Lymphovascular Invasion is Independently Associated With Poor Prognosis in Patients With Localized Upper Urinary Tract Urothelial Carcinoma Treated Surgically

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Purpose: We explored the prognostic impact of lymphovascular invasion in patients with localized upper urinary tract urothelial carcinoma.

Materials and Methods: The clinical records of 135 patients treated surgically for localized upper urinary tract urothelial carcinoma (pTa-3N0M0) were reviewed retrospectively. Lymphovascular invasion was defined as cancer cells in an endothelium lined space. Actuarial survival curves were calculated by the Kaplan-Meier method. Differences between survival curves were evaluated by the log rank test. Multivariate analysis was performed using the Cox proportional hazard model.

Results: Median followup was 55 months (range 3 to 232). Lymphovascular invasion was present in 57 patients (42.2%) and it was associated with higher pathological T stage and higher tumor grade. Recurrence-free and disease specific survival rates in patients with lymphovascular invasion were significantly worse than those in patients without lymphovascular invasion ($p = 0.001$ and 0.001, respectively). Multivariate analysis revealed that lymphovascular invasion, patient age and pathological T stage were significant prognostic factors for recurrence-free and disease specific survival. Based on multivariate analysis patients were divided into 4 risk groups, including pT2 or less/negative lymphovascular invasion, pT2 or less/positive lymphovascular invasion, pT3/negative lymphovascular invasion and pT3/positive lymphovascular invasion. Recurrence-free and disease specific survival rates in patients with pT3/positive lymphovascular invasion were significantly worse than rates in the other 3 groups (each $p < 0.001$).

Conclusions: The current study indicates that positive lymphovascular invasion predicts poor survival in patients with pathologically localized upper urinary tract urothelial carcinoma. Risk stratification based on lymphovascular invasion status and pathological T stage would be helpful for selecting patients at high risk who would be appropriate candidates for clinical trials.

Key Words: urothelium, lymph nodes, carcinoma, ureter, neoplasm invasiveness

Although UUT-UC is relatively uncommon, accounting for approximately 5% to 7% of all urothelial malignancies,[1] the incidence of UUT-UC has increased in the last 20 years.[2] In general the prognosis of UUT-UC is worse than that of bladder tumors. Disease specific 5-year survival rates of 60% to 80% have been reported following surgical management for organ confined renal pelvic UC.[3] The number of patients who have recurrence and/or metastasis within a few years after surgery has been reported to be not negligible.[4] Although systemic adjuvant chemotherapy with the methotrexate, vinblastine, doxorubicin and cisplatin regimen is widely applied for UC,[5,6] its moderate to severe side effects make it difficult to deliver to a considerable number of patients. Thus, specific indicators of patient prognosis should be evaluated to determine a better therapeutic approach.[7,8]

Previous reports of UUT-UC showed that pT stage, pathological grade, tumor location, LNI and surgical procedure are prognostic factors.[4,9–11] Recently the prognostic impact of LVI was reported.[12,13] However, those studies included patients with LNI, which is a strong negative predictor of survival in patients with UUT-UC.[14] After urothelial cancer has metastasized treatment options such as radiotherapy and systemic chemotherapy do not significantly change the overall survival rates. Identifying risk factors for recurrence and/or metastasis in patients with pathologically localized UUT-UC without LNI would be more beneficial for understanding the risk of disease progression to death and improve survival rates. Therefore, a detailed analysis of prognostic factors is warranted in patients with pathologically localized UUC-UC without LNI. We clarified the impact of LVI status on the prognosis in patients with localized UUT-UC treated surgically at a single institution.

MATERIALS AND METHODS

Patients

A total of 189 consecutive patients with newly diagnosed UUT-UC were treated surgically at our institution between 1983 and 2005. Nephroureterectomy with bladder cuff removal was performed with partial ureterectomy done in select patients. Regional lymph node dissection was per-

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formed in patients with enlarged nodes on preoperative evaluation or intraoperative inspection. Extended lymphadenectomy was not performed routinely. Five patients with distant metastasis at diagnosis, 24 with T4 and/or positive LNI and 11 with a diagnosis other than urothelial carcinoma were excluded from study. Eight patients were lost to followup within 3 months after surgery. Information on clinicopathological data was not available in 6 patients. Consequently 135 patients with pathologically localized UUT-UC (pTa-3N0M0) formed the current study cohort.

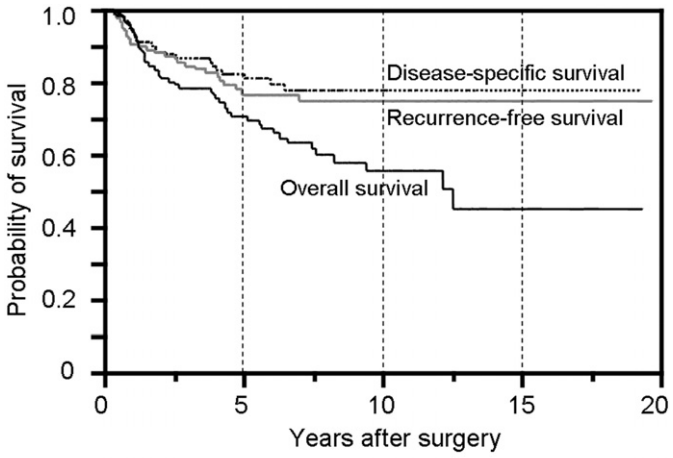
Nephroureterectomy specimens were macroscopically and microscopically examined to determine the extent of invasion, degree of lymph node metastasis and LVI. Tumor stage and grade were determined according to the 1997 TNM system and the 1973 WHO grading system, respectively. LVI was defined as cancer cells in an endothelium lined space without underlying muscular walls. A clear-cut endothelial lining was required to distinguish an endothelium lined space from the retraction space artifact that is common in invasive urothelial carcinoma. In the current analysis any equivocal focus was considered negative. No attempt was made to distinguish between vascular and lymphatic vessels because of the difficulty and lack of reproducibility when using routine light microscopic examination. Immunohistochemistry for endothelial cells was not done, in keeping with pathologist practice.

Postoperative followup included urinary cytology and cystoscopy every 3 months for 2 years and every 6 months thereafter. Computerized tomography, and chest x-ray and/or magnetic resonance imaging were performed every 6 months for 5 years and annually thereafter. Bladder recurrence was not considered in the recurrence-free survival rate calculation because it did not impact survival in the current population.

A total of 30 patients received 1 to 6 courses of postoperative adjuvant chemotherapy. After disease recurred patients were treated with systemic chemotherapy and/or radiotherapy according to the recurrence site and general patient condition.

TABLE 1. *Baseline characteristics of 135 patients*

	No. Pts	No. Neg LVI (%)	No. Pos LVI (%)	p Value
Overall	135	78	57	
Age:				
Younger than 70	68	37 (47.4)	31 (54.4)	0.43
70 or Older	67	41 (52.6)	26 (45.6)	
Sex:				
M	94	61 (78.2)	33 (57.9)	0.011
F	41	17 (21.7)	24 (42.1)	
Laterality:				
Lt	76	46 (59.0)	30 (52.6)	0.41
Rt	58	31 (39.7)	27 (47.4)	
Bilateral	1	1 (1.3)	0 (0)	
pT:				
a–2	73	55 (70.5)	18 (31.6)	<0.001
3	62	23 (29.5)	39 (68.1)	
Grade:				
1/2	81	60 (76.9)	21 (36.8)	<0.001
3	54	18 (23.1)	36 (63.2)	
Ureteral tumor:				0.50
Absence	59	36 (46.2)	23 (40.4)	
Presence	76	42 (53.9)	34 (59.6)	
Surgical procedure:				0.39
Nephroureterectomy	124	73 (93.6)	51 (89.5)	
Partial ureterectomy	11	5 (6.4)	6 (10.5)	



Patients at risk				
Years after surgery	0	5	10	15
Overall survival	135	65	20	4
Disease-specific survival	135	65	20	4
Recurrence-free survival	135	60	19	4

FIG. 1. Overall, disease specific and recurrence-free survival curves for entire cohort.

Data Analysis

Continuous values are expressed as the median unless indicated otherwise. Associations were evaluated based on the Fisher exact test for nominal valuables. Overall, disease specific and recurrence-free survival curves were calculated by the Kaplan-Meier method. We compared survival rates according to certain clinicopathological variables using the log rank test, including patient age, sex, tumor laterality, pT, tumor grade, LVI and tumor location (presence or absence of ureteral tumor). Factors related to survival were analyzed by Cox proportional hazards regression models. On multivariate analysis pT and tumor grade were divided into 2 groups (pTa-2 vs pT3 and G1/2 vs G3, respectively). For all analyses differences were considered significant at $p < 0.05$. All analyses were performed using JMP®, version 5.0.0.

RESULTS

Oncological Outcome

Table 1 lists the clinicopathological characteristics of the 135 patients. Figure 1 shows overall disease specific and recurrence-free survival curves for the entire cohort. During the median 55-month followup (range 3 to 232) 48 of the 135 patients (35.6%) died. Five and 10-year overall survival rates were 70.8% and 55.8%, respectively. Disease recurred in 27 of the 135 patients (20.0%) during the study period. Five and 10-year recurrence-free survival rates were 77.2% and 75.6%, respectively. Of the 135 patients 23 (17.0%) died of the disease. Five and 10-year disease specific survival rates were 82.5% and 78.2%, respectively.

Patients with LVI

LVI was present in 57 patients (42.2%). We defined these patients as the positive LVI group. In the positive LVI group pT and grade were higher than in the negative LVI group (each $p = 0.001$). LVI was found in 0 of 23 (0%), 7 of 29 (24%),