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Original Article

Prognostic Factors Influencing Survival after Nephroureterectomy for Transitional Cell Carcinoma of the Upper Urinary Tract

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We analyzed the prognostic factors influencing survival after surgeries for upper urinary tract urothelial carcinoma (UUT-UC) with longer follow-up periods than in previous studies. Between January 2000 and December 2004, 386 patients underwent nephroureterectomy for UUT-UC. The data for the 221 patients with UUT-UC were retrospectively reviewed. Nine variables were evaluated for association with the survival outcomes of cause-specific survival. The prognostic significance was tested univariately with the log-rank test. The simultaneous effects of multiple prognostic factors were estimated by multiple regression analysis using the Cox proportional hazards model. The median follow-up was 38.4 months. The 5-year over all survival was 62.3%. Significant prognostic factors for disease-specific survival rate on univariate analysis were pathological stage ($p < 0.0001$), tumor grade ($p = 0.0324$), and venous invasion ($p < 0.0001$). Multivariate analysis revealed that only venous invasion was significant for disease-specific survival rate ($p = 0.0205$). Venous invasion was the only independent prognostic factor in pathologically localized UUT-UC.

Key words: nephroureterectomy, transitional cell carcinoma, upper urinary tract

Open radical nephroureterectomy (ONU) with excision of a bladder cuff has been the gold standard of treatment for upper urinary tract urothelial cancer (UUT-UC). Recently, this concept has been challenged due to the development of more advanced techniques for diagnosis, surgery, and follow-up. Minimally invasive procedures are gaining acceptance with regard to laparoscopic radical nephroureterectomy (LNU) [1-3]. We have already revealed that LNU does not negatively affect oncological control by

a comparative multi-institute study enrolling a relatively large number of patients with UUT-UC and without prior or concomitant bladder cancer [4, 5]. Although the survival data suggested that the clinical progression reflected the cancer stage of the initial disease and not the surgical procedure, the follow-up periods in LNU might have been too short to confirm this conclusion.

In the current study, we reveal the prognostic factors influencing survival and urinary bladder recurrence after surgeries for UUT-UC with longer follow-up periods than in previous studies.

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Materials and Methods

A total of 386 patients underwent nephroureterectomy for upper tract transitional cell carcinoma between January 2000 and December 2004 in Okayama University Hospital and 17 related hospitals. Patients with a previous history of bladder cancer, with concomitant bladder cancer and with metastasis were excluded from the analysis. The clinicopathologic data for the remaining 221 patients with upper tract transitional cell carcinoma were retrospectively reviewed. Upper urinary tract TCC was diagnosed by intravenous urography, retrograde pyelography, computed tomography of the abdomen, magnetic resonance imaging, and ureteroscopy with or without biopsy. In all patients, preoperative cystoscopy and radiologic examinations were performed to rule out metastasis and concomitant bladder tumors. Patient characteristics are given in Table 1.

ONU ($n = 163$) was performed with a broad median incision or with lumbar and lower pararectal abdominal incisions. LNU ($n = 58$) was performed using ret-

roperitoneoscopy. The distal ureter, including the intraluminal portion and the ureteral orifice, was removed en bloc by extravesical resection. Regional lymphadenectomy was not performed routinely. None of the patients received neoadjuvant chemotherapy and thirty-four patients (15%) received adjuvant chemotherapy consisting of various multidrug regimens and a varying number of cycles (9 patients received methotrexate, epirubicin, and cisplatin [MEC]; 25 patients received methotrexate, vinblastine, adriamycin and cisplatin [M-VAC]). Sixteen other patients received oral 5-fluorouracil.

Cystoscopy was performed every 3 months for 2 years after nephroureterectomy, then every 4 months from 2 to 3 years, every 6 months from 3 to 5 years, and annually after 5 years. Urine cytology was examined at cystoscopy. Intravenous urography, computed tomography, and chest radiography were performed annually.

Cause-specific survival from time of surgery was defined as the end point for this retrospective analysis. Distribution of event times was calculated for each of the prognostic factors by Kaplan-Meier. The following variables were evaluated for association with the survival outcomes of disease-specific survival: sex (male vs. female), age (younger than 70 vs. 70 or older), tumor stage (Tis, Ta or T1 vs. T2-T4), tumor grade (G1 or G2 vs. G3), venous invasion (yes vs. no), lymphatic invasion (yes vs. no), tumor site (ureter involvement vs. no ureter involvement), multifocality (yes vs. no), and surgical technique (laparoscopic vs. open). Venous invasion and lymphatic invasion was defined by the presence of cancer cells in the endothelium. Immunohistochemistry for endothelial cells was not done. The prognostic significance of each variable was tested univariately with the log-rank test. The simultaneous effects of multiple prognostic factors were estimated by multiple regression analysis using the Cox proportional hazards model. Only factors that had a prognostic impact at a significance level (p) of 0.05 according to the univariate analyses were entered into the multiple regression model. Statistical significance in this study was set as $p < 0.05$.

Results

The median follow-up after nephroureterectomy

Table 1 Patients characteristics

Median age (range)	72 (46-92)
Sex (%)	
Male	153 (69.2)
Female	68 (30.8)
Tumor side (%)	
Right	116 (52.5)
Left	105 (47.5)
Tumor site (%)	
Pelviccalyceal	110 (49.8)
Ureter	111 (50.2)
Tumor number (%)	
Single	168 (76)
Multiple	53 (24)
Management of tumors	
Open	163 (73.8)
Laparoscopic	58 (26.2)
Pathologic stage (%)	
pTa	21 (10)
pT1	58 (27.5)
pT2	22 (10.4)
pT3	96 (45.5)
pT4	7 (3.3)
pTis	7 (3.3)
Grade (%)	
1	18 (8.1)
2	117 (52.9)
3	86 (38.9)

was 38.4 months (range 0.8 to 92.2 months). Of the 221 patients, 42 (19.2%) died of metastatic urothelial cancer. The 5-year over all survival was 62.3%. Bladder tumor recurrence occurred in 91 patients (41.1%).

Nine clinical and pathologic parameters (sex, age, pathologic stage, tumor grade, venous invasion, lymphatic invasion, surgical technique, tumor site, multifocality) were subjected to univariate analysis to determine weather they were statistically significant predictors of disease-specific survival. In the analysis, age was reclassified into 2 subgroups: younger than

70 vs. 70 or older, and tumor stage and grade were each classified into 2 subgroups: pTa, pTis or pT1 versus pT2-4 and G1 or G2 versus G3, respectively. On univariate analysis, pathologic stage (Fig. 1), tumor grade (Fig. 2), and venous invasion (Fig. 3) were found to be statistically significant predictors of disease-specific survival. Table 2 summarizes the univariate analysis of risk factors. Significant prognostic factors for the disease-specific survival rate on univariate analysis were pathological stage ($p < 0.0001$), tumor grade ($p = 0.0324$), and venous invasion ($p < 0.0001$). Multivariate analysis revealed that

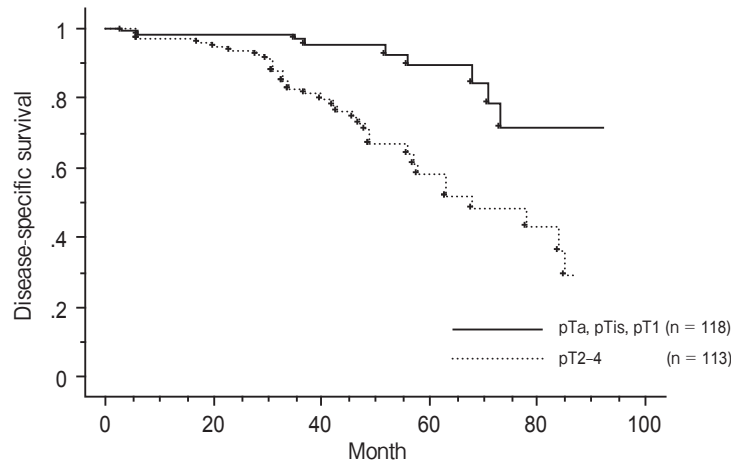


Fig. 1 Kaplan-Meier disease-specific survival curves for patients with stage pTa, pTis or pT1 and pT2-4 are statistically distinct. ($p < 0.0001$, Log-rank test)

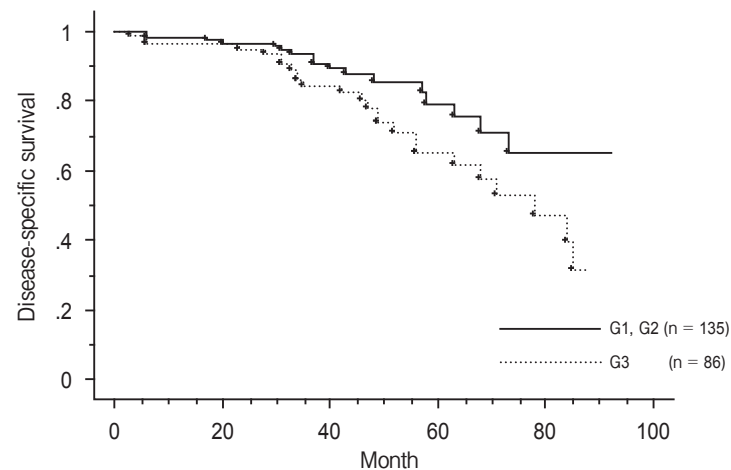


Fig. 2 Kaplan-Meier disease-specific survival curves for patients with tumor grade 1 or 2 and G3 are statistically distinct. ($p < 0.0324$, Log-rank test)

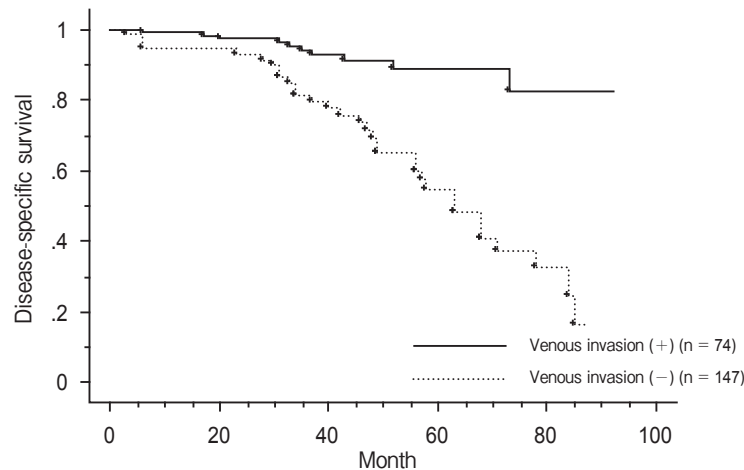


Fig. 3 Kaplan-Meier disease-specific survival curves for patients with venous invasion and without venous invasion are statistically distinct. ($p < 0.0001$, Log-rank test)

Table 2 Univariate analysis of risk factors for disease-specific survival

Variable	No. Pts	<i>P</i> value
Sex		
Male	153	0.3559
Female	68	
Age		
Younger than 70	87	0.3274
70 or older	134	
Pathologic stage		
Tis, Ta or T1	118	<0.0001
T2–T4	103	
Tumor grade		
G1 or G2	135	0.0324
G3	68	
Venous invasion		
Yes	73	<0.0001
No	148	
Lymphatic invasion		
Yes	60	0.8995
No	161	
Surgical technique		
Open	163	0.6345
Laparoscopic	58	
Tumor site		
Ureter involvement	111	0.2905
No ureter involvement	110	
Multifocality		
Yes	52	0.7
No	169	

Table 3 Multivariate analysis of risk factors for disease-specific survival

Variable	HR	95% CI	<i>P</i> value
Age	0.623	0.297–1.306	0.2099
Sex	0.775	0.399–1.509	0.4538
Pathologic stage	0.492	0.181–1.336	0.1639
Tumor grade	1.102	0.491–2.088	0.9734
Venous invasion	3.354	1.205–9.337	0.0205
Lymphatic invasion	0.808	0.392–1.665	0.5628
Surgical technique	1.342	0.641–2.810	0.4354
Tumor site	0.806	0.414–1.569	0.525
Multifocality	1.135	0.548–2.349	0.7332

Table 4 Recurrence location of 73 venous invasion positive patients

Location of recurrence	No. Pts
Lymph node	21
Lung	5
Liver	8
Bone	6
Local	3

only venous invasion was significant for disease-specific survival rate ($p = 0.0205$) (Table 3).

Venous invasion was present in 73 patients (33.3%). Eleven (9.3%) of 113 T1 stage patients were positive, and 62 (60.2%) of 103 T3 stage patients were positive. In tumor grade, 2 (9%) of 18 G1 patients were positive, 22 (18.8%) of 117 G2 patients were positive and 49 (56.9%) of 86 G3 patients were positive. Recurrence occurred in 37

(50%) of 73 patients. Lymph node metastasis occurred in 37 patients (28.7%), distant metastasis occurred in 19 patients (26%) and local recurrence occurred in 3 patients (4.1%) (Table 4). Mean period until recurrence was 14.5 months.

Discussion

Nephroureterectomy is considered the standard treatment for UUT-UC. However, UUT-UC shows a significantly high local failure even after radical surgery. Various prognostic factors influencing survival after nephroureterectomy for UUT-UC have been reported by investigators. However, in recent years, a drastic change in the surgical approach for UUT-UC has occurred; that is, although conventional ONU remains a standard therapeutic modality for patients with upper urinary tract cancer, LNU has been widely applied to clinical practice with advances in laparoscopic technology and surgical skills. This change may influence the prognosis for UUT-UC, including the development of recurrent bladder cancer. Only a few studies have reported on prognostic factors for UUT-UC in this new era of laparoscopic surgery [6, 7]. Our study is one of the larger studies and has a longer follow-up than others employing multivariate analysis. Tumor location, tumor grade and pathologic stage have been traditionally documented as major prognostic factors in patients with UUT-UC. In our study, pathologic stage and tumor grade were also found to be statistically significant predictors of cause-specific survival on univariate analysis. However, on multivariate analysis, venous invasion was the only independent prognostic factor in pathologically localized UUT-UC. Venous invasion was detected in 33.3% of cases in our series. It was associated with high tumor stage and grade, and proved to be the strongest predictor of poor patient outcome. Therefore, our results demonstrate that the aggressiveness of the pathologically localized UUT-UC is better characterized by venous invasion than by stage or tumor grade.

Whereas comparable observations have been reported in some studies employing multivariate analyses and detecting vascular invasion in 25–47% of

cases [1, 3, 8, 9], lymph vascular invasion was regarded as the strongest prognostic factor in them.

Although the clinical value of extended lymphadenectomy in localized UUT-UC is still controversial, further study should be done to reveal the value of extended lymphadenectomy by the laparoscopic approach.

Our study is the largest study that has been evaluated using multivariate analysis. In the surgical management of UUT-UC, laparoscopic nephroureterectomy does not negatively affect long-term oncological control and can be an alternative modality. Venous invasion is the only independent prognostic factor in pathologically localized UUT-UC.

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