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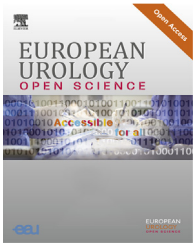

Review – Urothelial Cancer

Bladder Recurrence Following Upper Tract Surgery for Urothelial Carcinoma: A Contemporary Review of Risk Factors and Management Strategies

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Abstract

Context: Bladder recurrences have been reported in 22–47% of patients after surgery for upper urinary tract urothelial carcinoma (UTUC). This collaborative review focuses on risk factors for and treatment strategies to reduce bladder recurrences after upper tract surgery for UTUC.
Objective: To review the current evidence on risk factors and treatment strategies for intravesical recurrence (IVR) after upper tract surgery for UTUC.
Evidence acquisition: This collaborative review is based on a literature search of PubMed/Medline, Embase, Cochrane Library, and currently available guidelines on UTUC. Relevant papers on bladder recurrence (etiology, risk factors, and management) after upper tract surgery were selected. Special attention has been paid to (1) the genetic background of bladder recurrences, (2) bladder recurrences after ureterorenoscopy (URS) with or without a biopsy, and (3) postoperative or adjuvant intravesical instillations. The literature search was performed in September 2022.
Evidence synthesis: Recent evidence supports the hypothesis that bladder recurrences after upper tract surgery for UTUC are often clonally related. Clinicopathologic risk factors (patient, tumor, and treatment related) have been identified for bladder recurrences after UTUC diagnosis. Specifically, the use of diagnostic ureteroscopy before radical nephroureterectomy (RNU) is associated with an increased risk of bladder recurrences. Further, a recent retrospective study suggests that performing a biopsy during ureteroscopy may further worsen IVR (no URS: 15.0%; URS without biopsy: 18.4%; URS with biopsy: 21.9%). Meanwhile, a single postoperative instillation of intravesical chemotherapy has been shown to be associated with a reduced bladder recurrence risk after RNU compared with no instillation (hazard ratio 0.51, 95% confidence interval 0.32–0.82). Currently, there are no data on the value of a single postoperative intravesical instillation after ureteroscopy.

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Conclusions: Although based on limited retrospective data, performing URS seems to be associated with a higher risk of bladder recurrences. Future studies are warranted to assess the influence of other surgical factors as well as the role of URS biopsy or immediate postoperative intravesical chemotherapy after URS for UTUC.
Patient summary: In this paper, we review recent findings on bladder recurrences after upper tract surgery for upper urinary tract urothelial carcinoma.

1. Introduction

Urothelial carcinoma (UC) is the sixth most common tumor in developed countries [1]. It can be located in the lower (bladder and urethra) and/or the upper (pyelocaliceal cavities and ureter) urinary tract. UC in the upper urinary tract (UTUC) accounts for 5–10% of UCs [1], with an estimated annual incidence of approximately two cases per 100 000 persons. This rate has risen in the past few decades as a result of improved detection [2,3].

The outcome of UTUC is closely associated with the stage of the disease at presentation [4]. For this reason, proper risk categorization and staging of UTUC is essential to determine the best treatment. Key investigations for UTUC are computed tomography/magnetic resonance urography and urine cytology [5]. Ureterorenoscopy (URS) with or without a biopsy is commonly used to confirm the diagnosis of UTUC and to determine the grade and subsequent risk category.

UTUCs can be stratified into two risk categories: low and high risk. The standard treatment for high-risk UTUC is radical nephroureterectomy (RNU) with bladder cuff excision, while renal-sparing surgery is a valid alternative in low-risk patients or for patients with a solitary kidney or advanced staged chronic kidney disease [5]. Postoperatively, bladder recurrences occur frequently [6,7]. Whether metachronous bladder tumors are considered recurrences or second primary tumors is up for debate. Moreover, it is difficult to predict which patients will develop bladder recurrences after upper tract surgery. Given the implications of bladder recurrences (eg, therapeutic consequences, additional surgical procedures, patient discomfort, and health care costs), strategies to reduce this risk have become highly relevant.

In this collaborative review, we summarized current knowledge on risk factors for bladder recurrence(s) after upper tract surgery for UTUC and possible ways to reduce this risk.

2. Evidence acquisition

A literature search in English was performed using PubMed/Medline, Embase, the Cochrane Library, and the currently available guidelines on UTUC (European Association of Urology [EAU] and National Comprehensive Cancer Network [5,8]).

For the literature search, the keywords used were "upper tract urothelial carcinoma; UTUC", "upper tract surgery; nephroureterectomy; distal ureterectomy; ureteroscopy; ureterorenoscopy; nephron-sparing surgery; kidney-sparing surgery; renal-sparing surgery", and "bladder recurrence; intravesical recurrence". The results between 2012 and 2022 were considered. Relevant papers on bladder recurrence after upper tract surgery were selected. Special attention has been paid to (1) the genetic background of bladder recurrences, ([2) the occurrence of bladder recurrences after URS with or without a biopsy, and ([3) postoperative or adjuvant intravesical instillations after upper tract surgery. The search strategy is specified in Supplementary Figure 1. The literature search was performed in September 2022.

3. Evidence synthesis

3.1. *(Genetic) Background of bladder recurrences*

3.1.1. *Generality about bladder recurrence following upper tract surgery*

There are two hypotheses explaining these high rate of bladder recurrences: intraluminal seeding (epithelial spread) and in-field cancerization (according to this theory, urothelial cells are primed to undergo transformation by previous carcinogenic events) [9]. Strikingly, after upper tract surgery, intravesical recurrences are seen in up to half of cases, compared with 2–5% in the contralateral upper tract [10]. This would support the seeding hypothesis over the field-change hypothesis. However, a resolution to this question has not been established definitively.

The incidence of bladder recurrence after RNU ranges between 22% and 47% [6,7], with the most frequent site being around the excised bladder cuff. The incidence bladder recurrences after distal ureterectomy also vary substantially in the literature: from 28% [11] to 69% [11–13].

Data are limited with regard to bladder recurrences after diagnostic URS, preoperatively, followed by RNU [14,15]. Thus, data on bladder recurrences after URS alone are lacking. Several studies have recently been conducted to further elucidate the high rate of bladder recurrences after upper tract surgery, focusing on the genetic background.

3.1.2. *Molecular disparity between UTUC versus UC of the bladder*

UTUC and UC of the bladder display similar histologic characteristics; however, these malignancies have distinct epidemiologic and clinicopathologic differences. For example, 60% of UTUCs are invasive at diagnosis, compared with only 15–25% of bladder tumors [16]. Delay in diagnosis as well as anatomical and biological disparities may be of influence. Moreover, multiple studies have demonstrated that UTUC and urothelial bladder cancer exhibit significant differences in the prevalence of common genomic alterations (eg, in

FGFR3, *TP53*, and *HRAS*, and epigenetic genes, eg, *KDM6A* and *KMT2A-C*). For instance, UTUC shows more alterations in *FGFR* genes and a higher incidence of microsatellite instability, while UC of the bladder more often shows mutations in *TP53* [17–19]. These findings are summarized in a collaborative review by Sfakianos et al [20], indicating that UTUC and UC of the bladder share mutations in similar genes but at varying frequencies. Furthermore, subtyping of UTUC and UC of the bladder has identified similar expression subtypes, although UTUC has been found to be more often luminal, with more T-cell depletion. Therefore, evidence supports that UTUC has different genomic features from UC of the bladder [21]. Clinically, therefore, such data support approaching UTUC and UC of the bladder as (related but) distinct diseases.

3.1.3. Clonal relation between UTUC and bladder recurrences

Whether UTUC and subsequent bladder recurrences are clonally related or represent separate primary tumors is debatable. Evidence to support a clonal relation between metachronous UTUC and UC of the bladder has been summarized in a systematic review, based on nine studies published up to 2019 [22]. The authors concluded that, taking into account the limitations of microsatellite technology in comparison with next-generation sequencing and currently accepted concepts of tumor heterogeneity and evolution, most, if not all, UTUCs and paired UCs of the bladder are clonally related [22]. However, in this review, the sequence of events was not taken into account (UTUC first or bladder first, duration of the interval). Hence, no definitive conclusions could be drawn regarding the clonal relation between UTUC and subsequent bladder recurrences.

The most recent study included in the systematic review was by Audenet et al [19]. In a cohort of 195 UTUC patients, the investigators sequenced tumors and matched germline DNA using a targeted next-generation sequencing platform. In a subgroup of 29 patients with UTUC who underwent RNU and developed bladder recurrences, both tumors were analyzed to assess their clonal relation and these were found to be consistently clonally related. Tumors with alterations in FGFR3, KDM6A, and CCND1 were associated with a high risk of developing bladder recurrences, whereas TP53 alterations were associated with a lower risk [19].

In 2021, a report published by Van Doeveren et al [23] targeted DNA sequencing of a panel of 41 genes on matched normal and tumor tissue of 15 primary UTUC patients treated by RNU who later developed 19 bladder recurrences. Based on the detected tumor-specific DNA aberrations, the paired UTUC and intravesical recurrence(s) of 11 patients (73%) showed a clonal relation, whereas in four patients, the molecular results did not indicate a clear clonal relationship.

Also in 2021, Petros et al [24] focused on the molecular subtypes in same-patient metachronous UTUC and urothelial bladder cancer. They performed whole transcriptome RNA sequencing in a total of 95 samples (UTUC = 61, UC of the bladder = 34) from 40 untreated patients. A gene expression analysis showed that the majority of bladder tumors developing after UTUC appeared luminal like, similar to the initial UTUC tumors. In addition, it was found that metachronous tumors largely maintain the molecular subtype of the initial tumor regardless of chronologic development or anatomical origin [24]. However, the results of this study should be interpreted with caution, especially given the known heterogeneity of tumors when it comes to molecular subtypes. In addition, bladder recurrences do not necessarily appear to be identical to the UTUC in terms of disease stage and grade.

3.1.4. Summary of genetic background

UTUC has distinct genomic features, which are different from the genomic features of UC of the bladder. Nevertheless, recent evidence supports the hypothesis that bladder recurrences after upper tract surgery for UTUC are mostly clonally related recurrences and not new primary tumors. Moreover, these largely maintain the molecular subtype of the initial UTUC. This genetic evidence may aid in resolving the debate about metachronous bladder tumors, as it suggests that these tumors represent seeding from the initial tumors versus second primary lesions.

3.2. Risk factors for bladder tumor recurrence after upper tract surgery

Clinical and pathologic factors for bladder recurrence after upper tract surgery for UTUC have been described over the past two decades. However, the studies to date are primarily retrospective in nature and vary in the number of patients included, duration of follow-up, variables analyzed, and statistical analyses.

3.2.1. Patient-, tumor-, and treatment-specific factors after RNU

In a meta-analysis of 18 retrospective studies each of which included >100 patients treated with RNU between 2007 and 2014, significant predictors of bladder recurrence after RNU were identified [7]. Three categories of predictors for an increased risk of bladder recurrence were identified, which are also mentioned in current guidelines (level of evidence: 3) [5]:

1. Patient-specific factors such as male gender, previous bladder cancer, and preoperative chronic kidney disease. Smoking at diagnosis is also associated with an increased risk for bladder recurrences after RNU [25].
2. Tumor-specific factors such as positive preoperative urinary cytology, tumor grade, multifocality, tumor diameter, pT stage, and the presence of carcinoma in situ [26]. In addition, ureteral tumor location has been considered a risk factor for bladder recurrence (vs tumor location in the renal pelvis) [26], although conflicting results exist. Most reports state that the closer the tumor to the bladder, the greater the risk of bladder recurrence.
3. Treatment-specific factors such as extravesical bladder cuff removal and positive surgical margins [23]. Failure to completely remove the bladder cuff also increases the risk of bladder cancer recurrence [27].

These risk factors are largely consistent with one of the most recent analyses [28].

In addition to the risk factors mentioned, several multivariable models for predicting bladder recurrences after RNU have been developed [29,30]. Both studies suffered from substantial biases and showed conflicting evidence regarding significant predictive factors. Therefore, these cannot yet be introduced into routine clinical practice.

3.2.2. Bladder recurrence after distal ureterectomy

Distal ureterectomy with ureteroneocystostomy are indicated for low-risk tumors in the distal ureter that cannot completely be removed endoscopically and for high-risk tumors if kidney-sparing surgery is desired [5,13]. Currently, there is no direct evidence for specific risk factors for developing bladder recurrence after distal ureterectomy, although it seems likely that the same risk factors as for RNU would apply.

3.2.3. Bladder recurrence after URS

A specific area of recent interest has been the link between URS and bladder recurrence. URS is used to visualize the ureter, renal pelvis, and collecting system, and to allow for a biopsy of suspicious lesions [31]. Combining imaging findings, urine cytology, URS, and URS biopsy may help in the decision-making process between radical RNU and kidney-sparing therapy. Hence, the tendency is to perform diagnostic URS when in doubt. In addition, URS is regularly used for endoscopic treatment (laser ablation and tumor vaporization) and for follow-up thereafter.

It has been assumed that URS or the URS biopsy–related manipulation leads to intravesical recurrences, consistent with the hypothesis that UTUC manipulation may increase tumor seeding into the downstream urothelium [14]. In the current EAU guideline [5], it is described that the use of diagnostic URS indeed has been associated with a two- to three-time higher risk of developing bladder recurrence after RNU. This is based on two systematic reviews and meta-analyses [32,33], published in 2017 and 2018, which included largely the same retrospective series. Another recent retrospective study reported bladder recurrences after RNU in 7.7% of patients who did not undergo diagnostic URS versus in 30.8% patients who underwent diagnostic URS [15].

Discussion continues regarding whether bladder recurrences are caused by the URS (visual confirmation without a biopsy) procedure itself or whether performance of a biopsy during URS in particular increases the risk of bladder recurrence. Although in URS without a biopsy, there is no clear tumor manipulation as in URS with a biopsy, manipulation of the ureteroscope and the irrigation backflow are hypothesized to increase the risk of seeding as well.

Sharma et al [14] performed a recent retrospective single-institution analysis among 834 RNU patients. Patients were classified according to the diagnostic approach to UTUC, with the largest groups consisting of (1) no URS and no biopsy (straight to RNU), (2) URS without a biopsy, and (3) URS with a biopsy. Two-year bladder recurrence rates were 15%, 18%, and 22%, respectively. On a multivariable analysis, it was found that the biopsy group was associated with increased intravesical recurrences relative to the group that did not undergo URS (2-yr intravesical recurrence rate 21.9% vs 15.0%; hazard ratio [HR] 1.40, $p = 0.04$), while the group that underwent URS without a biopsy (18.4% vs 15.0%; HR 1.15, $p = 0.54$) did not. Hence, the authors concluded that URS with a biopsy of UTUC prior to RNU is associated with an increased risk of intravesical recurrences, whereas URS without a biopsy did not have a large enough effect size to be statistically significant [14]. Importantly, caution must be applied when considering these conclusions, as no direct comparison was made between the URS biopsy group and the URS no-biopsy group, nor was the study powered to draw this conclusion. Other confounding factors include the retrospective nature and instability of baseline characteristics among the groups (ie, there were significant differences in terms of tumor stage, grade, location, and multifocality). In addition, technical operative information was lacking, and the use of access sheaths during or ureteral stents after URS was not accounted for.

These results were subsequently entered into a meta-analysis [14] including 11 other series. In a total of 1913 patients who had received URS before the RNU and 3140 who did not receive URS before RNU, URS was associated with an increased risk of intravesical recurrence compared with no URS (HR 1.47, 95% confidence interval [CI] 1.32–1.64, $p < 0.01$). The influence of a biopsy was recounted in another systematic review of 16 studies [34]. Although based on few data, this review concluded that a diagnostic URS alone is not significantly associated with intravesical recurrence, whereas URS with a biopsy significantly increases the risk of subsequent intravesical recurrence [34].

To date, there are no separate data focusing on risk factors of intravesical recurrence after therapeutic URS (for kidney-sparing treatment), although stringent monitoring of the lower urinary tract is advised [35].

3.2.4. Summary of risk factors

Several clinicopathologic risk factors are known for developing bladder recurrence after UTUC. The use of diagnostic URS before RNU is associated with increased bladder recurrences, although recent literature suggests that the tumor manipulation from the biopsy during URS may be more associated with bladder recurrences than with visual URS itself. Thus, the risk/benefit of perming a biopsy should be individualized (eg, if there is a large endoscopically unmanageable tumor discovered on URS, discretion should be paid to whether a biopsy is needed or whether the patient should go straight to RNU).

3.3. Strategies to reduce the risk of bladder recurrence

Strategies to reduce to the risk of bladder recurrence after RNU for UTUC can broadly be classified into (1) (surgical) technique for diagnosing and treating UTUC and (2) intravesical treatment afterwards.

3.3.1. Surgical

Open RNU with bladder cuff excision has historically been the standard of care for high-risk UTUC, regardless of tumor location [5]. A recent EAU guideline systematic review of 42 studies of 7554 patients comparing the oncologic outcomes of laparoscopic with open RNU found that all but one of the included studies were retrospective series, and most reported similar oncologic outcomes between laparoscopic

and open RNU [36]. The prospective study by Simone et al [37] showed poorer oncologic outcomes in patients with locally advanced tumors who were treated laparoscopically. 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 [36]. These results should be interpreted with caution as most of the studies had a small sample size and were underpowered to detect a difference in oncologic efficacy between surgical approaches.

Management of the distal ureter is another important issue. Generally, three different methods have been used to excise the intramural ureter and bladder cuff: extravesical, transvesical, and endoscopic techniques. It has been shown in a large retrospective study of 2681 patients who underwent RNU with various methods for the bladder cuff excision in 24 international institutions to have no differences in cancer-specific or overall survival among the three methods, but the endoscopic technique has a higher risk of intravesical recurrence [27]. Current EAU guidelines do not recommend one method over the other.

Early ureteral ligation has been proposed as a means of preventing seeding of upper urinary tract cells to the bladder, to bladder recurrences. 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 [38]. In that study, bladder cuff resection was performed via a lower abdominal incision, and early ureteral ligation was defined as ligation of the ureter as quickly as possible after expanding the retroperitoneal space. Of the patients who had early ureteral ligation, 23% developed a bladder recurrence with a median follow-up of 24 mo. 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 (2-yr intravesical recurrence-free survival rate in the early ureteral ligation group: 86% vs 64% in the control group, $p = 0.025$). Multivariate analyses identified early ureteral ligation as an independent predictor of reduced intravesical recurrence in patients with UTUC located in the renal pelvis.

3.3.2. *Intravesical instillation after RNU*

With intravesical recurrence rates of up to 50% after RNU, there has been considerable interest in adjuvant bladder installations to reduce this risk. Two prospective randomized trials [39,40], a meta-analysis [41], and a Cochrane systematic review [42] have demonstrated that a single postoperative instillation of intravesical chemotherapy 2–10 d after surgery lowers the bladder cancer recurrence rate following RNU over time compared with no instillation (Cochrane: HR: 0.51, 95% CI 0.32–0.82). After 12 mo of follow-up, this would result in 127 fewer bladder recurrences (95% CI 182–44) per 1000 patients. The two prospective randomized trials consisted of the ODMIT-C trial, performed in the UK, in which 40 mg mitomycin C administered on removal of the urinary catheter [39], and a Japanese study, in which 30 mg thiotepa was administered within 48 h after RNU [40]. Based on this evidence (level of evidence: 2), the EAU guideline strongly recommended to deliver a postoperative bladder instillation of chemotherapy to lower the intravesical recurrence rate after RNU [5]. Prior to instillation, a cystogram may be considered in case of any concerns about drug extravasation.

Based on current evidence, it is unlikely that additional instillations beyond one perioperative instillation of chemotherapy will further reduce the risk of intravesical recurrence [43]. One low-level evidence study suggested that bladder irrigation might reduce the risk of bladder recurrence after RNU [44]. Future trials are needed to assess the head-to-head comparisons of chemotherapeutic drugs and also to determine the optimal timing of chemotherapy instillations. For instance, a trial where the intravesical instillation is given before instead of after RNU will hopefully provide more insight once it reads out [45].

3.3.3. *Intravesical instillations after URS*

Based on low-level evidence only, a single dose of intravesical chemotherapy after diagnostic/therapeutic ureteroscopy of nonmetastatic UTUC has been suggested to lower the rate of intravesical recurrence, similarly to that after RNU [35]. However, no comparative studies have been reported in this setting.

3.3.4. *Intravesical instillations after kidney-sparing surgery*

There are currently no data to support the use of a bladder instillation of chemotherapy after kidney-sparing surgery as the available randomized controlled trials included only patients who received RNU. Adjuvant mitomycin C instillations in the upper tract have been evaluated in one prospective trial, but the rate of bladder recurrences was not reported [46]. While there is no direct evidence supporting the use of an intravesical instillation of chemotherapy after kidney-sparing surgery, single-dose chemotherapy might be effective in this setting as well. The benefit of an intravesical instillation after URS needs to be evaluated prospectively.

4. Conclusions

Bladder recurrences occur frequently after upper tract surgery for UTUC. Recent evidence supports the hypothesis that bladder recurrences after upper tract surgery for UTUC are clonally related and not separate entities. Since tumors with certain genetic alterations have been linked with a higher recurrence risk, this may warrant stricter follow-up or more precautionary measures in patients at the highest risk.

Regarding risk factors, several clinicopathologic factors (patient, tumor, and treatment related) are known for developing bladder recurrence after UTUC. The use of diagnostic URS before RNU seems to have a negative impact on the occurrence of bladder recurrence. Recent literature suggests that performing a biopsy during URS is associated with a higher risk of bladder recurrence, and this should be kept in mind when performing URS. If imaging and cytology are not sufficient for diagnosis and/or staging of UTUC, and URS is needed, it seems reasonable to evaluate whether a biopsy is really necessary or whether URS can be performed without a biopsy. Future studies should be directed toward the potential influence of other factors and alterna-

tives to establish the diagnosis and/or stage (eg, noninvasive diagnostic methods such as urine- and blood-based biomarkers, percutaneous biopsy [47], etc.).

A single postoperative instillation has shown to be beneficial to reduce the risk of a bladder recurrence after RNU. Although there is a lack of data on an intravesical instillation after URS, it seems conceivable that such an instillation will also be beneficial after URS with or without a biopsy. Ideally, this should be investigated in a randomized trial.

Given the high risk of intravesical recurrence(s), it is mandatory for patients with UTUC to undergo endoscopic surveillance after upper tract surgery. There is little evidence to guide the frequency of surveillance or risk-adapted strategies for follow-up. In addition, there is a lack of data addressing the natural history of intravesical recurrences and progression in patients with UTUC after upper tract surgery. Consequently, so far, management of a bladder recurrence following RNU remains similar to the current guideline-based treatment strategy for primary bladder cancer.

Author contributions: Laura S. Mertens had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Mertens, van Rhijn, Masson-Lecomte, Boorjian, Thompson.
Acquisition of data: Mertens, van Rhijn, Masson-Lecomte, Boorjian, Thompson, Sharma, Matin.
Analysis and interpretation of data: Mertens, van Rhijn, Masson-Lecomte, Boorjian, Thompson.
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Critical revision of the manuscript for important intellectual content: Mertens, van Rhijn, Masson-Lecomte, Boorjian, Thompson, Sharma, Matin.
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Appendix A. Supplementary data

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