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Original article

The effect of tumor location on oncologic outcomes in patients with upper urinary tract urothelial carcinoma stratified by pathologic stage

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Abstract

Objectives: The aim of this study was to investigate the effect of tumor location on oncologic outcomes in patients with upper urinary tract urothelial carcinoma (UTUC) stratified according to pathologic stage.

Material and methods: Between January 1996 and March 2009, 503 patients with UTUC were enrolled who had undergone radical nephroureterectomies and had no nodal or distal metastases. Preoperative chemotherapy or radiation therapy was not administered to any study patient. Clinicopathologic patient characteristics were obtained and used to analyze recurrence-free survival (RFS), cancer-specific survival, and overall survival with the Cox proportional hazards model.

Results: During the median follow-up of 52 months, patients with pathologic tumor (pT) stage 3 ureteral tumors had a shorter duration of RFS compared with those with pT3 renal pelvis tumors (5-y RFS: 50% and 71%, $P = 0.047$). There was no prognostic relevance to the tumor location in pTa/Tis/T1 and pT2 diseases. RFS and cancer-specific survival were significantly shorter in duration in pT3 ureteral disease compared with pT2 diseases ($P < 0.001$ and $P = 0.028$). No differences were found in oncologic outcomes between pT3 renal pelvic and pT2 diseases. The presence of pT3 ureteral tumors actually increased the risks of disease recurrence (hazard ratio [HR] = 7.82, $P < 0.001$), cancer-specific death (HR = 5.08, $P < 0.001$), and overall mortality (HR = 3.25, $P = 0.031$).

Conclusions: Patients with UTUC and pT3 ureteral tumors had an increased risk of disease recurrence and cancer-specific death. These results underscore the need for close follow-up and the consideration of adjuvant chemotherapy for patients with pT3 ureteral cancer.

Keywords: Upper urinary tract urothelial carcinoma; Ureteral tumor; Tumor stage; disease recurrence

Introduction

Upper urinary tract urothelial carcinoma (UTUC) is a rare disease, accounting for <5% of all urothelial carcinomas worldwide [1]. The incidence of UTUC in Taiwan is unusually higher than that in other countries and comprises 20% to 33% of all urothelial cancers [2,3].

The prognostic effect of primary tumor location on oncologic outcomes in patients with UTUC is still controversial. In some study cohorts, ureteral locations have been found to be significantly associated with worse recurrence-free survival (RFS). Ureteral tumors are an independent risk factor that indicates a poor prognosis for cancer-specific survival (CSS) and RFS in patients with pathologic tumor stage (pT) 3 UTUCs [4,5]. Renal pelvic tumors that invade the renal parenchyma have been associated with a better prognosis than tumors invading peripelvic or periureteral fat [6]. Some studies have not reported any differences in oncologic outcomes between patients with ureteral and renal pelvis tumors [7–9].

In this study, we investigated the effect of tumor location on oncologic outcomes in patients with UTUC by stratifying patients according to pT stage.

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Material and methods

Patient population and enrollment criteria

Between January 1996 and March 2009, 598 consecutive Taiwanese patients with UTUC who underwent radical nephroureterectomies (RNUs) at our institution were enrolled. Of the 598 patients, 95 were excluded for the following reasons: incomplete tumor stage (11), bladder urothelial carcinoma before RNU (33), radical cystectomies with concomitant RNU (7), previous systemic chemotherapy, including neoadjuvant therapy for UTUC (7), previous radiotherapy to the pelvis (2), and nodal metastases (35). This study focused on the remaining 503 patients.

All 503 RNUs were performed by either the open or laparoscopic method. Bladder cuff resections were obtained through the open approach. The hilar and regional lymph nodes were resected if enlarged or if palpable nodes were identified preoperatively or intraoperatively. There was no adjuvant chemotherapy performed for pTa-3 diseases postoperatively (which included 495 patients). All of the 8 patients with pT4 disease underwent cisplatin-based chemotherapy after RNU and were excluded from the survival analyses.

The Research Ethics Committee of the National Taiwan University Hospital (201304027RINC) approved this study.

Clinical data collection

Patient medical records were used to obtain information about age, sex, diabetes mellitus status, hypertension status, serum creatinine levels, dialysis history, herbal medications, smoking status, and pathologic characteristics of UTUC tumors.

Estimated glomerular filtration rate was calculated using the Modification in Diet in Renal Disease Study equation [10]. The tumor location was defined as the dominantly advanced lesion at the ureteral or renal pelvis according to pathology reports. In all, 39 patients with equally advanced tumors at both ureteral and renal pelvis locations were excluded from the analyses of the association between the tumor locations and oncologic outcomes. Tumor multifocality was defined as the synchronous appearance of ≥ 2 pathologically confirmed tumors in the urinary tract. Heavy smokers were defined as people who had a cumulative smoking history of 20 pack-years or more.

Pathologists at our institution reviewed all surgical specimens. Tumors were graded according to 2004 World Health Organization classifications and staged based on 2002 TNM classifications.

Follow-up protocol

After RNU, all patients were followed regularly with cystoscopic examinations, urine cytologic tests, and renal sonography every 3 months in the first year, then every 6 months for 2 years, and annually afterward. Computed tomography or magnetic resonance imaging or both were performed annually to detect local recurrence, contralateral UTUC occurrence, and distal metastasis. Disease recurrence was defined as tumor relapse in the operative field, regional lymph nodes, or distant metastasis. Cisplatin-based chemotherapy is the primary treatment of all types of recurrent disease. A physician determined each patient's cause of death. All patients who died of UTUC had previous disease recurrence.

Statistical methods

The chi-square test was used to analyze associations between clinicopathologic parameters. The log-rank test was used to compare RFS, CSS, and overall survival (OS) periods among patient groups. The Cox proportional hazards model was used to evaluate the risk of oncologically adverse events. Prognosticators used in the multivariate model were designated from factors with a $P < 0.15$ in the univariate analysis. A $P < 0.05$ was considered statistically significant.

Results

Population characteristics

Patient demographics and clinical features stratified by tumor location are listed in Table 1. Our cohort included 249 men (49.5%) and 254 women (50.5%). The median age of all patients was 68 years (interquartile range [IQR]: 60.0–74.8 y). Overall, 280 patients had renal pelvic tumors (55.7%) and 184 patients had ureteral tumors (36.6%). The remaining 39 patients had the same T stage tumors at both the renal pelvis and ureter (7.7%). Ureteral and combined pelvic and ureteral tumors are more likely associated with high-grade disease compared with renal pelvic tumors alone (64.1%, 60%, and 50.7%, respectively; $P = 0.012$). It was also more common for patients with ureteral tumors to have advanced chronic kidney disease stages (3, 4, and 5) than patients with renal pelvic and combined tumors (69.1%, 50.3%, and 48.7%, respectively; $P < 0.001$). The presence of locally advanced disease (pT3/T4) was more frequent in renal pelvic tumors (37.5%) than in the combined locations (30.7%) and ureteral tumors (20.2%) ($P < 0.001$). No significant difference was found in the rest of the clinicopathologic characteristics among patient groups (Table 1).

Patient survival

In all, 495 patients with pTa-T3N0M0 diseases were enrolled for the survival analyses. Table 2 demonstrates disease recurrence, cancer-specific death, and overall mortality rates stratified by tumor stages and locations.