Original Study

Predictive and Prognostic Value of Preoperative Thrombocytosis in Upper Tract Urothelial Carcinoma

Beat Foerster,[1,2] Marco Moschini,[1,3] Mohammad Abufaraj,[1,4] Francesco Soria,[1,5] Kilian M. Gust,[1,6] Morgan Rouprêt,[7] Pierre I. Karakiewicz,[8] Alberto Briganti,[3] Michael Rink,[9] Luis Kluth,[9] Romain Mathieu,[10] Vitaly Margulis,[11] Yair Lotan,[11] Atiqullah Aziz,[9] Hubert John,[2] Shahrokh F. Shariat,[1,6,11,12] for the UTUC Collaboration

Abstract

We evaluated the predictive and prognostic role of preoperative thrombocytosis (TC) in upper tract urothelial carcinoma. Records of 2492 patients undergoing radical nephroureterectomy between 1990 and 2008 were retrospectively analyzed. Preoperative TC predicts non–organ-confined disease ($P < .001$) and lymph node metastases ($P < .001$) at radical nephroureterectomy. Among other biomarkers, TC could benefit preoperative risk stratification and help guide treatment decisions.

Purpose: The purpose of this study was to evaluate the predictive and prognostic role of preoperative thrombocytosis (TC) in upper tract urothelial carcinoma (UTUC) after radical nephroureterectomy (RNU) in a large multi-institutional cohort of patients. **Methods:** Records of 2492 patients undergoing RNU for non-metastatic UTUC between 1990 and 2008 were retrospectively analyzed. Preoperative TC was defined as a platelet count $> 400 \times 10^9$/L, irrespective of gender type. Logistic regression analyses were performed to evaluate its association with pathologic features. Cox proportional hazards regression was used for estimation of recurrence-free survival, cancer-specific survival, and overall survival. **Results:** Preoperative TC was found in 309 (12.4%) patients and was associated with advanced tumor stage and grade, lymph node metastasis, lymphovascular invasion, tumor architecture, necrosis, and concomitant carcinoma in situ (P-values $\leq .027$). Preoperative TC independently predicted $\geq$ pT2 ($P < .001$), non–organ-confined ($P < .001$), and lymph node-positive ($P < .001$) disease in a preoperative model that adjusted for the effects of age, gender, location, multifocality, and tumor architecture. Within a median follow-up of 45 months, recurrence occurred in 663 (26.6%) patients with 545 (21.9%) dying of UTUC. In univariable Cox proportional hazard regression analysis, TC was significantly associated with recurrence-free survival (hazard ratio [HR], 1.32; $P = .015$) and overall survival (HR, 1.4; $P < .001$), but not cancer-specific survival (HR, 1.17; $P = .2$). In both pre- and postoperative multivariable models, when adjusted for the effects of standard clinicopathologic features, TC did not retain its association with survival outcomes. **Conclusions:** Preoperative TC is associated with adverse clinicopathologic features and predicts worse pathology at RNU. Among other serum biomarkers, TC could benefit preoperative risk stratification and help guide treatment decisions.

Clinical Genitourinary Cancer, Vol. ■, No. ■, ■-■

Keywords: Cancer of urinary tract, Platelet count, Prognostic factors, Radical nephroureterectomy, Urothelium

[1]Department of Urology, Medical University of Vienna, Vienna, Austria
[2]Department of Urology, Kantonsspital Winterthur, Winterthur, Switzerland
[3]Department of Urology, Urological Research Institute, Vita-Salute University, San Raffaele Scientific Institute, Milan, Italy
[4]Division of Urology, Department of Special Surgery, Jordan University Hospital, The University of Jordan, Amman, Jordan
[5]Division of Urology, Department of Surgical Sciences, San Giovanni Battista Hospital, University of Studies of Torino, Turin, Italy
[6]Karl Landsteiner Institute of Urology and Andrology, Vienna, Austria
[7]Department of Urology, Pitié-Salpétrière, Assistance-Publique Hôpitaux de Paris and Faculté de Médecine Pierre et Marie Curie, University Paris VI, Paris, France
[8]Department of Urology, University of Montreal, Montreal, Canada
[9]Department of Urology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[10]Department of Urology, Rennes University Hospital, Rennes, France
[11]Department of Urology, University of Texas Southwestern Medical Center, Dallas, TX
[12]Department of Urology, Weill Cornell Medical College, New York, NY

Submitted: Feb 22, 2017; Revised: Jun 9, 2017; Accepted: Jun 13, 2017

Address for correspondence: Shahrokh F. Shariat, MD, Department of Urology and Comprehensive Cancer Center, Vienna General Hospital, Medical University of Vienna, Währinger Gürtel 18-20, Vienna A-1090, Austria
E-mail contact: shahrokh.shariat@meduniwien.ac.at

1558-7673/$ - see frontmatter
http://dx.doi.org/10.1016/j.clgc.2017.06.003

Introduction

The standard treatment for nonmetastatic high-risk upper tract urothelial carcinoma (UTUC) is radical nephroureterectomy (RNU) with bladder cuff excision.[1] In low-risk cases, endoscopic kidney-sparing procedure (KSP) is the treatment of choice. Despite adequate therapy, 28% of patients experience disease recurrence, and 24% eventually succumb to UTUC within 5 years of RNU.[2-4] The current proposed risk stratification into high- and low-risk is insufficient to guide management of patients with UTUC.[5] Moreover, the role of perioperative systemic therapies and lymphadenectomy in UTUC is still unclear. To improve prediction of patients likely to fail RNU or those likely to benefit from KSP, lymphadenectomy, or perioperative chemotherapy, we need more accurate pre-RNU predictive tools. This is particularly important since ureteroscopic biopsy and cross-sectional imaging is inadequate for staging UTUC. Biological markers have been investigated for this purpose, but none has yet been implemented into clinical practice, partially because of the difficulty in obtaining them and the associated cost.[6,7] New, fast and easily obtainable, better, and cost-efficient biomarkers are needed to help improve current risk prediction and thereby clinical decision-making.

Hematologic and inflammatory changes of serum markers have been shown to be of prognostic value in various urologic and non-urologic malignancies,[8,9] with platelet count being one of them.[10] Abnormal levels of C-reactive protein,[11] hemoglobin,[12] neutrophil-to-lymphocyte ratio,[13] and platelet count[14] have been associated with tumor aggressiveness and adverse outcome in UTUC. In urothelial carcinoma of the bladder, preoperative thrombocytosis (TC) has been identified as a predictor for oncologic outcome and survival after radical cystectomy.[15,16] To date, only studies with limited sample size (n = 269) have investigated the prognostic significance of elevated platelet count in UTUC after RNU.[14]

Therefore, the aim of the current study was to evaluate the value of preoperative TC for staging and prediction of outcomes in a large multi-institutional cohort of patients treated with RNU for UTUC.

Patients and Methods

Patient Selection

This retrospective multicenter collaboration was approved by the institutional review boards of all participating sites and provided the obligated data-sharing agreements before initiation. Records of 2492 patients undergoing RNU for non-metastatic UTUC (N0-1, M0) between 1990 and 2008 were included.[17] Each center provided a computerized database. After merging, the dataset was checked for inconsistencies of variables and integrity problems, which were reported and solved through regular communication between the institutions. Prior to any analysis, all identified anomalies were resolved, and the final database was created. Patients who received pre-RNU treatment, either chemo- or radiotherapy, were excluded from the analysis.

Data Collection and Pathologic Evaluation

Preoperative platelet count was assessed within 30 days before RNU. TC was defined as a platelet count $> 400 \times 10^9$/L. This cutoff was used in the previously published studies on thrombocytosis in UTUC[14] and bladder cancer.[15]

RNU specimens were evaluated at each institution in accordance with standard pathologic practice. For determination of pathologic stage, the 2002 American Joint Committee on Cancer/International Union Against Cancer TNM classification of malignant tumors was used. Pathologic grading was set according the 1998 World Health Organization/International Society of Urologic Pathologists consensus classification system. All samples were reviewed for reclassification under the staging and grading systems stated above. Tumor location was categorized into renal pelvicalyceal or ureteral.[18] The predominant tumor architecture pattern was categorized as papillary or sessile.[19] Concomitance of 2 or more pathologically confirmed urothelial cancers in any location of the upper urinary tract was considered as multifocal.[20] Lymphovascular invasion was present when cancer cells were within endothelium-lined space without underlying muscular walls.[21]

Follow-up

RNU was performed either laparoscopically or open, together with bladder cuff excision by trans- or extravesical approach, with a curative intent. Lymph node dissection (LND) was conducted at the discretion of the surgeon, based on preoperative computed tomography staging or intraoperative suspect palpation.

The follow-up regimen consisted of visits every 3 to 4 months for the first year after RNU, every 6 months between the second and fifth year, and annually afterwards. Examinations included medical history taking, physical examination, routine blood work, urinary cytology, chest radiography, cystoscopy, and radiographic imaging of the contralateral upper tract. Whole-body skeletal scintigraphy and chest computed tomography or magnetic resonance imaging were only conducted when clinically indicated. Recurrence was considered as tumor relapse in the operative field and/or regional lymph nodes and/or distant metastasis. New tumor in the bladder or contralateral upper urinary tract was not considered as recurrence. The cause of death was asserted by the responsible physician and confirmed by chart review and/or death certificates.[22] For all patients with determination of cancer death, a previously stated disease recurrence was obligate. Deaths in the perioperative period (within 30 days of surgery) were regarded as non−cancer-specific and were censored at that particular time for cancer-specific survival (CSS) analyses.

Statistical Analysis

The association of clinic-pathologic characteristics with TC was assessed using χ^2 and Mann-Whitney U tests for categorical and continuous variables, respectively. For estimation of recurrence-free survival (RFS), CSS, and overall survival (OS) according to TC, Kaplan-Meier curves were created; comparison was done with the log-rank test. Univariable and multivariable Cox regression analyses were performed to evaluate the prognostic effect of TC on survival. Predictive value on definitive pathologic features was measured with univariable and multivariable logistic regression analyses. Model accuracy was defined by receiver operating characteristic analysis. Statistical analyses were performed using STATA 11.2 (Stata Corp, College Station, TX). All tests were 2-sided, and $P < .05$ was considered as statistically significant.

Results

Table 1 shows the clinical and pathologic characteristics and their association with TC. Of the 2492 patients, 309 (12.4%)