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## Kidney Cancer

# Renal Cell Carcinoma with Isolated Lymph Node Involvement: Long-term Natural History and Predictors of Oncologic Outcomes Following Surgical Resection

Boris Gershman<sup>a</sup>, Daniel M. Moreira<sup>b</sup>, R. Houston Thompson<sup>c</sup>, Stephen A. Boorjian<sup>c</sup>, Christine M. Lohse<sup>d</sup>, Brian A. Costello<sup>e</sup>, John C. Cheville<sup>f</sup>, Bradley C. Leibovich<sup>c,\*</sup>

<sup>a</sup> Division of Urology, Rhode Island Hospital and The Miriam Hospital, Providence, RI, USA; <sup>b</sup> Department of Urology, University of Illinois, Chicago, IL, USA; <sup>c</sup> Department of Urology, Mayo Clinic, Rochester, MN, USA; <sup>d</sup> Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA; <sup>e</sup> Department of Oncology, Mayo Clinic, Rochester, MN, USA; <sup>f</sup> Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA

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### Abstract

**Background:** Renal cell carcinoma (RCC) with isolated lymph node (LN) involvement has historically been associated with poor prognosis. However, a subset of patients may experience long-term survival.

**Objective:** To examine the natural history of RCC with isolated LN involvement following surgical resection with long-term follow-up, and to evaluate clinicopathologic features associated with disease progression and survival.

**Design, setting, and participants:** A total of 138 patients with isolated pN1M0 RCC underwent partial or radical nephrectomy and LN dissection from 1980 to 2010.

**Intervention:** Partial or radical nephrectomy with LN dissection.

**Outcome measurements and statistical analysis:** Metastasis-free survival (MFS), cancer-specific survival (CSS), and overall survival (OS) were estimated using the Kaplan-Meier method. Associations between clinicopathologic features and oncologic outcomes were evaluated using Cox regression models.

**Results and limitations:** Median follow-up among survivors was 8.5 yr. The 5-yr and 10-yr MFS, CSS, and OS rates were 16% and 15%, 26% and 21%, and 25% and 15%, respectively. The median time to development of metastases was only 4.2 mo. On multivariable analysis, symptoms at presentation (hazard ratio [HR] 2.40;  $p = 0.03$ ), inferior vena cava tumor thrombus (HR 1.99;  $p = 0.003$ ), clear cell (HR 2.21;  $p = 0.01$ ) and collecting duct/not otherwise specified (HR 4.28;  $p < 0.001$ ) histologic subtypes, pT4 stage (HR 2.64;  $p = 0.005$ ), and coagulative tumor necrosis (HR 2.51;  $p < 0.001$ ) were independently associated with development of metastases. MFS rates at 1 yr after surgery were 71%, 63%, 33%, and 7% for patients with one, two, three, and four to five adverse features, respectively. Limitations include surgical selection bias.

**Conclusions:** Although isolated pN1 disease portends a poor prognosis, a small subset of patients experience durable long-term survival after surgical resection of isolated lymphatic metastases. Adverse prognostic features may enhance patient risk stratification and facilitate multimodal management approaches.

**Patient summary:** Although isolated lymph node metastases portend a poor prognosis, a small subset of patients experience long-term survival following surgical resection.

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\* Corresponding author. Department of Urology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. Tel. +1 507 2660191; Fax: +1 507 2844951.

E-mail address: [leibovich.bradley@mayo.edu](mailto:leibovich.bradley@mayo.edu) (B.C. Leibovich).

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## 1. Introduction

The role of lymph node dissection (LND) in the surgical management of renal cell carcinoma (RCC) has been controversial [1–3]. Although LND allows undisputed pathologic assessment of nodal stage, its impact on oncologic outcomes has been uncertain. Older retrospective studies suggested a potential oncologic benefit [4–8], yet data from both randomized trials [9] and more recent investigations [10–12] have revealed no impact on survival.

Isolated lymph node (LN) involvement in the absence of systemic disease provides an important case study in this context, since a therapeutic benefit for nonmetastatic RCC may be expected exclusively in this population [13]. Historically, isolated LN involvement has been associated with poor prognosis, dating back to the original report by Robson et al on the outcomes of radical nephrectomy [4,14,15]. However, a subset of such patients may experience durable long-term survival following surgical resection [16–19].

A critical analysis of isolated LN involvement may provide insight into the apparent lack of oncologic benefit of LND in M0 RCC. Accordingly, the objectives of this study were twofold. First, we examined the natural history of RCC with isolated LN involvement following surgical resection with long-term follow-up. Second, we evaluated clinicopathologic features associated with disease progression and survival in order to guide preoperative and postoperative risk stratification and management.

## 2. Patients and methods

### 2.1. Patient population

After obtaining institutional review board approval, we identified 3830 patients with sporadic, unilateral, M0 RCC treated with partial or radical nephrectomy from 1980 to 2010 at the Mayo Clinic. Of these, 769 (20%) underwent LND, and 139 were found to have pN1M0 RCC. We excluded one patient who died intraoperatively, leaving 138 patients for the study cohort. LND was performed at the surgeon's discretion, and a standardized template was not utilized. Staging was based on surgical pathology and preoperative radiographic evaluation, which included imaging of the chest, abdomen, and pelvis, with additional imaging (eg, bone, brain) as clinically indicated.

### 2.2. Clinicopathologic and radiographic features

Clinicopathologic features recorded included year of surgery, age at surgery, sex, symptoms at presentation, smoking status, Eastern Cooperative Oncology Group performance status (ECOG PS), Charlson comorbidity index (non-age-adjusted and excluding RCC), body mass index (BMI), receipt of neoadjuvant systemic therapy, surgical approach (open or laparoscopic), stage according to the 2010 American Joint Committee on Cancer classification, pathologic tumor size, histologic subtype, grade according to the World Health Organization/International Society of Urological Pathology classification, number of LNs removed, number of positive LNs, presence of coagulative tumor necrosis, and presence of sarcomatoid differentiation. Patients with a palpable flank or abdominal mass, discomfort, gross hematuria, acute-onset varicocele, or constitutional symptoms including rash, sweats, weight loss, fatigue, early satiety, or anorexia were considered symptomatic. All pathology slides were re-reviewed by one urologic pathologist (J.C.C.) who was

unaware of patient outcome. In addition, the following preoperative radiographic features were recorded from medical records: lymphadenopathy (cN1) on computed tomography (CT), renal vein involvement on CT or magnetic resonance imaging (MRI), and inferior vena cava (IVC) involvement on CT or MRI.

### 2.3. Statistical methods

Continuous variables were summarized using the median and interquartile range (IQR) and categorical variables using the frequency count and percentage. Distant metastases-free survival (MFS), cancer-specific survival (CSS), and overall survival (OS) were estimated using the Kaplan-Meier method for the overall cohort and among patients who underwent extended LND, defined as removal of  $\geq 13$  LNs [20]. Associations of clinicopathologic features with the development of distant metastases, cancer-specific mortality (CSM), and all-cause mortality (ACM) were evaluated using Cox proportional hazards regression models and summarized using a hazard ratio (HR) and 95% confidence interval (CI). Multivariable models were constructed using forward stepwise selection with  $p = 0.05$  set as the cutoff for a feature to enter or leave the model. Six patients died from unknown causes and were excluded from analysis of CSS/CSM.

Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). All tests were two-sided and  $p < 0.05$  was considered statistically significant.

## 3. Results

A total of 138 patients with isolated LN metastases formed the study cohort. Clinicopathologic features are summarized in Table 1. The median number of LNs removed was five (IQR 2–14) and the median number of positive LNs was two (IQR 1–3), with 57 (46%) patients found to have only one positive LN. Overall, 125 (91%) patients had symptoms at presentation, 60 (43%) had preoperative radiographic lymphadenopathy (cN1), 33 (24%) had a radiographic IVC tumor thrombus, and 106 (77%) had pT3/T4 disease. There was a high incidence of adverse pathologic features, including grade 4 in 55 (40%) patients, coagulative tumor necrosis in 111 (80%) patients, and sarcomatoid differentiation in 30 (22%) patients. Five patients received adjuvant systemic therapy (in the absence of recurrence or metastases) at 27, 41, 78, 105, and 111 d following surgery.

Median follow-up among survivors was 8.5 yr (IQR 5.6–10.9), during which time 108 patients developed distant metastases and 117 died, including 99 from RCC. Sites of distant metastases are summarized in Supplementary Table 1. A total of 31 patients developed recurrence in the retroperitoneal LNs, though only two of these were in the absence of concurrent distant metastases. MFS, CSS, and OS are illustrated in Fig. 1. The 5-yr and 10-yr MFS, CSS, and OS rates were 16% and 15%, 26% and 21%, and 25% and 15%, respectively. Notably, median time to development of distant metastases was only 4.2 mo (IQR 2.1–11.7), and MFS at 1 yr was only 37%. However, nearly all patients who remained free of distant metastases at 5 yr after surgery experienced durable MFS at longer follow-up. In patients who underwent extended LND (defined as removal of  $\geq 13$  LNs), MFS, CSS, and OS were similar to rates for patients with  $< 13$  LNs removed (Supplementary Figs. 1–3).

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