



Original Article

# Survival benefit with extended lymphadenectomy for advanced renal malignancy: A population-based analysis

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## KEYWORDS

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**Abstract** *Objective:* We used population-based data to examine the possible benefit of extended lymphadenectomy for patients with renal malignancy in the setting of more advanced disease.

*Methods:* The Surveillance, Epidemiology, and End Results (SEER) database was utilized to identify non-metastatic, T3-T4 renal cancer patients from 2004–2015 treated with removal of  $\geq 1$  lymph node at the time of nephrectomy. Non-parametric bivariate statistics were used to assess associations between covariates of interest and extended lymphadenectomy ( $\geq 10$  lymph nodes removed). Cancer-specific survival (CSS) and overall survival (OS) benefit was evaluated using Kaplan–Meier analysis.

*Results:* Of the 4397 patients identified, 816 (18.6%) underwent extended lymphadenectomy. For patients with T3a disease, 5-year CSS and OS benefit with extended lymphadenectomy did not reach statistical significance (CSS: hazard ratio [HR] 0.98, 95% confidence interval [CI] 0.77–1.24; OS: HR 0.96, 95% CI 0.77–1.20). Conversely, for those with T3b-T3c disease, extended lymphadenectomy led to statistically significant improvements in both 5-year CSS and OS compared to non-extended lymphadenectomy (CSS: HR 0.78, 95% CI 0.61–0.99; OS: HR 0.72, 95% CI 0.58–0.90). Finally, for those with T4 disease, use of extended lymphadenectomy had OS benefit after 5 years (OS: HR 0.51, HR 0.29–0.90,  $p = 0.02$ ).

*Conclusion:* Based on population-level data, extended lymphadenectomy was associated with improved survival in select patients with advanced renal malignancy treated with surgical nephrectomy. Understanding the basis of these real-world findings in the face of conflicting randomized trial results will be key, moving forward.

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## 1. Introduction

For patients undergoing oncologic surgery, lymph node dissection (LND) provides important staging information that allows for a more accurate assessment of prognosis. For instance, patients with node-positive kidney cancer have a markedly lower 5-year relative survival (66.7%) compared to those with localized disease (92.6%) [1]. For patients with certain cancers, receipt of an extended lymphadenectomy (eLND) may also be associated with a survival benefit (e.g., esophageal cancer) [2]. In renal malignancy, the potential survival benefit for eLND has not been clearly demonstrated to date. At a population-level, results from analyses using Surveillance, Epidemiology, and End Results (SEER) cancer registry data before 2009 were conflicting [3–6]. Another large institutional study of kidney cancer patients from 1990–2010 at Mayo Clinic did not demonstrate any benefit from lymphadenectomy—extended or otherwise—for patients with non-metastatic kidney cancer [7].

A number of targeted and immune-based systemic therapies are now options for advanced kidney cancer patients [8–11]. Extended lymphadenectomy could identify more candidates for these novel therapies with earlier and more frequent use potentially impacting survival at a population level. Moreover, diagnosis of advanced disease would allow for enhanced patient prognostication, and potentially allow for inclusion into a number of clinical trials. Conversely, delaying identification of node-positive disease by not performing an extensive node-dissection may delay timely administration of beneficial targeted therapies. However, the potential benefits of eLND for advanced renal malignancy in the targeted therapy era have not completely been evaluated.

We hypothesize that there is a survival benefit with eLND for patients with locally advanced renal tumors diagnosed after 2004, which is a time frame in which new targeted therapy was first used in routine clinical practice. To test this, we utilized SEER data to identify patients treated with nephrectomy and LND from 2004–2014, and examined whether removal of  $\geq 10$  lymph nodes was associated with improved cancer-specific survival (CSS) and overall survival (OS). If a survival benefit was demonstrated, this work would represent an important initial step to further characterizing which patients benefit most from this approach and what extent of lymphadenectomy is required to gain such survival advantage.

## 2. Materials and methods

### 2.1. Dataset

We utilized SEER cancer registry data to identify our cohort of interest. This database, managed by the National Cancer

Institute, captures all new cancer diagnoses within specific geographically-defined registries. The database includes detailed information on patient demographics, tumor characteristics, treatments received and outcomes, including CSS and OS.

### 2.2. Cohort

The process used to generate our analytic cohort is shown in Fig. 1. We identified patients with kidney cancer, based on ICD-O-3 code C64.9. We limited the cohort to patients with clear cell, papillary, sarcomatoid, and chromophobe carcinomas. We excluded patients with prior malignancies, lack of histologic diagnosis and those with a diagnosis by death certificate/autopsy. We also limited the cohort to adults over 18 years of age diagnosed from 2004–2015 and to those who received surgical treatment with either radical or partial nephrectomy. Regarding cancer staging, we restricted the cohort to those with non-metastatic (M0/Mx), T3-T4 tumors based on American Joint Committee on Cancer (AJCC) criteria. Finally, we limited our analysis to patients who had  $\geq 1$  lymph node removed during nephrectomy.

### 2.3. Primary exposure and outcomes

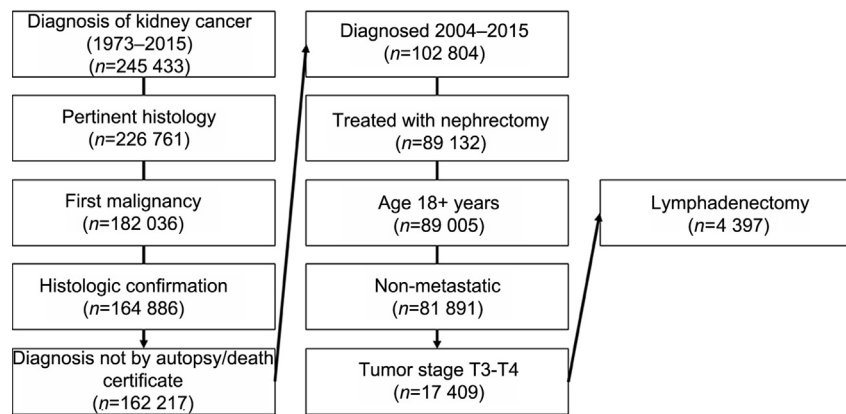
Our primary exposure of interest was eLND, defined by the removal of  $\geq 10$  lymph nodes at the time of nephrectomy. Our primary outcomes were CSS and OS, as captured by the SEER database.

### 2.4. Additional covariates of interest

We also considered potentially pertinent variables captured by SEER that would be important to adjust for as possible confounders in our analysis of eLND performance. Patient demographics included age at diagnosis, sex, race/ethnicity (Non-Hispanic Caucasian, Spanish/Hispanic/Latino, African American, Other) and marital status (married, not married, unknown). Cancer characteristics included year of diagnosis (categorized as 2004–2006, 2007–2010, 2011–2014), tumor size (in centimeters), tumor stage (T3a, T3b-T3c, T4) and histology (clear cell, papillary, other). Treatment factors included type of surgery (radical versus partial nephrectomy) and lymph node count.

### 2.5. Statistical analysis

We used non-parametric bivariate statistics to evaluate associations between our covariates of interest and receipt of eLND. Kaplan–Meier survival curves were generated for all available covariates of interest with a potential impact on CSS and OS, *a priori*. These curves were statistically



**Figure 1** Cohort generation. Lymphadenectomy cohort generation using Surveillance, Epidemiology, and End Results data through application of select exclusion criteria is shown. Extended lymphadenectomy patients were further selected from this lymphadenectomy cohort based on the patient’s receipt of 10 or more lymph nodes removed at the time of surgery.

evaluated with non-parametric log rank tests. For continuous covariates, bivariate Cox proportional hazards models were used to test for statistical significance.

For CSS, multivariable competing-risks survival models were constructed including all covariates with  $p < 0.10$  on prior log rank or bivariate Cox proportional hazard testing. We considered interactions between (a) tumor stage and eLND and (b) pathologic nodal stage and eLND based on the theory that eLND benefits would vary based on presence of higher-risk disease, and kept interactions with  $p < 0.20$ . We planned to stratify our analysis across levels of any significant interactions. As we found a significant interaction between tumor stage and eLND, our final models were stratified between T3a, T3b-T3c and T4 tumors. To confirm that models met the proportionality assumption, we added time-dependent covariates using the *tvc* and *tevp* functions in STATA. If time-dependent covariates were statistically significant, they were kept in the model and reported estimates were based on a final extended competing-risks survival model. Similar techniques were used for OS, but with Cox proportional hazards models instead of competing-risk models. Patients missing data from  $\geq 1$  covariates were excluded from regression models. Sensitivity analyses were carried out using six nodes as a cutoff for eLND.

Statistical significance was considered at  $p < 0.05$  for final estimates, and all analyses were two-sided and performed using STATA/SE v14.1 (STATA Corp, College Station, TX, USA). As data were publically available and de-identified, this analysis was deemed exempt from IRB oversight.

### 3. Results

Our analytic cohort consisted of 4397 kidney cancer patients who underwent nephrectomy with  $\geq 1$  lymph nodes removed at surgery (Table 1). Of these, 816 (18.6%) underwent eLND with  $\geq 10$  lymph nodes removed. Patients treated with eLND were younger ( $p < 0.001$ ), had larger tumors ( $p < 0.001$ ) and were diagnosed more recently ( $p < 0.001$ ). Patients with eLND had an average of 15.7 lymph nodes removed versus 3.2 lymph nodes in non-eLND patients ( $p < 0.001$ ).

For the cohort, median follow-up was 30 months (interquartile range [IQR] 12–65 months). Among 3385 cases with complete data, 1101 (32.5%) died from cancer, 242 (7.1%) died from other causes and 2042 (60.3%) were alive and censored at the end of follow-up. Among 2024 patients with T3a tumors, 474 (23.4%) died from cancer, 129 (6.4%) died from other causes and 1421 (70.2%) were censored. Among 1138 patients with T3b-T3c tumors, 501 (44.0%) died from cancer, 101 (8.9%) died from other causes and 536 (47.1%) were censored. Among 223 patients with T4 tumors, 126 (56.5%) died from cancer, 12 (5.4%) died from other causes and 85 (38.1%) were alive at the end of follow-up. Kaplan–Meier curves displaying OS by tumor stage are shown in Fig. 2 (see Table 1).

#### 3.1. CSS

Regarding CSS, we adjusted for age at diagnosis (continuous and centered at age 60 years), marital status, tumor size, tumor grade and nodal stage as time-dependent covariates. We noted a significant interaction between tumor stage and eLND in our competing-risks and Cox regression models, so models were stratified by tumor stage. There was no significant difference in survival among patients with T3a tumors based on eLND (5-year survival: 69.0% with eLND vs. 70.5% without eLND, HR 0.98, 95% CI 0.77–1.24) (Table 2). We did observe a significant CSS advantage among patients with T3b-T3c tumors undergoing eLND (5-year survival: 61.4% with eLND vs. 55.2% without eLND, HR 0.78, 95% CI 0.61–0.99). Similar findings were seen among patients with T4 tumors, but did not reach statistical significance (5-year survival: 50.0% with eLND vs. 33.1% without eLND, HR 0.58, 95% CI 0.32–1.06).

#### 3.2. OS

The final regression models assessing OS were stratified by tumor stage (T3a, T3b-T3c and T4) and adjusted for age at diagnosis (continuous and centered at 60 years), tumor size, race/ethnicity, marital status, tumor grade (low grade vs. high grade; time-dependent) and nodal stage (positive vs. negative; time-dependent). We had similar findings

**Table 1** Characteristics of cohort based on performance of extended lymphadenectomy.

Characteristics	Extended lymphadenectomy (n=816)	No extended lymphadenectomy (n=3581)	p-Value
Patient demographics			
Age at diagnosis (mean±SD, year)	58.1±11.3	60.7±11.9	<0.001
Male sex, n (%)	556 (68.1)	2464 (68.8)	0.709
Race/ethnicity <sup>a</sup> , n (%)			0.225
Non-hispanic Caucasian	558 (68.9)	2484 (69.5)	
Hispanic/Latino	138 (17.0)	527 (14.8)	
African American	56 (6.9)	304 (8.5)	
Other	58 (7.2)	257 (7.2)	
Marital status, n (%)			0.060
Married	514 (63.0)	2229 (62.3)	
Not married	261 (32.0)	1229 (34.3)	
Unknown/missing	41 (5.0)	123 (3.4)	
Cancer characteristics			
Year of diagnosis, n (%)			<0.001
2004–2006	134 (16.4)	810 (22.6)	
2007–2010	230 (28.2)	1206 (33.7)	
2011–2014	452 (55.4)	1565 (43.7)	
Tumor size (mean±SD, cm) <sup>b</sup>	10.2±4.2	9.4±4.0	<0.001
Tumor stage <sup>c</sup> , n (%)			0.689
T3a	447 (59.1)	1920 (59.5)	
T3b-T3c	260 (34.4)	1070 (33.2)	
T4	50 (6.6)	237 (7.3)	
Fuhrman grade 3–4 <sup>d</sup> , n (%)	526 (74.0)	2279 (72.1)	0.322
Histology, n (%)			0.024
Clear cell	691 (84.7)	3064 (85.6)	
Papillary	45 (5.5)	259 (7.2)	
Other	256 (7.1)	80 (9.8)	
Clinical node-positive, n (%)	774 (21.6)	180 (22.1)	0.781
Treatment characteristics			
Radical nephrectomy, n (%)	801 (98.2)	3465 (96.8)	0.034
Lymph node count (mean±SD) <sup>e</sup>	15.7 (5.0)	3.2 (2.4)	<0.001

SD, standard deviation.

<sup>a</sup> Missing in 15 cases.<sup>b</sup> Missing in 71 cases.<sup>c</sup> Missing in 413 cases.<sup>d</sup> Missing in 527 cases.<sup>e</sup> Missing in 257 cases.

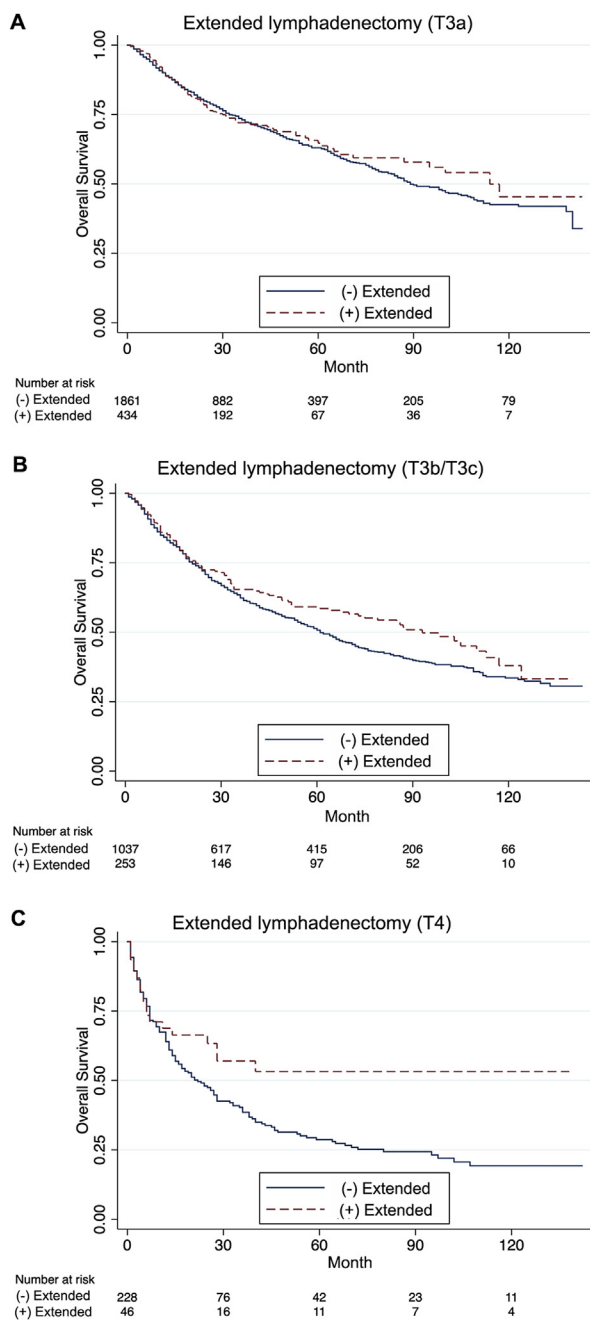
regarding OS; no OS benefit was noted among patients with T3a tumors (HR 0.96, 95% CI 0.77–1.20), but was seen among those with T3b-T3c tumors (HR 0.72, 95% CI 0.58–0.90). We also noted a OS benefit for the smaller subgroup of patients with T4 tumors (HR 0.51, 95% CI 0.29–0.90). Sensitivity analyses using a cutoff of six lymph nodes did not demonstrate any CSS or OS advantage (data not shown).

#### 4. Discussion

Our population-based analysis of contemporary eLND use in patients undergoing nephrectomy has three major findings. First, the most significant survival benefit associated with eLND was seen in patients with venous involvement of their disease (e.g., T3b/T3c tumors). Second, eLND did not demonstrate any observable survival benefit for patients

with T3a tumors. Finally, the small subgroup of patients with T4 disease may also derive a survival benefit from eLND.

To date, a number of studies have assessed the performance and extent of lymphadenectomy for renal malignancy. Although guideline statements endorse lymphadenectomy in the setting of preoperative or intraoperative suspicion of abnormal loco-regional lymph nodes, this ancillary procedure is not recommended in the setting of low risk disease or without grossly positive nodal involvement [12]. The only randomized trial (i.e., EORTC 30881) showed no survival benefit with lymphadenectomy for those with renal cell carcinoma [13]. However, this study was criticized for the large proportion of the study population with low risk (T1-T2) tumors, which may mask any benefit for higher risk patients [6]. In a small institutional study, Pantuck et al. [14] noted statistically significant survival benefit in those undergoing lymphadenectomy



**Figure 2** Overall survival for kidney cancer patients with and without extended lymphadenectomy. Kaplan-Meier analysis showing overall survival data for patients with and without receipt of extended lymphadenectomy by tumor stage (Figure 2A: T3a disease; Figure 2B: T3b/T3c disease; Figure 2C: T4 disease). The Y-axis shows overall survival probability. The X-axis shows time (in months) from receipt of surgery with lymphadenectomy or extended lymphadenectomy. The dashed graph line represents patients who underwent extended lymphadenectomy in each analysis. The solid graph line represents patients who underwent non-extended lymphadenectomy in each analysis. Statistically significant overall survival benefit was demonstrated for those undergoing extended lymphadenectomy in the setting of T3b/T3c and T4 disease (Figure 2B and 2C), but not T3a disease (Figure 2A) compared to performance of less extensive lymphadenectomy.

during cytoreductive nephrectomy for those with known nodal disease, compared to those not treated with LND. Schafhauser et al. [15] performed a retrospective analysis of 1035 RCC patients and noted that long-term survival was improved with systematic lymphadenectomy (57%) versus targeted lymphadenectomy (50%) and no lymphadenectomy (44%) performed, despite having more advanced overall tumor stage in this first group. Capitanio et al. [16] studied 44 patients with T4 disease and showed improved CSS with increasing number of lymph node removal (with each lymph node removed providing an 8% decrease in the risk of mortality whereas presence of each positive lymph node was associated with a 16% increase in mortality in these patients). This same group examined a large cohort of kidney cancer patients to show that certain subgroups benefited most from more extensive dissections (e.g., larger tumor size, sarcomatoid histology) [17,18]. Nini et al. [19] assessed anatomic locations of lymph node spread in 415 RCC patients treated with radical nephrectomy and eLND (median LN removed 14, IQR 9–19), of which 23% ( $n=95$ ) were pN1 status. Despite supporting a high inter-patient variability for advanced RCC nodal disease dissemination patterns, the presence of interaortocaval lymph node involvement was found to be an independent predictor of cancer specific mortality (HR 2.3, 95% CI, 1.3–3.9,  $p<0.1$ ), thus representing a potential anatomic target for inclusion in extended lymph node dissection templates.

Recent developments in the understanding of cancer dissemination pathophysiology may provide insight into the detected survival benefit with eLND for those with more advanced renal malignancy within our analysis. A 2018 study by Pereira et al. [20] examined the spread of malignant cells (expressing a photoconvertible protein, Dendra2) that were implanted within murine lymph node tissue. They ultimately discovered that a portion of these photo-detectable Dendra2 tumor cells were found to migrate directly into nodal blood vessels, thus facilitating systemic hematogenous dissemination and contributing to deposition within distant host organ tissue. Similarly, Brown et al. [21] analyzed the migration of cancer cells after infusing them into the afferent lymphatic vessels of host mice, finding evidence of tumor cell infiltration and invasion within local nodal vasculature contributing to distant metastatic lung spread without passage through expected lymphatic channels, such as the thoracic duct. Although additional work is needed to better elucidate such dissemination patterns in human models, the concept of direct hematogenous dissemination from local lymph node tissue (as an alternative route of tumor cell propagation to that of traditional lymphogenous spread to sentinel nodal targets) remains an important area of future consideration in our developing understanding of advanced tumor pathophysiology. In more advanced forms of renal malignancy, presence of even microscopic malignant nodal involvement may provide a key mechanism for distant metastatic disease seeding with implications on a patient's future survival and disease progression. Thus identifying appropriate candidates for eLND at the time of renal extirpative surgery remains an important consideration in these patient populations.

In contrast to these studies that endorse the use of lymphadenectomy, Joslyn et al. [3] analyzed the SEER



**Table 2** Cancer-specific and overall survival from extended lymphadenectomy.

	n	5-year survival (% , 95% CI)		HR (95% CI)	p-Value
		Extended lymphadenectomy	No extended lymphadenectomy		
Cancer-specific survival <sup>a</sup>					
T3a	2295	69.0 (63.5–73.9)	70.5 (68.0–72.9)	0.98 (0.77–1.24)	0.87
T3b-T3c	1290	61.4 (54.6–67.4)	55.2 (52.0–58.3)	0.78 (0.61–0.99)	0.04
T4	274	50.0 (33.8–64.2)	33.1 (26.9–39.6)	0.58 (0.32–1.06)	0.08
Overall survival <sup>b</sup>					
T3a	2295	66.3 (60.7–71.3)	64.9 (62.2–67.3)	0.96 (0.77–1.20)	0.72
T3b-T3c	1290	59.2 (52.4–65.3)	51.1 (48.0–54.3)	0.72 (0.58–0.90)	<0.01
T4	274	50.0 (33.8–64.2)	30.1 (24.0–36.3)	0.51 (0.29–0.90)	0.02

CI, confidence interval; HR, hazard ratio.

<sup>a</sup> Competing-risks regression model stratified by tumor stage, adjusted for age at diagnosis, tumor size, marital status, tumor grade and pathologic nodal stage.

<sup>b</sup> Cox extended regression model stratified by tumor stage, adjusted for age at diagnosis, race/ethnicity, marital status, tumor grade and pathologic nodal stage.

database from 1983–1998 showing no clear statistical survival benefit with performing lymphadenectomy (or extended variations) in patients with RCC. More recently, Whitson et al. [5] analyzed nearly 11 000 patients using SEER from 1998–2006. They concluded that eLND provides a significant survival benefit for those with node positive disease. However, these results have been scrutinized for bias due to multiple imputation (replacement of missing data based on plausible input values) to derive tumor grade for a large portion of the study cohort. Sun et al. [6] recapitulated Whitson's study and showed that the survival benefit associated with lymphadenectomy lost statistical significance in all groups except for that in which imputation was utilized to artificially complete tumor grade data points, illustrating the impact that the method of data handling can have on determining survival benefit and outcome variability. A more recent study by Marchioni et al. [22] concluded that the number of lymph nodes removed did not impact cancer specific mortality in a cohort of nonmetastatic T2-T3 RCC patients, despite finding that the number of positive lymph nodes present did correlate with increased cancer specific mortality with T3 disease and that the number of nodes removed was associated with reduced cancer specific mortality specifically for those with positive nodal disease. Similarly, Gershman et al. [23] analyzed a multi-institutional cohort of 2722 M0 RCC patients treated by radical nephrectomy with or without LND (of which 171 patients had pN1 disease) showing no mortality benefit or reduction of distant metastasis with LND performance, regardless of extent. This included patients who showed clinical radiographic evidence of nodal involvement on preoperative imaging. Finally, a recent multicenter cohort study of nearly 1978 kidney cancer patients with tumor thrombus showed no detectable survival benefit with more extensive lymph node dissections among patients treated with nephrectomy, tumor thrombectomy, and lymphadenectomy [24].

Despite these previously conflicting studies, there are a number of strengths to this study that support the validity of our findings. First, a modern SEER cohort focusing on RCC patients from 2004–2015 was utilized, representing an era when novel targeted therapies were in use. Early

results from randomized trials (e.g., S-TRAC, ASSURE) are conflicting regarding the benefits for adjuvant use of targeted therapies after nephrectomy [25,26]. However, there is some signal that adjuvant use of sunitinib among the highest-risk patients prolongs disease-free survival [26]. We await more mature results to evaluate their impact on survival. Second, given the concerns raised regarding the use of multiple imputation with previous SEER analyses, we excluded patients with unknown tumor stage from our analysis [6]. Thus, all patients with a given disease stage in our analytic cohort had this information based on reported, as opposed to derived, input values in an effort to ensure consistency and accuracy with our data handling. Finally, our use of a competing-risk survival analysis accounted for death from other causes as a competing event for CSS.

However, our findings must be viewed in context of the inherent limitations of our analysis. First, due to its non-randomized, retrospective nature, it is difficult to determine causal benefit of eLND versus more limited LND in the setting of advanced RCC management. Moving forward, randomized trials can help determine the benefits of eLND for kidney cancer patients, particularly in the setting of targeted therapy modalities. A second limitation lies in the relatively small representation of patients with certain disease staging (such as those with T4 disease) within our study. Third, this study did not allow assessment of specific templates for LND or surgeon intent. Further work will be needed to better delineate specific nodal targets for eLND to optimize capture of extrarenal tumor involvement. As a possible adjunctive measure to aid in this determination, Sherif et al. [27] assessed the feasibility of sentinel lymph node mapping for renal malignancy, finding improved disease detection although no correlation to survival benefit. Regardless, improving the selection of RCC patients who are most appropriate for varying extents of LND should remain a primary consideration for future investigation. Finally, as with any registry-based retrospective study, we cannot account for unmeasured confounders such as patient performance status, symptomatic disease or receipt of adjuvant therapy that may have impacted our outcomes of interest.

Despite these limitations, our results endorse the consideration of eLND for advanced kidney cancer patients undergoing nephrectomy in the targeted therapy era. As previously mentioned, future work will have to help identify the best candidates for this approach, as well as the ideal surgical techniques that are applied. As we move toward increasing utilization of robotic-assisted techniques for advanced kidney cancer surgery, there will be further need to assess the impact of these approaches on performance of lymphadenectomy [28,29]. Additionally, multi-center registries and linked population level data (e.g., SEER-Medicare) may provide the necessary resources to test the interaction between LND and response to adjuvant targeted and immune therapies.

## 5. Conclusion

Contemporary population-based data demonstrate a survival benefit associated with eLND for select patients with advanced RCC treated with nephrectomy. Use of eLND at the time of extirpative surgery for patients with T3-T4 tumors remains an important adjunctive treatment consideration, particularly in the setting of novel systemic targeted and immune-based therapies.

## Author contributions

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*Critical Revision of the Manuscript:* Dean Laganosky, Christopher P. Filson, Viraj A. Master.

## Conflicts of interest

The authors declare no conflict of interest.

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