

Impact of the Extent of Regional Lymphadenectomy on the Survival of Patients With Urothelial Carcinoma of the Upper Urinary Tract

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Purpose: We determined the impact of the extent of regional lymphadenectomy on survival in patients with urothelial carcinoma of the upper urinary tract.

Materials and Methods: Between January 1989 and January 2006, 169 patients with nonmetastatic urothelial carcinoma of the upper urinary tract underwent curative surgery. We previously reported the primary sites of nodal metastases in urothelial carcinoma of the upper urinary tract. Nodal sites where the incidence of metastases was 30% or more were considered regional lymph nodes. When all primary sites were resected, this was considered complete lymphadenectomy. Regional lymphadenectomy without the removal of all primary sites was considered incomplete lymphadenectomy. We retrospectively analyzed the influence of the extent of lymphadenectomy on patient survival.

Results: A total of 45 patients (26.6%) underwent complete lymphadenectomy. Lymphadenectomy was performed in an additional 36 patients (21.3%) but it was incomplete. Lymphadenectomy was not performed in 88 patients. Cancer specific survival did not significantly differ between the groups when all patients were analyzed. However, patient survival significantly depended on the extent of lymphadenectomy when we focused on patients with T stage pT3 or higher. Patient survival was likely to improve when the number of lymph nodes removed increased. Multivariate analysis showed that complete lymphadenectomy was a significant prognostic factor for cancer specific survival ($p = 0.009$) as well as T stage (pT3 or less $p = 0.0004$) and tumor grade (G3 $p = 0.0001$).

Conclusions: Although further investigation is required to make a definite conclusion, the extent of lymphadenectomy may significantly influence its therapeutic effect, especially for patients with advanced disease.

Key Words: ureter; kidney; carcinoma, transitional cell; lymph node excision, mortality

Lymph nodes are the major sites of UCUUT metastases.^{1,2} It was reported that the incidence of lymph node metastasis is about 30% to 40%. Nodal involvement is a poor prognostic indicator and chemotherapy or radiotherapy rarely results in improved patient survival.³ Thus, the control of nodal involvement is an important issue in the treatment of UCUUT.

Nephroureterectomy is the standard surgical procedure for the majority of patients with UCUUT.^{4,5} However, to our knowledge whether routine LND is beneficial for patient survival remains undetermined.^{6,7} Recently the importance of LND was demonstrated in bladder cancer since extended radical LND improved staging and prognosis.⁸⁻¹⁰ Since UCUUT is histologically similar to bladder cancer, we hypothesized that radical LND for UCUUT may be as important as for bladder cancer for improving tumor staging and/or patient prognosis after radical surgery. To examine our hypothesis we analyzed and recently reported the primary sites of lymphatic metastases of UCUUT according to

the primary tumor location using surgically excised specimens and/or imaging analysis.¹¹

In the current study we determined the primary sites of nodal metastases as the regional nodes according to our previous results. We then retrospectively examined the influence of the extent of LND on patient survival in UCUUT.

MATERIALS AND METHODS

Patients and Tumors

Between January 1988 and January 2006, 190 patients with UCUUT were treated at our department, of whom 169 underwent curative surgery. Tumor staging was done according to the UICC TNM classification.¹² Table 1 lists patient characteristics. Location of the primary tumor was categorized into 8 regions, including the right RP, right UU, right MU, right LU, left RP, left UU, left MU and left LU. The UU was designated the upper third of the ureter which is superior to the inferior mesenteric artery, the MU was designated the middle third from the level of the inferior mesenteric artery to the crossing with the common iliac artery and the LU was designated as below the crossing. All tumors were histologically transitional cell carcinoma.

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TABLE 1. *Characteristics of patients with UCUUT who underwent curative surgery*

No. pts	169	
Mean/median age (range)	67.5/69.2 (38.7–85.5)	
No. men/women	113/56	
Mean/median mos followup (range)	49.0/37.3	(1–209)
No. primary tumor site:		
Rt RP	47	
Rt UU	5	
Rt MU	15	
Rt LU	26	
Lt RP	53	
Lt UU	4	
Lt MU	5	
Lt LU	14	
No. treatment:		
Radical nephroureterectomy (open/retroperitoneoscopic)	153	(146/7)
Radical nephrectomy	5	
Segmental ureterectomy	7	
Endoscopic ablation	4	
No. LND:		
CompLND	45	
IncompLND	36	
None	88	

Surgical Procedure

Surgery was performed based on a previously described procedure.¹³ Nephroureterectomy is primarily indicated for the surgical treatment of UCUUT. Open standard nephroureterectomy was performed in 146 patients, and retroperitoneoscopic surgery in conjunction with open distal ureter and bladder cuff removal was done in 7. The procedure of open standard nephroureterectomy has not changed during the last 20 years. Radical nephrectomy was performed only in patients diagnosed with renal cell carcinoma by preoperative imaging analysis. Segmental ureterectomy or endoscopic ablation was performed only in patients with superficial disease or a solitary kidney.

Regional Lymph Node, LND and Pathological Findings

Table 2 lists the primary sites of lymphatic metastases according to primary tumor location. Nodal sites where the incidence of metastasis was 30% or more were considered regional lymph nodes (table 2). For tumors of the right RP, and the upper and MU the renal hilar, paracaval and retrocaval nodes (and interaortocaval nodes for the ureteral tumor) were considered regional lymph nodes.

We did not observe lymphatic metastasis to the renal hilar or paracaval nodes in tumors of the right upper and

MU. This may have resulted from the small number of patients in this study. Thus, we thought that these nodes should be removed en bloc, in addition to the interaortocaval and retrocaval nodes, as should be done for right RP tumors. For tumors of the left upper and MU the renal hilar and para-aortic nodes were the regional nodes. There was no lymphatic metastasis of the left UU tumor and no hilar nodes involvement was found in the left MU tumor. As mentioned, the renal hilar nodes should be removed en bloc, in addition to the para-aortic nodes, as for left RP tumors. For tumors of the LU the common iliac, external iliac, obturator and internal iliac nodes were included as the regional lymph nodes, as for bladder cancer.

Figure 1 shows the anatomical regions of lymph node dissection according to primary tumor location. When the regional nodes were dissected, this was considered CompLND. When the extent of LND did not include all regional sites, it was considered IncompLND. We did not use clear criteria for the indication for LND. The extent of LND was determined by the surgeons based on preoperative stage and/or patient comorbidity.

All LNDs were performed by open surgery and not laparoscopically. Lymph node specimens were sampled en bloc with the surrounding adipose tissue. Packets were examined to identify lymph nodes visually and by palpation. The lymph nodes were then sent to a single pathologist for histological examination. The fat tissue was not reexamined to identify additional lymph nodes.

Adjuvant Chemotherapy

The indication for adjuvant chemotherapy was nodal involvement and/or disease infiltrating the surrounding adipose tissue. However, we finally determined the indication after considering patient comorbidity, performance status and willingness to receive therapy. Chemotherapy consisted of 1 to 3 courses of a regimen including methotrexate, vinblastine, doxorubicin and cisplatin.

Statistical Analysis

Univariate analysis was performed using the Mann-Whitney U test to compare the number of lymph nodes between groups. The chi-square test was used to compare the proportion of patients between groups. Cancer specific survival was calculated with the Kaplan-Meier method and statistical significance was analyzed with the log rank test. Univariate and multivariate analysis for the prognostic fac-

TABLE 2. *Primary sites of nodal involvement and regional lymph nodes according to tumor location*

Primary Tumor Site	No. Pts With Nodal Metastasis	No. Metastatic Lymph Nodes (%)							
		Hilar	Paracaval	Retrocaval	Interaortocaval	Para-aortic	Common Iliac	Obturator	Internal Iliac
Rt:									
RP*	15	8 (53)	5 (33)	5 (33)	—	—	—	—	—
UU*	2	—	—	1 (50)	1 (50)	—	—	—	—
MU*	3	—	—	1 (33)	2 (67)	—	—	—	—
LU*	2	—	—	—	—	—	1 (50)	1 (50)	—
Lt:									
RP	15	9 (60)*	—	—	1 (7)	8 (53)*	—	—	—
MU	3	—	—	—	—	3 (100)	—	—	—
LU	2	—	—	—	—	—	1 (50)	—	1 (50)

No suprahilar, external iliac or left UU metastases.

* Regional nodes according to primary tumor site.

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