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

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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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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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Table 1 – Clinicopathologic and radiographic parameters for the study cohort (n = 138)

Parameter	Result
Age at surgery (yr)	63 (54–72)
Charlson comorbidity index	0 (0–1)
Body mass index (kg/m^2)	27.2 (24.0–31.1)
Tumor size (cm) (n = 137)	10.0 (8.0–13.0)
Number of lymph nodes removed (n = 124)	5 (2–14)
Number of positive lymph nodes (n = 124)	2 (1–3)
Year of surgery	
1980–1991	34 (25)
1992–2004	60 (43)
2005–2010	44 (32)
Sex	
Female	47 (34)
Male	91 (66)
Symptoms	125 (91)
Constitutional symptoms	69 (50)
Smoking history	
Never	54 (39)
Current	36 (26)
Former	48 (35)
Eastern Cooperative Oncology Group performance status (n = 137)	
0	107 (78)
1	23 (17)
2	6 (4)
3	1 (1)
Body mass index	
<30 kg/m^2	91 (66)
≥30 kg/m^2	47 (34)
Radiographic evidence of:	
Lymphadenopathy	60 (43)
Renal vein involvement	50 (36)
Inferior vena cava tumor thrombus	33 (24)
Preoperative systemic therapy	1 (1)
Type of surgery	
Open radical nephrectomy	132 (96)
Laparoscopic radical nephrectomy	5 (4)
Open partial nephrectomy	1 (1)
Renal cell carcinoma histologic subtype	
Clear cell	105 (76)
Papillary	15 (11)
Chromophobe	5 (4)
Collecting duct	4 (3)
Clear cell papillary	1 (1)
Not otherwise specified	8 (6)
2010 pT classification (n = 137)	
pT1a	3 (2)
pT1b	10 (7)
pT2a	11 (8)
pT2b	7 (5)
pT3a	62 (45)
pT3b	31 (23)
pT3c	2 (1)
pT4	11 (8)
Grade	
2	6 (4)
3	77 (56)
4	55 (40)
Coagulative tumor necrosis	111 (80)
Sarcomatoid differentiation	30 (22)
Number of lymph nodes removed (n = 124)	
<13	88 (71)
≥13	36 (29)
Number of positive lymph nodes (n = 124)	
1	57 (46)
≥2	67 (54)

Data are reported as median (interquartile range) for continuous variables and as n (%) for categorical variables.

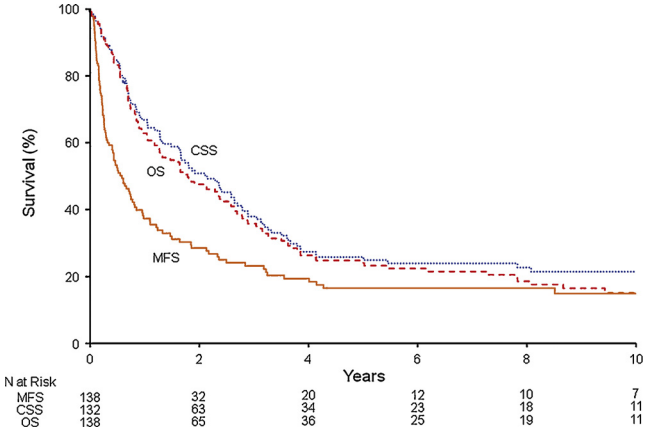

Fig. 1 – Distant metastases–free survival (MFS), cancer-specific survival (CSS), and overall survival (OS).

We further examined the subset of 16 patients who remained free of metastases at 5 yr. Clinicopathologic features for these patients are summarized in Table 2. These patients had more indolent tumor biology, as evidenced by lower pT stage, lower grade tumors, and lower incidence of adverse pathologic features such as coagulative tumor necrosis and sarcomatoid differentiation.

Next, we examined the associations of clinicopathologic features with the development of distant metastases, CSM, and ACM to identify prognostic factors to aid patient risk stratification and identify candidates for consideration of a multimodal management approach. Univariable associations are summarized in Table 3. Interestingly, neither the number of LNs removed nor the number of positive LNs was associated with oncologic outcomes. Similarly, the presence of preoperative radiographic lymphadenopathy (cN1) was not associated with oncologic outcomes (Supplementary Fig. 4). On multivariable analysis (Table 4), several features were associated with the development of distant metastases: symptoms at presentation (HR 2.40, $p = 0.03$), IVC tumor thrombus (HR 1.99; $p = 0.003$), clear cell (HR 2.21; $p = 0.01$) and collecting duct/not otherwise specified (NOS; HR 4.28; $p < 0.001$) histologic subtypes, pT4 stage (HR 2.64; $p = 0.005$), and coagulative tumor necrosis (HR 2.51; $p < 0.001$). Three features were associated with both CSM and ACM: ECOG PS ≥1, coagulative tumor necrosis, and sarcomatoid differentiation, each associated with a 2.2–2.5-fold higher risk of CSM and ACM. This probably reflects both the risk of disease progression, as captured by adverse pathologic features, and patient functional status, which may reflect candidacy for systemic therapies. In stepwise multivariable models with forced inclusion of the number of LNs removed and number of positive LNs, neither feature was significantly associated with oncologic outcomes (Supplementary Table 2).

To facilitate clinical application of the above results, we estimated MFS stratified according to the number of adverse prognostic features present (Fig. 2). All patients in the study had at least one of the five adverse features (symptoms at presentation, IVC tumor thrombus, histologic subtype of clear cell, collecting duct, or NOS, tumor stage

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Table 2 – Clinicopathologic features for patients free of distant metastases at 5 yr after surgery (n = 16)

Parameter	Result
Age at surgery (yr)	57 (49–75)
Charlson comorbidity index	0 (0–1.5)
Body mass index (kg/m^2)	26.4 (24.1–30.4)
Tumor size (cm) (n = 15)	10.0 (6.6–13.3)
Number of lymph nodes removed	6 (2.5–19)
Number of positive lymph nodes	1.5 (1–2.5)
Year of surgery	
1980–1991	3 (19)
1992–2004	9 (56)
2005–2010	4 (25)
Sex	
Female	5 (31)
Male	11 (69)
Symptoms	13 (81)
Constitutional symptoms	6 (38)
Smoking history	
Never	9 (56)
Current	3 (19)
Former	4 (25)
Eastern Cooperative Oncology Group performance status	
0	14 (88)
1	1 (6)
2	1 (6)
Body mass index	
<30 kg/m^2	10 (62)
≥30 kg/m^2	6 (38)
Radiographic evidence of:	
Lymphadenopathy	4 (25)
Renal vein involvement	3 (19)
Inferior vena cava tumor thrombus	2 (13)
Preoperative systemic therapy	0
Type of surgery	
Open radical nephrectomy	15 (94)
Laparoscopic radical nephrectomy	1 (6)
Renal cell carcinoma histologic subtype	
Clear cell	13 (81)
Papillary	2 (13)
Clear cell papillary	1 (6)
2010 pT classification (n = 15)	
pT1a	1 (7)
pT1b	2 (13)
pT2a	2 (13)
pT2b	0
pT3a	7 (47)
pT3b	2 (13)
pT3c	1 (7)
pT4	0
Grade	
2	3 (19)
3	9 (56)
4	4 (25)
Coagulative tumor necrosis	7 (44)
Sarcomatoid differentiation	1 (6)
Number of lymph nodes removed	
<13	11 (69)
≥13	5 (31)
Number of positive lymph nodes	
1	8 (50)
≥2	8 (50)

Data are reported as median (interquartile range) for continuous variables and as n (%) for categorical variables.

pT4, or coagulative tumor necrosis). There were eight (6%) patients with one adverse feature, 34 (25%) with two, 66 (48%) with three, 27 (20%) with four, and three (2%) with all five. MFS rates at 1 yr after surgery were 71%, 63%, 33%, and 7% for patients with one, two, three, and four or five adverse features, respectively.

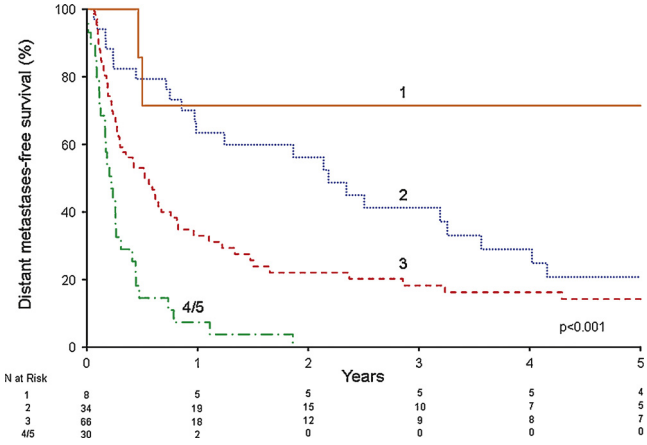

Fig. 2 – Distant metastases–free survival stratified according to the number of adverse prognostic features.

4. Discussion

Isolated LN involvement in the absence of clinically evident systemic metastases portends a poor prognosis. In this study, the probability of MFS at 5 yr after surgery was only 16%. More importantly, the median time to progression was only 4.2 mo, and MFS at 1 yr was only 37%. In addition, CSM and OS were very similar, suggesting that the majority of patients with LN metastases die of disease without substantial incidence of competing causes of mortality. Taken together, these observations suggest the presence of occult systemic disease in the majority of patients with clinically isolated pN1 disease. However, the subset of patients who do not harbor occult systemic disease at the time of surgery experience durable long-term survival following surgical resection of LN metastases: nearly all patients who were free of progression at 5 yr remained free of progression at long-term follow-up.

Improved risk-stratification is critical in guiding both preoperative and postoperative management in these patients. For instance, patients suspected of having occult systemic disease may benefit from consideration of up-front systemic therapy before nephrectomy, while in the postoperative setting such patients may benefit from consideration of adjuvant systemic therapy or enrollment into a clinical trial. To this end, we identified several features that were associated with systemic progression following surgery that may be used to facilitate risk stratification. It is clear from Fig. 2 that patients with three or more adverse features have poor prognosis with surgery alone, and may benefit from consideration of a multimodal management approach. Some of these prognostic factors may be assessed preoperatively, as in the case of symptoms at presentation, IVC tumor thrombus, and pT4 stage; others require preoperative renal mass biopsy or surgical pathology, and may be limited to the postoperative setting. The presence of such risk factors may identify patients who

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Table 3 – Univariable associations of clinicopathologic features with the development of distant metastases, CSM, and ACM.

Feature	Distant metastases		Cancer-specific mortality		All-cause mortality	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Year of surgery						
1980–1991	1.0 (reference)		1.0 (reference)		1.0 (reference)	
1992–2004	0.72 (0.45–1.16)	0.2	0.91 (0.57–1.47)	0.7	0.88 (0.57–1.38)	0.6
2005–2010	0.93 (0.57–1.53)	0.8	0.81 (0.48–1.37)	0.4	0.85 (0.52–1.38)	0.5
Age at surgery	0.95 (0.82–1.10) [a]	0.5	1.10 (0.94–1.29) [a]	0.3	1.17 (1.01–1.36) [a]	0.04
Male	1.00 (0.67–1.51)	0.9	0.87 (0.58–1.32)	0.5	0.89 (0.61–1.31)	0.6
Symptoms	2.16 (1.00–4.66)	0.050	2.10 (0.92–4.79)	0.08	2.02 (0.94–4.35)	0.07
Constitutional symptoms	1.67 (1.14–2.44)	0.009	1.71 (1.15–2.55)	0.009	1.66 (1.15–2.40)	0.007
Smoking history						
Never	1.0 (reference)		1.0 (reference)		1.0 (reference)	
Current	1.46 (0.92–2.34)	0.1	1.09 (0.66–1.79)	0.7	1.02 (0.64–1.63)	0.9
Former	1.16 (0.74–1.82)	0.5	1.28 (0.80–2.04)	0.3	1.24 (0.81–1.90)	0.3
ECOG PS ≥1	1.52 (0.96–2.40)	0.08	2.56 (1.60–4.10)	<0.001	2.42 (1.57–3.77)	<0.001
Charlson comorbidity index	1.07 (0.94–1.23) [b]	0.3	1.03 (0.90–1.17) [b]	0.7	1.02 (0.90–1.16) [b]	0.8
Body mass index	1.03 (0.99–1.06) [b]	0.2	1.00 (0.97–1.04) [b]	0.9	1.00 (0.96–1.03) [b]	0.8
Body mass index ≥30 kg/m^2	1.09 (0.73–1.62)	0.7	0.91 (0.60–1.39)	0.7	0.87 (0.59–1.29)	0.5
Radiographic evidence						
Lymphadenopathy	1.34 (0.92–1.96)	0.1	1.10 (0.74–1.64)	0.6	1.10 (0.76–1.59)	0.6
Renal vein involvement	1.70 (1.15–2.52)	0.008	1.56 (1.04–2.32)	0.03	1.47 (1.01–2.14)	0.04
IVC involvement	2.03 (1.32–3.13)	0.001	1.61 (1.04–2.48)	0.03	1.43 (0.94–2.17)	0.09
Type of surgery						
Open (radical or partial)	1.0 (reference)		1.0 (reference)		1.0 (reference)	
Laparoscopic radical	1.25 (0.51–3.08)	0.6	0.99 (0.31–3.13)	0.9	0.77 (0.28–2.08)	0.6
Tumor size	1.02 (0.97–1.07) [b]	0.5	1.01 (0.96–1.06) [b]	0.8	1.01 (0.96–1.05) [b]	0.8
RCC histologic subtype						
All others	1.0 (reference)		1.0 (reference)		1.0 (reference)	
Clear cell	2.16 (1.20–3.89)	0.01	1.55 (0.84–2.85)	0.2	1.37 (0.79–2.37)	0.3
Collecting duct or NOS	4.92 (2.18–11.14)	<0.001	3.44 (1.51–7.84)	0.003	3.21 (1.49–6.89)	0.003
2010 pT classification						
pT1–2	1.0 (reference)		1.0 (reference)		1.0 (reference)	
pT3–4	1.41 (0.89–2.24)	0.1	1.51 (0.91–2.49)	0.1	1.31 (0.83–2.05)	0.3
2010 pT classification						
pT1–3	1.0 (reference)		1.0 (reference)		1.0 (reference)	
pT4	2.51 (1.29–4.90)	0.007	1.62 (0.82–3.21)	0.2	1.42 (0.73–2.74)	0.3
Grade						
2–3	1.0 (reference)		1.0 (reference)		1.0 (reference)	
4	1.56 (1.06–2.30)	0.02	1.78 (1.20–2.65)	0.005	1.70 (1.17–2.47)	0.006
Coagulative tumor necrosis	2.08 (1.23–3.52)	0.006	2.40 (1.35–4.27)	0.003	2.51 (1.48–4.25)	<0.001
Sarcomatoid differentiation	1.46 (0.93–2.32)	0.1	2.50 (1.59–3.92)	<0.001	2.45 (1.60–3.74)	<0.001
Number of LNs removed	1.00 (0.98–1.02) [b]	0.9	0.99 (0.97–1.01) [b]	0.3	0.99 (0.97–1.01) [b]	0.5
Number of LNs removed ≥13	1.02 (0.66–1.59)	0.9	0.84 (0.53–1.35)	0.5	0.86 (0.56–1.34)	0.5
Number of positive LNs	1.01 (0.95–1.07) [b]	0.8	1.02 (0.97–1.08) [b]	0.5	1.03 (0.97–1.08) [b]	0.3
Number of positive LNs ≥2	1.09 (0.73–1.64)	0.7	1.19 (0.78–1.81)	0.4	1.19 (0.81–1.75)	0.4

HR = hazard ratio; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; IVC = inferior vena cava; RCC = renal cell carcinoma; NOS = not otherwise specified; LNs = lymph nodes.
[a] HR represents a 10-unit increase.
[b] HR ratio represents a 1-unit increase.

Table 4 – Multivariable associations of clinicopathologic features with the development of distant metastases, cancer-specific mortality, and all-cause mortality

Feature	Distant metastases		Cancer-specific mortality		All-cause mortality	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Symptoms at presentation	2.40 (1.10-5.21)	0.03	–	–	–	–
IVC tumor thrombus	1.99 (1.27-3.12)	0.003	–	–	–	–
RCC histologic subtype			–	–	–	–
All others	1.0 (reference)					
Clear cell	2.21 (1.21-4.04)	0.010				
Collecting duct or NOS	4.28 (1.87-9.80)	<0.001				
pT4 stage (vs pT1–3)	2.64 (1.34-5.21)	0.005	–	–	–	–
Coagulative tumor necrosis	2.51 (1.46-4.32)	<0.001	2.24 (1.22-4.10)	0.009	2.50 (1.44-4.33)	0.001
Sarcomatoid differentiation	–	–	2.30 (1.45-3.62)	<0.001	2.21 (1.43-3.40)	<0.001
ECOG PS ≥1	–	–	2.41 (1.50-3.87)	<0.001	2.40 (1.55-3.71)	<0.001

HR = hazard ratio; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status.

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would benefit from consideration of preoperative systemic therapy, adjuvant systemic therapy, or enrollment into a clinical trial.

Interestingly, three clinicopathologic features were prognostic of CSM and ACM: ECOG PS $\geq$1, coagulative tumor necrosis, and sarcomatoid differentiation. This suggests that unlike the development of distant metastases, which appears to be largely driven by tumor biology, the endpoints of CSM and ACM reflect not only disease biology (as captured by adverse pathologic features) but also patient functional status. The latter may indicate eligibility for systemic therapy or, alternatively, cancer-related functional decline.

Historically, LN involvement has been associated with a poor prognosis [4,14,15]. Indeed, in the original account of the outcomes of radical nephrectomy by Robson et al in 1969, the authors reported 3-yr survival of approximately 35% for pN1M0 disease [15]. Perhaps more notable is that the survival figure in that study (Figure 1 in [15]) appears to capture the underlying biology of isolated LN involvement: the survival of patients with LN involvement parallels that of patients with distant metastases, probably because of progression from occult systemic disease, until the LN survival curve plateaus, reflecting the subset of durable survivors without occult systemic disease at the time of surgery.

Several contemporary series have examined isolated LN disease. Investigators from the MD Anderson center reported on a series of 40 patients with surgically resected pN1M0 disease, and observed that disease recurred in 70% at a median of 4.9 mo [17]. An updated report on 68 patients with longer follow-up noted 22.1% progression-free survival at a median of 43.5 mo after surgery [16]. Favorable prognostic features included ECOG PS of 0 and the absence of sarcomatoid features. In a multi-institution series of 171 patients with median follow-up of 1.3 yr, median CSS was 1.2 yr, and the presence of systemic symptoms was the strongest predictor of poor survival [18]. More recently, Trinh and colleagues [19] conducted a population-based study of 799 patients with median follow-up of only 17 mo, reporting median OS of 28 mo and actuarial CSS of 38% at 5 yr. Adverse prognostic features included higher Fuhrman grade, clear cell histology, advanced pT stage, and percentage of positive nodes. Randomized trials examining adjuvant therapies have observed similar survival in the setting of node-positive disease [21,22]. Some of the differences in oncologic outcomes reported may be related to differences among study populations.

RCC has been associated with predominantly hematogenous, rather than lymphogenous, spread [3,23]. For instance, in one autopsy study that included 80 patients with pN1 RCC, only five (6.3%) were without concurrent distant metastatic disease [24]. Anatomic studies provide several mechanisms to explain these findings. Lymphatic drainage from the kidney is unpredictable, and direct lymphatic drainage into the IVC and thoracic duct have both been described [25]. Alternatively, hematogenous spread may reflect tumor biology rather than anatomic considerations [26].

Despite these findings, there does appear to be a small subset of patients without occult systemic disease in whom resection of isolated LN disease is associated with durable long-term survival. These patients are characterized by pathologic nodal involvement (pN1) in the absence of adverse prognostic features, as identified in this and other studies. However, the majority of existing prediction tools to identify patients with pN1 disease [27–29] utilize the same clinicopathologic features that have been associated with occult systemic disease and early progression, probably reflecting the association of nodal disease with systemic disease. Alternative prediction tools are required to identify patients with nodal metastases independent of features associated with systemic disease [30].

This retrospective study has several limitations. Most importantly, it reflects a surgical cohort and the selection bias inherent to surgical candidacy. In addition, LND was performed at the surgeon's discretion, which may introduce additional selection bias. LND boundaries were not standardized, and it is possible that more extensive LND may be associated with different oncologic outcomes. Moreover, variability has been reported in the assessment of LN counts. Neither the location of positive lymph nodes nor specific pathologic features of positive lymph nodes, such as the presence of extranodal extension or sarcomatoid features, was available. Furthermore, given the rarity of isolated pN1 disease, a larger cohort may improve the statistical power for detection of associations between clinicopathologic features and oncologic outcomes. Finally, assessment of pathologic features may not be available preoperatively without renal mass biopsy. Still, this is the largest single-institution study to examine the topic. Accordingly, it benefits from the availability of a comprehensive set of clinical, radiographic, and pathologic features, utilization of re-reviewed pathology, and long-term follow-up.

5. Conclusions

Isolated pN1 disease portends poor prognosis, with a 5-yr probability of metastasis-free survival of only 16%. Nevertheless, a subset of patients experience durable long-term survival to 10 yr after surgical resection of isolated lymphatic metastases. Adverse prognostic features including symptoms at presentation, radiographic IVC involvement, pT4 stage, coagulative tumor necrosis, and clear cell, collecting duct, or NOS histologic subtypes were independently associated with the development of distant metastases, and may enhance patient risk stratification and facilitate multimodal management approaches.

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Study concept and design: Gershman, Thompson, Moreira, Boorjian, Lohse, Costello, Cheville, Leibovich.
Acquisition of data: Lohse, Thompson, Leibovich.
Analysis and interpretation of data: Gershman, Thompson, Moreira, Boorjian, Lohse, Costello, Cheville, Leibovich.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2016.12.027.

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