnosis (5-7).

In accordance with clinical guidelines, the primary treatment of non-metastatic UTUC is mainly determined by the pathological grading of the tumor (8,9). Options for managing low-grade tumors include renal-sparing interventions, such as segmental ureteral resection and endoscopic resection or ablation. For high-grade tumors, the recommended treatment options are surgical resection in the form of radical nephroureterectomy (RNU) or, in select cases, distal ureterectomy, with bladder cuff excision (BCE) and regional lymphadenectomy (8-10).

Rationale and knowledge gap

Despite endoscopic or surgical treatment(s), disease recurrence involves the bladder in 22% to 47% of cases, thus surveillance with a combination of cross-sectional imaging, cystoscopy, and cytology should be performed first 3 to 5 years with follow-up intervals guided by pathologic staging (5,8-10). The leading theory of bladder recurrences (BRs) after primary treatment is clonal expansion of carcinoma, which proposes that multifocal UCC is due to intraluminal spread and seeding of cells that originated from a single, malignantly transformed cell (11,12). There are multiple predictors of BR that have been identified. Specifically, regarding BR after RNU, a meta-analysis by Seisen *et al.* reported three distinct domains of significant predictors for BR (13). First, patient-specific factors are male gender, history of non-muscle invasive bladder cancer (NMIBC), preoperative chronic kidney disease, and smoking at the time of diagnosis (13-15). Second, the tumor-specific factors include preoperative urine cytology positive for abnormal urothelial cells, ureteral tumor location, tumor multifocality, invasive pT stage, tumor necrosis, and presence of carcinoma *in situ* (13,14,16). Lastly, treatment-specific factors include a laparoscopic approach to RNU, extravesical or transurethral bladder cuff removal, positive surgical margins, and postoperative intravesical chemotherapy (pIVC) (13,17-20).

Of the predictors for BR following RNU, the treatment-specific risk factors are optimal, modifiable targets for improving patient outcomes. While there is an absence of consensus guidelines on surgical approach and bladder cuff management, the use of single dose, postoperative instillation of intravesical chemotherapeutic agents has been integrated into several clinical guidelines following multiple retrospective studies, meta-analyses, and randomized controlled trials (8-10,17,18,21,22).

Objective

The objective of this review is to concisely describe foundational literature that supported the use of single dose, pIVC for reducing BR of patients undergoing RNU + BCE for UTUC, review pIVC practice patterns, and discuss the future directions of this treatment adjunct.

Development of pIVC

The early days

For decades, IVC has been used to kill malignant urothelial cells before implantation and BR has occurred in patients treated for UCC in the bladder (23). One of the first studies of pIVC for decreasing BR after RNU was published by Tari *et al.* in 1987. Their study included 16 patients that received pIVC, in the form of either mitomycin C (MMC), carboquone, or cytosine arabinocide, and 11 patients that did not receive pIVC. Within 2 years after RNU, recurrence rates in the patients that received pIVC were significantly lower, at 12.5%, versus patients that did not, at 42.3%, respectively (24). In the time that followed, multiple regimens of additional IVC agents were investigated, including thiotepa, adriamycin, epirubicin, and pirarubicin (THP) (21,25,26).

Fundamental clinical trials

The modern evidence supporting pIVC came from the One Dose Mitomycin C (ODMIT-C) trial reported on in 2011 by O'Brien *et al.* (22). This prospective, randomized, multicenter trial in Britain accrued 284 patients from 46 centers between 2000 to 2006 and investigated the utility of a single postoperative dose of 40 mg of MMC for preventing BR in 1 year after RNU. MMC was administered at the time of urinary catheter removal which typically occurred 7 to 10 days following RNU. In their intention-to-treat analysis of 239 patients, the authors demonstrated a decrease in BR from 27% in the control group to 17% in the MMC treatment arm (P=0.055). Additionally, the per-protocol analysis of 220 patients yielded an absolute risk reduction of 11% (P=0.03) and number needed to treat of

Table 1 Consensus guidelines on pIVC for upper tract urothelial carcinoma

Organization	Guideline statement	Year of first release
EAU	Deliver a postoperative bladder instillation of chemotherapy to lower the intravesical recurrence rate	2013
	Level of evidence: 1b (evidence based on at least one randomized clinical trial)	
	Strength rating: strong (advantages of intervention clearly outweigh the disadvantages)	
NCCN	Perioperative IVC with mitomycin or gemcitabine should be considered following nephroureterectomy with cuff of bladder resection	2017
	Category 2A (based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate)	
AUA/SUO	In patients undergoing RNU or segmental ureterectomy (including distal ureterectomy) for upper UTUC, a single dose of perioperative IVC should be administered in eligible patients to reduce the risk of BR	2023
	Strong recommendation, level of evidence: A (benefits > risks/burdens; net benefit is substantial; applies to most patients in most circumstances and future research is unlikely to change confidence)	

pIVC, postoperative intravesical chemotherapy; EAU, European Association of Urology; NCCN, National Cancer Center Network; IVC, intravesical chemotherapy; AUA, American Urological Association; SUO, Society of Urologic Oncology; RNU, radical nephroureterectomy; UTUC, upper urinary tract urothelial carcinoma; BR, bladder recurrence.

nine to prevent one BR. The safety of pIVC was excellent with no events related specifically to the instillations. Due to BR defined by cystoscopic appearance only, there was a lack of histologic confirmation of BR. Despite the trial's flaws, it did provide level 1 evidence to support MMC as a safe and efficacious treatment after RNU.

In 2013, Ito *et al.* added to the body of evidence supporting pIVC after RNU with their prospective, randomized, multicenter trial in Japan. The THP Monotherapy Study Group Trial accrued 77 patients from 2005 to 2008 and investigated the utility of a single postoperative instillation of 30 mg of THP for preventing BR within 2 years after RNU (21). The THP instillation was performed within 48 hours postoperatively. Patients with history of synchronous bladder cancer were excluded. The 1-year BR rate in pIVC patents was 16.9%, compared to 31.8% in the control group. Furthermore, the 2-year BR rate was 16.9% in the treatment arm compared to 42.2% in the control group. The multivariable analysis supported the administration of the THP as an independent predictor of decreased BR. Lastly, as in the ODMIT-C trial, there were no complications attributable to pIVC.

As a result of the encouraging evidence presented in these two trials, single dose pIVC appeared in multiple international guidelines on UTUC. Based on the OMDIT-C trial, the European Association of Urology (EAU) provided the first recommendations advocating for pIVC after RNU to reduce the rates of BR in the 2013 update of the UTUC guidelines (22,27). Next, the Japanese Urologic Association (JUA) 2014 edition of the UTUC guideline referenced the results of the OMDIT-C trial and THP study as data that strongly indicated the preventative value of single dose pIVC (21,22,28). Following this, the UTUC section of the National Cancer Center Network (NCCN) 2017 bladder cancer guidelines provided recommendation to strongly consider single dose, immediate pIVC after RNU (29). Most recently, the collaboration of the American Urological Association (AUA) and the Society of Urologic Oncology (SUO) published the 2023 guidelines for non-metastatic UTUC with a strong recommendation for single dose, pIVC to reduce the risk of BR after RNU or segmental ureterectomy (including distal ureterectomy) (10). The current guideline recommendations and grade of evidence are outlined in *Table 1*.

Assessing utilization

The clinical guidelines discussed here are similar in nature to the medical treatises dating back to the time of Hippocrates (30). For as long as there have been guidelines, there have been questions about adherence. After the first EAU position statement on pIVC, several groups sought to assess pIVC utilization and identify barriers to use among urologic oncologists.

First, in 2014, Lu *et al.* conducted a self-report survey by e-mail of 722 urologic oncologists in the SUO over a

consecutive 8-week period (31). The response rate was low at 22%, of which 14 of 158 respondents were not performing RNU. In the cohort performing RNU (n=144), 55% were surgeons with ≥10 years in practice and 90% were those performing <10 cases annually (<5 cases: 41%, 6 to 10 cases: 49%). Of the surgeons performing RNU, only 51% reported using pIVC. In this group, 70% provided pIVC routinely in all patients and 30% only to patients with a history of NMIBC. Furthermore, 94% performed a single instillation and MMC was the most common intravesical agent at 88. Administration was performed at varying time intervals after RNU, with 77% within 1 week postoperative, including 33% intraoperatively. Among the 49% of respondents that reported not using pIVC, their rationale was as follows: lack of data supporting use (44%), urologist's preference (19%), office infrastructure (17%), overtreatment concerns (12%), extravasation concern (6%), and patient preference (2%) (31).

Similarly, in 2014, Kikuchi *et al.* assessed UTUC management in Japan after the JUA comments acknowledging potential role of pIVC (28,32). The investigators conducted a mail-based survey assessing UTUC management of 1,119 urology institutes with a response rate of 59% response rate (32). Of the respondents, less than 2% were <10 years into practice while the 78% majority had been practicing for 20 to 40 years. RNU volume was <10 cases/year for 69% of the entire cohort in the year prior to the survey. Only 12% of respondents reported performing a single dose of pIVC after RNU with 49% using THP, followed by 19% MMC, 13% epirubicin, and 8% doxorubicin. Notably, this survey did not assess for the rationale non-utilizers of pIVC.

Most recently, in 2017, an e-mail based survey on UTUC management was conducted by Dobé *et al.* of 1,053 participants in the EAU Section of Oncological Urology (ESOU) over a consecutive 3-month period with a 12% response rate (33). Interestingly, despite the EAU guideline, there were numerous similarities to the results of the SUO cohort's utilization. Of the 127 participants, 40% had been in practice for <10 years and 88% had RNU volume of <10 cases per year. Within this cohort, 47% of respondents were using pIVC and there was no correlation with years in practice or RNU volume. Regarding choice of pIVC, 85% reported using MMC and 10% doxorubicin. Timing of administration was performed within 10 days postop or intraoperatively in 74% and 10% of participants, respectively. The leading rationale for those not utilizing pIVC was a lack of supporting evidence (55%), concern about potential side effects (18%), and organizational deficiencies (15%). It is difficult to assess whether there are healthcare system-specific factors hindering European centers from widespread adoption of IVC.

The above studies share several key limitations. First, the distribution of surveys was specifically to urologic oncologists and major teaching hospitals, excluding urologists that may otherwise perform RNU outside of these contexts. Next, the surveys provided were not externally validated. Lastly, the low response rates introduce a significant nonresponse bias, potentially underestimating the degree of non-utilization of pIVC. The low response rate may be due to poor dissemination of the surveys, as e-mail based may be easily overlooked. Future endeavors in assessing pIVC utilization may benefit from distributing validated surveys in multiple formats (e.g., e-mail or letter based, in-person at national meetings, social media) to providers in multiple practice settings (e.g., outside high-volume centers, non-fellowship trained urologists) over a broader period (e.g., 3 to 6 months minimum) to enhance response rate and validity.

Despite inherent limitations listed above, surveys continue to be an efficient means to understanding practice patterns for pIVC use. Clinical data from multicenter, international robotic surgery for upper tract urothelial cancer study group (ROBUUST) data set provides an additional avenue for examining trends in pIVC utilization as well) (34). Briefly, the ROBUUST groups includes retrospective data from 17 academic medical centers worldwide that performed minimally invasive (laparoscopic or robotic) RNU between 2006 and 2020. The analysis included 618 RNU cases performed after the inclusion of pIVC in the 2013 EAU UTUC guidelines. Despite the theoretical expectation for academic centers to better incorporate evidence-based practice, the aggregate data revealed pIVC utilization rate of 24%, significantly lower than previously reported. The annuals trends in usage increased over the study period with none of the 17 centers exceeding 25% utilization. Additionally, there were significant regional discrepancies between the sites (e.g., one Asian center reporting 93% pIVC use and another 0%) that are poorly understood and may be driven by institutional practices or geographic factors not captured in the study. Of note, the ROBUUST group did not present the types of intravesical agents, timing of administration, surgeon demographics, or rationale for non-utilization.

The following sections address three of the leading rationale for non-utilization reported by the SUO and ESUO cohorts: lack of supporting evidence, safety

concerns, and clinical infrastructure to provide context. Herein we encourage consideration of the information presented to lower the barriers to implementing pIVC after RNU into clinical practice.

Growing body of supporting research

In nearly 10 years since the last clinical trial that highlighted the utility of pIVC, the space for research studies in this arena remains an open opportunity. Growing the existing foundation of research may serve to guide urologists who cite non-utilization due to lack of data. Alongside the level 1 evidence from the OMDIT-C and THP trials, two meta-analyses demonstrated a significantly decreased risk of BR after RNU in patients that received pIVC (17,35). The utility of single dose pIVC after RNU was further validated in a 2019 Cochrane systematic review that concluded pIVC may increase time to BR (18). The completion of additional randomized clinical trials has potential to supplement supporting research to encourage increased utilization of single dose IVC to decrease BR.

Understanding safety concerns

One of the most commonly used agent for pIVC, MMC, is generally regarded as a safe and effective intravesical therapy, despite the feared major complications associated with extravasation (36). Reports of MMC leakage during transurethral resection of bladder tumor (TURBT) causing massive necrosis of the perivesical and rectal tissue have been published (37,38). By performing a BCE during RNU for UTUC, there is a theoretical risk of extravasation of the instilled IVC at the site of the bladder cuff. Utilizers of pIVC have reported performing cystogram to verify no extravasation of contrast prior to instillation therapy (31,33). In a retrospective cohort study, Gulamhusein *et al.* report an alternative method to decrease risk of extravasation, where in the surgeon performed an intraoperative bladder leak test to ensure a watertight closure prior to MMC instillation (39). The study group demonstrated that postoperative MMC (administered within 48 hours postoperative) had no significant adverse events specific to MMC instillation. Multiple studies have corroborated these findings of MMC's safety profile when administered after RNU (22,25,40,41). Beyond MMC, investigators should turn to the NMIBC literature in which the intravesical chemotherapeutic, gemcitabine, has been extensively investigated (35). In randomized controlled trials and meta-analyses, gemcitabine has demonstrated a favorable safety profile when used immediately after TURBT for patients with NMIBC (42,43). In the UTUC realm, the practice of gemcitabine as pIVC for RNU was explored in a retrospective analysis that demonstrated efficacy that was comparable to MMC (44). As support for pIVC grows, the urologist previously choosing to avoid pIVC due to safety concerns may find solace in using the less toxic agent, gemcitabine, after RNU.

Overcoming limitations of clinical infrastructure

The utilization of clinical resources is significant for instillations, requiring outpatient resources, personnel trained in handling chemotherapy agents, and means of properly disposing the hazardous waste (31). Non-utilization due to clinical infrastructure is fertile ground for integration of pIVC regimens that do not rely on the outpatient setting. First, single instillation (as opposed to multiple postoperative instillations) should be performed as it would minimize resource utilization without compromising on oncologic outcomes in this setting (8,9,17). Furthermore, shifting the timing of single dose pIVC administration to the intraoperative setting (as opposed to outpatient) can further reduce resource utilization without compromising outcomes and may potentially increase pIVC utilization (44). Future studies in this realm may include a comparative analysis of health care costs associated with intraoperative versus postoperative administrations and randomized clinical trials comparing the oncologic efficacy of different pIVC regimens (e.g., single versus multiple dose).

Trajectory of pIVC use

The integration of single dose pIVC after RNU continues to grow, albeit at a slow pace. In the study by Kenigsberg *et al.*, the included 17 academic institutions reported an upward annual trend for pIVC use of 8% between 2013 and 2019, following the release of the EAU guidelines (34). The adherence to the updated UTUC management guidelines appears to follow a similar course of progressive utilization seen pIVC after TURBT for NMIBC. For reference, a cross-sectional study following the SWOG S0337 trial ("Effect of Intravesical Instillation of Gemcitabine versus Saline Immediately Following Resection of Suspected Low-Grade NMIBC on Tumor Recurrence") did not indicate an increased use of immediate post-TURBT gemcitabine in the nearly 2 years following publication, thus highlighting

the limitations of prominent studies to impact utilization (42,45).

The phenomenon of non-adherence to guidelines despite the cumulative evidence, such as pIVC after RNU, is rich with opportunities for the growing field of implementation science. Multiple evidence-based frameworks exist to guide researchers in addressing the gaps between guideline recommendations and real-world practice, with the goal of developing interventions for improvement (46-48). Such implementation research is well underway in the NMIBC community regarding pIVC administration after TURBT for low to intermediate grade bladder tumors. Investigators in the United Kingdom identified numerous barriers to pIVC utilization in this setting that included, among others, a of lack of supporting evidence, safety concerns, and clinical infrastructure to provide context. These studies contributed to the development of the Transurethral Resection and Single Instillation Intravesical Chemotherapy Evaluation in Bladder Cancer Treatment (RESECT) randomized clinical trial that was developed in part to assess the impact of implementation (49). The aim is to conduct a multicenter international observation study of NMIBC management that will inform investigators as to the interventions (such as provider education and organizational auditing) on pIVC utilization and subsequent patient outcomes. This study is currently recruiting. Given the similarities in oncologic goals between pIVC after TURBT and pIVC after RNU, these studies should serve as an ideal reference for implementation strategies that may improve patient outcomes.

Conclusions

The utilization of single dose pIVC to decrease BRs after RNU for UTUC is supported by multiple RCTs and clinical practice guidelines. Despite the cumulative evidence in support of oncologic control with pIVC, utilization is reportedly low. The reasons for non-utilization are complex and implementation science can fill the gaps to encourage adherence to guidelines for better patient outcomes.

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Footnote

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