

Original article

Effect of tumor size on recurrence-free survival of upper tract urothelial carcinoma following surgical resection

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Abstract

Objective: To identify predictors of recurrence-free survival (RFS) based on the clinicopathological features of patients with upper tract urothelial carcinoma (UTUC) who have undergone radical nephroureterectomy (RNU) with bladder cuff resection.

Materials and methods: We retrospectively reviewed the records of patients from October 1998 to July 2012 at our tertiary institution and identified 120 patients with sufficient data who underwent RNU for UTUC. We recorded various clinical and histopathological parameters as potential predictors of outcome. Recurrence was defined as any occurrence of urothelial carcinoma after RNU either intravesically, local/regionally, or at distant sites. Univariate, multivariate, and RFS analyses were conducted using the Cox regression and Kaplan-Meier methods.

Results: The median age of our cohort was 71 years (interquartile range: 64–78). Median RNU-specimen tumor size was 3.0 cm (interquartile range: 2.0–5.0 cm). Fifty-four patients (45%) had a tumor <3.0 cm and 66 (55%) had a tumor ≥3.0 cm. Eighty patients (66.7%) had organ-confined UTUC (≤pT2) and 40 (33.3%) had non-organ-confined UTUC (≥pT3). Sixty-five patients (54.2%) experienced at least 1 recurrence. Forty-three patients (35.8%) had at least 1 episode of intravesical recurrence and 28 (23.3%) had distant recurrence. A multivariate analysis revealed non-organ-confined disease (hazard ratio [HR] = 3.62, *P* < 0.001), tumor diameter ≥3 cm (HR = 1.97, *P* = 0.011), and male gender (HR = 1.81, *P* = 0.047) to be significant independent predictors of disease recurrence. The 5-year RFS rate was 46.9% and 25.8% for patients with tumor size <3 and ≥3 cm, respectively.

Conclusions: Following RNU, the incidence of recurrence remains high among patients with UTUC. In our cohort of patients, tumor diameter ≥3.0 cm, non-organ-confined UTUC, and male gender constitute important risk factors for poor RFS outcomes following RNU. These patients require diligent postoperative surveillance and may potentially benefit from perioperative systemic therapy. © 2014 Elsevier Inc. All rights reserved.

Keywords: Upper tract urothelial carcinoma; Recurrence; Tumor size; Risk factors; Pathology

1. Introduction

Upper tract urothelial carcinoma (UTUC) is rare and only comprises 5% to 7% of all urothelial tumors with an incidence of 2 cases per 100,000 person-years [1,2]. It notably carries a high risk of recurrence, despite aggressive surgical resection consisting of a radical nephroureterectomy (RNU) with bladder cuff excision, with reported recurrence

rates of 22% to 66% [1–3]. The outcomes of patients with UTUC have not significantly changed over time even though surgical techniques are continually being refined and the usage of perioperative systemic chemotherapy is increasing as adjunctive treatment [4,5]. One of the more obvious reasons for such disappointing outcomes is that UTUC is difficult to stage preoperatively. Tissue biopsies are limited by access to the tumor location, the relative thinness of the upper urinary tract, and by the ability of current equipment to obtain an adequate tissue sample for evaluation. Radiographic imaging offers marginal aid in staging of UTUC and may be limited by the often-impaired

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renal function in patients with a host of comorbidities, which are common amongst patients with UTUC.

The relatively lower incidence of UTUC combined with the difficulty in assessing risk preoperatively in these patients has resulted in efforts to delineate risk groups pertaining to the likelihood of disease recurrence and the necessity for stringent postoperative surveillance. Previous studies have identified other potential risk factors such as age, gender, concomitant carcinoma in situ (CCIS), lymphovascular invasion, multifocal tumors, and tumor architecture to supplement the proven tumor-node-metastasis classification [1,6]. Tumor size, which is widely recognized as a prognostic factor in bladder cancer for recurrence and progression, has been examined in a relatively few studies for UTUC, however only in the context of the ancillary risk of intravesical recurrence [5–8]. The aim of the present study was to determine whether tumor size along with other identified risk factors has an effect on the recurrence-free survival (RFS) of patients with UTUC.

2. Materials and methods

After obtaining approval from the institutional review board, we identified 155 patients who underwent either open or minimally invasive RNU with bladder cuff resection at our tertiary institution specifically for UTUC from October 1998 to July 2012. Minimally invasive RNU consisted of exclusively laparoscopic, hand-assisted, or robotic-assisted laparoscopic RNU. The distal ureter and bladder cuff were managed by endoscopic, extravesical, or open techniques. A lymph node dissection (LND) was performed when there was a high degree of clinical suspicion despite negative biopsy finding and in cases where suspicious lymph nodes were unamenable to biopsy. In 19 RNU cases, LND was performed as a part of a modified-template retroperitoneal LND single-arm prospective series, whose anatomical boundaries have been previously described [9]. Excluded from this study were 21 patients who had radical cystectomy with concomitant RNU and 14 patients who had previously undergone radical cystectomy. The demographic, operative, and clinicopathological data of the remaining 120 patients were reviewed in an institutional review board–approved retrospective study.

Follow-up data were obtained retrospectively through patient charts and from our institutional cancer registry. Patients were generally followed up postoperatively every 3 months for the first 2 years, then every 6 months for the next 2 years, and annually thereafter. The follow-up consists of a history, physical examination, complete blood count and metabolic panel, urine cytology, and cystoscopy. Routine imaging was obtained at the clinician's discretion every 6 to 12 months and consisted of chest x-ray and either computerized tomography or magnetic resonance imaging

of the abdomen and pelvis (with intravenous contrast depending on adequate renal function and no contraindications). Elective imaging consisting of bone scans, chest computerized tomography, or magnetic resonance imaging was obtained when clinically indicated.

Recurrence was defined as any occurrence of urothelial carcinoma after RNU intravesically, locally within the prior operative field, in the regional lymph nodes, or at distant metastatic sites.

3. Pathological findings

The 2002 American Joint Committee on Cancer tumor-node-metastasis classification was used for pathological staging [10]. Tumor grading was assessed using the 2004 World Health Organization classification [11]. All surgical specimens were processed in a standard fashion according to the guidelines of the College of American Pathologists [12]. Slides were reviewed by a genitourinary pathologist. Tumor size was reported as the maximum diameter during gross surgical specimen examination.

4. Statistical analysis

The time to recurrence was calculated from the time of RNU. Recurrence rates and RFS were estimated using the Kaplan-Meier method with comparisons made using the log-rank test. Univariable and multivariable Cox proportional hazard regression analyses were used to determine potential prognostic predictors of RFS. Variables with $P < 0.2$ in univariate Cox models were selected for multivariate analysis. Backward elimination based on likelihood ratio was used to determine a multivariate final model. Comparisons between categorical data were made using the chi-square test. Statistical analyses were conducted using SPSS 19.0 (IBM Software division, Somers, NY, USA). All reported P values are 2-sided, with statistical significance set at $P < 0.05$.

5. Results

The descriptive variables of the 120 patients who met our inclusion criteria are shown in Table 1. Pathological stage, when subdivided by organ confinement, was \leq pT2 in 80 patients (66.7%) and \geq pT3 in 40 (33.3%). The median RNU-specimen tumor diameter was 3.0 cm (interquartile range [IQR]: 2.0–5.0 cm). Of the 66 patients with a tumor size \geq 3.0 cm, 40 (33.3%) had organ-confined disease and 26 (21.7%) had non-organ-confined disease. Eleven (9.2%) patients received neoadjuvant chemotherapy, 14 (11.7%) patients received adjuvant chemotherapy, and 2 (1.7%) patients had additional adjuvant chemotherapy after being treated in the neoadjuvant setting.

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