

Strategies to reduce bladder tumor recurrences following surgery for upper tract urothelial carcinoma

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Abstract

The incidence of upper tract urothelial carcinoma (UTUC) has been on the rise and the malignancy is more commonly managed surgically as higher proportions of *in situ* disease are being detected. One challenge facing urologists is the high rate of post-treatment intravesical recurrence (IVR) of UTUC (23 – 50%). Genomic research indicated that cells of recurrent bladder lesions are most often clonally derived from the primary UTUC and are likely to seed into the bladder after tumor manipulation. This calls for effective strategies to prevent the spread of UTUC. The methods we discuss here are the use of a ureteral access sheath during diagnostic ureteroscopy, application and timing of intravesical chemoprophylaxis, early ureteral ligation distal to UTUC, and formal bladder cuff excision. Urologic surgeons should aim to achieve a reduced rate of IVR when applying these techniques.

Keywords: Chemoprophylaxis, Nephroureterectomy, Ureteroscopy

1. INTRODUCTION

Upper tract urothelial carcinoma (UTUC) accounts for approximately 5% of urothelial cancers, with an increasing incidence over the past 30 years [1]. The proportion of *in situ* UTUC in databases reportedly has grown from 7.2% during the 1970s to 31% at present [1]. It is likely that improved diagnostics and formal guidelines have contributed to earlier and more timely diagnosis and, as a result, a larger proportion of patients can be managed by urologic surgery [1].

UTUC has been traditionally treated with radical nephroureterectomy (RNU) and bladder-cuff excision (BCE). RNU remains the gold standard for bulky, high-grade, or invasive UTUC. Endoscopic ablation has emerged as a treatment option for low-grade UTUC while increasing alternatives of chemotherapy and immunotherapy are available for patients requiring systemic therapy [2-4].

Even after management, however, UTUC is associated with the development of urothelial carcinoma in the bladder in 23 – 50% of the patients [5-8]. A wide array of risk factors has been reported to be responsible for intravesical recurrence (IVR) following UTUC. Patient factors, such as female gender and active tobacco use, pathological factors, including tumor size, focality, stage, and grade, and treatment variables, such as incomplete distal ureteral resection and post-operative systemic chemotherapy, all have been suggested as potential risks for IVR [5-7,9]

In reality, some of the associated risks are non-modifiable. However, emerging research underscored certain strategies related to all urologic practices that could reduce IVR following UTUC surgery. In this paper, we present and discuss practical approaches to reduce IVRs following ureteroscopy (URS) and RNU.

2. CLONALITY

A question presents itself: Are bladder tumors clonally related to antecedent UTUC cancer? Two theories have been proposed to explain the high rates of recurrence of UC in the bladder after treatment of UTUC (through either URS or RNU). One theory, called “field change,” proposes that panurothelial genetic mutations are present either

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congenitally, from infection, or toxin exposure, and render the entire urothelium independently susceptible to further mutations leading to cancer [10,11]. This could account for UC forming in both the upper and lower urinary tracts [11,12]. The other theory postulates that UTUC cells are displaced into the ureteral lumen during manipulation and instrumentation and seeded downstream into the bladder to cause UC in the bladder [11,12]. The rationale behind this theory is, in part, supported by the timing of the development of IVR after UTUC procedures, and by the occurrence of multifocal UTUC in an ipsilateral ureter, which suggests local spread. In addition, high-grade UTUC is associated with a five-fold increased rate of high-grade bladder recurrence, suggesting a possible clonal relationship between the upper and lower tract cell lines [5].

This origin of the IVR cancer cells has been studied by Audenet *et al.*, who compared genetic mutations of three cohorts of tumors: urothelial carcinoma of the bladder alone, UTUC alone, and bladder carcinoma occurring after UTUC treatment [12]. The study reported differences between UTUC and bladder UC in certain genes, such as HRAS, FGFR3, TP52, ERBB2, and RB1 [12]. Notably, however, in the 29 patients with prior UTUC and subsequent bladder cancer, 86% of somatic mutations were present in both tumors [12]. These observations imply a high likelihood of clonal relatedness [12].

Similarly, Van Doeveren *et al.* found recurrent bladder cancer originated from UTUC cell lines by analyzing a panel of 41 genes and comparing tumor tissue to normal tissue in post-RNU patients [11]. The tumor tissue of the UTUC and recurrent bladder lesions shared specific DNA mutations, indicating a clonal relation in 11 out of 15 patients (73%) [11]. The authors concluded that the need for diagnostic URS should be carefully considered before RNU due to the risk of seeding cancer cells into the bladder [11]. They also called for steps to be taken during RNU to minimize the displacement of upper tract cells into the bladder and for intravesical chemotherapy to be administered perioperatively to minimize the viability of any potentially seeded cancer cells [11].

3. IVRS FOLLOWING URS FOR UTUC

There is concern about seeding cancer cells intraluminally through URS and associated endoscopic therapies for UTUC [13,14]. The majority of data regarding URS seeding was from patients who underwent RNU either with or without a prior diagnostic URS (d-URS). One such study found that d-URS had an odds ratio of 4.0 (95% CI [1.4 – 11.9], $P = 0.01$) for recurrence of cancer in the bladder [15]. Another similar study noted a hazard ratio of 5.6 (95% CI [1.7 – 18.5], $P < 0.004$) for d-URS before RNU [8]. One meta-analysis observed an IVR range of 39.2 – 60.7% with d-URS and a

range of 16.7 – 46% without d-URS [16]. Due to the risks of cancer dissemination, it is recommended to avoid performing URS and instrumenting a normal contralateral ureter when performing d-URS for suspected UTUC [4].

Diagnostic URS has immense value in the evaluation of UTUC. Endoscopy provides key diagnostic information, including tumor appearance, focality, size, and pathological information (if biopsied). However, the approach to diagnosis and management of UTUC cannot be dogmatic. Certain clinical scenarios may preclude URS or render the risk of URS to outweigh the benefit. For example, when it comes to ureteral stricture disease, the risk of ureteral perforation exists and diagnosis may be better achieved by upper tract cytology through renal barbotage along with high-quality cross-sectional imaging of the tumor [4]. The AUA 2023 UTUC guidelines state that there are cases for which URS evaluation is not necessary and give the following examples: (1) high-grade selective cytology or another source of tissue diagnosis; (2) radiographic findings strongly indicating high-grade disease, such as an obvious enhancing, urothelial-based soft-tissue filling defect on contrast-enhanced imaging with urography; and (3) URS findings will not influence decision making, such as patients who are not willing or able to undergo treatment for UTUC [4]. Proceeding directly to RNU is permitted in the AUA and EAU guidelines in cases strongly suspected of high-grade disease based on cytological and imaging criteria even in the absence of pathohistological results [4,17].

Interestingly, a lower recurrence rate has been reported with d-URS using a ureteral access sheath (11.5% with sheath vs. 39.7% without sheath) [8]. In a single study, when a sheath was used, multivariate analysis revealed that the risk of d-URS for bladder cancer was mitigated, though insignificantly (HR 1.3, [0.3 – 6.4], $P = 0.76$) [8]. Therefore, although the evidence is limited, it is advisable to use a ureteral access sheath when performing d-URS for suspected UTUC. The rationale is two-fold. First, as discussed above, this can potentially decrease downstream bladder recurrences. Second, ureteral access sheath likely decreases intrapelvic pressures which may cause seeding of UTUC through pyelovenous backflow [16,18]. Importantly, the latter consideration remains theoretical. Indeed, Nison *et al.* found that d-URS did not impact extravesical recurrence in a multicenter study of 500 patients [16,18]. In either case, judicious use of a ureteral access sheath for UTUC d-URS is recommended whenever feasible [8]. Importantly, it is critical to first evaluate the ureter before sheath placement. Specifically, we recommend that urologists perform free-hand diagnostic URS to first evaluate the entire length of the ureter before sheath placement. Such a practice allows for adequate characterization of ureteral disease and avoids disruption of tissue architecture when a

ureteral tumor is present. If a ureteral disease exists, an access sheath may still facilitate ureteroscopic intervention although the sheath must remain distal to the tumor site.

Limited data are available regarding IVR rates when placing a stent following diagnostic URS. Lee *et al.* found no significant difference in IVR-free survival when a stent was placed in a 41-patient retrospective cohort, with 53% receiving a stent following d-URS [19]. Our practice is similar to the management of urinary stone disease. Namely, the use of stents should be predicated on the clinical scenario. We believe that the management of ureteral tumors benefits from a ureteral stent for some duration (3 – 14 days), given the inherent edema that may occur post-procedure. Conversely, an uncomplicated treatment of a renal pelvic or calyceal lesion in an unobstructed system may not require temporary stenting. Future studies investigating the impact of stent placement on IVR rates would be of benefit.

The potential for intraluminal seeding from endoscopic ablation surgery for UTUC has not been well studied. Many cohort studies included a mix of UTUC disease with respect to grade, focality, and location, all of which could confound bladder recurrence rates. However, we can assume, for now, that the risks of IVR are at least equal to those of d-URS [20]. In a pooled analysis of the literature, Petros *et al.* noted a bladder cancer recurrence rate standing between 40% and 50% [20]. To minimize this risk, following tumor ablation and after ensuring there is no perforation of the upper or lower tracts, urologists may give one dose of pelvicalyceal or intravesical chemoprophylactic agent immediately after operation to kill displaced UTUC cells in the lumen of the ureter and bladder [4]. At present, there is no specific consensus on the specific drug type, instillation method, or dosing frequency. However, these authors believe that either 2 g of gemcitabine in 100 cc normal saline or 1 g of mitomycin-C in 50 cc normal saline post-URS are practical adjuvant therapies. Given the increase in low-grade cancer and strong recommendations of endoscopic ablation for low-grade UTUC by the AUA and EAU guidelines, more research is needed in this area [1,4].

4. IVRS FOLLOWING RNU

Recurrence of UC in the bladder after nephroureterectomy is attributable to multiple risks, including patient-specific factors (e.g., smoking at the time of diagnosis), tumor-specific factors (e.g., tumor grade/stage/size), and treatment-specific factors (e.g., surgical techniques). Of these, urological oncologists are most equipped to optimize the treatment-specific factors in an effort to reduce recurrence rates in the bladder. We discuss certain techniques that can be implemented to minimize the chances of recurrence due to surgical management.

The dissemination of UTUC to the bladder during RNU is likely due to kidney manipulation causing intraluminal displacement and drainage into the lower tract [21-23]. Retrospective studies of open versus laparoscopic RNU suggested that the surgical approach alone exerted little to no impact on IVR rates. Notably, one study found that the laparoscopic approach had a slightly higher IVR, possibly due to high abdominal pressure during laparoscopic approaches increasing flow into the lower tract [21-25]. In both open and minimally invasive approaches, early ureteral ligation is a key method used to reduce this risk. Specifically, the ureter is ligated immediately on gaining access to the retroperitoneal space and before ligating the renal artery [21]. This was studied in a prospective, multicenter trial by Yamashita *et al.* and the rate of IVR was 36% in the control group against 23% in the early ureteral ligation group [21]. In this study, the benefit was most notable for renal pelvic UTUC tumors. Admittedly, the efficacy of early ureteral ligation in UTUC of the ureter may be limited. Here, if the ureter is ligated cephalad to the tumor site, cancer cells can still migrate into the lower tract and adhere to the injured urothelium near the cystotomy site. Thus, it is advised to ligate below the tumor whenever possible [21,26].

Another method that urologists should focus on to lower IVR is adequate bladder cuff excision, which is recommended during RNU for the purpose of avoiding incomplete ureterectomy and subsequent IVR [4]. In other words, it is imperative not to leave any component of the ipsilateral upper urinary tract *in situ*. Multiple large retrospective studies have found high rates of IVR with incomplete bladder cuff excision, one of which reported a hazard ratio of 3.536 (95% CI, [2.245 – 5.568]) [27,28]. The approach for BCE can be extravesical, transvesical, or a combined endoscopic “pluck” technique [4,29]. The “pluck” technique has been criticized by some for possible tumor seeding through endoscopic manipulation, and mixed evidence showed that this technique had higher rates of IVR [4,29-31]. The extravesical and transvesical approaches are preferable given that they do not raise such concern, provided that the excision has achieved clean margins and the bladder is closed in a water-tight fashion to allow for the use of intravesical chemoprophylaxis [10]. Our personal practice uses an extravesical approach for lesions above the iliac vessels, whereas a transvesical approach is preferred for lesions below the iliac vessels.

Another method to reduce IVR is to instill a single dose of intravesical chemotherapeutic agent (mitomycin-C, gemcitabine, or pirarubicin) perioperatively when performing RNU or segmental ureterectomy [4,32,33]. While only half of urological oncologists endorsed administering bladder chemoprophylaxis after RNU in a 2016 survey, the data for use

are quite compelling with current guidelines now supporting such treatment through a strong recommendation [4,34]. A large, prospective, randomized, and non-blinded control trial out of the United Kingdom by O'Brien *et al.* demonstrated an 11% absolute risk reduction and a 40% relative risk reduction in IVR after one dose of mitomycin-C was instilled into the bladder postoperatively after RNU [32]. A phase two clinical trial by Ito *et al.* yielded an IVR of 16.9% 2 years after pirarubicin treatment was administered postoperatively compared with 42.2% IVR in the control group [33]. A Cochrane database review similarly found a reduced risk of bladder cancer recurrence using bladder chemoprophylaxis over time, with a hazard ratio of 0.51 (95% CI: 0.32 – 0.82) [35]. Some urologists are also using gemcitabine due to its efficacy on UC of the bladder. However, the chemotherapeutic agent has not been formally studied prospectively in the context of preventing UTUC IVR [4,36-38]. Potential advantages of gemcitabine are as follows: (1) it is less likely to cause chemical peritonitis in the event of extravascular extravasation; (2) it does not require alkalization of the urine; (3) it is relatively cheaper; and (4) it is easy to formulate by hospital pharmacies [4,37,38].

The timing of using bladder chemoprophylaxis in the context of RNU varies with institutions. There is some evidence that intraoperative bladder chemoprophylaxis is safe and associated with lower bladder recurrence rates compared to post-operative administration. These observations are comparable to the decreased recurrence of low-grade bladder cancers that are well-established with immediate administration following resection [39-41]. Our practice involves instilling 2 g of gemcitabine in 100 cc normal saline into the bladder through a catheter clamped for the first 90 – 120 min of the RNU until the ureter is ligated distal to the tumor. Thereafter, the bladder may be drained with no additional chemoprophylaxis. One dose of chemoprophylaxis is thought to be sufficient to kill any displaced UTUC in the bladder lumen and this is supported by a study in which maintenance intravesical chemotherapy did not impact the rates of bladder recurrence compared to a single perioperative dose within 48 h of RNU [42].

5. CONCLUSIONS

Multiple factors impacting rates of IVR can be altered by practicing urologists. Such proactive strategies include the use of a ureteral access sheath during diagnostic URS, the use and timing of intravesical chemoprophylaxis, early ureteral ligation distal to UTUC, and formal bladder cuff excision. Surgeons employing each of these measures should appreciate the benefit of lower rates of IVR. Close surveillance after RNU is still required. Prospective data of recurrence rates after intraoperative bladder chemoprophylaxis are needed to

recommend this practice more strongly. Further studies are regarding IVR after endoscopic ablation are also warranted since this technique is now strongly recommended for the treatment of low-grade UTUC.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: Jay D. Raman

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Methodology: All authors

Writing – original draft: All authors

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

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Not applicable.

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