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Original article

Influence of late-stage chronic kidney disease on overall survival in patients with upper tract urothelial carcinoma following radical nephroureterectomy

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ABSTRACT

Objectives: The prevalence of both chronic kidney disease (CKD) and upper tract urothelial carcinoma (UTUC) in Taiwan is unusually high, and we aimed to investigate the impact of preoperative renal function on UTUC after radical nephroureterectomy.
Materials and methods: Between 2000 and 2013, 248 UTUC patients were enrolled in this retrospective study after excluding patients who had concomitant muscle-invasive bladder cancer, whose tumor metastasized at initial presentation, and who received perioperative chemotherapy or radiotherapy. The significance of CKD on overall survival (OS), cancer-specific survival (CSS), and bladder recurrence-free survival (BRFS) was evaluated by Cox proportional hazard model.
Results: The median follow-up time was 45.41 months. Overall 5-year OS, CSS, and BRFS rates were 78.27%, 87.81%, and 70.42%, respectively. Aging, late-stage CKD, and nonorgan-confined primary tumor stage were independent predictors for OS after adjustment. Nonorgan-confined primary tumor stage and lymph node involvement were two independent predictors for CSS after adjustment. Concomitant bladder tumor was the only significant predictor for BRFS after adjustment.
Conclusion: Patients with late-stage CKD had a higher risk of having poor OS. Patients with concomitant bladder tumor had a greater risk of having bladder cancer recurrence despite primary tumor stage. Concomitant bladder tumor, however, had no effect on OS and CSS in this study.

1. Introduction

Upper tract urothelial carcinoma (UTUC) is an uncommon disease, and the incidence rate of all UCs in the West is around 5%.[1] However, the incidence of UTUC is extraordinarily high in Taiwan, accounting for about 30% of all UCs.[2] Although nephron-sparing surgery, including partial nephrectomy, segmental ureterectomy, and endoscopic management, is feasible in selected UTUC patients, radical nephroureterectomy (RNU) remains the gold standard for high-grade, invasive UTUC.

Chronic kidney disease (CKD) is another popular disease in Taiwan. According to the 2013 annual report of the United States Renal Data System, the prevalence of end-stage renal disease in Taiwan is the highest in the world, and the high dialysis rate leads to a substantial increase in medical expenses. In addition, the CKD population have a worse all-cause mortality, increased cardiovascular events, and more frequent hospitalization.[3,4] It has been demonstrated that evaluation of the serum creatinine level alone is not an ideal tool to estimate renal function.[5] Coresh et al[6] showed that around 5% of patients with stage III or greater CKD have normal serum creatinine levels. Instead, estimated glomerular filtration rate (eGFR) was clinically applied to represent patients' renal function.

UTUC is a major cancer in patients with CKD/end-stage renal disease in Taiwan, but the investigation of the association

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between CKD and UTUC remains limited to date. The aim of this study was to evaluate the impact of a variety of clinicopathological factors as well as preoperative renal function on overall survival (OS), cancer-specific survival (CSS), and bladder recurrence-free survival (BRFS) in a cohort of patients following RNU for primary UTUC.

2. Materials and methods

2.1. Patients and data collection

We conducted this study by retrospective chart review. The study protocol was approved by the Institutional Review Board of Kaohsiung Medical University Hospital, Kaohsiung, Taiwan. A total of 248 patients with UTUC undergoing RNU between January 2000 and June 2013 were enrolled. The exclusion criteria included concomitant muscle-invasive bladder cancer, metastatic or bilateral UTUC at initial presentation, perioperative chemotherapy or radiotherapy, and incomplete clinical information. Clinical and pathological data were recorded for each patient. Open or laparoscopic RNU was performed according to surgeons' preference. Seventy-two patients (29.03%) received transurethral resection of bladder tumor due to concomitant nonmuscle-invasive bladder cancer (NMIBC).

Patients were followed-up postoperatively with urine cytology and cystoscopy (every 3 months for the first 2 years and every 6 months for the next 2 years, and every year thereafter). Chest X ray, abdominal ultrasound, intravenous urography, and abdominal computed tomography were arranged every 3–6 months according to physician's consideration. The cause of death was confirmed by chart review and/or death certificate.

2.2. Statistical analysis

Parameters including age, sex, cigarette smoking, estimated renal function within 3 weeks prior to surgery, tumor location (either pelvis or ureter, or simultaneously in both regions), pathological tumor stage, lymph node metastasis, surgical modality, bladder cuff management, and concomitant NMIBC were documented. As mentioned earlier, preoperative renal function was estimated by eGFR, calculated using the Modification of Diet in Renal Disease study equation[7]:

$$186 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}).$$

Patients with late-stage CKD (stage IV or V), characterized by high hemodialysis rates, were qualitatively different from those with early stage (stage I, II, or III) CKD in the disease complexity, mortality, and economic impact.[8] Therefore, patients were dichotomized into the early (eGFR $\geq$ 30 mL/min/1.73 m^2) and late (eGFR < 30 mL/min/1.73 m^2) CKD groups. Tumors were staged according to the American Joint Committee on Cancer tumor, node, and metastasis classification, 7th edition and graded using the 2004 World Health Organization/International Society of Urologic Pathology consensus classification. Bladder cuff was resected by the transvesical, extravesical, or transurethral incision (TUI) method. The detailed surgical technique was described previously.[9]

Survival rates were calculated from the date of RNU to the date of all-cause mortality, cancer-specific death, bladder cancer recurrence, or last visit. All variables included were entered into multivariate Cox proportional hazard model to identify independent predictors for OS, CSS, and BRFS. All statistical tests were performed using SPSS version 19.0 (IBM Corp., Armonk, NY, USA) and statistical significance of p was set at 0.05.

3. Results

Patients' demographic data are listed in Table 1. The median age was 68 years (range, 24–95 years) with a slight female predominance (59.68%). Forty-seven cases (18.95%) were current smokers and nearly one third of the patients (31.85%) had late-stage CKD. Tumors were similarly located at the renal calyx/pelvis and ureter (43.95% and 41.53%, respectively). As for pathological distribution, 47 patients (18.95%) were noninvasive (pT_a/pT_{is}), 73 patients (29.44%) were pT_1, 71 patients (28.63%) were pT_2, 48 patients (19.35%) were pT_3, and nine patients (3.63%) were pT_4. Seven cases (2.82%) had lymph node metastasis and most were of high grade (74.60%). Of the 248 patients, 152 (61.29%) underwent open RNU, and 96 (38.71%) were treated by laparoscopic approach. As for bladder cuff management, most patients received TUI or extravesical methods (43.95% and 42.34%, respectively). In addition, all clinicopathological parameters analyzed were not significantly different between the early and late-stage CKD groups except sex.

3.1. Survival analysis

The median follow-up was 45.4 months (range, 1–144 months). Overall and cancer-specific death was recorded in 58 (23.39%) cases and 32 (12.90%) cases, respectively, and 61 (24.60%) patients had bladder cancer recurrence. The 5-year OS, CSS, and BRFS rates were 78.27%, 87.81%, and 70.42%, respectively.

In univariate analysis, aging, high-grade, nonorgan-confined primary tumor stage (pT_{3-4}), lymph node involvement, and bladder cuff management were significantly associated with poor OS (Table 2). Late-stage CKD had a marginal effect on OS ($p = 0.073$). After multivariate adjustment, the independent predictors for OS were aging [hazards ratio (HR), 1.78; 95% confidence interval (CI), 1.04–3.04, $p = 0.037$], late-stage CKD (HR, 1.96; 95% CI, 1.10–3.50, $p = 0.023$), and nonorgan-confined primary tumor stage (HR, 2.00, 95% CI, 1.05–3.81, $p = 0.035$).

As shown in Table 3, nonorgan-confined primary tumor stage and lymph node involvement were the only two significant prognostic factors associated with worse CSS in both univariate ($p < 0.001$ in both cases) and multivariate ($p = 0.022$ and $p = 0.017$, respectively) analyses.

Lastly, the presence of concomitant bladder tumor was a significant predictor for BRFS in univariate analysis (Table 4). In multivariate Cox proportional hazard model, concomitant bladder tumor posed an 11.76-fold increase in the risk of bladder cancer recurrence (95% CI, 6.39–21.65; $p < 0.001$).

4. Discussion

UTUC is an uncommon cancer but its incidence in Taiwan is much higher than across the world.[2] RNU remains the gold-standard treatment for UTUC although a number of nephron-sparing surgeries are being developed. Several clinicopathological factors have been reported to be associated with outcome of UTUC patients following RNU, such as aging, multifocality, pathological stage, lymphovascular invasion, surgical approach, and bladder cuff management.[10–15] Although the relationship between CKD and UTUC has been discussed before,[16–18] the influence of CKD on UTUC outcome was seldom mentioned.

CKD is a rather common disorder in Taiwan with a prevalence rate of 12% (95% CI, 11.66–12.28%).[4] Patients having dialysis therapy due to end-stage renal disease were at higher risk of various cancers, including UC.[19–21] The underlying mechanism of cancer development may possibly be related to impaired DNA repair, immunocompromised status, nutritional deficiencies, and persistent urinary tract irritation resulting from chronic infection/