The Impact Factors on Prognosis of Patients With pT3 Upper Urinary Tract Transitional Cell Carcinoma

Ching-Fang Wu,* See-Tong Pang, Chih-Shou Chen, Cheng-Keng Chuang, Yu Chen and Paul-Yann Lin

From the Division of Urology, Department of Surgery (CFW, CSC) and Department of Pathology (PYL), Chang Gung Memorial Hospital, Chia-Yi, Division of Urology, Department of Surgery, Chang Gung Memorial Hospital, Lin-Kou (STP, CKC, YC), and Graduate Institute of Clinical Medical Science, Chang Gung University College of Medicine, Kaohsiung (CFW) and Lin-Kou (STP), Taiwan, Republic of China

Purpose: Stage 3 upper urinary tract transitional cell carcinoma is a heterogeneous disease including different tumor locations (pelvis vs ureter) and invasion patterns (renal parenchyma, peripelvic fat and periureteral fat). Unfortunately the outcomes of patients with pT3 disease with different invasion pattern are largely unknown. This study presents the clinical outcome of patients with pT3 disease with upper urinary tract transitional cell carcinoma.

Materials and Methods: We retrospectively reviewed the medical records of all patients with pT3 disease with upper urinary tract transitional cell carcinoma. Four patient groups were classified according to tumor location and tumor invasion pattern. Prognostic factors including age, gender, tumor grade, tumor size, tumor number, tumor location and microscopic finding of vascular invasion were analyzed with respect to disease recurrence and survival.

Results: A total of 72 patients were included in this study. The most common complaint and tumor relapse pattern were painless gross hematuria and distant metastasis, respectively. Patients with pT3 disease with superficial parenchymal invasion had better disease-free and recurrence-free survival than the other 3 groups. Initial tumor location ($p = 0.02$) and vascular invasion ($p = 0.02$) were independent factors for disease-free survival, and vascular invasion ($p = 0.001$) was the only predictive factor for recurrence-free survival.

Conclusions: The present study demonstrated that patients with pT3 disease with superficial parenchymal invasion should be considered to have lower stage disease, and that vascular involvement is the only independent prognostic factor for patients with pT3 disease for disease-free and recurrence-free survival. Systemic adjuvant therapy should be recommended for patients with pT3 disease with vascular involvement.

Key Words: vascular invasion, parenchyma invasion, transitional cell carcinoma, upper urinary tract

Urothelial carcinoma of the upper urinary tract, including renal pelvis and ureter, accounts for approximately 5% of all urothelial tumor and 10% of all renal tumor cases.[1,2] Tumor stage and grade have been documented as major prognostic factors in patients with upper urinary tract transitional cell carcinoma. According to the AJCC TNM classification, pT3 stage UUT-TCC is a heterogeneous disease including tumor invasion into peripelvic fat, parenchymal and periureteral fat. However, the prognostic value of pattern of invasion or tumor location of pT3 UUT-TCC has seldom been studied systematically.[3] To clarify influence of traditional prognostic factors, invasion pattern and tumor location of pT3 UUT-TCC on survival, this retrospectively study reviews our experience in treating patients with pT3 UUT-TCC.

MATERIALS AND METHODS

From January 1988 to December 2003, patients with UUT-TCC treated at Lin-Kou and Chia-Yi Chang Gung Memorial Hospital were retrospectively reviewed. Nephroureterectomy with bladder cuff excision and lymph node dissection was adapted as standard treatment in our institute. Lymph node dissection depends on location of primary tumor. In cases of renal pelvis and upper ureter tumors the lymph nodes on the ipsilateral side from the midline of aorta or vena cava between the renal hilus and inferior mesenteric artery were removed. In middle ureter tumor, ipsilateral lymph nodes between the renal hilus and bifurcation of the common iliac artery were excised. In low ureter tumor, pelvic lymph nodes including common iliac, external iliac and external iliac lymph nodes on the ipsilateral side were excised. Inclusion criterion was patients with pT3 (stage 3) without lymph node involvement or metastasis. Previous studies at this medical institution revealed different clinical presentations between patients with UUT-TCC on dialysis and patients with normal renal function.[4] Our exclusion criterion was patients with dialysis or uremic stage (preoperative creatinine larger than 2.0). Excretory urography, cytology,

Submitted for publication December 10, 2006.

* Correspondence and requests for reprints: Division of Urology, Department of Surgery, Chang Gung Memorial Hospital, No. 6, Chia-Pu West Rd., Pu-Zu, Chia-Yi, Taiwan, 613 Republic of China (telephone: 886-5-3621000 ext. 2865; FAX: 886-5-3621000 ext. 2761; e-mail: wuchingf@ms3.hinet.net).

For another article on a related topic see page 677.

***Editor's Note*: This article is the second of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 732 and 733.**

DOI:10.1016/j.juro.2007.03.115

cystoscopy and ureterorenoscopy were used for the diagnosis, while computerized tomography or magnetic resonance urography was used for preoperative staging. Tumor grade was determined using the World Health Organization grading system, and tumor stage was determined using the AJCC TNM classification. Patients with pT3 were classified into 4 groups according to pathological findings: 1) superficial or focal parenchyma invasion, indicating parenchyma invasion depth of less than 5 mm from basement membrane,[3] 2) extensive parenchyma invasion indicating deeper invasion or easily noticeable from gross specimen, 3) peripelvic fat invasion, and 4) periureteral fat invasion. The remaining analytical factors included patient age, sex, adjuvant treatments and relapse pattern (table 1). The possibility of chemotherapy, radiotherapy or concurrent chemoradiotherapy for postoperative adjuvant therapy was discussed with all patients. Chemotherapy agents included cisplatin (50 mg/m^2 on day 1) and fluorouracil (750 mg/m^2 on days 1, 2 and 3). Radiotherapy treatment volume consisted of the tumor bed and regional lymph node. The total dose of postoperative adjuvant radiotherapy was 45 Gy at 1.8 Gy per fraction. Recurrent disease was defined as local failure in tumor bed, lymph node recurrence or distant metastasis. Because recurrence in the bladder did not impact survival in the current patient population, it was not included in the estimation of recurrence-free survival and overall survival. Survival time was calculated based on definitive treatment of TCC until final followup or disease specific death. Disease specific actuarial survival and recurrence-free survival curves were derived by the Kaplan-Meier method and compared by the log rank test. Univariate analysis with the log rank test and Cox hazards regression was applied to assess the value of the prognostic factors patient age (exceeding the mean age of the patient population), gender (male vs female), tumor grade (1 and 2 vs 3), tumor size (exceeding the mean size), number of tumors (1 focus vs multiple foci), tumor location (pelvis and/or ureter), and microscopic findings of vascular involvement in predicting recurrence-free and disease specific survival. Vascular involvement included lymphatic, vessel and perineural involvement. Efficacy of postoperative adjuvant therapies was also evaluated. Statistical calculations were performed using commercial statistical software (SPSS®).

RESULTS

A total of 72 patients with pT3 UUT-TCC were included in the study. Mean patient age was 66.7 years (range 35 to 89), and the male-to-female ratio was 1:1. Postoperative followup ranged from 3 to 92 months (median 26.5, mean ± SD 34.2 ± 26.3). Painless gross hematuria (88.9%) was the most common presentation. Of 9 patients 4 had previous and 5 had synchronous bladder TCC. The most common tumor relapse pattern was distant metastasis (14), including liver (7), lung (5) and bone (2). Table 1 lists clinical demographic characteristics of the 4 groups of patients with pT3 UUT-TCC.

The present study demonstrated that there were statistically significant differences of disease-free ($p = 0.014$) and recurrence-free ($p = 0.035$) survival rates among 4 groups using the Kaplan-Meier method with the log rank test (figs. 1 and 2). Rate of disease-free survival of patients with pT3 disease with superficial invasion of parenchyma was higher than the other 3 groups (table 2). Furthermore, patients with pT3 disease with superficial invasion of parenchyma also had a higher recurrence-free survival rate than those with extensive parenchyma invasion or periureteral fat invasion (table 2). Disease-free and recurrence-free survival rates in groups 2, 3 and 4 did not statistically differ.

The 7 variables listed in tables 3 and 4 were analyzed for correlation with overall patient survival and recurrence-free survival, respectively. According to the univariate and Cox

TABLE 1. *Characteristics of patients with pT3 UUT-TCC*

	Superficial	Extensive	Peripelvic Fat	Periureteral Fat	Total
No. pts	18	25	10	19	72
Mean pt age ± SD (median)	67.7 ± 2.3 (68)	67.4 ± 2.1 (67)	67.8 ± 2.9 (66.5)	64.2 ± 3.1 (67)	66.7 ± 1.3 (67)
No. gender (%):					
Female	11	11	5	9	36 (50)
Male	7	14	5	10	36 (50)
No. grade (%):					
Low (1, 2)	13	10	3	7	33 (46)
High (3)	5	15	7	12	39 (54)
No. tumor cm (%):					
Less than 4	11	6	6	16	39 (54)
4 or Greater	7	19	4	3	33 (46)
No. multiplicity (2 or more) (%)	2	8	6	1	17 (24)
No. concomitant bladder TCC (%)	1	2		2	5 (7)
No. history of bladder TCC (%)	1		1	2	4 (6)
No. tumor location (%):					
Pelvis	16	20	4		40 (56)
Pelvis + ureter	2	5	6		13 (18)
Ureter				19	19 (26)
No. vascular invasion (%)		7	2	4	13 (18)
No. relapse pattern (%):					
Bladder	4	3	3	3	13 (18)
Local failure	1	3		1	5 (7)
Lymph node		2		1	3 (4)
Metastasis	1	6	2	6	14 (19)
Contralat UUT-TCC	1		1		2 (3)
No. adjuvant therapy:					
Chemotherapy		2	3	4	9
Radiotherapy		1	3	4	8
No. CCRT		2		5	7