Impact of Lymph Node Dissection on Cancer Specific Survival in Patients With Upper Tract Urothelial Carcinoma Treated With Radical Nephroureterectomy

Marco Roscigno,*,† Shahrokh F. Shariat,† Vitaly Margulis,† Pierre Karakiewicz,† Mesut Remzi,† Eiji Kikuchi,† Cord Langner,† Yair Lotan,† Alon Weizer,† Karim Bensalah,† Jay D. Raman,† Christian Bolenz,† Charles C. Guo,† Christopher G. Wood,‡ Richard Zigeuner,† Jeffrey Wheat,§ Wareef Kabbani,† Theresa M. Koppie,† Casey K. Ng,† Nazareno Suardi,† Roberto Bertini,† Mario I. Fernández,† Shuji Mikami,† Masaru Isida,† Maurice Stephan Michel† and Francesco Montorsi‖

From the Vita-Salute University San Raffaele, Milan, Italy (MR, RB, FM), Clinica Alemana de Santiago, Santiago, Chile (MIF), University of Vienna, Vienna (MR), and Medical University Graz, Graz (CL, RZ), Austria, University Medical Center Mannheim, University of Heidelberg, Mannheim, Germany (CB, MSM), Keio University School of Medicine, Tokyo, Japan (EK, SM, MI), University of Rennes, Rennes, France (KB), University of Montreal, Montreal, Quebec, Canada (PK, NS), University of Texas Southwestern Medical Center, Dallas (SFS, YL, WK), and University of Texas M. D. Anderson Cancer Center, Houston (VM, CCG, CGW), Texas, University of Michigan, Ann Arbor, Michigan (AW, JW), University of California Davis, Sacramento, California (TMK), and Cornell University, New York, New York (JDR, CKN)

Abbreviations and Acronyms

CIS = carcinoma in situ
CSS = cancer specific survival
DFS = disease-free survival
ECOG PS = Eastern Cooperative Oncology Group performance status
LN = lymph node
LND = lymphadenectomy
LVI = lymphovascular invasion
RNU = radical nephroureterectomy
UTUC = upper tract urothelial cancer

Submitted for publication October 15, 2008.
Study received institutional review board approval.

* Correspondence: Vita Salute University San Raffaele, Via Olgettina 60, 20132, Milan, Italy (telephone: +39-2-2643-4199; FAX: +39-2-26437298; e-mail: roscigno.marco@hsr.it).

† Nothing to disclose.

‡ Financial interest and/or other relationship with Antigenics Inc., Pfizer Inc., Bayer/Onyx, Kidney Cancer Association and Ethicon.

§ Financial interest and/or other relationship with Johnson & Johnson.

‖ Financial interest and/or other relationship with Pfizer, Bayer, Eli Lilly, Pierre Fabre, AMS and GSK.

See Editorial on page 2412.

Editor's Note: This article is the third of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 2834 and 2835.

Purpose: We examined the impact of lymphadenectomy on the clinical outcomes of patients with upper tract urothelial cancer treated with radical nephroureterectomy.

Materials and Methods: Data were collected on 1,130 consecutive patients with pT1-4 upper tract urothelial cancer treated with radical nephroureterectomy at 13 centers worldwide. Patients were grouped according to nodal status (pN0 vs pNx vs pN+). The choice to perform lymphadenectomy was determined by the treating surgeon. All pathology slides were reevaluated by dedicated genitourinary pathologists. Univariable and multivariable Cox regression models measured the association of nodal status (pN0 vs pNx vs pN+) with cancer specific survival.

Results: Overall 412 patients (36.5%) had pN0 disease, 578 had pNx disease (51.1%) and 140 had pN+ disease (12.4%). The 5-year cancer specific survival estimate was lower in patients with pN+ compared to those with pNx disease (35% vs 69%, $p < 0.001$), which in turn was lower than that in those with pN0 disease (69% vs 77%, $p = 0.024$). In the subgroup of patients with pT1 disease (345) cancer specific survival rates were not different in those with pN0 and pNx. In pT2-4 cases (813) cancer specific survival estimates were lowest in pN+, intermediate in pNx and highest in pN0 (33% vs 58% vs 70%, $p = 0.017$). When adjusted for the effects of standard clinicopathological features pN+ was an independent predictor of cancer specific survival ($p < 0.001$). pNx was significantly associated with worse prognosis than pN0 in pT2-4 upper tract urothelial cancer only.

Conclusions: Nodal status is a significant predictor of cancer specific survival in upper tract urothelial cancer. pNx is significantly associated with a worse prognosis than pN0 in pT2-4 tumors. Patients expected to have pT2-4 disease should undergo lymphadenectomy to improve staging and thereby help guide decision making regarding adjuvant chemotherapy.

Key Words: lymph node excision; prognosis; urologic neoplasms; carcinoma, transitional cell; survival

0022-5347/09/1816-2482/0
THE JOURNAL OF UROLOGY®

Vol. 181, 2482-2489, June 2009
Printed in U.S.A.
DOI:10.1016/j.juro.2009.02.021

UPPER tract urothelial carcinoma is a relatively rare neoplasm, accounting for about 5% of all urothelial cancers.[1] Approximately 30% of patients have muscle invasive UTUC of the renal pelvis or of the ureter at presentation and the incidence of lymph node metastasis ranges from 30% to 40% at surgery.[2,3] Nodal involvement is a poor prognostic indicator, and chemotherapy and radiotherapy rarely result in significantly improved survival.[4] However, lymphadenectomy is not currently performed in all patients treated with radical nephroureterectomy for UTUC because it remains controversial whether this procedure improves patient survival.[5,6] Nevertheless, LND is known to be an essential component of the surgical management of bladder cancer because it allows not only postoperative risk stratification[7] but also seems to improve disease specific and overall survival.[8–12] Recently several studies reported that LND at RNU provides a survival benefit in patients with locally advanced UTUC.[13–15] Nonetheless these reports are comprised of small sample sizes and single institution analyses. Thus, we used a large multicenter cohort to evaluate the impact of LND on clinical outcomes of patients with UTUC treated with RNU. We further hypothesized that LND improves staging, thereby altering outcomes in patients undergoing radical surgery for UTUC.

PATIENTS AND METHODS

Patients

This study received institutional review board approval and all participating sites provided the necessary institutional data sharing agreements before study initiation. A total of 13 centers worldwide provided data. A computerized data bank was generated for data transfer. After combining the data sets reports were generated for each variable to identify data inconsistencies and other data integrity problems. Through regular communication with all sites resolution of all identified anomalies was achieved before analysis. Before the final analysis the database was frozen and the final data set was produced for the current analysis.

This study comprised 1,453 patients who underwent RNU with ipsilateral bladder cuff resection between 1987 and 2007. Patients with pTa (295) and pTis disease (28) were excluded from analysis as they had no risk of lymph node metastasis. Patients affected by muscle invasive bladder cancer before or during followup were also excluded from study, leaving 1,130 available for analysis. Median patient age was 69.9 years (range 27 to 94).

Treatment

Of the 1,130 patients 924 (82%) underwent open RNU and 206 (18%) underwent laparoscopic RNU. Overall 552 patients (49%) underwent LND (open 84%) in addition to RNU (laparoscopic 16%). The choice to perform LND was determined by the surgeon based on clinical presentation as well as the location and laterality of the primary tumor. LND normally included the para-aortic, paracaval or interaortocaval nodes from the renal hilum to the inferior mesenteric artery in renal pelvis and proximally ureteral tumors. In mid and lower ureteral tumors nodes from the renal hilum to the bifurcation of the common iliac artery and ipsilateral pelvic nodes were removed, respectively. The standardization of LND was impossible due to the multicenter and retrospective design of the study. Overall 187 patients (16.6%) received adjuvant chemotherapy, including 128 in the subgroup treated with LND. The criteria for the delivery of adjuvant chemotherapy were not standardized due to the retrospective and multicentric design of the study. In 97% of the patients chemotherapy was platinum based, consisting mainly of methotrexate, vinblastine, doxorubicin and cisplatin.

Pathological Findings

Only primary UC tumors were included in this study. All surgical specimens were processed according to standard pathological evaluation procedures and all slides were rereviewed by genitourinary pathologists according to identical strict criteria. All pathologists were blinded to clinical outcomes. LNs were identified macroscopically and/or by palpation. The total number of identified LNs and the number of LNs involved with tumor were documented. All pathological slides were rereviewed according to strict criteria by genitourinary pathologists blinded to the original pathology slides and clinical outcomes. Pathological staging was performed according to the 2002 TNM classification of the American Joint Committee on Cancer. Tumor grade was assessed according to the 1998 World Health Organization/International Society of Urological Pathology consensus classification.[16] Lymphovascular invasion was defined as the presence of tumor cells within an endothelium lined space without underlying muscular walls.[17] The presence of concomitant CIS and tumor architecture were also assessed in every representative section.[18]

To ensure the validity of the pathological data extraction 2 pathologists independently reviewed specimens from 145 patients while blinded to patient clinical parameters and the finding of the other reviewer. Inter-reader reliability measured using the intraclass correlation coefficient was greater than 0.95 for each pathological characteristic.

Followup

Patients were generally followed every 3 to 4 months for the first year following RNU, every 6 months from the second through the fifth years and annually thereafter. Followup consisted of a history, physical examination, routine blood work and serum chemistry studies, urinary cytology, chest radiography, cystoscopic evaluation of the bladder and radiographic evaluation of the contralateral upper urinary tract. Elective bone scans, chest computerized tomography or magnetic resonance imaging were performed when clinically indicated. Median followup for patients alive at last followup was 45 months (range 1 to 250).

Cause of death was determined by the treating physicians, by chart review corroborated by death certificates or by death certificates alone. Death certificates were retrieved from the archived death certificates and reviewed for cause of death. Attribution of cause of death on the death certificate is in 2 parts. Part I lists death caused by immediate cause of death (final disease or condition re-