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ORIGINAL ARTICLE – UROLOGIC ONCOLOGY

Risk of Cancer-specific Mortality following Recurrence After Radical Nephroureterectomy

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ABSTRACT

Purpose. To describe the natural history and identify predictors of cancer-specific survival in patients who experience disease recurrence after radical nephroureterectomy (RNU) for upper tract urothelial carcinoma (UTUC).

Methods. Of 2,494 UTUC patients treated with RNU without neoadjuvant chemotherapy, 597 patients experienced disease recurrence. A total of 148 patients (25 %) received adjuvant chemotherapy before disease recurrence. Multivariable Cox regression model addressed time to cancer-specific mortality after disease recurrence.

Results. The median time from RNU to disease recurrence was 12 months (interquartile range 5–22). A total of 491 (82 %) of 597 patients died from UTUC, and 8 patients (1.3 %) died from other causes. The median time from disease recurrence to death of UTUC was 10 months. Actuarial cancer-specific survival estimate at 12 months after disease recurrence was 35 %. On multivariable analysis that adjusted for the effects of standard clinicopathologic characteristics, higher tumor stages [hazard ratio (HR) pT3 vs. pT0–T1: 1.66, $p = 0.001$; HR pT4 vs. pT0–T1: 1.90, $p = 0.002$], absence of lymph node dissection (HR 1.28, $p = 0.041$), ureteral tumor location (HR 1.44, $p < 0.0005$) and a shorter interval from surgery to disease recurrence ($p < 0.0005$) were significantly associated with cancer-specific mortality. The adjusted 6-, 12- and 24-month postrecurrence cancer-specific mortality was 73, 60 and 57 %, respectively.

Conclusions. Approximately 80 % of patients who experience disease recurrence after RNU die within 2 years after recurrence. Patients with non-organ-confined stage, absence of lymph node dissection, ureteral tumor location and/or shorter time to disease recurrence died of their tumor more quickly than their counterparts. These factors should be considered in patient counseling and risk stratification for salvage treatment decision making.

Upper tract urothelial carcinoma (UTUC) is a rare and potentially lethal disease.[1] Radical nephroureterectomy (RNU) with excision of a bladder cuff is the standard of care for the treatment in patients with a normal contralateral kidney for high-grade and/or invasive tumors of the

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renal pelvicaliceal system and ureters, offering adequate local tumor control and long-term survival.[2,3] Although most post-RNU disease recurrences seem to occur within the first 2–3 years after surgery, disease recurrence can occur at any time after RNU.[2,4,5] The natural history of UTUC from RNU to disease recurrence has been intensively investigated.[2,5–9] However, to our knowledge, there is no study determining the outcomes and prognostic factors of patients who have experienced disease recurrence after RNU. Indeed, from clinical experience, the natural history of these patients is highly variable. Improved understanding of the natural history and clinical outcome prognosticators after disease recurrence could help in patient counseling and, more importantly, clinical trial design and interpretation.

We hypothesized that standard clinicopathological features could help predict outcomes in UTUC patients even after disease recurrence. Moreover, we hypothesized that a shorter time to disease recurrence after RNU would be associated with an unfavorable clinical course. Therefore, we set out to analyze the clinical outcomes of UTUC patients after RNU and to identify the risk factors for cancer-specific mortality in a large international multicenter cohort of patients who experienced disease recurrence after RNU for UTUC.

PATIENTS AND METHODS

Patient Selection

This was an institutional review board–approved study, with all participating sites providing the necessary data-sharing agreements before initiation. A total of 16 international centers 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. The database was closed for follow-up in 2009, and before final analysis, the database was frozen.

From 2494 patients who underwent RNU between 1987 and 2007 for UTUC, 597 (24 %) experienced disease recurrence within a median time of 12 months from surgery. Sixty-two patients (2.5 %) were excluded from analysis as a result of missing data. No patient received preoperative systemic chemotherapy or perioperative radiotherapy. Patients with a history of muscle-invasive urothelial carcinoma of the urinary bladder were excluded. RNU was performed according to the standard described elsewhere.[4] Hilar or regional lymphadenectomy was generally performed in patients with suspicious lymph nodes (LNs) on preoperative imaging or with suspicious intraoperative findings. The indication and extent of lymphadenectomy performed was at the discretion of individual surgeons. Tumor multifocality was defined as the synchronous presence of two or more pathologically confirmed tumors in any location (renal pelvicaliceal system or ureter).[10] Adjuvant chemotherapy was administered to 148 patients (25 %) at the clinicians' discretion on the basis of tumor stage and overall health status. Ninety-four percent of patients received cisplatin-based therapy, and 6 % received carboplatin-based systemic chemotherapy.

Pathologic Evaluation

All surgical specimens were processed according to standard pathologic procedures at each institution. Uropathologists who were blinded to clinical outcomes reexamined all specimens according to standardized criteria and confirmed urothelial carcinoma histology. Tumors were staged according to the 2010 American Joint Committee on Cancer–Union Internationale Contre le Cancer tumor, node, metastasis staging system.[11] Tumor grading was performed according to the 2004 World Health Organization/International Society of Urological Pathology consensus classification.[12] Histopathologic assessment included concomitant carcinoma-in-situ, tumor architecture (papillary or sessile based on the predominant feature of the index lesion), lymphovascular invasion (defined as the presence of tumor cells within an endothelium-lined space without underlying muscular walls) and tumor necrosis (defined as the presence of microscopic coagulative necrosis in more than 10 % of the tumor area).[5,8,9] Tumor location was defined as either renal pelvicaliceal or ureteral on the basis of the index cancer.[13]

Follow-up Regimen

Patients were generally followed 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, urinary cytology, chest radiography, cystoscopic evaluation of the urinary bladder and radiographic evaluation of the contralateral upper urinary tract. Elective bone scans, chest computerized tomography scans or magnetic resonance imaging were performed when clinically indicated at the physician's discretion.

Disease recurrence was defined as tumor relapse in the operative field, regional LNs, and/or distant metastasis. Occurrences of urothelial carcinoma in the bladder or contralateral upper tract were not considered as disease recurrence. Cause of death was determined by treating

physicians, by chart review corroborated by death certificates or by death certificates alone.[14] All patients who were coded as dead of cancer had previous disease recurrence. Perioperative mortality (i.e., any death within 30 days of surgery or before discharge) was censored at time of death for cancer-specific survival analyses.

Statistical Analysis

The aim of this analysis was to describe the relationship between risk of cancer-specific mortality after a disease recurrence and time from RNU to disease recurrence. To assess this relationship, we constructed a Cox proportional hazard regression model. The time to death from UTUC was calculated as months from disease recurrence to death. The Cox model included months from RNU to disease recurrence, age, gender, pathologic T stage, tumor architecture (sessile vs. papillary), lymphovascular invasion, nodal status, tumor necrosis, tumor location (pelvicaliceal system vs. ureter) and concomitant carcinoma-in-situ as covariates. Months from RNU to recurrence was added to the model with restricted cubic splines with knots at the tertiles to account for nonlinearity. The model was created using varying knot locations, and the location had little effect on the model results. Adjuvant chemotherapy was not included as a covariate in the Cox regression model because many patients experienced recurrence before 3 months after RNU and potentially did not have the opportunity to receive adjuvant chemotherapy. Additionally, adjuvant chemotherapy is not expected to improve survival after disease recurrence.

As a sensitivity analysis, we repeated our previous analysis including adjuvant therapy and omitting patients with less than 3 months of follow-up. Because of the very low number of patients who received non-cisplatin-based chemotherapy, all patients receiving adjuvant chemotherapy were analyzed as one group. Kaplan-Meier curves were constructed to illustrate cancer-specific survival after disease recurrence. All reported *p*-values are two-sided, and a *p*-value of 0.05 was considered to be statistically significant. All statistical analyses were performed by Stata 11.0 software (StataCorp, College Station, TX).

TABLE 1 Descriptive characteristics of 597 upper tract urothelial carcinoma patients treated with radical nephroureterectomy who experienced disease recurrence

Characteristic	Value
Age (years), median (IQR)	69 (63–76)
Gender	
Male	393 (66)
Female	204 (34)
Surgical approach	
Open	517 (87)
Laparoscopic	80 (13)
Pathologic stage	
pT0	1 (0.2)
pTa	28 (5)
pTis	6 (1)
pT1	60 (10)
pT2	110 (18)
pT3	304 (51)
pT4	88 (15)
Tumor architecture	
Papillary	322 (54)
Sessile	275 (46)
Concomitant carcinoma-in-situ	
Absent	412 (69)
Present	185 (31)
Tumor location	
Pelvicaliceal system	386 (65)
Ureter	211 (35)
Lymphovascular invasion	
Absent	340 (57)
Present	257 (43)
Tumor necrosis	
Absent	388 (65)
Present	209 (35)
Nodal status	
pN negative	127 (21)
pN positive	135 (23)
pNX	335 (56)
Time from surgery to recurrence (month), median (IQR)	12 (5, 22)

IQR interquartile range

RESULTS

Table 1 summarizes the clinicopathologic characteristics of the 597 UTUC patients with disease recurrence after RNU. Most patients showed features of biologically aggressive disease such as advanced tumor stage (66 %) and high-grade disease (100 %). All patients had negative surgical margins. Most patients who received a LN dissection had muscle-invasive or advanced UTUC ($n = 136$; 84 %). Of those patients with LN metastasis, 2 (1 %) had pT1, 12 (9 %) pT2, 74 (55 %) pT3 and 47 (35 %) pT4 UTUC, respectively. The median time from RNU to disease recurrence was 12 months (interquartile range 5–22), with a minimum of 1 month and maximum of nearly 10 years.

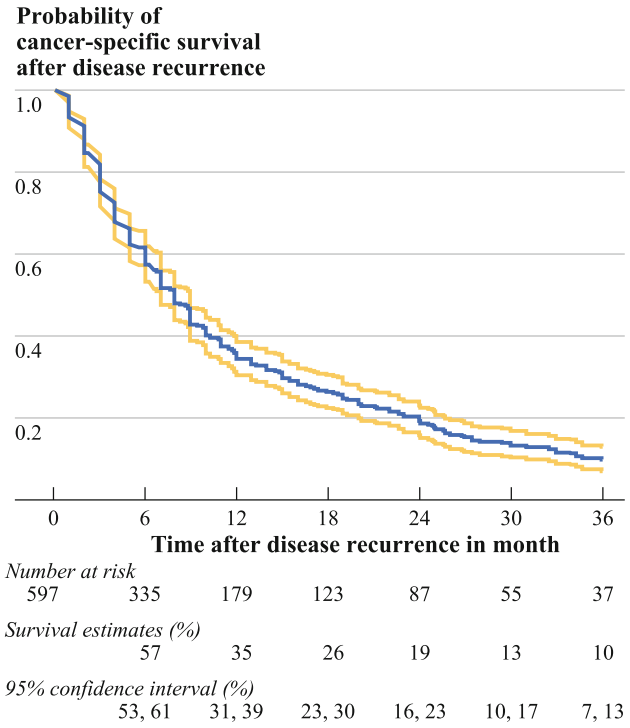


FIG. 1 Kaplan–Meier plot of cancer-specific survival estimates after disease recurrence in 597 UTUC patients treated with RNU. *Dashed lines* represent 95 % confidence intervals

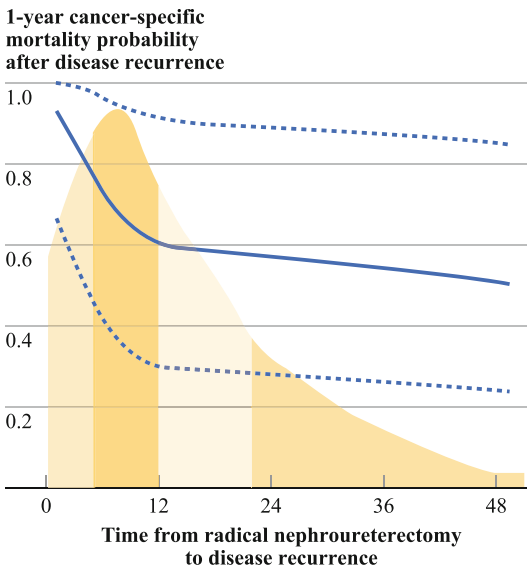
Overall, 491 of 597 patients with disease recurrence died from UTUC, and 8 patients died from other causes. The median time from disease recurrence to death was 10 months (interquartile range 3–20). Actuarial cancer-specific survival estimates at 6, 12 and 24 months after disease recurrence were 57 % (95 % confidence interval [CI] 53–61), 35 % (95 % CI 31–39) and 19 % (95 % CI 16–23), respectively (Fig. 1).

Figure 2 shows the risk of cancer-specific mortality within 1 year of disease recurrence by months from RNU to disease recurrence. The curve is adjusted to the average UTUC patient in our cohort: 69 year-old man with papillary tumor architecture in the pelvicaliceal system, no lymphovascular invasion, concomitant carcinoma-in-situ or tumor necrosis, without lymphadenectomy (pNx) performed and with pT3 tumor stage. The adjusted probability of cancer-specific mortality at 1 year after disease recurrence was 86, 73 and 60 %, if disease recurred within 3, 6 or 12 months of RNU, respectively. After 12 months of RNU, the risk of dying of UTUC continues to fall as time from RNU to disease recurrence increases; however, the decline in risk is less steep, compared to the sharp decline in risk between 0 and 12 months.

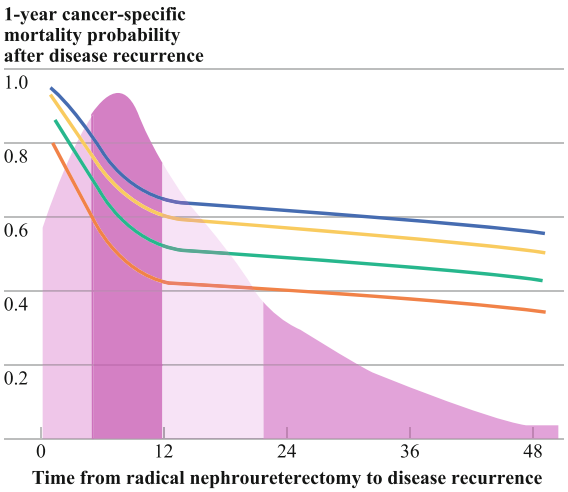
The estimated 6 month risk of cancer-specific mortality after disease recurrence stratified by pathologic stage and time from RNU to disease recurrence is shown in Fig. 3. The risk of death from UTUC was influenced adversely by increased pathologic stage and decreased time to disease recurrence: although an increase in the pathologic stage also increased the risk of cancer-specific mortality at any time, the increase in time from RNU to disease recurrence led to a linear decrease in the cancer-specific mortality risk at any stage. As before, the steepest decline in survival was seen in patients who experience disease recurrence within 12 months after RNU; the probability of survival remained relatively stable for patients who experienced disease recurrence after 12 months within each pathologic subgroup.

In the multivariable Cox regression analysis that adjusted for the effects of standard clinicopathologic characteristics, higher tumor stages [hazard ratio (HR) pT3 vs. pT0/Ta/Tis/T1: 1.66, $p = 0.001$; HR pT4 vs. pT0/Ta/

FIG. 2 Risk of cancer-specific mortality within 1 year after RNU according to the time to recurrence after RNU in months for a 69 year-old man with a pT3 tumor with a papillary tumor in the pelvicaliceal system, without lymphovascular invasion, concomitant carcinoma-in-situ or lymphadenectomy (pNx). *Dashed lines* represent 95 % confidence intervals. *Overlaid* is the density plot of months from RNU to disease recurrence with quantiles highlighted



Months from RNU to disease recurrence	1-year probability of cancer-specific mortality	95% confidence interval
3	0.86	0.56–0.99
6	0.73	0.41–0.96
9	0.64	0.33–0.93
12	0.60	0.30–0.91
15	0.59	0.29–0.90
18	0.58	0.29–0.89
21	0.58	0.29–0.89
24	0.57	0.28–0.89
27	0.57	0.28–0.88
30	0.56	0.27–0.88
33	0.55	0.27–0.87
36	0.54	0.26–0.87
39	0.54	0.25–0.86



Pathologic T-stage	Probability of cancer-specific mortality (95% CI) Time from RNU to disease recurrecne 6 months	12 months	18 months	24 months	30 months	36 months
pT0/Ta/Tis/T1	0.55 (0.30, 0.83)	0.42 (0.21, 0.72)	0.41 (0.20, 0.70)	0.40 (0.20, 0.69)	0.39 (0.19, 0.68)	0.38 (0.18, 0.67)
pT2	0.67 (0.36, 0.94)	0.52 (0.25, 0.85)	0.50 (0.24, 0.83)	0.49 (0.23, 0.82)	0.48 (0.23, 0.82)	0.47 (0.22, 0.80)
pT3	0.73 (0.41, 0.96)	0.60 (0.30, 0.91)	0.58 (0.29, 0.89)	0.57 (0.28, 0.89)	0.56 (0.27, 0.88)	0.54 (0.26, 0.87)
pT4	0.78 (0.44, 0.98)	0.65 (0.32, 0.94)	0.63 (0.31, 0.93)	0.62 (0.30, 0.93)	0.61 (0.30, 0.92)	0.60 (0.29, 0.92)

FIG. 3 Stage-dependent estimates of the risk of cancer-specific mortality after disease recurrence in 597 patients treated with RNU for UTUC. The *black line* represents patients with pathologic stages pT0–1, *red line* pT2, *orange line* pT3 and *blue line* pT4 disease at RNU

Tis/T1: 1.90, $p = 0.002$], absence of LN dissection (HR 1.28, $p = 0.041$), absence of concomitant carcinoma-in-situ (HR 0.79, $p = 0.025$), ureteral tumor location (HR 1.44, $p < 0.0005$) and a reduced time from surgery to disease recurrence ($p < 0.0005$) were significantly associated with cancer-specific mortality (Table 2).

In the sensitivity analysis including adjuvant chemotherapy and excluding patients with less than 3 months of follow-up (97 died from disease and 9 were censored), adjuvant chemotherapy was not significantly associated with cancer-specific mortality after disease recurrence (HR 0.80; 95 % CI 0.63–1.03; $p = 0.086$). Additionally, including adjuvant chemotherapy did not change the HRs of the other covariates in the model, suggesting adjuvant chemotherapy is not a confounding factor in this analysis.

DISCUSSION

UTUC patients who experience disease recurrence after RNU with curative intent have very poor outcomes. Most of these patients died from UTUC within 1 year after disease recurrence, and only few patients (19 %) survived beyond 2 years after disease recurrence. This underscores the lethal nature of UTUC once the disease recurs and becomes systemic.[2,4,5] However, the fact that 10 % of patients are still alive at 3 years after disease recurrence demonstrates the highly variable natural history of UTUC. Accurate prediction of clinical outcomes after disease recurrence could help in patient counseling and clinical trial design and analysis. However, to our knowledge, no study has analyzed risk factors for outcomes in UTUC patients who experience disease recurrence after RNU.

Shorter time from RNU to disease recurrence is associated with poorer survival after disease recurrence. Interestingly, it seems that the time to death after disease recurrence becomes longer as time to recurrence extends beyond the first 12 months. After 12 months, the time to death is still associated with the time to disease recurrence, but rate of decrease in survival becomes minimal. This change in proportionality between time to recurrence and rate of mortality was present within each pathologic stage, i.e., the shorter the time to disease recurrence the greater the mortality, the change in rate becomes less significant after the first 12 months after RNU. Our findings are similar to those of Mitra et al.[15] who reported that a time to disease recurrence <12 months is associated with unfavorable outcomes in patients with urothelial carcinoma of the bladder. These findings intuitively seem reasonable, as a shorter time from RNU to disease recurrence probably reflects more biologically aggressive disease. Previously, Margulis et al.[2] also reported that median time from RNU to disease recurrence was less than 12 months in a large cohort of 1,363 UTUC patients. However, the prognostic value of time to disease recurrence on UTUC outcomes was not assessed.

TABLE 2 Multivariable Cox proportional hazard regression model predicting cancer-specific mortality in 597 patients treated with radical nephroureterectomy for upper tract urothelial carcinoma

Characteristic	HR	95 % CI	*p*
Time from surgery to disease recurrence (month)	NA[a]	NA[a]	<0.0005
Sessile tumor architecture	0.96	0.78–1.17	0.7
Lymphovascular invasion	1.16	0.96–1.41	0.13
Age (per 10 years)	1.09	0.96–1.19	0.073
Nodal status			
pN negative	–	–	Ref.
pN positive	1.19	0.892–1.60	0.2
pNx	1.28	1.01–1.63	0.041
Pathologic T stage			
pT0/Ta/Tis/T1	–	–	Ref.
pT2	1.33	0.96–1.84	0.091
pT3	1.66	1.23–2.25	0.001
pT4	1.90	1.27–2.84	0.002
Male gender	1.08	0.89–1.31	0.4
Tumor necrosis	1.06	0.87–1.30	0.5
Tumor location			
Pelvicaliceal system	–	–	Ref.
Ureter	1.44	1.18–1.75	<0.0005
Concomitant carcinoma-in-situ	0.79	0.65–0.971	0.025

HR hazard ratio, *CI* confidence interval, *Ref.* reference

[a] Hazard ratio and confidence interval not provided because of nonlinear modeling. See Fig. 2 for relationship between time to disease recurrence and risk of death from upper tract urothelial carcinoma after disease recurrence

We found that non-organ-confined pathologic stage, absence of lymphadenectomy and ureteral tumor location were also significant predictors of cancer-specific mortality on multivariable analysis. These factors should be taken into consideration for patient counseling and risk stratification after disease recurrence, particularly because outcomes are variable and some patients might benefit from additional treatments with different grades of associated morbidity. Pathologic stage is an established predictor for outcomes prognostication after RNU.[2,5,6,16,17] However, there is still controversy regarding the value of tumor location and lymphadenectomy in UTUC.[18–21] Various large recent studies have reported that retroperitoneal lymphadenectomy can improve disease staging and potentially have therapeutic benefit in patients with advanced UTUC.[20,22–24] In our study, absence of lymphadenectomy (56 % of the study cohort) was a predictor for poorer cancer-specific mortality. This finding might be explained by a potentially beneficial effect of systemic adjuvant chemotherapy in LN-positive patients.[25,26] Moreover, the Will-Rogers phenomenon might have influenced this result; patients without LN dissection who experienced disease recurrence may have harbored LN metastasis at time of surgery. On the basis of the cumulative data from the literature, it seems that lymphadenectomy could offer a more accurate staging and also may remove (micro-)metastasis thereby resulting into improved outcomes.[20,24] However, we did not control for the LN count or for the anatomical template of lymphadenectomy, both of which might have influenced our results.[20,27] Only a prospective study with standardized criteria and a clearly defined template may shed more light on the value of LN dissection. In addition, a prospective study is needed to better elucidate the differences in outcomes between patients with renal pelvis tumors and ureteral tumors.[13,28] In accordance with several single- and multicenter studies that analyzed the impact of tumor location on outcomes after RNU, ureteral tumor location was associated with cancer-specific mortality after disease recurrence in our study.[28–30] A possible explanation for this finding may be a reduced barrier effect of the ureter compared to the renal parenchyma in advanced tumors.

Our study has some limitations. First and foremost are limitations inherent to the multicenter and retrospective design including a lack of data regarding prior treatments, delay between diagnosis and surgery, patient preferences, and comorbidities.[31] We also could not adjust for the number of surgeons at each institution as well as surgeons' preferences, experience, or surgical techniques. However, all surgeons operated at tertiary care centers with experience in UTUC. Another limitation includes possible interobserver variability between pathologists; a central pathology review was not performed. Bajorin et al.[32] have demonstrated that patients' performance status, as well as number and location of metastases impact survival in patients with metastatic urothelial carcinoma of the bladder. It is likely that these factors also might have influence outcomes in UTUC, but, unfortunately, these data were not available, and our analyses therefore remained unadjusted for them. Differences in the indication for and protocols of adjuvant chemotherapy as well as number of administered cycles were not controlled for in our study. However, the role of adjuvant chemotherapy is undetermined in UTUC because large retrospective studies have shown no (or only limited) survival benefit in patients with UTUC.[33] Data on salvage therapies after disease recurrence were missing and therefore remained unadjusted for in this study. Finally, we did not adjust analyses for local or distant disease recurrence which might influence outcomes.[32] Therefore, our results need to be validated in a robust prospective cohort. Moreover, our findings emphasize the urgent need for new biomarkers allowing a better tumor characterization and therefore improved outcomes prognostication and prediction of response to therapy.[34,35]

Most patients die of UTUC once their disease recurs after RNU. Time from RNU to disease recurrence is an important predictor for cancer-specific mortality, particularly if disease recurrence occurs within the first 12 months after RNU. In addition, non-organ-confined pathologic stage, failure to perform a LN dissection and ureteral tumor location are strongly associated with cancer-specific mortality after recurrence. These factors should be considered in patient counseling, as well as design and analysis of salvage chemotherapy protocols/clinical trials. In addition, our findings further support the notion that every patient treated with RNU for high-risk UTUC should undergo a lymphadenectomy for a more accurate staging.

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