ELSEVIER

Urologic Oncology: Seminars and Original Investigations 29 (2011) 383–387

UROLOGIC ONCOLOGY

Original article

Bladder cancer after nephroureterectomy in patients with urothelial carcinoma of the upper urinary tract

Ja Hyeon Ku, M.D., Woo Seok Choi, M.D., Cheol Kwak, M.D., Hyeon Hoe Kim, M.D., Ph.D.*

Department of Urology, Seoul National University College of Medicine, Seoul, Korea

Received 24 February 2009; received in revised form 6 April 2009; accepted 7 April 2009

Abstract

Objectives: To determine the independent risk factors of bladder recurrence in patients with upper urinary tract (UUT) urothelial carcinoma (UC).

Materials and methods: A total of 181 patients with UUT-UC were enrolled in this study. Their median age was 63 years (range 36–90), and median follow-up after total nephroureterectomy was 37.5 months (range 1.0–174.0). The end-point of this study was defined as the initial intravesical recurrence of UC.

Results: Of the 181 patients, 64 (35.4%) developed subsequent bladder tumors at a median interval of 6.3 months (range 1.7–50.1) after initial treatment. By univariate analysis, a previous bladder tumor history ($P = 0.046$) and tumor necrosis ($P < 0.001$) were found to have a significant prognostic impact on bladder tumor-free survival in patients with superficial UUT-UC, whereas surgical margin status ($P = 0.045$) and the use of adjuvant chemotherapy ($P = 0.003$) were found to be prognostic factors for bladder tumor-free survival in those with invasive UUT-UC. However, by multivariate analysis, only tumor necrosis ($P = 0.012$, relative risk = 6.512) was found to have a significant impact on intravesical recurrence in patients with superficial UUT-UC. However, surgical margin status ($P = 0.007$, relative risk = 5.846) and the use of adjuvant chemotherapy ($P = 0.001$, relative risk = 0.223) were retained as independent predictors of bladder tumor survival in those with invasive UUT-UC.

Conclusions: Our findings may be useful in patients with UUT-UC who may require more stringent follow-up by cystoscopy to detect bladder tumors.

Keywords: Urothelial carcinoma; Ureter; Urothelial cancer; Bladder neoplasms

1. Introduction

Urothelial carcinoma (UC) of the upper urinary tract is relatively uncommon. Since the formation of tumors, either synchronously and/or metachronously, in multiple foci throughout the urinary tract is an important feature of UC, the development of bladder tumors is possible in patients with upper urinary tract UC. However, although several studies have focused on the risk factors of the subsequent development of bladder cancer after total nephroureterectomy, results have exhibited significant differences from setting to setting [1–6]. This is partly because cancer of high stage and grade in the upper urinary tract tends to develop distant metastasis, and, thus, often patients succumb to the original disease before recurrence in the bladder becomes clinically apparent. The clinical and pathologic features that affect the subsequent intravesical recurrence of cancer remain to be elucidated. The aim of the present study was to identify the independent risk factors of bladder recurrence in patients with upper urinary tract UC.

2. Patients and methods

Approval of the study was obtained from the Institutional Review Board. We reviewed clinical data of the 204 patients who received surgical management for an upper urinary tract tumor at our institution from 1991 to 2006. Those excluded from this study included 2 patients who had undergone radical cystectomy, 5 who underwent concomitant radical cystectomy due to invasive bladder tumor, 4 who

* Corresponding author. Tel.: +82-2-2072-2425; fax: +82-2-742-4665.
E-mail address: hhkim@snu.ac.kr (H.H. Kim).

1078-1439/$ – see front matter
doi:10.1016/j.urolonc.2009.04.007

received neoadjuvant systemic chemotherapy, 6 with distant metastasis at diagnosis, 2 who underwent upper urinary tract UC managed by ureterectomy, 3 with a nontransitional histology, and 1 with CIS only. The clinicopathologic data of the remaining 181 patients were retrospectively reviewed.

Median patient age was 63 years (range 36–90). Of the 181 patients included, 164 (90.6%) received nephroureterectomy with removal of the bladder cuff, while nephroureterectomy was performed in the remaining 17 (9.4%) without bladder cuff excision. Postoperatively, cisplatin-based adjuvant chemotherapy was performed in 48 patients (29.4%) including methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) regimen in 32, gemcitabine and cisplatin (G-C) in 14, or cisplatin, cyclophosphamide, and doxorubicin (CISCA) in 2. Pathologic stages and tumor grades were diagnosed according to the TNM and World Health Organization classifications, respectively. Lymphovascular invasion was defined as the unequivocal presence of tumor cells within the endothelial linings of lymphatic and/or vascular channels [7]. The presence of tumor necrosis was evaluated based on macroscopic tumor descriptions, and tumors were considered necrotic only if they exhibited >10% macroscopic necrosis, which is apparent to experienced pathologists by gross examination of surgical specimens [8]. Patients underwent cystoscopy and urinary cytology every 3 months, with chest X-ray, intravenous urography, and abdominal and/or pelvic computed tomography every 6 months. In the absence of urothelial cancer relapse within 2 years after surgery, re-examination intervals were extended.

The end-point of this study was defined as the initial intravesical recurrence of UC. Bladder tumor-free survival was defined as the period between the date of total nephroureterectomy to the date of initial intravesical recurrence. Survival data was analyzed by the Kaplan-Meier method using a log-rank test. Multivariate analysis using Cox's proportional hazards model was used to determine the contribution of several clinicopathologic factors to the bladder tumor-free survival rates of patients with upper urinary tract UC. All P values were two-sided and P values < 0.05 were regarded significant. All statistical analyses were performed with SPSS software (Statistical Package for the Social Sciences, SPSS Inc., Chicago, IL).

3. Results

Median follow-up after total nephroureterectomy was 37.5 months (range 1.0–174.0). Of the 181 study subjects, 64 (35.4%) developed subsequent bladder tumors at a median interval of 6.3 months (range 1.7–50.1) after initial treatment. Pathologic stages and grades of initial intravesical recurrence were distributed as follows: 31 patients had a pTa tumor, 22 a pT1 tumor, 1 a pT2 tumor, 1 a pT4 tumor, 6 a grade 1 tumor, 38 a grade 2 tumor, and 9 had a grade 3 tumor. Patients with tumor necrosis had larger tumor size than those without tumor necrosis (3.5 ± 0.2 vs. 5.2 ± 0.8, $P = 0.008$). No differences were found between patients with and without bladder recurrence in terms of metastasis free survival ($P = 0.605$), cancer specific survival ($P = 0.416$), or overall survival ($P = 0.236$) (data not shown).

Table 1
Clinical and pathological characteristics

Variables	No recurrence	Recurrence	P value (Log-rank test)
Age (years)			0.205
<60	46 (70.8%)	19 (29.2%)	
≥60	71 (61.2%)	45 (38.8%)	
Sex			0.300
Male	90 (63.4%)	52 (36.6%)	
Female	27 (69.2%)	12 (30.8%)	
Body mass index (kg/cm^2)			0.065
<25	63 (58.3%)	45 (41.7%)	
≥25	54 (74.0%)	19 (26.0%)	
ASA score			0.779
1	43 (69.4%)	19 (30.6%)	
2–3	74 (62.2%)	45 (37.8%)	
Previous bladder tumor history			0.461
Absent	107 (65.2%)	57 (34.8%)	
Present	10 (58.8%)	7 (41.2%)	
Tumor location			0.852
Pelvis	57 (64.8%)	31 (35.2%)	
Ureter	60 (64.5%)	33 (35.5%)	
Tumor size (cm)			0.254
<3	57 (67.9%)	27 (32.1%)	
≥3	60 (61.9%)	37 (38.1%)	
Procedure			0.657
Without cuff excision	10 (58.8%)	7 (41.2%)	
With cuff excision	107 (65.2%)	57 (34.8%)	
Pathologic T stage			0.360
pTa-T1	40 (67.8%)	19 (32.2%)	
pT2-4	77 (63.1%)	45 (36.9%)	
Tumor grade			0.747
1–2	80 (65.0%)	43 (35.0%)	
3	37 (63.8%)	21 (36.2%)	
Lymph node status			0.913
Negative	111 (64.5%)	61 (35.5%)	
Positive	6 (66.7%)	3 (33.3%)	
Concomitant CIS lesion			0.477
Absent	110 (65.5%)	58 (34.5%)	
Present	7 (53.8%)	6 (46.2%)	
Lymphovascular invasion			0.842
Absent	86 (64.7%)	47 (35.3%)	
Present	31 (64.6%)	17 (35.4%)	
Tumor necrosis			0.149
Absent	108 (66.7%)	54 (33.3%)	
Present	9 (47.4%)	10 (52.6%)	
Surgical margin			0.036
Negative	114 (65.9%)	59 (34.1%)	
Positive	3 (37.5%)	5 (62.5%)	
Adjuvant chemotherapy			0.049
No	82 (61.7%)	51 (38.3%)	
Yes	35 (72.9%)	13 (27.1%)	

ASA = American Society of Anesthesiologists; CIS = carcinoma in situ.