Bladder tumor recurrence after urothelial carcinoma of the upper urinary tract

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Abstract: Upper tract urothelial carcinoma (UTUC) is a relatively uncommon and poorly investigated malignancy, however, bladder recurrence after radical nephroureterectomy (RNU) is a frequent event. In this review, we summarize the current knowledge on risk prediction of bladder tumor recurrence after RNU, including surgical strategies and adjuvant intravesical treatments to reduce the risk of recurrence. Finally, we outline some of the more recent advances in genomics that will likely lead to new prognostic markers and risk stratification tools that may refine UTUC treatment in the future.

Keywords: Upper tract urothelial carcinoma (UTUC); intravesical recurrence; nephroureterectomy; surveillance

Incidence & epidemiology

Urothelial carcinomas are the 5th most frequently diagnosed non-cutaneous cancer in the US (1) and may be located in the lower genitourinary tract (urethra and bladder) or upper genitourinary tract (ureter and pyelocaliceal system). Upper tract urothelial carcinoma (UTUC) is a relatively rare entity, accounting for 5–7% of all renal tumors and 5–10 % of all urothelial tumors. The estimated annual incidence is 1–2 cases per 100,000 (1,2). Recent advances in imaging and endoscopic techniques, as well as improved bladder cancer survival has led to an increase in the detection of UTUC. The mean age at diagnosis has also increased over the last 30 years from 68 to 73 years (3). The cause of UTUC is still unknown, however several environmental factors, such as cigarette smoking, herbal medicines (e.g., aristolochic acid), chronic infection, and occupational carcinogenesis, have been linked to the development of UTUC (4). Due to the low prevalence of the disease, racial differences in the development of UTUC is inconclusive. Asian ethnicity appears to be associated with higher-grade disease compared

with other ethnicities (5). However, stage for stage, there appears to be no racial differences. Differences in epigenetic and genetic factors such as occupation/environmental exposures as well as socioeconomic factors may explain these differences.

The standard of care for surgical management of UTUC is radical nephroureterectomy (RNU) with excision of bladder cuff (6). Intravesical recurrence occurs in approximately 50% of patients during follow-up surveillance with ureteric tumors and high tumor grade independent predictors of a bladder recurrence (7). The majority of these recurrences occur in the first year after surgery (8).

Risk prediction

UTUC and bladder cancer have common pathological mechanisms and show analogous tumor characteristics with similar prognostic risk factors (9,10). As a result, clinical decision-making for UTUC is often inferred from the larger evidence base on primary bladder cancer (11). However, UTUC remains an aggressive disease with high

progression and recurrence rates. Conversely, certain patients with lower risk disease may benefit from a more conservative approach, such as segmental resection or endoscopic ablation. Pre-operative risk stratification with individualized risk prediction of bladder recurrences after RNU may inform the frequency of surveillance and identify patients who are most likely to benefit from adjuvant intravesical treatments. A recent meta-analysis identified three categories of predictors of intravesical recurrence after RNU: (I) patient-specific factors including pre-existing renal impairment, male gender, smoking and a prior history of bladder cancer; (II) tumor-specific factors including multifocality, location with the ureter, positive preoperative cytology, $\geq$ pT2 and histological evidence of necrosis; (III) treatment-specific factors including positive surgical margins, extravesical bladder cuff excision and a laparoscopic approach (12). However, it is difficult to draw robust conclusions from many of these studies as they are limited by their small sample size, single-center series, heterogeneous cohorts and multivariable risk models which do not adequately integrate surgery and tumor specific variables.

Two multivariable models for predicting intravesical recurrences after RNU are currently available. Xylinas and colleagues from the UTUC Collaboration Group (13) developed and validated a risk stratification nomogram predicting bladder recurrences at 3, 6, 9, 12, 18 and 36 months. In a cohort of 1,839 patients managed with RNU at 15 European and North American centers over a 20-year period, 31% of patients had a bladder recurrence at a median of 24 months. In multivariable models, advanced age, male gender, ureteral tumor location, laparoscopic surgical technique, endoscopic distal ureteral management, previous bladder cancer, higher tumor stage, concomitant carcinoma *in situ* (CIS), and lymph node involvement were all associated with intravesical recurrence. The authors proposed two versions of the nomogram—a full model and a reduced model, with discriminative accuracies of 69.0% and 67.8% respectively in the validation cohort. The reduced model was based exclusively on previously described clinicopathologic features of patients with UTUC, whereas the full model incorporated the surgical approach (e.g., open versus laparoscopic approach) and endoscopic management or stripping of distal ureter versus transvesical approach.

Another nomogram has also been developed in a cohort of 754 patients in 13 institutions in Japan (14). In this study, the incidence of intravesical recurrence at 12 months was

15% and 29% at 5 years with a median time to recurrence of 10 months. Multivariate analysis found that papillary tumor architecture, absence of lymphovascular invasion and higher pathological T stage ($\geq$ pT2) were independently significant predictive factors and that male gender was a marginally significant predictive factor for intravesical recurrence. Age, laterality, body mass index, smoking status, tumor location, multiplicity, tumor grade, concomitant CIS, hydronephrosis, positive preoperative urine cytology, management of distal ureter, surgical approach and adjuvant chemotherapy were not associated with recurrence in the bladder.

Both studies have inherent limitations which should be acknowledged. Centralized pathologic review was not performed in either study and may have led to misinterpretation of pathologic specimens and underreporting of certain features such as CIS. Neither study controlled for smoking status or cumulative exposure, which this has been previously shown to be associated with bladder recurrences after RNU (13). Evolving surgical technique related to the long time periods in both studies were not accounted for and may have profound effects on the outcomes. The effect of the laparoscopic approach on risk of bladder recurrence still remains unclear.

While these studies hold promise for predicting intravesical recurrences after RNU and raise important questions regarding appropriate follow up endoscopic surveillance and adjuvant treatment, they must be rigorously externally validated before they can be introduced into routine clinical practice.

Strategies to reduce the risk of bladder recurrence

Strategies to reduce to the risk of intravesical recurrence after RNU for UTUC fall under two broad categories: (I) surgical technique and (II) intravesical treatments. Open RNU with bladder cuff excision has historically been the standard-of-care for high risk UTUC, regardless of tumor location (6). Initially described by Clayman and colleagues (15) almost 30 years ago, laparoscopic RNU has been widely adopted in the last decade. Numerous techniques to manage the bladder cuff during laparoscopic RNU have also been described: via an open approach (intravesical or extravesical excision), a laparoscopic approach (standard excision, laparoscopic stapling, laparoscopic bipolar sealer/divider instrument), or via an endoscopic approach (transurethral resection with ureter stripping). A robot-assisted laparoscopic approach has been recently

described in order to facilitate management of the distal ureter (16). Most published series suggest better perioperative outcomes using a minimally invasive approach (17), with favorable oncologic outcomes. A recent European Association of Urology (EAU) Guidelines systematic review of 42 studies of 7,554 patients comparing the oncologic outcomes of laparoscopic compared with open RNU found that all but 1 of the included studies were retrospective series, and most reported similar oncologic outcomes between laparoscopic and open RNU (18). Only 26 of the included studies reported bladder recurrence-free survival and most studies reported equivalent or better bladder recurrence-free survival with a laparoscopic approach (18). These results should be interpreted with caution as most of the studies were small-sample and underpowered to detect a difference in oncologic efficacy between surgical approaches. Only 9 of the 41 retrospective series adjusted for confounders, therefore their findings are difficult to interpret with the selection bias favoring the laparoscopic group in most studies. Finally, a meta-analysis of the data was not possible due to the underlying heterogeneity of the studies (18).

Several precautions have been advocated by the EAU in order to reduce the risk of tumor recurrence: (I) avoid entering the urinary tract; (II) avoid direct contact between instruments and the tumor; (III) laparoscopic RNU must take place in a closed system including avoiding morcellation of the tumor and the use an endobag for tumor extraction; (IV) removal of the kidney and ureter *en bloc* with the bladder cuff; (V) invasive or large (T3/T4 and/or N+/M+) tumors are possible contraindications for laparoscopic RNU (6,18).

Early ureteral ligation has also been proposed as a means of preventing seeding of upper urinary tract cells to the bladder as a cause of intravesical recurrence. This has been evaluated in a single-arm prospective trial in 74 patients undergoing RNU and compared with a propensity score-matched historical control cohort. Twenty-three percent of patients who had early ureteral ligation during RNU developed a bladder recurrence with a median follow-up of 24 months. Although there was no difference in the intravesical recurrence-free survival rates in patients with ureteral disease, a significant difference was observed in patients with UTUC of the renal pelvis. Multivariate analyses also identified early ureteral ligation as an independent predictor of intravesical recurrence in patients with UTUC located in the renal pelvis (19).

With intravesical recurrence rates up to 50% after RNU there has been considerable interest in adjuvant bladder

installations to reduce the risk of bladder recurrence. Two prospective randomized trials (20,21), a meta-analysis (22) and a Cochrane systematic review (23) have shown that a single post-operative instillation of intravesical chemotherapy [mitomycin C (MMC), pirarubicin (THP)] in the early post-operative period reduces the risk of bladder tumor recurrence within the first year following RNU.

The prospective ODMIT-C (One Dose Mitomycin C) Trial was undertaken in 46 UK centers in 284 patients with no previous or concurrent history of bladder cancer undergoing RNU for suspected UTUC. Forty mg MMC was administered on removal of the urinary catheter. Intravesical recurrence was assessed by visual inspection at cystoscopy at 3, 6, and 12 months after RNU. Overall, a single dose of post-operative intravesical MMC led to an absolute reduction in risk of intravesical recurrence of 11% and the number needed to treat to prevent one bladder tumor was nine (20). The principle limitations of the trial were the lack of histological confirmation of recurrence and also the lack of standardized timing of the administration of MMC which occurred at least a week after RNU. Although the trial was not designed to investigate the efficacy of surgical approaches for RNU, 29 of 284 patients (10%) underwent laparoscopic RNU, and a recurrence within the bladder was only found in 3 (10%) patients. At the time the trial was opened, laparoscopic urologic surgery was in its infancy and the low level of recurrence may be due to case selection bias favoring smaller tumors for laparoscopic approaches.

The efficacy of a single intravesical instillation of 30 mg THP within 48 hours after RNU has also been evaluated in a prospective trial in 77 patients from 11 institutions in Japan (21). Follow-up cystoscopy and urinary cytology were repeated every 3 months for 2 years or until the first recurrence. Overall, the investigators found that fewer patients who received THP had a recurrence compared to the control group (16.9% at 1 year and 16.9% at 2 years in the THP group compared with 31.8% at 1 year and 42.2% at 2 years in the control group; log-rank P=0.025). On multivariable analysis THP instillation [hazard rate (HR), 0.26; 95% CI, 0.07–0.91; P=0.035] and open surgery (HR, 0.28; 95% CI, 0.09–0.84; P=0.024) were independently predictive of a decreased incidence of intravesical recurrence. In this study, histologic confirmation of the bladder recurrence was required. Multivariable analysis did find that laparoscopic surgery was associated with an increased risk of intravesical recurrence. As with the previous trial, this study was not designed to evaluate the

surgical approach for managing UTUC. Future trials are needed to assess the head-to-head comparisons of chemotherapeutic drugs, as well as determine the optimal timing of chemotherapy instillations.

Surveillance and treatment of bladder recurrences

With the high risk of intravesical recurrences, it is mandatory for patients with UTUC to undergo endoscopic surveillance after RNU. Surveillance schedules consist of cystoscopy and urinary cytology for at least 5 years regardless of the stage or grade of primary UTUC (6), however there is little evidence to guide the frequency of surveillance or risk-adapted strategies for follow-up. The two available multivariable models for predicting intravesical recurrences after RNU do not recommend specific cut offs for determining recurrence risk in the context of endoscopic surveillance and these thresholds cannot be easily derived from the decision curve analysis in either study (13,14).

Recent data using conditional survival analysis suggest that the risk of intravesical recurrence evolves during surveillance after RNU. The concept of conditional survival probability shows the likelihood of surviving for an additional duration after the initial diagnosis or disease treatment because the patient has already survived for a certain time. It provides a more accurate and dynamic estimate of outcome probability at each surveillance follow-up point and has been recently assessed in UTUC (24,25). Conditional intravesical recurrence-free survival has been reported in 364 patients with Ta-3N0M0 disease who underwent either open or laparoscopic RNU (24). Bladder recurrences were detected in 176 (48.4%) patients and based on 1, 2, 3 and 4-year survivorship the 5-year conditional intravesical recurrence-free survival rate increased from 41.5% to 60.5%, 73.4%, 79.5% and 96.7%, respectively. Predictive factors of bladder recurrences including laparoscopic RNU and pT stage 2 or less remained independent risk factors over time and bladder recurrences typically developed within 18 months, particularly 6 to 12 months after RNU. As a result, patients with pT2 or lower T stage who undergo laparoscopic RNU may be recommended for longer follow-up (24). The study was limited by its small sample size and retrospective nature, as well as a lack of information regarding established prognostic factors such as smoking status.

The management of a bladder recurrence following

RNU is similar to the current guideline-based treatment strategy for primary bladder cancer, however, there is a lack of data addressing the natural history of intravesical recurrences and progression in patients with UTUC after treatment with RNU. Tanaka and colleagues reviewed the records of 241 patients with an intravesical recurrence after RNU (pTa-4N0M0) (26). All patients were treated with transurethral resection of the bladder recurrence and 101 (41.9%) underwent Bacillus Calmette-Guerin (BCG) treatment, whereas 49 (20.3%) underwent intravesical chemotherapy. Multivariate analysis found that pT1 disease and the number of tumor recurrences at the time of first bladder recurrence were independent risk factors for a recurrence. Disease progression within the bladder was associated with pT1 tumors, concomitant CIS and no prior BCG treatment (26).

Genomic advances

UTUC is histologically similar to urothelial bladder cancer however genomic studies have shown they are distinct entities (27). Although UTUC shares many of the same genomic alterations with urothelial carcinoma of the bladder, some key differences have been identified as oncogenic drivers of UTUC (28). As a result, there has been considerable interest in elucidating genomic alterations in UTUC which could lead to novel prognostic markers that may refine UTUC treatment and post-treatment surveillance.

One particular recent study has offered a new insight into the genomic differences between UTUC and bladder cancer by defining the clonal relatedness of temporally distinct tumors (29). The investigators prospectively sequenced tumors and matched germline DNA in a cohort of 195 UTUC patients and 454 primary bladder cancer patients using a targeted next-generation sequencing platform. Although the spectrum of genomic alterations was similar between UTUC and primary bladder cancer, significant differences in the prevalence of mutations in individual genes were found, including a higher frequency of *FGFR3* and *HRAS* alterations and a lower frequency of *TP53*, *RB1*, and *ERBB2* alterations in UTUC as compared with bladder cancer. Of the 195 patients with UTUC, 137 underwent RNU, with 57 (42%) later developing an intravesical recurrence. In a subgroup of 29 patients with UTUC and a history of intravesical recurrence, both tumors were analyzed to assess their clonal relatedness and were found to be consistently clonally related. After adjusting for clinical

factors associated with intravesical recurrences, alterations in *FGFR3*, *KDM6A* and *CCND1* were associated with a high risk of developing a subsequent bladder recurrence, whereas *TP53* alterations were associated with a lower risk (29). This result is of particular importance as it confirms that UTUC with subsequent bladder recurrence are clonally related, justifying developing methods to prevent lower tract seeding during RNU and the identification of patients with genetic alterations that may require more rigorous surveillance after surgery.

Conclusions

In summary, although UTUC is a relatively rare entity, bladder recurrence after RNU is a relatively frequent event. In recent years, considerable advances have been made in developing prognostic tools to identify patients at a higher risk of intravesical recurrence who may benefit from intensified therapy and those who could be spared from the side effects of unnecessary intervention and follow up surveillance. In the future it is likely that routine genomic characterization of UTUC will provide more clinically relevant information, including identification of patients who could be candidates for molecularly driven clinical trials or for the evaluation of the risk of bladder recurrence, which may help guide the selection of adjuvant treatment and intensity of follow-up surveillance.

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Footnote

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