Prognostic Role of Lymphovascular Invasion in Patients with Urothelial Carcinoma of the Upper Urinary Tract

Manel Mellouli[1]*, Slim Charfi[1], Walid Smaoui[2], Rim Kallel[1], Abdelmajid Khabir[1], Mehdi Bouacida[2], Mohamed Nabil Mhiri[2], Tahya Sellami Boudawara[1]

Purpose: To evaluate the impact of lymphovascular invasion on the prognosis of patients treated for upper urinary tract urothelial carcinomas.

Materials and methods: Clinical records of 49 patients treated surgically at our institute for upper urinary tract urothelial carcinomas were reviewed retrospectively. LVI was defined as the presence of cancer cells within an endotheluim-lined space without underlying muscular walls. Actuarial survival curves were analysed by Kaplan-Meier method. Multivariate analysis was performed using Cox's proportional hazard model.

Results: Median follow-up was 32 months. Lymphovascular invasion was present in 26 (53%) patients. Lymphovascular invasion was associated with higher pathological tumor stage (pT) and higher tumor grade. The disease-free and overall survival rates of the patients with lymphovascular invasion were significantly worse than those of the patients without lymphovascular invasion ($p < 0.001$ and $p = 0.027$ respectively). Multivariate analysis revealed that lymphovascular invasion as well as tumor grade and pathological tumor stage were significant prognostic factors for disease-free and overall survival.

Conclusion: The presence of lymphovascular invasion was a strong predictor of a poor outcome for UTUC. This finding could help identify patients at greater risk for disease recurrence who would benefit from close follow-up and early adjuvant therapy.

Keywords: transitional cell carcinoma; urinary tract; lymphovascular invasion; prognosis.

INTRODUCTION

Upper urinary tract urothelial carcinomas (UTUC) are rare tumors representing only 5% of all urothelial carcinomas.(1) The estimated incidence of UTUC in Europe is 1 to 4 cases per 100,000 individuals per year.(1) In Tunisia, according to the register of the southern Tunisian cancers (2007 edition), the estimated incidence of UTUC is 0.21 cases per 100,000 individuals in women and 0.67 cases per 100,000 individuals in men (Sellami A, 2007, unpublished data). To date, radical nephroureterectomy (RNU) remains the gold standard treatment for non-metastatic UTUC.(2) Despite surgery, UTUC remains a malignancy with a high potential for local and distant relapse, especially in patients with advanced disease.(3) Numerous criteria, such as age, multifocality, tumor stage, grade and architecture, and lymphovascular invasion (LVI) have been established as determinant prognostic factors in UTUC.(1) In UTUC, LVI is detected in 15 to 20% of cases and is associated with high stage and grade.(3-8) However, the prognostic role of LVI has not still been routinely assessed, checked and described in pathological reports. The aim of the current study was to further delineate the prognostic significance of LVI by analyzing survival outcome for patients with UTUC treated by surgery.

MATERIALS AND METHODS

We retrospectively analyzed 49 patients who underwent surgery for UTUC between 1992 and 2013 in the CHU Habib Bourguiba of Sfax. Surgical procedures were performed in one center by various surgeons. All grossly involved lymph nodes were removed during surgery.

Clinical features

Clinical data were collected via medical file review. They included age, gender, history of bladder carcinoma or synchronous bladder carcinoma and outcomes.

Pathological Evaluation

All surgical specimens (partial ureterectomy, Nephrectomy or RNU) were processed according to standard pathologic procedures and all slides were re-reviewed by two pathologists. All specimens were evaluated for tumor location, tumor multifocality, tumor size, tumor architecture, pathological stage, histological grade, presence of LVI, tumor necrosis, concomitant carcinoma in situ (CIS), surgical margin status and lymph node status. Tumors were staged according to the 2009 American Joint Committee on Cancer–International Union against Cancer (AJCC/UICC) TNM staging system.(9) Tumor grade was assessed according to the 2004 World Health Organization grading system.(10) Multifocality was defined by the presence of two or more synchronous tumors. Tumor architecture was defined as

[1]Department of pathology, Habib Bourguiba Hospital, 3029 Sfax, Tunisia.
[2]Department of urology, Habib Bourguiba Hospital, 3029 Sfax, Tunisia.
*Correspondence: Department of pathology, Habib Bourguiba Hospital, 3029 Sfax, Tunisia.
Tel : 00216 21 027 852. Fax : 00216 74 243 427. Email : mellouli.manel@yahoo.fr.
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Table 1. Characteristics of 49 patients with UTUC.

	Total, n=49 (%)	LVI negative, n=23	LVI positive, n=26	*P*-value
Age (years)				0.357
<60	18 (36.8)	10	8	
>60	31 (63.2)	13	18	
Sex	0.174			
Men	41 (83.6)	21	20	
Women	8 (16.3)	2	6	
History of bladder carcinoma				0.319
Yes	14 (28.6)	5	9	
No	35 (71.4)	18	17	
Tumor location				0.622
Renal pelvis	39 (79.5)	19	20	
Ureter	10 (20.4)	4	6	
Tumor size (cm)				0.786
<4	14 (28.5)	7	7	
>4	35 (71.5)	16	19	
Multifocality				0.012
Unifocal	34 (69.3)	20	14	
Multifocal	15 (30.6)	3	12	
Tumor architecture				0.062
Papillary	42 (85.7)	22	20	
Sessile	7 (14.3)	1	6	
Pathologic stage				0.117
<pT3	24 (49)	14	10	
≥pT3	25 (51)	9	16	
Tumor grade				0.069
Low	17 (34.7)	11	6	
High	32 (65.3)	12	20	
Associated squamous or glandular differentiation				0.674
Absent	37 (75.5)	18	19	
Present	12 (24.4)	5	7	
Tumor necrosis				0.073
Absent	17 (34.6)	5	12	
Present	32 (65.3)	18	14	
Concomitant CIS				0.173
Present	13 (26.5)	4	9	
Absent	36 (73.4)	19	17	
Surgical margin status				0.189
R0	40 (81.6)	17	23	
R+	9 (18.4)	6	3	
Lymph node status				0.118
N0	26 (53)	15	11	
N+	7 (14)	1	6	
Nx	16 (33)	7	9	

papillary or sessile. LVI was defined, on H&E stained slides, as the presence of tumor cells within an endothelium-lined space without underlying muscular wall. No immunohistochemistry techniques were used to determine the presence of LVI.

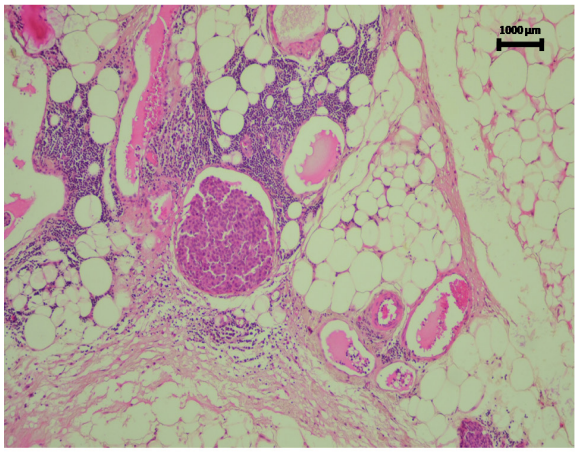

Figure 1. High-grade urothelial carcinoma within a vessel in a radical nephroureterectomy (HE x 100).

The extent of lymph node dissection was not standardized and thus was not available for analysis. Nodal status was determined by pathological assessment of retrieved lymph nodes at time of surgery.

Follow-up regimen

Patients were followed every 3-4 months for the first year following surgery, every 6 months from the second through the fifth years, and annually thereafter. They underwent physical examination, cystoscopy, urine cytology and abdominal-pelvic CT at each visit.
Recurrence was defined as the disease occurring in the bladder or in the contralateral upper urinary tract.

Statistical analysis

Clinicopathologic features of patients were evaluated. In the analysis, age was reclassified into 2 groups: younger than 60 versus 60 or older. Tumor size was reclassified into 2 groups: less than 4 cm or more than 4 cm. Tumour stage was classified into 2 groups: pTa, pT1 and pT2 versus pT3 and pT4. In multifocal tumors, clinicopathologic factors were defined according to the site with the highest stage. Qualitative variables were compared by the chi-square test and quantitative variables by the student *t*-test. Patient disease free-survival (DFS) was computed from the day of surgery until

Table 2. Multivariate analysis of prognostic factors for disease-free survival.

	HR	95% CI	*P*-value
Lymph node status	0.513	0.28 - 0.91	0.024
Pathologic stage	3.319	1.03 – 10.67	0.044
Tumor grade	19.862	2.1 – 187.49	0.009
LVI	3.081	1.0 – 9.129	0.042

Abbreviations : CI, confidence interval ; HR, hazard ratio

Table 3. Multivariate analysis of prognostic factors for overall survival.

	HR	95% CI	*P* value
Lymph node status	0.700	0.39 - 1.24	0.226
Pathologic stage	6.351	1.02 - 39.45	0.047
Tumor grade	27.947	2.99 – 260.76	0.003
LVI	6.839	1.99 – 23.40	0.002
Tumor necrosis	2.775	0.86 – 8.87	0.085
CIS	0.539	0.16 – 1.78	0.313
Tumor size	1.272	0.32 – 4.93	0.728

Abbreviations : CI, confidence interval ; HR, hazard ratio

disease recurrence or until the most recent follow-up visit. Patient overall survival (OS) was computed from the day of surgery until death or until the most recent follow-up visit. Estimation of DFS and OS was performed using the Kaplan-Meier method. Prognostic significance of clinicopathological factors were tested with the log-rank test.

The potential prognostic factors (e.g. LVI status) were established by univariate analysis, and only the significant factors were entered into multivariate Cox proportional hazard regression models. Statistical significance in this study was set as P< 0.05. Statistical analyses were performed using SPSS v.19.0 (IBM Corp., Armonk, NY, USA).

The study protocol was approved by the Ethics and Scientific committee of each participating institution. The study was performed in compliance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

RESULTS

Study population Characteristics

Table 1 lists clinical and pathological patient characteristics. LVI was present in 26 (53%) patients (Figure 1).

Association between LVI and clinicopathological factors

Association between clinical and pathological characteristics and LVI are shown in **Table 1**.

Tumor multifocality was significantly associated with the presence of LVI ($P = 0.012$). The prevalence of LVI increases with higher tumor grade and advanced pathological stage but these associations were not significant.

Outcome and survival data

10 patients (20.4%) received adjuvant chemotherapy. The median follow-up was 32 months (range from 2 to 92 months). During follow-up, 28 patients (57.1%) experienced disease recurrence and 22 patients (44.8%) died of UTUC.

Univariate analysis revealed that LVI were associated with DFS and OS. The 5-year DFS rate was 66.2%in the absence of LVI and 15.4% in the presence of LVI ($P < 0.001$) (**Figure 2A**). The 5-year OS rate was 62.1% in the absence of LVI and 28.5% in the presence of LVI ($P = 0.027$) (**Figure 2B**).

In multivariate analysis, pathologic stage ($P = 0.044$), tumor grade ($P = 0.009$), LVI ($P = 0.04$) and Lymph node involvement ($P = 0.024$) were identified as independent predictive factors of recurrence (**Table 2**). Multivariate analysis showed also that pathologic stage ($P = 0.047$), tumor grade ($P = 0.003$) and LVI ($P = 0.002$) were associated with lower overall survival rates (**Table 3**).

DISCUSSION

Previous well-designed studies have analyzed the prognostic factors in patients with UTUC for determining the subgroup of patients who have biologically aggressive tumour and who might receive close follow-up and adequate adjuvant therapy. Many features such as pathological stage, tumor grade and presence of lymph node metastases have been identified as prognostic variables for recognizing risk groups among patients with UTUC.[11-15] The prognostic implications of LVI has also been investigated in previous studies. However,

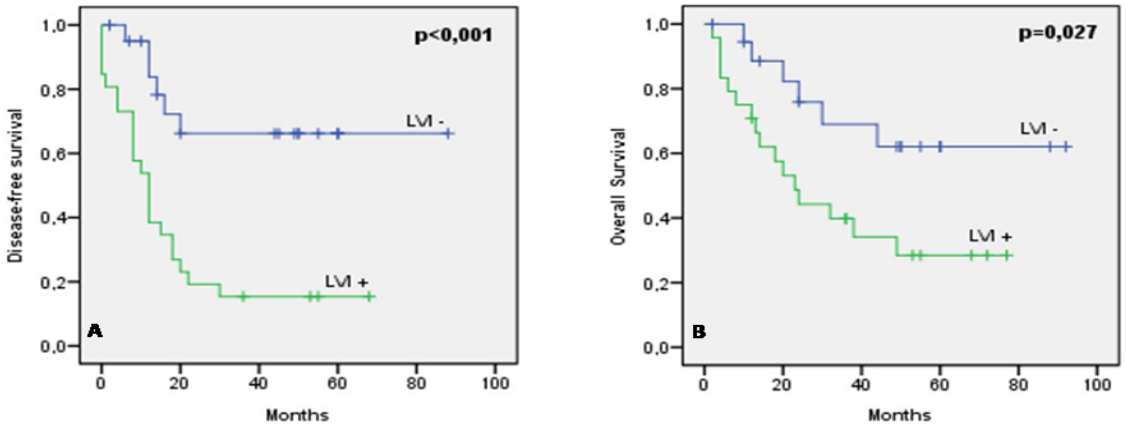

Figure 2. Kaplan-Meier curves of disease-free survival (A) and overall survival (B) stratified by LVI in 49 patients with UTUC. The blue line indicates LVI negative status and the green line indicates LVI positive status.

the results were controversial and the exact role that LVI has in predicting the prognosis of UTUC remains unclear. We tried to assess the prognosis impact of the presence or absence of LVI in our patients.

LVI is an obligatory step in lymph node involvement and distant metastases.[7,16] Consequently, the identification of LVI may permit the determination of patients without lymph node metastases who are at increased risk for distant metastases and disease-related death.

The definition of LVI is not well established. Many authors define LVI as "the presence of malignant cells within an endothelial-lined space with no underlying muscular walls on HE stained sections" but in other studies, diagnostic criteria are not specified.[17]

In most previous studies, LVI was detected in 13 to 42% of patients with UTUC.[3-8] However, the presence of LVI is not routinely mentioned in pathological reports.[4] In our study, the incidence of LVI was higher (53.1%) than previously described. This could be explained by the fact that most UTUC have been diagnosed at an advanced stage. In fact, 63.26% of patients had UTUC invading the muscularis at the time of surgery (pT2) and 51% of patients were in pathological stages of pT3 and pT4.

Several single-center studies have reported that LVI is significantly associated with higher tumor stage and grade.[8,16,17] These studies have also shown that LVI independently predicts worse disease-free and disease specific survival rates. Kikuchi et al. reported that LVI is an independent significant predictor of disease recurrence and poorer prognosis, in their retrospective study of 1450 patients.[4] These results were recently corroborated by the work of Novara et al. and Hong et al. (5,18) These findings were supported by two others multi-institutional studies, which demonstrated that LVI was associated with well-known prognostic factors of UTUC, such as high tumor grade, advanced stage, metastasis to lymph nodes, tumor necrosis, sessile tumor architecture, and concomitant CIS.[4-5] In addition, these studies validated the independent value of LVI for predicting both disease-free survival and cancer specific survival. Our findings were in agreement with those of recent series. We showed that LVI was associated with a significant decline in disease-free and overall survival on both univariate ($P = 0.001$ and $P = 0.027$, respectively) and multivariate analyses ($P = 0.042$ and $P = 0.002$, respectively) at a median follow-up of 32 months.

Based on these data, LVI status should be mentioned in the pathologic report of RNU specimens, and it might be included in the TNM staging system for UTUC. In this case, the standardization of diagnostic criteria in evaluation of LVI might be necessary to limit the inter-observer variability.

One of the limitations of our study was its single-center nature and small study population. Moreover, the inclusion of patients with lymph nodes involvement, made it difficult to determine the correct prognostic value of LVI in patients with pathologically localized UTUC.

CONCLUSIONS

LVI status is a powerful prognosis factor in UTUC, is strongly correlated with poorer disease-free and overall survival. We thus advocate that LVI should be carefully sought in histological specimens. The LVI status could be a useful tool to identify those patients who are at higher risk of disease recurrence and who may need adjuvant therapy.

CONFLICT OF INTEREST

None declared.

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