



# Prognostic Importance of Lymphovascular Invasion in Urothelial Carcinoma of the Renal Pelvis

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**BACKGROUND:** The current study was conducted to assess the impact of lymphovascular invasion on the survival of patients with urothelial carcinoma of the renal pelvis. **METHODS:** Patients with urothelial carcinoma of the renal pelvis who underwent radical nephroureterectomy from 2010 through 2015 were identified in the National Cancer Data Base. Patients were characterized according to demographic and clinical factors, including pathologic tumor stage and lymphovascular invasion. Associations with overall survival were assessed through proportional hazards regression analysis. **RESULTS:** A total of 4177 patients were identified; 1576 had lymphovascular invasion. Patients with T3 disease and lymphovascular invasion had 5-year survival that was significantly worse than that of patients with T3 disease without lymphovascular invasion (34.7% vs 52.6;  $P < .001$  by the log-rank test), and approached that of patients with T4 disease without lymphovascular invasion (34.7% vs 26.5%;  $P = .002$ ). On multivariate analysis controlling for age, comorbidities, grade, lymph node status, surgical margin status, race, sex, and chemotherapy administration, patients with T3 disease and lymphovascular invasion also were found to have significantly worse survival compared with patients with T3 disease without lymphovascular invasion (hazard ratio, 1.7; 95% confidence interval, 1.4-1.91). **CONCLUSIONS:** Lymphovascular invasion status is a key prognostic marker that can stratify the risk of patients with pT3 upper tract urothelial carcinoma further. Patients with this pathologic feature should be carefully considered for clinical trials exploring existing and novel therapies. *Cancer* 2018;124:2507-14. © 2018 American Cancer Society.

**KEYWORDS:** lymphovascular invasion, upper tract urothelial carcinoma, cancer staging, prognosis, survival.

## INTRODUCTION

The incidence of upper tract urothelial cancer (UTUC) has increased over recent decades, with 1.88 cases per 100,000 person-years reported in 2005.<sup>1</sup> The American Joint Committee on Cancer (AJCC) seventh edition staging system classifies UTUC into categories of worsening prognosis.<sup>2</sup> Staging is based on the TNM system, with lymph node-negative and metastasis-negative T1, T2, and T3 tumors assigned stages I, II, and III, respectively; T4 tumors and cases with positive lymph nodes or metastases are assigned stage IV.

The AJCC system was constructed from available evidence that T classification is highly prognostic of survival outcomes after surgical intervention.<sup>3,4</sup> To our knowledge, due to low disease incidence, evidence to guide staging and prognostication historically has been limited to small retrospective series. However, recent multi-institutional data-sharing collaborations have published results reaffirming the centrality of T classification to prognosis with greater statistical power.<sup>5-7</sup>

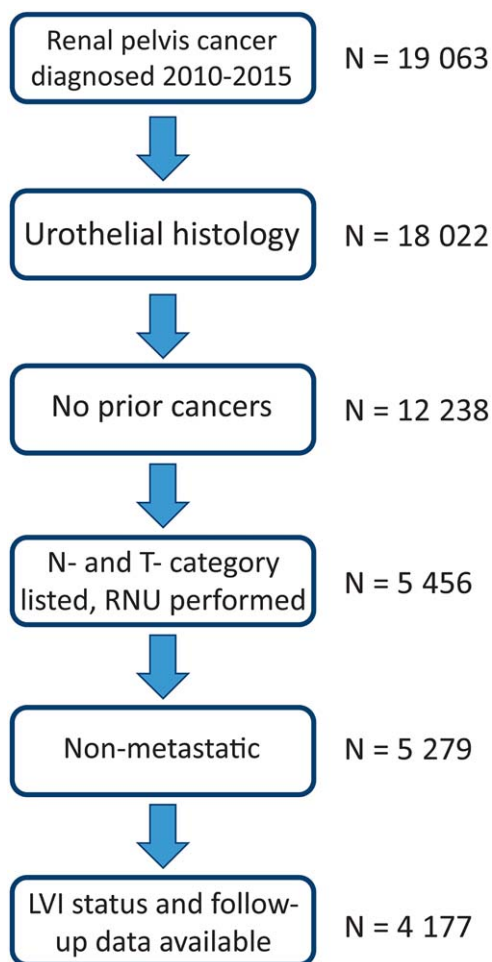
Interest also recently has emerged in lymphovascular invasion (LVI) as a prognostic modulator in patients with UTUC. Several studies have found LVI to be an important predictor of survival outcomes, but again, to our knowledge these largely have been confined to small retrospective series.<sup>8,9</sup> Since 2010, the National Cancer Data Base (NCDB) has collected data regarding LVI status for all newly diagnosed solid tumors, including renal pelvis cancer. Currently, data are available for cases diagnosed through 2015. The broad nature of the data collected by the NCDB provides an excellent opportunity to reassess the influence of LVI in UTUC and potentially affirm findings from previous studies.

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**Figure 1.** Selection criteria. LVI indicates lymphovascular invasion; RNU, radical nephroureterectomy.

The objective of the current study was to determine the impact of LVI on survival in patients with UTUC of the renal pelvis, and to determine whether LVI status might usefully inform the UTUC staging system by improving the prognostic usefulness of T classification.

## MATERIALS AND METHODS

The NCDB is a collaborative clinical registry between the American College of Surgeons' Commission on Cancer and the American Cancer Society. Approximately 70% of incident cancer cases in the United States from >1500 facilities are included.<sup>10</sup>

The database was queried for patients aged  $\geq 18$  years who were diagnosed with renal pelvic cancer from January 1, 2010 to December 31, 2015. Only patients who had undergone radical nephroureterectomy (RNU) were included, both because this is the standard treatment of UTUC of the renal pelvis and because patients

undergoing other treatment modalities lacked data regarding pathologic staging and LVI status in high percentage. Patients with nonurothelial histology or rare urothelial variant histology were excluded; the final cohort had *International Classification of Diseases for Oncology, 3rd Edition* (ICD-O-3) codes 8120 or 8130. Patients also were excluded due to: 1) prior malignancies; 2) known metastatic disease; 3) unknown pathologic T or N classification; 4) unknown LVI status; or 5) missing date elements needed to calculate follow-up or survival. The selection process is summarized in Figure 1.

## Statistical Analysis

Descriptive statistics were calculated. The Charlson-Deyo Comorbidity Scores were grouped into categories of 0, 1, or  $\geq 2$ . A proportional hazards model was used to calculate 2-year, 3-year, 4-year, and 5-year overall survival (OS), stratified by pathologic T classification and LVI status. Pathologic T classification was used because clinical T classification was unavailable for a large percentage of patients, and because of the significant upstaging that occurs when clinical and pathologic T classifications are compared.<sup>5,11</sup> Patients listed as having N classification N0 or Nx were both considered to be without known lymph node-positive disease. Age-adjusted survival analysis then was performed using proportional hazards regression and represented graphically in Kaplan-Meier plots. Only patients with lymph node-negative disease were included in both age-adjusted and age-unadjusted univariate survival analyses. Survival differences between T classification and LVI groups were assessed using log-rank comparisons in unadjusted analyses.

Multivariate proportional hazards survival analysis then was performed, adjusting for demographic and clinical covariates. Pathologic T classification and LVI status were combined into a single composite category. Patients with both N0 and N+ disease were included in the multivariate proportional hazards regression model; our intention was to demonstrate that LVI is an important predictor of survival independent of lymph node status, and is not merely a surrogate marker for lymph node positivity. Hazard ratios (HRs) were recalculated using different T classification and LVI combinations as reference groups. The model was repeated with subsequent primary malignancies as a covariate (the number, site, and other pathologic and clinical details of subsequent malignancies were unavailable). Finally, a separate model was created including T classification and LVI status as separate variables rather than a single composite variable. This allowed for the inclusion of an interaction term between LVI

status and lymph node positivity to further assess the effect of LVI on survival independent of its relationship to lymph node status.

All *P* values were the result of 2-sided tests and *P* values < .05 were considered to be statistically significant. Statistics were performed with SAS statistical software (version 9.4; SAS Institute Inc, Cary, North Carolina).

## RESULTS

A total of 4177 patients in 963 different facilities met selection criteria. Of these, 1576 patients (38%) were LVI positive. Baseline demographics are summarized in Table 1. A total of 522 patients (12%) had known lymph node-positive disease with a pathologic N classification of N1 to N3. A total of 372 patients (9%) had positive surgical margins. Chemotherapy, of any intent, was administered during the treatment course of 959 patients (23.0%). Subsequent primary malignancies were noted in 14% of patients, including 13% of patients with a pathologic T classification of T3 (15% of patients with pT3 LVI-negative [LVI-] disease, and 12% of patients with pT3 LVI-positive [LVI+] disease). Among patients alive at the time of last contact, the median follow-up was 922 days (interquartile range, 513-1488 days). The median follow-up for the entire cohort was 723 days (23.7 months).

During follow-up, 1529 patients (37%) died of any cause; 2648 were alive at the time of last contact. Unadjusted OS for the 3655 patients without known lymph node-positive disease is shown in Table 2. The 95% confidence intervals (95% CIs) for OS overlapped for the T1 LVI+ and T2 LVI- groups, for the T2 LVI+ and T3 LVI- groups, and for the T3 LVI+ and T4 LVI- groups. The 95% CIs did not overlap for the T3 LVI- and T3 LVI+ groups. The OS rates were recalculated in an age-adjusted fashion. These are shown in Supporting Table S1. Age adjustment did not appear to alter the calculated survival rates substantially and did not affect which groups did or did not have overlapping CIs.

Among patients with pT3 disease without known lymph node-positive disease, 8% had positive surgical margins, including 3% of patients with pT3 LVI- disease and 10% of patients with pT3 LVI+ disease. The 4-year OS for patients with pT3 LVI- disease was 62.3 months (95% CI, 58.5-66.4 months) for patients without positive surgical margins and 40.1 months (95% CI, 23.5-68.3 months) for patients with positive surgical margins. The 4-year OS for patients with pT3 LVI+ disease was 43.6 months (95% CI, 39.1-48.7 months) for those without positive margins and 12.5 months (95% CI, 5.9-26.8 months) for patients with positive surgical margins.

**TABLE 1.** Clinical and Pathologic Characteristics (N=4177)

Parameter	No. of Patients	%
Y of diagnosis		
2010	681	16.3
2011	597	14.3
2012	690	16.5
2013	730	17.5
2014	815	19.5
2015	664	15.9
Age at diagnosis, y		
18-39	32	0.8
40-49	142	3.4
50-59	564	13.5
60-69	1108	26.5
70-79	1384	33.1
≥80	948	22.7
Race		
White (includes Hispanic)	3763	90.1
Black	215	5.1
Other/unknown	199	4.8
Sex		
Male	2379	56.95
Female	1796	43.0
Other	2	.05
Charlson-Deyo Comorbidity Score		
0	2854	68.3
1	956	22.9
≥2	367	8.8
WHO grade		
Low	451	10.8
High	3495	83.7
Unknown	231	5.5
Pathologic T classification		
1	1183	28.3
2	481	11.5
3	2076	49.7
4	437	10.5
Pathologic N classification		
No known lymph node-positive disease	3655	87.5
Known lymph node-positive disease	522	12.5
Lymphovascular invasion		
Present	1576	37.7
Absent	2601	62.3
Surgical margins		
Positive	372	8.9
Negative	3754	89.9
Unknown	51	1.2
Chemotherapy administration		
Yes	959	23.0
No	3077	73.7
Unknown	141	3.4
Status at time of last follow-up		
Dead	1529	36.6
Alive	2648	63.4

Abbreviation: WHO, World Health Organization.

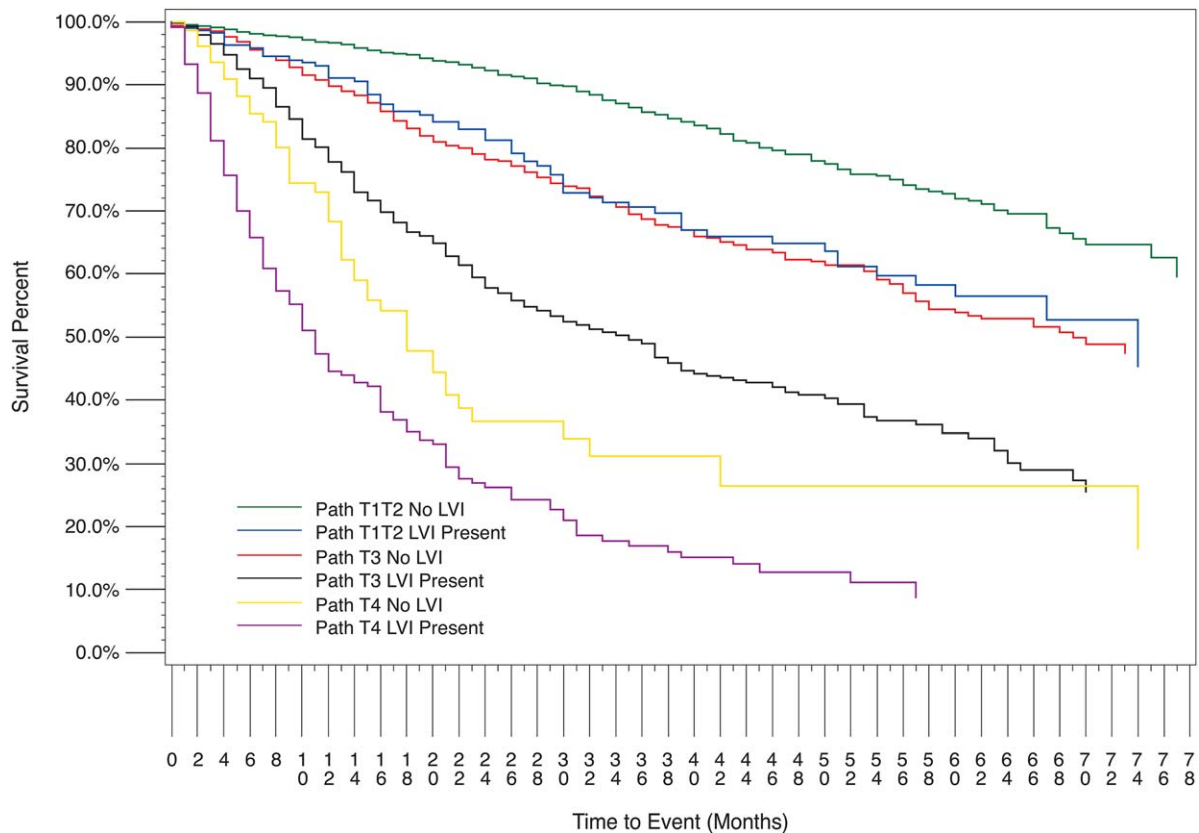
Among patients with pT3 LVI- disease, chemotherapy was administered to 4% of patients before surgery and 20% of patients after surgery. Among patients with pT3 LVI+ disease, chemotherapy was administered to 4% of patients before surgery and 33% of patients after surgery.

Age-adjusted proportional hazards survival for patients without known lymph node-positive disease,

**TABLE 2.** OS in Patients Without Known Lymph Node-Positive Disease (N=3655)

Cohort	Patients	2-Year OS, %	95% CI	3-Year OS, %	95% CI	4-Year OS, %	95% CI	5-Year OS, %	95% CI
T1 LVI-	1065	92.5	90.8-94.2	86.5	84.0-89.0	80.4	77.3-83.7	74.8	70.9-79.0
T1 LVI+	105	83.5	76.4-91.3	77.4	69.0-87.0	73.9	64.7-84.4	64.8	52.8-79.5
T2 LVI-	349	89.3	85.8-92.9	79.4	74.3-84.9	70.3	63.9-77.4	58.9	50.9-68.1
T2 LVI+	102	76.4	68.0-85.9	59.9	49.7-72.1	52.2	41.5-65.7	44.4	33.1-59.6
T3 LVI-	989	76.9	74.1-79.8	67.4	64.1-70.9	60.9	57.2-64.9	52.6	48.2-57.4
T3 LVI+	768	56.7	53.1-60.6	48.3	44.4-52.5	40.7	36.5-45.3	34.7	30.1-40.0
T4 LVI-	72	35.4	25.2-49.7	30.5	20.5-45.4	26.5	16.3-43.0	26.5	16.3-43.0
T4 LVI+	205	25.5	19.9-32.7	16.6	11.7-23.5	12.6	8.0-19.7	9.1	4.8-17.3

Abbreviations: -, negative; +, positive; 95% CI, 95% confidence interval; LVI, lymphovascular invasion; OS, overall survival. Pathologic T classification was used.



**Figure 2.** Kaplan-Meier analysis of age-adjusted overall survival for patients without known lymph node-positive disease (N = 3655). The number at risk for each group was as follows: T1/T2 lymphovascular invasion (LVI) negative (-), 1414 patients; T1/T2 LVI positive (+), 207 patients; T3 LVI-, 989 patients; T3 LVI+, 768 patients; T4 LVI-, 72 patients; and T4 LVI+, 205 patients. Path indicates pathologic.

stratified by pathologic T classification and LVI status, is shown in Figure 2. Log-rank unadjusted comparisons between selected pairs of groups without known lymph node-positive disease are as follows: T1T2 LVI + versus T1T2 LVI-:  $P \leq .0001$ ; T1T2 LVI + versus T3 LVI-:  $P = .6069$ ; T1T2 LVI + versus T3 LVI +,  $P < .0001$ ; T1/T2 LVI + versus T3 total (not shown),  $P < .0041$ ; T3 LVI + versus T3 LVI-,  $P < .0001$ ; T3 LVI + versus T4

LVI-,  $P = .0019$ ; T3 LVI + versus T4 LVI+,  $P < .0001$ ; and T3 LVI + versus T4 total,  $P < .0001$ .

The same graphical survival analysis was performed with patients with T1 and T2 disease separated (see Supporting Fig. S1). The T1 and T2 groups also were graphed separately for greater visual clarity (see Supporting Fig. S2). The following additional log-rank comparisons were performed to further elucidate the relative

**TABLE 3.** Effect of Pathologic T Classification and LVI on OS (N=4177)

Group	HR	95% CI	P
T1/T2 LVI-	Referent	Referent	
T1/T2 LVI+	1.8	1.4-2.3	<.001
T3 LVI-	2.1	1.8-2.5	<.001
T3 LVI+	3.7	3.1-4.3	<.001
T4 LVI-	5.3	4.0-7.1	<.001
T4 LVI+	7.1	5.8-8.7	<.001

Abbreviations: -, negative; +, positive; 95% CI, 95% confidence interval; HR, hazard ratio; LVI, lymphovascular invasion; OS, overall survival.

Multivariate competing risks regression analysis was adjusted for age, sex, race, Charlson-Deyo Comorbidity Score, World Health Organization grade, pathologic N classification, surgical margin status, and chemotherapy administration. Cofactors with statistically significant independent effects included older age (continuous) (HR, 1.03; 95% CI, 1.02-1.04), Charlson-Deyo Comorbidity Score  $\geq 2$  (HR, 1.5; 95% CI, 1.3-1.8), pathologic N + disease (HR, 1.5; 95% CI, 1.3-1.7), high grade (HR, 1.9; 95% CI, 1.5-2.4), unknown grade (HR, 2.0; 95% CI, 1.4-2.7), positive surgical margins (HR, 2.0; 95% CI, 1.8-2.4), unknown surgical margins (HR, 1.5; 95% CI, 1.0-2.2), and chemotherapy administration (HR, 0.8; 95% CI, 0.7-0.9).

impact of categories T1 and T2: T1 LVI + versus T1 LVI-,  $P = .0132$ ; T1 LVI + versus T2 LVI-,  $P = .9000$ ; T2 LVI + versus T2 LVI-,  $P = .0007$ ; and T2 LVI + versus T3 LVI-,  $P = .2229$ . Table 3 shows risk-adjusted HRs for the effect of LVI and pathologic T classification on OS, controlling for demographic and pathologic cofactors in a multivariate proportional hazards model. Substantially overlapping 95% CIs were observed for the T1/T2 LVI + and T3 LVI- groups, as well as for the T3 LVI + and T4 LVI- groups. The model also was calculated with subsequent primary malignancy included as a cofactor. Subsequent primary malignancy did not affect survival ( $P = .45$ ), and we opted to omit this variable from our primary reported model due to the lack of specific detail available as previously noted. The analysis also was repeated with patients with T1 and T2 disease considered separately (see Supporting Table S2). The 95% CIs for the T2 LVI + and T3 LVI- groups overlapped substantially, and the 95% CIs for the T1 LVI + and T3 LVI- groups overlapped as well.

When T3 LVI- was set as the statistical referent, a direct comparison of T3 LVI + versus T3 LVI- disease yielded an HR of 1.7 (95% CI, 1.5-2.0). Comparison of T1/T2 LVI + versus T3 LVI- disease yielded an HR of 0.9 (95% CI, 0.7-1.1). Finally, when T3 LVI + was set as the statistical referent, a direct comparison of T4 LVI- versus T3 LVI + disease yielded an HR of 1.4 (95% CI, 1.0-1.9).

An additional multivariate competing-risks survival model was created to assess the interaction between LVI and pathologic lymph node status. In this model, T classification and LVI were entered as independent variables,

**TABLE 4.** Effect of Interaction Between Pathologic N Classification and LVI on OS (N=4177)

	N0		N+	
	HR	95% CI	HR	95% CI
LVI	1.8	1.6-2.0	1.1	0.8-1.5
		LVI-		LVI+
	HR	95% CI	HR	95% CI
Lymph node positivity	2.2	1.6-2.9	1.3	1.1-1.6

Abbreviations: -, negative; +, positive; 95% CI, 95% confidence interval; HR, hazard ratio; LVI, lymphovascular invasion; OS, overall survival.

Multivariate competing risks regression analysis was adjusted for age, sex, race, Charlson-Deyo Comorbidity Score, World Health Organization grade, pathologic T classification, surgical margin status, and chemotherapy administration. Cofactors with statistically significant independent effects included older age (continuous) (HR, 1.03; 95% CI, 1.02-1.04), high grade (HR, 1.9; 95% CI, 1.5-2.4), unknown grade (HR, 2.0; 95% CI, 1.4-2.7), Charlson-Deyo Comorbidity Score  $\geq 2$  (HR, 1.5; 95% CI, 1.3-1.8), positive surgical margins (HR, 2.1; 95% CI, 1.8-2.4), and chemotherapy administration (HR, 0.8; 95% CI, 0.7-0.9).

rather than being combined into a composite variable as shown in Figure 2 and Tables 2 and 3. T classification, lymph node status, and LVI status all were independent predictors of survival ( $P < .001$  for each). The T3 classification versus the T1/T2 classification carried an HR of 2.1 (95% CI, 1.8-2.5). The T4 classification versus the T1/T2 classification carried an HR of 5.3 (95% CI, 4.0-7.1-5.4). The interaction between LVI and lymph node status was found to be statistically significant ( $P = .003$ ). Table 4 shows the calculated HRs.

## DISCUSSION

In the current study, LVI was found to be a key predictor of poor prognosis in patients with UTUC of the renal pelvis treated with RNU. Patients with pathologic (p) T3, LVI + tumors represented individuals with a particularly aggressive category of disease, with survival that was substantially worse than that of patients with pT3 LVI- disease and that approached that of patients with pT4 LVI-disease. Survival differences between the pT3 LVI- and pT3 LVI + groups were both clinically meaningful (with an 18% difference in the 5-year OS) and statistically robust owing to the large sample size.

There is a known interaction between LVI and lymph node positivity.<sup>12</sup> In our multivariate competing risks regression analysis, LVI maintained significance when controlling for lymph node status. In addition, the interaction term between LVI and lymph node status was statistically significant when added to the model, indicating synergism of risk beyond the additive effect of the 2 variables. Both findings suggest that LVI has an

independent impact on survival, distinct from its relationship with lymph node status. The data from the current study do suggest that the impact of LVI is substantially greater in patients without known lymph node-positive disease, which is consistent with prior evidence.<sup>9,12,13</sup> This finding is rational given the significance of LVI as an early step in tumor dissemination; it is logical that the impact of LVI would be diminished when overt lymph node spread is present.

We believe these data, particularly the strong effect of LVI within the pT3 category, have implications for pathologic staging. Although a reorganization of risk stratification schema to merge patients with pT3 LVI + with those with pT4 may be premature, a subcategorization of the AJCC pT3 category into 2 categories based on the presence of LVI may be reasonable. Although the current study data also suggest a role for LVI in substratifying other T classifications in addition to T3, the relatively small number of patients in the T1/T2 and T4 subgroups limited analytic power and limits the strength of the conclusions that can be drawn from the current study data. However, it is notable that patients with category pT1/T2, LVI + disease had significantly worse prognosis compared with their pT1/T2, LVI- counterparts. Furthermore, neither patients with pT1/T2 LVI + disease nor those with pT2 LVI + disease had survival that differed significantly from that of patients with pT3 LVI- tumors on proportional hazards survival analysis. The relatively smaller sample sizes in these subgroups preclude overly strong conclusions; for this reason, we grouped pT1 and pT2 together in the main analyses and included subanalyses with pT1 and pT2 separated in the Supporting material. Despite these caveats, the results are provocative, and further investigation into the clinical behavior of these subgroups is warranted, as is consideration of a role for LVI in the selection of patients for adjuvant systemic therapy.

LVI is known to be of prognostic significance in patients with urothelial cell carcinoma of the bladder.<sup>14</sup> In a multicenter review of 750 patients, LVI predicted local and distant recurrence, OS, and cause-specific survival after cystectomy.<sup>13</sup> In a 2013 meta-analysis of 21 studies, LVI was found to predict recurrence-free survival, OS, and cancer-specific survival after cystectomy.<sup>14</sup> This relationship is observed in nonurothelial cell solid organ tumors as well.<sup>15,16</sup>

Although prior studies have investigated the prognostic significance of LVI in patients with UTUC, the low incidence of UTUC has limited study quality; to our knowledge, the majority of analyses are small,

retrospective, single-center series. Thus, in 2009, the Upper Tract Urothelial Carcinoma Collaboration combined data from 8 countries to produce a cohort of 1453 patients undergoing RNU for UTUC.<sup>9</sup> LVI was found to be present in approximately 24% of patients and was associated with lower 5-year recurrence-free survival rate (77% vs 44%) and cancer-specific survival rate (79% vs 47%). Another multicenter study from 2010 combined data from 6 countries to produce a cohort of 762 different patients undergoing RNU for UTUC.<sup>12</sup> LVI was present in 19.4% of patients and was associated with lower 5-year recurrence-free survival rate (79.3% vs 45.1%) and cancer-specific survival rate (82.1% vs 45.8%). That group included LVI in a nomogram predicting disease recurrence and survival after RNU.<sup>17</sup> Other large collaborative studies and a nearly 5000-patient meta-analysis further supported the importance of LVI in predicting survival in patients with UTUC.<sup>6,18</sup>

These findings have led investigators to suggest using LVI status to risk stratify patients with UTUC after RNU. Godfrey et al found LVI to be predictive of worse survival in their cohort of 211 patients, and noted similar survival between patients with  $\leq$ T1 LVI + disease and patients with muscle-invasive LVI- disease.<sup>8</sup> The authors suggested consideration of including LVI in the TNM system for UTUC pending larger studies. Data from the current study, emanating from a broadly inclusive national database, further support substratification of the UTUC TNM system using LVI status.

Developments in pathologic staging and postoperative risk stratification in oncology have important implications for selecting patients for the receipt of adjuvant therapy or participation in clinical trials. In UTUC, there has been mixed evidence supporting adjuvant chemotherapy in patients with high-risk (stage III-IV) tumors.<sup>2,19-22</sup> However, when only cisplatin-based regimens are considered, disease-free survival and OS may be improved,<sup>23</sup> as observed in patients with urothelial carcinoma of the bladder.<sup>24</sup> The POUT trial, a randomized controlled trial of adjuvant chemotherapy versus surveillance after RNU for patients with UTUC, opened in 2012.<sup>25</sup> Historically, neoadjuvant therapies for UTUC have received greater emphasis than adjuvant therapies due to the limitation on cisplatin administration to patients with reduced renal function after RNU.<sup>26</sup> However, novel nonplatinum agents such as checkpoint inhibitors and immunotherapies currently being tested in patients with urothelial carcinoma of the upper urinary tract may expand our ability to deliver adjuvant treatment to high-risk patients.<sup>27-29</sup> This

would elevate the usefulness of enhanced risk stratification using variables such as LVI.

The strengths of the current study include its large sample size and generalizability, capturing a majority of incident cases of UTUC in the United States during the study period, including cases managed at community centers. It is interesting to note that many prior studies represent institutional cohorts from tertiary referral centers, with an inherent risk of selection bias. The prospective nature of the data collection, and the NCDB's rigorous and standardized methodology for data collection, ensure robust data quality and reduce the potential for measurement bias.

Limitations of the current study include its limited follow-up duration; however, prior studies have suggested that a large percentage of UTUC mortality occurs early in the disease course. Margulis et al found a median time to cancer-specific mortality of 18.5 months.<sup>5</sup> Underrepresentation of certain subgroups is discussed above. No centralized pathologic rereview to verify LVI status was performed; however, we contend that this reflects real-world practice. Incomplete availability of data regarding specific patient and pathologic factors resulted in a diminished cohort size and a less extensive set of covariates for analytical models, which ultimately included age, sex, race, Charlson-Deyo Comorbidity Score, World Health Organization grade, pathologic N classification, surgical margin status, and chemotherapy administration. Specific pathologic features contributing to pT classification, such as renal parenchyma invasion versus peripelvic fat involvement in patients with pT3 disease, were unavailable, as were data regarding tumor multifocality. Specifics of the location and nature of subsequent malignancies were unavailable, and we could not determine their clinical significance or whether they represented unrelated malignancies versus bladder or contralateral upper tract recurrences.

The cohort in the current study was in some ways unrepresentative of the US population, although not dissimilar from previously reported populations with UTUC; it was 90% white (including Hispanic) and nearly 23% of the patients included were aged  $\geq 80$  years. As noted, age adjustment did not meaningfully alter survival rates.

We also were limited in our ability to assess the impact of chemotherapy within this cohort for 2 reasons. The first is a low use rate of chemotherapy, which is reflective of real-world clinical practice.<sup>30</sup> The second is insufficient data capture, because the NCDB identifies the

timing of chemotherapy but lacks sufficient detail to accurately determine therapeutic intent.

A persistent difficulty in studying UTUC is the large percentage of patients with pNx disease due to low rates of lymphadenectomy during RNU (well below 50% in the United States and Europe).<sup>31-33</sup> We elected to categorize patients with pN0 and pNx disease as those without known lymph node-positive disease, in contrast to patients with pN1 to pN3 disease, who we identified as having lymph node-positive disease, because the alternative of excluding patients with pNx disease would artificially enrich the cohort for patients with lymph node-positive disease and distort the data.

### Conclusions

In the current study, LVI was able to risk stratify patients after RNU for UTUC of the renal pelvis and identify those at highest risk of death. Therefore, we believe LVI represents a key factor in the selection of optimal candidates for adjuvant treatment, clinical trials, or heightened surveillance. Although to the best of our knowledge the survival benefits of adjuvant chemotherapy for patients with UTUC are incompletely proven, many novel agents currently are in development, with demonstrated activity in the metastatic setting and potential effectiveness in the adjuvant setting as well.<sup>27-29</sup> In the future, a wide pool of effective and tolerable adjuvant therapy options will render a thorough understanding of each patient's risk profile more valuable. Pathologic features such as LVI may be important contributors to that risk stratification.

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### CONFLICT OF INTEREST DISCLOSURES

Walter Stadler has acted as a paid consultant for and received grants for research support to his institution from Astra-Zeneca, Bayer, Bristol-Myers Squibb, Genentech, and Pfizer; received grants for research support to his institution from Astellas (Medivation), Boehringer Ingelheim, Dendreon, Exelixis, Johnson & Johnson, Merck, Novartis, and X4Pharmaceuticals; has acted as a paid consultant for Caremark/CVS, Eisai, Nordic Biotech, and Sotio; and has acted as a paid member of the Speakers' Bureau for Applied Clinical Education, Dava Oncology, Global Academy for Medical Education, and Vindico for work performed outside of the current study. Cheryl T. Lee is an American Joint Committee on Cancer eighth edition genitourinary subcommittee member.

### AUTHOR CONTRIBUTIONS

**Matthew R. Danzig:** Conceptualization, methodology, writing—original draft, and editing. **Katherine Mallin:** Methodology, editing, data curation, formal analysis, and visualization. **James M.**

**McKiernan:** Conceptualization. **Walter M. Stadler:** Conceptualization, editing, and supervision. **Srikala S. Sridhar:** Conceptualization and editing. **Todd M. Morgan:** Methodology and editing. **Bernard H. Bochner:** Conceptualization and supervision. **Cheryl T. Lee:** Conceptualization, methodology, editing, project administration, and supervision.

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