

REVIEW ARTICLE

Urothelial carcinoma: Recurrence and risk factors

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Summary

Urothelial carcinomas are malignant tumors that arise from the urothelial epithelium and may involve the lower and upper urinary tract. They are characterized by multiple, multifocal recurrences throughout the genitourinary tract. Bladder tumors account for 90-95% of urothelial carcinomas and are the most common malignancies of the urinary tract. Upper urinary tract urothelial carcinomas (UTUC) are relatively rare, accounting for 5% of urothelial tumors. The incidence of subsequent bladder cancer after surgical treatment for UTUC is approximately 15–50%. In contrast, patients with a primary tumor of the bladder have

a low risk (2-6%) the development of UTUC. Identification of prognostic factors and early detection of recurrent disease provide a better strategy for postoperative monitoring, surveillance, and potentially improve patient outcomes. In this review study we discuss the main risk factors for UTUC recurrence after radical cystectomy, and risk factors for intravesical recurrence after radical nephroureterectomy.

Key words: bladder cancer, prognosis, recurrence, survival, urothelial carcinoma

Introduction

Urothelial carcinomas are malignant tumors that arise from the urothelial epithelium and may involve the lower urinary tract (bladder and urethra) or the upper urinary tract (renal pelvis and ureter). The mechanisms of carcinogenesis are thought to be similar along the urinary tract but recent epidemiologic data and genetic studies do not support this theory. It is clear that strong differences exist regarding the tumor location and behavior between the lower and the upper urinary tract [1,2].

UTUC are relatively rare, accounting for 5% of urothelial tumors [3]. Tumors of the renal pelvis are about twice as common than ureteral tumors [4]. The incidence of subsequent bladder cancer after surgical treatment for UTUC is approximately 15–50% [5-8]. In contrast, patients with a primary tumor of the bladder have a low risk (2-6%) for

development of UTUC [9]. However, the risk is significantly higher with multifocal, pathologically confirmed tumors, in any upper urinary tract location (renal pelvis or ureter) if they are associated with carcinoma *in situ* (CIS) [10]. In such cases the risk of developing urinary tract tumors within 5 to 10 years is 26% [10].

In this review study we discuss the main risk factors for UTUC recurrence after radical cystectomy (RC), and risk factors for intravesical recurrence after radical nephroureterectomy (RNU).

Review criteria

A systematic review of the literature has been performed using Pubmed without timeline restriction and using the following keywords: urothelial carcinoma; ureter; renal pelvis; bladder cancer; prognosis; recurrence; survival; radi-

cal cystectomy; radical nephroureterectomy. All papers identified were English-language full text papers. We also searched the reference lists of identified articles to locate further papers.

Risk factors for upper tract urothelial cancer development after radical cystectomy

Urothelial carcinomas are characterized by multiple, multifocal recurrences along the genitourinary tract. About 3% of the patients treated by RC for invasive urothelial carcinoma of the bladder will subsequently develop a subsequent UTUC [9]. Up to 50% of the patients undergoing RC for urothelial carcinoma will develop a local recurrence or metastasis, usually within the first 2 to 3 years after surgery [11,12].

If it comes to relapse of disease after RC, in 80% of the cases it is extraurothelial recurrence and in 20% it is urothelial recurrence [13,14]. By contrast, late recurrences are most common in the UTUC and are detected only after developing tumor-related symptoms (i.e. primarily gross haematuria and flank pain), despite routine surveillance [13–15].

The potential risk factors for developing UTUC in patients surgically treated for primary bladder tumors are pathological stage, grade, multiplicity of bladder tumors, the presence of vesico-ureteric reflux, repeated CIS after immunotherapy (BCG), multifocal CIS of the bladder at the time of cystectomy, and the presence of bladder tumors in the ureter near the orifice [9-17] (Table 1). De Torres et al. have shown that patients who are being treated for bladder cancer have a higher risk of developing UTUC if they have vesico-ureteral reflux [18]. This confirmed the hypothesis that vesico-ureteral reflux has a role in the dissemination of cancer cells from the bladder to the ureter and renal pelvis [19].

Zincke et al. [20] reported that 8 of 14 patients with an UTUC after cystectomy had CIS in the cystectomy specimen. In that series, patients with CIS had 3-fold higher possibility to develop an UTUC. Similar findings were reported by others [15]. Studies that assessed variables influencing survival, e.g. pT stage, are more appropriate for assessing the impact of CIS on the rate of UTUC recurrence [21]. When considered in this aspect, the bulk of data from well-controlled studies does not support a greater risk of UTUC recurrence in patients with bladder CIS [21].

Ureteral tumor involvement has also been proposed as a factor predictive of UTUC recurrence. Raj et al. [22] reported a significant association between histologically positive frozen and final ureteral margin with subsequent UTUC recurrence. However, the authors found that sequential resection of the ureter in an attempt to achieve a negative anastomotic margin did not eliminate the increased risk of UTUC recurrence in these patients. Interestingly, Schoenberg et al. [23] reported that there was no increased rate of UTUC recurrence following completion of ureteroileal anastomosis despite the presence of ureteral abnormalities on frozen section analysis. Similarly, Sanderson et al. [9] found no increased rate of UTUC recurrence or anastomotic recurrence in 5% of patients with a positive frozen section or in 2% of patients with a positive final ureteral margin.

A multivariate analysis by Sved et al. [24] confirmed prostatic urethral tumor to be an independent risk factor for UTUC recurrence. More recently, a series confirmed that urothelial carcinoma of the male prostatic ducts or glands (pT1) and urothelial carcinoma of the female urethra were associated with 4-6 fold higher UTUC recurrence, respectively [9].

Patients with good prognostic factors at the time of RC, e.g. organ-confined (\leq pT2N0) disease, are more likely to develop a secondary urotheli-

Table 1. Risk factors for upper tract urothelial cancer development after radical cystectomy

Study First author (Ref. No.)	Number of patients	Follow-up (months)	Incidence of UTUC (%)	Risk factors
Akkad [16]	85	56	4.7	Recurrent and multifocal bladder cancer
Balaji [15]	529	49.1	3	Pathologic stage
Kenworthy [30]	430	40	2.6	Distal ureteral involvement at cystectomy
Yossepowitch [17]	483	/	4.6	Distal ureteral involvement at cystectomy
Solsona [14]	357	24	4.7	Multiple tumors, prostate involvement and organ-confined tumors in cystectomy specimen
Sved [24]	235	52.2	2	Prostatic urethral involvement at cystectomy

al tumor than patients with extravesical (>pT2) or node-positive bladder cancer [14]. However, pathological stage is not an independent risk factor for UTUC recurrence, but rather a predictor of prolonged survival after RC, and therefore a greater time at risk to develop a late relapse [9,14,25].

Patients undergoing cystectomy for urothelial carcinoma need long-term monitoring for disease recurrence and assessment of the urinary diversion function. With the known aggressive natural history of urothelial carcinomas, surveillance after cystectomy for locally and/or regionally confined disease has traditionally been performed frequently and includes multiple organ systems. The majority of patients will be identified after symptoms develop but can achieve prolonged disease-free survival when treated with RNU.

Metachronous UTUC after radical cystectomy were most often identified in symptomatic (hematuria in 60-80% flank pain, pyelonephritis, and weight loss) vs asymptomatic patients (62 vs 38%) [25]. With the progress of imaging technologies and future advances in biomarker development, we should be able to detect these lesions at early phases and stages, while the patient is still asymptomatic.

Carcinoma in situ of the bladder

The impact of a history of bladder CIS on the clinical outcomes after RNU for metachronous UTUC has not been clearly defined. CIS is a flat intraepithelial lesion characterized by marked cytologic abnormalities and has constituted about 10% of all bladder cancer cases. It is high grade, potentially aggressive, and unpredictable manifestation of transitional cell carcinoma of the

bladder [26]. In bladder cancer, CIS is associated with an increased risk of disease recurrence and cancer specific survival [10,27].

Considered as a marker of genetic instability of the urothelium, CIS has been associated with the development of multifocal metachronous tumors [28].

Tumor recurrence in the distal ureters and proximal urethra often is associated with the presence of CIS in the bladder's primary tumor and/or in the positive margins; it is usually considered recurrent disease and not a second primary lesion by the majority of the authors. These cases tend to relapse sooner after radical cystectomy. Youssef et al. have shown that metachronous UTUC developing after bladder CIS demonstrates pathologic features indicating aggressive tumor behavior. These patients have a greater risk of recurrence and death from cancer after RNU. These findings suggest the need for aggressive surveillance programs and multimodal management strategies for patients who develop UTUC in the setting of a previous bladder CIS [29].

Specifically, in patients with a history of bladder CIS, yearly upper urinary tract imaging and frequent urinary cytology should be implemented in the surveillance program. The development of UTUC in patients with a history of bladder CIS should alert the clinician to the biologic aggressiveness of the UTUC.

Prognostic factors for bladder cancer development after radical nephroureterectomy

Although it is well known that bladder tumors are associated with UTUC, it is still not clearly defined which clinical and histopathological factors

Table 2. Risk factors for bladder cancer development after radical nephroureterectomy

Study First author (Ref. No.)	Number of patients	Follow-up (months)	Incidence of bladder cancer (%)	Risk factors
Koga [7]	85	35	34	Female gender, postoperative systemic chemotherapy, and incomplete distal ureterectomy
Hisataki [8]	69	53	35	Multifocality of UTUC and the pathologic stage
Raman [5]	103	39	50	Positive history of bladder cancer
Terakawa [41]	177	31	36	Multifocality of UTUC and the pathologic stage
Kang [42]	189	91	31	Multifocality of UTUC
Milojevic [31]	92	39.5	21.7	Multifocality of UTUC
Elalouf [33]	237	44	35.9	Previous history of bladder cancer, tumor location and concomitant carcinoma <i>in situ</i>

affect the occurrence of bladder cancer in patients with UTUC. The incidence of subsequent bladder cancer after surgical treatment for UTUC has been shown to be approximately 15–50% [4-8,30].

Only few studies to date have focused on the potential risk factors for the development of bladder tumors after managing UTUC tumor [4-8,31-33] (Table 2). Reported risk factors include tumor multiplicity, stage, grade, size, ureteric location, and surgical method. However, the clinical and pathologic features that affect subsequent intravesical recurrence of cancer are yet to be elucidated. This is partly because cancer in the upper urinary tract of a high stage and grade tends to develop distant metastasis so often that patients die of the original disease before recurrence in the bladder becomes clinically apparent [4,34,35].

On the other hand, the significance of a positive history of bladder cancer in patients with UTUC has been the subject of many studies. Muller et al. [36] showed that a positive history of bladder tumors is a poor prognostic sign for patients with tumors of the upper urinary tract. Specifically, the presence of previous or simultaneous bladder cancer is an independent predictor of poor cancer-specific survival (CSS) and survival without recurrence of disease in patients with UTUC. Similar to these results, in a multicenter European study Novara et al. [37] demonstrated that a positive history of bladder cancer and the presence of invasive bladder cancer at the time of RNU were independent predictors of lower CSS. Prognostic significance of previous or simultaneous bladder cancer was also confirmed by a Taiwanese study and a multicenter Japanese study [38,39]. Tran et al. [40] have shown that patients who have had any invasion of the ureter before RC have a high risk of recurrence in the upper urinary tract. In patients with UTUC it is necessary to establish the possible presence of previous bladder tumors, because these patients require more aggressive treatment and frequent clinical assessment.

Raman et al. reported that 82% of patients de-

veloped an intravesical tumor less than 2 years after managing their UTUC at a mean interval of 13.2 months (range 1-45) [5]. Milojevic et al. have shown that 85% of the patients developed an intravesical tumor less than 2 years after managing their UTUC, at a mean interval of 16.3 months (range 3-85) [31].

Koga et al. identified female gender, postoperative systemic chemotherapy, and incomplete distal ureterectomy as risk factors for subsequent bladder tumors at a median follow-up of 35 months among 85 patients surgically treated for UTUC [7]. Hisataki et al. identified that the multifocality of the UTUC and the pathologic stage independently influenced intravesical recurrence [8] while Raman et al. reported that only a history of bladder cancer predicted the development of subsequent bladder tumors [5]. Terakawa et al. showed that patients with low-stage tumors and those with multifocal tumors were likely to undergo subsequent intravesical recurrence [41]. Multifocality of the UTUC as an independent risk factor for development of bladder tumor has also been shown by Kang et al. in a study with 189 patients [42]. More complete data of these studies are listed in Table 2. A number of studies on the molecular level explain the occurrence of multiple tumors as a result of clonal evolution of a progenitor cell [43,44]. Kakizoe et al. demonstrated that patients with UTUC have at the same time neoplastic microscopic changes (atypical hyperplasia and CIS) of the bladder and the prostatic portion of the urethra [45].

Hisataki et al. identified that multifocality of UTUC and tumor size independently influenced intravesical recurrence [8]. Zigeuner et al. were able to show the significance of the localization of the primary tumor for intravesical recurrence-free survival [46]. Nevertheless, they included the multiplicity of the tumor as another factor when the localization of the UTUC was concerned [46]. Milojevic et al. [31] showed that the multiplicity of the tumor of the upper urothelium is an inde-

Table 3. Most commonly studied risk factors for development of metachronous bladder cancer after treatment for UTUC

Characteristics	Comment	Study First author (Ref. No.)
Multifocality of the UTUC	Independent risk factor for the occurrence of bladder cancer	Hisataki [8] Milojevic [31]
Tumor stage	Patients with low-stage tumors are likely to undergo subsequent intravesical recurrence	Terakawa [41]
Tumor grade	Higher tumor grade is independent predictor of muscle-invasive bladder cancer recurrence	Elalouf [33]
Primary tumor location	Incomplete distal ureterectomy is a risk factor for subsequent bladder recurrence	Koga [7]

pendent risk factor for the occurrence of bladder cancer.

Of the most commonly studied risk factors for development of metachronous bladder lesions after treatment for UTUC, the most significant reported factors are multifocality, tumor stage and grade, site of the primary tumor, and disease volume (Table 3) [7,8,31,33,41].

Because the risk of occurrence of bladder cancer in patients with multiple primary tumors of the upper urothelium is increased in the first 2 years after the operation, frequent follow-up including cystoscopy is required for the the early detection of tumors. Since the multiplicity of UTUC is an independent risk factor for bladder cancer development, data on UTUC multiplicity should be searched in the pathological studies. Identification of prognostic factors for bladder cancer development after surgical management of UTUC provides a better strategy for postoperative monitoring and surveillance.

Radical nephroureterectomy, surgical approach

Radical nephroureterectomy with bladder cuff removal is the reference standard for patients with UTUC. Less radical approaches are historically reserved for imperative indications, such as the presence of a solitary kidney or other conditions predisposing to significant decline in global renal function post-RNU, and the need for lifelong renal replacement therapy. Djokic et al. reported that urothelial tumors can be managed conservatively, if pathological and anatomical conditions are taken into consideration and combined with radical surgical treatment [47].

Koda et al. reported that intravesical recurrence after surgery for UTUC was not related to the type of the surgical procedure (i.e., laparoscopy-assisted or open nephroureterectomy) performed, in their study of 106 patients with follow-up time of 24 months [48]. Type of surgical techniques that are used in the treatment of UTUC is not a significant risk factor for bladder cancer development [49].

Laparoscopic RNU (LNU) and robotic RNU have emerged as minimally invasive alternatives to open RNU, with advantages in terms of less blood loss, shorter length of hospital stay, and shorter convalescence [50,51]. To date, only one prospective randomized trial has shown no difference in terms of disease recurrence and CSS between LNU and open RNU [52]. A population-based study and a meta-analysis of retro-

Table 4. Recurrence free survival and cancer specific survival after treatment for UTUC

<i>Study First author (Ref. No.)</i>	<i>5-year RFS (%)</i>	<i>5-year CSS (%)</i>
Lucas [56]	-	83
Grasso [57]	-	64
Fajkovic [58]	37.1	91
Cutress [59]	33	92
Milojevic [34]	47	70.5
Elalouf [33]	66	71

RFS: recurrence free survival, CSS: cancer specific survival

spective studies confirmed the safety of LNU with regard to oncologic outcomes compared with open RNU [50,51]. Excision of the bladder cuff is mandatory in invasive or high-risk non-invasive UTUC [53].

Resection of the distal ureter and its orifice is performed because these areas are part of the urinary tract and present a considerable risk for tumor recurrence. Recent publications on survival after RNU have concluded that removal of the distal ureter (bladder cuff) improves prognosis after RNU [54].

Lymph node dissection during RNU allows for optimal staging of the disease and may have a therapeutic role [55]. Cumulative data from the literature on this subject suggests that LND should be performed during RNU or distal ureterectomy for invasive UTUC [53,55].

Most series suggest that RNU provides an improved recurrence free and CSS benefit compared with simple nephrectomy [33,34,56-59]. CSS at 5 years has been reported to be 64-92% (Table 4). When RNU is performed, local recurrence is rare, and risk of distant metastases is directly related to the risk factors listed in Table 3.

Radical nephroureterectomy by either open or laparoscopic approach is the gold standard therapy for UTUC; however, less invasive alternatives such as endoscopic ablation or segmental ureterectomy also have a therapeutic role.

Conclusions

Early detection of recurrent disease results in timely administration of appropriate therapy and potentially improves patient outcomes. However, postoperative surveillance should be tailored to the natural course of the cancer and

the patients' risk of cancer recurrence or progression. Therefore, creating a model using independent predictors of recurrence allows the clinician to perform effective screening in those at high risk of site-specific progression while avoiding unnecessary testing and costs for

those at lower risk.

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