

Clinical Significance of Lymph Node Dissection in Patients with Muscle-Invasive Upper Urinary Tract Transitional Cell Carcinoma Treated with Nephroureterectomy

We investigated the value of lymph node dissection in patients with cN0 muscle-invasive transitional cell carcinoma of the upper urinary tract (UUT-TCC). Medical records of 152 patients with cN0 muscle-invasive UUT-TCC, who underwent nephroureterectomy between 1986 and 2005, were reviewed. Sixty-three patients (41.4%) underwent lymph node dissection. The median number of lymph nodes harvested was 6 (range, 1 to 35), and from these, lymph node involvement was confirmed in 9 patients (14.3%). Locoregional recurrence (LR) and disease-recurrence (DR) occurred in 29 patients and 63 patients, respectively. Fifty-five patients (36.2%) had died of cancer at the last follow-up. The number of lymph nodes harvested was associated with the reduction of LR ($\chi^2_{\text{trend}}=6.755$, $P=0.009$), but was not associated with DR ($\chi^2_{\text{trend}}=1.558$, $P=0.212$). In the survival analysis, N stage ($P=0.0251$) and lymph node dissection ($P=0.0073$) had significant influence on LR, but not on DR or disease-specific survival. However, the number of lymph nodes harvested did not affect LR-free, DR-free, or disease-specific survival. We conclude that lymph node dissection may improve the control of locoregional cancer, as well as staging accuracy, in cN0 muscle-invasive UUT-TCC, but that it does not clearly influence survival.

Key Words : Carcinoma, Transitional Cell; Ureter; Kidney Pelvis; Recurrence; Lymph Node Excision

Kang Su Cho¹, Hyun Min Choi¹,
Kyochul Koo¹, Sung Jin Park¹,
Koon Ho Rha¹, Young Deuk Choi¹,
Byung Ha Chung¹, Nam Hoon Cho²,
Seung Choul Yang¹, and Sung Joon Hong¹

Department of Urology¹, the Urological Science
Institute, and Department of Pathology², Yonsei
University College of Medicine, Seoul, Korea

Received : 14 June 2008
Accepted : 26 September 2008

Address for correspondence

Sung Joon Hong, M.D.
Department of Urology and the Urological Science
Institute, Yonsei University College of Medicine, 134
Shinchon-dong, Seodaemun-gu, Seoul 120-752, Korea
Tel : +82.2-2228-2315, Fax : +82.2-312-2538
E-mail : sjhong346@yuhs.ac

INTRODUCTION

Radical nephroureterectomy with bladder cuff resection is the standard treatment for patients with transitional cell carcinoma of the upper urinary tract (UUT-TCC). Even after this radical procedure (1, 2), however, UUT-TCC shows high rates of local recurrence and systemic disease, with lymph nodes as the major site of metastases (3-5).

In bladder cancer, extended lymphadenectomy improves both staging and prognosis (6-8). The role of lymphadenectomy in the surgical treatment of UUT-TCC is more difficult to establish, because the disease is relatively rare. Several recent studies have suggested a possibly curative effect of lymph node dissection in the treatment of patients with infiltrative UUT-TCC (9-13).

Nonetheless, lymphadenectomy is not used routinely, for either therapy or staging, especially in clinically N0 UUT-TCC. In this study, we investigated the clinical significance of lymph node dissection (LND) in patients with cN0 muscle-invasive UUT-TCC who underwent nephroureterectomy.

MATERIALS AND METHODS

Study population

We reviewed the medical records of patients with muscle-invasive UUT-TCC who underwent open nephroureterectomy in a single institution between January 1986 and December 2005. Patients with distant metastasis at diagnosis, unresectable lesions, and concomitant invasive bladder cancer were excluded. Patients in whom lymph node involvement was suspected on preoperative imaging studies or operative findings were also excluded. A total of 152 patients were eligible for this study, including 103 male patients (67.8%), and 49 female patients (32.2%). The median age was 65 yr (range, 25 to 86 yr), and the median follow-up duration was 53 months (range, 6 to 214 months) (Table 1).

Treatments and follow-ups

All patients had undergone nephroureterectomy with bladder cuff excision. Regional LND and its extent were determined at the surgeon's discretion, because the role of LND is

not yet established, especially in UUT-TCC patients without evidence of lymph node involvement. The indication for adjuvant chemotherapy was disease infiltrating the surrounding adipose tissue, or histological confirmation of lymph node involvement. The final decision on chemotherapy, however, was

based on a combination of factors, including coexisting conditions, and the patient's ability and willingness to comply. Patient follow-up was relatively uniform and included surveillance cystoscopy, urinary cytology, abdomen-pelvis computed tomography (CT), whole body bone scan, and chest radiography, performed at 3-month intervals for the first 2 yr, at 6-month intervals for the subsequent 3 yr, and annually thereafter.

Table 1. Subject characteristics

Parameters	Number (%) of patients
Sex	
Female	49 (32.2)
Male	103 (97.8)
Age	
<65 yr	76 (50.0)
> 65 yr	76 (50.0)
Location	
Ureter	72 (47.4)
Renal pelvis	80 (52.6)
Tumor size	
<3 cm	66 (43.4)
≥3 cm	86 (56.6)
Multiplicity	
Single	119 (78.3)
Multiple	33 (21.7)
T-stage	
T2	47 (30.9)
T3	98 (64.5)
T4	7 (4.6)
Tumor grade	
Low grade	14 (9.2)
High grade	138 (90.8)
No. of lymph nodes harvested	
0	89 (58.6)
1 to 5	30 (19.7)
≥6	33 (21.7)
N stage	
pN0	54 (35.5)
pNx	89 (58.6)
pN+	9 (5.9)
Adjuvant chemotherapy	
Not performed	105 (69.1)
Performed	47 (30.9)
Total	152 (100.0)

Study methods

Clinical information was obtained by a retrospective review of all relevant medical records. Locoregional recurrence (LR) was defined as ipsilateral pelvic lymph node enlargement, or iliac fossa tumor recurrence in lower ureteral tumors, and para-aortic, paracaval, aortocaval, renal hilar lymph node enlargement, or renal fossa tumor recurrence in renal pelvic or upper 2/3 ureteral tumors. A lymph node of 1 cm or more, based on an abdomen-pelvis CT scan, was considered a metastasized node. Disease recurrence (DR) was defined as distant metastasis and/or LR. The T-stage and tumor grade of each tumor were determined according to the 2002 American Joint Committee on Cancer (AJCC) TNM staging system and the 1998 World Health Organization/International Society of Urologic Pathologists (WHO/ISUP) classification of papillary urothelial neoplasia (14, 15).

We investigated the difference in LR and DR according to the number of lymph nodes harvested, using the chi-square test and linear-by-linear association. To evaluate the impact of various clinical and pathological features on LR, DR, and disease-specific survival, we used the Kaplan-Meier methods and log-rank test. The multivariate Cox proportional hazards model was used for multivariate survival analyses. Calculations were performed with the Statistical Package for Social Sciences (SPSS) for Windows, version 12.0, and a two-tailed *P* value of less than 0.05 was considered to be significant.

RESULTS

Sixty-three patients (41.4%) underwent LND, with a medi-

Table 2. Comparisons of locoregional recurrence and disease recurrence according to T stage and number of lymph nodes harvested

T stage	Number of patients with recurrence/Number of patients							
	Locoregional recurrence				Disease recurrence			
	NLN=0	0<NLN<6	NLN≥6	Total	NLN=0	0<NLN<6	NLN≥6	Total
T2	10/34	0/7	0/6	10/47	14/34	0/7	4/6	18/47
	$\chi^2_{trend}=4.095, P_{trend}=0.043$				$\chi^2_{trend}=0.093, P_{trend}=0.760$			
T3, 4	14/55	2/23	3/27	19/105	21/55	10/23	14/27	45/105
	$\chi^2_{trend}=3.157, P_{trend}=0.076$				$\chi^2_{trend}=1.357, P_{trend}=0.244$			
Total	24/89	2/30	3/33	29/152	35/89	10/30	18/33	63/152
	$\chi^2_{trend}=6.755, P_{trend}=0.009$				$\chi^2_{trend}=1.558, P_{trend}=0.212$			

NLN, number of lymph nodes harvested.

an number of 6 lymph nodes harvested (range, 1 to 35). Of these 63 patients, 9 patients showed lymph node involvement (14.3%) (Table 1). During follow-up, LR occurred in 29 patients (19.1%), DR in 63 patients (41.4%), and disease-specific death in 55 patients (36.2%). Five-year LR-, DR-free, and disease-specific survival rates were 78.2%, 56.9%, and

66.1%, respectively.

A chi-square test of linear trend showed that when patients were subdivided into three groups, based on median number of lymph nodes harvested ($n=0$, $0 < n < 6$, $n \geq 6$), an increase in the number of lymph nodes harvested was associated with the reduction of LR ($\chi^2_{\text{trend}}=6.755$, $P=0.009$), especially in the T2 subgroup ($\chi^2_{\text{trend}}=4.095$, $P=0.043$). The T3, T4 subgroups showed a linear trend with borderline significance ($\chi^2_{\text{trend}}=3.157$, $P=0.076$). However, the number of lymph nodes harvested and DR ($\chi^2_{\text{trend}}=1.558$, $P=0.212$) were not related (Table 2).

Table 3. Survival analysis of locoregional recurrence, disease recurrence, and disease-specific death

	Locoregional recurrence		Disease recurrence		Disease-specific death	
	5 yr RFS (%)	P value	5 yr RFS (%)	P value	5 yr DSS (%)	P value
Location		0.7089		0.9403		0.7828
Renal pelvis	81.0		58.9		67.1	
Ureter	75.1		54.8		65.0	
Tumor size		0.7472		0.1515		0.0526
<3 cm	74.2		60.9		69.3	
≥ 3 cm	81.6		53.9		61.4	
Multiplicity		0.2385		0.5932		0.2846
Single	75.8		53.3		62.8	
Multiple	86.3		63.6		72.0	
T-stage		0.0002		0.0002		0.0009
T2	82.2		62.7		68.6	
T3	77.2		54.1		63.8	
T4	26.7		14.3		28.5	
Tumor grade		0.2099		0.2826		0.3420
Low grade	91.6		67.7		65.9	
High grade	76.8		56.0		64.4	
N stage		0.0251		0.1318		0.4598
pN0	90.9		59.5		72.3	
pN+	80.0		29.6		66.7	
pNx	70.6		58.2		62.7	
Lymph node dissection		0.0073		0.6665		0.9473
Not performed	70.6		58.2		62.7	
Performed	89.9		55.0		71.0	
Adjuvant chemotherapy		0.1234		0.1074		0.0650
Not performed	75.0		53.0		60.4	
Performed	85.8		68.3		82.6	

RFS, recurrence-free survival rate; DSS, disease-specific survival rate.

In the survival analysis, T stage had a significant influence on LR-free ($P=0.0002$), DR-free survival ($P=0.0002$), and disease-specific survival ($P=0.0009$), but tumor location, size, multiplicity, grade, and adjuvant chemotherapy did not affect LR-free, DR-free, or disease-specific survival ($P>0.05$) (Table 3). The N stage ($P=0.0251$) and LND ($P=0.0073$) had a significant influence on LR-free survival, but not on DR-free and disease-specific survival ($P>0.05$) (Table 3). Multivariate Cox proportional hazards models revealed that N stage ($P=0.041$) and LND ($P=0.012$) were independently related to LR-free survival (Table 4). Although patients who did not undergo LND had a higher probability of LR than those who did, there was no difference in LR-free, DR-free, and disease-specific survival curves according to the number of lymph nodes harvested ($0 < n < 6$ vs. $n \geq 6$) (Fig. 1). Patients with pNx tumors showed a poorer LR-free survival curve than those with pN0 tumors ($P=0.0074$, Fig. 1); however, there was no difference between these two tumor types in the DR-free or disease-specific survival curves ($P>0.05$).

DISCUSSION

Regional lymphadenectomy is widely accepted in the management of bladder cancer, because extended lymphadenectomy improves staging and prognosis (6-8). In UUT-TCC, the role of LND is less clear. Although UUT-TCC is histologically similar to bladder cancer, and LND improves staging, data do not yet support a therapeutic benefit from this

Table 4. Multivariate Cox proportional hazards model for locoregional recurrence

	Model (A)			Model (B)		
	HR	95% CI	P value	HR	95% CI	P value
T stage			0.001			0.002
T3 vs. T2	0.909	0.402-2.054	0.818	0.936	0.418-2.096	0.872
T4 vs. T2	6.850	2.106-22.280	0.001	6.774	2.084-22.013	0.001
N stage			0.041			-
N+ vs. N0	2.446	0.266-22.470	0.429	-	-	-
Nx vs. N0	3.912	1.351-11.327	0.012	-	-	-
Lymph node dissection						
Not performed vs. performed	-	-	-	3.460	1.312-9.127	0.012

HR, hazard ratio; CI, confidence interval.

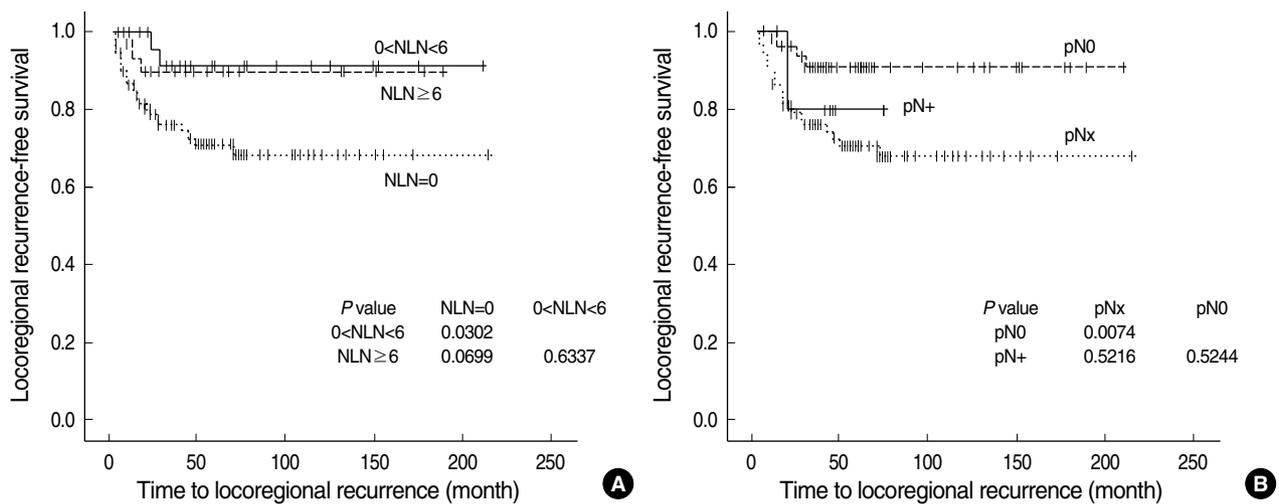


Fig. 1. Locoregional recurrence-free survival curves according to number of lymph nodes harvested (A) and N stage (B). NLN, number of lymph nodes harvested.

procedure, and the variability in the lymphatic drainage precludes a standard template for LND. Urologists tend to omit lymphadenectomy at the time of nephroureterectomy if no evidence is found for lymph node involvement by surgical or radiological evaluation. Our study shows, however, that approximately 15% of patients with cN0 muscle-invasive UUT-TCC experience LR.

Komatsu et al. first suggested a therapeutic benefit for lymphadenectomy based on two long-term survivors with lymph node metastases, one of whom received adjuvant chemotherapy and one who did not (10). Park et al. reported a more favorable outcome for patients with UUT-TCC treated with lymphadenectomy, as compared with previous studies, and suggested that this surgical procedure had specifically increased survival (16). However, the therapeutic effect of routine lymphadenectomy for patients with UUT-TCC has not been specifically evaluated.

Although not yet confirmed prospectively, two recent retrospective studies support the therapeutic use of lymphadenectomy, in conjunction with nephroureterectomy, for UUT-TCC. Brausi et al. maintained that retroperitoneal LND (with five or more lymph nodes removed) and T-stage independently influence prognosis. A Japanese study showed that patients who underwent complete lymphadenectomy (with a median of seven lymph nodes removed) had a better prognosis than those who did not, especially among patients with advanced disease ($\geq pT3$) (11). However, our study demonstrated that an increased number of lymph nodes harvested was associated with the reduction of LR, and that LND had a significant influence on LR-free survival, but not on DR-free and disease-specific survival. This is because distant metastasis usually coincides with locoregional spread in UUT-TCC. Miyake et al. showed that lymphadenectomy improves prognosis in patients with no lymph vessel invasion, but not in those with lymph vessel invasion (12). They concluded that patients

with lymph vessel invasion have systemic disease, and that these patients should receive aggressive systemic adjuvant therapies rather than regional lymphadenectomy. These observations are consistent, in part, with ours.

Kondo et al. showed that the primary site of lymph node metastasis depends on the primary tumor location and lateral orientation (17). Although this study does not provide a well-defined template for LND that may be generally applied, it does take a significant step toward determining the optimal extent of lymphadenectomy. They recommend that radical lymphadenectomy for right renal pelvic and ureteral tumors should extend to the posterior aspect of the inferior vena cava by transection of the lumbar veins. When the tumors are located at the upper and middle ureter, the dissection should extend further, to the inter-aortocaval nodes. In contrast, lymphadenectomy for tumors of the left renal pelvis and upper two-thirds of the left ureter should extend only to the renal hilum and para-aortic nodes. Clearly, either a hilar or a limited LND will not remove all of the primary lymphatic drainage area of the kidneys or ureters.

It is well known that lymph node involvement is closely associated with T stage and tumor grade (10, 13, 17). Kondo and his colleagues reported that the incidence of lymphatic involvement varied according to stage and grade, with 0%, 5%, 24%, and 84% of Tis-1, T2, T3, and T4 tumors, and 0%, 11%, and 35% of G1, G2, and G3 tumors, respectively, showing such involvement (17). Regional lymphadenectomy might be safely omitted in UUT-TCC patients with low-grade or low-stage tumors at preoperative biopsy or imaging evaluation. However, CT or magnetic resonance imaging prior to surgery may not clearly reveal T1 and T2 disease, and sampling error, particularly with larger tumors, may limit the accuracy in grading. Relevant to this are recent studies showing that laparoscopic procedures for radical nephroureterectomy may facilitate patient recovery, with disease control

comparable to that of traditional open surgery. But although oncological outcomes for the two procedures compare favorably, questions remain concerning lymphadenectomy, especially if radical in extent, because laparoscopic retroperitoneal LND in conjunction with nephroureterectomy presents a technical challenge (18-20). Typically, the use, extent, and pattern of LND in UUT-TCC have been left to the surgeon's discretion, and for this reason, a large number of patients with UUT-TCC has rarely, if ever, received lymphadenectomy in the same clinical setting (13). From this point of view, prospective randomized studies are needed to define the indications, most effective techniques, and optimal anatomical range for lymphadenectomy.

In conclusion, we found that approximately 15% of patients with cN0 muscle-invasive UUT-TCC who received LND showed lymph node involvement on pathologic examination. Our results suggest that LND can improve the control of locoregional cancer, as well as staging accuracy, but that LND does not clearly influence survival in patients with this disease.

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