Biological Behavior and Long-Term Outcomes of Carcinoma In Situ in Upper Urinary Tract Managed by Radical Nephroureterectomy

Teruo Inamoto,* Hideyasu Matsuyama, Naokazu Ibuki, Kazumasa Komura, Kiyoshi Takahara, Kiyohide Fujimoto, Hiroaki Shiina, Shigeru Sakano, Kazuhiro Nagao, Makito Miyake, Yoshihiro Tatsumi, Hiroaki Yasumoto, Haruhito Azuma and the Nishinihon Uro-Oncology Collaborative Group

From the Departments of Urology, Osaka Medical College (TI, NI, KK, KT, HA), Takatsuki, Graduate School of Medicine, Yamaguchi University (HM, SS, KN), Ube, Nara Medical University (KF, MM, YT), Kashihara and Shimane University School of Medicine (HS, HY), Izumo, Japan

Purpose: In patients with urothelial carcinoma CIS (carcinoma in situ) generally has a poor prognosis. However, to our knowledge the outcomes of pure/primary CIS and the behavior of CIS concomitant with pTa-pT4 upper tract urothelial carcinoma managed by nephroureterectomy have not been previously specified. We explored the biological and prognostic features of concomitant CIS compared with those of pure/primary CIS.

Materials and Methods: We queried a multicenter upper tract urothelial carcinoma database. Data from NUOG (Nishinihon Uro-Oncology Group) were analyzed, including patient gender, age, presence of bladder cancer and pT stage. Clinicopathological features were compared between the different subtypes. Cancer specific and overall survival, and the relative excess risk of death were estimated by CIS subtype.

Results: We identified 163 patients with CIS in the upper urinary tract, of whom pure/primary CIS was noted in 24.5%. In the concomitant CIS cohort the pathological diagnosis of the nonCIS region was pTa, pT1, pT2, pT3 and pT4 in 4.9%, 22.8%, 25.2%, 44.7% and 1.6% of patients, respectively. The sensitivity of a selective urine cytology test was higher in the pure/primary CIS group than in the concomitant CIS group (60.0% vs 37.4%). At a median followup of 32 months 10-year estimated mean cancer specific survival was 92.4 months (range 83.7 to 101.0) in the overall CIS cohort. Ten-year estimated mean cancer specific survival in patients with pure/primary CIS was significantly longer than in patients with concomitant carcinoma in situ (111.8 months, range 101.0 to 122.6 vs 85.89, range 75.3 to 96.5, log rank p = 0.007).

Conclusions: Patients presenting with concomitant CIS have a worse outcome than those who present with pure/primary CIS, suggesting a need to differentiate these 2 entities in the treatment decision process.

Key Words: ureter, kidney, carcinoma in situ, urothelium, prognosis

Abbreviations and Acronyms

BCG = bacillus Calmette-Guérin
B-CIS = bladder CIS
c-CIS = concomitant CIS
CIS = carcinoma in situ
CSS = cancer specific survival
p-CIS = pure/primary CIS
RNU = radical nephroureterectomy
UTUC = upper tract urothelial carcinoma
UTUC-CIS = CIS of renal pelvicalyceal system and ureters

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* Correspondence: Department of Urology, Osaka Medical College, 2-7 Daigaku-machi, Takatsuki City, Osaka 569-8686, Japan (telephone: 81-72-683-1221; FAX: 81-72-684-6546; e-mail: tinamoto@osaka-med.ac.jp).

UROTHELIAL carcinoma is the fourth and the sixth most common solid malignancy in men and women, respectively.[1,2] However, primary UTUC is less common and accounts for only 5% to 10% of all urothelial tumors.[1,2] To date RNU with bladder cuff excision has been the gold

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standard treatment in patients with a normal contralateral kidney for high grade and invasive tumors, offering adequate local tumor control and survival. However, kidney sparing treatment using endoscopic approaches plus laser vaporization has been established for a select patient group with low grade and noninvasive disease.[3,4] At diagnosis the disease is often multifocal and 50% to 60% of UTUCs are invasive compared with 15% to 25% of all bladder tumors.[2] Correct tumor characterization is necessary to make the optimal treatment choice.

To our knowledge the therapeutic impact of RNU on long-term survival in patients with UTUC-CIS remains unknown. The retrograde ureteroorenoscopic approach is preferred for tumors smaller than 15 mm. It is important and often difficult to visually differentiate inflammation or guidewire trauma from CIS or low grade Ta disease.[5]

B-CIS and UTUC-CIS are thought to behave differently, although they appear to be pathologically identical.[6] B-CIS typically progresses to higher stage disease in approximately 50% of patients without treatment, and 10 and 15-year cancer specific survival is 79% and 74%, respectively.[6] Conversely the progression rate of UTUC-CIS is 5% with topical therapy and it has a 95% 5-year disease specific survival rate.[6] However, in most studies of conservative therapy the absence of a solid upper tract tumor and the presence of positive retrograde selective urine cytology results were combined to define UTUC-CIS.

Flat tumors or CIS are often difficult to see with white light endoscopy.[7] The usefulness of the fluorescence in situ hybridization assay of UTUC is still debated with its limitations of false-positive and positive predictive values. Urine cytology examination has low sensitivity and around 60% specificity for low grade UTUC, although it is more accurate for detecting high grade lesions and CIS.[8]

The natural history and prognosis, and the positive cytology rate in p-CIS and c-CIS cases has not yet been specified to our knowledge. A concomitant muscle invasive region with CIS may represent the determinant of prognosis. In the current study we compared the prognosis of patients with pure CIS and c-CIS, and assessed the background of whole UTUC-CIS.

METHODS

Study Design and Population

We performed a retrospective study of data from academic centers. The study included consecutive patients with UTUC who underwent RNU between 1995 and 2009. The study cohort comprised 1,510 patients from a total of 4 academic or cancer referral centers. Data sharing agreements and institutional review board approval were obtained at each study site.

Of these patients 163 with CIS were identified for the current analyses. Pathological confirmation of CIS coupled with confirmation of absent papillary tumors was defined as p-CIS. The presence of CIS in association with another pathological stage was defined as c-CIS. All patients had previous, histologically confirmed transitional cell carcinoma with no evidence of distant metastases (anyT, N0, M0). They were followed with office based cystoscopy and voided urinary cytology.

Patients were included in study at various stages of followup. None had a prior history of bladder cancer or bladder CIS and none of them were treated with BCG in the bladder or the upper tract. Patients who received neoadjuvant chemotherapy, those with previous contralateral UTUC and those with a history of muscle invasive bladder cancer were excluded from study. Those who underwent ureteroscopy and endoscopic treatment or other surgery simultaneously were also excluded.

Voided urine cytology was invariably obtained before cystoscopy. Patients with suspicious cystoscopy and/or positive cytology results were evaluated with retrograde transureteral biopsies with or without biopsy of suspicious lesions. At each participating institution all histology slides were reviewed by a dedicated pathologist. Cytology was considered positive only when malignant cells were present. Computerized tomography was performed every 6 months for 5 years and annually thereafter.

Urothelial recurrence was defined as the first histologically documented tumor relapse in the bladder. Of the 163 patients in the CIS cohorts 85 experienced tumor recurrence in the urinary tract, including 65 in c-CIS cohorts and 20 in p-CIS cohorts. Grade according to the 1973 WHO classification was missing in 7 patients included in study because tumor stage according to the 1997 TNM classification was available.

Patients with UTUC were treated with RNU with a bladder cuff with curative intent. None of the patients in the current analysis received systemic preoperative chemotherapy or radiotherapy.

Statistical Methods

Patients were followed until death or the date of loss to followup. CSS and overall survival were obtained and evaluated as functions of age (discrete and continuous). Overall survival events included all deaths in the cohort under investigation. Death from the disease of interest was not separated from death from another cause.

The Kaplan-Meier method was used to estimate the survival rate and log rank test was used to compare the survival rate among the 4 age cohorts. Tests of association and correlation were performed with the Pearson chi-square test or the Fisher exact test when appropriate. One-way ANOVA was applied to compare continuous variables between 2 or more groups. Statistical significance was considered at $p < 0.05$. Statistical analyses were performed with IBM® SPSS®, version 24.0.

RESULTS

Table 1 lists patient characteristics. Of the 163 patients included in study 122 had no bladder