

# Lymphadenectomy Improves Survival of Patients With Renal Cell Carcinoma and Nodal Metastases

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**Purpose:** In a population based cohort we determined whether an increase in the number of lymph nodes removed is associated with improved disease specific survival of patients with renal cell carcinoma treated with nephrectomy.

**Materials and Methods:** Patients in the Surveillance, Epidemiology and End Results database with renal cell carcinoma and no evidence of distant metastases were identified. Those patients included in the study underwent radical or partial nephrectomy with lymphadenectomy. Cox regression analyses were performed to identify factors associated with disease specific survival including an interaction between lymph node status and the number of lymph nodes removed.

**Results:** Between 1988 and 2006, 9,586 patients with renal cell carcinoma met the study inclusion criteria. Median followup was 3.5 years (range 1.4 to 6.8). Of the patients 2,382 (25%) died of renal cell carcinoma, including 1,646 (20%) with lymph node negative disease and 736 (58%) with lymph node positive disease. There was no effect on disease specific survival with increasing the extent of lymphadenectomy in patients with negative lymph nodes (HR 1.0, 95% CI 0.9–1.1,  $p = 0.93$ ). However, patients with positive lymph nodes had increased disease specific survival with extent of lymphadenectomy (HR 0.8 per 10 lymph nodes removed, 95% CI 0.7–1.0,  $p = 0.04$ ). An increase of 10 lymph nodes in a patient with 1 positive lymph node was associated with a 10% absolute increase in disease specific survival at 5 years ( $p = 0.004$ ).

**Conclusions:** This study shows an association between increased lymph node yield and improved disease specific survival of patients with lymph node positive nonmetastatic renal cell carcinoma who underwent lymphadenectomy. Patients at high risk for nodal disease should be considered for regional or extended lymphadenectomy. Clinical variables to predict risk and validation of dissection templates are important areas for future research.

**Key Words:** carcinoma, renal cell; nephrectomy; lymph node excision; survival

APPROXIMATELY 58,000 new cases of renal cell carcinoma were diagnosed in the United States in 2010.<sup>1</sup> Lymph node status is a strong prognostic indicator in patients with kidney cancer.<sup>2,3</sup> Although most patients with positive LNs will also have distant

metastatic disease, approximately 3% to 10% of patients in modern series will have spread confined only to LNs.<sup>4,5</sup> These patients could potentially be cured by lymphadenectomy alone. In fact, 5-year DSS for patients with node positive disease (but not

## Abbreviations and Acronyms

DSS = disease specific survival  
EORTC = European Organization for the Research and Treatment of Cancer  
KM = Kaplan-Meier  
LN = lymph node  
RCC = renal cell carcinoma  
SEER = Surveillance, Epidemiology and End Results

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distant metastases) who underwent lymphadenectomy is reported between 21% and 38%.<sup>4,6-8</sup>

A randomized trial of LN dissection in patients with clinically negative LNs revealed no survival advantage to lymphadenectomy.<sup>9</sup> However, only 4% of patients who underwent lymphadenectomy had positive nodes and, therefore, the trial was likely underpowered to detect a therapeutic benefit of node dissection. In contrast, cohort studies which have specifically examined patients with node positive disease have found a benefit to lymphadenectomy, although these were primarily single institution studies with relatively small numbers of patients.<sup>5,6,8</sup> In a population based cohort we determined whether an increase in the number of LNs removed was associated with improved survival of patients with RCC undergoing nephrectomy.

## MATERIALS AND METHODS

### Study Population

The study cohort was derived from the SEER database, a population based cancer registry managed by the National Cancer Institute. In lieu of institutional review board approval an exemption was obtained from the University of California San Francisco Committee on Human Research.

Site rec B (which codes for organ involvement) was used to identify patients with tumors originating in the kidney. RCC histologies were further selected based on the codes for clear cell (8310), papillary (8050, 8260, 8342), chromophobe (8270, 8290, 8317), collecting duct (8319), medullary (8510), granular (8320), sarcomatoid (8318) and RCC not otherwise specified (8312). The years of diagnoses were limited to 1988 to 2006, corresponding to the period during which detailed information regarding LN dissection was available. All patients treated with radical or partial nephrectomy and concomitant lymphadenectomy were included in this analysis. Patients with distant metastases at presentation and pediatric patients (younger than 18 years old) were excluded from analysis.

### Variables

The primary predictor was the number of LNs retrieved at lymphadenectomy, derived from the SEER variable "eod10lnexam" (which codes for number of lymph nodes examined). Covariates included year of diagnosis, age, gender, race/ethnicity, marital status, tumor size, grade, histology, T stage, N stage<sup>10</sup> and the number of positive nodes.

Centered continuous variables were used for analysis (year of diagnosis, age at diagnosis, tumor size, number of LNs retrieved and number of positive LNs). There was a sharp break from linearity at values of LNs retrieved more than 30 (155) and LNs positive more than 9 (44), suggesting that these values represented coding errors. These values were changed to missing.

Race/ethnicity was categorized as white, black, Hispanic or other (Asian, American Indian/Alaska Native and Native Hawaiian/Pacific Islanders). Marital status was

classified as married or not (single, divorced, separated and widowed). Histology was classified into clear cell (clear cell and granular), papillary, chromophobe and other (collecting duct, medullary, sarcomatoid). RCC not otherwise specified was changed to missing. The primary outcome was disease specific survival. The SEER variable "Code to site rec KM" (which codes for vital status) was used to identify subjects as living, dead of disease or dead of other causes.

### Statistical Analysis

The Student t test and chi-square test were used to assess differences in baseline characteristics between subjects with and without positive nodes. Disease-free survival curves were plotted using the KM method. Multivariable Cox regression analyses were performed to determine factors associated with DSS. This model included an interaction term to test whether the impact of the number of LNs retrieved on DSS was dependent upon LN status. As there were significant missing data for grade and histology, models were generated with and without these covariates. In addition, ordered logistic regression was performed to impute values of grade (using gender, tumor size, T stage and N stage) and this variable was used in the final model. There were no strong predictors of histology and, therefore, imputation was not performed. Tests for linear trend were performed for ordered categorical predictors.

A separate multivariable Cox model was created to assess the impact of additional positive nodes on survival of patients with LN positive disease. An interaction term between the number of positive LNs and the number of LNs retrieved was included to determine whether the impact of increased LN retrieval on DSS was dependent on the number of positive nodes.

Finally, KM survival curves were generated according to the number of LNs retrieved. These curves were adjusted for those variables significantly associated with DSS in the multivariable model (year of diagnosis, age, tumor size, grade, T stage, N stage, number of positive LNs). Adjustment was performed using the mean value for continuous variables and the mode for categorical variables.

The alpha value was set at 0.05 and 95% confidence intervals were determined. Tests for interaction were considered significant if  $p < 0.2$ . Data were analyzed using STATA@ version 11.0.

## RESULTS

Between 1998 and 2006 a total of 9,586 patients underwent nephrectomy and concomitant lymphadenectomy. The baseline characteristics of the study cohort were stratified by node status (table 1). Patients with positive nodes were more likely to have larger tumors ( $p < 0.0001$ ), higher nuclear grade ( $p < 0.001$ ), a greater proportion with papillary histology ( $p < 0.001$ ) and higher T stage ( $p < 0.001$ ). Patients with node positive disease were significantly older ( $p < 0.0001$ ), more often male ( $p = 0.002$ ) and diagnosed more recently ( $p = 0.02$ ) than those without nodal involvement. A median of 2 nodes was sam-

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