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LYMPHOVASCULAR INVASION INDEPENDENTLY PREDICTS INCREASED DISEASE SPECIFIC SURVIVAL IN PATIENTS WITH TRANSITIONAL CELL CARCINOMA OF THE UPPER URINARY TRACT

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ABSTRACT

Purpose: We investigated the prognostic impact of lymphovascular invasion (LVI) and traditional prognostic factors for survival in a large series of patients treated surgically for upper tract transitional cell carcinoma (TCC). We also developed a prognostic factors based model for risk stratification of upper tract TCC.

Materials and Methods: We identified a study population of 173 consecutive patients treated surgically for upper tract TCC at our institution between 1980 and 2002. We compared LVI with other pathological features and determined the disease specific survival rate.

Results: LVI was found in 52 patients (30.1%). As tumor grade and pathological stage increased, the incidence of LVI increased significantly. LVI was found in 12 of 133 patients (9.0%) without lymph node metastasis compared with 40 of 40 patients (100%) with lymph node metastasis. Five and 10-year disease specific survival rates were 84.9% and 80.4% in the absence of LVI, and 40.2% and 21.1% in the presence of LVI, respectively ($p < 0.001$). In multivariate analysis LVI, pathological T stage and tumor grade were independent predictors for disease specific survival. The relative risk of death could be expressed with the formula, $\exp(0.729 \times \text{tumor grade} + 1.659 \times \text{pathological T stage} + 1.160 \times \text{LVI})$. Using this equation the patients were stratified into low risk (grade 1 or 2, LVI negative, stage pT2 or lower), high risk (any tumor grade, LVI positive, stage pT3 or greater) and intermediate risk (all others) groups with significant differences in survival. Five and 10-year disease specific survival rates were 93.0% and 89.4% in the low risk group (82 patients), 66.8% and 62.9% in the intermediate risk group (53 patients), and 25.6% and 0% in the high risk group (38 patients), respectively.

Conclusions: In addition to pathological stage and tumor grade, LVI is an independent prognostic factor for disease specific survival in upper tract TCC. Patients in the high and/or intermediate risk groups may benefit from integrated therapies with surgery and postoperative systemic chemotherapy.

KEY WORDS: lymphatic metastasis, urologic neoplasms; carcinoma, transitional cell; survival

Renal pelvic transitional cell carcinoma (TCC) accounts for 5% of all urothelial tumors and 10% of all renal tumors.[1] Ureteral tumors are less common, occurring with one fourth the incidence of renal pelvic tumors.[2] In this relatively uncommon malignancy there are few systemic reports involving more than 100 cases, and discussing the factors provides prognostic information derived systemically from the long-term followup of a group of patients.[3–5] In previous studies on upper tract TCC several clinical factors have been associated with patient outcome, namely age, pathological grade, T stage, tumor location, lymph node involvement and surgical procedures.[3,4,6,7] In patients with other malignancies, lymphovascular invasion (LVI) by tumor cells has been shown to be associated with a high incidence of lymph node or distant metastases and a poor prognosis.[8,9] In fact, LVI is the first and essential process in initiating the metastatic cascade. However, in upper tract TCC few reports have shown associations between LVI and distant metastases or poor prognosis.[10] We investigated the possible significance of LVI in terms of survival, along with standard prognostic factors in patients with upper tract TCC followed for a long time after surgery.

Risk stratification is an important issue in cancer treatment because it can facilitate a more accurate prediction of outcome and provide a more homogenous population for the most appropriate therapeutic approach. However, to our knowledge no previous investigation has attempted to set up a risk stratification model for upper tract TCC. In this study the records of 173 patients with upper tract TCC treated at our institution were retrospectively analyzed to develop a prognostic factors based model for risk stratification.

MATERIALS AND METHODS

A total of 185 consecutive patients were treated surgically for upper tract TCC at our institution from January 1980 through December 2002. Exclusion criteria were distant metastasis at diagnosis, presence of concomitant invasive bladder tumor or incomplete data. We identified a study population of 173 consecutive patients who had complete data based on pathological features. Mean patient age was 65.5 years (range 37 to 89). Patients were followed postoperatively with urinary cytology every 3 months for 2 years and then every 6

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months. Computerized tomography and cystoscopy, and/or magnetic resonance imaging and/or excretory urogram were performed every 6 months for 5 years and annually thereafter. Median followup was 43 months (mean 58, range 1 to 265).

Nephroureterectomy with removal of the bladder cuff was the most common procedure (165 patients, 95.4%). Partial ureterectomy and nephrectomy were performed in 7 patients and 1 patient, respectively. Dissection of regional lymph nodes was performed in patients with enlarged nodes on a preoperative evaluation or in those who were suspected of having enlarged nodes at intraoperative inspection. Extended lymphadenectomy was not routinely performed. Cisplatin based neoadjuvant and adjuvant chemotherapy regimens were administered to 8 (4.6%) and 48 (27.7%) patients, respectively. Postoperative adjuvant radiotherapy regimens were not routinely used at our institution.

LVI was defined as the unequivocal presence of tumor cells within endothelial lined lymphatic and vascular channels.[10] Associations between LVI and clinical or pathological features were assessed with the chi-square test for trends. The actuarial probabilities obtained using a Kaplan-Meier analysis were reported as median ± 2 standard errors (95% CI) and were compared using the log rank test. Prognostic factors assessed were age (greater vs less than mean patient age of 65 years), gender, tumor laterality, tumor location (pelvis vs ureter), tumor grade (G1/2 vs G3), pathological T stage (pTa-T2 vs pT3/4), surgical margin status, lymph node involvement and LVI. We used the Cox proportional hazards regression analysis to assess the prognostic indicators for survival, and $p < 0.05$ indicated statistical significance. These analyses were performed with the STATA® version 7.0 statistical software package.

RESULTS

LVI of upper tract TCC was found in 52 patients (30.1%). Associations between clinicopathological features and the incidence of LVI are shown in table 1. Patients older than 65 years or female patients had a significantly higher incidence of LVI than their counterparts. The incidence of LVI was significantly associated with increasing tumor grade, increasing extent of cancer, presence of positive surgical margin and lymph node involvement. LVI was found in 1 of 11 patients (9%) with grade 1 tumors, 17 of 105 patients (16%) with grade 2 tumors and 34 of 57 patients (60%) with grade 3 tumors ($p < 0.001$). LVI was noted in 0 of 44 (0%), 5 of 36 (14%), 9 of 23 (39%), 31 of 61 (51%) and 7 of 7 (100%) patients with pTa, pT1, pT2, pT3 and pT4, respectively ($p < 0.001$). LVI was found in 12 of 133 patients (9.0%) without lymph node metastasis compared to 40 of 40 patients (100%) with lymph node metastasis.

A total of 43 patients died of the disease. The disease specific survival rate was 72.3% at 5 years and 65.1% at 10 years. Univariate analysis revealed age, gender and all pathological factors examined were significant independent predictors of disease specific survival. LVI, pathological stage and tumor grade provided independent prognostic information when controlled for the effects of other variables in multivariate analysis (table 2). Five and 10-year survival rates were 40.2% and 21.1%, respectively in patients with LVI compared to 84.9% and 80.4% in patients without LVI (fig. 1, $p < 0.001$). According to tumor grade, 5 and 10-year survival rates were 86.1% and 79.7% for G1/2, and 38.1% and 31.8% for G3 disease (fig. 2, $p < 0.001$). According to pathological T classification, 5 and 10-year survival rates were 91.0% and 85.8% for pT2 or less, and 42.8% and 31.4% for pT3/4 disease, respectively (fig. 3, $p < 0.001$). LVI was found in 6 of 88 patients (6.8%) with G1/2 and pathological stage pT2 or less, compared to 26 of 40 patients (65%) with G3 and pathological stage pT3/4.

Using the 3 statistically significant variables in the multivariate Cox regression analysis (tumor grade, pT stage and LVI), the relative risk of death could be calculated with the formula, $\exp(0.729 \times \text{grade} + 1.659 \times \text{pT stage} + 1.160 \times \text{LVI})$. In this equation grade equaled 1 if tumor grade was G3, and grade equaled 0 if tumor grade was G1/2. pT stage equaled 1 if pathological stage was pT3/4 and 0 if pT2 or less. LVI equaled 1 if LVI was present and 0 if absent. Based on the relative risk of death, patients with upper tract TCC were divided into 3 risk groups of low (relative risk of death = 1), intermediate (2.07 to 10.89) and high (16.78 to 34.73). According to the prognostic factors based risk stratification for upper tract TCC, 82 patients were in the low risk group (grade 1 or 2, LVI negative and stage pT2 or lower), 38 patients in the high risk group (any tumor grade, LVI positive and stage pT3 or greater) and 53 patients in the intermediate risk group (all others). Five and 10-year disease specific survival rates were 93.0% and 89.4% in the low risk

TABLE 1. *Clinicopathological characteristics of patients with or without LVI*

	All Pts	Pts With LVI (%)	Pts Without LVI (%)	p Value
No. pts	173	52 (30.1)	121 (69.9)	
Age:				0.029
Younger than 65 yrs	75	16 (21.3)	59 (78.7)	
Older than 65 yrs	98	36 (36.7)	62 (63.3)	
Gender:				0.027
Male	132	34 (25.8)	98 (74.2)	
Female	41	18 (43.1)	23 (56.1)	
Tumor laterality:				0.249
Lt	91	31 (34.1)	60 (65.9)	
Rt	78	21 (26.9)	57 (73.1)	
Bilat	4	0 (0)	4 (100)	
Tumor location:				0.958
Pelvis	97	29 (29.9)	68 (70.1)	
Ureter	76	23 (30.3)	53 (67.4)	
Grade:				<0.001
1 or 2	116	18 (15.6)	98 (84.5)	
3	57	34 (59.7)	23 (40.3)	
pT Stage:				<0.001
pTa–T2	105	14 (13.3)	91 (86.7)	
pT3, 4	68	38 (55.9)	30 (44.1)	
Surgical margin:				0.002
Pos	18	11 (61.1)	7 (38.9)	
Neg	155	41 (26.4)	114 (73.6)	
Lymph node involvement:				<0.001
Pos	40	40 (100)	0 (0)	
Neg	133	12 (9.0)	121 (91.0)	