ELSEVIER

Urologic Oncology: Seminars and Original Investigations 30 (2012) 666–672

UROLOGIC ONCOLOGY

Original article

Macroscopic sessile tumor architecture is a pathologic feature of biologically aggressive upper tract urothelial carcinoma

Hans-Martin Fritsche, M.D.,[a] Giacomo Novara, M.D.,[b] Maximilian Burger, M.D.,[a] Amit Gupta, M.D.,[c] Kazumasa Matsumoto, M.D.,[d] Wassim Kassouf, M.D.,[e] Kanishka Sircar, M.D.,[e] Filiberto Zattoni, M.D.,[b] Tom Walton, M.D.,[f] Stefan Tritschler, M.D.,[g] Shiro Baba, M.D.,[d] Patrick J. Bastian, M.D.,[g] Juan I. Martínez-Salamanca, M.D.,[h] Christian Seitz, M.D.,[i] Wolfgang Otto, M.D.,[a] Wolf Ferdinand Wieland, M.D.,[a] Pierre I. Karakiewicz, M.D., M.P.H.,[j] Vincenzo Ficarra, M.D.,[b] Arndt Hartmann, M.D.,[k] Shahrokh F. Shariat, M.D., Ph.D.[l,*]

[a] *Caritas St. Josef Medical Center, University of Regensburg, Regensburg, Germany*
[b] *University of Padua, Padua, Italy*
[c] *University of Texas Southwestern Medical Center, Dallas, TX 75390, USA*
[d] *Kitasato University School of Medicine, Sagamihara, Japan*
[e] *McGill University Health Centre, Montréal, Canada*
[f] *Nottingham City Hospital, Nottingham, United Kingdom*
[g] *Ludwig Maximilians University, Klinikum Grosshadern, Munich, Germany*
[h] *Hospital Universitario Puerta de Hierro-Majadahonda, Universidad Autónoma de Madrid, Madrid, Spain*
[i] *General Hospital Bolzano, Bolzano, Italy*
[j] *University of Montréal, Montréal, Canada*
[k] *Institute of Pathology, University of Erlangen, Erlangen, Germany*
[l] *Weill Medical College of Cornell University, New York, NY 10021, USA*

Received 14 May 2010; received in revised form 13 July 2010; accepted 16 July 2010

Abstract

Objective: Macroscopic sessile tumor architecture was associated with adverse outcomes after radical nephroureterectomy (RNU) for upper tract urothelial carcinoma (UTUC). Before inclusion in daily clinical decision-making, the prognostic value of tumor architecture needs to be validated in an independent, external dataset. We tested whether macroscopic tumor architecture improves outcome prediction in an international cohort of patients.

Material and methods: We retrospectively studied 754 patients treated with RNU for UTUC without neoadjuvant chemotherapy at 9 centers located in Asia, Canada, and Europe. Tumor architecture was macroscopically categorized as either papillary or sessile. Univariable and multivariable Cox regression analyses were used to address recurrence-free (RFS) and cancer-specific survival (CSS) estimates.

Results: Macroscopic sessile architecture was present in 20% of the patients. Its prevalence increased with advancing pathologic stage and it was significantly associated with established features of biologically aggressive UTUC, such as tumor grade, lymph node metastasis, lymphovascular invasion, and concomitant CIS (all P values < 0.02). The median follow-up for patients who were alive at last follow-up was 40 months (IQR: 18–75 months, range: 1–271 months). Two-year RFS and CSS for tumors with papillary architecture were 85% and 90%, compared with 58% and 66% for those with macroscopic sessile architecture, respectively (P values < 0.0001). On multivariable Cox regression analyses, macroscopic sessile architecture was an independent predictor of both RFS (hazard ratio {HR}: 1.5; $P = 0.036$) and CSS (HR: 1.5; $P = 0.03$).

Conclusion: We confirmed the independent prognostic value of macroscopic tumor architecture in a large, independent, multicenter UTUC cohort. It should be reported in every pathology report and included in post-RNU predictive models in order to refine current clinical decision making regarding follow-up protocol and adjuvant therapy.

Keywords: Tumor architecture; Upper urinary tract; Urothelial carcinoma; Nephroureterectomy; Growth pattern

* Corresponding author. Tel.: (469) 363-8500; fax: (212) 746-0975.
E-mail address: sfshariat@gmail.com (S.F. Shariat).

1078-1439/$ – see front matter
doi:10.1016/j.urolonc.2010.07.010

1. Introduction

Upper urinary tract urothelial carcinoma (UTUC) comprises approximately 5% of all urothelial tumors and 10% of all renal tumors [1]. Radical nephroureterectomy (RNU) with bladder cuff resection and regional lymphadenectomy is regarded as the standard treatment in most of the patients with UTUC [2]. Biological markers for UTUC are lacking. Only tumor stage, lymph node metastasis, and grade have been documented as major prognostic factors [3–11], while the prognostic value of potential important features, such as tumor architecture, presence of necrosis, and lymphovascular invasion, remains to be proven [6,7,12–15].

Macroscopic sessile tumor architecture has been independently associated with adverse outcomes after RNU for UTUC in a single large multi-institutional retrospective study [14]. Before inclusion in daily clinical decision-making, the prognostic value of macroscopic tumor architecture needs to be validated in an independent, external dataset.

2. Materials and methods

This was an institutional review board approved study with all participating sites providing the necessary institutional data sharing agreements before initiation of the study. A total of 9 academic centers worldwide provided data. None of these institutions participated in the mentioned study by Remzi et al. [14]. A computerized databank 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 final analysis, the database was frozen, and the final data set was produced for the current analysis.

The database comprised 785 patients treated with RNU with ipsilateral bladder cuff resection between 1987 and 2008. No patient received preoperative chemotherapy or radiation therapy. Patients with concurrent urothelial carcinoma of the urinary bladder (UCB) and those in whom the macroscopic tumor architecture was not mentioned in the histopathologic report were also excluded. This left 754 patients for analysis.

Surgery was performed by several surgeons according to the standard criteria for RNU, i.e., extrafascial dissection of the kidney with the entire length of ureter and adjacent segment of the bladder cuff. The hilar and regional lymph nodes adjacent to the ipsilateral great vessel generally were resected along with enlarged lymph nodes if abnormal on preoperative computed tomography scans or palpable intra-operatively. Extended lymphadenectomy was not routinely performed.

2.1. Pathologic evaluation

All surgical specimens were processed according to standard pathologic procedures at each institution. Tumors were staged according to the American Joint Committee on Cancer–Union Internationale Contre le Cancer (UICC) TNM classification [16]. Tumor grading was assessed according to the 1998 WHO/International Society of Urologic Pathology (ISUP) consensus classification. Tumor architecture is defined based on the predominant macroscopic feature by pathologic gross examination. If present, macroscopic sessile growth was defined as being predominant. The information on macroscopic architecture was taken from the histopathologic report. Microscopic tumor architecture like trabecular, nodular, or infiltrative pattern of invasion or inverted papillary architecture was not judged [17].

2.2. Follow-up regimen

Patients were generally observed every 3 to 4 months for the first year after RNU, every 6 months from the second through the fifth years, and annually thereafter. Follow-up consisted of a history, physical examination, routine blood work and serum chemistry studies, urinary cytology, chest radiography, cystoscopic evaluation of the urinary bladder, and radiographic evaluation of the contralateral upper urinary tract. Elective bone scans, chest computed tomography, and magnetic resonance imaging were performed when clinically indicated.

Disease recurrence was defined as local failure in the operative site, regional lymph nodes, or distant metastasis. Bladder recurrences were not considered in the analysis of recurrence-free survival rate. Cause of death was determined by the treating physicians, by chart review corroborated by death certificates, or by death certificates alone. Most patients who were identified as having died of UTUC had progressive, widely disseminated metastases at the time of death. Patients who died in the perioperative period (i.e., death within 30 days of surgery) were censored at time of death for UTUC-specific survival analyses.

2.3. Statistical analysis

The Fisher's exact test and the χ^2 test were used to evaluate the association between categorical variables. Differences in variables with a continuous distribution across dichotomous categories were assessed using the Mann-Whitney U test. The Kaplan-Meier method was used to calculate survival functions, and differences were assessed with the log-rank statistic. Univariable and multivariable Cox regression models addressed time to recurrence and cancer-specific mortality after RNU. Statistical significance in this study was set as $P \leq 0.05$. All