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ORIGINAL ARTICLE

Concomitant carcinoma in situ as an independent prognostic parameter for recurrence and survival in upper tract urothelial carcinoma: a multicenter analysis of 772 patients

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Abstract
Purpose The purpose of this study is to assess the association of concomitant carcinoma in situ (CIS) with disease recurrence and cancer-related death in a multi-institutional series of patients treated with radical nephroureterectomy (RNU) for upper tract urothelial carcinoma (UTUC).
Methods We collected retrospectively the data of 772 patients treated with RNU and ipsilateral bladder cuff excision at 9 international institutions in Asia, Europe, and Northern America from 1987 to 2008. Surgical specimens were processed according to standard pathologic procedures at each institution. Univariable and multivariable Cox regression models addressed time to recurrence and cancer-specific mortality.
Results Concomitant CIS was present in 88 patients (11.4%); it was associated with more advanced pathologic stage, higher tumor grade, and presence of lymphovascular invasion (all P-values < 0.05). The five-year recurrence-free (RFS) and cancer-specific survival (CSS) estimates were 74.4 and 76.3%, respectively, in the absence of CIS compared with 56.4 and 59.9%, respectively, in the presence of CIS (P-values < 0.0001 for RFS and 0.002 for CSS, respectively). On multivariable Cox regression analyses, concomitant CIS was an independent predictor of both RFS (hazard ratio (HR): 1.9; $P = 0.007$) and CSS (HR: 1.7, $P = 0.048$). Similar findings were reconfirmed in subgroups analyses limited to T2, organ confined, and N0/Nx UTUC, or patients who did not receive adjuvant chemotherapy.
Conclusions Presence of concomitant CIS is an independent predictor of both RFS and CSS in patients treated with RNU for UTUC. This information may be useful in

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risk stratification of UTUC patients for follow-up and additional therapy.

Keywords Upper tract urothelial carcinoma · Carcinoma in situ · UTUC collaboration group · Cancer-specific survival · Transitional cell carcinoma

Purpose

Upper urinary tract urothelial carcinoma (UTUC) is a rare malignant disease. Only 4–15% of all primary kidney cancers are urothelial carcinomas [1, 2], and of all urothelial tumors, only 5% are found in ureter and kidney [3]. Radical nephroureterectomy (RNU) with bladder cuff resection and regional lymphadenectomy is the mainstay of treatment for invasive and/or high-grade UTUC. Following RNU, the prognostic role of several pathologic variables such as tumor stage, tumor grade, lymph node metastasis, lymphovascular invasion, tumor necrosis, tumor location, and tumor architecture has been established [4–16]. Carcinoma in situ (CIS) is a high-grade and potentially aggressive manifestation of urothelial carcinoma (UC). Within the bladder, CIS is a well-known prognostic factor in non-muscle invasive [17–19] and muscle-invasive UC [20, 21].

In UTUC, the prevalence of concomitant CIS with UTUC has been reported to be between 27 and 36% [13, 14, 22]. However, the data available on the prognostic impact of concomitant CIS in UTUC remain sparse, and very recently, Wheat et al. [23] reported that the presence of concomitant CIS was associated with a higher risk of disease recurrence and cancer-specific mortality only in patients with organ-confined UTUC. Consequently, the purpose of this present study is to evaluate the prognostic role of the presence of concomitant CIS in an international, multicenter series of patients treated with RNU for UTUC.

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 9 institutions worldwide provided data. A computerized databank 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. We excluded patients who received neoadjuvant chemotherapy ($n = 13$), which left 772 patients for analysis.

Surgery was performed by multiple surgeons according to the standard criteria for RNU, i.e., extrafascial dissection of the kidney with the entire length of ureter and adjacent segment of the bladder cuff. 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 [24]. Tumor grading was assessed according to the 1973 World Health Organization/International Society of Urologic Pathology consensus classification [25]. Lymphovascular invasion (LVI) was defined as the presence of tumor cells within an endothelium-lined space without underlying muscular walls. No central revision of the pathological slides was performed.

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 years, 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 the treating physicians, chart review corroborated by death certificates, or 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.

Table 1 Association of concomitant carcinoma in situ with clinical and pathologic characteristics of 772 patients treated with radical nephroureterectomy and ipsilateral bladder cuff excision for upper tract urothelial carcinoma

	Cases (%)	Concomitant carcinoma in situ		
		Absent ($n = 684$, 89%)	Present ($n = 88$, 11%)	*P*-value
Age (years; median and interquartile range)	68 (61–75)	68 (61–75)	68.4 (64–74.2)	0.218
Race				0.01
Caucasian	623 (81%)	543 (87%)	80 (13%)	
Asiatic	149 (19%)	141 (95%)	8 (5%)	
Gender				0.393
Male	532 (69%)	475 (89%)	57 (11%)	
Female	240 (31%)	209 (87%)	31 (13%)	
Type of surgery				0.232
Open RNU	703 (91%)	626 (89%)	77 (11%)	
Laparoscopic RNU	69 (9%)	58 (84%)	11 (16%)	
Lymph node dissection				0.233
Yes	586 (76%)	524 (89%)	62 (11%)	
No	186 (24%)	160 (86%)	26 (14%)	
Tumor location[a]				0.185
Renal pelvis only	409 (59%)	372 (91%)	37 (9%)	
Ureter only	234 (34%)	206 (88%)	28 (12%)	
Both renal pelvis and ureter	48 (7%)	40 (83%)	8 (17%)	
Pathologic stage				0.039
pTa	165 (21%)	154 (93%)	11 (7%)	
pT1	196 (25%)	179 (91%)	17 (9%)	
pT2	147 (19%)	128 (87%)	19 (13%)	
pT3	220 (29%)	185 (84%)	35 (16%)	
pT4	44 (6%)	38 (86%)	6 (14%)	
Grade				<0.001
G1	98 (13%)	95 (97%)	3 (3%)	
G2	225 (29%)	214 (95%)	11 (5%)	
G3	449 (58%)	375 (84%)	74 (16%)	
Number of removed lymph nodes (median and interquartile range)	3 (2–6)	3 (2–6)	3 (2–8)	0.668
Lymphovascular invasion[b]				0.026
Absent	610 (80%)	551 (90%)	59 (10%)	
Present	150 (20%)	126 (84%)	24 (16%)	
Lymph node stage				0.300
N0	134 (17%)	117 (87%)	17 (13%)	
Nx	586 (76%)	524 (89%)	62 (11%)	
N1/2	52 (7%)	43 (83%)	9 (17%)	
Adjuvant chemotherapy				0.510
Yes	705 (91%)	623 (88%)	82 (12%)	
No	67 (9%)	61 (91%)	6 (9%)	
Follow-up (median and interquartile range)	33.5 (15–64.7)	35 (16–65.7)	27 (12–47.5)	0.012

[a] Tumor location missing in 81 cases

[b] Lymphovascular invasion missing in 12 cases

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 Mann–Whitney *U* 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 vers 16.0 (SPSS Inc, Chicago, IL, USA).

Results

Association of concomitant CIS with clinical and pathologic characteristics

Concomitant CIS was present in 88 patients (11.4%). Table 1 shows the association between concomitant CIS and clinical and pathologic characteristics. Prevalence of concomitant CIS increased with advancing pathologic stage (7, 9, 13, 16, and 14%, for Ta, T1, T2, T3, and T4, respectively; $P = 0.039$), higher tumor grade, and presence of lymphovascular invasion (*P*-values < 0.05). The median follow-up duration was significantly longer in patients without concomitant CIS compared with those with concomitant CIS ($P = 0.012$).

Association of concomitant CIS with clinical outcomes

The median follow-up for all patients was 33.5 months (interquartile range (IQR) 15–64.7). At last follow-up, 260 patients (34%) were dead from whom 158 (20%) had died of UTUC. Overall 185 patients (24%) developed disease recurrence. The median follow-up for patients who were alive at last follow-up was 40 months (IQR: 18–75 months).

The overall 3- and 5-year RFS estimates were 75% (standard error (SE) 1.7) and 72.3% (SE 1.8), respectively. The overall 3- and 5-year CSS estimates were 79.0% (SE 1.7) and 74.7% (SE 1.9), respectively.

Table 2 Univariable and multivariable Cox regression analyses of concomitant CIS for prediction of disease recurrence in 772 patients treated with radical nephroureterectomy and ipsilateral bladder cuff excision for upper tract urothelial carcinoma (185 recurrences)

Parameter	Univariable analyses			Multivariable analysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age	1.0	1.004–1.04	0.01	1.02	1.001–1.04	0.045
Race	1.1	1.002–1.2	0.046	1.1	0.9–1.2	0.072
Gender	0.9	0.7–1.3	0.627	0.8	0.5–1.1	0.160
Surgery	1.5	0.9–2.4	0.137	0.8	0.4–1.5	0.443
Tumor location			0.030			0.005
Renal pelvis only	1	Reference	–	1	Reference	–
Ureter only	1.1	0.8–1.6	0.483	1.3	0.9–1.9	0.136
Both ureter and renal pelvis	2.0	1.2–3.4	0.008	2.5	1.4–4.3	0.001
Pathologic stage			<0.0001			<0.0001
pTa	1	Reference	–	1	Reference	–
pT1	1.6	0.8–3.3	0.210	0.9	0.3–2.1	0.745
pT2	4.0	2.0–7.9	<0.0001	2.8	1.3–6.3	0.011
pT3	7.9	4.2–14.8	<0.0001	4.9	2.3–10.5	<0.0001
pT4	44.7	22.4–89.6	<0.0001	13.5	5.2–34.8	<0.0001
Grade			<0.0001			0.293
G1	1	Reference	–	1	Reference	–
G2	2.1	0.9–4.9	0.107	1.6	0.6–4.4	0.378
G3	6.7	2.9–15.1	<0.0001	2.0	0.8–5.3	0.162
Lymphovascular invasion	3.8	2.8–5.2	<0.0001	1.7	1.2–2.5	0.003
Lymph node stage			<0.0001			0.001
N0	1	Reference	–	1	Reference	–
Nx	0.9	0.6–1.3	0.457	1.2	0.7–2.0	0.419
N1/2	5.5	3.4–9.0	<0.0001	2.9	1.5–5.3	0.001
Concomitant CIS	2.0	1.4–3.0	<0.001	1.9	1.2–3.0	0.007

Table 3 Univariable and multivariable Cox regression analyses of concomitant CIS for the prediction of cancer-specific survival in 772 patients treated with radical nephroureterectomy and ipsilateral bladder cuff excision for upper tract urothelial carcinoma (158 cancer-specific deaths)

Parameter	Univariable analyses			Multivariable analysis		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Age	1.0	1.007–1.04	0.006	1.02	1.004–1.04	0.022
Race	1.1	0.96–1.2	0.251	1.0	0.9–1.2	0.483
Gender	0.8	0.6–1.2	0.263	0.7	0.5–1.0	0.075
Surgery	0.9	0.5–1.8	0.867	0.9	0.4–1.9	0.701
Tumor location			0.065			0.036
Renal pelvis only	1	Reference	–	1	Reference	–
Ureter only	1.1	0.7–1.5	0.771	1.2	0.8–1.8	0.360
Both ureter and renal pelvis	1.9	1.1–3.4	0.021	2.2	1.2–4.0	0.01
Pathologic stage			<0.0001			<0.0001
pTa	1	Reference	–	1	Reference	–
pT1	1.6	0.7–3.8	0.254	0.9	0.4–2.4	0.843
pT2	4.4	2.0–9.6	<0.0001	2.6	1.1–6.3	0.033
pT3	10.0	4.8–20.8	<0.0001	5.5	2.4–12.6	<0.0001
pT4	59.0	26.7–130.2	<0.0001	13.9	5.0–38.9	<0.0001
Grade			<0.0001			0.502
G1	1	Reference	–	1	Reference	–
G2	1.6	0.7–3.9	0.301	1.4	0.5–3.9	0.521
G3	5.6	2.5–12.8	<0.0001	1.7	0.6–4.6	0.298
Lymphovascular invasion	4.5	3.2–6.2	<0.0001	1.9	1.3–2.8	0.001
Lymph node stage			<0.0001			0.001
N0	1	Reference	–	1	Reference	–
Nx	0.9	0.6–1.5	0.900	1.5	0.9–2.6	0.154
N1/2	6.6	3.8–11.4	<0.0001	3.4	1.7–6.9	0.001
Concomitant CIS	1.8	1.2–2.9	0.003	1.7	1.01–2.8	0.048

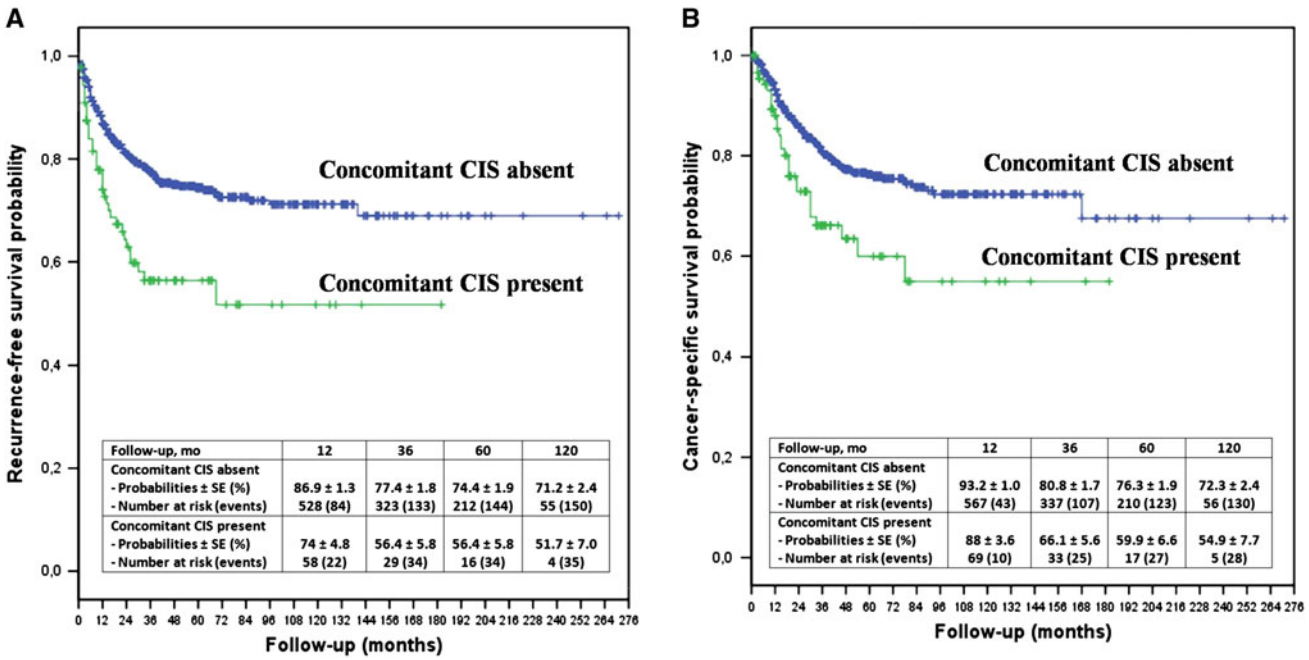
Presence of concomitant CIS was significantly associated with a decrease in RFS and CSS (Tables 2, 3, respectively). The 5-year RFS and CSS rates were 74.4% (SE 1.9%) and 76.3% (SE 1.9%), respectively, in the absence of CIS compared with 56.4% (SE 5.8%) and 59.9% (SE 6.6%), respectively, in the presence of CIS (Fig. 1a, b, respectively; log-rank *P*-values < 0.0001 and 0.002, respectively). Stratifying by pT stage, presence of concomitant CIS was significantly associated with both RFS and CSS in T2 (Fig. 2a, b, respectively) and organ-confined (pTa-T2 N0-x) disease.

On multivariable Cox regression analyses that adjusted for the effects of age, race, gender, type of surgery, tumor location, stage, grade, and lymph node status, concomitant CIS was an independent predictor of both RFS (Hazard ratio (HR): 1.9; $P = 0.007$) and CSS (HR: 1.7; $P = 0.048$). Results did not change substantially when patients with positive nodes (HR of concomitant CIS for RFS: 2.4, $P = 0.001$; HR for CSS: 2.1, $P = 0.011$) or those who received adjuvant chemotherapy were excluded (HR of concomitant CIS for RFS: 2.5, $P = 0.001$; HR for CSS: 2.5, $P = 0.002$). When analyses were restricted to patients with T2 disease, concomitant CIS was an independent predictor of both RFS (HR 4.0; $P = 0.011$) and CSS (H.R. 3.8; $P = 0.036$). Similar figures were obtained in organ-confined cancers (HR: 2.5, $P = 0.02$ for RFS; HR: 2.4, $P = 0.042$ for CSS). Conversely, concomitant CIS was not significantly associated with the outcome of the patients with non-organ-confined disease (pT3-4Nany) (HR: 1.5, $P = 0.180$ for RFS; HR: 1.2, $P = 0.504$ for CSS).

Conclusions

We found that concomitant CIS was present in about 11% of RNU specimens. In addition, we found that concomitant CIS conferred a worse prognosis such as lower RFS and CSS rates, even after adjustment for the effects of standard prognostic factors.

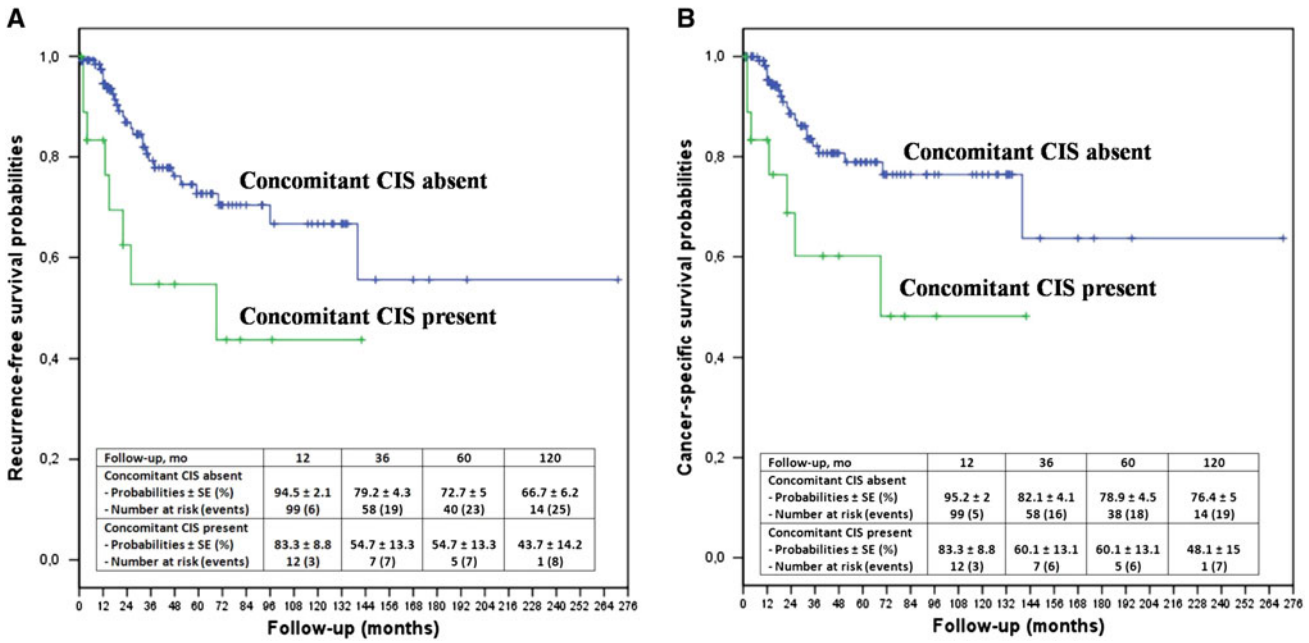
Although CIS is an established prognostic factor in bladder UC, the literature on its prognostic role in UTUC is limited. The prevalence of concomitant CIS in our study is lower than that in previous studies (i.e., 27–36%)



Follow-up, mo	12	36	60	120
Concomitant CIS absent				
- Probabilities ± SE (%)	86.9 ± 1.3	77.4 ± 1.8	74.4 ± 1.9	71.2 ± 2.4
- Number at risk (events)	528 (84)	323 (133)	212 (144)	55 (150)
Concomitant CIS present				
- Probabilities ± SE (%)	74 ± 4.8	56.4 ± 5.8	56.4 ± 5.8	51.7 ± 7.0
- Number at risk (events)	58 (22)	29 (34)	16 (34)	4 (35)

Follow-up, mo	12	36	60	120
Concomitant CIS absent				
- Probabilities ± SE (%)	93.2 ± 1.0	80.8 ± 1.7	76.3 ± 1.9	72.3 ± 2.4
- Number at risk (events)	567 (43)	337 (107)	210 (123)	56 (130)
Concomitant CIS present				
- Probabilities ± SE (%)	88 ± 3.6	66.1 ± 5.6	59.9 ± 6.6	54.9 ± 7.7
- Number at risk (events)	69 (10)	33 (25)	17 (27)	5 (28)

Fig. 1 Kaplan–Meier curves of **a** recurrence-free survival and **b** cancer-specific survival stratified by presence or absence of concomitant CIS in 772 patients treated with radical nephroureterectomy and ipsilateral bladder cuff excision for upper tract urothelial carcinoma (P-values < 0.0001 and 0.002, respectively)



Follow-up, mo	12	36	60	120
Concomitant CIS absent				
- Probabilities ± SE (%)	94.5 ± 2.1	79.2 ± 4.3	72.7 ± 5	66.7 ± 6.2
- Number at risk (events)	99 (6)	58 (19)	40 (23)	14 (25)
Concomitant CIS present				
- Probabilities ± SE (%)	83.3 ± 8.8	54.7 ± 13.3	54.7 ± 13.3	43.7 ± 14.2
- Number at risk (events)	12 (3)	7 (7)	5 (7)	1 (8)

Follow-up, mo	12	36	60	120
Concomitant CIS absent				
- Probabilities ± SE (%)	95.2 ± 2	82.1 ± 4.1	78.9 ± 4.5	76.4 ± 5
- Number at risk (events)	99 (5)	58 (16)	38 (18)	14 (19)
Concomitant CIS present				
- Probabilities ± SE (%)	83.3 ± 8.8	60.1 ± 13.1	60.1 ± 13.1	48.1 ± 15
- Number at risk (events)	12 (3)	7 (6)	5 (6)	1 (7)

Fig. 2 Kaplan–Meier curves of **a** recurrence-free survival and **b** cancer-specific survival stratified by presence or absence of concomitant CIS in 147 patients treated with radical nephroureterectomy and ipsilateral bladder cuff excision for pT2 upper tract urothelial carcinoma (P-values 0.01)

[13, 14, 22]. The reasons underlying this discrepancy are multifold such as differences in disease severity, pathologic evaluation, and reporting.

With regard to the prognostic role of concomitant CIS, in a study of 1,363 patients with UTUC, concomitant CIS has been associated with RFS and CSS in univariable analyses, but this association was lost after adjustment for the effects of standard pathologic features in multivariable analyses [10]. In a recent large analysis on 1,387 patients treated with RNU, Wheat et al. [23], indeed, failed to demonstrate a

prognostic role for concomitant CIS on the whole cohort, but in subgroup analyses limited to organ-confined UTUC demonstrated that such pathological feature was an independent predictor of both disease recurrence and cancer-related death. In the current study, indeed, concomitant CIS was an independent predictor of both RFS and CSS in all patients as well as in subgroup analyses of patients with T2, organ confined, and N0/Nx UTUC, or patients who did not receive adjuvant chemotherapy.

The present study is important for some reasons. Our study supports that searching and reporting concomitant CIS in RNU specimens maybe important. Moreover, the discrepancy in the prevalence of CIS might warrant a standardization of pathologic assessment. Finally, since patients with T2 or organ-confined UTUC and concomitant CIS are at increased risk of disease recurrence compared with patients without concomitant CIS, they should be considered for closer follow-up or inclusion into clinical trials of adjuvant therapy.

There are several limitations to our study. First and foremost are the limitations inherent in retrospective analyses. Although we have done multiple internal and external reviews of our consortium data set, we excluded from this analysis patients for whom we could not obtain complete information, which could possibly create selection bias. In addition, the population in this study underwent RNU by multiple surgeons; indication and extension of lymph node dissection were not standardized, and specimens were evaluated by multiple pathologists without standardization of the pathological protocol and central slide review. Finally, the study period spans more than 20 years, and the data in the present study may not represent current practice patterns. However, about 60% of the patients in the study were treated in the year 2000 or thereafter.

Concomitant CIS was present in 11% of our RNU specimens. The prevalence of concomitant carcinoma in situ increased with worsening pathologic features such advancing pathologic stage, presence of lymph node metastasis, and presence of lymphovascular invasion. Patients with concomitant CIS are at significantly higher risk of both disease recurrence and cancer-related death. Presence of concomitant CIS should be included in the reports of RNU specimens, and patients with concomitant CIS should be considered for closer follow-up and/or clinical trials of adjuvant therapy following RNU.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Genega EM, Porter CR (2002) Urothelial neoplasms of the kidney and ureter. An epidemiologic, pathologic, and clinical review. Am J Clin Pathol 117(Suppl):S36
2. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ (2009) Cancer statistics, 2009. CA Cancer J Clin 59(4):225–249
3. Cai G, Liu X, Wu B (2009) Treatment of upper urinary tract urothelial carcinoma. Surg Oncol (Epub ahead of print)
4. Raman JD, Ng CK, Scherr DS et al (2010) Impact of tumor location on prognosis for patients with upper tract urothelial carcinoma managed by radical nephroureterectomy. Eur Urol 57(6):1072–1079
5. Remzi M, Haitel A, Margulis V et al (2009) Tumour architecture is an independent predictor of outcomes after nephroureterectomy: a multi-institutional analysis of 1363 patients. BJU Int 103(3):307–311
6. Isbarn H, Jeldres C, Shariat SF et al (2009) Location of the primary tumor is not an independent predictor of cancer specific mortality in patients with upper urinary tract urothelial carcinoma. J Urol 182(5):2177–2181
7. Novara G, De Marco V, Gottardo F et al (2007) Independent predictors of cancer-specific survival in transitional cell carcinoma of the upper urinary tract: multi-institutional dataset from 3 European centers. Cancer 110(8):1715–1722
8. Bolenz C, Shariat SF, Fernandez MI et al (2009) Risk stratification of patients with nodal involvement in upper tract urothelial carcinoma: value of lymph-node density. BJU Int 103(3):302–306
9. Kikuchi E, Margulis V, Karakiewicz PI et al (2009) Lymphovascular invasion predicts clinical outcomes in patients with node-negative upper tract urothelial carcinoma. J Clin Oncol 27(4):612–618
10. Margulis V, Shariat SF, Matin SF et al (2009) Outcomes of radical nephroureterectomy: a series from the upper tract urothelial carcinoma collaboration. Cancer 115(6):1224–1233
11. Novara G, Matsumoto K, Kassouf W et al (2010) Prognostic role of lymphovascular invasion in patients with urothelial carcinoma of the upper urinary tract: an international validation study. Eur Urol 57(6):1064–1071
12. Roscigno M, Shariat SF, Margulis V et al (2009) Impact of lymph node dissection on cancer specific survival in patients with upper tract urothelial carcinoma treated with radical nephroureterectomy. J Urol 181:2482
13. Roscigno M, Shariat SF, Margulis V et al (2009) The extent of lymphadenectomy seems to be associated with better survival in patients with nonmetastatic upper-tract urothelial carcinoma: how many lymph nodes should be removed? Eur Urol 56(3):512–518
14. Zigeuner R, Shariat SF, Margulis V et al (2010) Tumour necrosis is an indicator of aggressive biology in patients with urothelial carcinoma of the upper urinary tract. Eur Urol 57(4):575–581
15. Roscigno M, Shariat SF, Freschi M et al (2009) Assessment of the minimum number of lymph nodes needed to detect lymph node invasion at radical nephroureterectomy in patients with upper tract urothelial cancer. Urology 74(5):1070–1074
16. Lughezzani G, Jeldres C, Isbarn H et al (2010) A critical appraisal of the value of lymph node dissection at nephroureterectomy for upper tract urothelial carcinoma. Urology 75(1):118–124
17. Sylvester RJ, van der Meijden AP, Oosterlinck W et al (2006) Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol 49(3):466–475
18. Shariat SF, Weizer AZ, Green A et al (2000) Prognostic value of P53 nuclear accumulation and histopathologic features in T1 transitional cell carcinoma of the urinary bladder. Urology 56(5):735–740
19. Shariat SF, Pahlavan S, Baseman AG et al (2001) E-cadherin expression predicts clinical outcome in carcinoma in situ of the urinary bladder. Urology 57(1):60–65

20. Shariat SF, Palapattu GS, Karakiewicz PI et al (2007) Concomitant carcinoma in situ is a feature of aggressive disease in patients with organ-confined tcc at radical cystectomy. Eur Urol 51(1):152–160
21. Shariat SF, Palapattu GS, Amiel GE et al (2006) Characteristics and outcomes of patients with carcinoma in situ only at radical cystectomy. Urology 68(3):538–542
22. Kojima Y, Tozawa K, Kawai N, Sasaki S, Hayashi Y, Kohri K (2006) Long-term outcome of upper urinary tract carcinoma in situ: effectiveness of nephroureterectomy versus bacillus Calmette-Guérin therapy. Int J Urol 13(4):340–344
23. Wheat JC, Weizer AZ, Stuart Wolf J et al (2010) Concomitant carcinoma in situ is a feature of aggressive disease in patients with organ confined urothelial carcinoma following radical nephroureterectomy. Urol Oncol (Epub ahead of print)
24. Greene FL, Page DL, Fleming ID et al (2002) American Joint Committee on Cancer (AJCC) staging manual, 6th edn. Springer, Philadelphia
25. Mostofi FK, Sobin LH, Torloni H (1973) Histological typing of urinary bladder tumours. World Health Organisation