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The natural history of renal cell carcinoma with isolated lymph node metastases following surgical resection from 2006 to 2013

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Abstract

Introduction: Renal cell carcinoma (RCC) with isolated lymph node (LN) involvement (pN1 M0 RCC) is a rare clinical entity associated with a poor prognosis. Prior studies comprised cohorts treated predominantly prior to the introduction of targeted systemic therapy. We therefore examined the natural history of pN1M0 RCC following surgical resection in a contemporary cohort, and evaluated clinicopathologic features associated with survival.

Patients and methods: We identified patients aged 18 to 89 years who underwent radical or partial nephrectomy with LN dissection for pN1 M0 RCC from 2006 to 2013 in the National Cancer Database. The associations of clinicopathologic features with overall survival (OS) were evaluated using Cox regression models, and a simplified risk score was developed.

Results: A total of 2,679 patients were found to have pN1 M0 RCC after nephrectomy. Median follow-up was 19.2 (interquartile range 8.2, 39.8) months, during which time 1,782 patients died. One-, 5-, and 8-year OS rates were 68%, 28%, and 19%, respectively. On multivariable analysis, older age (HR 1.50; $P< 0.001$ for ≥70 vs, 18−<50 years old), rural location (HR 1.49; $P= 0.01$), larger tumor size (HR 1.29; $P= 0.01$ for 5−<10 cm; HR 1.34; $P= 0.01$ for 10−<15 cm; HR 1.43; $P= 0.01$ for ≥15 cm vs. <5 cm); higher pT stage (HR 1.25; $P= 0.04$ for pT3; HR 2.41; $P< 0.001$ for pT4 vs. pT1), positive surgical margins (HR 1.55; $P< 0.001$), number of positive LNs (HR 1.18; $P= 0.01$ for 2−3; HR 1.37; $P< 0.001$ for >3 vs. 1), and nonclear cell histologic subtype (HR 1.32; $P< 0.001$) were independently associated with decreased OS. A simplified risk score was developed based on the multivariable results. Five-year OS was 49%, 28%, 22%, and 10% for patients with scores of <4, 4 to 6, 7 to 9, and >9, respectively.

Conclusions: In this large, contemporary cohort, pN1 M0 RCC was associated with a poor prognosis, with 5-year survival less than 30%. A simplified risk score was developed to facilitate postoperative risk-stratification and selection of patients for consideration of adjuvant therapy and clinical trial enrollment.

Keywords: Renal cell carcinoma; Lymph nodes; Metastasis; Lymphadenectomy; Targeted therapy

Abbreviations: HR, hazard ratio; IVC, inferior vena cava; LND, lymph node dissection; NCDB, National Cancer Database; OS, overall survival; RCC, renal cell carcinoma

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1. Introduction

Renal cell carcinoma (RCC) with isolated lymph node (LN) involvement (pN1 M0) is a rare clinical entity [1]. Although pN1 M0 RCC is associated with a poor prognosis, a subset of patients demonstrates long-term survival, with 10-year overall survival ranging from 5% to 39% [1−4]. Unfortunately, data regarding pN1 M0 RCC have been largely limited to small, institutional or multi-institutional series, and comprised cohorts treated predominantly prior to the introduction of targeted therapy [2−13]. Moreover, there is evidence for substantial heterogeneity in the clinical outcomes of patients with pN1 M0 RCC [2], highlighting a need for predictive tools to facilitate postoperative prognostication and risk-adapted management.

In this study, we examined the natural history of pN1M0 RCC following surgical resection in a large, contemporary cohort treated from 2006 to 2013, and evaluated clinicopathologic features associated with survival to create a risk prediction model.

2. Patients and methods

2.1. Study cohort

After obtaining exempt status from the Institutional Review Board, we identified 2,679 patients aged 18 to 89 years who underwent radical or partial nephrectomy with LN dissection (LND) for pTany pN1 M0 RCC from 2006 to 2013 in the National Cancer Database (NCDB) (Supplementary Fig. 1). LND was defined as removal of 1 or more LNs. LND templates were not standardized, and LND was performed at the surgeon's discretion.

2.2. Clinicopathologic features and outcome

We identified the following baseline characteristics as recorded in the NCDB: age, year of diagnosis, sex, race, Hispanic status, Charlson comorbidity index, insurance status, geographic location, facility type, distance to hospital, rurality, income level, education status, clinical and pathologic TNM stage, tumor size, surgical margin status, and tumor grade. For patients treated from 2010 to 2013, the following Collaborative Stage (CS) Site-Specific Factors were also available: presence of histologic tumor necrosis, sarcomatoid differentiation, invasion beyond renal capsule, renal vein or inferior vena cava thrombus, and ipsilateral adrenal gland invasion.

The primary outcome was overall survival (OS).

2.3. Statistical analyses

Baseline characteristics were summarized as frequency count/percentage or median/interquartile range (IQR). Overall survival was estimated using the Kaplan-Meier method. The associations of clinicopathologic features with OS were evaluated using Cox proportional hazards regression models. Two multivariable models were developed using only features significant on univariable analysis: Model 1 included all patients in the cohort and was adjusted for all covariates except CS Site-Specific Factors; Model 2 was restricted to patients treated from 2010 to 2013 and was adjusted for all available features, including CS Site-Specific Factors. Observations with missing data were dropped from regression models, except where noted and modeled as "Unknown."

To simplify clinical application, we developed a risk score using features that were statistically significant on multivariable analysis (Model 1). The parameter estimates for selected features on multivariable analysis Model 1 were normalized by the smallest parameter estimate to create "points." We excluded rurality from the risk score model to produce survival estimates averaged over this covariate as distributed in the study cohort. OS was then estimated according to risk score groups.

Statistical analyses performed using R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria). All tests were 2-sided, and P values <0.05 were considered statistically significant.

3. Results

A total of 2,679 patients were found to have pN1 M0 RCC following partial or radical nephrectomy. Baseline characteristics are summarized in Table 1. Median age at diagnosis was 60 (IQR 52, 69) years, and 68% of the cohort was male. The median number of LNs removed was 3 (IQR 1, 8), and the median number of positive LNs was 2 (IQR 1, 3). Tumors demonstrated aggressive pathologic features—72% of patients had ≥pT3 disease, and among patients treated from 2010 to 2013, 35% had histologic tumor necrosis, while 23% had sarcomatoid differentiation. Among patients treated from 2010 to 2014, select baseline characteristics and OS, stratified by surgical approach, are presented in Supplementary Table 1 and Supplementary Fig. 2. Although the agent is not captured in the NCDB, a total of 830 (31%) patients received systemic therapy after surgery.

Median follow-up was 19.1 (IQR 8.2, 39.8) months, during which time 1,782 patients died of any cause. Overall survival is summarized in Fig. 1 and Table 2. One-, 5-, and 8-year OS rates were 68%, 28%, and 19%, respectively. Although the cohort demonstrated poor survival over the first 5 years after surgery, there was a small subset of patients who demonstrated durable long-term survival.

We examined the associations of clinicopathologic features with OS. Univariable and multivariable results are summarized in Table 3. On multivariable analyses using the entire cohort (*Model 1*), older age (HR 1.50; 95% CI 1.21−1.86; $P < 0.001$ for ≥70 vs. 18−<50 years old), rural location (HR 1.49; 95% CI 1.10−2.02; $P = 0.01$), larger tumor size (HR 1.29; 95% CI 1.07−1.56; $P = 0.01$ for 5−<10 cm; HR 1.34; 95% CI 1.09−1.64; $P = 0.01$ for

Table 1
Clinicopathologic features for the cohort ($N = 2,679$).

Patient features	N (%)
Age (y)	
Median (IQR)	60 (52, 69)
18−<50	506 (18.9)
50−<60	754 (28.1)
60−<70	803 (30.0)
≥70	616 (23.0)
Year of diagnosis	
2006−2007	799 (29.8)
2008−2009	694 (25.9)
2010−2011	587 (21.9)
2012−2013	599 (22.4)
Sex	
Male	1824 (68.1)
Female	855 (31.9)
Race	
White	2210 (82.5)
Black	350 (13.1)
Other	82 (3.1)
Unknown	37 (1.4)
Hispanic	
No	2379 (88.8)
Yes	131 (4.9)
Unknown	169 (6.3)
Charlson Comorbidity index	
0	1972 (73.6)
1	528 (19.7)
≥2	179 (6.7)
Insurance status	
Not insured	109 (4.1)
Private	1346 (50.2)
Medicaid	170 (6.3)
Medicare	979 (36.5)
Other government	34 (1.3)
Unknown	41 (1.5)
Geographic location	
New England	111 (4.1)
Middle Atlantic	351 (13.1)
South Atlantic	521 (19.4)
East North Central	514 (19.2)
East South Central	194 (7.2)
West North Central	230 (8.6)
West South Central	229 (8.5)
Mountain	102 (3.8)
Pacific	272 (10.2)
Missing	155 (5.8)
Facility type	
Community Cancer Program	184 (6.9)
Comp Community Cancer Prog.	850 (31.7)
Academic/Research Program	1240 (46.3)
Other (Integrated Network)	250 (9.3)
Missing	155 (5.8)
Distance from facility (miles)	
Median (IQR)	14.7 (5.9, 41.6)
≤ 60	2162 (80.7)
61−120	293 (10.9)
> 120	174 (6.5)
Missing	50 (1.9)
Rurality	
Metropolitan	2017 (75.3)
Urban	495 (18.5)
Rural	72 (2.7)
Missing	95 (3.5)
Median zip code income	
< $30,000	375 (14.0)
$30,000−35,999	463 (17.3)
$36,000−45,999	790 (29.5)
≥ $46,000	951 (35.5)
Missing	100 (3.7)
No high-school education within residential zip code	
> 29%	457 (17.1)
20−28.9%	649 (24.2)
14−19.9%	633 (23.6)
< 14%	838 (31.3)
Missing	102 (3.8)
Type of nephrectomy	
Partial nephrectomy	80 (3.0)
Radical nephrectomy	2599 (97.0)
Surgical approach[a]	
Open	831 (70.1)
Laparoscopic	161 (13.6)
Robotic	98 (8.3)
Missing	96 (8.1)
Systemic therapy	
None	1822 (68)
Presurgical	27 (1)
Postsurgical	749 (28)
Pre- and postsurgical	81 (3)
cN Stage	
cN0	542 (20.2)
cN1	1126 (42)
cNX	1001 (37.4)
Missing	10 (0.4)
Pathologic Features	
pT Stage	
pT1	286 (10.7)
pT2	357 (13.3)
pT3	1718 (64.1)
pT4	220 (8.2)
Missing	98 (3.6)
Tumor size (cm)	
Median (IQR)	9 (6.5, 12.0)
≤ 5	397 (14.8)
5−<10	1212 (45.2)
10−<15	810 (30.2)
≥15	237 (8.8)
Missing	23 (0.9)
Lymph nodes examined	
Median (IQR)	3 (1.0, 8.0)
Lymph nodes positive	
Median (IQR)	2 (1.0, 3.0)
1	1254 (46.8)
2−3	801 (29.9)
>3	619 (23.1)
Missing	5 (0.002)
Positive margin	
No	2010 (75.0)
Yes	600 (22.4)
Missing	69 (2.6)
Histologic subtype	
Clear cell	1072 (40.0)
Papillary	477 (17.8)
Chromophobe	81 (3.0)
Collecting duct	65 (2.4)
Cyst-associated RCC	1 (0.0)
Sarcomatoid	283 (10.6)

(*continued*)

Table 1 (***Continued***)

(*continued*)

Table 1 (*Continued*)

Patient features	N (%)
Not otherwise specified (NOS)	700 (26.1)
Tumor grade	
1	18 (0.7)
2	340 (12.7)
3	1150 (42.9)
4	776 (29.0)
Missing	395 (14.7)
Tumor necrosis[b]	
No	642 (54.1)
Yes	418 (35.2)
Missing	126 (10.6)
Sarcomatoid differentiation[b]	
No	867 (73.1)
Yes	270 (22.8)
Missing	49 (4.1)
Invasion beyond capsule[b]	
No	522 (44.0)
Yes	624 (52.6)
Missing	40 (3.4)
Renal vein/IVC involvement[b]	
None	695 (58.6)
Renal vein only	330 (27.8)
IVC	130 (11.0)
Missing	31 (2.6)
Ipsilateral adrenal gland invasion[b]	
No	1001 (84.4)
Yes	94 (7.9)
Missing	91 (7.7)

IQR = interquartile range; IVC = inferior vena cava; RCC = renal cell carcinoma.

[a] Only available for 2010 to 2014.

[b] CS site-specific factors (SSFs) from 2010 to 2014.

Table 2
Overall survival for the cohort.

Time point	Overall survival (95% CI)
1 y	68% (67%–70%)
2 y	49% (47%–51%)
3 y	39% (37%–41%)
4 y	32% (31%–34%)
5 y	28% (26%–30%)
6 y	24% (22%–27%)
7 y	22% (20%–24%)
8 y	19% (17%–22%)
9 y	18% (16%–21%)

10–<15 cm; HR 1.43; 95% CI 1.11–1.85; $P = 0.01$ for ≥15 cm vs. <5 cm); higher pT stage (HR 1.25; 95% CI 1.00–1.56; $P = 0.04$ for pT3; HR 2.41; 95% CI 1.81–3.20; $P < 0.001$ for pT4 vs. pT1), positive surgical margins (HR 1.55; 95% CI 1.37–1.77; $P < 0.001$), number of positive LNs (HR 1.18; 95% CI 1.03–1.34; $P = 0.01$ for 2–3; HR 1.37; 95% CI 1.18–1.58; $P < 0.001$ for >3 vs. 1), and histologic subtype (HR 1.32; 95% CI 1.17–1.48; $P < 0.001$ for nonclear cell vs. clear cell) were associated with increased mortality (Table 3, *Model 1*). In a model that was further adjusted for additional pathologic features available in patients treated from 2010 to 2013, results were overall similar, but the presence of histologic tumor necrosis (HR 1.38; 95% CI 1.09–1.74; $P = 0.01$), sarcomatoid differentiation (HR 1.52; 95 CI 1.12–2.06; $P = 0.01$), and ipsilateral adrenal gland invasion (HR 1.80; 95% CI 1.14–2.83;

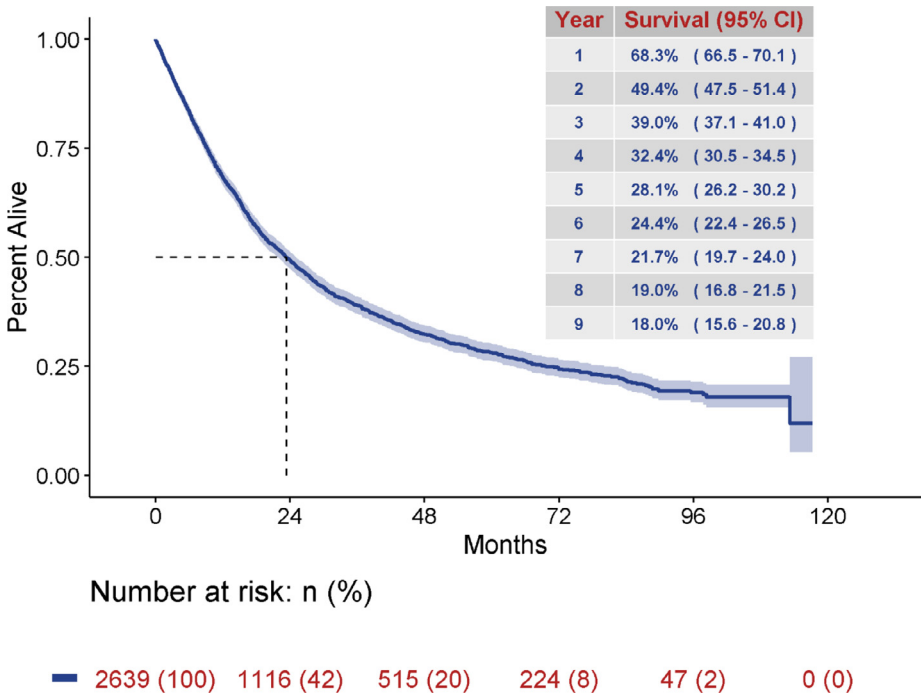


Fig. 1. Overall survival for the cohort. Shaded area represents 95% CI.

Table 3
Univariable and multivariable associations of clinicopathologic features with OS.

	Univariable			Multivariable Model 1 ($N = 1965$)			Multivariable Model 2 ($N = 645$)		
Feature	HR	95% CI	*P* value	HR	95% CI	*P*value	HR	95% CI	*P*value
Age (y)									
18−<50	ref.			ref.			ref.		
50−<60	1.11	0.96, 1.29	0.14	1.11	0.94, 1.32	0.22	1.38	0.95, 1.99	0.09
60−<70	1.18	1.02, 1.36	0.02	1.17	0.98, 1.40	0.09	1.41	0.97, 2.05	0.07
≥70	1.53	1.32, 1.77	<0.001	1.50	1.21, 1.86	<0.001	1.61	1.04, 2.48	0.03
Year of diagnosis									
2006/2007	ref.			ref.			−		
2008/2009	0.88	0.78, 0.99	0.03	1.00	0.86, 1.16	0.99	−		
2010/2011	0.74	0.65, 0.85	<0.001	0.87	0.73, 1.02	0.09	ref.		
2012/2013	0.75	0.65, 0.87	<0.001	0.88	0.73, 1.07	0.20	1.01	0.79, 1.29	0.94
Sex									
Male	ref.			ref.			ref.		
Female	1.12	1.01, 1.24	0.03	1.08	0.96, 1.21	0.22	1.00	0.78, 1.29	0.99
Race									
White	ref.			ref.			ref.		
Black	0.99	0.86, 1.14	0.87	0.98	0.82, 1.17	0.79	0.89	0.62, 1.28	0.54
Other	0.95	0.72, 1.26	0.74	1.07	0.78, 1.48	0.66	1.17	0.63, 2.20	0.62
Hispanic									
No	ref.			−			−		
Yes	1.01	0.81, 1.26	0.94	−			−		
Unknown	1.01	0.84, 1.22	0.93	−			−		
Charlson Comorbidity index									
0	ref.			ref.			ref.		
1	1.15	1.03, 1.30	0.02	1.10	0.96, 1.26	0.18	1.36	1.04, 1.79	0.03
≥2	1.27	1.06, 1.53	0.01	1.22	0.99, 1.51	0.07	1.37	0.89, 2.11	0.15
Insurance status									
Private	ref.			ref.			ref.		
Uninsured	1.01	0.79, 1.30	0.92	1.13	0.84, 1.52	0.43	1.48	1.89, 2.47	0.13
Medicaid	1.00	0.82, 1.22	0.99	1.13	0.89, 1.42	0.32	1.78	1.06, 2.99	0.03
Medicare	1.23	1.11, 1.36	<0.001	1.00	0.85, 1.17	0.96	1.17	0.86, 1.59	0.33
Other Gov't	1.09	0.70, 1.67	0.71	0.94	0.57, 1.55	0.79	1.34	0.42, 4.30	0.63
Geographic location									
New England	ref.			−			−		
Mid Atlantic	1.04	0.80, 1.36	0.76	−			−		
South Atlantic	1.11	0.86, 1.43	0.42	−			−		
East North Central	1.15	0.89, 1.49	0.28	−			−		
East South Central	1.23	0.93, 1.64	0.15	−			−		
West North Central	1.21	0.91, 1.60	0.19	−			−		
West South Central	1.13	0.85, 1.50	0.40	−			−		
Mountain	1.15	0.83, 1.61	0.40	−			−		
Pacific	1.02	0.78, 1.35	0.86	−			−		
Facility type									
Community Cancer Program	ref.			−			−		
Comprehensive Community	1.11	0.91, 1.35	0.28	−			−		
Academic/Research Program	0.99	0.82, 1.20	0.93	−			−		
Int. Network Cancer Program	1.21	0.96, 1.53	0.10	−			−		
Unknown	0.83	0.63, 1.09	0.19	−			−		
Distance from facility (miles)									
Continuous	1.00	1.00, 1.00	0.37	−			−		
≤ 60	ref.			−			−		
61−120	0.89	0.76, 1.04	0.14	−			−		
>120	0.93	0.76, 1.14	0.47	−			−		
Rurality									
Metropolitan	ref.			ref.			ref.		
Urban	1.02	0.91, 1.16	0.71	0.99	0.86, 1.14	0.86	1.22	0.93, 1.60	0.15
Rural	1.48	1.13, 1.93	0.005	1.49	1.10, 2.02	0.01	1.80	0.99, 3.30	0.06
Median zip code income									
<$30,000	ref.			−			−		
$30,000−$35,999	0.98	0.83, 1.16	0.81	−			−		

(*continued*)

Table 3 (***Continued***)

	Univariable			Multivariable Model 1 ($N = 1965$)			Multivariable Model 2 ($N = 645$)		
Feature	HR	95% CI	*P* value	HR	95% CI	*P*value	HR	95% CI	*P*value
$36,000–$45,999	0.88	0.76, 1.03	0.10	–			–		
>$46,000	0.91	0.79, 1.06	0.24	–			–		
No high-school education within residential zip code									
≥29%	ref.			–			–		
20–28.9%	1.00	0.86, 1.16	0.97	–			–		
14–19.9%	0.97	0.83, 1.12	0.67	–			–		
<14%	0.96	0.83, 1.11	0.57	–			–		
cN Stage									
cN0	ref.			ref.			ref.		
cN1	1.25	1.09, 1.44	0.001	1.01	0.86, 1.19	0.88	1.01	0.77, 1.34	0.93
cNx	1.47	1.28, 1.68	<0.001	1.10	0.93, 1.31	0.25	0.98	0.68, 1.40	0.90
pT Stage									
pT1	ref.			ref.			ref.		
pT2	1.08	0.87, 1.35	0.48	0.98	0.75, 1.29	0.91	2.03	1.11, 3.71	0.02
pT3	1.81	1.51, 2.16	<0.001	1.25	1.00, 1.56	0.04	2.17	1.25, 3.78	0.01
pT4	4.00	3.20, 4.99	<0.001	2.41	1.81, 3.20	<0.001	3.17	1.53, 6.59	0.002
Size (cm)									
Continuous	1.02	1.01, 1.03	<0.001	–			–		
<5	ref.			ref.			ref.		
5–<10	1.35	1.17, 1.57	<0.001	1.29	1.07, 1.56	0.01	0.99	0.67, 1.47	0.90
10–<15	1.48	1.27, 1.73	<0.001	1.34	1.09, 1.64	0.01	0.85	0.56, 1.29	0.45
≥15	1.67	1.36, 2.04	<0.001	1.43	1.11, 1.85	0.01	1.24	0.74, 2.11	0.41
Number of LNs removed (continuous)	1.01	1.00, 1.01	0.07	–			–		
Number of positive LNs									
1	ref.			ref.			ref.		
2–3	1.24	1.11, 1.39	<0.001	1.18	1.03, 1.34	0.01	0.97	0.74, 1.28	0.84
>3	1.57	1.40, 1.77	<0.001	1.37	1.18, 1.58	<0.001	1.20	0.90, 1.61	0.22
Positive margin	1.91	1.72, 2.13	<0.001	1.55	1.37, 1.77	<0.001	1.89	1.43, 2.51	<0.001
Histologic subtype									
Clear cell	ref.			ref.			ref.		
Nonclear cell	1.33	1.21, 1.47	<0.001	1.32	1.17, 1.48	<0.001	1.25	0.98, 1.59	0.07
Tumor grade									
1	ref.			ref.			ref.		
2	1.50	0.70, 3.18	0.29	1.01	0.47, 2.17	0.97	1.54	0.20, 11.54	0.68
3	2.35	1.11, 4.94	0.02	1.44	0.68, 3.06	0.34	2.19	0.30, 16.06	0.44
4	3.85	1.83, 8.11	<0.001	2.19	1.03, 4.65	0.04	3.44	0.47, 25.42	0.23
Tumor necrosis[a]									
No	ref.			–			ref.		
Yes	1.52	1.28, 1.80	<0.001	–			1.38	1.09, 1.74	0.01
Sarcomatoid differentiation[a]	2.12	1.77, 2.52	<0.001	–			1.52	1.12, 2.06	0.01
Invasion Beyond Capsule[a]	1.69	1.43, 1.99	<0.001	–			1.10	0.83, 1.47	0.50
Renal vein/IVC involvement[a]									
None	ref.			–			ref.		
Renal Vein	1.36	1.14, 1.63	<0.001	–			1.03	0.78, 1.37	0.81
IVC	1.70	1.34, 2.16	<0.001	–			0.98	0.66, 1.45	0.91
Ipsilateral adrenal gland invasion[a]									
No	ref.			–			ref.		
Yes	2.79	2.19, 3.56	<0.001	–			1.80	1.14, 2.83	0.01
Operative approach[b]									
Open	ref.			–			ref.		
Laparoscopic	0.75	0.58, 0.96	0.02	–			0.80	0.55, 1.16	0.24
Robotic	0.82	0.61, 1.12	0.21	–			0.88	0.59, 1.32	0.54

[a] CS site-specific factors (SSFs) from 2010 to 2013.
[b] Only available for 2010 to 2013.

P = 0.01) were also independently associated with increased mortality (Table 3, *Model 2*). Although year of diagnosis was associated with OS on univariable analysis, it was not associated with OS after multivariable adjustment. In sensitivity analyses further adjusted for receipt of postsurgical systemic therapy (Supplementary Table 2), receipt of postsurgical systemic therapy was not statistically significantly associated with OS in multivariable models, and point estimates for the other covariates were essentially unchanged.

To simplify clinic prediction using the prognostic features identified in multivariable analyses, we developed a risk score based on multivariable *Model 1* (Table 4). Points are added for each feature as noted in Table 4 to calculate the risk score total for each patient. Overall survival, estimated according to the risk score, is summarized in Fig. 2. Five-year OS was 49%, 28%, 22%, and 10% for patients with scores of <4, 4–6, 7–9, and >9, respectively. As an example, a 65-year-old patient with a 7 cm, grade 3, pT3, clear cell tumor with 2 positive LNs and negative margins would have a risk score of 4 points, which corresponds to an estimated 5-year OS of 28%.

4. Discussion

In this study, we examined the natural history of pN1 M0 RCC in a large, contemporary cohort of patients treated from 2006 to 2013. Although overall survival was poor, there remained a small subset of patients who demonstrated long-term survival, with 5- and 8-year OS of 28% and 19%, respectively. On multivariable analysis, several clinicopathologic features were independently associated with poor survival, including larger tumor size, higher pT stage, higher tumor grade, nonclear cell histologic subtype, and presence of histologic tumor necrosis or sarcomatoid differentiation. A simplified risk score was developed based on these results to facilitate postoperative prognostication and selection of patients for consideration of adjuvant therapy.

Table 4
Simplified risk score based on multivariable Model 1. Points are added for each feature below as noted to calculate the risk score for each patient. Overall survival, according to risk score point total, is summarized in Fig. 2.

Feature	Points
Age (y)	
18–<70	0
≥70	2
Tumor size (cm)	
<5	0
≥5	2
# positive LNs	
1	0
2–3	1
>3	2
pT Stage	
≤pT2	0
pT3	1
pT4	5
Positive margin	
No	0
Yes	3
Histologic subtype	
Clear cell	0
Nonclear cell	2
Tumor grade	
1–3	0
4	5

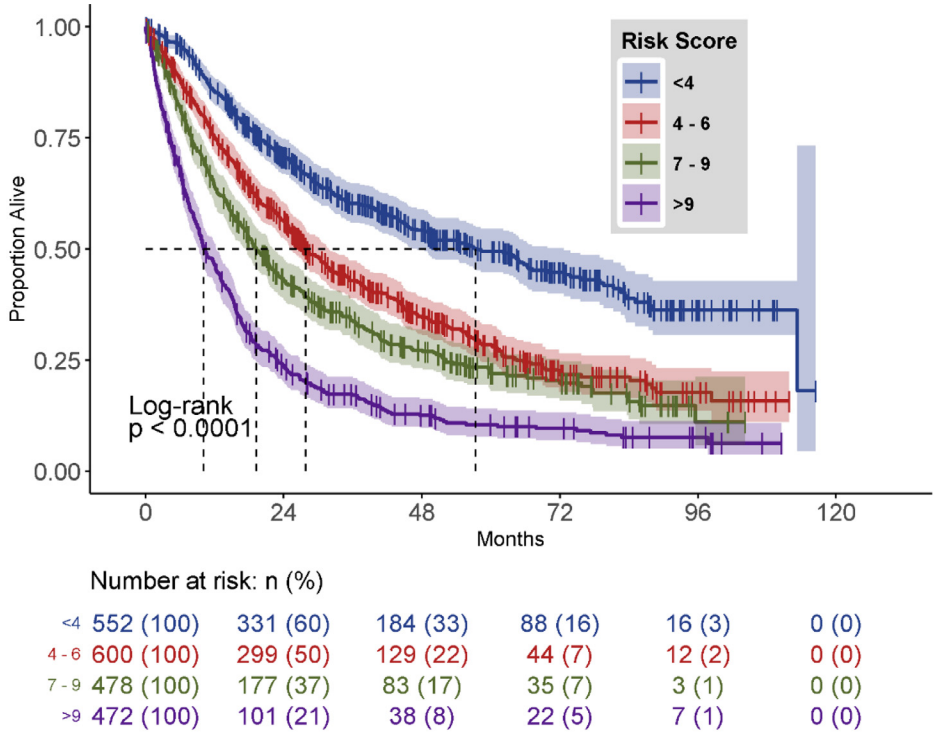
LNs = lymph nodes.

To our knowledge, this is the largest series of patients with pN1 M0 RCC, and the only cohort treated exclusively following the introduction of targeted therapy [1]. It is interesting that overall survival rates are similar to those reported in studies comprised of patients treated in the immunotherapy era [2–4]. Although causal inference is not possible comparing across descriptive studies, these results suggest that contemporary survival rates for pN1 M0 RCC have not dramatically improved compared to earlier studies.

Moreover, although the present study evaluated overall survival, as this is the only endpoint captured in the NCDB, results were consistent with cancer-specific survival reported in prior studies (10-year CSS ranging from 21% to 31%, [2,9,12]). This likely reflects that pN1 M0 RCC has a low incidence of competing causes of mortality. Indeed, pN1 M0 RCC is often associated with occult metastatic disease at the time of surgery—in 1 institutional report 63% of patients developed metastases by 1 year after surgery, and the median time to development of distant metastases was only 4.2 months [2].

Prior studies have evaluated features associated with survival for patients with pN1 M0 RCC [1,2,5,6,9,11,12]. In multivariable analyses, pT stage, tumor grade, and histologic subtype have each been independently associated with survival across multiple studies. For instance, in 1 multiinstitutional series of 171 patients, more advanced pT stage, higher tumor grade, and nonclear cell histologic subtype were independently associated with worse cancer-specific survival [9]. In another series of 799 patients in SEER, higher pT stage, and higher tumor grade were associated with worse cancer-specific survival [12]. In the largest single-institutional series of 138 patients, more advanced pT stage, collecting duct or RCC not otherwise specified histologic subtype, and presence of coagulative tumor necrosis were independently associated with development of distant metastases [2]. The results of the present study overall reinforce those of prior investigations, highlighting that, in an adequately powered sample, most adverse clinicopathologic features confer an independently worse prognosis in patients with pN1 M0 RCC.

The role of LND in the management of RCC has received renewed interest in recent years [1]. Although early studies suggested a potential survival benefit to LND, [14–19] more recent investigations have not confirmed a survival benefit, even in high-risk patient populations [20–25]. These results reinforce those of the only randomized trial to evaluate the therapeutic benefit of LND, EORTC 30881 [26]. In this context, the natural history of patients with pN1 M0 RCC—wherein a small subset of patients demonstrates durable long-term survival following resection of nodal metastases—seems to contradict the apparent lack of a survival benefit to LND. There are multiple potential explanations to reconcile these disparate findings. Most importantly, it is not possible to make inference regarding the survival benefit of LND from



Year	Risk Score <4	Risk Score 4 - 6	Risk Score 7 - 9	Risk Score >9
1	85.5% (82.5 - 88.5)	75.2% (71.7 - 78.8)	63.9% (59.7 - 68.4)	46.4% (42.1 - 51.2)
2	70.6% (66.8 - 74.7)	56.4% (52.5 - 60.7)	42.9% (38.5 - 47.7)	23.9% (20.3 - 28.2)
3	60.2% (55.9 - 64.7)	42.9% (38.9 - 47.3)	33.9% (29.7 - 38.7)	17.1% (13.9 - 21.0)
4	54.2% (49.7 - 59.0)	34.8% (30.8 - 39.3)	27.2% (23.2 - 32.0)	12.6% (9.7 - 16.3)
5	49.4% (44.8 - 54.5)	28.4% (24.5 - 33.0)	22.0% (18.0 - 26.7)	10.4% (7.7 - 14.1)
6	44.7% (39.9 - 50.1)	21.7% (17.8 - 26.5)	19.8% (15.9 - 24.7)	9.6% (7.0 - 13.3)
7	38.8% (33.5 - 45.0)	21.2% (17.2 - 26.0)	15.7% (11.6 - 21.2)	7.6% (5.1 - 11.3)
8	36.2% (30.7 - 42.8)	17.7% (13.5 - 23.2)	11.1% (5.8 - 21.3)	7.6% (5.1 - 11.3)
9	36.2% (30.7 - 42.8)	15.8% (11.0 - 22.5)	0.0% (0.0 - 0.0)	6.3% (3.7 - 10.8)

Fig. 2. Overall survival stratified by risk score points. Shaded area represents 95% CI. Points are added for each feature in Table 4 noted to calculate the risk score for each patient. Overall survival, according to risk score point total, is summarized below.

descriptive studies—the long-term survivors may have demonstrated favorable outcomes in the absence of LND. Indeed, such patients have been reported to have more indolent disease than those with pN1 M0 RCC who do not demonstrate long-term survival [2]. Alternatively, it may be possible that LND does confer a survival benefit in a very small subset of patients, but existing studies are either underpowered to detect this treatment effect or do not examine the appropriate patient subset.

The current study has a number of limitations. Most importantly, we were unable to examine endpoints other than overall survival, such as development of distant metastases or cancer-specific survival. Still, for a disease entity with a low incidence of competing risks of mortality, overall survival is a reliable long-term endpoint. In addition, surgical pathology is not rereviewed in the NCDB, and select features, such as presence of histologic tumor necrosis or sarcomatoid differentiation, were only available from 2010 onward. Furthermore, the cohort reflects the outcomes of patients who underwent surgical resection, and results cannot be extended to patients who did not undergo surgery, such as those with radiographically enlarged LNs preoperatively. Given the retrospective, multi-institutional nature of data in the NCDB, neither the decision to perform LN dissection nor the LN dissection templates were standardized. Finally, we did not evaluate the comparative effectiveness of therapeutic interventions, nor potential heterogeneity in the treatment effect of adjuvant therapies according to the risk score, as the primary aim of this study was descriptive. Despite these limitations, this study reflects the outcomes of a large, contemporary cohort.

5. Conclusions

In this large, contemporary cohort of patients treated from 2006 to 2013, pN1 M0 RCC was associated with a poor prognosis, with a 5-year estimated OS of only 28%. A simplified risk score was developed to facilitate postoperative risk-stratification and selection of patients for consideration of adjuvant therapies.

Conflict of interest

The authors have no conflicts of interest to disclose.

The National Cancer Data Base (NCDB) is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The CoC's NCDB and the hospitals participating in the CoC NCDB are the source of the deidentified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.08.003.

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