International Journal of Urology (2007) **14**, 26–32 doi: 10.1111/j.1442-2042.2006.01664.x

Evaluation of regional lymph node dissection in patients with upper urinary tract urothelial cancer

Fernando P Secin,[1] Theresa M Koppie,[1] Juan I Martinez Salamanca,[1] Shahid Bokhari,[1] Ganesh V Raj,[1] Semra Olgac,[2] Angel Serio,[1] Andrew Vickers[3] and Bernard H Bochner[1]

[1]Department of Urology, Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan-Kettering Cancer Center, [2]Department of Pathology, Memorial Sloan-Kettering Cancer Center, and [3]Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, New York, USA

Objective: The role of the lymph node dissection (LND) in conjunction with nephroureterectomy (NU) in upper tract urothelial cell carcinoma (UT-UCC) remains undefined. We evaluated the manner in which the LND was applied at NU, the patterns of lymph node (LN) involvement and the preoperative variables that could identify patients at high risk for lymph node metastasis (LNM).

Methods: We examined clinical, radiological and pathological records of patients who underwent NU for UT-UCC between 1985 and 2004. The central pathology laboratory reviewed all specimens and graded tumors using the 2002 World Health Organization/International Society of Urologic Pathologists grading system.

Results: Of the NU performed in 252 patients for UT-UCC, 105 (42%) were N0, 28 (11%) N+ and 119 (47%) Nx. Some form of LN resection was performed with NU in 53% of patients, with a median of four LN sampled (interquartile range, 2–10). After adjustment for tumor and patient characteristics, surgeon remained a significant predictor of LN resection ($P < 0.0005$). Of the evaluated variables, suspicious LN on preoperative computed tomography, present in 60% of N+ patients, was the only preoperative variable associated with the pathological finding of LNM ($P < 0.0005$).

Conclusions: LND in patients with UT-UCC is surgeon-dependent. Given the prognostic importance of LN status and the limited accuracy of preoperative staging of the regional LN, surgeons should perform a regional LND at the time of NU.

Key words: kidney neoplasms, lymph nodes, metastasis, survival, ureteral neoplasms.

Introduction

Despite encouraging reports of renal-sparing treatment of low-grade ureteral or renal pelvis tumors in selected patients,[1,2] nephroureterectomy (NU) with bladder cuff resection remains the gold standard of treatment for high-grade upper tract urothelial cell carcinoma (UT-UCC).[1] The natural history of the disease, specifically its multifocal nature, frequent recurrences after conservative therapy, propensity for local invasion and poor outcome once invasive disease is present, strongly argues for aggressive treatment for most cases. As with bladder cancers, high-grade invasive UT-UCC is frequently associated with regional lymph node metastasis (LNM), which can precede the development of distant disease. Extrapolating results from urothelial bladder cancer studies,[3] it seems reasonable to believe that lymph node dissection (LND) in conjunction with NU may provide not only useful staging and prognostic information but also a therapeutic benefit in selected patients with UT-UCC. Nonetheless, it is impossible to draw any consistent conclusion on either way as previously published NU series present few details regarding practice patterns, including selection criteria, indications or LND templates. Published practice patterns vary greatly among institutions with patients receiving LND from large NU series ranging from 44%[4] to 67%[5] for open NU series;[1,2,6–12] therefore, the role of the regional retroperitoneal LND in patients with UT-UCC remains undefined.

Our objective was to describe the manner in which the LND was applied at NU and the pattern of LNM at NU in patients with primary UT-UCC. We also sought to determine preoperative predictors of LNM to identify a population of patients who may eventually benefit from LND and/or could be selected for neoadjuvant therapy trials. Additionally, we analyzed the pathological features associated with LNM to identify which may be used as high-risk characteristics on preoperative biopsy or endoscopic resection specimens.

Correspondence: Bernard Bochner, MD, Department of Urology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, USA. Email: bochnerb@mskcc.org

Received 27 April 2006; accepted 19 July 2006.

Materials and methods

Clinical, pathological and radiographic information was collected in 255 NU performed in 252 patients between December 1985 and March 2004 at Memorial Sloan-Kettering Cancer Center. Three patients underwent NU of the contralateral unit; data for only the first NU were included in the analysis. All NU were performed either open ($n = 248$) or laparoscopically ($n = 7$) by one of 10 specialized urological oncologist. The use, extent and template of the LND was at the surgeon's discretion.

After internal review board approval, preoperative information was recorded for each patient, including age, gender, body mass index (BMI), prior bladder cancer, prior radical cystoprostatectomy, tobacco history (former or current vs non-smoker), grade of the biopsy (negative, low grade or high grade), tumor side, urine cytology result (positive, suspicious or negative), presence of suspicious regional lymph node (LN) enlargement on preoperative computed tomography (CT), administration of neoadjuvant therapy, and age-adjusted Charlson comorbidity index.[13] All operative notes were reviewed in detail to determine intraoperative LN status, if described, as well as the extent and location of the LN dissection or sampling.

All specimens, including location and number of the dissected and metastatic LN, were analyzed per protocol at the pathology department of Memorial Sloan-Kettering Cancer Center (MSKCC). Tumors were

graded using the World Health Organization (WHO) grading system (low, intermediate, and high grade), and staged according to the 2002 American Joint Committee on Cancer and tumor-node-metastasis (AJCC-TNM) staging system. Tumors were evaluated for location (renal pelvis, ureter or both), size, pathological stage, laterality, parenchymal invasion, capsular invasion, sinus invasion, surgical margins status (defined as malignant cells at the inked margin), ureteral margin status (presence of carcinoma *in situ* and/or invasive carcinoma at the ureteral line of resection), lymphovascular invasion, cell differentiation (presence of squamous, glandular or sarcomatoid features), associated carcinoma *in situ*, multifocality and perineural invasion.

Patients were followed postoperatively with physical examination, periodic cystoscopy, urine cytology, serum evaluations and imaging studies at the discretion of their individual physicians. Cancer-specific mortality was defined as death in the setting of local recurrence or distant metastasis as recorded by death certificates and/or medical record review. Cancer-specific survival was defined as the time from the NU to the date of last follow up or cancer-specific death; patients with non-disease related deaths were censored at the time of death.

Administration of perioperative chemotherapy varied from case to case over time. Thirty-one selected patients received perioperative chemotherapy, 17 received adjuvant therapy (most of them methotrexate, vinblastine, adriamycin, cisplatinum combination [MVAC] and platinum-based regimens), another seven received neoadjuvant (mostly MVAC and platinum-based regimens) and the other seven were unclear whether they received adjuvant or neoadjuvant. Among all N+-patients, 15 received some form of perioperative chemotherapy: nine adjuvant, two neoadjuvant and four were unclear.

Logistic or linear regression included the aforementioned preoperative variables to identify factors associated with LND and LNM at the time of NU. When analyzing predictors of LND and number of LN retrieved, we fitted a multivariate mixed model (using the *xtlogit* command in Stata, College Station, TX, USA) in which surgeon was entered as a random effect. In the mixed model, surgeons with less than 20 cases were grouped together in the same cluster. BMI was analyzed as a continuous variable. Neoadjuvant therapy was not entered into the predictive model as only nine patients received preoperative chemotherapy. Histological grade and presence of perineural invasion could not be used in the model because, respectively, only one-third of the patients were biopsied and there were no cases of perineural invasion among patients without LNM (Table 1). When analyzing predictors of LNM, we excluded patients who did not have LND performed (Nx patients) because they provided no information about LNM. Due to the low number of patients with LNM ($n = 28$), associations with LNM were assessed univariately. Statistical analyses were conducted on Stata 8.2.

Results

Regional LN dissection

Of the 252 NU, 105 (42%) were N0, 28 (11%) N+, and 119 (47%) Nx. Table 1 shows the characteristics of patients according to LN status. Noteworthy variability was observed in the number of LN retrieved (Fig. 1). The median number of LN removed was four (interquartile range [IQR], 2–10). A third of patients had negative preoperative voided or cystoscopic urine cytology. Thirty-seven percent of patients had a preoperative biopsy performed, with 22% of these reported as negative or indeterminate. Almost half of all patients had a history of bladder cancer, and 15% of all patients had undergone prior or simultaneous radical cystoprostatectomy. The extent of the LND ranged from a limited node sampling to a formal retroperitoneal LND; no standard template was followed. See Table 2 for full description of the location and laterality of all LN and positive LN removed.

Variables associated with performance of LND and number of LN identified

Overall, 133 (53%) of 252 patients had evidence that LN tissue was evaluated on the final pathology report. On multivariate analysis, positive urine cytology (odds ratio [OR], 2.53; 95% confidence interval [CI], 1.21, 5.28; $P = 0.01$) was significantly associated with the performance of LND; BMI (OR, 1.07; 95% CI, 0.99, 1.14; $P = 0.07$) and female gender (OR, 1.87; 95% CI, 0.9, 3.91; $P = 0.10$) approached statistical significance with the performance of LND (Table 3). After adjustment for the aforementioned tumor and patient characteristics, surgeon remained a significant predictor of LND ($P < 0.0005$). For example, surgeon A performed LND on 40% of patients, whereas surgeon B performed LND on 73% of patients.

Of 28 patients with LNM, 12 (43%) had N1, 15 (54%) N2, and one (4%) N3 disease. Among N+ patients, a median of nine LN were resected (IQR, 2–13), and a median two LN were identified as positive (IQR, 1–6).

On multivariate linear regression analysis, tumor side was the only variable significantly associated ($P = 0.036$) with number of LN removed (after Box-Cox transformation for normality). A mean of 8.6 nodes were removed for left-sided tumors compared to 4.3 for right-sided tumors. BMI, positive urine cytology, presence of LN enlargement on CT and age were not significantly associated with number of LN reported.

Among the 10 node-positive patients with right UT-UCC, the location of positive nodes was: four paracaval, three retrocaval, one precaval, one hilar, one interaortocaval, one retroperitoneal and one periureteral. Among the 18 node-positive patients with left UT-UCC, the positive nodes were: 11 paraaortic, six hilar, two mesenteric, one interaortocaval and one pelvic region. The location of positive nodes was not clearly described in three patients.

Preoperative factors associated with LNM

Only the presence of suspicious LN on CT scan was significantly associated with LNM at the time of the NU in univariate logistic

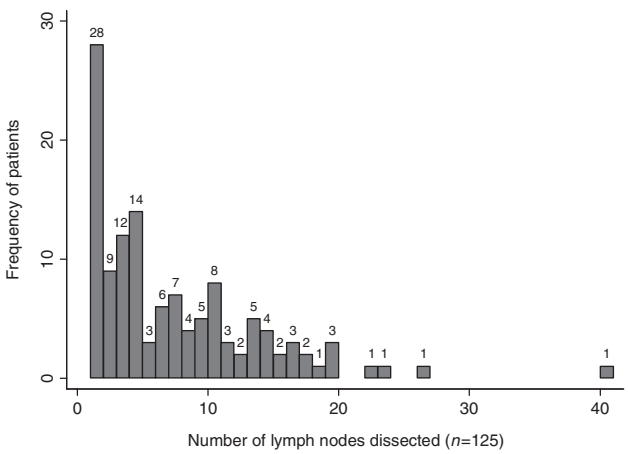

Fig. 1 Histogram showing the number of lymph nodes dissected. Data on number of nodes evaluated were missing for eight patients.

Table 1 Patient characteristics according to lymph node status

	Nx *n* (%)	N0 *n* (%)	N1-3 *n* (%)	Total *n* (%)
Number of patients	119 (47%)	105 (42%)	28 (11%)	252
Age median (IQR) (*n* = 252)	70 (61, 76)	70 (62, 75)	68 (56, 76)	69 (60, 75)
Gender (*n* = 252)				
Female	33 (28%)	41 (39%)	12 (43%)	86 (34%)
Male	86 (72%)	64 (61%)	16 (57%)	166 (66%)
Side (*n* = 252)				
Right	58 (49%)	56 (53%)	18 (64%)	132 (52%)
Left	61 (51%)	49 (47%)	10 (36%)	120 (48%)
Preoperative urine cytology (*n* = 216)				
Negative	43 (42%)	24 (26%)	3 (14%)	70 (32%)
Positive	60 (58%)	68 (74%)	18 (86%)	146 (68%)
Biopsy (*n* = 93)				
Negative or indeterminate	12 (33%)	7 (15%)	1 (9%)	20 (22%)
Low Grade	21 (58%)	25 (54%)	6 (55%)	52 (56%)
High Grade	3 (8%)	14 (30%)	4 (36%)	21 (23%)
Ever smoked (*n* = 208)				
No	24 (25%)	21 (23%)	5 (24%)	50 (24%)
Yes	73 (75%)	69 (77%)	16 (76%)	158 (76%)
Prior bladder cancer (*n* = 247)				
No	60 (52%)	57 (55%)	15 (54%)	132 (53%)
Yes	55 (48%)	47 (45%)	13 (46%)	115 (47%)
Prior or simultaneous radical cystoprostatectomy (*n* = 244)				
No	95 (85%)	91 (88%)	22 (79%)	208 (85%)
Yes	17 (15%)	13 (13%)	6 (21%)	36 (15%)
Suspicious nodes on preoperative CT (*n* = 209)				
No	82 (83%)	69 (81%)	10 (40%)	161 (77%)
Yes	17 (17%)	16 (19%)	15 (60%)	48 (23%)
BMI median (IQR) (*n* = 219)	26 (23, 29)	27 (24, 30)	27 (23, 30)	27 (24, 29)
Age-adjusted Charlson index median (IQR) (*n* = 252)	4 (3, 6)	4 (3, 6)	4 (2, 5)	4 (3, 5)
ASA Score (*n* = 209)				
1	4 (4%)	1 (1%)	1 (5%)	6 (3%)
2	60 (59%)	51 (59%)	13 (62%)	124 (59%)
3	38 (37%)	34 (40%)	7 (33%)	79 (38%)
Number LN dissected median (IQR) (*n* = 125)	–	4 (2, 10)	9 (2, 13)	4 (2, 10)

ASA, American Society of Anesthesiology; BMI, body mass index; IQR, interquartile range.

regression analysis (OR, 6.47; 95% CI, 2.46, 17.0; $P < 0.0005$; Table 4). However, 40% of N+ patients did not have suspicious LN enlargement on preoperative CT scan. Positive urine cytology was not predictive of LNM, with 14% of N+ patients having negative urine cytology. Preoperative biopsy also lacked predictive capacity. Of all N+ patients with a preoperative biopsy ($n = 11$), 55% ($n = 6$) had low-grade histology (Table 1). In contrast, all N+ patients had high-grade disease in the final specimen (Table 5).

Pathological factors associated with LNM

Lymph node metastasis at the time of the NU was significantly associated with multiple pathological features in univariate analysis, including parenchymal invasion ($P = 0.01$), capsular invasion ($P < 0.0005$), sinus fat invasion ($P = 0.002$), positive surgical margins ($P = 0.008$), lymphovascular invasion ($P < 0.0005$), cell differentiation ($P = 0.01$) and tumor size ($P = 0.02$). Presence of carcinoma *in situ* (CIS), tumor location and multifocality were not significantly associated with N+ disease (Table 5).

Recurrence and cancer-specific survival

Overall, 75 patients died of disease (28 were N0, 32 were Nx and 17 were N+). Median follow up for survivors was 3.1 years. The cancer-specific survival (CSS) probabilities at 5 and 10 years were 61%

Table 2 Distribution of lymph nodes dissected according to nephroureterectomy (NU) side

NU side		Total *n*	N0 *n*	N1 *n*	N2 *n*	% N 1–2
Right	Paracaval	27	23	1	3	15
	Hilar	13	12	1	0	8
	Pelvic	14	13	0	1	7
	Retrocaval	4	2	0	2	50
	Inter aorto-caval	4	4	0	0	0
	Precaval	2	2	0	0	0
	Periureteral	2	1	1	0	50
	Retroperitoneal	1	0	1	0	100
	Total	67	57	4	6	15
Left	Paraaortic	46	35	5	6	24
	Hilar	26	22	1	3	15
	Pelvic	11	10	1	0	9
	Mesenteric	3	1	0	2	67
	Preaortic	2	2	0	0	0
	Inter aorto-caval	2	1	0	1	50
	Periureteral	1	1	0	0	0
	Retroperitoneal	1	1	0	0	0
	Total	92	73	7	12	21

Some patients were counted more than once as they had their lymph nodes removed from more than one location.

Table 3 Multivariate logistic regression analysis of variables associated with performance of lymph node dissection at the time of surgery

	Odds ratio	95% CI	*P*-value
BMI	1.07	0.99, 1.14	0.07
Age-adjusted Charlson index	1.10	0.90, 1.35	0.3
Prior bladder cancer	0.74	0.33, 1.69	0.5
Suspicious lymph nodes on CT	1.45	0.63, 3.37	0.4
Tumor side (left vs right)	1.28	0.63, 2.60	0.5
Gender (female vs male)	1.87	0.90, 3.91	0.10
Positive cytology	2.53	1.21, 5.28	0.01
Surgeon	Random effect	Random effect	<0.0005

'Other surgeons' compile urologists who performed less than 20 cases. CI, confidence interval; CT, computed tomography.

Table 4 Univariate logistic regression analysis of preoperative variables associated with lymph node metastasis

	Odds ratio	95% CI	*P*-value
Age	0.97	0.94, 1.01	0.16
Urine cytology	2.12	0.57, 7.83	0.3
Preoperative biopsy			
Negative	Reference	–	0.8
Low grade	1.68	0.17, 16.4	–
High grade	2.00	0.19, 21.4	–
Tobacco exposure	0.97	0.32, 2.98	0.9
Prior bladder cancer	1.05	0.46, 2.43	0.9
Prior or simultaneous RCP	1.91	0.65, 5.59	0.2
Suspicious LN enlargement on CT	6.47	2.46, 17.0	<0.0005
BMI	0.99	0.90, 1.10	0.9
Tumor side	1.58	0.66, 3.73	0.3
Gender	1.17	0.50, 2.73	0.7

Patients without lymph node dissection (Nx) were excluded from this analysis, because they provide no information about lymph node metastasis. RCP, radical cystoprostatectomy.

(95% CI, 53%, 68%) and 53% (95% CI, 43%, 61%), respectively. The 3- and 5-year CSS probabilities were 79% and 56% for N0 patients, 80% and 73% for Nx patients, and 41% and 0% for N+ patients ($P < 0.0005$ for N0 = N+ = Nx) (Fig. 2). For N+ patients, the median survival time was 25 months There was no statistically significant difference in cancer-specific survival between N0 and Nx disease ($P = 0.4$). The hazard ratio for Nx compared to N0 was 0.81 (95% CI, 0.48, 1.36), and the hazard ratio for N+ in relation to N0 was 3.38 (95% CI, 1.82, 6.25). We identified 11 nodal or retroperitoneal recurrences in the 105 patients with N0 disease and another 11 in the 28 patients with N+ disease. In addition to the 75 disease-specific deaths, 25 patients died from other causes.

Discussion

Although the overall benefit of LND for patients undergoing NU for UT-UCC remains unresolved, the potential benefits include accurate pathological assessment of the regional LN. Knowledge of the regional LN status is important because it identifies a high-risk group for recurrence and poor CSS (Fig 2).[4,14] Accurate knowledge of the regional LN status (ideally preoperatively) may aid in the appropriate patient

Table 5 Univariate logistic regression analysis of pathologic (postoperative) variables associated with lymph node metastasis

Pathological characteristics	LN Status *n* (%)			N1-3 vs N0		
	Nx *n* = 119	N0 *n* = 105	N1-3 *n* = 28	Odds ratio	95% CI	*P*-value
pT Stage (*n* = 244)						<0.0005*
Ta	40 (34%)	30 (29%)	1 (4%)			
CIS	9 (8%)	3 (3%)	0 (0%)			
T1	27 (23%)	18 (17%)	1 (4%)			
T2	15 (13%)	20 (19%)	0 (0%)			
T3	23 (20%)	31 (30%)	18 (75%)			
T4	2 (2%)	2 (2%)	4 (17%)			
(+) SM (*n* = 184)	1 (2%)	3 (3%)	5 (20%)	8.0	1.8 ,36	0.008*
(+) Ureteral margin (*n* = 189)	11 (17%)	13 (13%)	1 (4%)	0.3	0.04 ,2.3	0.2
PNI (*n* = 186)	2 (3%)	1 (1%)	5 (20%)	25	2.74 ,223	0.001*
LVI (*n* = 192)	10 (15%)	15 (15%)	14 (56%)	7.4	2.8 ,19	<0.0005
CIS (*n* = 203)	40 (51%)	28 (28%)	11 (44%)	2.0	0.8 ,4.9	0.13
Grade (*n* = 245)						<0.0005*
1	42 (37%)	22 (21%)	0 (0%)			
2	21 (18%)	17 (16%)	0 (0%)			
3	51 (45%)	65 (63%)	27 (100%)			
Parenchymal invasion (*n* = 191)	20 (29%)	23 (23%)	11 (50%)	3.4	1.3 ,8.8	0.01
Capsular invasion (*n* = 188)	7 (11%)	4 (4%)	10 (40%)	16	4.4 ,58	<0.0005
Sinus invasion (*n* = 187)	6 (10%)	15 (15%)	11 (44%)	4.5	1.7 ,12	0.002
Multifocality (*n* = 248)	23 (20%)	12 (12%)	4 (14%)	1.3	0.4 ,4.3	0.7
Location (*n* = 249)						0.6
Ureteral	26 (22%)	26 (25%)	5 (18%)	Reference	–	–
Renal pelvis	61 (53%)	49 (47%)	16 (57%)	1.7	0.6 ,5.2	–
Combined	29 (25%)	30 (29%)	7 (25%)	1.2	0.3 ,4.3	–
Cell differentiation (*n* = 249)	10 (9%)	10 (10%)	8 (29%)	3.8	1.3 ,11	0.01
Size, mean in cm (SD) (*n* = 205)	3.4 (2.5)	3.5 (1.8)	4.7 (2.6)	1.3	1.0 ,1.6	0.02

Patients without lymph node dissection (Nx) were excluded from this analysis, because they provide no information about lymph node metastasis. **P*-values determined by Fisher's exact test because of small cell counts. CSI, carcinoma *in situ;* LVI, lymphovascular invasion; PNI, perineural invasion; SM, surgical margins.

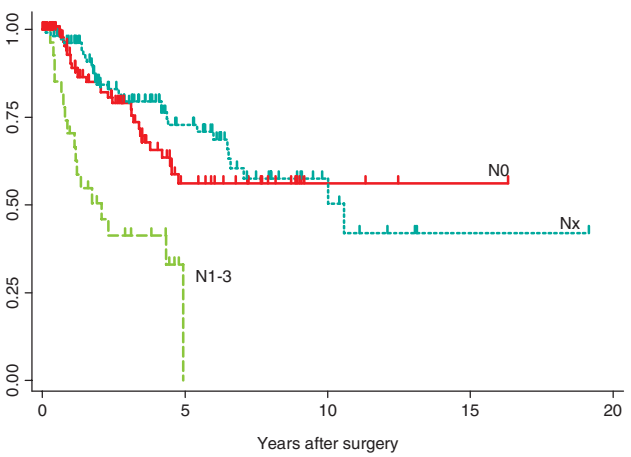

Fig. 2 Cancer-specific survival probabilities after surgery according to lymph node status.

selection for adjuvant (or possibly neoadjuvant) therapy including chemotherapy, which is particularly significant given the ongoing progress in the development of non-nephrotoxic chemotherapy agents active against urothelial cancer.[15]

Despite the recognition that the pathways for progression of UT-UCC include involvement of regional retroperitoneal and pelvic LN, no standards have been defined for when to perform LND or how extensive dissection should be. Hesitancy and lack of standardization still exists even among academic institutions (including our series), where the proportion of patients undergoing any form of LND varies from 44%[4] to 67%[5] for open NU series.[1,2,4,6–12] LND rates are even lower during minimally invasive approaches such as hand-assisted laparoscopic NU[9,12] or fully laparoscopic NU,[6,12] being approximately 15%. At our institution, LND has become more frequently performed (increasing from 40% to 61% over the last 5 years), yet criteria for its performance still are not uniform. Similarly, it is difficult to draw conclusions regarding local recurrence rates as many series do not report frequency or extent of the LND.[6,7,10]

Preoperative staging still represents a challenge, and it is not sufficient to identify patients with LNM. Suspicious CT findings was the only variable significantly predicting LNM, similar to reports of Garcia Garcia *et al.* [16] Importantly, 40% of our N+ patients had no sign of LN enlargement on CT.

Tumor size was also not predictive of biological behavior. In our series, two patients with LNM had tumors measuring less than 2 cm. One of them subsequently developed liver metastasis and died of disease. Similarly, patients with low-stage or low-grade tumors are not

exempt from developing distant metastasis and death.[7,10] None of our patients with LNM had low-grade disease, but one had a Ta tumor. In addition, the pathological variables predicting LNM in multivariate analysis, such as presence of lymphovascular invasion, capsular invasion and sinus fat invasion, are almost impossible to diagnose either on imaging studies or on preoperative biopsy analyses.

Can we select patients that should undergo LND? Given the listed limitations in preoperative staging, we would suggest that proper staging requires LND be performed in all patients with high-grade UT-UCC.

Defining the surgical limits of the LND is important, because the primary lymphatic drainage area of the kidneys and ureters may be extensive and complex, as described by Parker in 1935.[17] The lymphatic drainage from the kidneys to regional nodes is somewhat predictable; however, beyond the regional nodes it becomes varied. Of note, malignant disease may disrupt drainage patterns, making the locations of LNM far less predictable. Clearly, either a hilar or a limited LN dissection will not remove all of the primary lymphatic drainage area of the kidneys or ureters.

In addition to its prognostic value, LND may play a therapeutic role for patients with UT-UCC, as suggested by other authors.[14,18] Theoretically, a regional LND could remove microscopic regional disease that has not progressed distantly. However, there have been no well designed prospective studies to support the therapeutic value of LND in patients with UT-UCC. Miyake *et al.* [18] reported no significant difference in CSS between patients with and without LND; however, among patients with no lymphovascular invasion identified in the specimen, 5-year CSS was 86% for the 19 patients with LND, significantly higher than the 50% CSS for the 25 patients without LND ($P < 0.05$). They concluded that lymphadenectomy might provide a therapeutic advantage in patients with UT-UCC in the absence of lymphovascular invasion. In addition, it is not unreasonable to extrapolate results from cystectomy studies, which demonstrated that selected patients with positive LN during cystectomy can obtain survival benefit from extended LND.[3] Of note, many patients will have a solitary kidney and thus are not candidates for adjuvant platinum-based chemotherapy; therefore, removal of all identifiable disease may afford the best chance for cure.

The lack of any standardized pattern of side-specific dissection in our cohort represents a limitation in drawing definite conclusions regarding the therapeutic role of LND. Mapping information is also not available because LN were removed in only half of the cohort, with a tendency to perform LN sampling rather than formal LND. While the criteria for performing a LND were difficult to assess retrospectively, it is of interest that survival curves of both Nx and N0 patients were similar. This likely represents an undefined selection bias in that patients with lower risk for LNM were most likely included in a large percentage of the Nx group.

This communication does not pretend to demonstrate the therapeutic benefit of LND, but what it clearly states is the need for therapeutically-focused prospective, randomized protocols that adequately define the techniques and extent of LND in order to find a solution this unsolved urological dilemma.

Conclusion

Our retrospective study demonstrates that imaging, cytological and/or biopsy findings cannot reliably identify patients with LNM preoperatively. CT was the only variable significantly associated with LNM; however, CT failed to show LN enlargement in 40% of patients with LNM. Based on the poor prognosis of N+ patients and on the impossibility to accurately stage patients preoperatively, we recommend a more systematic approach to LND during nephroureterectomy in patients with UT-UCC. LND is clearly indicated for accurate staging and possibly to select patients for adjuvant chemotherapy. Although its therapeutic value has not been proven prospectively, the lack of a sensitive preoperative test for LNM argues for consideration of LND in all patients.

Acknowledgments

We would like to thank Janet Novak and Barbara Kristaponis for their expert editorial review; and Kinjal Vora and Jason Stasi for assistance with data retrieval.

References

1 Elliott DS, Segura JW, Lightner D *et al.* Is nephroureterectomy necessary in all cases of upper tract transitional cell carcinoma? Long-term results of conservative endourologic management of upper tract transitional cell carcinoma in individuals with a normal contralateral kidney. *Urology* 2001; **58**: 174–8.
2 Iborra I, Solsona E, Casanova J *et al.* Conservative elective treatment of upper urinary tract tumors: a multivariate analysis of prognostic factors for recurrence and progression. *J. Urol.* 2003; **169**: 82–5.
3 Herr HW, Donat SM. Outcome of patients with grossly node positive bladder cancer after pelvic lymph node dissection and radical cystectomy. *J. Urol.* 2001; **165**: 62–4.
4 Park S, Hong B, Kim CS *et al.* The impact of tumor location on prognosis of transitional cell carcinoma of the upper urinary tract. *J. Urol.* 2004; **171**: 621–5.
5 Charbit L, Gendreau MC, Mee S *et al.* Tumors of the upper urinary tract: 10 years of experience. *J. Urol.* 1991; **146**: 1243–6.
6 Bariol SV, Stewart GD, McNeill SA *et al.* Oncological control following laparoscopic nephroureterectomy: 7-year outcome. *J. Urol.* 2004; **172**: 1805–8.
7 Cozad SC, Smalley SR, Austenfeld M *et al.* Transitional cell carcinoma of the renal pelvis or ureter: patterns of failure. *Urology* 1995; **46**: 796–800.
8 Hall MC, Womack S, Sagalowsky AI *et al.* Prognostic factors, recurrence, and survival in transitional cell carcinoma of the upper urinary tract: a 30-year experience in 252 patients. *Urology* 1998; **52**: 594–601.
9 Hsueh TY, Huang YH, Chiu AW *et al.* A comparison of the clinical outcome between open and hand-assisted laparoscopic nephroureterectomy for upper urinary tract transitional cell carcinoma. *BJU Int.* 2004; **94**: 798–801.
10 Huben RP, Mounzer AM, Murphy GP. Tumor grade and stage as prognostic variables in upper tract urothelial tumors. *Cancer* 1988; **62**: 2016–20.
11 Matin SF, Gill IS. Recurrence and survival following laparoscopic radical nephroureterectomy with various forms of bladder cuff control. *J. Urol.* 2005; **173**: 395–400.
12 Stifelman MD, Sosa RE, Andrade A *et al.* Hand-assisted laparoscopic nephroureterectomy for the treatment of transitional cell carcinoma of the upper urinary tract. *Urology* 2000; **56**: 741–7.
13 Charlson ME, Pompei P, Ales KL *et al.* A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J. Chronic. Dis.* 1987; **40**: 373–83.
14 Komatsu H, Tanabe N, Kubodera S *et al.* The role of lymphadenectomy in the treatment of transitional cell carcinoma of the upper urinary tract. *J. Urol.* 1997; **157**: 1622–4.
15 Bamias A, Deliveliotis C, Fountzilas G *et al.* Adjuvant chemotherapy with paclitaxel and carboplatin in patients with advanced carcinoma of

the upper urinary tract: a study by the Hellenic Cooperative Oncology Group. *J. Clin. Oncol.* 2004; **22**: 2150–54.
16 Garcia Garcia F, Fontana Compiano LO, Garcia Ligero J *et al.* [Personal and histopathological factors as prognostic variables in upper urothelial tumors undergoing surgery]. *Arch. Esp. Urol.* 2002; **55**: 503–8.
17 Parker A. Studies on the main posterior lymph channels of the abdomen and their connections with the lymphatics of the genitourinary system. *Am. J. Anat.* 1935; **56**: 409–43.
18 Miyake H, Hara I, Gohji K *et al.* The significance of lymphadenectomy in transitional cell carcinoma of the upper urinary tract. *Br. J. Urol.* 1998; **82**: 494–8.