Dissecting the role of lymphadenectomy in the management of renal cell carcinoma: past, present, and future

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ABSTRACT

Lymph node involvement in renal cell carcinoma (RCC) portends a poor prognosis. However, the role of lymph node dissection (LND) at the time of tumor resection is not fully understood. Conflicting data have been published regarding the survival implications of LND during RCC surgery, and the optimal patient population for which LND might be beneficial has yet to be identified. Based on recent data characterizing the outcomes of node-positive RCC, some have advocated for revising the current staging guidelines to better reflect these findings. Given the paucity of high-quality evidence supporting or refuting the routine use of LND in RCC, further research is needed to shed light on this important topic. There are a number of ongoing clinical trials evaluating the role of perioperative (neoadjuvant and adjuvant) systemic therapy, which include patients with node-positive RCC, and will serve to guide changes in treatment practices for this patient population moving forward.

KEYWORDS: • Renal Cell Carcinoma • lymphadenectomy • lymph node dissection • kidney cancer • survival •

INTRODUCTION

Renal cell carcinoma (RCC) is one of the most common solid organ malignancies, with over 74,000 new cases and 15,000 deaths anticipated in the United States in 2020 alone[1]. Staging of RCC allows clinicians to characterize disease based on similar survival outcomes, which further aids in prognostication, selection of optimal treatment modalities, and clinical trial eligibility. The criteria for RCC staging as outlined by the American Joint Committee on Cancer (AJCC) are highlighted in Table 1[2].

For many urologic malignancies, concurrent lymph node dissection (LND) at the time of primary tumor resection offers essential treatment and diagnostic value. Removing malignant lymph nodes may significantly reduce a patient's overall tumor burden. Furthermore, detection of positive lymph nodes critically informs the probability of disease risk stratification and the requirement for additional treatments. For example, immediate administration of androgen deprivation therapy for node-positive prostate cancer, which was detected by pelvic LND, has demonstrated clinically significant survival benefits[3]. Patients with pathologically node-positive bladder cancer after pelvic LND achieve a greater survival benefit from adjuvant chemotherapy compared to node-negative patients[4-6]. Similarly, adjuvant chemotherapy has been shown to lower recurrence rates among nonseminomatous germ cell testis cancer patients who have positive nodal disease after retroperitoneal LND[7].

However, existing literature remains unclear regarding the clinical utility of LND for RCC. The American Urologic Association (AUA) and the National Comprehensive Cancer Network (NCCN) have published contemporary guidelines, but these recommendations are not supported by strong evidence. The AUA states that LND should be performed only when there is suspicion of lymphadenopathy, as LND could potentially aid in staging[8], and NCCN guidelines recommend that LND should only be performed when there are palpable or enlarged lymph nodes on preoperative imaging tests[9]. Still, the supporting literature has not identified which patients derive the greatest benefit, if any, from LND. This uncertainty is exacerbated by unpredictable lymphatic drainage patterns of the kidneys, as well as the fact that there is no universal template for LND during kidney cancer surgery[10, 11].

While retrospective studies have shown a survival benefit of LND for RCC[12, 13], the only randomized clinical trial to have studied LND for RCC, EORTC 30881, showed no oncologic benefit of LND with regards to overall survival, time to progression, or progression-free survival[14]. In this review, we consider lymph node positivity in RCC as it relates to staging, outcomes, patient selection for lymph node dissection, and the role of systemic therapy.

Patient Selection for Lymph Node Dissection

Given the uncertainty behind the benefit of LND in treating RCC, fewer urologists have been performing LND over the past decade[15, 16]. In an analysis of 37,279 patients who underwent radical nephrectomy for RCC between 1988 and 2015 selected from the Surveillance, Epidemiology, and End Results (SEER) registry, Kates et al. identified a 63% reduction in LND rates among localized tumors[16]. In 2005, LND rates in the US

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Stage	8E AJCC[2]	Proposed staging		
		Shao *et al.*[30]	Yu *et al.*[29]	Patel *et al.*[35]
I	T1N0M0	1a: T1N0M0 1b: T2N0M0	T1N0M0	T1N0M0
II	T2N0M0	T3N0M0	T2N0M0	T2N0M0
III	T1-2N1M0, T3N$_{any}$M0	T1-3N1M0, T4N0M0	T3N0M0	T3N0M0
IV	T4N$_{any}$M0, T$_{any}$N$_{any}$M1	T4N1M0, T$_{any}$N$_{any}$M1	T1-3N1M0, T4N$_{any}$M0, T$_{any}$N$_{any}$M1	IVa: T3N1M0, T3N0M1, T4N0M0 IVb: T4N1M0, T4N0M1, T4N1M1

TABLE 1 | Comparison of AJCC staging groups to other proposed classification schemes. Modified, with permission, from Patel *et al*[35].

had fallen below 5% for all RCC surgeries[17]. This decrease in LND rate can, at least partially, be attributed to the clinical stage migration toward early-stage RCC (i.e. patients who are unlikely to receive LND), which has followed advancements in imaging capabilities since the 1980s[18].

In a retrospective analysis of 110,963 patients with non-metastatic RCC from the National Cancer Database (NCDB), Radadia et al. reported that only 11,867 (11%) had LND at time of surgery[19]. Those patients undergoing LND were more likely to have clinically node-positive disease (OR: 18.68, 95% CI: 16.62 – 21.00, p<0.01) and less likely to undergo minimally invasive / robotic surgery (OR: 0.73, 95% CI: 0.64 – 0.77, p<0.01)[19]. In this same cohort, however, only 14.8% of patients receiving LND had clinically node-positive disease, suggesting a large majority of patients who received LND had no preoperative evidence of nodal disease[19]. In a subsequent analysis of this patient population, Farber et al. showed that a disproportionate amount of LNDs were performed for low-stage RCC. Surgeons performed LND in 5% and 23% of patients with pT1 and pT2 RCC, respectively, despite lymph node involvement in only 1.1% and 2.3% of cases, respectively[20]. This apparent overutilization of LND for lower risk renal tumors likely reflects the ambiguity surrounding guidelines and the lack of strong contemporary evidence for LND implementation.

Part of this ambiguity may reflect limitations in preoperative staging. Determining candidacy for LND

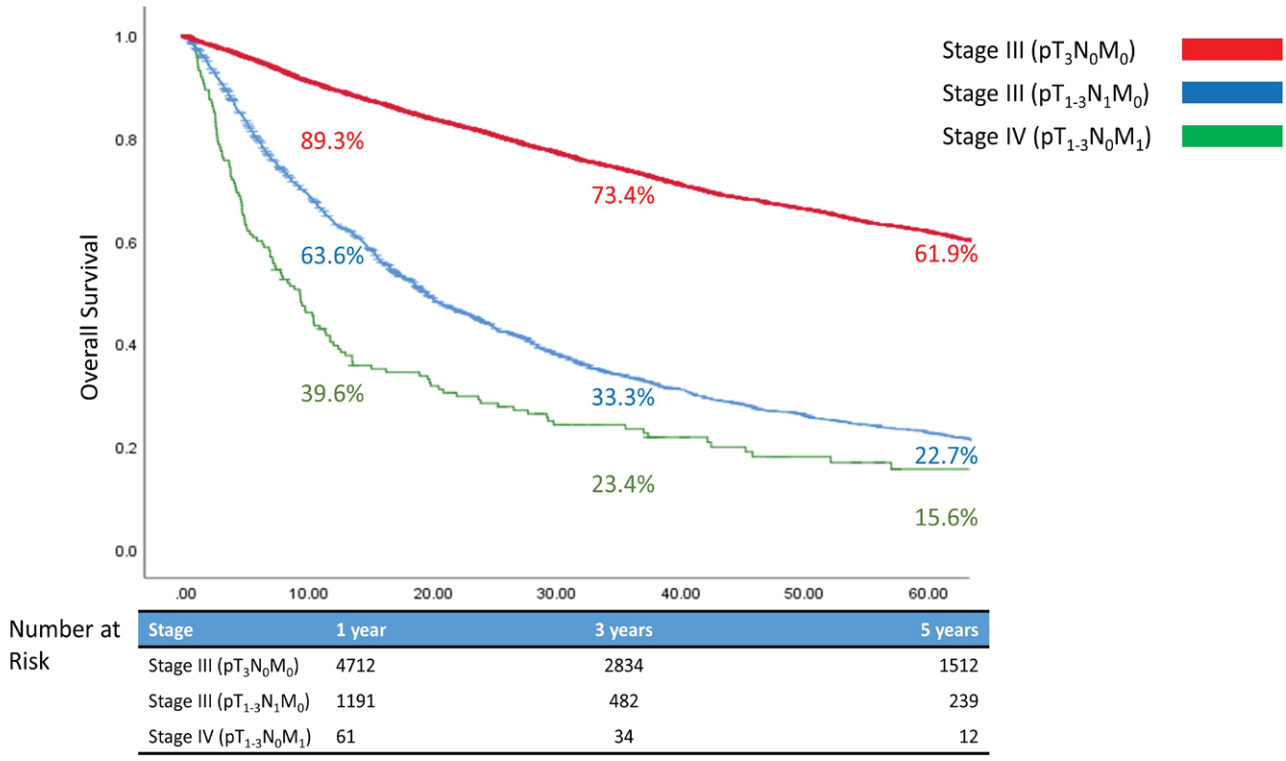

FIGURE 1 | Overall survival of NCDB patients with renal cell carcinoma stratified by American Joint Committee on Cancer stage of disease and lymph node status. Red indicates lymph node–negative stage III disease (pT3N0M0); blue, lymph node–positive stage III disease (pT1-3N1M0); green, stage IV metastatic disease (pT1-3N0M1). Reproduced, with permission, from Srivastava *et al.*[31].

currently relies heavily on clinical lymph node (cLN) status and lymph node size, as determined by preoperative imaging[19,21]. Preoperative computed tomography (CT) and magnetic resonance imaging (MRI) are the primary methods used to detect nodal metastases, but have sensitivities of only 77% and 73%, respectively, and have limited ability to identify nodal micro-metastases[21]. Unpredictable lymphatic drainage of the kidney makes it difficult to identify a consistent template for LND, which may contribute to overlooked nodal disease on preoperative imaging[22]. Additionally, the correlation between cLN status and pathological lymph node (pLN) status can be difficult to determine. In a retrospective analysis of 2,954 patients with RCC who underwent either partial or radical nephrectomy with LND, only 29% of patients with lymphadenopathy on preoperative CT were confirmed to be pLN positive after LND[23].

Furthermore, in EORTC 30881, only 20% of patients with palpable lymphadenopathy had nodal disease after LND[14]. Aside from lymph node size, some have proposed using other imaging findings to determine candidacy for LND, such as evidence of perinephric or renal sinus fat invasion on CT[24]. Others have proposed utilizing alternative imaging techniques to better identify LND candidates. A pilot study investigating lymphotrophic nanoparticle enhanced MRI (LNMRI) showed promising results in diagnosing pLN status, with 100% sensitivity and 96% specificity[25]. Clearly, current modalities for staging RCC are insufficient for determining cLN and pLN status, and more accurate and reproducible preoperative methods are needed to identify optimal LND candidates.

Outcomes in Node-Positive Disease and Implications for Staging

Prior studies have established that lymph node-positive disease portends worse survival in RCC[26]. Cancer-specific survival (CSS) in patients with lymph node positivity ranges from 21-38% at 5 years and 11-29% at 10 years, and those patients with positive nodes have nearly 8-fold higher risk of mortality compared to those with negative nodes[27, 28]. Notably, current AJCC staging criteria consider both pT3N0M0 (node negative) and pT1-3N1M0 (node positive) patients to have stage III RCC. However, this common grouping has been studied more closely in recent years. Several studies have proposed modification of current AJCC staging groups, lending support to the role of LND among patients with advanced RCC[29-31]. More specifically, these studies note that patients with node-positive Stage III RCC have survival more closely resembling Stage IV patients, including those with metastasis, rather than their node-negative Stage III counterparts. In an institutional retrospective analysis of 4,652 patients with advanced RCC, Yu et al. reported comparable oncologic outcomes between pT1-3N1M0 (Median CSS = 2.8 years, 95%CI: 1.8-4.8 years) and pT1-3N0/xM1 (Median CSS = 2.4 years, 95%CI: 2.1-3.0 years); however, both had distinctly inferior outcomes compared to pT1-3N0M0 patients (Median CSS = not reached, 95% 10.2 – no estimate years)[29]. Shao et al. conducted an analogous study of 2,120 patients from a single institution which was then validated with over 74,000 patients from the SEER database. The authors noted longer overall survival (OS) for T3N0M0 compared to T1-3N1M0 (72.7% vs 38.1%), similar survival for T1-3N1M0 and T4N0M0 (38.1% vs 36.2%), and greater survival for T1-3N1M0 compared to TanyNanyM1 disease (38.1% vs 12.6%)[30]. Using the NCDB, Srivastava et al. conducted a retrospective analysis of 8,988 patients with stage III/IV RCC, which compared patients with pT-3N0M0, pT1-3N1M0, and pT1-3N0M1 disease. The results, depicted in Figure 1, showed greater 5-year OS among patients with pT3N0M0 (61.9%) compared to pT1-3N1M0 (22.7%), and similar OS between pT1-3N1M0 and pT1-3N0M1 (15.6%) disease. Of note, the results of this study also showed node positivity to be predictive of OS among Stage III-IV patients[31]. Similar survival outcomes of pN1 and metastatic RCC suggest that many patients with lymph node involvement may have occult metastases at time of surgery. In a series described by Gershman et al., metastasis-free survival at 1-year was only 37%, and CSS rates were expectedly poor[32].

Trial	Status	Treatment Compared	Stage for inclusion	Histology	Primary Outcome	Reference
ASSURE	Reported	Sunitinib Vs. sorafenib Vs. placebo	pT1b (G3-4), pT2-4, or pTanyN1	Clear cell or non-clear cell	DFS; no difference	48
S-TRAC	Reported	Sunitinib Vs. placebo	pT3-4	Clear cell only	DFS; improved	49
PROTECT	Reported	Pazopanib Vs. placebo	pT2 (G3-4), pT3-4, or pTanyN1	Clear cell or predominantly clear cell	DFS; no difference	51
ATLAS	Reported	Axitinib Vs. placebo	pT2 or pTanyN1	Clear cell or predominantly clear cell	DFS; no difference, stopped early due to futility	50

TABLE 2 | Reported clinical trials evaluating perioperative or adjuvant tyrosine kinase inhibitors for RCC

Based on the results of these studies, some have advocated for reclassifying T1-3N1M0 RCC as stage IV instead of stage III[33-35]. These proposed staging revisions are shown in Table 1. In an era where the precise genomic and epigenetic factors are not entirely understood, cancer staging offers clinical insight into tumor biology based on objective factors. As such, in addition to its prognostic implications, revamping the classification of localized node-positive RCC could potentially better inform treatment modalities and refine eligibility for clinical trials.

Given the mortality associated with nodal disease, one might expect that LND at the time of nephrectomy would offer a survival benefit, however, mixed results have been published on this matter over the past several decades. Early work from Herrlinger et al. showed an OS advantage among patients undergoing complete LND compared to those undergoing partial or absent node dissection[12, 36]. Similarly, other studies found increased OS and CSS among patients with node-positive

Trial	Status	Treatment Arms	Stage for Inclusion	Histology	Primary Outcome	Reference
SOURCE	Ongoing	Sorafenib (3 years) vs. sorafenib (1 year) vs. placebo	Leibovich score 3 to 11	Clear cell or non-clear cell	DFS	NCT00492258
EVEREST	Ongoing	Everolimus vs. placebo	pT1b (G3-4) pT2-4 pTanyN1	Clear cell or non-clear cell	RFS	NCT01120249
Checkmate 914	Ongoing	Nivolumab vs nivolumab + ipilimumab vs. placebo	pT2a(G3-4) N0M0 pT2a(Gany) N0M0 pT3(Gany) N0M0 pT4Gany N0M0 pTany(Gany)N1M0	Predominant clear cell histology	DFS	NCT03138512
RAMPART	Ongoing	Durvalumab + tremelimumab vs. durvalumab	Leibovich score 3 to 11	All RCC (except pure oncocytoma, collecting duct, medullary and transitional cell cancer)	DFS and OS	NCT03288532
PROSPER RCC	Ongoing	Nivolumab vs. observation	≥ T2Nx TanyN+ M1 NED	All RCC histology	EFS	NCT03055013
KEYNOTE	Ongoing	Pembrolizumab vs. placebo	pT2(G4 or sarcomatoid)N0M0 pT3-4(Gany)N0M0 pTanyN+M0 M1 NED	Clear cell component +/- sarcomatoid features	DFS	NCT03142334
IMmotion010	Ongoing	Atezolizumab vs. placebo	TanyNanyM0	Clear cell or sarcomatoid	DFS	NCT03024996

TABLE 3 | Ongoing clinical trials evaluating perioperative or adjuvant tyrosine kinase, mTOR inhibitors, and/or checkpoint inhibitors for RCC. RCC: renal cell carcinoma; DFS: disease-free survival; RFS: recurrence free survival; OS: overall survival; NED: no evidence of disease; EFS: event free survival.

disease who underwent LND compared to those who did not[13, 37, 38]. To date, only one prospective, randomized phase 3 trial has assessed the utility of LND in RCC. The EORTC 30881 trial, published in 2009, showed no survival benefit among patients who underwent nephrectomy with LND compared to patients who underwent nephrectomy alone[14]. However, multiple limitations to this study make it difficult to interpret and implement the findings of this study for clinical practice. Most notably nearly 70% of the study population had pT1 or pT2 disease, and only 4% of patients in the trial population had nodal metastasis[39]. Therefore, the majority of patients in the trial were unlikely to benefit from node dissection[40]. EORTC 30881 was also limited in that there was no universal LND template required, and therefore results could have varied significantly based on surgeon, template, and center. Despite these shortcomings, subsequent retrospective studies attempting to clarify the impact of LND have shown similar results to EORTC 30881[20, 41-44]. In a study of the NCDB, Farber et al. did not find any survival benefit associated with LND when comparing 11,867 patients with non-metastatic RCC undergoing partial or radical nephrectomy with LND to a propensity-score matched cohort of patients who did not receive LND (OS 34.7 vs. 34.9 months, respectively)[20]. The NCDB has also been used to emulate the methods of EORTC 30881 using propensity score matching, with results showing no survival advantage of LND, even when adjusted to include a greater proportion of high-risk patients[41].

The Role of Adjuvant and Perioperative Therapy in Node-Positive RCC

While nephrectomy is considered the gold standard treatment for non-metastatic RCC, up to 40% of patients may recur after an extirpative intervention[45]. Recurrence rates can be as high as 80% in those with node-positive disease, with 5-year survival as low as 11-35%[46, 47]. Thus, exploration of multimodal therapy is vital to addressing the shortcomings of nephrectomy and improving outcomes in node-positive RCC. Due to the significant risk of progression to metastatic disease, patients with node-positive RCC are prime candidates for early intervention[33].

Thus far, four adjuvant trials that included patients with node-positive RCC have reported their results (Table 2). The ASSURE trial randomized 1,943 patients with completely resected pT1b, pT2-4, or TanyN+ RCC to one of three arms: sunitinib, sorafenib, or placebo, for 54 weeks[48]. The analysis showed no difference in disease free survival (DFS) for either sunitinib or sorafenib compared to placebo (HR 1.02, 97.5% CI 0.85 – 1.23; p=0.8038 and HR 0.97, 97.5% CI 0.80 – 1.17; p=0.7184, respectively)[48]. The S-TRAC trial randomized 615 pT3-4 or TanyN+ to sunitinib or placebo. The results of S-TRAC were more encouraging than those of ASSURE, concluding that patients in the sunitinib arm had significantly longer DFS compared to placebo (HR 0.76, 95% CI 0.59 – 0.98; p=0.03)[49]. The ATLAS trial randomized 724 patients with previously-resected RCC (≥pT2 and/or N+) to axitinib or placebo. On the primary analysis of DFS, there was no significant difference in the intention-to-treat population (HR 0.87, 95% CI 0.660 – 1.147; p=0.3211)[50]. The PROTECT trial randomized 1,538

patients with pT2, pT3, and pT4 disease to pazopanib or placebo. Initially, the dose was set at 800 mg daily, but was later reduced to 600 mg due to significant adverse effects. Interestingly, while the 600 mg group showed no significant reduction in DFS (HR 0.86, 95% CI 0.70 – 1.06; p = 0.165), the 800 mg group did (HR 0.69, 95% CI 0.51 – 0.94; p=0.02)[51].

Akin to the prior efforts to orchestrate immune-mediated antineoplastic activity through cytokines, checkpoint inhibitors have come to the forefront as a promising therapeutic option for metastatic RCC. In the Checkmate 025 trial, the checkpoint inhibitor nivolumab showed significant improvement in OS with fewer adverse effects when compared to everolimus (HR of death 0.73, 98.5% CI 0.59 – 0.93; p=0.002)[52]. Checkmate 214, the landmark phase III trial that compared nivolumab plus ipilimumab versus sunitinib in metastatic RCC, demonstrated improved complete response rate (9% vs 1%) and improved OS for the checkpoint inhibitor arm (HR 0.63, 99.8% CI 0.44-0.89, p<0.001)[53]. Given the success of these agents in the management of metastatic RCC, integrating these therapies as adjuvant therapies may be a logical next step for patients at high-risk for metastatic progression, such as node-positive RCC. However, to date there have been no reported results from trials examining the role of checkpoint inhibitors as adjuvant therapy.

Noteworthy ongoing phase III trials for perioperative/adjuvant therapy are highlighted in Table 3. SORCE (NCT00492258) is an ongoing trial comparing sorafenib 3 years vs. sorafenib 1 year vs. placebo. However, preliminary results presented at European Society for Medical Oncology 2019 showed no significant increase in DFS for patients in the sorafenib arms[54]. Similarly, EVEREST (NCT01120249) is an ongoing clinical trial investigating the potential of the mTOR inhibitor everolimus. The recent success of Checkpoint 025 and Checkpoint 214 in demonstrating clinical utility of nivolumab and ipilimumab for RCC has led to five ongoing phase III clinical trials to implement checkpoint inhibitors in the adjuvant/perioperative space: Checkmate 914 (NCT03138512) – nivolumab plus ipilimumab vs. versus nivolumab vs. placebo, RAMPART (NCT03288532) – durvalumab plus tremelimumab vs. durvalumab vs. observation, PROSPER RCC (NCT03055013) – perioperative nivolumab vs. observation, KEYNOTE (NCT03142334) – pembrolizumab vs. observation, and IMmotion010 (NCT03024996) – atezolizumab vs. observation. Notably, PROSPER RCC incorporates a neoadjuvant aspect, potentially allowing for translational studies of tissue and sera by comparing pre- and post-nivolumab treated tissue[55].

There is a significant need to address the limitations of nephrectomy and LND in node-positive RCC. However, there is a dearth of evidence to direct the therapy for those with nodal disease. While 5%-47% of the patient population in the aforementioned trials – ASSURE, S-TRAC, ATLAS, PROTECT, Checkmate 025 and Checkmate 214 – were node-positive, no study completed a subgroup analysis in this population of interest[48-53]. It is imperative that investigation into this unique population is included in future trials exploring the role of systemic therapies in the treatment of locally advanced and metastatic RCC.

Conclusions

The presence of pathologic lymph nodes in patients with non-metastatic kidney cancer has crucial prognostic value. Outcomes from several recent studies suggest that revising staging categories may lead to improved prognostication for patients with advanced RCC and have implications for therapy selection and clinical trial participation.

It remains unclear whether LND can be a beneficial surgical option for a select subset of patients with RCC. Much of this uncertainty stems from a lack of level one evidence regarding nodal disease in RCC. However, with several ongoing and upcoming clinical trials that include patients with node-positive RCC, anticipated results may lead to a paradigm shift in the management of this disease. It is imperative that physicians work to enroll patients in clinical trials in order to gain a better understanding of the complexities of this disease, and ultimately improve the care of our patients.

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