ELSEVIER

Urologic Oncology: Seminars and Original Investigations ▮ (2017) ▮▮▮–▮▮▮

UROLOGIC ONCOLOGY

Original article

# Variant histology as a significant predictor of survival after radical nephroureterectomy in patients with upper urinary tract urothelial carcinoma

Jung Kwon Kim, M.D.[a], Kyung Chul Moon, M.D., Ph.D.[b], Chang Wook Jeong, M.D., Ph.D.[c], Cheol Kwak, M.D., Ph.D.[c], Hyun Hoe Kim, M.D., Ph.D.[c], Ja Hyeon Ku, M.D., Ph.D.[c,*]

[a] *Department of Urology, Center for Prostate Cancer, Research Institute and Hospital of the National Cancer Center, Goyang, Korea*
[b] *Department of Urology, Seoul National University Hospital, Seoul, Republic of Korea*
[c] *Department of Pathology, Seoul National University Hospital, Seoul, Republic of Korea*

Received 17 October 2016; received in revised form 2 January 2017; accepted 12 February 2017

## Abstract

**Objectives:** To investigate the effect of variant histology (VH) on survival after radical nephroureterectomy in patients with upper urinary tract urothelial carcinoma (UTUC) and the effect of adjuvant chemotherapy on the survival of patients with UTUC with VH.

**Materials and methods:** A total of 452 patients who underwent radical nephroureterectomy for UTUC without neoadjuvant chemotherapy in our institution between 1991 and 2012 were retrospectively analyzed. We performed a comparative analysis between pure UTUC and UTUC with VH groups. The Kaplan-Meier method was used to calculate survival estimates for cancer-specific survival (CSS) and overall survival (OS), and log-rank test was used to conduct comparisons between the groups. Univariate and multivariate Cox-proportional hazard regression analyses were performed to evaluate significant variables associated with CSS and OS.

**Results:** UTUC with VH was present in 41 (9.1%) patients. UTUC with VH showed aggressive clinicopathological features in comparison with pure UTUC. The Kaplan-Meier curves showed significantly decreased 5-year CSS and OS (both, $P < 0.001$) in UTUC with VH group. Multivariate analysis revealed that VH was an independent predictor of CSS ($P < 0.001$) and OS ($P < 0.002$). The Kaplan-Meier curves also showed significantly decreased 5-year CSS and OS in UTUC with the VH group compared to the pure UTUC group in patients who received adjuvant chemotherapy.

**Conclusions:** We found that UTUC with VH harbored aggressive biologic features, and VH was an independent prognostic factor for CSS and OS on both univariate and multivariate analyses. In addition, UTUC with VH group had poorer survival outcomes than pure UTUC group in patients who received adjuvant chemotherapy. Consequently, adjuvant treatment modalities other than adjuvant chemotherapy should be considered in this group. 

*Keywords:* Radical nephroureterectomy; Upper urinary tract urothelial carcinoma; Variant histology

## 1. Introduction

Upper urinary tract urothelial carcinoma (UTUC) is a rare malignant neoplasm accounting for only 5% to 10% of UCs [1]. Radical nephroureterectomy (RNU) with bladder cuffing is still the standard of care for invasive, nonmetastatic UTUC [1,2]. Despite its durable long-term disease control in early-stage patients, UTUC is a biologically aggressive malignant neoplasm with the potential for disease recurrence and cancer-specific mortality [1,3]. Several subsequent studies aimed to determine potential prognostic factors of survival after RNU in patients with UTUC [2,4,5].

Variant histology (VH) in UC of the bladder is generally an unfavorable prognostic factor in association with high grade and advanced pathologic T stage at the time of presentation [6–10]. In addition, several UTUC-focused studies associated VH with poorer survival outcomes than

This work was supported by the National Research Foundation of Korea, South Korea (NRF) grant funded by the Korea government (MSIP) (No. 2016R1A2B4011623).

* Corresponding author. Tel.: +82-2-2072-0361; fax: +82-2-742-4665.
*E-mail address:* kuuro70@snu.ac.kr (J.H. Ku).

http://dx.doi.org/10.1016/j.urolonc.2017.02.010
1078-1439/

pure UTUC [11–16]. Accordingly, some patients with VH were recommended to receive adjuvant chemotherapy and intensive surveillance protocols [11,13,15,17]. However, most studies failed to achieve statistical significance on multivariate analysis [12–15].

In the current study, we investigated the effect of VH on survival after RNU in patients with UTUC and the effect of adjuvant chemotherapy on the survival of patients with UTUC with VH.

## 2. Methods

### 2.1. Ethics statement

The Institutional Review Boards of the Seoul National University Hospital approved this study (Approval number: H-1606-027-768). As this study was carried out retrospectively, written informed consent from patients was waived. Personal identifiers were completely removed, and the data were analyzed anonymously. Our study was conducted according to the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

### 2.2. Study cohort

A total of 461 patients who underwent RNU for clinically localized UTUC between 1991 and 2012 at our institution were included in this study. Clinical data in the medical records were retrospectively reviewed. Patients who had a diagnosis of non-UC ($n = 3$) following analysis of their final RNU specimen and those with a history of treatment with neoadjuvant chemotherapy ($n = 6$) were excluded from the study. Consequently, a total of 452 cases were finally analyzed. The workup, surgery, pathologic review, and follow-up have been previously detailed [3].

### 2.3. Acquisition and definition of data

RNU was performed in cases of highly suspected UTUC in preoperative computed tomography (CT) or retrograde urography or both. Ureteroscopy or ureterscopic biopsy was performed in some patients with ambiguous preoperative evaluations.

Among the patients, open ($n = 332$) and laparoscopic ($n = 120$) RNU were performed by various surgeons at our institution using standard techniques. The hilar or regional lymph nodes (LNs) adjacent to the great vessel were generally resected if palpable intraoperatively or enlarged on preoperative CT scan. The extent of lymphadenectomy performed was at the discretion of the individual surgeons.

The evaluation of pathological specimens of RNU was conducted by staff pathologists with genitourinary expertise according to the standard pathological procedure at our institution. Pathological staging was assigned to the 2002 TNM classification by the American Joint Committee on Cancer-Union for International Cancer Control (AJCC/UICC) [18], and pathological grading was assessed according to both the recommended 1973 world health organization (WHO) system and the 1998/2004 International Society of Urological Pathology/WHO consensus classification [1,19]. T staging was categorized into pT0/a/is/1, pT2, and pT3/4 to facilitate statistical analyses.

Other analyzed covariates, including age, sex, body mass index, American Society of Anesthesiologists (ASA) score, preoperative ureteroscopic evaluation and biopsy, pathologic N stage, number of removed LNs and positive LNs, lymphovascular invasion (LVI), carcinoma in situ, multifocality, surgical margin status, hydronephrosis, tumor location, adjuvant chemotherapy, intravesical recurrence (IVR), follow-up duration, cancer-specific death, and all-cause death, were obtained from medical records. The duration of survival was calculated from the date of surgery to the date of last follow-up or death. Cause of death was determined by the responsible physicians and death certificates.

### 2.4. Adjuvant chemotherapy

Adjuvant chemotherapy was defined as receiving any regimen of treatment that started within 3 months after RNU. In addition, administration of less than 3 cycles of adjuvant chemotherapy was also excluded. Notably, adjuvant chemotherapy in patients reported as high-risk tumors was based on our institutional policy during this period. Accordingly, cisplatin-based chemotherapy regimen was the most common regimen, as described previously, depending on the patient's eligibility and renal function [20,21].

### 2.5. Follow-up protocol

According to our standardized postoperative protocol, patients were generally followed up after RNU at least every 3 to 4 months for the first year and then were followed up semiannually from the year 2 through year 5. After 5 years, patients were seen annually. Follow-up consisted of physical examination, serum chemistry evaluation, urinary cytology, cystoscopic evaluation of the urinary bladder, chest X-rays, renal ultrasound, or CT scan.

### 2.6. Statistical analyses

The clinicopathological characteristics were compared between pure UTUC and UTUC with VH groups using chi-squared test for categorical variables, and independent *t*-test or Mann-Whitney *U* test for continuous variables. The Kaplan-Meier method was used to calculate survival estimates for cancer-specific survival (CSS) and overall survival (OS), and log-rank test was used to conduct comparisons between the groups. Univariate and multivariate Cox-proportional hazard regression analyses were