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Urothelial Cancer

Prognostic Role of Lymphovascular Invasion in Patients with Urothelial Carcinoma of the Upper Urinary Tract: An International Validation Study

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Abstract

Background: Lymphovascular invasion (LVI) identified following pathologic slide review has been shown to be an independent predictor of recurrence-free survival (RFS) and cancer-specific survival (CSS) in a multicenter series of patients undergoing radical nephroureterectomy (RNU) for upper urinary tract urothelial carcinoma (UTUC). However, the validity of LVI in everyday practice, where pathologic re-review of all slides is uncommon, has not been assessed.
Objective: Our aim was to evaluate the prognostic role of LVI in an international cohort of patients treated with RNU for UTUC without pathologic slide review.
Design, setting, and participants: Data from 762 patients treated with RNU for UTUC without neoadjuvant chemotherapy were collected at nine centers located in Europe, Asia, and Canada.
Measurements: We evaluated patients' characteristics, RFS, and CSS.
Results and limitations: LVI was present in 148 patients (19.4%). At a median follow-up of 34 mo, 23.5% of the patients developed disease recurrence and 19.8% died of UTUC. The 5-yr RFS and CSS rates were 79.3% and 82.1%, respectively, in the absence of LVI compared with 45.1% and 45.8%, respectively, in the presence of LVI (p values <0.0001). On multivariable Cox regression analyses, LVI was an independent predictor of RFS (hazard ratio [HR]: 3.3; $p = 0.005$) and CSS (HR: 5.9; $p < 0.0001$). Similarly, among patients with pN0/Nx disease, LVI was an independent predictor of RFS (HR: 2.1; $p = 0.001$) and CSS (HR: 2.3; $p < 0.0001$).
Conclusions: In a large multicenter series of patients treated with RNU for UTUC and for which no pathologic slide review was performed, LVI was present in approximately 20% and was an independent predictor of both RFS and CSS. LVI status should always be included in the pathologic report of RNU specimens, and patients with LVI should be considered for adjuvant therapy studies.

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1. Introduction

Upper urinary tract urothelial carcinoma (UTUC) is rare, comprising 10% of all renal tumors and 5% of urothelial malignancies overall [1,2]. Although selected patients with small well-differentiated tumors may be amenable to a nephron-sparing surgery through endourologic approaches, radical nephroureterectomy (RNU) with bladder cuff resection and regional lymphadenectomy is the mainstay of treatment [3].

Despite efforts, little is known regarding the natural history and impact of prognostic variables in UTUC. Although the prognostic value of pathologic stage, lymph node metastasis, and tumor grade has been established [4–12], that of potential important features in clinical decision making, such as tumor architecture, tumor necrosis, and lymphovascular invasion (LVI), remains to be elucidated or validated [7–9,13–17]. Several small single-institution studies have suggested that LVI may be an important feature of biologically and clinically aggressive UTUC [18,19]. In a large multicenter study, the Upper Tract Urothelial Carcinoma Collaboration (UTUCC) reported that LVI is a powerful independent predictor of both disease recurrence and cancer-specific mortality in patients without lymph node metastasis [20]. Before a new biomarker such as LVI can be integrated into clinical decision making, it needs external confirmation in an independent data set. Moreover, in the UTUCC study, all pathologic slides were re-reviewed by genitourinary pathologists according to identical strict criteria. This may limit the relevance of the findings to everyday clinical practice in which nongenitourinary pathologists review slides and the criteria for LVI may vary among pathologists. Therefore, the aim of the current study was to externally validate the prognostic role of LVI in a second international cohort of patients treated with RNU for UTUC where pathologic slide review was not performed.

2. Patients and methods

This study was approved by an institutional review board with all participating sites providing the necessary institutional data-sharing agreements before initiation of the study. A total of nine academic centers worldwide provided data. A computerized 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. Following exclusion of patients who received neoadjuvant chemotherapy ($n = 12$) and patients in whom the presence of LVI was unknown ($n = 13$), the 762 remaining patients were the subjects of the present analysis.

Specifically, 27 patients (3.5%) were treated in Bolzano, Italy; 155 (20.3%) in Kitasato, Japan; 51 (6.7%) in Madrid, Spain; 89 (11.7%) in Montreal, Canada; 138 in Derby, United Kingdom; 58 (7.6%) in Munich, Germany; 98 (12.9%) in Padua, Italy; 85 (11.2%) in Regensburg, Germany; and 61 (8%) in Verona, Italy. None of these patients had been included in the study from Kikuchi et al [20].

Surgery was performed by several surgeons according to the standard criteria for RNU (ie, 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 (CT) scans or palpable intraoperatively. Extended lymphadenectomy was not routinely performed.

2.1. 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 (AJCC)/Union Internationale Contre le Cancer TNM classification [21]. Tumor grading was assessed according to the 1973 World Health Organization/International Society of Urologic Pathology consensus classification [22]. LVI was defined as the presence of tumor cells within an endothelium-lined space without underlying muscular walls. Immunohistochemistry for endothelial cells was not performed in keeping with the standard practice of pathologists. Any equivocal foci and foci in which tumor cells merely encroached on a vascular lumen were considered negative. No attempt was made to differentiate between vascular and lymphatic vessels because of the difficulty and lack of reproducibility when using routine light microscopic examination.

2.2. Follow-up regimen

Patients were generally observed every 3–4 mo for the first year after RNU, every 6 mo 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 CT, 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 the recurrence-free survival (RFS) rate. Cause of death was determined by the treating physicians, by chart review corroborated by death certificates, or by death certificates alone. Most patients who were identified as having died of UTUC had progressive, widely disseminated metastases at the time of death. Patients who died in the perioperative period (ie, death within 30 d of surgery) were censored at time of death for cancer-specific survival (CSS) analyses.

2.3. Statistical analysis

The Fisher exact test and the χ^2 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. All the Cox multivariable models included an interaction term, which consisted of LVI and pathologic N stage. The interaction term was meant to test the hypothesis that the magnitude of the effect of LVI on the RFS and CSS survival probabilities depends on N stage in a manner in which a simple additive effect might be inappropriate. Statistical significance in this study was set as $p \leq 0.05$. All reported p values are two-sided. Analyses were performed with SPSS v.16.0 (SPSS Inc, Chicago, IL, USA).

Table 1 – Association of lymphovascular invasion with clinical and pathologic characteristics of 762 patients treated with radical nephroureterectomy and bladder cuff excision for upper tract urothelial carcinoma

	Cases (%)	Lymphovascular invasion		
		Absent (%) (n = 614, 81%)	Present (%) (n = 148, 19%)	p value
Gender				0.489
Male	527 (69)	421 (80)	106 (20)	
Female	235 (31)	193 (82)	42 (18)	
Age, yr, median (interquartile range)	68 (61–75)	68 (61–74.4)	69.1 (63.5–76.5)	0.061
Year of surgery				0.858
1987–1989	40 (5)	31 (78)	9 (22)	
1990–1999	297 (39)	241 (81)	56 (19)	
2000–2008	425 (56)	342 (81)	83 (19)	
Tumor location*				0.046
Renal pelvis only	401 (53)	316 (79)	85 (21)	
Ureter only	232 (30)	201 (87)	31 (13)	
Both renal pelvis and ureter	48 (6)	38 (79)	10 (21)	
Pathologic stage				<0.001
pTa	159 (21)	156 (98)	3 (2)	
pTis	9 (1)	9 (100)	0	
pT1	195 (26)	177 (91)	18 (9)	
pT2	145 (19)	125 (86)	20 (14)	
pT3	211 (28)	133 (63)	78 (37)	
pT4	43 (5)	14 (33)	29 (67)	
Grade				<0.001
G1	97 (12.7)	90 (93)	7 (7)	
G2	223 (29.3)	208 (93)	15 (7)	
G3	442 (58)	316 (72)	126 (28)	
Number of removed lymph nodes (median and interquartile range)**	3 (2–6)	3 (2–6)	2 (2–7)	0.967
Concomitant CIS				0.08
Absent	677 (89)	552 (82)	125 (18)	
Present	85 (11)	62 (73)	23 (27)	
Lymph node stage				<0.001
N0	131 (17)	99 (76)	32 (24)	
Nx	582 (76)	490 (84)	92 (16)	
N1/2	49 (6)	25 (51)	24 (49)	

CIS = carcinoma in situ.
* Tumor location missing in 81 cases.
** Computed on 175 of the 180 patients for which lymphadenectomy was performed.

3. Results

3.1. Association of lymphovascular invasion with clinical and pathologic features

LVI was present in 148 of 762 patients (19.4%). Table 1 shows the association between LVI and clinical and pathologic features in this cohort. Prevalence of LVI increased with higher pathologic stage (2%, 9%, 14%, 37%, and 67%, for Ta, T1, T2, T3, and T4, respectively; $p < 0.001$) and was associated with higher tumor grade and lymph node metastasis (p values <0.001).

3.2. Association of lymphovascular invasion with clinical outcomes

The median follow-up of the whole cohort was 34 mo (interquartile range: 15–65 mo). At last follow-up, 179 patients (23.5%) had developed disease recurrence and 151 (19.8%) were dead of UTUC. Moreover, 99 patients (13%) experienced non–cancer-related deaths. The median follow-up for patients alive at last follow-up was 40 mo (interquartile range: 18–75 mo). The overall 2- and 5-yr RFS estimates were 79.3% (standard error [SE]: 1.6%) and 73.2% (SE: 1.8%), respectively. The overall 2- and 5-yr CSS estimates were 84.4% (SE: 1.4%) and 75.7% (SE: 1.9%), respectively.

LVI was significantly associated with an increased risk of disease recurrence and cancer-specific death (Tables 2 and 3, respectively). The 5-yr RFS and CSS rates were 79.3% (SE: 1.9%) and 82.1% (SE: 1.9%), respectively, in the absence of LVI compared with 45.1% (SE: 5.1%) and 45.8% (SE: 5.2%), respectively, in the presence of LVI (Fig. 1a and b, respectively; p values <0.0001).

On multivariable Cox regression analyses that included age, year of surgery, tumor location, stage, grade, presence of concomitant carcinoma in situ (CIS), and lymph node status, LVI was an independent predictor of both RFS (hazard ratio [HR]: 3.3, 95% confidence interval [CI], 1.4–7.7, $p = 0.005$) and CSS (HR: 5.9; 95% CI, 2.2–16.2, $p < 0.0001$). Notably, the interaction term describing the combined effect of LVI and lymph node stage on CSS ($p = 0.037$) was

Table 2 – Univariable and multivariable Cox regression analyses of lymphovascular invasion for prediction of disease recurrence in 762 patients treated with radical nephroureterectomy and ipsilateral bladder cuff excision for upper tract urothelial carcinoma (179 recurrences)

Parameter	Univariable analysis			Multivariable analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	1.02	1.004–1.03	0.02	1.01	0.993–1.03	0.237
Year of surgery			0.957			
1987–1989	1	Referent	–	1	Reference	0.025
1990–1999	0.9	0.5–1.8	0.943	0.7	0.39–1.44	0.386
2000–2008	1.0	0.54–1.9	0.942	0.4	0.24–0.95	0.036
Tumor location			0.017			0.015
Renal pelvis only	1	Referent	–	1	Reference	–
Ureter only	1.19	0.83–1.70	0.346	1.3	0.89–1.9	0.163
Both ureter and renal pelvis	2.15	1.27–3.65	0.004	2.2	1.27–3.77	0.005
Pathologic stage			<0.0001			<0.0001
pTa/Tis	1	Referent	–	1	Reference	–
pT1	1.3	0.7–2.7	0.342	0.7	0.32–1.8	0.549
pT2	3.4	1.8–6.5	<0.0001	2.4	1.1–5.1	0.021
pT3	6.5	3.6–11.8	<0.0001	4.3	2.1–8.9	<0.0001
pT4	38.7	20–74.3	<0.0001	14.8	5.9–37.1	<0.0001
Grade			<0.0001			0.123
G1	1	Referent	–	1	Reference	–
G2	2.5	0.96–6.4	0.058	2.1	0.71–6.5	0.175
G3	7.7	3.2–18.9	<0.0001	2.8	0.96–8.29	0.058
Concomitant CIS	1.9	1.3–2.8	0.001	1.7	1.09–2.74	0.018
Lymph node stage			<0.0001			0.001
N0	1	Referent	–	1	Referent	–
Nx	0.4	0.5–1.3	0.49	1.4	0.75–2.7	0.268
N1/2	5.6	3.4–9.3	<0.0001	4.4	1.98–10.1	<0.001
Lymphovascular invasion	3.8	2.8–5.1	<0.0001	3.3	1.42–7.75	0.005
Lymphovascular invasion and lymph node stage interaction						0.138
N0				1	Referent	–
Nx				0.5	0.2–1.42	0.210
N1/2				0.3	0.1–0.9	0.047

CI = confidence interval; CIS = carcinoma in situ; HR = hazard ratio.

statistically significant, which indicates that the risk associated with the presence of LVI and N stage is synergistic and significantly exceeded statistically the additive combination of the individual risks. Conversely, the interaction term addressing the combination of LVI and lymph node status on RFS failed to reach statistical significance ($p = 0.138$), indicating that the risk associated with the presence of LVI and N stage did not appear to exceed the additive contribution of these risk variables. Nonetheless, the individual contributions of LVI and N stage were statistically significant and should be interpreted as such.

Analyses were rerun after excluding 66 patients who received adjuvant chemotherapy. This resulted in consistent statistical patterns and *p* values (HR of LVI for RFS: 3.1, $p = 0.022$; HR for CSS: 7.0, $p = 0.002$). Moreover, considering only the patients who had lymph node dissections, similar results were obtained (HR of LVI for RFS: 3.2, $p = 0.008$; HR for CSS: 6.1, $p = 0.001$).

3.3. *Association of lymphovascular invasion with clinical outcomes in lymph node–negative patients and patients who did not undergo lymphadenectomy*

Overall, 49 patients (6.5%) had positive lymph nodes, 131 (17%) had negative lymph nodes, and 582 (76%) did not undergo a lymphadenectomy. Among patients who had either negative lymph nodes or who did not undergo lymphadenectomy, LVI was present in 124 cases (17%). LVI was an independent predictor of RFS (HR: 2.1, 95% CI, 1.4–3.3, $p = 0.001$) and CSS (HR: 2.3, 95% CI, 1.4–3.7, $p < 0.001$) (Table 4). Exclusion of 38 patients who received adjuvant chemotherapy did not alter the statistical significance of these associations.

Among 49 patients with positive lymph nodes, 24 (49%) had LVI. However, LVI was not associated with RFS (HR: 1.1, $p = 0.9$) or CSS (HR: 1.1, $p = 0.9$).

4. Discussion

In accordance with previous studies [18,20], we found that LVI was present in about 20% of patients treated with RNU for UTUC. Presence of LVI was associated with established features of aggressive UTUC such as advanced pT stage, higher tumor grade, and lymph node metastasis. Moreover, patients with LVI were at a significantly increased risk of disease recurrence and cancer-specific mortality, even after controlling for the effects of standard clinicopathologic features. Subgroup analyses revealed that presence of LVI increased the risk of both disease recurrence and cancer-specific mortality in patients with pN0 and pNx disease; conversely, the presence of LVI was not associated with the clinical outcome of lymph node–positive patients.

Table 3 – Univariable and multivariable Cox regression analyses of lymphovascular invasion for prediction of cancer-specific mortality in 762 patients treated with radical nephroureterectomy and ipsilateral bladder cuff excision for upper tract urothelial carcinoma (152 cancer-specific deaths)

Parameter	Univariable analysis			Multivariable analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	1.02	1.007–1.04	0.006	1.02	0.99–1.04	0.081
Year of surgery			0.834			0.461
1987–1989	1	Reference	–	1	Reference	–
1990–1999	1.1	0.6–2.3	0.709	0.98	0.46–2.1	0.973
2000–2008	1.2	0.6–2.5	0.583	0.78	0.34–1.6	0.514
Tumor location			0.043			0.054
Renal pelvis only	1	Reference	–	1	Reference	–
Ureter only	1.07	0.73–1.57	0.725	1.1	0.76–1.7	0.505
Both ureter and renal pelvis	2.03	1.16–3.56	0.013	2.0	1.01–2.65	0.016
Pathologic stage			<0.0001			<0.0001
pTa/Tis	1	Reference	–	1	Reference	–
pT1	1.5	0.7–3.4	0.319	0.8	0.32–2.1	0.699
pT2	3.9	1.8–8.4	<0.001	2.3	1.01–5.3	0.049
pT3	8.8	4.4–17.7	<0.0001	5.1	2.28–11.3	<0.0001
pT4	53.0	24.8–113.5	<0.0001	14.0	5.1–38.1	<0.0001
Grade			<0.0001			0.310
G1	1	Reference	–	1	Reference	–
G2	1.9	0.74–5.1	0.175	1.9	0.61–5.78	0.266
G3	6.5	2.67–15.9	<0.0001	2.3	0.76–6.8	0.143
Concomitant CIS	1.7	1.1–2.7	0.01	1.6	1.004–2.6	0.048
Lymph node stage			<0.0001			<0.001
N0	1	Reference	–	1	Reference	–
Nx	0.9	0.6–1.6	0.988	2.3	1.05–5.3	0.036
N1/2	6.7	3.8–11.9	<0.0001	7.0	2.6–18.7	<0.0001
Lymphovascular invasion	4.6	3.3–6.3	<0.0001	5.9	2.2–16.2	<0.0001
Lymphovascular invasion and lymph node stage interaction						0.037
N0				1	Reference	–
Nx				0.3	0.1–0.95	0.040
N1/2				0.2	0.05–0.69	0.011

CI = confidence interval; CIS = carcinoma in situ; HR = hazard ratio.

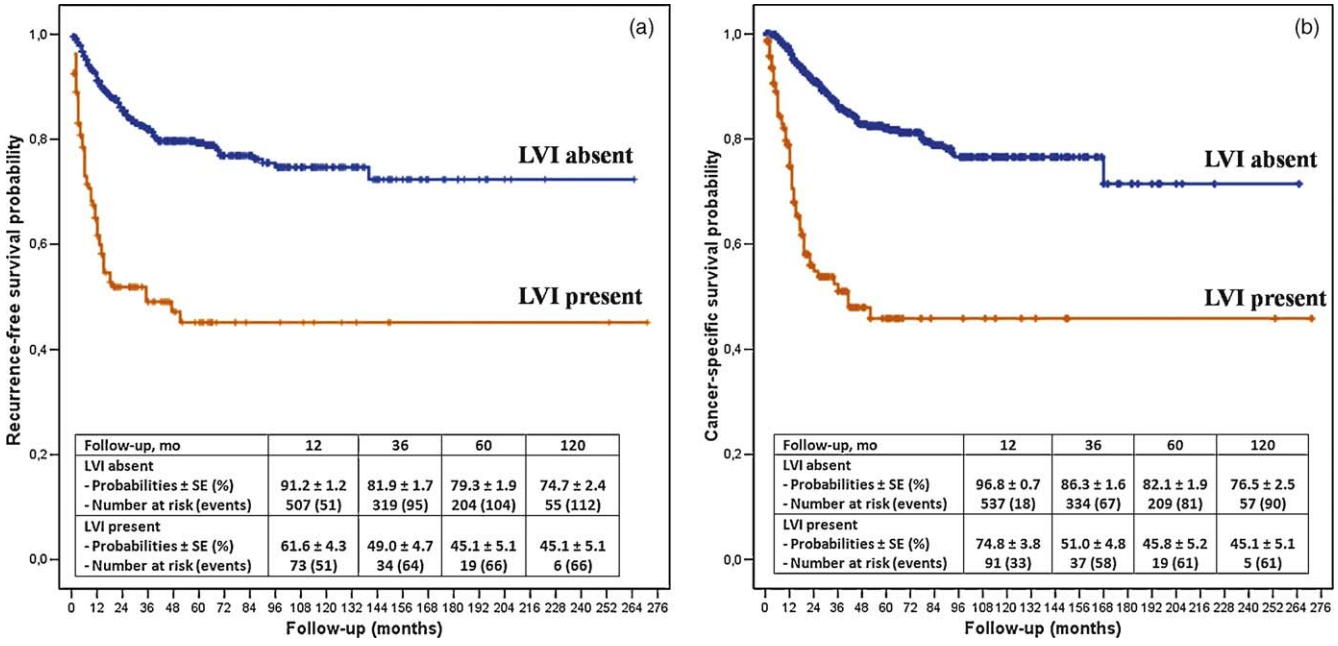

Fig. 1 – Kaplan-Meier curves of (a) recurrence-free survival and (b) cancer-specific survival stratified by lymphovascular invasion (LVI) status in 762 patients treated with radical nephroureterectomy and ipsilateral bladder cuff excision for upper tract urothelial carcinoma (*p* values <0.0001). SE = standard error.

Table 4 – Multivariable Cox regression analyses of lymphovascular invasion for prediction of disease recurrence (*n* = 705; 145 recurrences) and cancer-specific mortality (*n* = 705; 122 deaths) in patients who either had negative lymph nodes or did not undergo lymphadenectomy

Parameter	Recurrence			Cancer-specific mortality		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age	1.01	0.99–1.03	0.379	1.02	0.99–1.04	0.153
Year of surgery			0.034			0.208
1987–1989	1	Referent	–	1	Referent	–
1990–1999	0.6	0.31–1.39	0.274	0.649	0.29–1.43	0.649
2000–2008	0.4	0.19–0.91	0.029	0.493	0.21–1.13	0.493
Tumor location			0.002			0.028
Renal pelvis only	1	Referent	–	1	Referent	–
Ureter only	1.6	1.06–2.48	0.024	1.43	0.91–2.25	0.124
Both ureter and renal pelvis	2.6	1.49–4.66	0.001	2.23	1.2–4.14	0.011
Pathologic stage			<0.0001			<0.0001
pTa/Tis	1	Referent	–	1	Referent	–
pT1	0.7	0.3–1.69	0.447	0.7	0.31–2.0	0.626
pT2	2.2	1.04–4.65	0.039	2.2	0.93–5.0	0.073
pT3	3.6	1.74–7.64	0.0001	4.3	1.9–9.76	<0.0001
pT4	19.3	6.55–56.8	<0.0001	24.9	7.8–79.1	<0.0001
Grade			0.168			0.507
G1	1	Referent	–	1	Referent	–
G2	1.9	0.64–5.96	0.235	1.7	0.57–5.40	0.327
G3	2.5	0.87–7.61	0.085	1.9	0.64–5.77	0.246
Concomitant CIS	2.1	1.31–3.51	0.002	2.0	1.2–3.49	0.009
Lymphovascular invasion	2.1	1.35–3.26	0.001	2.3	1.46–3.69	<0.0001

CI = confidence interval; CIS = carcinoma in situ; HR = hazard ratio.

LVI is an important prognostic factor in various malignancies such as liver, testis, and penile cancer. Indeed, in some of these malignancies, it has been included in the AJCC TNM staging criteria where its presence upstages the patient. However, its prognostic role in UTUC has not yet been established. In two small single-center studies, Kikuchi et al [18] and Saito et al [19] reported that the presence of LVI was an independent predictor of CSS in Japanese men treated with RNU. Conclusions from these studies were limited by their single-center nature and small sample sizes (<200 patients and <60 patients with LVI). Therefore the UTUCC used a large multi-institutional data set including >1400 patients to assess the prognostic value of LVI in UTUC. They found that 24% of patients had LVI and that 5-yr RFS and CSS probabilities were 77% and 71% for patients without LVI, respectively, compared with 44% and 47% for patients with LVI, respectively. In multivariable analyses, the authors found that the presence of LVI was an independent predictor for both disease recurrence and cancer-specific mortality in the entire cohort of patients and in patients with pN0/Nx UTUC [20]. All the slides of patients included in that study were re-reviewed by genitourinary pathologists according to identical strict criteria, which might limit the application of the study findings in everyday clinical practice. The current study was performed to validate these findings externally in a real-world scenario without re-review of all slides.

The prognostic value of LVI increased in patients with pNx/pN0 status, but it was lost in patients with pN1–2. Infiltration of the vascular and/or lymphatic structures by tumor cells is an important step in tumor dissemination because the initial entry of neoplastic cells into the circulation occurs through the local microvascular network, including the lymphatic and blood vessels. The strong association of LVI with lymph node metastasis and disease recurrence/progression after apparently effective local treatment suggests that LVI plays a role in the metastatic process and may be used as a surrogate for occult metastasis [23].

The important prognostic value of LVI status supports that it should always be included in the pathologic report of RNU specimens. Moreover, patients with LVI should be considered at increased risk of disease recurrence compared with patients with similar features but without LVI, and therefore they should be counseled for adjuvant therapy following RNU. Unfortunately, radiotherapy and chemotherapy currently have limited efficacy in the adjuvant setting.

Notably, in our series the presence of concomitant CIS turned out to be an independent predictor of both RFS and CSS probabilities, which had not been found in prior studies [7,9]. Moreover, tumor locations were shown to play an independent predictive role for recurrence and survival, with patients with concomitant pelvis and ureteral cancer having a worse outcome, similar to prior studies [7].

There are several limitations to our study. First and foremost are the limitations inherent to 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 slide review. However, all surgeons operated at selected centers with significant experience in urothelial cancer management, which might increase the external validity of the data compared with the single-center single-surgeon setting. Similarly, whereas it may be preferable for

a single pathologist specialized in genitourinary pathology to review each specimen, using immunohistochemical staining to maximize the diagnostic accuracy in detecting LVI, the present study reflects a real-world practice. Nevertheless, all specimens were examined by dedicated genitourinary pathologists at selected centers. Finally, the study period spans >20 yr, and the data in the present study may not represent current practice patterns. However, 56% of the patients in the study were treated in the year 2000 or thereafter. Moreover, LVI rates were stable along the study period, although year of surgery was significantly associated with disease recurrence in multivariable analyses.

5. Conclusions

LVI is present in approximately 20% of patients treated with RNU. We externally validated that LVI is associated with established features of biologically and clinically aggressive UTUC and, more importantly, disease recurrence and cancer-specific mortality. Subgroup analyses revealed that presence of LVI increased the risk of both disease recurrence and cancer-specific mortality in patients with pN0/pNx disease; however, LVI has no prognostic value in patients with lymph node metastases. LVI status should always be included in the pathologic report of RNU specimens, and patients with LVI should be considered for studies of adjuvant therapy following RNU.

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