Mortality trends and the impact of lymphadenectomy on survival for renal cell carcinoma patients with distant metastasis

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Abstract

Introduction: Current treatment paradigms for metastatic renal cell carcinoma (mRCC) invoke a combination of surgical and systemic therapies. We sought to quantify trends in mortality and performance of lymphadenectomy, as well as impact on survival for patients with mRCC.

Methods: The Surveillance, Epidemiology, and End Results registry (SEER) (1988–2011) identified patients with mRCC. Kaplan-Meier curves and Cox proportional hazards models with competing risks regression were employed to assess survival.

Results: 15 060 patients with mRCC were identified, with 6316 (41.9%) undergoing cytoreductive nephrectomy. Mean number of lymph nodes removed was 6.2, with mean 3.3 positive nodes among 1018 (43.9%) patients with positive nodes. Median overall survival (OS) increased from seven to 11 months (1999–2010), and finding a positive node decreased median cancer survival from 22 to nine months. Cancer-specific survival (CSS) showed significant decreases in mortality after 2005 (hazard ratio [HR] 0.71 [0.60–0.83] comparing 2010 to 1990). Lymphadenectomy was associated with decreased OS (HR 1.10 [1.03–1.16]; p=0.002) due to decreased CSS (HR 1.10 [1.04–1.17]; p<0.001) without increase in other-cause mortality (HR 0.94 [0.79–1.11]; p=0.455). However, more extensive lymphadenectomy ≥3 lymph nodes removed did not significantly impact OS or CSS. Number of positive lymph nodes was associated with decreased CSS.

Conclusions: mRCC continues to carry a poor prognosis, but current treatment paradigms have led to modest improvements in OS and CSS in recent years. Lymphadenectomy was found to play a prognostic rather than therapeutic role in the management of mRCC. The performance of lymphadenectomy should be limited based on clinical judgment and better incorporated into randomized trials of new systemic therapies to identify scenarios where implementation may improve survival.

Introduction

A quarter of patients with renal cell carcinoma (RCC) present with distant metastatic disease at the time of diagnosis.[1] Current treatment paradigms invoke an integration of surgical and systemic therapies to optimize survival, but a number of controversies persist.[2] Cytoreductive nephrectomy (CN) before systemic therapy has been the dominant treatment paradigm since 2001. A combined analysis of two randomized trials showed longer median survival for CN preceding immunotherapy (interferon-alpha) compared to immunotherapy alone (13.6 vs. 7.8 months).[3-5] While preoperative selection is necessary for surgery, based on performance status and other factors identified by Culp et al, both CN and metastasectomy appear to play potential therapeutic roles in the management of metastatic RCC (mRCC).[2,6,7] Less certain, however, is whether the performance of lymphadenectomy (LND) at the time of CN exerts an effect on survival.

Reviews of the literature and available randomized trial data suggest LND plays a therapeutic role in clinical nodal disease without distant metastasis, but that it is not generally therapeutic for pT1-2 disease and has an uncertain effect in localized high-risk disease (T3–4N0M0).[8,9] Minimal data is available on the role of LND in mRCC, with a general belief that there would be negligible, if any benefit at the cost of increased time and morbidity during surgery. It would then follow that LND may be expected to have no impact on cancer survival while possibly being detrimental to overall survival (OS). Therefore, we sought to quantify trends in mortality and the performance of LND for patients with mRCC before and after the implementation of systemic therapy, and assess the effect of LND on survival for patients diagnosed with mRCC. We hypothesized that LND for patients with mRCC would show no impact on cancer-specific survival (CSS) while increasing other-cause mortality.

Methods

Study cohort, variables, and outcomes

After obtaining Institutional Review Board approval, the Surveillance, Epidemiology, and End Results (SEER) registry was used to identify patients diagnosed with mRCC (M1 disease based on TNM stage) from 1988–2011. The time period allowed a number of years prior to and after the introduction of systemic therapy to assess trends. Demographics and clinical data were assessed, including age, sex, race, year of diagnosis, surgical treatments (CN and LND), radiation therapy, tumour size, and Fuhrman grade. If LND was performed, the number of lymph nodes (LNs) sampled, as well as number of positive LNs was determined. Followup began from the time of diagnosis, and outcomes to assess survival included any cause of death (OS) and RCC cause of death (CSS).

Statistical analysis

Absolute survival was tabulated using median survival, mean time to death, and Kaplan-Meier curves for survival probabilities. Survival was stratified by the overall cohort, patients receiving CN and/or LND, the number of positive LNs, and year of diagnosis. Relative survival was assessed using multivariable Cox proportional hazards models, along with sensitivity analyses restricting the cohort to CN patients and specific time periods. Sensitivity analyses also varied cutoffs for the number of LNs removed, defined as LND (directly reported are ≥1, ≥3, and ≥8 based on a prior study[10]) given that the removal of one or very few LNs could indicate a LN biopsy rather than attempt at formal LND. The final relative survival estimates employed competing risks regression considering non-cancer causes of death (other-cause mortality) as a competing risk of death. Statistical analyses were performed using STATA software v.12.0 (STATA Corp, College Station, TX, U.S).

Results

A total of 15 060 patients with mRCC met the inclusion criteria, with 6316 (41.9%) undergoing CN, of which 2318 (36.7%) also had at least one LN removed at the time of surgery (Appendix A). The concurrent removal of any LN increased from 26.1% in 1995 to 43.5% in 2009 (+1.2% per year), but decreased somewhat to 37.4% in 2011. Fig. 1A shows LND over time defined as the removal of ≥3 and ≥8 LNs based on previous research.[10] Using the strictest definition (≥8), the performance of LND increased from about 2.3% in 1990 to about 5% in recent years. The mean number of LNs was 6.2 (7.9) for surgeries with at least one LN removed, and there was an average of 3.3 (4.3) positive LNs among the 1018 patients with positive nodes (Appendix B). Median overall survival increased about four months, from six to seven months before 1999 to 10 to 11 months after 2005, which paralleled improvement in CSS and one-year Kaplan-Meier survival probabilities (Fig. 1B). Cancer survival was about eight months for the overall cohort, 19 months for patients receiving a CN, and 15 months for patients receiving CN along with LN sampling (Table 1). Among the latter group, patients found to have no positive nodes after surgery had a median cancer survival of 22 months, while survival decreased to nine months with the finding of any positive node. OS and CSS generally decreased with increasing number of positive LNs.

Relative CSS improved during the time period, with adjusted hazard ratios (HRs) over the years plotted in Fig. 1C showing significant improvement after 2005, with a HR

Table 1. Stratified survival data (overall and cancer-specific) for metastatic renal cell carcinoma patients, SEER 1988–2011

	N	%	Followup (months)[a]	Death	%	Time to death (months)[a]	SD	RCC death	%	Time to RCC death (months)[a]	SD	Median K-M RCC survival (months)
Cohort	15 060	100.0	15.8	13 026	86.5	12.2	19.5	11 319	75.2	11.6	17.3	8
No LND	12 742	84.6	14.4	11 199	87.9	11.3	18.7	9679	76.0	10.8	16.7	7
CN only	3998	26.5	26.9	3106	77.7	21.0	25.9	2687	67.2	19.4	23.0	19
CN + LN sampling	2318	15.4	23.4	1827	78.8	17.6	23.2	1640	70.8	16.4	19.8	15
Any positive node	1018	43.9	15.9	879	86.3	12.8	17.8	797	78.3	11.9	15.1	9
# LNs positive												
0	1300	56.1	29.2	948	72.9	22.0	26.7	843	64.8	20.6	22.8	22
1	454	19.6	18.8	383	84.4	14.7	19.8	344	75.8	13.6	17.5	10
2	201	8.7	14.7	181	90.0	12.9	16.3	166	82.6	12.6	15.8	10
3	110	4.7	15.7	94	85.5	13.1	24.3	83	75.5	10.3	10.8	9
4+	253	10.9	11.7	230	90.9	9.2	8.8	204	80.6	9.2	9.1	8

[a]Mean. CN: cytoreductive nephrectomy; LND: lymphadenectomy; K-M: Kaplan Meier; LN: lymph node; RCC: renal cell carcinoma; SD: standard deviation; SEER: Surveillance, Epidemiology, and End Results registry.

of 0.71 (0.60–0.83) comparing 2010 to 1990. The adjusted overall competing risks survival model showed a significant decrease in survival associated with removal of ≥1 LN (HR 1.10 [1.03–1.16]; p=0.002). Removal of ≥1 LN was not associated with decreased survival due to other causes (HR 0.94 [0.79–1.11]; p=0.455), but was associated with decreased CSS (HR 1.10 [1.04–1.17]; p<0.001] (Table 2, Fig. 2A). However, higher threshold definitions for LND (≥3 and ≥8) more likely to estimate performance of a true LND did not show any difference in OS, other-cause survival, or CSS in competing risks models (Figs 2B, 2C; further sensitivity analyses and modes for variation in LNs removed are shown in Table 2). CSS with mRCC did not vary depending on age at diagnosis, but survival decreased for female sex, White race, and increasing primary tumour size. Subanalyses, including restriction to only CN patients and to patients diagnosed with mRCC in more recent years, showed the same associations for LND. Among patients undergoing LND, the number of positive LNs had the strongest association with decreased CSS, ranging from HR 1.56 (1.37–1.77; p<0.001) for one positive node to HR 2.30 (1.96–2.70; p<0.001) for four or more positive nodes (Appendix C; Fig. 2D).

Discussion

Metastatic RCC continues to carry a poor prognosis despite advances in treatment paradigms over the past two decades. However, our results show modest improvements in OS and CSS in recent years. Integrating surgical and systemic therapies has been key to providing effective therapeutic options to patients with mRCC.[2] This likely explains the increased survival rates for mRCC patients in SEER over the study period. While CN and metastasectomy are thought to have potential therapeutic roles and are often integrated in parallel with systemic therapy, the role of LND has been uncertain and inconsistently employed.[2,6-9,11] Our results suggest that LND does not play a therapeutic role for patients with mRCC. The removal of any LN was associated with decreased OS. The reason for this detrimental effect was not due to increased other-cause mortality, as we had hypothesized, but was attributable to decreased CSS. However, this is likely due to selective sampling of suspicious nodes in some patient. A stricter definition for LND (≥3 to ≥8 LNs removed) to account for inadvertent or selective removal (biopsy) of LNs showed LND had no impact on OS, CSS, or other-cause mortality. The latter finding is considered to more accurately reflect performance of LND with clinical therapeutic intent.

Early evidence had suggested LND might play a therapeutic role in mRCC, with a significant survival advantage in a study comparing 17 patients undergoing CN to 112 patients undergoing CN and LND.[12] However, a more recent mRCC cohort of 258 patients from Memorial Sloan Kettering

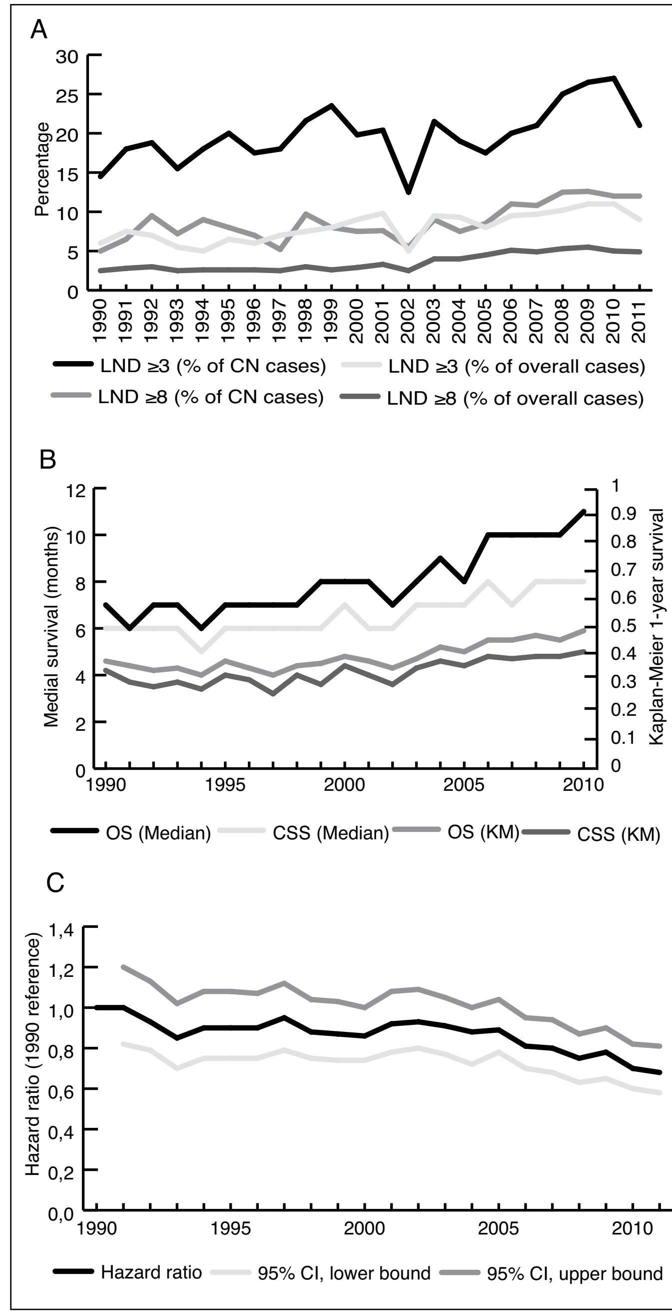

Fig. 1. Trends over time in ***(A)*** the performance of lymphadenectomy (for definitions based on ≥3 and ≥8 lymph nodes removed); ***(B)*** median survival and Kaplan-Meier survival probabilities; and ***(C)*** adjusted cancer-specific survival for metastatic renal cell carcinoma patients, Surveillance, Epidemiology, and End Results registry 1988–2011. CI: confidence interval; CSS: cancer-specific survival; LND: lymphadenectomy; OS: overall survival.

indicated LND did not provide a survival advantage, with a comparative five-year survival of 21% for patients undergoing CN with LND and 31% for patients undergoing CN without LND.[10] Although survival was lower for patients undergoing LND, the difference was not significant due to small sample size. Furthermore, cause of death was not

Table 2. Cox proportional hazards competing risks regression models for associations with cancer-specific survival, SEER 1988–2011

		95% CI		
	HR	Low	High	p value
Univariate model				
≥1 LN	0.66	0.63	0.70	<0.001
≥3 LN	0.65	0.61	0.69	<0.001
≥8 LN	0.66	0.60	0.72	<0.001
Model 1: Multivariable[a]				
≥1 LN	0.71	0.67	0.75	<0.001
≥3 LN	0.72	0.67	0.77	<0.001
≥8 LN	0.73	0.66	0.81	<0.001
Model 2: Multivariable[b]				
≥1 LN	1.12	1.05	1.19	<0.001
≥3 LN	1.06	0.99	1.14	0.11
≥8 LN	1.04	0.95	1.15	0.39
Model 3: Competing risks[c]				
≥3 LN	1.03	0.96	1.10	0.42
CN	0.51	0.49	0.53	<0.001
Age				
<45	REF	-	-	-
45–54	0.98	0.90	1.06	0.61
55–64	0.97	0.89	1.05	0.43
65–74	0.93	0.86	1.01	0.10
75–84	0.96	0.87	1.05	0.33
85+	0.96	0.83	1.11	0.57
Sex				
Female	1.08	1.04	1.13	<0.001
Race				
White	REF	-	-	-
Black	0.93	0.87	0.99	0.03
Hispanic	0.90	0.85	0.96	0.00
Other	0.87	0.80	0.94	<0.001
Radiation				
None	REF	-	-	-
Therapy	1.12	1.08	1.16	<0.001
Unknown	1.17	0.97	1.41	0.11
Tumour size				
≤4	REF	-	-	-
>4 to ≤7	1.20	1.11	1.30	<0.001
>7 to ≤10	1.36	1.26	1.46	<0.001
>10 to ≤20	1.51	1.40	1.63	<0.001
>20	1.79	1.46	2.18	<0.001
Unknown	1.17	1.08	1.27	<0.001

Table 2 (cont'd). Cox proportional hazards competing risks regression models for associations with cancer-specific survival, SEER 1988–2011

		95% CI		
	HR	Low	High	p value
Sensitivity analyses[d]				
LND[d]				
≥1 node	1.10	1.04	1.17	<0.001
≥2 nodes	1.07	1.01	1.14	0.03
≥3 nodes	1.03	0.96	1.10	0.42
≥4 nodes	0.99	0.93	1.07	0.84

[a]Adjusted for year, age, sex, race, radiation, and tumour size (not shown); not adjusted for CN; [b]adjusted for CN, year, age, sex, race, radiation, and tumour size (not shown); [c]competing risks model accounting for other-cause mortality and adjusted for CN, year, age, sex, race, radiation, and tumour size; [d]sensitivity analyses varying the cutoff for number of nodes removed to qualify as a LND. CI: confidence interval; CN: cytoreductive nephrectomy; HR: hazard ratio; LND: lymphadenectomy; SEER: Surveillance, Epidemiology, and End Results registry.

specified to separate deaths due to cancer from other causes. Our analysis captures a larger population-based cohort and verifies more recent thoughts that LND may have negligible, if any benefit in mRCC.

Interestingly, we found other-cause mortality was comparable between groups even with variation in the extent of LND, while CSS was decreased for patients with a few LNs removed rather than equivalent, as initially expected. There are a few possible explanations for this effect. One important reason could be a tendency to perform a LN biopsy on mRCC patients with a worse prognosis — choosing clinically suspicious LNs to resect intraoperatively, which would lead to identification of more advanced locoregional disease. While a validated model by Heng et al, the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model, now exists to stratify patients based on risk, SEER does not provide sufficient laboratory or performance data to compare patients based on risk groups.[13] A second explanation may be related to coding of the cause of death. Mortality incurred from the removal of LNs, either directly or indirectly due to postoperative morbidity, could be attributed to the cancer instead of iatrogenic etiology because of the fact the surgery was performed for mRCC. Our sensitivity analysis showed higher threshold definitions for LND, such as ≥3 or ≥8 LNs removed, were not significantly associated with OS, CSS, or other-cause mortality. The data support the notion that LND may add minimal morbidity and be unlikely to translate into a significant detriment to survival among patients with mRCC. The findings are similar to those from EORTC 30881, although the trial was limited to patients without nodal or distant metastatic disease at presentation.[8]

Before the widespread implementation of systemic therapies, mortality for patients with mRCC was fairly static. The development of novel categories of systemic and targeted treatments for mRCC has led to improved cancer survival in recent years (2010 vs. 1990: HR 0.71 [0.60–0.83]; p<0.001). However, there is significant variation in prognosis leading to a need for prognostic models to help advise patients and determine the best options for therapy. Although LND does not appear to play a therapeutic role in the treatment of mRCC, the number of positive nodes found during surgery does provide additional prognostic survival data that could aid in risk-stratification. The International Metastatic Renal-Cell Carcinoma Database Consortium prognostic

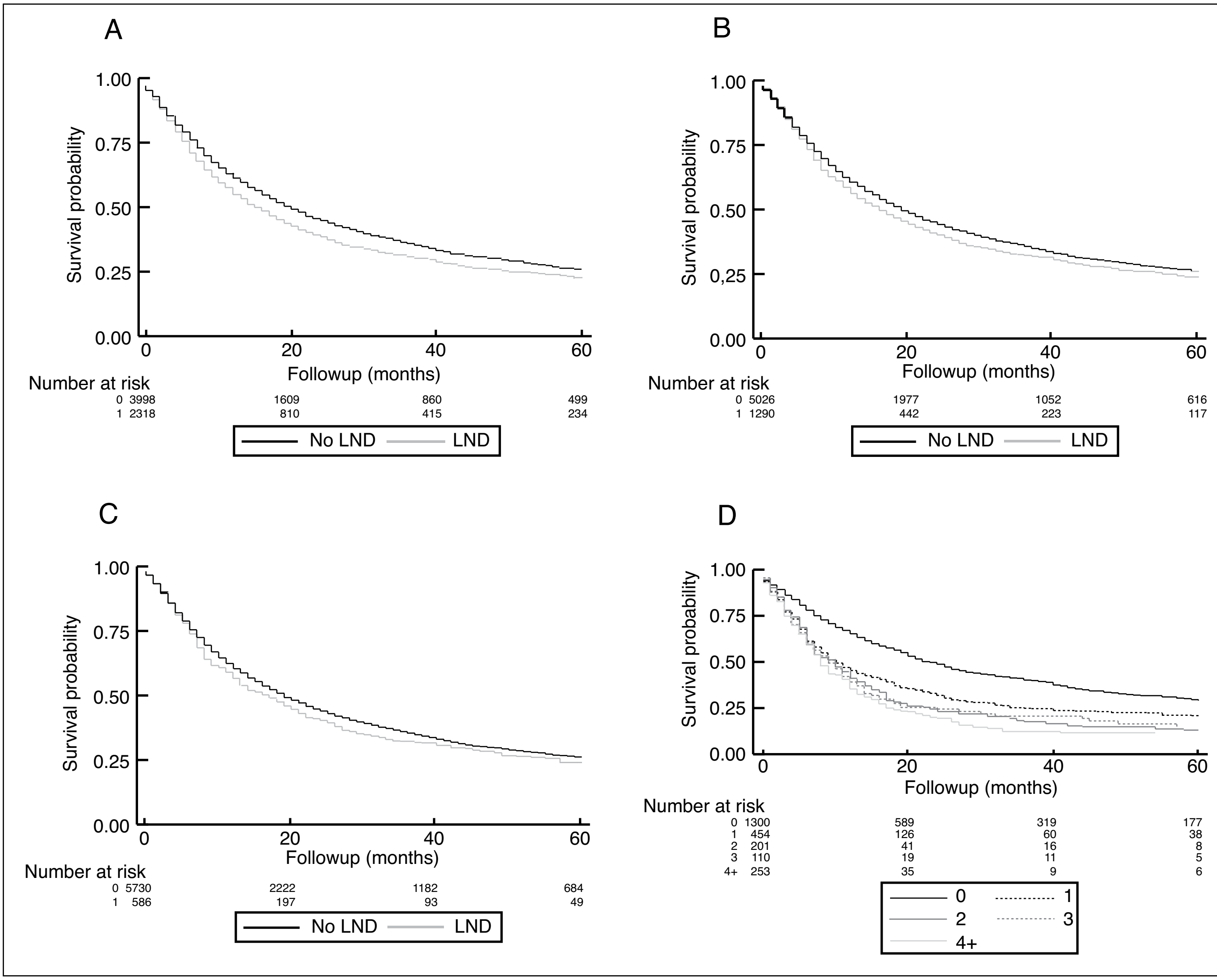

Fig. 2. Kaplan-Meier survival curves of cancer-specific survival for metastatic renal cell carcinoma patients stratified by the performance of lymphadenectomy (LND), defined as ***(A)*** ≥1 lymph node removed; ***(B)*** ≥3 lymph nodes removed; and ***(C)*** ≥8 lymph nodes removed among patients receiving cytoreductive nephrectomy, and by the ***(D)*** number of positive lymph nodes found for patients receiving lymphadenectomy, Surveillance, Epidemiology, and End Results registry 1988–2011.

model includes risk factors that can be determined in a non-invasive fashion, but in a clinical trial setting, the number of positive LNs could also be useful to determine differential effects of treatment based on LN burden. Many authors note lack of evidence in performing LND in mRCC, but some suggest it could play a role for tyrosine kinase inhibitors, among other new systemic therapies.[14] Therefore, level one evidence on the effect of LND on survival in mRCC could be readily obtained by randomizing the practice of LND into randomized control trials already planning to evaluate new systemic agents.[15] Until then, if LND can be performed without increasing morbidity, select patients may benefit from this additional surgical extirpation.

The primary limitations of the present study, besides those already mentioned above, include its retrospective nature and lack of data on comorbidity and metastatic burden. Furthermore, data on the use of systemic agents is not available through SEER, allowing a finer level of association between improved survival over time and new treatments. However, the association of LND with survival was stable across a number of multivariable subset analyses, including time, and important sensitivity analyses were performed with different threshold definitions for LND. Despite the limitations, the results use a competing-risks analysis to demonstrate mortality trends for mRCC patients over a broad number of years and argue for a prognostic, rather than therapeutic role of LND in the management of mRCC.

Conclusion

In summary, mRCC continues to carry a poor prognosis, but current treatment paradigms invoking an integration of surgical and systemic therapies have led to modest improvements in OS and CSS in recent years. Using a competing-risks approach, LND was found to play a prognostic rather than therapeutic role in the management of mRCC. The performance of LND should be limited based on clinical judgment and better incorporated into randomized trials of new systemic therapies to identify scenarios where implementation may improve survival.

Competing interests: Dr. Pierorazio is an unpaid member of the kidney cancer advisory board for Myriad Genetics. The remaining authors report no competing personal or financial interests.

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Appendix A. Demographics, tumour characteristics, and intervention data for patients with metastatic renal cell carcinoma, SEER 1988–2011

	All mRCC		Cytoreductive nephrectomy	
	Value	% or SD	Value	% or SD
Overall	15060	100.0	6316	100.0
Age (SD)				
Mean	62.9	12.1	60.16	11.2
<45	900	6.0	485	7.7
45–54	2851	18.9	1489	23.6
55–64	4524	30.0	2095	33.2
65–74	4009	26.6	1570	24.9
75–84	2297	15.3	634	10.0
85+	479	3.2	43	0.7
Sex				
Male	10133	67.3	4331	68.6
Race				
White	10818	71.8	4665	73.9
Black	1385	9.2	457	7.2
Hispanic	1889	12.5	785	12.4
Other	968	6.4	409	6.5
Lymph nodes sampled	2318	15.4	2318	36.7
Cytoreductive nephrectomy	6316	41.9	6316	100.0
Radiation				
None	10055	66.8	4576	72.5
Therapy	4855	32.2	1676	26.5
Unknown	150	1.0	64	1.0
Tumour size (cm)				
≤4	1232	8.2	445	7.0
>4 to ≤7	3170	21.0	1413	22.4
>7 to ≤10	3862	25.6	2027	32.1
>10 to ≤20	3601	23.9	2029	32.1
>20	165	1.1	98	1.6
Unknown	3029	20.1	304	4.8
Fuhrman grade				
1	331	2.2	152	2.4
2	1611	10.7	1126	17.8
3	3105	20.6	2186	34.6
4	1626	10.8	1345	21.3
Unknown	8387	55.7	1507	23.9

mRCC: metastatic renal cell carcinoma; SEER: Surveillance, Epidemiology, and End Results registry; SD: standard deviation.

Appendix B. Number of lymph nodes removed at lymphadenectomy and number of positive lymph nodes, SEER 1988–2011

	Value	%
Cohort	15060	100.0
# LNs sampled		
0	12742	84.6
1	689	4.6
2	339	2.3
3	222	1.5
4	165	1.1
5–10	490	3.3
11–25	329	2.2
>25	84	0.6
Mean (SD)		
Overall	0.9	3.8
If LN removed	6.2	7.9
Any LN removed	2318	15.4
Any positive node(s)	1018	6.8
# LNs positive		
0	1300	8.6
1	454	3.0
2	201	1.3
3	110	0.7
4	60	0.4
5–10	138	0.9
>10	55	0.4
Mean (SD)	1.4	3.3
If any positive LN	3.3	4.3
% positive nodes	32.4%	-

LN: lymph node; SD: standard deviation; SEER: Surveillance, Epidemiology, and End Results registry.

Appendix C. Cox proportional hazards competing risks regression models among patients undergoing lymphadenectomy for associations with cancer-specific survival, SEER 1988–2011

		95% CI		
	HR[a]	Low	High	p value
Positive LNs				
0	REF	-	-	-
1	1.56	1.37	1.77	<0.001
2	1.96	1.66	2.33	<0.001
3	1.78	1.41	2.25	<0.001
4+	2.30	1.96	2.7	<0.001
Age				
<45	REF	-	-	-
45–54	0.92	0.77	1.11	0.40
55–64	0.96	0.81	1.15	0.69
65–74	1.02	0.84	1.23	0.84
75–84	1.26	0.99	1.60	0.06
85+	1.28	0.65	2.52	0.48
Sex				
Female	1.10	0.99	1.23	0.06
Race				
White	REF	-	-	-
Black	1.23	1.02	1.48	0.03
Hispanic	0.93	0.80	1.07	0.30
Other	0.86	0.70	1.06	0.16
Radiation				
None	REF	-	-	-
Therapy	1.36	1.21	1.53	<0.001
Unknown	1.55	0.98	2.45	0.06
Tumour size				
≤4	REF	-	-	-
>4 to ≤7	0.92	0.72	1.19	0.54
>7 to ≤10	1.09	0.86	1.38	0.48
>10 to ≤20	1.12	0.89	1.42	0.34
>20	1.50	1.02	2.20	0.04
Unknown	0.98	0.65	1.49	0.94

[a]Multivariable Cox model adjusted for year (not shown), cytoreductive nephrectomy, age, sex, race, radiation, and tumour size. CI: confidence interval; CN: cytoreductive nephrectomy HR: hazard ratio; LN: lymph node. SEER: Surveillance, Epidemiology, and End Results registry.