Lymphovascular Invasion in Transurethral Resection Specimens as Predictor of Progression and Metastasis in Patients With Newly Diagnosed T1 Bladder Urothelial Cancer

Kang Su Cho, Ho Kyung Seo, Jae Young Joung, Weon Seo Park, Jae Y. Ro, Kyung Seok Han, Jinsoo Chung and Kang Hyun Lee*

From the Urologic Oncology Clinic (KSC, HKS, JYJ, KSH, JC, KHL) and Department of Pathology (WSP), Center for Specific Organs Cancer, National Cancer Center, Goyang, Korea, and Department of Pathology, Methodist Hospital and Research Institute, Weill Medical College of Cornell University (JYR), Houston, Texas

Purpose: We evaluated the clinical significance of lymphovascular invasion in transurethral resection of bladder tumor specimens in patients with newly diagnosed T1 urothelial carcinoma of the bladder.

Materials and Methods: Enrolled in the study were 118 patients with newly diagnosed T1 urothelial carcinoma of the bladder who underwent transurethral resection of bladder tumor between 2001 and 2007. Patient records were retrieved from a prospectively maintained bladder cancer database. We evaluated the correlation between lymphovascular invasion and other clinicopathological features, and the impact of lymphovascular invasion on disease recurrence, disease progression and metastasis.

Results: Lymphovascular invasion was histologically confirmed in 33 patients (28.0%). While lymphovascular invasion correlated with tumor grade ($p = 0.002$), it was not associated with gender, age, bladder tumor history, tumor size, multiplicity or concomitant carcinoma in situ. Recurrence, progression and metastasis developed in 45 (38.1%), 19 (16.1%) and 10 patients (8.5%), respectively. Univariate analysis showed that lymphovascular invasion was marginally associated with recurrence and significantly associated with progression ($p = 0.011$) and metastasis ($p = 0.019$). Multivariate Cox proportional hazards analysis revealed that recurrence was significantly associated with lymphovascular invasion ($p = 0.029$), and with bladder tumor history ($p < 0.001$), tumor size ($p = 0.031$) and multiplicity ($p = 0.043$). Lymphovascular invasion was the only independent prognostic factor associated with progression ($p = 0.016$).

Conclusions: In patients with newly diagnosed T1 urothelial carcinoma of the bladder lymphovascular invasion in transurethral resection of bladder tumor specimens predicts disease progression and metastasis.

Key Words: urinary bladder; carcinoma, transitional cell; lymphatic metastasis; neoplasm invasiveness; urothelium

Abbreviations and Acronyms

LVI = lymphovascular invasion

TUR = transurethral resection

TURBT = TUR of bladder tumor

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Study received National Cancer Center institutional review board approval.

* Correspondence: Urologic Oncology Clinic, National Cancer Center, 111 Jungbalsan-ro, Ilsandong-gu, Goyang-si, Gyeonggi-do, 410-769, Republic of Korea (telephone: +82-31-920-1676; FAX: +82-31-920-1790; e-mail: uroonco@ncc.re.kr).

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Urothelial carcinoma of the bladder can present as a muscle invasive or nonmuscle invasive lesion. Approximately 75% of patients present with nonmuscle invasive tumors limited to the mucosa or lamina propria. For nonmuscle invasive bladder tumors the probability of recurrence after TURBT at 1 year is 15% to 70% and the probability of progression at 5 years is 7% to 40%.[1,2]

Prior radical cystectomy series showed a LVI incidence of 30% to 50%

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in cases of urothelial carcinoma of the bladder.[3–9] LVI is independently associated with overall, cancer specific and recurrence-free survival.[4,6,7,9] Although some studies failed to show that LVI has a statistically significant impact on prognosis on multivariate analysis,[3,5,8] LVI is generally considered a poor prognostic feature in patients with muscle invasive bladder cancer after radical surgery.

Lopez and Angulo first noted that vascular invasion in TURBT surgical specimens of T1 bladder cancer is an independent prognostic factor.[10] However, Larsen et al contradicted this finding.[11] There are limited data on the clinical significance of LVI in TURBT specimens in patients with nonmuscle invasive bladder cancer. Thus, the clinical significance of LVI for nonmuscle invasive bladder cancer remains an open issue. We evaluated the clinical significance of LVI in patients with newly diagnosed T1 urothelial carcinoma of the bladder.

MATERIALS AND METHODS

Study Population

This study was approved by the National Cancer Center institutional review board. We reviewed archived data on consecutive patients newly diagnosed with T1 bladder cancer between 2001 and 2007 in the prospectively maintained National Cancer Center bladder cancer database. Patients with concomitant urothelial carcinoma of the upper urinary tract or nonurothelial carcinoma histology were excluded. A total of 118 patients with newly diagnosed T1 urothelial carcinoma of the bladder were enrolled in this study, of whom 101 (85.6%) were male and 21 (17.8%) had a history of Ta bladder tumor. Median patient age was 67 years (range 39 to 91) and median followup was 35 months (range 12 to 89).

Treatment and Data Collection

All patients initially underwent TURBT. Repeat TURBT was done in 31 patients (26.3%) at surgeon discretion 2 to 6 weeks after initial surgery. Indications for repeat TURBT were an absent muscularis propria in initial TURBT specimens, suspicion of residual tumor and referral after initial TURBT was done elsewhere. The goal of repeat TURBT was to provide a wide resection margin and deep tumor removal to achieve complete resection of suspected residual tumor.

A total of 100 patients (84.7%) underwent intravesical therapy after TURBT. Intravesical therapy consisted of a 6-week course of mitomycin C in 65 patients, a 6-week course of bacillus Calmette-Guerin in 27 and an 8-week course of epirubicin in 8. Systemic chemotherapy was recommended in patients with multifocal LVI and the final decision on chemotherapy was based on a combination of factors, including coexisting conditions, and patient ability and willingness to comply. Two or 3 cycles of cisplatin based chemotherapy were administered in 11 patients (9.3%), including a gemcitabine plus cisplatin regimen in 5, and methotrexate, vinblastine and doxorubicin plus cisplatin in 6. Subsequently radical cystectomy and pelvic lymphadenectomy after TURBT were done in 4 patients (3.4%).

Followup was relatively uniform. Surveillance cystoscopy and urinary cytology were done at 3-month intervals in the first 2 years, at 6-month intervals in the next 3 years and annually thereafter. Generally abdominopelvic computerized tomography and chest radiography were done at 6 to 12-month intervals.

Patient clinical and pathological features, and followup information were retrieved from the database. T stage was determined using the 2002 American Joint Committee on Cancer TNM staging system and histological grade was determined with the WHO system. Routine LVI evaluations were done. LVI was considered present only when tumor cells were unequivocally noted within or attached to the wall of a vascular or lymphatic space on hematoxylin and eosin stained sections. Multiple serial sections

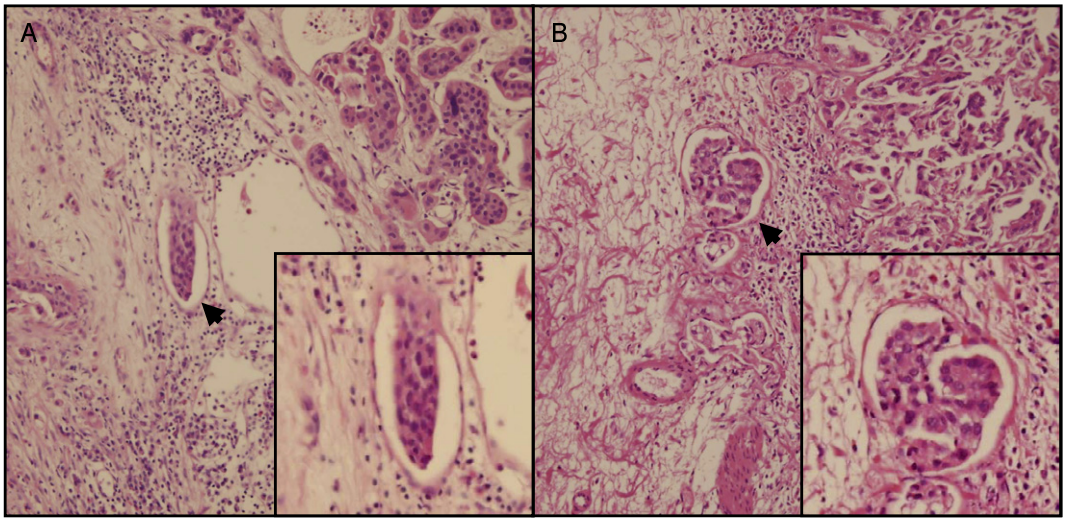

Figure 1. LVI in representative cases (*A* and *B*) of T1 bladder urothelial carcinoma. H & E, reduced from ×200 (*A* and *B*) and ×400 (insets).