

Prognostic value of prior history of urothelial carcinoma of the bladder in patients with upper urinary tract urothelial carcinoma: results from a retrospective multicenter study

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Abstract

Background Patients with urothelial carcinoma (UC) often develop multifocal metachronous tumors throughout the genitourinary tract. In the present study, we evaluated the prognostic value of prior history of UC of the bladder (UCB) in patients with upper tract urothelial carcinoma (UTUC) in an international multi-institutional cohort.

Patients and methods Data from 785 patients who underwent radical nephroureterectomy (RNU) with

ipsilateral bladder cuff resection at nine academic institutions in Europe and the USA between 1987 and 2008 were reviewed. Log-rank tests and Cox proportional hazards regression models were used for univariable and multivariable analyses.

Results The median follow-up of the whole cohort was 34 months (interquartile range 15–66 months). Five hundred and fifty-eight (72 %) patients had no UCB before the diagnosis of UTUC; a prior history of non-muscle-invasive and muscle-invasive UCB before the UTUC was found in 179 (23 %) and 36 (5 %), respectively. History of UCB

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before RNU was an independent predictor of both recurrence-free survival ($p = 0.012$; no UCB vs. non-muscle-invasive UCB: hazard ratio (HR) 1.4, $p = 0.082$; no UCB vs. muscle-invasive UCB: HR 2.1, $p = 0.007$) and cancer-specific survival ($p = 0.008$; no UCB vs. non-muscle-invasive UCB: HR 1.2, $p = 0.279$; no UCB vs. muscle-invasive UCB: HR 2.3, $p = 0.008$) on multivariable Cox regression analyses that included age, gender, surgical type, stage, grade, presence of concomitant carcinoma in situ, presence of lymphovascular invasion, and lymph node status.

Conclusions Prior history of muscle-invasive UCB was significantly associated with an increased risk of disease recurrence and cancer-specific death in patients with UTUC.

Keywords Bladder cancer · Prognosis · Urothelial carcinoma · Nephroureterectomy · Recurrence

Introduction

One classic characteristic of urothelial carcinoma (UC) is the development of frequent, multifocal metachronous lesions throughout the entire urinary tract [1–3]. According to the panurothelial field defect theory, this is explained by independent malignantly transformation of epithelial cells at different sites, and the intraluminal seeding and implantation of tumor cells that derived from an initial clone [4]. After diagnosis of UC of the bladder (UCB), UC of the upper urinary tract (UTUC) occurs in 2 to 7 % of all cases [3, 5]. In contrast, primary UTUC accounts for only up to 5 % of all renal and urothelial cancers of the upper urinary tract [3, 5]. Controversy still exists regarding the role of upper urinary tract surveillance in patients after diagnosis of UCB. However, it is also controversial whether patients with UTUC are at higher risk for recurrence and/or cancer-specific mortality from upper tract disease if they have a prior history of UCB. Due to the rarity of the disease, data of UTUC after primary bladder cancer are scarce [6]. In a multi-institutional data set of 293 patients from three European centers who had undergone radical nephroureterectomy (RNU) for UTUC, a history of UCB before the diagnosis of UTUC was an independent predictor of cancer-specific survival probabilities in addition to pathologic stage of the primary tumor and lymph nodes, the presence of synchronous muscle-invasive UCB, and tumor multifocality within the upper urinary tract [6]. In this cohort, 6 % of all patients developed contralateral UTUC. The only predictive variable for contralateral UTUC after RNU was a history of UCB before RNU [7].

In our multi-institutional series of 785 patients from nine academic centers in Europe and the USA, we assessed

the prognostic value of prior history of bladder cancer on recurrence and cancer-specific survival in patients with UTUC.

Patients and methods

This was an institutional review board—approved study with all participating sites providing the necessary institutional data sharing agreements before initiation of the study. A total of nine academic centers worldwide provided data. A computerized data bank was generated for data transfer. After combining the data sets, reports were generated for each variable to identify data inconsistencies and other data integrity problems. Through regular communication with all sites, resolution of all identified anomalies was achieved before analysis. Before final analysis, the database was frozen, and the final data set was produced for the current analysis.

The database comprised 785 patients who underwent RNU with ipsilateral bladder cuff resection between 1987 and 2008. Following exclusion of patients who received neoadjuvant chemotherapy ($n = 12$), 773 remaining patients were the subjects of the present analysis.

Surgery was performed by several surgeons according to the standard criteria of RNU, i.e., extrafascial dissection of the kidney with the entire length of ureter and adjacent segment of the bladder cuff. Careful cystoscopy was performed in all patients before ureteronephrectomy to prevent tumor seeding during resection of the distal ureter and its orifice. The hilar and regional lymph nodes adjacent to the ipsilateral great vessel generally were resected along with enlarged lymph nodes if abnormal on preoperative computed tomography scans or palpable intraoperatively. Extended lymphadenectomy was not routinely performed.

Pathologic evaluation

All surgical specimens were processed according to standard pathologic procedures at each institution. Tumors were staged according to the American Joint Committee on Cancer–Union Internationale Contre le Cancer TNM classification [8]. Tumor grading was assessed according to the 1973 WHO/International Society of Urologic Pathology consensus classification [9].

Follow-up regimen

Patients were generally observed every 3–4 months for the first year after RNU, every 6 months from the second through the fifth year, and annually thereafter. Follow-up consisted of a history, physical examination, routine blood work and serum chemistry studies, urinary cytology, chest

radiography, cystoscopic evaluation of the urinary bladder, and radiographic evaluation of the contralateral upper urinary tract. Elective bone scan, chest computed tomography, and magnetic resonance imaging were performed when clinically indicated.

Disease recurrence was defined as local failure in the operative site, regional lymph nodes, or distant metastasis. Bladder recurrences were not considered in the analysis of recurrence-free survival (RFS) rate. Cause of death was determined by treating physicians, by chart review corroborated by death certificates, or by death certificates alone. Most patients who were identified as having died of UTUC had progressive, widely disseminated metastases at the time of death. Patients who died in the perioperative period (i.e., death within 30 days of surgery) were censored at time of death for cancer-specific survival (CSS) analyses.

Statistical analysis

The Fisher's exact test and the Chi-square test were used to evaluate the association between categorical variables. Differences in variables with a continuous distribution across dichotomous categories were assessed using the Kruskal–Wallis test. The Kaplan–Meier method was used to calculate survival functions, and differences were assessed with the log-rank statistic. Univariable and multivariable Cox regression models addressed time to recurrence and cancer-specific mortality after RNU. Statistical significance in this study was set as $p \leq 0.05$. All reported p values are two-sided. Analyses were performed with SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

Association of prior history of bladder cancer with clinical and pathological features of UTUC

Five hundred and fifty-eight (72 %) patients had no bladder cancer before the diagnosis of upper tract transitional carcinoma; 179 (23 %) and 36 (5 %) had a prior history of non-muscle-invasive and muscle-invasive bladder transitional cell carcinoma before the upper tract transitional cell carcinoma, respectively. Specifically, 12 patients (2 %) had only bladder carcinoma in situ (CIS); 61 (8 %) Ta, 106 (14 %) T1, 22 (3 %) T2, 9 (1 %) T3, and 5 (1 %) T4 bladder cancer, respectively. One hundred and eighty-four patients (177 with non-muscle-invasive and seven with muscle-invasive cancers) were treated with transurethral resection plus intravesical therapies; conversely, 31 patients (two with non-muscle-invasive and 29 with muscle-invasive cancer) had radical cystectomy. Information on the time interval between diagnosis of UCB to diagnosis of UTUC was

available in 116 patients out of 773 patients. Median time period was 26 months (IQR 7.25–84.0).

Table 1 shows the association between prior history of bladder transitional cell carcinoma with clinical and pathological features of UTUC. Patient age and proportions of patients with lymphovascular invasion in the UTUC and concomitant CIS in the upper tract were significantly different across the three subgroups of patients (all p values <0.05).

Association of prior history of bladder cancer with clinical outcomes

The median follow-up of the whole cohort was 34 months (interquartile range 15–66 months). At last follow-up, 182 patients (23 %) had developed disease recurrence and 155 (20 %) were dead of UTUC. Moreover, 102 patients (13 %) experienced non-cancer-related deaths. The median follow-up for patients alive at last follow-up was 40 months (interquartile range 18–76 months). The overall 2- and 5-year RFS estimates were 79.1 % (standard error 1.6 %) and 73 % (SE 1.8 %), respectively. The overall 2- and 5-year CSS estimates were 84.3 % (SE 1.4 %) and 75.4 % (SE 1.8 %), respectively.

Prior history of bladder transitional cell carcinoma was significantly associated with an increased risk of disease recurrence and cancer-specific death (Tables 2, 3, respectively). Specifically, the 5-year RFS rates were 75.7 % (SE 2.0 %), 69.5 % (SE 4.1 %), and 45.5 % (SE 9.7 %), for patients without bladder cancer, with non-muscle-invasive, and with muscle-invasive bladder cancer, respectively (Fig. 1a; log-rank pooled over strata p value 0.001; no bladder cancer vs. non-muscle-invasive bladder cancer: $p = 0.455$; no bladder cancer vs. muscle-invasive bladder cancer: $p < 0.0001$). Similarly, the 5-year CSS rates were 77.1 % (SE 2.1 %), 76.7 % (SE 3.7 %), and 43 % (SE 9.8 %), for patients without bladder cancer, with non-muscle-invasive, and with muscle-invasive bladder cancer, respectively (Fig. 1b; log-rank pooled over strata p value 0.003; no bladder cancer vs. non-muscle-invasive bladder cancer: $p = 0.843$; no bladder cancer vs. muscle-invasive bladder cancer: $p < 0.0001$).

On multivariable Cox regression analyses, prior history of bladder cancer before RNU was an independent predictor of both RFS (p value 0.012; no bladder cancer vs. non-muscle-invasive bladder cancer: hazard ratio (HR) 1.4, $p = 0.082$; no bladder cancer vs. muscle-invasive bladder: HR 2.1, $p = 0.007$) and CSS (p value 0.008; no bladder cancer vs. non-muscle-invasive bladder cancer: HR 1.2, $p = 0.279$; no bladder cancer vs. muscle-invasive bladder: HR 2.3, $p = 0.008$), once adjusted for the effects of other covariates.

Analyses were rerun after excluding 66 patients who received adjuvant chemotherapy. This resulted in consistent statistical patterns and p values (data not extensively shown).

Table 1 Association of prior history of bladder cancer with clinical and pathologic characteristics of 773 patients treated with radical nephroureterectomy and bladder cuff excision for upper tract urothelial carcinoma

	Cases (%)	Prior history of bladder UC			<i>p</i> value
		No prior bladder UC (<i>n</i> = 558, 72 %)	Non-muscle-invasive bladder UC (<i>n</i> = 179, 23 %)	Muscle-invasive bladder UC (<i>n</i> = 36, 5 %)	
Age (years; median; and interquartile range)	68 (61–75)	67.5 (60–74.5)	69 (63–76)	69 (64–74)	0.033
Gender					0.056
Male	533 (69 %)	373 (70 %)	130 (24 %)	30 (6 %)	
Female	240 (31 %)	185 (77 %)	49 (20 %)	6 (3 %)	
Type of surgery					0.270
Open RNU	703 (91 %)	500 (71 %)	169 (24 %)	34 (5 %)	
Laparoscopic RNU	70 (9 %)	58 (83 %)	10 (14 %)	2 (3 %)	
Lymph node dissection					0.439
Performed	185 (24 %)	136 (74 %)	38 (20 %)	11 (6 %)	
Not performed	588 (76 %)	422 (72 %)	141 (24 %)	25 (4 %)	
Pathologic stage					0.735
pTa	163 (21 %)	119 (73 %)	40 (25 %)	4 (2 %)	
pTis	9 (1 %)	7 (78 %)	2 (22 %)	0	
pT1	195 (25 %)	138 (71 %)	49 (25 %)	8 (4 %)	
pT2	147 (19 %)	103 (70 %)	36 (25 %)	8 (5 %)	
pT3	215 (28 %)	156 (73 %)	46 (21 %)	13 (6 %)	
pT4	44 (6 %)	35 (80 %)	6 (14 %)	3 (6 %)	
Grade					0.401
G1	99 (13 %)	75 (76 %)	19 (19 %)	5 (5 %)	
G2	224 (29 %)	157 (70 %)	60 (27 %)	7 (3 %)	
G3	450 (58 %)	326 (73 %)	100 (22 %)	24 (5 %)	
Number of removed lymph nodes median and interquartile range)	3 (2–6)	3 (2–6)	3 (2–6)	2 (2–2)	0.132
Lymphovascular invasion*					0.003
Absent	614 (79 %)	436 (71 %)	154 (25 %)	24 (4 %)	
Present	148 (19 %)	115 (77 %)	21 (14 %)	12 (8 %)	
Concomitant CIS					0.044
Absent	683 (88 %)	503 (74 %)	150 (22 %)	30 (4 %)	
Present	90 (12 %)	55 (61 %)	29 (32 %)	6 (7 %)	
Lymph node stage					0.083
N0	135 (18 %)	104 (77 %)	26 (19 %)	5 (4 %)	
Nx	588 (76 %)	422 (72 %)	141 (24 %)	25 (4 %)	
N1/2	50 (6 %)	32 (64 %)	12 (24 %)	6 (12 %)	
Time from RNU to last follow-up or death (median and interquartile range)	34 (15–66)	36 (16–68)	30 (17–62)	16 (12–45)	0.023

CIS carcinoma in situ

* Lymphovascular invasion: status missing in 11 cases

Discussion

This series of 773 patients from nine academic institutions from Europe and the USA comprises one of the largest cohorts investigating UTUC. Our data revealed a history

of muscle-invasive UCB before RNU as an independent predictor for recurrence and cancer-specific mortality in patients with UTUC. Further independent prognosticators included pathological stage, grade, concomitant carcinoma in situ, lymphovascular invasion, and lymph node

Table 2 Univariable and multivariable Cox regression analyses of prior history of bladder cancer for prediction of disease recurrence in 773 patients treated with radical nephroureterectomy and ipsilateral bladder cuff excision for upper tract urothelial carcinoma (182 recurrences)

Parameter	Univariable analysis			Multivariable analysis		
	HR	95 % CI	<i>p</i> value	HR	95 % CI	<i>p</i> value
Age	1.0	1–1.03	0.025	1.0	0.7–1.03	0.125
Gender	0.9	0.7–1.3	0.622	0.9	0.7–1.3	0.707
Prior history of bladder cancer			0.001			0.012
No bladder cancer	1	Reference	–	1	Reference	–
Non-muscle-invasive bladder cancer	1.1	0.8–1.6	0.462	1.4	0.9–1.9	0.082
Muscle-invasive bladder cancer	2.7	1.6–4.5	<0.001	2.1	1.2–3.6	0.007
Type of surgery	1.4	0.9–2.3	0.103	1.4	0.9–2.3	0.132
Pathologic stage			<0.0001			<0.0001
pTa/Tis	1	Reference	–	1	Reference	–
pT1	1.4	0.7–2.8	0.316	1.1	0.6–2.2	0.797
pT2	3.5	1.9–6.8	<0.0001	2.4	1.2–4.7	0.012
pT3	6.7	3.7–12.0	<0.0001	3.5	1.8–6.8	<0.0001
pT4	40.3	20.9–77.6	<0.0001	15.2	7.0–33.0	<0.0001
Grade			<0.0001			0.034
G1	1	Reference	–	1	Reference	–
G2	2.5	0.9–6.5	0.055	1.9	0.7–5.1	0.190
G3	7.9	3.2–19.3	<0.0001	2.9	1.1–7.4	0.031
Concomitant CIS	1.9	1.3–2.8	0.001	1.5	1.0–2.3	0.045
Lymphovascular invasion	3.8	2.8–5.2	<0.0001	1.7	1.2–2.3	0.004
Lymph node stage			<0.0001			0.023
N0	1	Reference	–	1	Reference	–
Nx	0.9	0.6–1.3	0.455	1.0	0.7–1.6	0.838
N1/2	5.6	3.4–9.2	<0.0001	1.9	1.1–3.3	0.023

status for recurrence of UTUC and age, pathological stage, and lymphovascular invasion for cancer-specific mortality of UTUC. These findings echo various previous studies examining prognostic factors for cancer-specific outcomes after RNU [10–12]. Regarding prior history of UCB, it is important to distinguish between prior muscle-invasive and non-muscle-invasive UCB. Five-year RFS rates were 75.7, 69.5, and 45.5 % (SE 9.7 %) for patients without UCB, with non-muscle-invasive, and with muscle-invasive UCB, respectively. The 5-year CSS rates were 77.1, 76.7, and 43 % (SE 9.8 %) for patients without UCB, with non-muscle-invasive, and with muscle-invasive UCB, respectively. In Kaplan–Meier analysis, there was a significant difference in outcome only between patients with no history of UCB versus patients with prior history of muscle-invasive UCB. In addition, in the multivariable model, only muscle-invasive UCB was an independent predictor for RFS and CSS. A history of noninvasive UCB before RNU for UTUC did not increase the risk for recurrence and cancer-specific mortality in these patients.

Similarly, Novara et al. [6] reported from a series of 269 patients who underwent RNU for UTUC that a history of muscle-invasive bladder cancer was an independent predictor of the probability of cancer-specific survival in

UTUC, whereas noninvasive UCB had no prognostic role in cancer-specific survival of UTUC. In contrast, Mullerad et al. reported on a smaller series of 129 patients that had undergone RNU for UTUC. From these patients, 62 had a history of UCB, which was an independent predictor for cancer-specific mortality regardless of being superficial or invasive UCB [13].

In contrast to these findings, Rabbani et al. [14] demonstrated in a 1973 to 1996 United States Surveillance, Epidemiology, and End Results (SEER) database analysis that patients with a de novo UTUC had a 1.67-fold increased risk of cancer-related death compared to patients with secondary UTUC after UCB. While comparing the tumor characteristics of 657 patients who developed UTUC after a diagnosis of UCB with 7,839 patients with de novo UTUC, patients with UTUC after UCB presented with lower stage [14]. Unfortunately, the authors were not able to distinguish between muscle-invasive and non-muscle-invasive bladder cancer in this study. In addition, patients with UTUC were included irrespective of therapy. Since patients with more aggressive UTUC more often undergo RNU, the underlying patient population may explain the differences in outcomes between these studies.

Table 3 Univariable and multivariable Cox regression analyses of prior history of bladder cancer for prediction of cancer-specific mortality in 773 patients treated with radical nephroureterectomy and ipsilateral bladder cuff excision for upper tract urothelial carcinoma (155 cancer-specific deaths)

Parameter	Univariable analysis			Multivariable analysis		
	HR	95 % CI	<i>p</i> value	HR	95 % CI	<i>p</i> value
Age	1.02	1–1.04	0.010	1.0	1–1.04	0.041
Gender	0.8	0.6–1.2	0.268	0.8	0.6–1.2	0.277
Prior history of bladder cancer			<0.001			0.008
No bladder cancer	1	Reference	–	1	Reference	–
Non-muscle-invasive bladder cancer	1.0	0.7–1.5	0.855	1.2	0.8–1.9	0.279
Muscle-invasive bladder cancer	3.2	1.9–5.4	<0.001	2.3	1.3–4.0	0.008
Type of surgery	1.0	0.6–1.9	0.847	1.0	0.6–1.9	0.850
Pathologic stage			<0.0001			<0.0001
pTa/Tis	1	Reference	–	1	Reference	–
pT1	1.5	0.7–3.5	0.300	1.2	0.5–2.9	0.637
pT2	4.1	1.9–8.7	<0.0001	2.9	1.3–6.4	0.011
pT3	9.0	4.5–18.0	<0.0001	4.9	2.3–10.8	<0.0001
pT4	55.5	25.9–118.4	<0.0001	21.4	8.7–52.8	<0.0001
Grade			<0.0001			0.133
G1	1	Reference	–	1	Reference	–
G2	1.9	0.7–5.1	0.168	1.4	0.5–3.8	0.534
G3	6.7	2.7–16.3	<0.0001	2.0	0.7–5.5	0.148
Concomitant CIS	1.8	1.2–2.7	0.005	1.5	0.9–2.3	0.110
Lymphovascular invasion	4.6	3.3–6.3	<0.0001	1.9	1.3–2.7	0.001
Lymph node stage			<0.0001			0.063
N0	1	Reference	–	1	Reference	–
Nx	0.9	0.6–1.5	0.898	1.3	0.8–2.1	0.283
N1/2	6.6	3.8–11.4	<0.0001	2.0	1.1–3.8	0.022

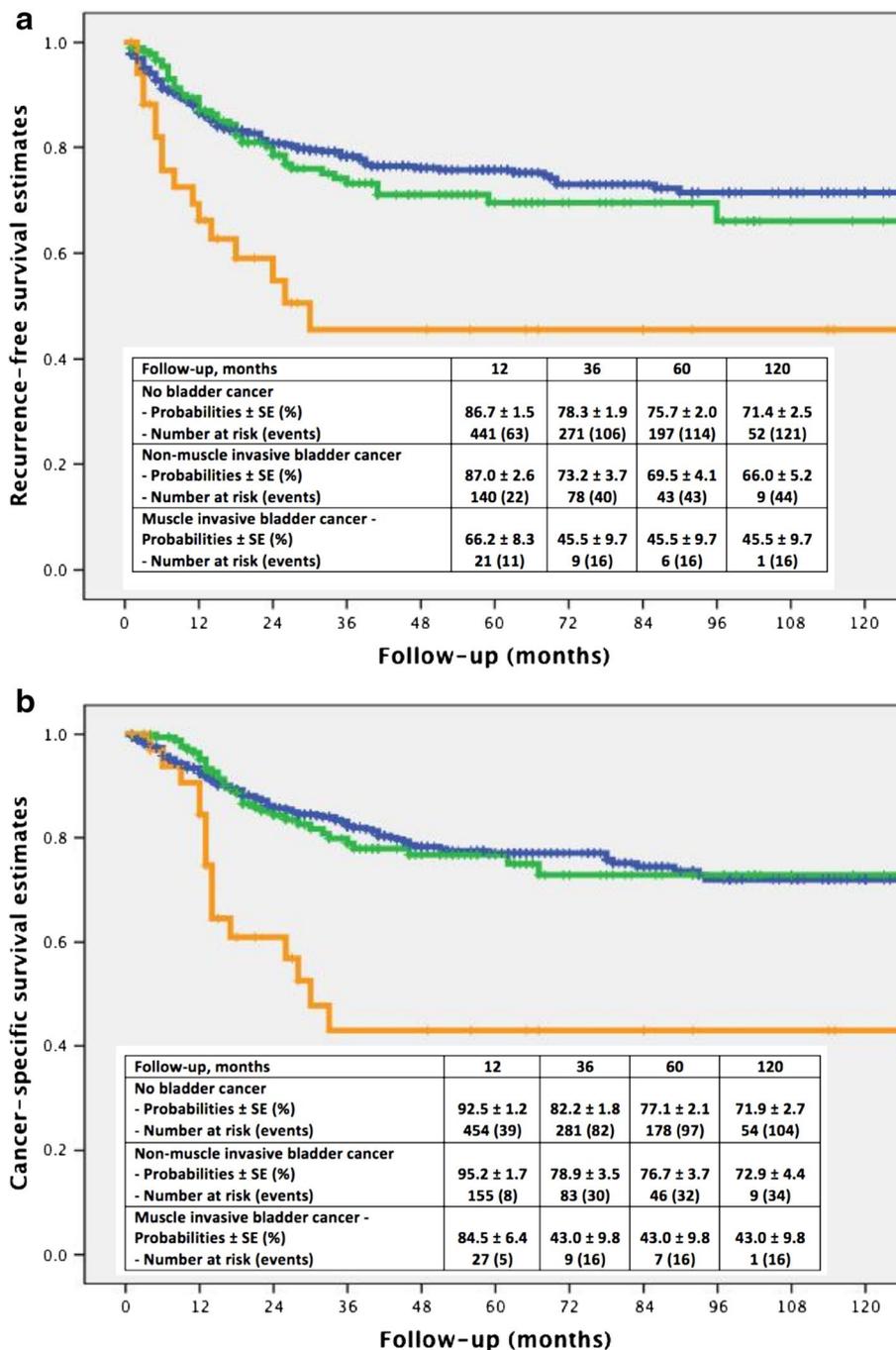
In a study from Milojevic et al. [15] with 221 patients treated with RNU for UTUC, patients with a history of non-muscle-invasive UCB had a higher risk of having multifocal disease and UTUC with higher tumor stages (pT3 or greater). However, there was no effect on cancer-specific survival, and the cohort did not include any patients with a history of muscle-invasive UCB. In another small study with 72 patients who had undergone RNU, Akdogan et al. [16] evaluated the effect of non-muscle-invasive bladder tumor history on clinical outcome after surgical management of UTUC. The authors showed that high tumor stage and grade, and ureteral tumor location were associated with a higher risk of cancer-specific mortality and recurrence, but history of UCB had no prognostic role.

In our study, 72 % of all patients had no prior diagnosis of UCB before RNU, whereas 23 % had non-muscle-invasive UCB and 5 % had muscle-invasive UCB before RNU for UTUC. These percentages are lower than in the series of Novara et al. [6] with about 50 % of all patients with a prior history of UCB and 7 % patients that underwent radical cystectomy for muscle-invasive UCB. However, previous studies reported even lower percentages of diagnosis of UCB prior RNU, ranging from 9 to 20 % [16–18].

Patients after radical cystectomy for UCB are at risk to develop recurrence in the upper urinary tract [2–5, 19]. Recently, Picozzi et al. [20] performed a meta-analysis based on 27 studies including a total of 13,185 patients to identify risk factors for UTUC recurrence after radical cystectomy for UCB. Patients with G1 tumors were at higher risk for UTUC recurrence than patients with G2 or G3 tumors. Also, patients with superficial tumors or CIS had a higher risk of recurrence, as well as patients with positive ureteral or urethral margins. Huguet-Pérez et al. [21] reported about a higher incidence of UTUC in patients with a history of superficial UCB that were cystectomized for superficial or invasive UCB. Similarly, Volkmer et al. [4] analyzed a cohort of 1,420 patients that underwent radical cystectomy for UCB with 25 patients showing UTUC recurrence. They identified four risk factors for upper urinary tract recurrence including history of CIS, recurrent UCB, non-muscle-invasive UCB, and tumor involvement of the distal ureter. Interestingly, patients with none of these risk factors showed UTUC recurrence in only 0.8 % of all cases within 15 years [4].

Older studies have revealed other risk factors, such as vesicoureteral reflux or occupational bladder cancer [22, 23]. Unfortunately, this was not investigated in newer studies and can thus not be commented on.

Fig. 1 a Kaplan–Meier curves of recurrence-free survival stratified by prior history of bladder cancer in 700 patients treated with radical nephroureterectomy and ipsilateral bladder cuff excision for upper tract urothelial carcinoma. *Blue curve*: patients without prior bladder cancer; *green curve*: patients with non-muscle-invasive bladder cancer; and *yellow curve*: patients with muscle-invasive bladder cancer. Log-rank pooled over strata p value 0.001; no bladder cancer versus non-muscle-invasive bladder cancer: $p = 0.455$; no bladder cancer versus muscle-invasive bladder cancer: $p < 0.0001$. **b** Kaplan–Meier curves of cancer-specific survival stratified by prior history of bladder cancer in 700 patients treated with radical nephroureterectomy and ipsilateral bladder cuff excision for upper tract urothelial carcinoma. *Blue curve*: patients without prior bladder cancer; *green curve*: patients with non-muscle-invasive bladder cancer; and *yellow curve*: patients with muscle-invasive bladder cancer. Log-rank pooled over strata p value 0.003; no bladder cancer versus non-muscle-invasive bladder cancer: $p = 0.843$; and no bladder cancer versus muscle-invasive bladder cancer: $p < 0.0001$



Upper tract urothelial carcinoma recurrence after radical cystectomy for UCB is a late oncological event [3]. According to the analysis of the SEER database, the median time to secondary UTUC was 33 months [5]. Although follow-up regimens for patients at risk to develop UTUC following primary bladder cancer are strict including regular endourological and/or radiological evaluation, most patients present due to novel symptoms [3, 14]. Sanderson et al. [3] reported that 78 % of all UTUC recurrences in 27 patients in a cohort of 1,359 patients who underwent radical cystectomy for

UCB were detected after the development of symptoms. One important factor that has to be drawn from studies looking into UTUC following primary cancer of the bladder is that long-term follow-up is mandatory as the incidence of UTUC is stable over time [14]. Contrary to this, the findings by Wright et al. [5] suggest that about 71 % of all UTUC cases following primary bladder cancer occur within the first 5 years of bladder cancer diagnosis.

In return, patients who underwent RNU for UTUC are also at higher risk to develop muscle-invasive UCB. Kim

et al. [24] showed in 422 patients who underwent RNU and 173 of these patients subsequently developing UCB, 28 with muscle-invasive disease, that an advanced pathological stage (pT3 or greater) and ureteral tumor location increased the risk of muscle-invasive UCB development. In a recent study, Ishioka et al. [25] developed a risk stratification model for the recurrence of UTUC in the bladder after RNU. This retrospective study was based on 754 UTUC patients without prior or concurrent bladder cancer and distant metastasis at 13 institutes in Japan. Papillary tumor architecture, absence of lymph vascular invasion, and higher pathologic T stage were independent risk factors for bladder cancer recurrence [25].

Overall, data on the prognostic value of a prior history of UCB in patients undergoing RNU for UTUC are controversial. Similarly to our study, the multi-institutional series of Novara et al. [6] revealed a prior history of muscle-invasive UCB as predictor for increased cancer-specific mortality and recurrence. Further prospective studies have to show whether prior history of muscle-invasive UCB is a risk factor for UTUC or whether these data partially reflect the mortality associated with the initial UCB. However, the rates for RFS and CSS after RNU emphasize that surgical treatment of upper tract tumor even in the case of locally advanced disease can achieve durable local control [26].

Our present study has several limitations. First, this study was a retrospective analysis, which includes patient data from two decades. Multiple specialized surgeons operated patients who underwent RNU at one of the nine centers. Also, surveillance protocols after surgery were different between the institutions. Furthermore, this data collection lacks a central pathological review, which may lead to interobserver variability causing potential misinterpretation of pathologic specimens.

Conclusion

In this retrospective analysis of a cohort of 784 patients who underwent RNU for UTUC, prior history of UCB was significantly associated with an increased risk of disease recurrence and cancer-specific death. This association is limited to a history of muscle-invasive UCB.

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