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ORIGINAL ARTICLE

Pattern and risk factors of intravesical recurrence after nephroureterectomy for upper tract urothelial carcinoma: A large Chinese center experience

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Background/purpose: There is currently no consensus about the pattern and risk factors of bladder recurrence after nephroureterectomy, especially in the Chinese population. We evaluated the pattern and risk factors based on data from a large Chinese center.

Methods: The clinical and pathological data of 438 patients with upper tract urothelial carcinoma (UTUC), who underwent nephroureterectomy at Peking University First Hospital, Beijing, China between 2000 and 2010, was retrospectively analyzed. Univariate analysis by log-rank test and multivariate analysis by Cox proportional hazards regression model were used to determine the independent risk factors.

Results: A total of 135 patients (30.8%) developed intravesical recurrence within a median follow-up of 45 months (range: 12–144 months). The median interval of bladder recurrence was 15 months (range: 2.0–98.0 months), and the two peaks for recurrence were 4–6 months and 17–19 months. Lower tumor grade, tumor multifocality, concomitant carcinoma *in situ* (CIS) and tumors located in the lower ureter were significant risk factors by univariate and multivariate analysis. A risk-scoring system was developed and a significant difference was found between different risk evaluations. Patients with concomitant CIS tended to develop a late bladder recurrence. One hundred and eighteen patients (87.4%) received transurethral resection after bladder tumor recurrence.

Conflicts of interest: None of the contributing authors have any conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

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Conclusion: Lower tumor grade, tumor multifocality, concomitant CIS and tumors located in the lower ureter tend to be predictive for bladder recurrence after nephroureterectomy, although the underlying mechanism is not fully elucidated, and the scoring system could help risk stratification. Most recurrent tumors could be treated by transurethral resection and there were two peaks for recurrence, which is probably related to the mechanisms and may be unique to the Chinese population.

Introduction

Radical nephroureterectomy with excision of the bladder cuff is the gold standard treatment for localized upper tract urothelial carcinomas (UTUC).[1] The reported recurrence rate within the bladder after treatment of a primary UTUC is about 20–50%.[2–13] Several studies have attempted to delineate the clinical and pathological criteria for predicting such recurrences.[2–13] However, most investigations analyzed a comparatively small number of patients, and to our knowledge, there are few published reports from research centers in China. Chinese herbs are mainly consumed in this cohort of population and have been proven to be related to urothelial carcinoma,[14] and the incidence of UTUCs in the Chinese population is different from that of the Western population, although the mechanism related to the ethnic difference is still unknown. Chinese UTUC patients are more likely to be female and females are less likely to be in a more advanced pathologic stage than males.[15] The recurrence pattern and predictive factors might be different and experience from Chinese centers could help understand the recurrence mechanism. We therefore conducted this study based on data from a nationwide high volume center in China, in order to identify these factors in this unique population.

Materials and methods

The follow-up data of patients who were treated at Peking University First Hospital, Beijing, China for newly diagnosed UTUC from 2000 to 2010 was reviewed. Among the 631 patients with complete follow-up, 193 were excluded from the study: 71 had concomitant/previous bladder tumors, 25 had bilateral synchronous UTUCs, 54 underwent other surgeries instead of radical nephroureterectomy, 39 had a follow-up period $<$ 12 months, two had metastasis disease, and two had a positive surgical margin. The remaining 438 patients were included in this study, and none of these patients received preoperative chemotherapy, although for some patients, adjuvant chemotherapy or radiotherapy was administered when evidence of distant metastasis or retroperitoneal recurrence was documented.

All patients were diagnosed by computed tomography, urologic ultrasound, magnetic resonance imaging (MRI), and in some patients, ureteroscopy with or without biopsy. Chest X-ray and preoperative cystoscopy were performed in all patients to rule out metastasis and concomitant bladder tumor. Urinary cytology specimens included voided specimens, catheterized bladder specimens, and selective ureteral washings. Surgical approaches included retroperitoneal open or laparoscopic nephroureterectomy. The ureter was ligated immediately after the control of the renal artery without dissecting around the kidney in all cases (for a tumor located in the lower ureter, the ureter was ligated in the proximal site of the tumor). Complete distal ureter and bladder cuff were removed entirely by extravesical dissection of the distal ureter and the intramural portion within the bladder wall through an open Gibson incision. Dissection of regional lymph nodes was performed in patients with suspicious lymph node invasion on preoperative imaging studies, or those suspected of having enlarged nodes during intraoperative inspection. All patients underwent surgery within 2 months after the occurrence of symptoms.

The follow-up regimen of affected patients included cystoscopy every 3 months for the first 2 years; cystoscopy intervals were extended to 1 year thereafter. Chest X-ray, serum creatine, abdominal ultrasound, and MRI or computed tomography were examined at the same time. We defined bladder recurrence as finding a subsequent bladder tumor during cystoscopy and confirmed it by pathology. The time of first bladder recurrence was used as the endpoint for the study. The follow-up of patients without tumor recurrence was censored to the date of their last visit. In case of death not related to the bladder cancer, follow-up was censored to the date of death.

Estimated glomerular filtration rate (eGFR) was calculated with the modified glomerular filtration rate estimating equation for Chinese patients.[16] Positive cytology was indicative of malignancy and the presence of atypical cells that were highly suggestive of urothelial carcinoma. Negative cytology was defined as no evidence of atypia, atypia without mention of malignancy, or scant cellular material. Tumor stage was assessed according to the UICC (Union for International Cancer Control) TNM classification of malignant tumors 2002. Tumor grading was assessed according to the World Health Organization (WHO) classification of 1973. Based on the site of the dominant lesion, tumor location was defined as renal pelvis or ureter, and ureter was classified as the upper ureter (above the upper border of the sacrum), the middle ureter (from the upper to the lower border of the sacrum), and the lower ureter (below the lower border of the sacrum).[17] Tumor multifocality was defined as the synchronous presence of two or more pathologically confirmed macroscopic tumors in any location.

All statistical tests were performed with SPSS version 20.0 (IBM Corp, Armonk, NY, USA); statistical significance was set at $p < 0.05$. Univariate analysis using the log-rank test and multivariate analysis using Cox's proportional hazards regression model were used. The Pearson test and the Chi-square test were used to test the distribution of categorical variables. Only variables significant by univariate analysis were considered for the multivariate analysis.