Prognostic Value of Extranodal Extension and Other Lymph Node Parameters in Patients With Upper Tract Urothelial Carcinoma

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Purpose: We assessed the prognostic value of extranodal extension and other lymph node parameters in a large multicenter cohort of patients with lymph node metastasis after radical nephroureterectomy.

Materials and Methods: We retrospectively analyzed the records of 222 patients with lymph node metastasis treated with radical nephroureterectomy for upper tract urothelial carcinoma without neoadjuvant therapy. Each lymph node metastasis was microscopically evaluated for extranodal extension.

Results: A median of 4 lymph nodes (IQR 8) was removed. Two lymph nodes (IQR 2) were positive. Lymph node density was 51.3% (IQR 71.7%). Overall 110 patients (49.5%) had extranodal extension, which was associated with more advanced pT stage ($p = 0.026$). On multivariable analysis extranodal extension was associated with disease recurrence ($p = 0.01$) and cancer specific mortality ($p = 0.013$). When stratified by a 30% cutoff, lymph node density was associated with disease recurrence and cancer specific mortality on univariable but not multivariable analysis ($p = 0.048$ and 0.049, respectively). Adding extranodal extension to a multivariable model including pT stage and tumor architecture improved predictive accuracy for disease recurrence from 70.3% to 74.5% ($p < 0.001$). Adding extranodal extension to a multivariable model including age, pT stage and tumor architecture improved predictive accuracy for cancer specific mortality from 70.6% to 74.4% ($p < 0.001$).

Conclusions: Extranodal extension is a powerful predictor of clinical outcomes in patients with upper tract urothelial carcinoma with lymph node metastasis. While other lymph node parameters seem to have limited clinical value, extranodal extension could help risk stratify patients with upper tract urothelial carcinoma and lymph node metastasis for better counseling and clinical trial design.

Key Words: urinary tract, urothelium, carcinoma, neoplasm metastasis, lymph node excision

Abbreviations and Acronyms

AJCC = American Joint Committee on Cancer
CIS = carcinoma in situ
ENE = extranodal extension
LN = lymph node
LNM = LN metastasis
RNU = radical nephroureterectomy
UTUC = upper tract urothelial carcinoma

Submitted for publication July 21, 2011.

Study received institutional review board approval.

Supplementary material for this article can be obtained at www.jurology.com.

* Financial interest and/or other relationship with Abbott, Aleve and Danone.

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0022-5347/12/1873-0845/0
THE JOURNAL OF UROLOGY®

Vol. 187, 845-851, March 2012
Printed in U.S.A.
DOI:10.1016/j.juro.2011.10.158

Patients with regional LNM at RNU are at considerable risk for disease recurrence and eventual death.[1,2] However, RNU with lymphadenectomy can achieve approximately 5% to 30% 5-year cancer specific survival.[1–3] Thus, while some patients with UTUC and LNM experience rapid disease progression after RNU, others can be cured with RNU and appropriate lymphadenectomy.[1–5]

Accurate prediction of outcomes in this heterogeneous population would allow for selective inclusion into clinical trials and counseling regarding adjuvant therapy. LN density was identified as a significant prognostic variable for bladder cancer in various studies.[6–11] The number of positive LNs is associated with radical cystectomy and lymphadenectomy outcomes.[6–11] A multi-institutional study of 135 patients with UTUC and LNM showed that LN density 30% or greater is associated with cancer recurrence and mortality.[12] In contrast to lower tract urothelial carcinoma, the number of LNs removed and the number of positive LNs were not associated with outcome in patients with LNM after RNU.

We assessed the prognostic value of the number of LNs removed, the number of positive LNs, LN density and ENE in a large multicenter cohort of patients with LNM after RNU and lymphadenectomy.

MATERIALS AND METHODS

Patient Selection and Data Collection

In this institutional review board approved study all participating sites provided the necessary institutional data sharing agreements before study initiation. A total of 18 worldwide centers provided data. A computerized databank was generated for data transfer. Before final analysis the database was frozen.

The records of 2,492 patients treated with RNU for UTUC between 1987 and 2007 were reviewed. All patients underwent RNU according to standard RNU criteria, ie extrafascial kidney dissection with the entire ureteral length and an adjacent segment of bladder cuff. No patient received chemotherapy and/or radiotherapy preoperatively. No patient had metastatic UTUC or invasive bladder cancer. Regional lymphadenectomy was generally performed at surgeon discretion if LNs were abnormal on preoperative computerized tomography or palpable intraoperatively. Extended lymphadenectomy was not routinely performed. Of the 2,492 patients 817 (32.8%) underwent lymphadenectomy, including 222 (27.2%) with LNM.

Pathological Evaluation

All surgical specimens were processed by standard pathological procedures. All slides were re-reviewed by genitourinary pathologists according to identical strict criteria while blinded to clinical outcome. Tumor grade was assigned according to the 2004 WHO classification system. Pathological stage was reassigned according to the 2009 AJCC TNM system. Each metastasis was microscopically evaluated for the presence or absence of ENE, defined as clear-cut perforation of an LN capsule by tumor tissue infiltrating perinodal tissue (fig. 1). LN density was defined as the ratio of the number of positive LNs to the total number of LNs removed.

Followup Regimen

Patients were generally followed every 3 to 4 months for year 1 after RNU, every 6 months from years 2 through 5 and annually thereafter.[5] Followup consisted of history, physical examination, routine blood studies, urinary cytology, chest radiography, cystoscopic evaluation of the bladder and radiographic evaluation of the contralateral upper urinary tract. Elective imaging was performed when clinically indicated.

Disease recurrence was defined as tumor relapse in the operative field or regional lymph nodes and/or distant metastasis. Urothelial carcinoma in the bladder or contralateral upper tract was not coded as recurrent disease. Patients who died in the perioperative period, ie within 30 days of surgery, were censored at time of death for UTUC specific survival analysis.

Statistical Analysis

The Fisher exact and chi-square tests were used to evaluate associations between categorical variables. Differences in variables with a continuous distribution across categories were assessed using the Mann-Whitney U and Kruskal-Wallis tests. Univariable recurrence and survival probabilities were estimated using the Kaplan-Meier method. Univariable and multivariable Cox regression models were created to address time to recurrence and mortality. The predictive accuracy of these models was quantified with the Harrell concordance index.[13] Predictive accuracy estimates are shown as proportions and were compared with the Mantel-Haenszel test. All reported p values are 2-sided with statistical significance considered at 0.05.

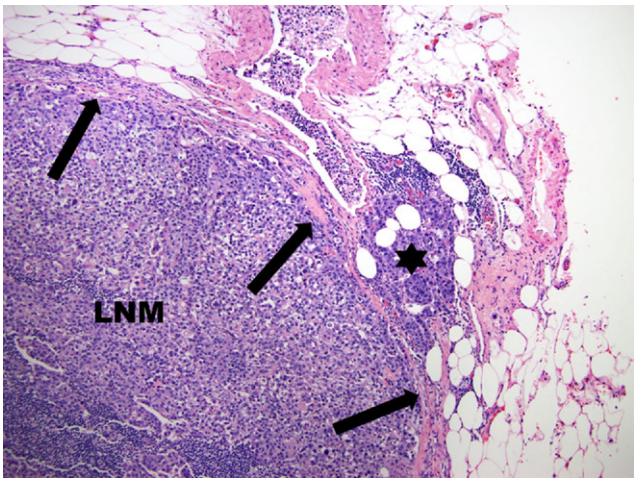

Figure 1. Representative image of urothelial carcinoma (asterisk) extranodal extension reveals tumor in adipose tissue beyond LN capsule (arrows). Reduced from ×100.