Lymph node density for stratification of survival outcomes with node positive upper tract urothelial carcinoma

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RAZA SJ, MILLER C, MAY A, DAVARO F, SIDDIQUI SA, HAMILTON Z. Lymph node density for stratification of survival outcomes with node positive upper tract urothelial carcinoma. *Can J Urol* 2019;26(4):9852-9858.

Introduction: *The use of lymph node density (LND) as a predictor of survival outcomes has been studied with urothelial carcinoma of the bladder. Similar results can be postulated to upper tract urothelial carcinoma (UTUC). This study aims to determine the overall survival of patients with lymph node positive UTUC based on LND, utilizing the National Cancer Database (NCDB).*

Materials and methods: *Data was derived from NCDB Participant User Kidney Dataset using the histology code 'transitional cell carcinoma', utilizing pN+ patients from 2004-2015. LND was calculated as number of positive nodes divided by total number of nodes removed. Patients were stratified by traditional AJCC pN stage and compared to LND groups (< 30%, ≥ 30%). Primary outcome was overall survival. Kaplan-Meier and Cox regression analyses were performed.*

Results: *A total of 2049 patients were identified (pN1 = 1022, pN2 = 1027; LND < 30% = 370, ≥ 30% = 1679). Mean LND was 71%. Cox regression for mortality using pN stage was not significant (p = 0.11); however, Cox regression for mortality using LND group noted significantly worsened survival with LND ≥ 30% (HR 1.54, p = 0.001). Kaplan Meier analysis for overall survival at 2 years showed no difference between pN1 and pN2 stages (35.3% versus 34.1%; log rank p = 0.37). Kaplan Meier analysis for overall survival at 2 years revealed significant difference between LND groups (LND < 30%, 47.3% versus LND ≥ 30%, 32.0%; log rank p < 0.001).*

Conclusions: *LND provides improved prognostic information regarding overall survival, compared to traditional AJCC pN staging. Future studies need to evaluate LND to improve prognostic understanding of lymph node positive UTUC.*

Key Words: kidney neoplasm, transitional cell carcinoma, lymph node excision, survival

Introduction

Upper tract urothelial carcinoma (UTUC) is an aggressive malignancy with a propensity for locally advanced disease or lymph node (LN) involvement, noted in up to 40% of patients at presentation.[1] Radical nephroureterectomy with bladder cuff excision is the treatment of choice for locally advanced disease, and LN dissection can be utilized for prognostic information in cases concerning for LN involvement.[2] Lymph node yield, both in the setting of negative or positive LN, may be associated with overall and recurrence free survival outcomes,[3,4] although this has not yet been confirmed in a prospective randomized trial and the use of lymph node dissection remains debatable. The current American Joint Committee on Cancer (AJCC) TNM staging system classifies pathologic nodal stage based on the number and size of the involved LN;[5] however, recent data analyzing the applicability of this system is lacking.

Accepted for publication April 2019

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Lymph node density (LND) is calculated as number of positive LN divided by total number of LN obtained. The use of LND as a predictor of survival outcomes has been previously studied with urological cancers. Studies have noted the prognostic role of LND for prostatic and penile carcinomas.[6,7] Similar results have also been reported for urothelial carcinoma of the bladder.[8] In one study, a threshold of 20% for LND was associated with cancer specific survival.[8,9] It can then be postulated that these results may translate to outcomes with UTUC.

LND has been briefly studied for UTUC. Results from a multi institutional database reported that LND ≥_30% was associated with worsened recurrence free and disease specific survival for patients with UTUC.[10] This study was novel in its analysis and implications for UTUC; however, to our knowledge it has not been replicated in a large national cohort. In this study we sought to determine the effect of LND on overall survival and compare the prognostic value of LND with standard AJCC TNM pathologic staging in patients with node disease positive UTUC, utilizing the National Cancer Database (NCDB). We hypothesized our analysis would echo previous findings and emphasize the need for further research into LND for prognosis with UTUC.

Materials and methods

The NCDB is a program that serves as nationwide oncology outcomes database. It is a joint initiative of American Cancer Society (ACS) and the American College of Surgeons Commission on Cancer (CoC).[11] The NCDB is a national cancer outcomes dataset that includes input from over 1500 CoC-accredited centers in the United States. Standardized coding definitions are utilized, and the data is freely available to participating institutions after application for projects are submitted and accepted by the NCDB. These data are used to identify trends in cancer treatments and provide a benchmark for participating institutions to compare their outcomes, serving for quality improvement. The NCDB is a large dataset that has been utilized for publications involving malignancies from different organ systems. It has previously included data regarding UTUC, providing validation for its merit.[12,13]

Data was derived from the NCDB Participant User File Kidney Dataset, using the database dictionary defined histology codes for 'transitional cell carcinoma' undergoing radical nephroureterectomy. Only patients with node positive status (pN+) and quantified node sampling from 2004 to 2015 were included. All patients with pN+ disease were subdivided into pN1 (metastasis in a single lymph node 2 cm or less) or pN2/N3 (metastasis in single lymph node greater than 2 cm or multiple lymph nodes) based on the 8th edition AJCC staging for UTUC. Patients with pN0 or pNx status were excluded from analysis. LND was determined by dividing number of positive lymph nodes by total number of lymph nodes removed. All patients were sub stratified in the LND group as < 30% or ≥ 30%, in order to elaborate on previous significant findings with UTUC.[9] Patients positive for metastatic disease (cM+) were excluded from analysis, and additional Cox analysis was performed with peri-operative chemotherapy, to determine its influence on survival. Patient age, race, Charlson's comorbidity index (CCI), clinical stage, income status, and insurance status were evaluated. Tumor nuclear grade was recorded, and postoperative outcomes including readmission rate, length of follow up and all-cause mortality were analyzed. The primary outcome was overall survival, analyzed by AJCC pN and predetermined LND sub groups with threshold of 30%. Our secondary outcome included readmission within 30 days.

One way ANOVA or Student's T-test was performed for continuous variables, and Fischer's exact or Pearson chi-square tests for categorical variables. Kaplan Meier and Cox regression analysis were performed to determine the overall survival at 2 and 5 years and hazard ratio for mortality, respectively. Data was analyzed using SPSS v25 (NY, USA) for all analyses, with p value of < 0.05 denoting statistical significance.

Results

A total of 2049 patients meeting inclusion criteria with UTUC and pN+ disease were identified from the database. Patient demographics are noted in Table 1. The mean age of the cohort was 70.4 years. Majority of the patients were white (91%) and predominantly male (56.3%). The number of patients with pN1 was almost equal to pN2/N3 (49.8% versus 50.1%, respectively). The pN1 and pN2 groups were well balanced with no significant differences regarding race, sex, or CCI. Of note, pN2/N3 patients had significantly lower age (69.4 versus 71.4 years, $p < 0.001$) and a higher rate of cT4 disease (32.5% versus 22.9%, $p < 0.001$). When comparing patients according to the LND groups, we noted the patients were well balanced with respect to sex, CCI, and cT stage. However, patients with LND ≥ 30% tended to have increasing age (68.4 versus 70.8, $p < 0.001$) and a significant difference in race ($p < 0.001$). The majority of patients had LND ≥ 30% (81.9%). Overall 41.7% patients received peri-operative

TABLE 1. **Patient details stratified by pN and lymph node density (LND)**

Variable	All (n = 2049)	pN1 (n = 1022)	pN2/N3 (n = 1027)	p value	LND < 30% (n = 370)	LND ≥ 30% (n = 1679)	p value
Patient demographics and clinical tumor characteristics							
Mean age	70.4 ± 11.0	71.4 ± 10.8	69.4 ± 11.2	< 0.001	68.4 ± 11.8	70.8 ± 10.8	< 0.001
Race				0.73			0.005
White	1865 (91.0%)	922 (91.3%)	932 (90.7%)		325 (87.8%)	1540 (91.7%)	
Black	107 (5.2%)	54 (5.3%)	53 (5.2%)		32 (8.6%)	75 (4.5%)	
Other	77 (3.8%)	35 (3.4%)	42 (4.1%)		13 (3.5%)	64 (3.8%)	
Male	1153 (56.3%)	558 (54.6%)	595 (57.9%)	0.13	210 (56.8%)	943 (56.2%)	0.86
Charlson				0.63			0.72
0	1476 (72.0%)	726 (71.0%)	750 (73.0%)		273 (73.8%)	1203 (71.6%)	
1	434 (21.2%)	227 (22.2%)	207 (20.2%)		74 (20.0%)	360 (21.4%)	
2	106 (5.2%)	51 (5.0%)	55 (5.4%)		16 (4.3%)	90 (5.4%)	
3^+	33 (1.6%)	18 (1.8%)	15 (1.5%)		7 (1.9%)	26 (1.5%)	
cT stage				< 0.001			0.05
cT1	136 (6.6%)	86 (8.4%)	50 (4.9%)		39 (10.5%)	97 (5.8%)	
cT2	42 (2.0%)	33 (3.2%)	9 (0.9%)		9 (2.4%)	33 (2.1%)	
cT3	190 (9.3%)	139 (13.6%)	51 (5.0%)		35 (9.5%)	155 (9.2%)	
cT4	569 (27.8%)	234 (22.9%)	335 (32.6%)		96 (25.9%)	473 (28.2%)	
Unknown	1112 (54.3%)	530 (51.9%)	582 (56.7%)		191 (51.6%)	921 (54.9%)	
Periop chemo				0.007			< 0.001
None	836 (40.8%)	440 (43.1%)	396 (38.6%)		144 (38.9%)	692 (41.2%)	
Neoadjuvant	125 (6.1%)	47 (4.6%)	78 (7.6%)		51 (13.8%)	74 (4.4%)	
Adjuvant	729 (35.6%)	348 (34.1%)	381 (37.1%)		129 (34.9%)	600 (35.7%)	
Unknown	359 (17.5%)	187 (18.3%)	172 (16.7%)		46 (12.4%)	313 (18.6%)	
Histology and survival outcomes							
High grade	1728 (84.3%)	865 (84.6%)	863 (84.0%)	0.71	311 (84.1%)	1417 (84.4%)	0.88
LND group				< 0.001			
< 30%	370 (18.1%)	228 (22.3%)	142 (13.8%)		370 (100%)	N/A	
≥ 30%	1679 (81.9%)	794 (77.7%)	885 (86.2%)		N/A	1679 (100%)	
pN Stage							< 0.001
pN1	1022 (49.9%)	1022 (100%)	N/A		228 (61.6%)	794 (47.3%)	
pN2/N3	1027 (50.1%)	N/A	1027(100%)		142 (38.4%)	885 (52.7%)	
Nodes pos	2.5 ± 2.9	1.5 ± 1.5	3.5 ± 3.6	< 0.001	1.7 ± 1.2	2.7 ± 3.2	< 0.001
Nodes total	5.4 ± 6.9	4.1 ± 5.9	6.7 ± 7.6	< 0.001	12.9 ± 9.6	3.8 ± 4.7	< 0.001
LND	71.3% ± 37.9	68.6% ± 36.4	74.1% ± 39.1	< 0.001	16.1% ± 7.3%	82.5% ± 24.3%	< 0.001
Length of stay	5.9 ± 6.1	6.0 ± 6.9	5.8 ± 5.4	0.15	5.4 ± 4.2	6.1 ± 6.5	0.08
Readmission	96 (4.7%)	46 (4.5%)	50 (4.9%)	0.77	18 (4.9%)	78 (4.6%)	0.93
Follow up (mo)	22.6 ± 23.7	22.7 ± 23.2	22.5 ± 24.3	0.37	28.1 ± 24.8	21.4 ± 23.4	< 0.001
Median (IQR)	15.1 (7.1-28.8)	15.7 (7.2-29.2)	14.7 (6.9-28.6)		20.3 (10.1-39.8)	14.0 (6.5-26.9)	
Mortality	1506 (73.5%)	743 (72.7%)	763 (74.3%)	0.41	215 (58.1%)	1291 (76.9%)	< 0.001

TABLE 2. **Cox regression for mortality**

Utilizing AJCC pN category				
Variable	**HR**	**95% CI low**	**95% CI high**	**p value**
Age	1.02	1.02	1.03	< 0.001
Charlson score (0 ref)				
1	1.00	0.93	1.19	0.45
2	1.36	1.09	1.73	0.007
3+	1.35	0.93	1.96	0.12
High nuclear grade	1.10	0.95	1.27	0.21
pN2/N3 (pN1 ref)	1.09	0.98	1.20	0.11
Utilizing LND category				
Variable	**HR**	**95%CI low**	**95%CI high**	**p value**
Age	1.02	1.06	1.03	< 0.001
Charlson score (0 ref)				
1	1.05	0.93	1.19	0.42
2	1.37	1.09	1.73	0.008
3+	1.44	0.99	2.10	0.06
High nuclear grade	1.09	0.94	1.26	0.24
LND ≥ 30%	1.54	1.33	1.78	< 0.001

chemotherapy, with significantly higher numbers noted for pN2/N3 and LND ≥ 30% cohorts.

Table 1 also lists the postoperative and survival outcomes. High nuclear grade disease was observed in the majority of patients (84.3%), while the mean number of lymph nodes removed was 5.4 and a mean of 2.5 lymph nodes positive. Overall mortality rate was 73.5%, with a median follow up of 15.1 (IQR 7.1-28.8) months. When comparing the pN1 versus pN2/N3 cohorts, we noted that pN2/N3 patients had a higher mean nodal count removed and mean nodal count positive, as expected based on the current AJCC staging system ($p < 0.001$). Furthermore, the rate of high grade disease, readmission rate, mean length of hospital stay, mean length of follow up, and overall mortality (72.7% versus 74.3%) was similar between AJCC pN cohorts. Similarly, there was no difference in the rate of high grade disease, readmission rate, or mean length of stay between LND groups. On the contrary, there was a significant difference in the overall mortality between LND cohorts, with an increasing rate of mortality associated with LND ≥ 30% (58.1% versus 76.9%, $p < 0.001$).

Cox regression analysis for mortality, Table 2, included age, CCI, high nuclear grade, and varying nodal status. The Cox regression was repeated with each individual nodal system (AJCC pN stage or LND category) to avoid collinearity. We noted that increasing age and CCI of 2 were associated with statistically significant risk of mortality, in both models utilizing pN or LND category. Of note, AJCC pN stage was not associated with mortality risk, in the model utilizing the pN category; however, in the model utilizing LND category, LND ≥ 30% was significantly associated with a risk of mortality (HR 1.54, $p < 0.001$). A subset Cox regression analysis of patients who received peri-operative chemotherapy, Table 3, revealed similar findings in terms of and and CCI. Interestingly in this subset pN2 disease was significantly associated with poorer overall survival (HR 1.16, p 0.01), and was LND ≥ 30% (HR 1.59, $p < 0.001$). Overall survival (OS) was plotted using Kaplan Meier survival curves. Using pN stage as a categorical variable showed no difference in OS, Figure 1; log-rank $p = 0.37$. However, a statistically significant difference was noted between the LND categories, Figure 2; log-rank $p < 0.001$).

Discussion

This study reports LND as a significant predictor of OS for non-metastatic UTUC through utilization of a large national tumor registry. Our study is novel in its comparison to AJCC staging and is supported by its large patient cohort. LND has previously been noted to predict recurrence free and cancer specific

TABLE 3. **Cox regression for mortality (includes only those with known perioperative chemotherapy status)**

Utilizing AJCC pN category				
Variable	**HR**	**95% CI low**	**95% CI high**	**p value**
Age	1.02	1.01	1.02	< 0.001
Charlson score (0 ref)				
1	1.06	0.92	1.22	0.41
2	1.45	1.12	1.86	0.004
3+	1.19	0.79	1.81	0.41
High nuclear grade	1.10	0.94	1.29	0.24
pN2 (pN1 ref)	1.16	1.04	1.31	0.01
POC (no POC ref)				
NAC	0.53	0.41	0.69	< 0.001
AC	0.56	0.49	0.64	< 0.001
Utilizing LND category				
Variable	**HR**	**95%CI low**	**95%CI high**	**p value**
Age	1.01	1.01	1.02	< 0.001
Charlson score (0 ref)				
1	1.05	0.92	1.21	0.46
2	1.45	1.13	1.87	0.004
3^{+}	1.24	0.82	1.89	0.31
High nuclear grade	1.08	0.92	1.27	0.32
LND ≥ 30%	1.59	1.35	1.87	< 0.001
POC (no POC ref)				
NAC	0.60	0.46	0.77	< 0.001
AC	0.55	0.49	0.63	< 0.001

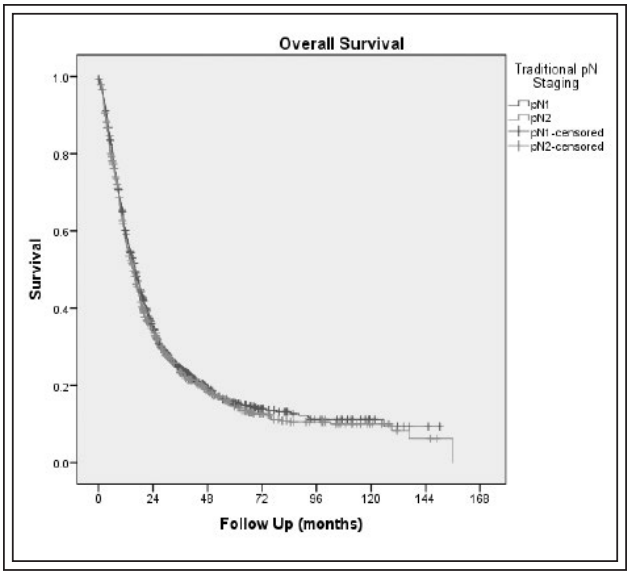

Figure 1. Kaplan Meier - overall survival by AJCC pN category.

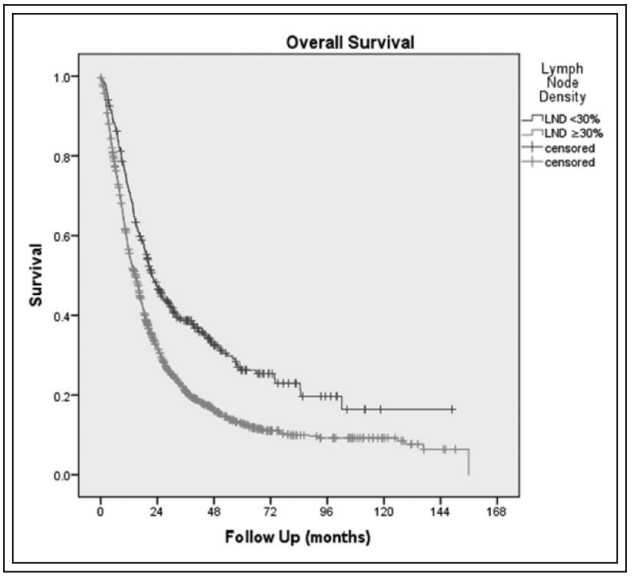

Figure 2. Kaplan Meier - overall survival by LND category

survival in UTUC patients providing further credence to this relationship; however, the previous study was limited to 135 patients, and there was no comparison with AJCC staging.[10] We utilized the National Cancer Database, which includes patients from oncologic centers across the United States, representing the overall national outcomes. A larger cohort of patients not only enhances the accuracy of previous findings, but also demonstrates the national trends of patient outcomes with respect to LND for UTUC.

Zareba et al have previously utilized the NCDB to report the association between LN dissection and survival outcomes of UTUC.[14] They reported that increasing total LN count was not an independent predictor of OS in patients with positive or negative disease. However it was noted that those with increasing positive LN yield had worse survival outcomes and those with increasing negative LN yield had improved survival outcomes, which may have been representing the underlying LND noted in our analysis. On a subset analysis utilizing only pN+ patients, Zareba et al reported LND as an independent predictor of lower OS with each 10% increase of LND, although the number of nodes yielded in this subset was not reported. Similarly, our study also noted a worsening survival outcome associated with LND, specifically using a cut off of 30% which has been previously reported.[10] On the contrary, Zareba et al did not compare the OS between LND and traditional AJCC pN staging. Our analysis noted that pN staging did not appear to correlate with OS outcomes; however, LND with a cutoff of 30% did provide prognostic information. Taken together, our study highlights the underlying relationship between LND and survival for UTUC, and the need for further study to delineate the specific relationship with LN involvement and LN yield for patient counseling.

The role of LN dissection at the time of nephroureterectomy is debatable. The indications for LN dissection with UTUC are not completely established and remain similar to those used for renal cell carcinoma.[2] Benefits may be related to improved staging and prognosis, as opposed to a true therapeutic benefit. However reports from a meta-analysis revealed an improved cancer specific survival for patients who undergo LN dissection at the time of nephroureterectomy.[15] Utilizing NCDB, Lenis et al analyzed predictors of LN dissection with UTUC.[16] They found high grade pathology, preoperative nodal enlargement, ureteral tumor site and academic centers were predictors of LN dissection. The overall median yield in that analysis was 3, with significantly higher yield noted for robot-assisted approach. Additionally, these authors identified an increasing utilization of LN dissection with the robotic approach over the study period, thus an increase in LN dissection could be predicted in coming years with more opportunity to evaluate LND against traditional AJCC staging.

At present, National Comprehensive Cancer Network guidelines recommend LN dissection with radical nephroureterectomy,[17] especially for advanced or high grade disease; however, the final AJCC staging of the disease incorporating LN status may not accurately stratify the survival outcomes. Based on the findings of our study, pN sub-staging does not reliably predict OS. This compares to the findings reported by Lee et al for bladder cancer.[9] Their study compared LND to the AJCC nodal staging in patients who underwent extended or super extended LN dissection following radical cystectomy with node positive disease. The study reported that LND was a significant predictor of recurrence free and overall survival compared to AJCC nodal staging, yet nodal disease was not a predictor of survival. Of note, the study utilized the LND as a continuous variable on multivariate cox regression model while the Kaplan Meier survival curves were plotted using quartiles of LND. Urothelial cell carcinoma of the bladder and UTUC have similar underlying pathology, and our analysis amplifies this relationship. We noted that pN staging for UTUC did not reliably predict the overall survival but LND was associated with stratification of outcomes.

Despite the emerging role of LN dissection at the time of NU and recent guideline recommendations, there still remain a limited number of patients who undergo this. Within the NCDB, Zareba et al reported a 20% rate of LN dissection. Such a low percentage of LN dissection performed may represent an underlying surgical disparity. Relatedly, if fewer LN dissections are being performed, there is limited evidence available for analysis to provide additional retrospective support. Furthermore, improved oncologic outcomes have been reported with LN dissection for UTUC. A recent review of literature by Siesen et al emphasized the therapeutic benefit of LN dissection for UTUC at the time of radical nephroureterectomy.[18] This analysis recommends LN dissection using the modified template,[19] with at least eight LN removed, and showed improve cancer specific survival for patients with invasive and locally advanced disease. In a prospective study, use of template based lymphadenectomy is reported to be an independent factor associated with improved cancer specific survival.[20] Since our study raises concerns regarding AJCC staging and its ability to predict survival, standard AJCC pathologic nodal staging alone may not be useful for prognostication as LN dissection is increasingly encouraged.

Our study contains inherent limitations related to its retrospective nature and selection bias. Additionally, the NCDB is limited by lack of recurrence free and cancer specific survival. These are the major limitations of utilizing the NCDB, which does not capture these variables. Additionally LN dissection template descriptions are not provided, as one would see from a single institutional study; thus we cannot determine the extent of LN dissection performed. Lack of centralized pathologic analysis, as well as the observational nature of the data collection with bias from other confounding factors at each institution must be considered as well. An inherent limitation of the lymph node density is the lack of a common denominator. The number of total nodes removed is dependent on the surgeon dissection and the pathologist interpretation. Taking this into consideration, there will always be some discrepancy for each patient and institution; however, it is worth noting that this limitation will be inherent even with a well-designed prospective study. For this reason, lymph node density is still in a hypothesis generating stage of investigation. Future research efforts should consider evaluation of LND as a predictor of survival outcomes in a prospective study. Until such results are available, urologists should continue to perform dedicated LN dissection with radical nephroureterctomy, in order to collect more information regarding the therapeutic benefits with UTUC.

Conclusions

In the setting of UTUC, LND provides prognostic information regarding overall survival, while traditional AJCC nodal staging does not correlate with this outcome in its current arrangement. Further research is necessary to evaluate LND for prediction of cancer specific outcomes. □

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