ELSEVIER

Urologic Oncology: Seminars and Original Investigations 37 (2019) 302.e1−302.e6

UROLOGIC ONCOLOGY

Clinical-Kidney cancer

The prognostic significance of nodal disease burden in patients with lymph node metastases from renal cell carcinoma

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Received 3 June 2018; received in revised form 6 February 2019; accepted 11 February 2019

Abstract

Objectives: To assess the relationship between nodal disease burden and overall survival (OS) among patients with lymph node (LN) metastases from renal cell carcinoma (RCC)

Methods: The National Cancer Data Base was used to identify 2,975 patients with RCC who were treated with radical nephrectomy and were found to have regional LN metastases. Associations between the number of positive and negative LN removed and OS were assessed using Cox proportional hazards regression. The median follow-up time among survivors was 3.6 years.

Results: The median number of positive LN was 1 (interquartile range 1−3). A higher number of positive LN was associated with higher all-cause mortality on multivariable analysis (HR 1.06 per 1 positive LN, 95% CI 1.04, 1.07, $P < 0.001$). Conversely, higher negative LN counts were associated with better OS (HR 0.97 per 1 negative LN, 95% CI 0.96, 0.99, $P < 0.001$). The adjusted probability of a patient with 1 LN removed that was positive surviving at least 2 years was 56%, a figure that increased to 64% when 1 out of 10 LN removed was positive and decreased to 38% when 10 out of 10 LN removed were positive.

Conclusions: Ours is the first study to show that differences in nodal disease burden translate into clinically significant differences in survival among patients with LN metastases from RCC.

Keywords: Renal cell carcinoma; Nephrectomy; Lymph node dissection; Lymphatic metastasis; Survival analysis

1. Introduction

Although the finding of pathologically-confirmed lymph node (LN) metastases at the time of surgery for renal cell carcinoma (RCC) generally portends a poor prognosis, there is a degree of heterogeneity in the clinical course of LN-positive (pN+) patients. While most develop distant metastases and die within 2 years of surgery, a small proportion of such patients enjoy a prolonged disease-free interval and may even be cured with surgery alone [1−3]. Despite the importance of identifying clinical factors that predict disease recurrence and progression in this high-risk population, the study of the natural history of pN+ RCC has, to date, been hampered by the fact that omission of LN dissection (LND) at the time of nephrectomy, even among patients at high risk of harboring LN metastases, is common [4], such that the number of patients found to have LN metastases at the time of surgery is low.

In other epithelial malignancies, the burden of metastatic disease in the regional LN has been shown to correlate with survival [5,6]. In contrast, there is a lack of consensus regarding the prognostic value of nodal disease burden among patients with pN+ RCC, with prior studies that assessed the association between nodal disease burden and survival reporting conflicting findings [7−9]. Consequently, prior (seventh) and current (eighth) editions of the American Joint Commission on Cancer tumor, nodes and metastasis (TNM) staging system group all RCC patients with LN metastases into a single N category (pN1) [10,11].

In the present study, we endeavored to clarify the relationship between nodal disease burden as measured by the

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https://doi.org/10.1016/j.urolonc.2019.02.006
1078-1439/

number of positive and negative LN and overall survival (OS) among patients with pN+ RCC using a national hospital cancer registry-based database.

2. Materials and methods

We identified 3,656 patients within the National Cancer Data Base (NCDB) who were 18 years of age or older, were diagnosed with RCC between 2004 and 2013, had no evidence of distant metastases, underwent radical nephrectomy and LND, and were found to have pathologically-confirmed LN metastases. Patients with a prior cancer diagnosis ($n = 482$) and those with missing data pertaining to vital status or follow-up time ($n = 107$) were excluded. To limit the influence of outliers, we also excluded 92 patients with more than 25 removed. The remaining 2,975 patients were included in the final analysis.

Our primary objective was to determine the association between the number of positive and negative LN removed and OS. Cox proportional hazards regression was used to model the association between LN counts and OS, adjusting for patient, tumor, and facility characteristics. Covariates of interest included age, sex, comorbidity burden as measured by the Charlson Comorbidity Index, race, insurance status, ZIP code-level income, location and designation (academic vs. nonacademic) of the treating facility, year of diagnosis, tumor histology and grade, presence of tumor necrosis, tumor stage, and surgical margin status. In addition to modeling positive and negative LN counts individually, we also performed a separate analysis in which survival was modeled as a function of the proportion of LN with metastatic disease (i.e., "LN density"). Interaction terms were used to determine whether the associations between positive LN count and survival differed according to clinical N stage, tumor histology, grade and pathologic T stage. Sensitivity analyses were performed by excluding patients with unknown histology and those with less than 5 LN removed.

Multiple imputation by chained equations was used to account for missing covariate data. The proportion of patients with missing data was highest for necrosis (63%) and grade (15%), with data for the remaining variables being more than 90% complete. We confirmed the absence of significant variable collinearity using a correlation matrix of parameter estimates. To account for clustering of outcomes at the facility level, we calculated robust standard errors. All statistical tests were 2-sided and P values less than 0.05 were considered significant. Statistical analyses were performed using Stata 14 (StataCorp LP, College Station, TX). Institutional review board approval for this study was waived because it used deidentified data.

3. Results

The median age of the patients included in the analysis was 61 years (interquartile range, IQR: 52−69; see Supplementary Table 1). Sixty-seven percent of the 1,759 patients whose clinical N stage was documented were classified as cN1. Thirty-six percent of tumors were classified as clear cell, 19% as papillary, 3% as chromophobe, and 2% as collecting duct/medullary. Histology was not specified for 40% of tumors. Of the tumors with known grade/stage, 83% were high-grade (III-IV) and 72% were locally-advanced (pT3−T4). The median LN yield was 3 (IQR: 1−7) and the median number of positive LN was 1 (IQR: 1−3).

The median follow-up time among survivors was 3.6 years (IQR: 1.9−6.1), with 1,948 deaths occurring during follow-up. The median survival time was 2.3 years (interquartile range, IQR: 0.9−6.4). The probabilities of surviving 1, 2 and 5 years were 73% (95% confidence interval, CI: 71%−74%), 54% (52%−56%), and 31% (29%−33%), respectively (see Fig. 1).

Patient, tumor and facility characteristics and their associations with OS are given in Table 1. Patients with tumors with collecting duct/medullary or unspecified histology demonstrated worse OS than those with tumors with clear cell histology. Higher tumor grade, presence of tumor necrosis, higher pathologic stage, and presence of positive surgical margins were likewise independent predictors of higher all-cause mortality.

After adjusting for patient, tumor, and facility characteristics, there remained a statistically-significant association between a higher number of positive LN removed and higher all-cause mortality (multivariable HR 1.06 per 1 positive LN, 95% CI: 1.04−1.07, $P < 0.001$). Higher negative LN counts were associated with better OS (HR 0.97 per 1 negative LN, 95% CI: 0.96−0.99, $P < 0.001$). The association between positive LN count and OS was similar across tumor histologies, grades, and pathologic T stages but was stronger among those patients who were classified as cN0 compared to those classified as cN1 ($p_{interaction} = 0.028$). The strength of the associations between positive and negative LN counts and OS did not change when limiting the analysis to patients with known histology (HR 1.06 per 1 positive LN, 95% CI: 1.01−1.08, $P < 0.001$; HR 0.97 per 1 negative LN, 95% CI: 0.95−0.99, $P < 0.001$) or those with at least 5 LN removed (HR 1.06 per 1 positive LN, 95% CI: 1.03−1.08, $P < 0.001$; HR 0.97 per 1 negative LN, 95% CI: 0.96−0.99, $P = 0.002$).

Absolute OS probabilities were found to differ markedly according to the number of positive and negative LN removed (see Table 2). For example, the adjusted probability of a patient who had a single LN removed that proved to be positive surviving at least 2 years was estimated to be 56%. Conversely, adjusted 2-year OS probabilities for patients with 1 and 10 positive LN out of 10 LN removed were 64% and 38%, respectively.

Replacing positive and negative LN counts with LN density in the model confirmed that there was a statistically significant increase in all-cause mortality with an increasing proportion of positive LN (HR 1.04 per 10% increase, 95% CI: 1.02−1.05, $P < 0.001$). However, the strength of this association differed according to the number of LN

Table 1
Associations between patient, tumor, and facility characteristics and overall survival on multivariable analysis

	HR (95% CI)	*P* value
Age (per 5 y)	1.05 (1.03–1.08)	<0.001
Sex		
Male	Ref.	
Female	1.09 (0.99–1.21)	0.074
Comorbidity burden (CCI)		
0	Ref.	
1	1.16 (1.04–1.30)	<0.001
≥2	1.36 (1.11–1.65)	
Race		
White	Ref.	
Black	1.14 (0.98–1.33)	0.093
Other	0.96 (0.73–1.26)	0.78
Insurance		
Private	Ref.	
Medicare	1.06 (0.93–1.20)	0.42
Medicaid	1.07 (0.85–1.35)	0.55
Other	1.01 (0.58–1.78)	0.96
Uninsured	1.24 (0.95–1.63)	0.12
Median income		
<$38,000	Ref.	
$38,000–$47,999	1.01 (0.87–1.19)	0.096
$48,000–$62,999	0.87 (0.74–1.01)	
≥$63,000	0.92 (0.79–1.07)	
Facility location		
Northeast	Ref.	
Midwest	1.10 (0.95–1.28)	0.19
South	0.98 (0.84–1.15)	0.82
West	1.15 (0.97–1.38)	0.11
Facility designation		
Academic	Ref.	
Nonacademic	1.10 (1.00–1.22)	0.054
Year of diagnosis		
2004–2008	Ref.	
2009–2013	0.87 (0.76–1.00)	0.054
Histology		
Clear cell	Ref.	
Papillary	1.15 (1.00–1.32)	0.045
Chromophobe	0.96 (0.71–1.31)	0.80
Collecting duct/medullary	1.86 (1.41–2.46)	<0.001
Unspecified	1.31 (1.17–1.48)	<0.001
Grade		
I/II	Ref.	
III	1.37 (1.19–1.57)	<0.001
IV	1.95 (1.67–2.28)	
Tumor necrosis		
Absent	Ref.	
Present	1.27 (1.07–1.52)	0.009
Pathologic T stage		
pT1-T2	Ref.	
pT3	1.35 (1.19–1.53)	<0.001
pT4	2.42 (1.96–2.98)	
Margins		
Negative	Ref.	
Positive	1.49 (1.32–1.69)	<0.001
Number of positive LN removed (per 1 LN)	1.06 (1.04–1.07)	<0.001
Number of negative LN removed (per 1 LN)	0.97 (0.96–0.99)	<0.001

removed; for patients with 5 LN removed, the absolute difference in 2-year OS between those with 20% of LN positive (i.e., 1 out of 5 LN) and those with 100% of LN positive (i.e., 5 out of 5 LN) was 11% (59% vs. 48%), compared to 23% (61% vs. 38%) for those with 10 LN removed and 46% (64% vs. 18%) for those with 20 LN removed (see Fig. 2).

4. Discussion

Although the incidence of LN metastases among patients with RCC has traditionally been thought to be low, it can approach 40% among those with multiple adverse pathologic features who are subjected to a thorough LND [12]. The presence of regional LN metastases portends a poor prognosis that more closely resembles that of patients with distant metastases than those with localized disease [13]. Given that a significant proportion of patients with RCC and distant metastases do not have regional LN involvement [14], it is thought that the principal route of RCC spread is not lymphatic but rather hematogenous. Conversely, autopsy studies have shown that greater than 90% of patients with retroperitoneal LN metastases have concurrent visceral and/or bone involvement [15], suggesting that isolated regional LN metastases are uncommon in this disease.

The natural history of pN+ M0 RCC has previously been described in several small single-center series and 1 large population-based study. In a cohort of 68 patients without evidence of distant metastases treated with nephrectomy and LND at MD Anderson Cancer Center, median OS was 32 months [7]. Of the patients that recurred, 67% did so within 1 year of surgery and only 1 patient recurred in the retroperitoneum in the absence of distant metastases. Among a cohort of 138 patients treated at the Mayo Clinic over a 30-year period, 10-year metastasis-free, cancer-specific (CSS), and OS probabilities were 15%, 21%, and 15%, respectively [9]. The median time to development of metastases was 4.2 months and only 2 patients recurred in the retroperitoneum in the absence of distant metastases. The largest cohort of patients with pN+ RCC described to date was derived from the Surveillance, Epidemiology, and End Results (SEER) registry, a study that reported a median OS of 28 months and 2, 5, and 10-year OS probabilities of 53%, 38%, and 26%, respectively, among 799 pN+ patients [8]. Of the patients who died of RCC, the median survival time was only 13 months. The generally rapid disease progression that occurs in most patients with pN+ RCC suggests that these patients harbor micrometastatic disease at distant sites at the time of nephrectomy that becomes clinically evident over time. Conversely, the prolonged disease-free survival seen in a small proportion of pN+ patients suggests that there exists a subset in whom the disease is truly limited to the regional LN and may be cured with LND

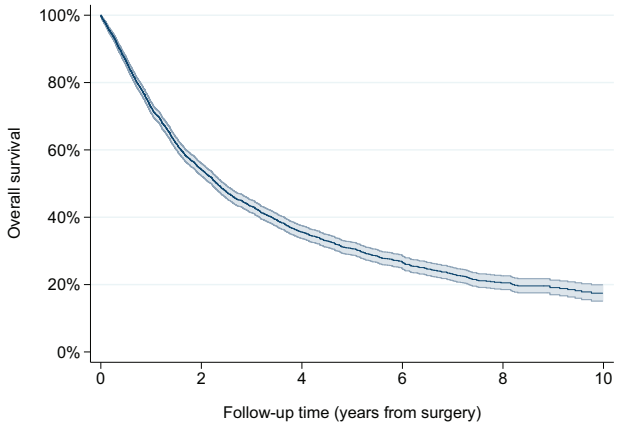

Fig. 1. Kaplan-Meier curve for overall survival.

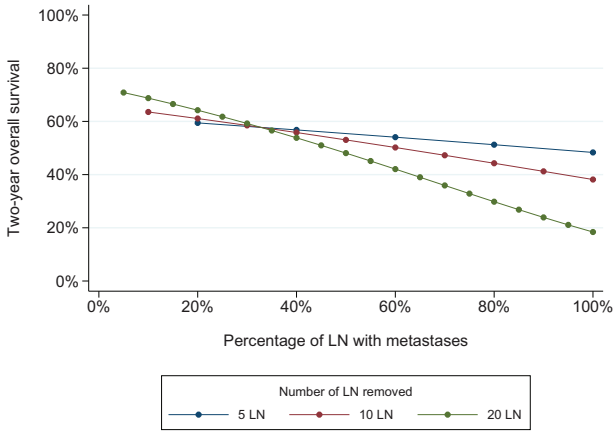

Fig. 2. Adjusted 2-year overall survival probabilities according to the percentage of lymph nodes with metastatic disease.

alone. This finding may inform the ongoing debate regarding the therapeutic value of LND in patients with RCC.

The previously cited studies also found that the prognosis of patients with pN+ RCC is primarily driven by pathologic features of the primary tumor. Consistent with our findings, they showed that patients with high-grade [8,13], necrotic [9], and locally-advanced (pT3-T4) [8,9] tumors are at increased risk of developing distant metastases and dying of the disease. Data pertaining to the influence of tumor histology on outcomes is more mixed. The presence of sarcomatoid differentiation was found to predict worse survival in 2 studies [7,9]. Meanwhile, patients with papillary histology were reported to have a better prognosis than those with clear cell tumors in 2 studies [7,8] and a worse prognosis in 1 [13]. In our study, patients with collecting duct/medullary tumors and those with unspecified histology had worse outcomes than patients with clear cell tumors, although the prognosis of patients with papillary tumors was no different than that of those with clear cell tumors. It must be noted, however, that our study has limited ability to assess the impact of tumor histology on outcomes given that the lack of expert pathologic review likely resulted in misclassification of histology in a significant proportion of tumors.

In multiple epithelial malignancies, the burden of disease within the regional LN has been shown to be an independent predictor of survival [5,6]. For example, among patients with urothelial carcinoma of the bladder, the number of involved LN forms the basis of the distinction between pN1 and pN2 disease in the seventh edition of the TNM staging system [10]. In contrast, whereas the sixth edition of the TNM staging system, published in 2002 and in use until 2009, did consider nodal disease burden in the N classification for RCC [16], with patients with a single positive LN classified as pN1 and those with multiple positive LN classified as pN2, this categorization was eliminated in the seventh edition, such that all patients with LN metastases are now grouped into 1 prognostic category (pN1) [10,11]. This change was made because, to date, studies examining the association between nodal disease burden and survival among patients with pN+ RCC have reported conflicting findings. In the recently published Mayo Clinic series, positive LN count was not an independent predictor of survival [9]. In a single-institution series of 88 patients, half of which had no evidence of distant metastases, Terrone et al. found that although patients with 2 or more positive LN did not have a worse CSS than those

Table 2
Adjusted 2-year overall survival probabilities according to the number of positive and negative lymph nodes removed

		Positive LN count									
		1	2	3	4	5	6	7	8	9	10
Negative LN count	0	56%	54%	52%	50%	48%	46%	44%	42%	40%	38%
	1	57%	55%	53%	51%	49%	47%	45%	43%	41%	39%
	2	58%	56%	54%	52%	50%	48%	46%	44%	42%	40%
	3	59%	57%	55%	53%	51%	49%	47%	45%	43%	41%
	4	59%	58%	56%	54%	52%	50%	48%	46%	44%	42%
	5	60%	59%	57%	55%	53%	51%	49%	47%	45%	43%
	6	61%	59%	58%	56%	54%	52%	50%	48%	46%	44%
	7	62%	60%	59%	57%	55%	53%	51%	49%	47%	45%
	8	63%	61%	59%	58%	56%	54%	52%	50%	48%	46%
	9	64%	62%	60%	58%	57%	55%	53%	51%	49%	47%
	10	64%	63%	61%	59%	58%	56%	54%	52%	50%	48%

with 1 positive LN, a cutoff of 5 or more positive LN did segregate patients into 2 groups with significantly different prognoses [17]. In contrast, involvement of more than 1 LN was found to be an independent predictor of both disease recurrence and OS in the MD Anderson series [7], whereas the previously cited SEER registry analysis reported a non-statistically significant association between an increasing number of positive LN and worse CSS on multivariable analysis [8]. The fact that our findings differ from those of some of these earlier studies can likely be explained by the fact that their analyses relied on small sample sizes and oftentimes categorized positive LN counts according to arbitrary cutpoints.

The number of positive LN is an incomplete measure of nodal disease burden as it does not factor in the extent of LND. Prior studies have used the concept of LN density, defined as the proportion of LN removed that are positive, to better define nodal disease burden among patients with RCC [8,17]. In the SEER registry analysis, Trinh et al. modeled positive LN count and LN density simultaneously and found that LN density >60% was an independent predictor of worse CSS. Of note, because these authors included both positive LN count and LN density in their model, LN density in actuality represented the negative LN count since LN density can only be made to vary by increasing or decreasing the negative LN count if the positive LN count is kept constant. Consequently, although the authors of this study concluded that LN density, but not positive LN count, should be considered an important prognostic factor in patients with pN+ RCC, we propose that their findings are congruent with ours in showing that both the number of positive and negative LN removed are important predictors of prognosis.

Our study is the first to show that differences in nodal disease burden translate into clinically meaningful differences in OS. For example, the absolute difference in the probability of surviving at least 2 years after nephrectomy for a patient with 1 positive LN out of 10 removed compared to a patient with 10 positive LN out of 10 removed was 26%. Our findings also underscore the fact that the prognostic value of nodal disease burden increases as the number of LN removed increases since a more thorough LND allows for a more accurate estimation of the true burden of disease. This provides an additional argument in favor of performing an extended LND in patients who are at high risk of harboring LN metastases, such as those with enlarged LN on preoperative imaging or palpably abnormal LN found at the time of surgery, irrespective of whether LND has any therapeutic value.

The main strength of the present study is its large sample size. Unlike in prior series, most patients in our cohort were treated in the targeted therapy era. The main limitation of the study is the lack of data pertaining to the presence, timing, and sites of disease recurrence. There was also no data pertaining to performance status, which has previously been shown to be an important prognostic factor in this patient population [7]. Centralized histopathologic review by expert genitourinary pathologists was also lacking. Furthermore, the low median LN yield suggests that most patients underwent sampling of suspicious LN as opposed to a formal template-based LND, although our findings suggest that this would tend to bias the association between nodal disease burden and survival towards the null. Lastly, given that only a small proportion of patients captured by the NCDB underwent an LND at the time of radical nephrectomy, our findings may not be generalizable to the broader population of patients with surgically treated RCC.

In summary, we confirm the generally poor outcomes of patients with pN+ RCC reported by prior studies. Conversely, our study is the first to show that differences in nodal disease burden translate into clinically significant differences in survival in this population.

Acknowledgments

The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed or the conclusions drawn from these data by the investigator. This work was supported by NIH/NCI Cancer Center support grant P30 CA008748 and the Sidney Kimmel Center for Prostate and Urologic Cancers.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.02.006.

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