Original Article

Outcomes of Radical Nephroureterectomy: A Series From the Upper Tract Urothelial Carcinoma Collaboration

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BACKGROUND: The literature on upper tract urothelial carcinoma (UTUC) has been limited to small, single center studies. A large series of patients treated with radical nephroureterectomy for UTUC were studied, and variables associated with poor prognosis were identified. **METHODS:** Data on 1363 patients treated with radical nephroureterectomy at 12 academic centers were collected. All pathologic slides were re-reviewed by genitourinary pathologists according to strict criteria. **RESULTS:** Pathologic review revealed renal pelvis location (64%), necrosis (21.6%), lymphovascular invasion (LVI) (24.8%), concomitant carcinoma in situ (28.7%), and high-grade disease (63.7%). A total of 590 patients (43.3%) underwent concurrent, lymphadenectomy and 135 (9.9%) were lymph node (LN) -positive. Over a mean follow-up of 51 months, 379 (28%) patients experienced disease recurrence outside of the bladder and 313 (23%) died of UTUC. The 5-year recurrence-free and cancer-specific survival probabilities (±SD) were 69% ± 1% and 73% ± 1%, respectively. On multivariate analysis, high tumor grade (hazards ratio [HR]: 2.0, $P < .001$), advancing pathologic T stage (P-for-trend <.001), LN metastases (HR: 1.8, $P < .001$), infiltrative growth pattern (HR: 1.5, $P < .001$), and LVI (HR: 1.2, $P = .041$) were associated with disease recurrence. Similarly, patient age (HR: 1.1, $P = .001$), high tumor grade (HR: 1.7, $P = .001$), increasing pathologic T stage (P-for-trend <.001), LN metastases (HR: 1.7, $P < .001$), sessile architecture (HR: 1.5, $P = .002$), and LVI (HR: 1.4, $P = .02$) were independently associated with cancer-specific survival. **CONCLUSIONS:** Radical nephroureterectomy provided durable local control and cancer-specific survival in patients with localized UTUC. Pathologic tumor grade, T stage, LN status, tumor architecture, and LVI were important prognostic variables associated with

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oncologic outcomes, which could potentially be used to select patients for adjuvant systemic therapy. **Cancer 2009;115:1224–33. © 2009 American Cancer Society.**

KEY WORDS: transitional cell carcinoma, urothelial carcinoma, radical nephroureterectomy, prognostic factors.

Upper urinary tract urothelial carcinoma (UTUC) arises from the urothelial lining of the urinary tract from the renal calyces to the ureteral orifice. With the incidence increasing over the past 2 decades, UTUC currently comprises 10% of all renal tumors and 5% of urothelial malignancies overall.[1,2] Although select patients with small, low-grade lesions may be candidates for endoscopic tumor ablation, radical nephroureterectomy (RNU) with excision of an ipsilateral bladder cuff, and retroperitoneal LN dissection is the gold-standard therapy for upper-tract cancers. To date, several contemporary, single-center series of patients treated with RNU for UTUC have been published.[3-7] While, these reports have contributed greatly to the current knowledge of the natural history and the prognostic factors important in UTUC, conclusions have been limited by small patient numbers and inhomogeneity of the study populations, as related to diagnosis, patient selection, staging, pathologic evaluation, and treatment. Nonetheless, these series have uniformly established that a significant proportion of UTUC patients eventually die of their disease due to unrecognized systemic metastases present at the time of surgery, underscoring the importance of thoughtful integration of adjuvant or neoadjuvant therapy strategies for patients at high risk of disease relapse.

Whereas tumor stage and histologic grade are well established prognostic factors of outcome after RNU, the oncologic significance of other potentially relevant variables, such as tumor site, architecture, histologic tumor necrosis, lymphovascular invasion (LVI), and the presence of concomitant carcinoma-in situ (CIS), among others, has not been clearly established.[4,8-15] Recognizing these limitations, we developed a comprehensive database incorporating the clinical and pathologic characteristics and outcomes of over 1300 patients treated with RNU for UTUC at 12 academic centers. Using this large international patient cohort, strict accrual criteria, and pathologic re-review of all slides, we sought to more clearly define the natural history, patterns of failure, and the impact of potential prognostic factors on relapse and survival after surgical management of UTUC.

MATERIALS AND METHODS

Patients

This was an institutional review board-approved study, with all participating sites providing the necessary institutional data use agreements before initiation of the study. A total of 12 centers worldwide provided data from their institutional databases for analysis. A computerized databank was generated for data transfer (UT M.D. Anderson Cancer Center, Houston, Tex). Multiple internal and external data reviews, and quality.

Assessments were performed to ensure the accuracy and completeness of data elements. The study comprised 1363 patients who underwent RNU with curative intent between 1992 and 2006. The indication for RNU was the presence of upper urinary tract transitional cell carcinoma, in the absence of systemic metastatic disease, deemed not appropriate or amenable to conservative treatment.

Treatment

Of 1363 patients, 1050 (77%) underwent open and 313 (23%) laparoscopic RNU, while 590 patients (43%) underwent concomitant lymphadenectomy. Operative note was used to determine whether LN dissection was performed. Of patients treated with open RNU, 491 (46.8%) underwent concomitant LN dissection, compared with 99 (31.6%) of patients treated with laparoscopic RNU ($P < .001$). The standardization of surgical technique and indications for lymphadenectomy was impossible due to the multicenter and retrospective design of the present study. Overall, the extent of LN dissection varied widely and was largely determined by surgeon preference. In general, para-aortic, paracaval, or interaortocaval lymph nodes from the hilus to the inferior mesenteric artery were removed in the case of renal pelvis and proximal ureteral tumors. For the mid- and lower ureteral tumors, LNs from the renal hilus to the bifurcation of the common iliac artery and ipsilateral pelvic LNs were removed, respectively. All patients underwent complete resection of distal ureter with a bladder cuff.

Neoadjuvant and/or adjuvant chemotherapy was administered to 3% and 13% of patients, respectively. Patients were chosen for neoadjuvant and adjuvant therapy at the discretion of the treating or referring physician, based on evidence of advanced disease by clinical or pathological staging, respectively. Systemic therapy regimens consisted of methotrexate, vinblastine, doxorubicin, and cisplatin in 34% of patients; methotrexate, cisplatin, and vinblastine in 29%; gemcitabine and cisplatin in 20%; and other platinum-based in 17%. Postoperative external beam radiotherapy was administered to 2% of the study cohort.

Pathologic Evaluation

All surgical specimens were processed according to standard pathologic procedures, and all slides were re-reviewed by genitourinary pathologists according to prospectively defined uniform criteria. All pathologists were blinded to clinical outcomes. Tumors were staged according to the American Joint Committee on Cancer — Union International Contre le Cancer (AJCC-UICC) Tumor-Node-Metastasis (TNM) classification.[16] Tumor grading was assessed according to the 1998 WHO/ISUP (International Society of Urologic Pathology) consensus classification.[17] In addition, all specimens were evaluated for tumor location, pattern of tumor growth (papillary vs sessile), presence of LVI, tumor necrosis, and concomitant CIS. Tumor growth pattern was assessed as previously described by Jimenez et al.[18] LVI was defined as the unequivocal presence of tumor cells in an endothelium lined space. With regard to tumor necrosis, cutoff was chosen at 10%, according to previously published data.[10]

Surveillance Regimen

Follow-up was performed according to institutional protocols. Patients were generally followed every 3 months to 4 months for the first year following 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 scans, chest computerized tomography (CT), or magnetic resonance imaging were performed when clinically indicated.

Cause of death was determined by the treating physicians, by chart review corroborated by death certificates, or by death certificates alone. Perioperative mortality (any death within 30 days of surgery or before discharge) was censored at time of death for urothelial disease-specific survival analyses.

Statistical Analysis

Disease recurrence was defined as local failure in the tumor bed, regional LNs, or distant metastasis. Bladder recurrences were not separately considered in the analysis of recurrence-free survival rate.

Univariate recurrence and survival probabilities after RNU were estimated using the Kaplan-Meier method. Univariate and multivariate Cox regression models addressed time to recurrence and cancer-specific mortality after RNU. In all models proportional hazards assumptions were systematically verified, using the Grambsch-Therneau residual-based test.[19] All reported P values are 2-sided and significance was set at $\leq .05$. All statistical tests were performed with SPSS version 13.0 (SPSS Inc., Chicago, Ill) and S-Plus Professional (MathSoft Inc., Seattle, Wash).

RESULTS

Patient Characteristics and Pathologic Staging

The median follow-up for 1363 patients treated with RNU was 37.2 months (range, 1.2 months to 250 months). Table 1 lists clinical and pathologic patient characteristics. For 1227 (90%) patients with Nx/N0 LN stage, the stage distribution was 22% Ta, 2% Tis, 24% T1, 19% T2, 30% T3, and 3% T4; and 61% had high grade UTUC. No pathologic evidence of malignancy was found in 9 patients (<1%), including 5 who received neoadjuvant chemotherapy.

In 590 patients who underwent regional LN dissection as an adjunct to RNU, the median number of LNs removed was 2.0 (range 0 to 41). Of these patients, 135 (10%) had metastasis to regional LNs. In patients with LN involvement, the median number of positive LNs was

Table 1. Clinical and Pathologic Characteristics of 1363 Patients Who Underwent Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma

Clinical Patient Characteristics	
Median age (y) ±SD	69.7±11.1
Sex (%)	
Women	442 (32.4)
Men	921 (67.6)
ECOG performance status (%)	
0	762 (66.8)
1	307 (26.9)
≥2	71 (6.3)
Previous bladder urothelial carcinoma diagnosis (%)	332 (24.4)
Previous upper tract endoscopic therapy (%)	192 (14.1)
Neoadjuvant systemic chemotherapy (%)	47 (3.4)
Adjuvant systemic chemotherapy (%)	170 (12.5)
Adjuvant external beam radiation (%)	22 (1.6)
Pathologic Tumor Characteristics	
pT stage (%)	
T0	9 (0.7)
Ta	264 (19.4)
Tis	28 (2.1)
T1	299 (21.9)
T2	252 (18.5)
T3	443 (32.5)
T4	68 (4.9)
pN stage (%)	
Unknown	773 (56.7)
Negative	455 (33.4)
Positive	135 (9.9)
Grade (%)	
Low	495 (36.3)
High	868 (63.7)
Concomitant carcinoma in situ (%)	391 (28.7)
Index tumor location (%)	
Renal pelvis	878 (64.4)
Ureter	463 (34.0)
Ureter-enteric anastomosis	22 (1.6)
Tumor growth architecture (%)	
Papillary	983 (72.1)
Sessile	380 (27.9)
Lymphovascular invasion (%)	338 (24.8)
Tumor necrosis (%)	294 (21.6)

2 (range 1 to 21) and the median LN density was 50% (range 30% to 100%). LN positivity increased incrementally with advancing pathological stage — <1% for T0/Ta/Tis, 2% for T1, 8% for T2, 17% for T3 and 46% for T4 ($P < .001$). High grade tumors were more likely to have positive LN (15% high grade vs 2% low grade, $P < .001$). Other factors associated with positive LN included LVI (29% present vs 4% absent, $P < .001$), architecture (31% sessile vs 6% papillary, $P < .001$), necrosis (26% present vs 6% absent, $P < .001$), concomitant CIS (15% present versus 8% absent, $P = .001$), but there was no association with tumor location ($P = .096$).

Neoadjuvant and adjuvant systemic therapy was administered to 13 (10%) and 59 (43%) LN-positive patients.

Recurrence-free and Cancer-specific Survival

Disease recurred in 379 (28%) patients at a median of 10.4 months (range 1 month to 143 months) after RNU (Fig. 1). Isolated local recurrences were observed in 41 (3%) of patients. A total of 510 (37%) patients died during the study follow-up, and 313 (61%) deaths were attributed to UTUC (Fig. 1). Median time to all cause and cancer-specific mortality was 24.0 months (range 1 to 227) and 18.5 months (range 1 month to 151 months), respectively.

Figures 2 through 6 demonstrate Kaplan-Meier estimates of recurrence-free survival and cancer-specific survival, stratified by pathologic stage, grade, LN status, LVI, and tumor architecture (all log rank $P < .001$), respectively. Multivariate Cox regression analysis demonstrated that pathological tumor stage, LN metastasis, LVI, and growth pattern were significantly associated with recurrence-free survival and cancer-specific survival (Tables 2 and 3).

DISCUSSION

This large multi-institutional series of patients with long-term follow-up after RNU supports the role of radical surgery for patients with organ confined UTUC. Despite the finding that majority of patients in this study had invasive, high grade UTUC, RNU afforded 5-year recurrence-free survival of 69% and 5-year cancer-specific survival of 73%. Remarkably, isolated local recurrence after RNU occurred in 3% of study patients, further supporting the role of radical surgery for these patients. Patients treated with RNU for noninvasive (<pT1) UTUC had 5-year recurrence-free and cancer-specific survival rates of 95% and 96%, respectively, a benchmark that other therapies, such as endoscopic tumor ablation, must be compared with in the absence of randomized trials. Oncologic

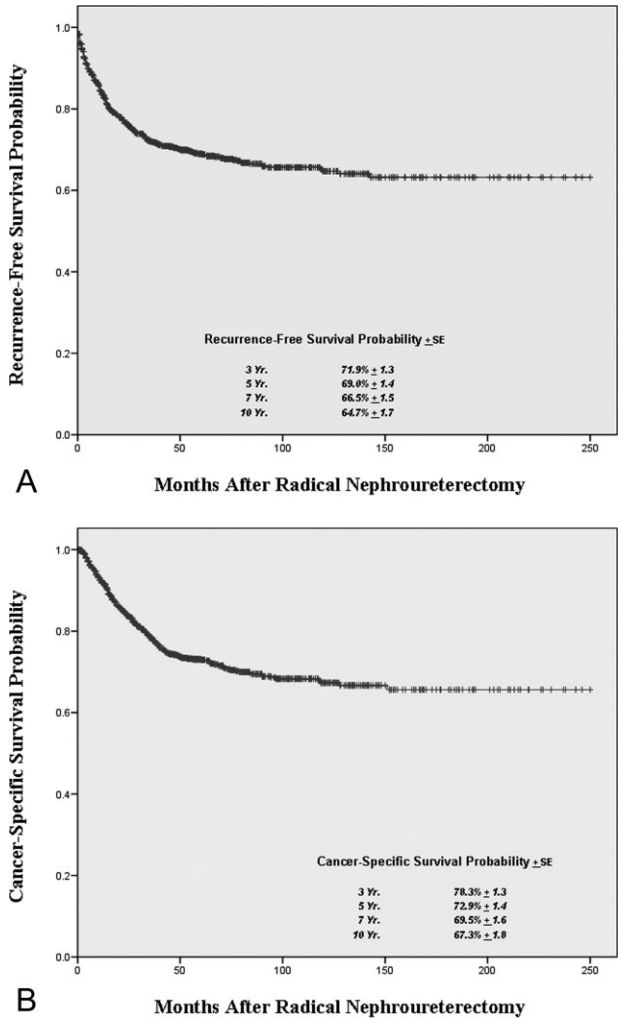

FIGURE 1. Kaplan-Meier estimates for (A) recurrence-free survival and (B) cancer-specific survival in 1363 patients treated with radical nephroureterectomy for upper tract urothelial carcinoma.

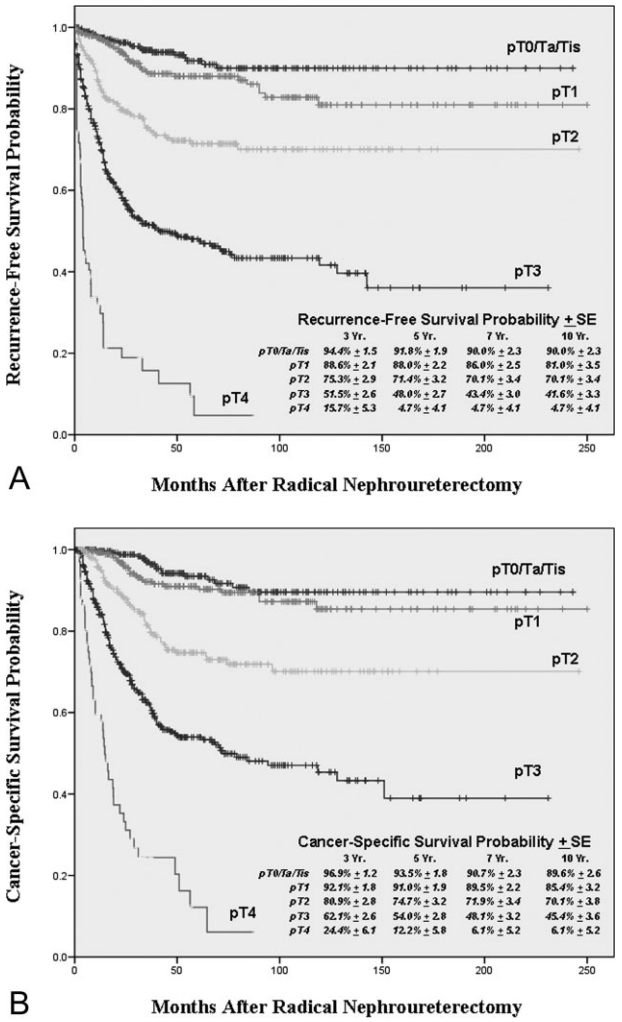

FIGURE 2. Kaplan-Meier estimates for (A) recurrence-free survival and (B) cancer-specific survival in 1363 patients treated with radical nephroureterectomy for upper tract urothelial carcinoma stratified by pathologic T stage.

outcomes reported herein are within the range reported in other studies, with 3 single-center series of >200 patients published to date, reporting 61%-76% 5-year cancer-specific survival after RNU.[3,4,6]

Despite adequate local tumor control afforded by RNU, a significant percentage of patients experience systemic disease progression after surgery. At a median follow-up of 37 months, 28% of patients experienced disease recurrence and 23% had died of UTUC. Herein we have strived to identify factors that predict for such adverse outcomes. Unique aspects of this study, such as strict entry criteria, pathologic re-review of all tissue slides, and large patient numbers enabled us to reliably identify prognostic variables associated with disease recurrence and cancer-specific mortality. We found that pathologic tumor stage, grade, tumor architecture, presence of LVI, and LN status, were all independently associated with probability of tumor recurrence and risk of death from UTUC. This information is critical for appropriate patient counseling, implementation of appropriate postoperative surveillance regimens, patient selection for adjuvant systemic therapy, and clinical trial design.

In contrast, prior studies have applied the 2-tiered urothelial carcinoma grading system to UTUC, and none have demonstrated tumor grade to be an independent predictor of oncologic outcome.[4,20,21] Unlike previous

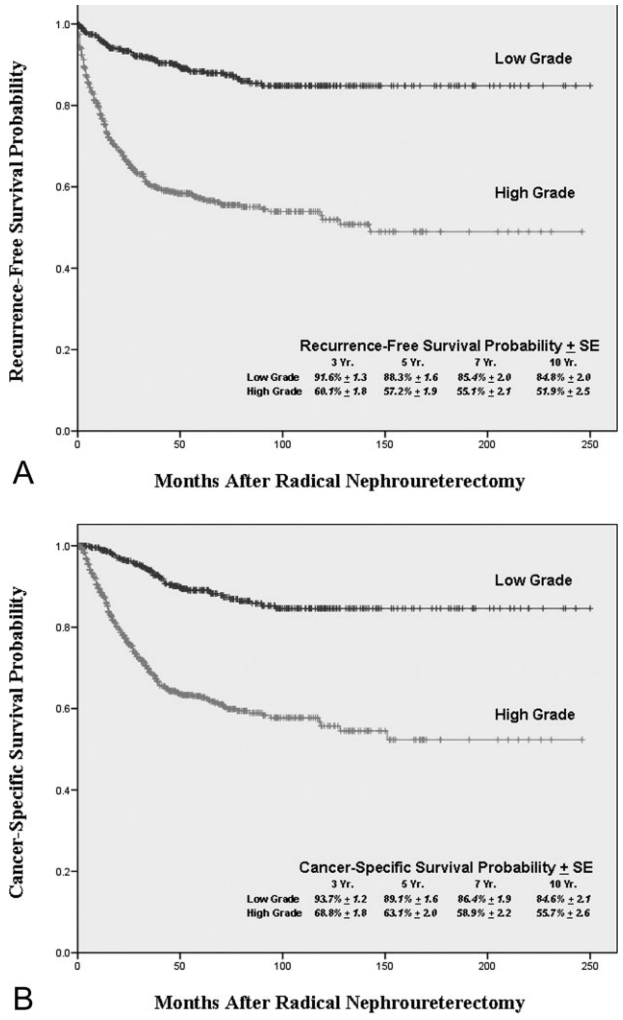

FIGURE 3. Kaplan-Meier estimates for (A) recurrence-free survival and (B) cancer-specific survival in 1363 patients treated with radical nephroureterectomy for upper tract urothelial carcinoma stratified by 1998 WHO grade classification.

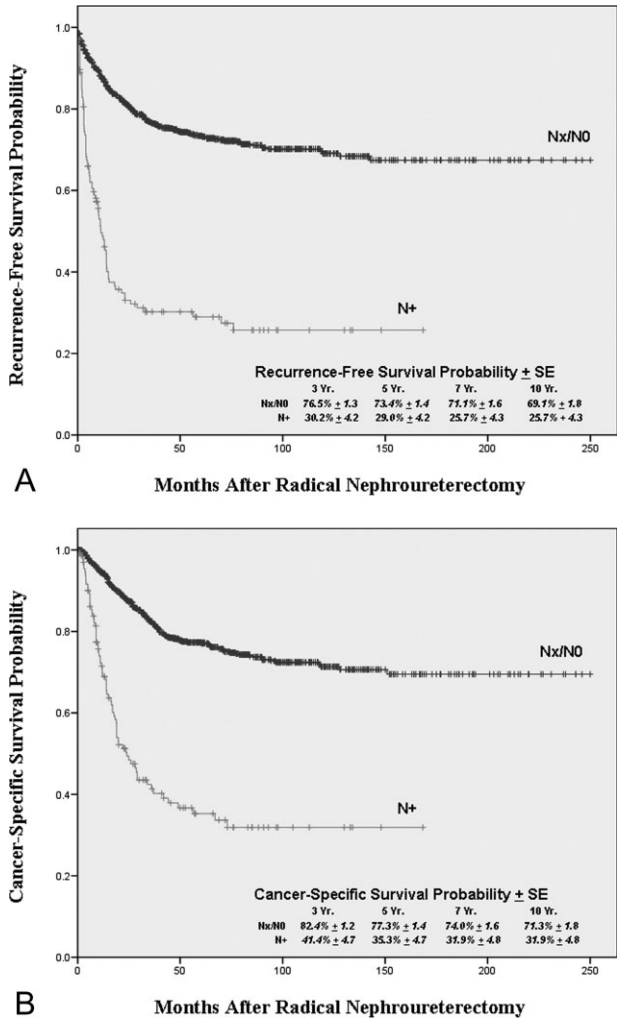

FIGURE 4. Kaplan-Meier estimates for (A) recurrence-free survival and (B) cancer-specific survival in 1363 patients treated with radical nephroureterectomy for upper tract urothelial carcinoma stratified by lymph node status.

reports, however, we provide compelling data that the new 2-tiered tumor grading system is a powerful independent predictor of recurrence and death from UTUC.

Largely depending on the stage of the primary tumor, 20-40 % of patients with UTUC are historically found to harbor LN metastases.[3,6,22] Similarly, positive LNs were seen in 23% of patients who underwent LN dissection in our series, underscoring the virulent capabilities of UTUC. Despite LN involvement, 35% of these patients were alive at 5 years and 32% were alive at 10 years after RNU, emphasizing that lymphadenectomy can be curative in a substantial subset of these patients. Whereas neoadjuvant or adjuvant therapy may have affected survival in this group of patients, the impact of systemic therapy in this setting is difficult to assess due to regimen variability, selections bias, as well as varying surgical templates used.

The role of LVI as a prognostic factor for progression and survival after RNU is controversial. Although several studies have identified LVI as a poor prognostic feature, only a few have controlled for possible confounding factors by using multivariate analyses.[4,8,12,23,24] In agreement with several single-center reports, our multiinstitutional study revealed that 25% of patients undergoing RNU for UTUC had histologically identifiable LVI. As previously reported in several cystectomy and

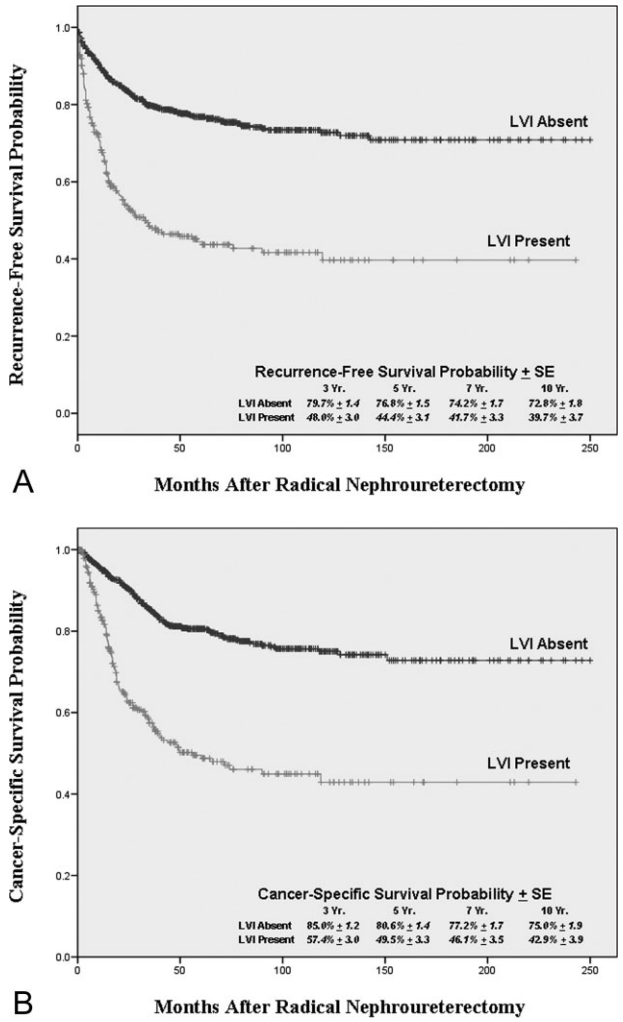

FIGURE 5. Kaplan-Meier estimates for (A) recurrence-free survival and (B) cancer-specific survival in 1363 patients treated with radical nephroureterectomy for upper tract urothelial carcinoma stratified by lymphovascular invasion (LVI).

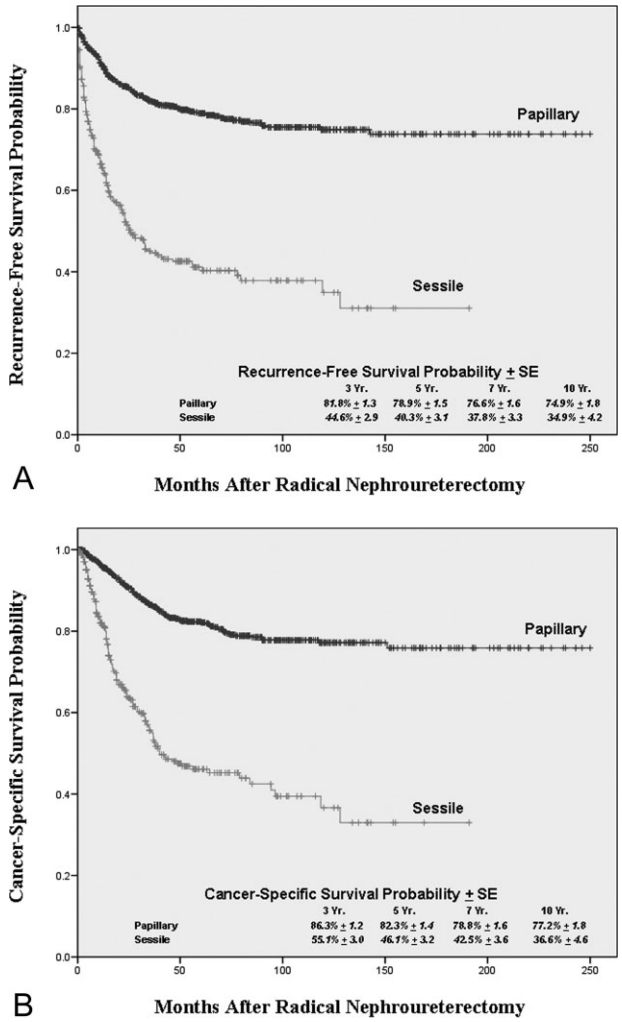

FIGURE 6. Kaplan-Meier estimates for (A) recurrence-free survival and (B) cancer-specific survival in 1363 patients treated with radical nephroureterectomy for upper tract urothelial carcinoma stratified by tumor architecture.

RNU series, LVI was associated with advanced stage, grade, and LN status.[4,8,9,12,23-26] Importantly, we found that LVI was also an independent predictor of relapse and death from UTUC.

Several investigators have reported that the tumor growth pattern, as defined by Jimenez at al is an independent predictor of oncologic outcome in patients treated with radical cystectomy for urothelial carcinoma of the urinary bladder.[18,27] Recently, Langner and colleagues have demonstrated that the infiltrative pattern was significantly associated with the development of metastatic disease and proved to be an independent prognostic marker of survival after RNU.[11] Approximately 28% of patients in our series demonstrated sessile tumor growth pattern, and this feature was independently associated with risk of tumor recurrence and cancer-specific survival, further affirming that tumor architecture is a reliable prognostic factor for patients with UTUC. We found that, at 5 years after RNU, 21% of patients with papillary growth pattern recurred and 18% died of UTUC, compared with 60% and 54% of patients whose tumors were sessile.

Several limitations of this study merit discussion. First and foremost are the limitations inherent to retrospective analysis. Although multiple internal and external reviews of the data set were performed, we excluded from

Table 2. Univariate and Multivariate Cox Regression Analyses for Prediction of Disease Recurrence After Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma

	Univariate			Multivariate		
	HR	95% CI	*P*	Risk Ratio	95% CI	*P*
Age	1.011	1.002-1.021	.023	1.009	0.999-1.018	.075
Sex	1.210	0.981-1.493	.074			
ECOG performance status	1.236	0.964-1.586	.095			
Previous bladder urothelial carcinoma	1.037	0.823-1.308	.756			
pT stage						
T0/Ta/Tis	1.000	Ref.		1.000	Ref.	
T1	1.720	0.990-2.988	.054	1.389	0.794-2.430	.250
T2	4.095	2.473-6.779	<.001	2.712	1.611-4.565	<.001
T3	9.907	6.257-15.687	<.001	5.059	3.077-8.318	<.001
T4	35.046	20.854-58.895	<.001	11.763	6.553-21.114	<.001
Trend			<.001			<.001
Nodal metastases	6.384	4.290-9.501	<.001	1.808	1.379-2.372	<.001
Grade	4.594	3.440-6.135	<.001	1.958	1.418-2.705	<.001
Concomitant carcinoma in situ	1.400	1.132-1.732	.002	0.898	0.717-1.123	.346
Location	0.428	0.245-0.748	.003	0.564	0.346-0.759	.568
Lymphovascular invasion	3.109	2.535-3.814	<.001	1.281	1.010-1.626	.041
Architecture	3.946	3.218-4.839	<.001	1.535	1.208-1.950	<.001
Necrosis	2.197	1.770-2.726	<.001	0.927	0.730-1.177	.532

HR indicates hazards ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group.

Table 3. Univariate and Multivariate Cox Regression Analyses for Prediction of Cancer-Specific Mortality After Radical Nephroureterectomy for Upper Tract Urothelial Carcinoma

	Univariate			Multivariate		
	HR	95% CI	*P*	Risk Ratio	95% CI	*P*
Age, y	1.019	1.008-1.030	.001	1.019	1.008-1.030	.001
Sex	1.199	0.948-1.504	.131			
ECOG performance status	1.306	0.997-1.710	.052			
Previous bladder urothelial carcinoma	1.158	0.902-1.485	.250			
Previous endoscopic treatment	0.811	0.568-1.158	.249			
pT stage						
T0/Ta/Tis	1.000	Ref.		1.000	Ref.	
T1	1.506	0.813-2.789	.193	1.263	0.677-2.356	.462
T2	4.116	2.386-7.099	<.001	2.811	1.599-4.943	<.001
T3	9.698	5.887-15.975	<.001	5.168	3.003-8.895	<.001
T4	33.381	19.034-58.543	<.001	11.040	5.794-21.035	<.001
Trend			<.001			<.001
Lymph node metastases	5.724	3.757-8.720	<.001	1.713	1.271-2.308	<.001
Grade	4.181	3.086-5.664	<.001	1.745	1.239-2.459	.001
Concomitant carcinoma in situ	1.316	1.039-1.667	.023	0.832	0.648-1.068	.148
Location	0.882	0.694-1.122	.306	0.564	0.346-0.759	.568
Lymphovascular invasion	3.109	2.535-3.814	<.001	1.370	1.050-1.787	.020
Architecture	4.876	3.223-5.630	<.001	1.532	1.174-2.000	.002
Necrosis	2.321	1.835-2.937	<.001	0.964	0.742-1.251	.780

HR indicates hazards ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group.

this analysis patients whose pathologic slides were not available for re-review and those without complete clinical information, thus introducing a possible selection bias. Similarly, we excluded patients in whom a clear source of systemic failure was not ascertainable, such as UTUC patients who went on to develop invasive urothelial carcinoma of the urinary bladder. The limited number of patients with UTUC, however, precludes organization of meaningful randomized prospective trials in this patient population. Consequently a retrospective study design, in

which rigorous clinical and pathologic review of patient data is implemented, provides a useful avenue to study patterns of failure and evaluate potential prognostic factors.

Our patient population underwent RNU by multiple surgeons, likely representing a significant case selection bias and variability of surgical techniques, especially pertaining to intraoperative management of retroperitoneal LNs. It should be noted that in our study, surgery was performed primarily by urologic oncologists at leading academic centers, and pathologists at these respective institutions evaluate a high volume of urologic cancers. While centralized pathologic review may have been preferable, results of this multi-institutional collaboration likely reflect real-world practice patterns.

CONCLUSION

Real progress in the treatment of UTUC is faced with several challenges. Most notably the rarity of this disease precludes significant advances by a single institutional experience. A collaborative effort among institutions using uniform diagnostic and treatment protocols could accelerate treatment advances, particularly for high risk patients who succumb to the disease. We hope that this initial retrospective report will serve to foster future multi-institutional collaborations and help overcome these obstacles.

Conflict of Interest Disclosures

The authors made no disclosures.

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