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Association between lymph node yield and survival among patients undergoing radical nephroureterectomy for upper tract urothelial carcinoma

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Abstract

Background—Prior studies examining the value of lymph node dissection (LND) in patients with urothelial carcinoma of the upper urinary tract (UTUC) have produced conflicting results. The objective of this study was to assess the relationship between lymph node (LN) yield and survival among patients undergoing radical nephroureterectomy (RNU).

Methods—The National Cancer Data Base was used to identify patients with non-metastatic UTUC who were treated with RNU between 2004 and 2012. The association between LN yield and overall survival (OS) was assessed using Cox proportional hazards regression, with adjustment for patient, tumor and facility characteristics.

Results—Of the 14,472 patients, 2,926 (20%) underwent LND. Median yield was two LN (IQR 1, 6). Among the entire cohort and the LN-negative (pN0) subgroup, higher LN yield was associated with lower all-cause mortality (multivariable HR 0.94 per five LN removed, 95% CI 0.89, 1.00, $p=0.034$ for the entire cohort; HR 0.86, 95% CI 0.79, 0.94, $p=0.001$ for the pN0 subgroup). Among LN-positive (pN+) patients, there was no association between total LN yield and OS; however, positive and negative LN counts were independent predictors of OS (HR 1.27 per five positive LN, 95% CI 1.16, 1.39, $p<0.001$; HR 0.90 per five negative LN, 95% CI 0.82, 1.00, $p=0.049$).

Conclusions—In this large, contemporary cohort of patients with UTUC, LND was found to be used infrequently despite evidence that higher LN yield is associated with lower all-cause mortality.

Precis

The National Cancer Data Base was used to assess the relationship between the extent of lymph node dissection performed at the time of radical nephroureterectomy for upper tract urothelial carcinoma and overall survival. Among a cohort of 2,926 patients, higher lymph node yield was found to be associated with lower all-cause mortality after adjustment for patient, tumor and facility characteristics.

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Conflicts of interest: None

Keywords

Transitional cell carcinoma; kidney; ureter; nephrectomy; lymph node dissection

Introduction

Urothelial carcinoma of the upper urinary tract (UTUC) is a rare but highly aggressive malignancy. UTUC has a propensity for early metastatic spread to the regional lymph nodes (LN), with LN metastases being found at the time of radical nephroureterectomy (RNU) in approximately 20–25% of patients with T2 tumors (invading into the muscularis propria) and as many as 60% of those with T3 or T4 tumors (invading into the renal parenchyma or perinephric/periureteric fat and adjacent organs, respectively).¹ LN metastases increase the risk of cancer-specific mortality almost three-fold such that approximately two-thirds of LN-positive (pN+) patients die of their disease within five years of surgery.²

Although the presence of LN metastases is an important prognostic factor in UTUC and the extent of lymph node dissection (LND) has been shown to be associated with survival in the related disease of urothelial carcinoma of the bladder,³ use of LND in patients with UTUC has not been standardized. This may be due to a lack of an established association between LND and survival in this patient population. Obtaining level one evidence for a therapeutic benefit of LND in patients with UTUC is a daunting proposition due in part to the rarity of the disease and the lack of consensus regarding standard dissection templates. Meanwhile, observational studies have produced somewhat conflicting findings. Specifically, while a recent analysis of the Surveillance, Epidemiology and End Results (SEER) registry found a positive association between LN yield and cancer-specific survival (CSS),⁴ an earlier multi-institutional study reported an association among LN-negative (pN0) patients only.⁵

Given the ongoing uncertainty regarding the prognostic and therapeutic value of LND in patients with UTUC, we set out to define the association between LN yield and survival using the National Cancer Data Base (NCDB).

Materials and Methods

The NCDB is a joint project of the American Cancer Society and the Commission on Cancer (CoC) of the American College of Surgeons that collects data from cancer registries at CoC-designated hospitals, which comprise one-third of all U.S. hospitals but diagnose approximately 70% of cancer cases nationwide.⁶ It contains information pertaining to patient and tumor characteristics, the initial course of treatment and vital status at last follow-up, but lacks data pertaining to tumor recurrence or cause of death. Institutional review board approval for this study was waived because it used de-identified data.

Our primary objective was to assess the relationship between LN yield, which was used as a surrogate of the extent of LND, and overall survival (OS) among patients with UTUC undergoing RNU. Secondary objectives were to assess the relationship between LN status (pN0 vs. pN+ vs. pNX) and OS among the entire cohort, and to identify patient, tumor and facility characteristics associated with receipt of LND, LN yield and LN positivity. The

study population was defined as patients 18 years of age or older who were diagnosed with UTUC between 2004 and 2012 and were treated with RNU ($n=23,884$). We excluded patients with metastatic disease at diagnosis ($n=790$), those with a prior cancer diagnosis ($n=8,092$) and those with missing data pertaining to whether LND was performed ($n=648$), LN yield ($n=3$) or follow-up time ($n=538$). The remaining 14,472 patients, of whom 2,926 underwent LND, were included in the analyses. Median follow-up time among survivors was 3.5 years (interquartile range, IQR, 2.0, 5.7).

Survival analyses were performed using Cox proportional hazards regression. Logistic regression was used to model LN positivity and receipt of LND, whereas zero-truncated negative binomial regression was used to model LN yield. Covariates included age (modeled as a continuous variable), sex, comorbidity burden as measured by the Deyo modification of the Charlson Comorbidity Index (categorized as 0 vs. 1 vs. 2), race (white vs. black vs. other), insurance status (private vs. Medicare vs. other), ZIP code-level income (quartiles), urbanicity of patient's county of residence (metropolitan vs. non-metropolitan), facility designation (academic comprehensive cancer program vs. other), facility location (Northeast vs. Midwest vs. South vs. West), annual facility RNU volume (continuous), year of diagnosis (modeled as a set of indicator variables), time from diagnosis to RNU (continuous), tumor site (renal pelvis vs. ureter), laterality, grade (well or moderately differentiated vs. poorly differentiated or anaplastic), pathologic T classification (T1, no invasion or invasion of subepithelial connective tissue only, vs. T2 vs. T3 vs. T4), surgical margin status and receipt of chemotherapy (none vs. neoadjuvant vs. adjuvant). Time from diagnosis to RNU was classified as missing if the date of diagnosis was the same as the date of RNU. With respect to the coding of tumor grade, although the AJCC Collaborative Staging System tumor grading scheme that is used by the NCDB differs from the World Health Organization/International Society of Urologic Pathology (WHO/ISUP) grading scheme for UC, a prior analysis of cases of UC of the bladder in the SEER database, which uses the same grading scheme as the NCDB, found that 98% of WHO/ISUP low-grade tumors and 97% of WHO/ISUP high-grade tumors were classified as well or moderately-differentiated and poorly-differentiated or anaplastic, respectively.⁷

Because it was hypothesized that the relationship between LN yield and outcomes may not be linear, LN yield was additionally modeled using restricted cubic splines with knots placed at 2, 6 and 18 LN (corresponding to the 50th, 75th and 95th percentiles of LN yield). Knots were placed at these points because the LN yield distribution was positively skewed.⁸ We also tested whether the associations between the number of total and negative LN removed and survival differed according to LN status (pN0 vs. pN+) via interaction terms. To assess whether the number of positive and negative LN had independent prognostic value among pN+ patients, these counts were also modeled separately. We likewise assessed the relationship between LN density (number of positive LN divided by the total number of LN removed) and survival among the pN+ subgroup.

Multiple imputation by chained equations was used to account for missing covariate data, the frequency of which varied from 27% for time from diagnosis to RNU to 10% for grade to less than 4% for all other covariates. To account for clustering of outcomes at the facility level, we calculated robust standard errors for all models. We confirmed that LN yield did

not violate the proportional hazards assumption. All statistical tests were two-sided and p -values less than 0.05 were considered significant. Statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC) and Stata 14 (StataCorp LP, College Station, TX).

Results

The median age of the patients included in the analysis was 71 years (IQR 63, 79) and 57% were male (see Table 1). Sixty-nine percent of tumors were located in the renal pelvis, 64% were high-grade and 47% were classified as T2 or higher. LND was performed in 2,926 patients (20%), with the median yield being two LN (IQR 1, 6). Increasing age and comorbidity burden were associated with a lower probability of receiving LND and lower LN yield on multivariable analysis, although the associations with LN yield did not reach conventional levels of statistical significance (see Table 2). Conversely, treatment at an academic facility and more recent year of diagnosis were positively associated with receipt of LND and LN yield. Patients with left-sided tumors and ureteric tumors were more likely to receive LND and have more LN removed. Higher tumor grade and T classification were associated with a higher likelihood of receiving LND but not LN yield (although patients with T4 tumors had, on average, higher LN yields than those with non-muscle-invasive disease, those with T2 or T3 tumors did not).

LN metastases were identified in 26% of patients who underwent LND. Tumor characteristics that were independently associated with LN positivity included tumor location in the renal pelvis and left side, high tumor grade, increasing T classification and positive surgical margins (see Table 3). LN yield was also an independent predictor of LN positivity: among patients who had one LN removed, the adjusted probability of finding LN metastases was 24%, a figure that increased in a non-linear fashion before peaking at 31% at a yield of approximately 15 LN (see Figure 2).

There were 5,816 deaths during follow-up. Five-year overall survival (OS) was 61% (95% CI 59%, 64%), 24% (20%, 27%) and 59% (58%, 60%) for patients classified as pN0, pN+ and pNX, respectively. The presence of LN metastases was an independent predictor of higher all-cause mortality (multivariable HR 1.89 for pN+ vs. pN0 patients, 95% CI 1.64, 2.17, $p<0.001$; see Table 4). All-cause mortality among patients who did not undergo LND was lower than that among pN+ patients (HR 0.56, 95% CI 0.49, 0.64, $p<0.001$) but not significantly different from that among pN0 patients (HR 1.05, 95% CI 0.97, 1.14, $p=0.21$). Other disease characteristics that were independent predictors of shorter survival included ureteric location, high tumor grade, increasing T classification and positive surgical margins. Receipt of adjuvant chemotherapy was associated with longer survival among the entire cohort and the pN+ subgroup, but not the pN0 subgroup (see Table 4).

Among the 2,926 patients who underwent LND, higher LN yield was associated with higher OS, with there being a 6% decrease in the hazard for every five LN removed (multivariable HR 0.94, 95% CI 0.89, 1.00, $p=0.034$). Modeling LN yield using splines suggested that the relationship between LN yield and OS was non-linear ($p=0.022$ for non-linearity; $p=0.010$ for overall non-linear association), with the nadir hazard occurring at a yield of approximately 15 LN (HR 0.75 for 15 vs. one LN removed, 95% CI 0.62, 0.90).

The test for interaction between LN yield and LN status was highly significant ($p=0.001$), indicating that the relationship between LN yield and OS differed between pN0 and pN+ patients. In contrast, there was no evidence of a statistically significant interaction between negative LN count and LN status ($p=0.08$). Subgroup analyses confirmed that higher LN yield was associated with higher OS among pN0 patients (HR 0.86 per five LN, 95% CI 0.79, 0.94, $p=0.001$) but not pN+ patients (HR 1.01 per five LN, 95% CI 0.94, 1.08, $p=0.89$). Among pN+ patients, modeling the number of positive and negative LN separately revealed that while an increasing number of positive LN was associated with lower OS (HR 1.27 per five positive LN, 95% CI 1.16, 1.39, $p<0.001$), an increasing number of negative LN was associated with higher OS (HR 0.90 per five negative LN, 95% CI 0.82, 1.00, $p=0.049$). Increasing LN density was likewise an independent predictor of lower OS among the pN+ subgroup (HR 1.04 per 10% increase, 95% CI 1.01, 1.07, $p=0.005$).

Discussion

In an analysis encompassing a large, diverse and contemporary group of patients with UTUC treated at over 1,000 U.S. hospitals, we found that LND constitutes a part of surgical management in only a fifth of such patients. Furthermore, the majority of patients who do undergo LND receive limited resections with low LN yields. These findings are likely a reflection of the ongoing uncertainty regarding the therapeutic value of LND in UTUC.

The low median LN yield and high rate of positivity in the LN sampled suggests that the attitude toward LND during RNU at most centers is that of a staging procedure, with selective removal of suspicious nodes (“node plucking”) being performed without interest in extending the dissection template in the setting of positivity. Given that standard cross-sectional imaging has limited accuracy in predicting pathologic LN positivity in patients with UTUC,^{9,10} LND has long been the gold standard for establishing nodal stage, which is a key determinant of prognosis.^{11,12} The adequacy of sampling is a central issue in surgical nodal staging and the question of the number and location of LN required for adequate staging is highly relevant. Our analysis shows that the likelihood of identifying positive LN continues to increase up to a yield of approximately 15 LN, suggesting that if LND was performed for staging purposes then the majority of cases in this series were under-sampled.

There is currently a lack of consensus regarding the value of LND in the surgical management of UTUC, which likely stems from inconsistent and sometimes contradictory findings reported by prior studies.^{4,5} One of the largest of these, from the Upper Tract Urothelial Carcinoma Collaboration, analyzed outcomes among 552 patients with UTUC treated at 13 centers worldwide.⁵ This study reported finding an association between higher LN yield and lower cancer-specific mortality among pN0 patients. Among the entire, unstratified cohort, higher LN yield was associated with a lower risk of disease recurrence on multivariate analysis (HR 0.97 per one LN removed, $p=0.04$), although there was only a non-significant association between LN yield and CSS (HR 0.97 per one LN removed, $p=0.12$). The significantly larger number of patients in our analysis is the likely reason why we were able to detect an association between LN yield and survival whereas this study had not. Alternately, because the relationship between LN yield and OS appears to be non-linear, the strength of the association detected in any study assuming a linear relationship would be

partially dependent on the LN yield distribution within the study sample. Although it is likewise possible that the discrepant results could be due to the fact that our study used OS as opposed to CSS as the outcome of interest, this is made less likely by the fact that we adjusted our multivariable analyses for both age and comorbidity burden. Furthermore, a recent population-based study using the SEER registry likewise found a higher LN yield to be an independent predictor of higher CSS among patients with UTUC undergoing RNU.⁴ These findings further support the notion that the link between a more extensive LND and longer survival in this population is a causal one.

The association between an increasing number of negative LN and survival within both the pN0 and pN+ subgroups is interesting. Among patients who are classified as pN0, an increasing number of LN removed and examined decreases the potential for misclassification of those with LN metastases as pN0. The prognostic value of an increasing number of negative LN among pN+ patients may be explained in a similar fashion, in that it more accurately defines the true burden of LN metastases by way of LN density. Although LN density has been previously established to be an important prognostic factor in patients with pN+ urothelial carcinoma of the bladder,^{13,14} this concept has yet to be validated in the setting of UTUC. Previously, a small series showed that LN density 30% was an independent predictor of higher cancer-specific mortality,¹⁵ although this finding was not replicated in a follow-up study.¹⁶ An alternate explanation of the association between the number of negative LN and survival among pN0 patients is that a thorough LND can be truly therapeutic if it eradicates unidentified microscopic foci of metastatic disease that are missed on routine pathologic examination. This hypothesis is supported by a recent study that reported finding micrometastatic disease by immunohistochemistry in 14% of UTUC patients who were initially classified as pN0 but later presented with disease recurrence.¹⁷

Irrespective of the putative therapeutic mechanisms, our findings offer evidence that a thorough LND has clinical value because it improves the accuracy of nodal staging, which may offer benefits for informed management strategies such as the use of adjunctive therapies. Patients in our study with LN metastases were more likely to receive adjuvant chemotherapy, and while there is currently no level one evidence for a benefit of perioperative chemotherapy in patients with UTUC undergoing RNU,¹⁸ we did find an association between receipt of adjuvant chemotherapy and higher OS among pN+ but not pN0 patients. More accurate nodal staging might also alter post-surgical surveillance strategies in ways that could impact identification, characterization and reporting of recurrence.

While our results suggest that a more thorough LND at the time of RNU is associated with longer survival, our study does not answer the lingering question as to which LN regions should be dissected to maximize the staging accuracy and therapeutic benefit of LND. To date, few studies have attempted to delineate the patterns of metastatic spread of UTUC to the regional LN within the retroperitoneum. In a recent multi-institutional study of 73 pN+ patients, most patients with right-sided renal pelvic and proximal ureteric tumors were found to have hilar and paracaval LN metastases, whereas those with left-sided tumors most commonly had metastases to the hilar and para-aortic LN.¹⁹ Involvement of the interaortocaval LN was common in patients with right-sided tumors and paracaval LN

metastases but not those with left-sided tumors. Although validation of these findings is required, an earlier observational study that compared patients with UTUC undergoing RNU with and without LND using templates similar to those described in the study above reported that patients with muscle-invasive (pT2) renal pelvic tumors who received template-based LND had a higher CSS compared to those treated with RNU alone.²⁰

The main strengths of our study are the large sample size and the fact that all patients were treated in the contemporary era. Nevertheless, its observational nature means that our results are susceptible to bias due to unmeasured or residual confounding. It is possible that the extent of LND may be modified by the surgeon based on his or her perception of cancer severity or therapeutic intent. For example, if a surgeon who believes that LND has no therapeutic value encounters palpably abnormal LN during RNU, he or she may simply sample a few of these LN to confirm the presence of LN metastases and go no further. Although LN metastases were detected less frequently in patients with lower LN yields, we cannot rule out that the true incidence of LN metastases or total metastatic LN burden was higher among patients who received limited versus more extensive LND. While it is also possible that the opposite is true, that patients who are expected to have pN+ disease are subjected to more extensive LND, such an association would tend to bias our results towards the null. Other factors might also influence the extent of dissection such as patient comorbidity, body habitus and prior surgery; all factors that could also influence the risk of complications and all-cause mortality. Lack of data pertaining to cause of death precluded an analysis of the relationship between LN yield and cancer-specific mortality. Although we controlled for patient age and comorbidity status in the multivariable analyses, CCI may not capture all nuances of an individual patient's comorbidities, such that the potential for residual confounding remains. Information pertaining to prior endoscopic treatment of the primary tumor, which has been associated with worse outcomes among those with high-grade disease,²¹ was not available. Finally, it must be acknowledged that LN yield is an imperfect surrogate of LND extent, as it may be related to other factors such as the manner in which LN are submitted (en bloc or as separate packets) and the thoroughness of subsequent histopathologic examination.

In summary, our study shows LND to be used infrequently in patients with UTUC and provides evidence of an association between increasing LN yield and longer survival in this population. It must be acknowledged that the question of therapeutic benefit from extended LND is complex, and answering it will require a firm understanding of nodal drainage patterns and prospective study in appropriately selected patients. Although the low incidence of UTUC and the inherent difficulties in randomizing surgical interventions for patients with highly lethal diseases make a randomized trial challenging to perform, our findings suggest that this question is important to address given the high degree of variability in existing practice and the potential for significant patient benefit.

Acknowledgments

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Figure 1.
Distribution of lymph node yield

Figure 2.
Adjusted probability of finding lymph node metastases as a function of lymph node yield.
Lymph node yield modeled using restricted cubic splines. Dashed lines represent 95% confidence interval.

Table 1

Patient, tumor and facility characteristics by lymph node status

	All (n=14,472)	pN0 (n=2,155)	pN+ (n=771)	pNX (n=11,546)
<i>Age (years)</i>	71 (63, 79)	69 (60, 77)	70 (61, 78)	72 (64, 79)
<i>Sex</i>				
Male	8,264 (57%)	1,254 (58%)	411 (53%)	6,599 (57%)
Female	6,208 (43%)	901 (42%)	360 (47%)	4,947 (43%)
<i>Comorbidity burden (CCI)</i>				
0	9,662 (67%)	1,498 (70%)	558 (72%)	7,606 (66%)
1	3,611 (25%)	503 (23%)	161 (21%)	2,947 (26%)
2	1,199 (8%)	154 (7%)	52 (7%)	993 (9%)
<i>Race</i>				
White	13,326 (93%)	1,949 (91%)	700 (92%)	10,677 (94%)
Black	604 (4%)	105 (5%)	40 (5%)	459 (4%)
Other	389 (3%)	84 (4%)	22 (3%)	283 (2%)
<i>Insurance</i>				
Private	4,222 (30%)	743 (35%)	254 (33%)	3,225 (28%)
Medicare	9,329 (65%)	1,235 (58%)	473 (62%)	7,621 (67%)
Other	732 (5%)	145 (7%)	36 (5%)	551 (5%)
<i>Median income</i>				
<\$38,000	2,221 (16%)	325 (15%)	111 (15%)	1,785 (16%)
\$38,000–\$47,999	3,484 (25%)	494 (23%)	189 (25%)	2,801 (25%)
\$48,000–\$62,999	3,935 (28%)	585 (28%)	201 (27%)	3,149 (28%)
\$63,000	4,577 (32%)	716 (34%)	255 (34%)	3,606 (32%)
<i>Urbanicity</i>				
Metropolitan	11,524 (83%)	1,687 (81%)	630 (85%)	9,207 (83%)
Non-metropolitan	2,427 (17%)	385 (19%)	112 (15%)	1,930 (17%)
<i>Facility designation</i>				
Academic	4,964 (35%)	1,021 (48%)	329 (43%)	3,614 (31%)
Non-academic	9,410 (65%)	1,106 (52%)	434 (57%)	7,870 (69%)
<i>Facility location</i>				
Northeast	3,108 (22%)	523 (25%)	157 (21%)	2,428 (21%)
Midwest	4,093 (28%)	590 (28%)	210 (28%)	3,293 (29%)
South	5,018 (35%)	666 (31%)	251 (33%)	4,101 (36%)
West	2,155 (15%)	348 (16%)	145 (19%)	1,662 (14%)
<i>Year of diagnosis</i>				
2004	1,317 (9%)	147 (7%)	79 (10%)	1,091 (9%)
2005	1,414 (10%)	168 (8%)	70 (9%)	1,176 (10%)
2006	1,437 (10%)	185 (9%)	63 (8%)	1,189 (10%)

	All (n=14,472)	pN0 (n=2,155)	pN+ (n=771)	pNX (n=11,546)
2007	1,567 (11%)	222 (10%)	88 (11%)	1,257 (11%)
2008	1,681 (12%)	240 (11%)	87 (11%)	1,354 (12%)
2009	1,702 (12%)	268 (12%)	101 (13%)	1,333 (12%)
2010	1,744 (12%)	281 (13%)	88 (11%)	1,375 (12%)
2011	1,753 (12%)	293 (14%)	106 (14%)	1,354 (12%)
2012	1,857 (13%)	351 (16%)	89 (12%)	1,417 (12%)
<i>Time from diagnosis to RNU (days)</i>	34 (19, 55)	35 (19, 58)	31 (16, 60)	34 (20, 54)
<i>Chemotherapy</i>				
None	12,401 (89%)	1,793 (86%)	346 (47%)	10,262 (92%)
Neoadjuvant	162 (1%)	62 (3%)	45 (6%)	55 (<1%)
Adjuvant	1,431 (10%)	235 (11%)	344 (47%)	852 (8%)
<i>Site</i>				
Renal pelvis	9,936 (69%)	1,360 (63%)	591 (77%)	7,985 (69%)
Ureter	4,536 (31%)	795 (37%)	180 (23%)	3,561 (31%)
<i>Laterality</i>				
Right	7,212 (50%)	990 (46%)	320 (42%)	5,902 (51%)
Left	7,193 (50%)	1,152 (54%)	442 (58%)	5,599 (49%)
<i>Grade</i>				
Low	4,628 (36%)	550 (29%)	39 (6%)	4,039 (39%)
High	8,360 (64%)	1,355 (71%)	667 (94%)	6,338 (61%)
<i>T classification</i>				
T0/Ta/Tis/T1	7,627 (53%)	1,017 (47%)	28 (4%)	6,582 (57%)
T2	1,873 (13%)	314 (15%)	74 (10%)	1,485 (13%)
T3	4,183 (29%)	707 (33%)	448 (58%)	3,028 (26%)
T4	765 (5%)	113 (5%)	217 (28%)	435 (4%)
<i>Surgical margins</i>				
Negative	13,190 (92%)	1,976 (93%)	564 (75%)	10,650 (94%)
Positive	1,072 (8%)	153 (7%)	184 (25%)	735 (6%)

Figures represent counts (percentages) for all variables except age and time from diagnosis to RNU, for which the figures represent medians (interquartile range, IQR); counts may not add up to reported totals because of missing data; percentages may not add up to 100% because of rounding; CCI, Charlson Comorbidity Index; pN0, lymph node-negative; pN+, lymph node-positive; pNX, lymph nodes not assessed; RNU, radical nephroureterectomy

Table 2

Patient, tumor and facility characteristics associated with receipt of lymph node dissection and lymph node yield

	Receipt of LND (n=14,472)		LN Yield (n=2,926)	
	OR (95% CI)	p-value	% (95% CI)	p-value
<i>Age (per five years)</i>	0.89 (0.87, 0.91)	<0.001	−4 (−7, 0)	0.08
<i>Sex</i>				
Male	Ref.		Ref.	
Female	1.12 (1.03, 1.21)	0.011	−11 (−21, 0)	0.044
<i>Comorbidity burden (CCI)</i>				
0	Ref.		Ref.	
1	0.90 (0.81, 1.00)	0.020 [‡]	−8 (−22, 9)	0.07 [‡]
2	0.86 (0.73, 1.02)		−20 (−37, 1)	
<i>Race</i>				
White	Ref.		Ref.	
Black	1.22 (0.99, 1.50)	0.06	−5 (−29, 27)	0.72
Other	1.21 (0.94, 1.55)	0.15	−7 (−35, 33)	0.70
<i>Insurance</i>				
Private	Ref.		Ref.	
Medicare	1.04 (0.91, 1.17)	0.58	−5 (−20, 13)	0.58
Other	1.13 (0.93, 1.38)	0.22	−10 (−33, 22)	0.51
<i>Median income</i>				
<\$38,000	Ref.		Ref.	
\$38,000–\$47,999	1.00 (0.86, 1.15)	0.59 [‡]	1 (−18, 24)	0.50 [‡]
\$48,000–\$62,999	1.00 (0.86, 1.17)		−5 (−23, 17)	
\$63,000	1.04 (0.88, 1.22)		−5 (−23, 17)	
<i>Urbanicity</i>				
Metropolitan	Ref.		Ref.	
Non-metropolitan	1.14 (0.98, 1.32)	0.10	−14 (−29, 5)	0.13
<i>Facility designation</i>				
Academic	Ref.		Ref.	
Non-academic	0.59 (0.50, 0.70)	<0.001	−62 (−69, −53)	<0.001
<i>Facility location</i>				
Northeast	Ref.		Ref.	
Midwest	0.94 (0.72, 1.24)	0.66	8 (−26, 56)	0.70
South	0.91 (0.71, 1.16)	0.43	−9 (−35, 26)	0.55
West	1.25 (0.95, 1.65)	0.11	36 (−13, 112)	0.17
<i>Annual facility RNU volume (per ten cases)</i>	1.15 (0.95, 1.38)	0.16	18 (−3, 43)	0.10

	Receipt of LND (n=14,472)		LN Yield (n=2,926)	
	OR (95% CI)	p-value	% (95% CI)	p-value
<i>Year of diagnosis</i>				
2004	Ref.		Ref.	
2005	0.95 (0.76, 1.18)	<0.001 [†]	54 (7, 122)	<0.001 [†]
2006	0.96 (0.79, 1.17)		54 (8, 119)	
2007	1.12 (0.92, 1.37)		48 (6, 107)	
2009	1.26 (1.04, 1.54)		57 (16, 112)	
2010	1.25 (1.03, 1.52)		85 (33, 157)	
2011	1.32 (1.07, 1.63)		77 (27, 146)	
2012	1.35 (1.11, 1.65)		97 (44, 170)	
<i>Time from diagnosis to RNU (per 90 days)</i>	1.04 (0.94, 1.15)	0.48	−10 (−22, 6)	0.20
<i>Chemotherapy</i>				
None	Ref.		Ref.	
Neoadjuvant	4.63 (3.02, 7.11)	<0.001	117 (52, 211)	<0.001
Adjuvant	1.81 (1.57, 2.08)	<0.001	11 (−8, 34)	0.29
<i>Site</i>				
Renal pelvis	Ref.		Ref.	
Ureter	1.29 (1.15, 1.43)	<0.001	22 (5, 41)	0.008
<i>Laterality</i>				
Right	Ref.		Ref.	
Left	1.31 (1.20, 1.43)	<0.001	36 (18, 56)	<0.001
<i>Grade</i>				
Low	Ref.		Ref.	
High	1.44 (1.28, 1.64)	<0.001	6 (−11, 26)	0.51
<i>T classification</i>				
T0/Ta/Tis/T1	Ref.		Ref.	
T2	1.43 (1.24, 1.65)	<0.001 [†]	−4 (−22, 18)	0.09 [†]
T3	1.88 (1.67, 2.10)		4 (−11, 22)	
T4	3.60 (2.94, 4.40)		31 (3, 65)	
<i>Surgical margins</i>				
Negative	Ref.		Ref.	
Positive	1.09 (0.93, 1.26)	0.29	5 (−17, 34)	0.69

[†]p-value derived from test for trend; CCI, Charlson Comorbidity Index; CI, confidence interval; LN, lymph node; LND, lymph node dissection; OR, odds ratio; ref., referent; RNU, radical nephroureterectomy; % , percent difference

Table 3

Patient, tumor and facility characteristics associated with lymph node positivity

	OR (95% CI)	p-value
<i>Age (per five years)</i>	1.09 (1.02, 1.16)	0.008
<i>Sex</i>		
Male	Ref.	
Female	1.13 (0.92, 1.38)	0.23
<i>Comorbidity burden (CCI)</i>		
0	Ref.	
1	0.84 (0.64, 1.10)	0.21 [†]
2	0.85 (0.56, 1.28)	
<i>Race</i>		
White	Ref.	
Black	1.20 (0.74, 1.94)	0.46
Other	0.76 (0.45, 1.28)	0.29
<i>Insurance</i>		
Private	Ref.	
Medicare	1.07 (0.81, 1.42)	0.63
Other	0.97(0.59, 1.60)	0.91
<i>Median income</i>		
<\$38,000	Ref.	
\$38,000–\$47,999	1.04 (0.73, 1.48)	0.09 [†]
\$48,000–\$62,999	0.83 (0.59, 1.18)	
\$63,000	0.80 (0.55, 1.16)	
<i>Urbanicity</i>		
Metropolitan	Ref.	
Non-metropolitan	0.78 (0.56, 1.07)	0.13
<i>Facility designation</i>		
Academic	Ref.	
Non-academic	1.21 (0.95, 1.55)	0.13
<i>Facility location</i>		
Northeast	Ref.	
Midwest	1.10 (0.81, 1.48)	0.55
South	1.15 (0.85, 1.56)	0.38
West	1.26 (0.90, 1.77)	0.18
<i>Annual facility RNU volume (per ten cases)</i>	1.01 (0.89, 1.16)	0.85
<i>Year of diagnosis</i>		
2004	Ref.	
2005	0.69 (0.41, 1.14)	0.007 [†]

	OR (95% CI)	<i>p</i>-value
2006	0.45 (0.26, 0.76)	
2007	0.67 (0.41, 1.08)	
2008	0.57 (0.34, 0.94)	
2009	0.57 (0.35, 0.93)	
2010	0.47 (0.29, 0.76)	
2011	0.66 (0.40, 1.07)	
2012	0.41 (0.25, 0.67)	
<i>Time from diagnosis to RNU (per 90 days)</i>	1.19 (0.94, 1.51)	0.15
<i>Chemotherapy</i>		
None	Ref.	
Neoadjuvant	3.08 (1.74, 5.46)	<0.001
Adjuvant	4.67 (3.58, 6.09)	<0.001
<i>Site</i>		
Renal pelvis	Ref.	
Ureter	0.51 (0.40, 0.65)	<0.001
<i>Laterality</i>		
Right	Ref.	
Left	1.30 (1.04, 1.63)	0.019
<i>Grade</i>		
Low	Ref.	
High	2.52 (1.71, 3.71)	<0.001
<i>T classification</i>		
T0/Ta/Tis/T1	Ref.	
T2	6.12 (3.83, 9.76)	<0.001 [†]
T3	9.70 (6.40, 14.70)	
T4	24.87 (15.33, 40.35)	
<i>Surgical margins</i>		
Negative	Ref.	
Positive	2.16 (1.62, 2.88)	<0.001
<i>Number of LN removed (per five LN)</i>	1.10 (1.01, 1.20)	0.033

[†] *p*-value derived from test for trend; CCI, Charlson Comorbidity Index; CI, confidence interval; LN, lymph node; OR, odds ratio; ref., referent; RNU, radical nephroureterectomy

Table 4

Associations between patient, tumor and facility characteristics and overall survival

	All (n=14,472)		pN0 (n=2,155)		pN+ (n=771)	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (per five years)	1.25 (1.23, 1.28)	<0.001	1.24 (1.18, 1.30)	<0.001	1.14 (1.08, 1.21)	<0.001
Sex						
Male	Ref.		Ref.		Ref.	
Female	0.91 (0.86, 0.96)	0.001	0.81 (0.69, 0.94)	0.007	0.98 (0.82, 1.17)	0.81
Comorbidity burden (CCI)						
0	Ref.		Ref.		Ref.	
1	1.20 (1.12, 1.28)	<0.001 [†]	1.25 (1.06, 1.48)	<0.001 [†]	0.94 (0.76, 1.16)	0.80 [†]
2	1.64 (1.49, 1.80)		1.76 (1.38, 2.25)		1.01 (0.67, 1.53)	
Race						
White	Ref.		Ref.		Ref.	
Black	1.11 (0.96, 1.28)	0.15	1.28 (0.95, 1.73)	0.11	0.72 (0.45, 1.14)	0.16
Other	1.01 (0.85, 1.19)	0.91	1.32 (0.89, 1.96)	0.17	0.81 (0.45, 1.43)	0.46
Insurance						
Private	Ref.		Ref.		Ref.	
Medicare	1.03 (0.95, 1.12)	0.44	1.36 (1.10, 1.68)	0.004	0.99 (0.76, 1.31)	0.97
Other	1.44 (1.24, 1.67)	<0.001	1.83 (1.29, 2.60)	0.001	1.54 (0.99, 2.38)	0.054
Median income						
<\$38,000	Ref.		Ref.		Ref.	
\$38,000–\$47,999	1.01 (0.92, 1.12)	0.009 [†]	1.05 (0.82, 1.34)	0.97 [†]	1.02 (0.75, 1.37)	0.09 [†]
\$48,000–\$62,999	0.99 (0.91, 1.09)		1.04 (0.81, 1.33)		0.97 (0.73, 1.27)	
\$63,000	0.89 (0.80, 0.99)		1.01 (0.78, 1.30)		0.81 (0.60, 1.08)	
Urbanicity						
Metropolitan	Ref.		Ref.		Ref.	
Non-metropolitan	1.05 (0.97, 1.13)	0.25	1.22 (0.98, 1.52)	0.07	0.92 (0.72, 1.17)	0.49
Facility designation						

	All (n=14,472)		pN0 (n=2,155)		pN+ (n=771)	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Academic	Ref.		Ref.		Ref.	
Non-academic	0.98 (0.91, 1.05)	0.49	0.94 (0.79, 1.12)	0.49	0.92 (0.73, 1.17)	0.52
<i>Facility location</i>						
Northeast	Ref.		Ref.		Ref.	
Midwest	1.11 (1.01, 1.21)	0.024	1.01 (0.81, 1.27)	0.91	1.20 (0.88, 1.62)	0.25
South	1.09 (1.00, 1.19)	0.06	1.05 (0.84, 1.31)	0.65	1.10 (0.81, 1.51)	0.53
West	0.98 (0.89, 1.08)	0.73	1.02 (0.80, 1.29)	0.88	0.90 (0.63, 1.28)	0.56
<i>Annual facility RNU volume (per ten cases)</i>	0.96 (0.92, 1.00)	0.037	0.89 (0.81, 0.98)	0.012	0.93 (0.83, 1.03)	0.14
<i>Year of diagnosis</i>						
2004	Ref.		Ref.		Ref.	
2005	0.95 (0.85, 1.06)	<0.001 [†]	0.90 (0.64, 1.25)	0.35 [†]	0.79 (0.55, 1.14)	0.06 [†]
2006	0.88 (0.78, 0.98)		0.91 (0.65, 1.29)		0.80 (0.54, 1.16)	
2007	0.84 (0.74, 0.94)		0.83 (0.59, 1.15)		0.59 (0.39, 0.88)	
2008	0.90 (0.81, 1.00)		0.74 (0.53, 1.04)		0.74 (0.50, 1.09)	
2009	0.90 (0.80, 1.00)		1.07 (0.76, 1.50)		0.79 (0.55, 1.15)	
2010	0.79 (0.71, 0.89)		0.76 (0.54, 1.08)		0.75 (0.51, 1.12)	
2011	0.80 (0.70, 0.91)		0.83 (0.58, 1.19)		0.57 (0.38, 0.85)	
2012	0.88 (0.77, 1.01)		0.85 (0.57, 1.25)		0.76 (0.49, 1.15)	
<i>Time from diagnosis to RNU (per 90 days)</i>	1.12 (1.05, 1.19)	<0.001	1.05 (0.87, 1.26)	0.61	1.14 (0.92, 1.41)	0.24
<i>Chemotherapy</i>						
None	Ref.		Ref.		Ref.	
Neoadjuvant	0.87 (0.65, 1.17)	0.36	1.22 (0.61, 2.42)	0.57	0.55 (0.34, 0.91)	0.020
Adjuvant	0.84 (0.76, 0.92)	<0.001	0.88 (0.69, 1.12)	0.29	0.55 (0.46, 0.67)	<0.001
<i>Site</i>						
Renal pelvis	Ref.		Ref.		Ref.	
Ureter	1.09 (1.03, 1.15)	0.005	0.94 (0.81, 1.10)	0.44	1.03 (0.84, 1.26)	0.81

	All (n=14,472)		pN0 (n=2,155)		pN+ (n=771)	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
<i>Laterality</i>						
Right	Ref.		Ref.		Ref.	
Left	1.00 (0.95, 1.05)	0.96	1.22 (1.05, 1.42)	0.009	0.99 (0.82, 1.20)	0.94
<i>Grade</i>						
Low	Ref.		Ref.		Ref.	
High	1.39 (1.29, 1.49)	<0.001	1.53 (1.25, 1.87)	<0.001	1.32 (0.90, 1.92)	0.16
<i>T classification</i>						
T0/Ta/Tis/T1	Ref.		Ref.		Ref.	
T2	1.52 (1.39, 1.65)	<0.001 [†]	1.33 (1.04, 1.71)	<0.001 [†]	1.60 (0.81, 3.17)	<0.001 [†]
T3	2.63 (2.46, 2.81)		2.57 (2.09, 3.15)		2.31 (1.21, 4.40)	
T4	4.40 (3.83, 5.04)		3.91 (2.71, 5.63)		3.52 (1.84, 6.72)	
<i>Surgical margins</i>						
Negative	Ref.		Ref.		Ref.	
Positive	1.73 (1.57, 1.91)	<0.001	1.94 (1.51, 2.49)	<0.001	1.34 (1.07, 1.68)	0.012
<i>LN status</i>						
pN0	Ref.		–		–	
pN+	1.89 (1.64, 2.17)	<0.001				
pNX	1.05 (0.97, 1.14)	0.21				
<i>Number of negative LN (per five LN)</i>	–		0.86 (0.79, 0.94)	0.001	0.90 (0.82, 1.00)	0.049
<i>Number of positive LN (per five LN)</i>	–		–		1.27 (1.16, 1.39)	<0.001

[†] p-value derived from test for trend; CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; LN, lymph node; pN0, lymph node-negative; pN+, lymph node-positive; pNX, lymph nodes not assessed; ref., referent; RNU, radical nephroureterectomy