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Urothelial Cancer

Transitional Cell Carcinoma of the Ureter: Prognostic Factors Influencing Progression and Survival

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Abstract

Objectives: We retrospectively evaluated prognostic factors for progression-free and disease-specific survival in a large cohort of patients with transitional cell carcinoma (TCC) of the ureter.
Methods: A single-centre series of 145 consecutive patients treated with partial resection of the ureter or nephroureterectomy between 1975 and 2004 was evaluated. Median follow-up was 96 mo. Routine preoperative laboratory parameters as well as clinical and tumour-specific data were assessed. Univariate and multivariate statistical analyses were performed.
Results: Five-year disease-specific survival ranged from 96.1% for stages pTa to 28.6% for pT4. Grade1 tumours were associated with 5-yr disease-specific survival rates of 100% compared with 84% for G2, and 51.9% for G3 tumours, respectively. Univariate analyses identified pT stage and grade, tumour diameter, cM and pN categories, weight loss, the presence of synchronous tumour in the renal pelvis as well as elevated levels for humoral factors such as serum alkaline phosphatase (AP), white blood cell (WBC) count, platelet count, γ-glutamyl transferase, creatinin, and blood urea nitrogen as prognostic factors. In multivariate analyses, tumour grade and WBC counts were predictive for low progression-free survival rates, whilst simultaneous tumour in the renal pelvis, high AP levels, and WBC counts were correlated with worse disease-specific survival.
Conclusions: Our retrospective analysis provides clinical factors to identify patients with TCC of the ureter at high risk for progression and death of disease. Interestingly, humoral factors such as elevated serum AP levels and high WBC counts were demonstrated to be of paramount prognostic significance besides tumour stage, grade and multifocality.

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1. Introduction

Upper urinary tract transitional cell carcinoma (UUT-TCC) is a rare disease, accounting for about 5% of all urothelial tumours [1,2]. The incidence accounts for more than 2500 new cases in the United States in 2005, with a male to female ratio of approximately 2:1 [3]. Amongst the known risk factors for the development of UUT-TCC are cigarette smoking, abuse of analgetics, occupational factors, chronic infection and stone disease, as well as antineoplastic agents such as cyclophosphamide [4]. UUT-TCC is often a multifocal disease. Whilst the incidence of bilateral tumours ranges between 2% to 8%, the ipsilateral upper urinary tract is affected in 27–36% by multifocal disease [1,4]. Only 2–4% of UUT-TCCs occur after the primary diagnosis of TCC of the urinary bladder [4,5]. In contrast, secondary TCC of the bladder after treatment of UUT-TCC occurs in up to 75% of cases [1,4,6].

Of all UUT-TCCs, about 75% are located in the collecting system of the kidney, whilst 25% occur in the ureter [1,7]. Seventy-three percent of ureteral malignancies involve the distal ureter, whilst 24% and 3% are primarily located in the middle and proximal ureter, respectively [2]. Because of the low incidence of the disease, most studies analyzing prognostic factors have included tumours of the ureter and the renal pelvis. Radical nephroureterectomy with a bladder cuff remains the standard treatment for UUT-TCC [4,7]. Survival at 5 yr following nephroureterectomy depends primarily on tumour grade and stage, and varies from 95% and 90%, respectively, for Ta/T1 tumours to 85% for T2/T3 tumours and 38% for T4 tumours [4,6]. Further prognostic factors with negative impact on survival are multiple tumours, renal insufficiency, and synchronous bladder tumours [8]. Additionally, tumour location has been demonstrated to be of prognostic importance in UUT-TCC with tumours of the renal pelvis having a better prognosis than ureteral tumours [9]. Tumours of the ureter seem to have a higher incidence of local recurrences and distant metastases compared with tumours of the renal pelvis [9]. Only a few studies have investigated prognostic factors in TCC of the ureter separately. We retrospectively evaluated a large cohort of 145 consecutive patients treated for TCC of the ureter in our institution, and performed univariate and multivariate analyses to identify prognostic factors influencing progression and survival.

2. Patients and methods

2.1. Patients

We identified 145 consecutive patients who underwent open surgery for TCC of the ureter in our department between 1975 and 2004. Patient charts were assessed for histopathologic data including tumour volume, World Health Organization grading and TNM classification [10]. Parameters such as blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum calcium, creatinin, lactate dehydrogenase (LDH), blood urea nitrogen, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transferase (γGT), bilirubin, alkaline phosphatase (AP), blood sugar, serum protein, and routine coagulation were assessed from patient charts. Furthermore, demographic and clinical data were evaluated, including preoperative body weight, size, and temperature, tumour-related symptoms such as haematuria, weight loss and/or pain, and blood pressure. Routine follow-up consisted of physical examination, ultrasound, cystoscopy, and urine cytology four times per year for the first 2 yr, twice for the third and fourth years, and once yearly thereafter. Additional studies such as intravenous urograms, computed or magnetic resonance tomography, bone scintigraphy, chest x-ray, and/or ureteroscopy were scheduled according to individual patients' risk profiles at the discretion of the responsible physician.

2.2. Statistical analyses

Progression-free survival and disease-specific survival from time of surgery were defined as end points for this retrospective analysis. Distribution of event times was calculated separately for each of the prognostic factors with the univariate product-limit method by Kaplan-Meier.

Continuous variables including tumour size, ESR, blood count, CRP, serum calcium, creatinin, LDH, blood urea nitrogen, ALT, AST, γGT, bilirubin, AP, blood sugar, serum protein, and routine coagulation parameters were dichotomized for this purpose according to the best cutoff value obtained from corresponding, single-factor receiver operator characteristic (ROC) curves with respect to the end points as reported previously [11]. If categoric factors were to be analyzed, all categories were introduced simultaneously into the statistical analysis, except when one category either did not contain or comprised only censored observations. Case censoring was applied in the analysis of progression-free analysis and disease-specific survival when the patient had no signs of recurrence or when death occurred unrelated to tumour during the observation period, respectively.

The prognostic significance of each variable was tested univariately with the log-rank test. The simultaneous effects of multiple prognostic factors were estimated by multiple regression analysis by using the Cox proportional hazards model in a forward-selection strategy. Only factors that had a prognostic impact at a significance level (p) of 0.05 according to the univariate analyses were entered into the multiple regression model. The proportional hazard assumption of these factors was met. Categoric values such as T classification