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Role of lymph node dissection in renal cell cancer

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Abstract

Lymph node metastasis in renal cell cancer (RCC) portends an extremely poor prognosis. Despite proven staging benefit, the therapeutic value of lymph node dissection in RCC remains questionable. The only prospective randomized trial examining its role failed to show any benefit. However, subsequent retrospective publications have attempted to identify high-risk cohorts and clinical scenarios where removal of nodes may improve survival. The aim of this article is to provide a comprehensive review looking at the role of lymph node dissection in RCC if any, the ideal extent of dissection, and also tools a clinician could employ to identify those who would most likely benefit from this exercise. © 2018 Elsevier Inc. All rights reserved.

Keywords: Lymph node dissection; Renal cell cancer; survival; prognosis; complications; biomarkers

Introduction

"Radical Nephrectomy" as described by Robson entailed removal of the lymphatic drainage field along with the disease bearing kidney as one of the important requirements for achieving cure [1]. Five decades later, despite proven staging benefit, the therapeutic benefit of lymph node dissection (LND) in renal cell carcinoma (RCC) remains questionable. The only prospective randomized controlled trial to date showed that complete lymph node removal from the crus of the diaphragm to the bifurcation of the aorta/vena cava failed to confer any survival benefit in "low risk" RCC [2]. Increased detection of small, indolent tumors; proliferation of minimally invasive nephron sparing surgery [3], and lack of perception of benefit has resulted in fewer urologists performing LND over the past decade [4].

However, some retrospective series claim that certain "high risk" groups may benefit from LND [5–10]. Hence, the aim of this review is to ascertain the role of LND in the management of RCC if any, and whether development of novel imaging, molecular and genomic tools have contributed to the identification of those who might benefit from LND.

Patterns of lymphatic spread in RCC

Since literature is still unclear regarding the role of LND in RCC, it makes sense to revisit the patterns of lymphatic drainage of the kidney and understand the reason why spread of RCC is so unpredictable. Detailed injection studies in cadavers carried out in the early half of the last century contributed to this knowledge [11] and helped in constructing the anatomic lymphatic drainage maps of the kidneys [12].

From the right kidney, efferent lymphatic vessels running anterior to the renal vein (anterior bundles) can drain into paracaval, precaval, retrocaval, and interaortocaval nodes. Retrocaval nodes are located close to the right crus of the diaphragm and connect with the thoracic duct [11,12]. Lymphatic vessels traveling posterior to the renal artery (posterior bundles) drain to the paracaval, retrocaval, and interaortocaval nodes [11,12]. From the left kidney, efferent lymphatic vessels running anterior to the renal vein can drain into the para-aortic and preaortic nodes [11,12]. Posterior efferent lymphatic vessels can drain to the para-aortic and retroaortic nodes [11]. Interconnections between the extensive retroperitoneal lymphatics between the first and the fifth lumbar vertebrae make drainage unpredictable [13,14]. In some cases, posterior efferent lymphatic vessels on both sides have been observed to connect directly to the

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thoracic duct without passing through any lymph nodes [11,15]. Direct drainage into the thoracic duct as shown in cadaver dissections by Assouad et al. [15] may explain the occurrence of distant metastasis without involvement of the retroperitoneum. This was confirmed in vivo by Brouwer et al. [13] using lymphoscintigraphy and SPECT/CT in a prospective study. Moreover, lack of involvement of ipsilateral hilar region with concurrent distant disease (skip lesion) has also been reported in up to 29% of cases [16].

Intraoperative identification of sentinel lymph nodes in RCC utilizing preoperative lymphoscintigraphy and SPECT/CT followed by intraoperative sampling with the help of a gamma camera has been reported by Bex et al. [17] and Sherif et al. [18]. The sentinel node detection rates were 70% and 77%, respectively. In the first study constituting 20 clinically node negative patients, none of the hilar, paraortic, and retrocaval sentinel nodes harvested contained tumor. Bex et al. also found nodes along the celiac trunk, internal mammary, mediastinal, and pleural spaces, highlighting the inconsistencies of renal lymphatic drainage. In Sherif's study of 13 arbitrarily chosen cT1b-T3b RCC patients, all clinically suspicious nodes on CT were confirmed to be sentinel nodes. These studies suffered from small sample sizes, a heterogeneous study population, and lack of a standard protocol. Hence, large scale lymph node mapping studies are required to corroborate these findings.

Staging benefit of LND

Knowing the complexity of lymphatic drainage of the kidney, it would be ideal if intraoperative assessment or imaging was accurate for assessing the extent of lymph node involvement. Unfortunately, in the EORTC 30881 trial, less than 20% of the palpably enlarged nodes during surgery were positive on histopathological examination [2]. Both CT and MRI are inadequate in detecting metastasis in nodes of normal shape and size [5]. Hence, LND is currently the only reliable way to stage accurately [3].

Presence of lymph node metastasis portends an extremely poor prognosis [9,19] and carries a 7.8-fold higher risk of dying of disease [19]. Cancer-specific survival of those with lymph node positive disease undergoing radical nephrectomy are 52%–72%, 21%–38%, and 11%–29% at 1, 5, and 10 years, respectively. Lymph node involvement has been established as an independent prognostic factor for poor oncologic outcomes in several studies [19,20]. It maintains this status in the presence of metastatic disease [21], even in those treated with targeted therapy [22].

Therapeutic benefit of LND

Although the role of LND in staging is well established, its role in improving oncological outcomes is debatable. Table 1 highlights some of the prominent publications focused on this issue. The only prospective, randomized phase III trial (EORTC 30881) which attempted to solve this controversy failed to show any survival benefit in clinically node negative patients [2]. However, these results could not be generalized due to various issues. The 4% incidence of lymph node involvement in the study cohort was very low. Most cases in this study were pT1–2 tumors based on more contemporary TNM classifications, and hence, had a very low risk of lymph node metastasis. Only 25% of the pT3 tumors underwent a complete LND, and the LND template used was unclear. A systematic review which included the EORTC trial and 5 non-randomized studies showed no survival benefit of LND in locally advanced (cT3–4) RCC [23]. The EORTC trial was not powered to look at this subgroup, and the overall quality of evidence in this review was poor. In another study, Feuerstein et al. did not find any gain in either RFS or OS in patients undergoing LND for tumors ≥7 cm in size [24]. A recent retrospective study using a propensity score-based analysis also failed to find any association between LND and improved oncological outcomes even in patients with radiographically positive nodes [25]. However, this study cohort suffers from low pathological node positivity (6.2%), lack of a prespecified LND template and suboptimal lymph node yields (IQR: 2–12).

Several studies have published contradictory results. A prospective cohort study of 511 patients by Herrlinger et al. [26] showed improvement in OS at 5 and 10 years with systematically extended LND. In Schafhauser's study of 1,035 patients (cT1–4), 51% received a systematic LND, and the median lymph node count was 18. Though most patients had negative lymph nodes, 27% of those with positive nodes survived > 5 years, translating into a 4% benefit for the LND cohort [27]. A study of 9,586 patients from the SEER database showed that patients with lymph node positive, nonmetastatic disease benefited from LND [9]. However, selection bias and lack of adjustment for important prognostic confounders make conclusions of all these studies unreliable.

More recently, some retrospective studies have attempted to identify "high risk" cohorts where LND could play a therapeutic role. Prominent among these was the study by Capitanio et al. [7] who showed that the LND resulted in improved CSS in some subcategories of RCC like pT2–4 stage, bulky tumors (>10 cm), or when sarcomatoid features were present. A more extensive LND was shown to improve CSS in pT4 RCC with the risk of dying decreasing by 8% for every lymph node removed [28]. In contrast, a secondary analysis of the ASSURE trial (ECOG-ACRIN 2805) looked at the role of LND in high risk, nonmetastatic RCC patients treated with adjuvant therapy and failed to find any survival benefit [29]. Although, LND was performed for all with resectable, clinically node positive disease, surgeon's discretion formed the basis for those with clinically negative nodes, introducing a selection

Table 1
Studies assessing therapeutic role of LND in nonmetastatic RCC

Study	Type of study	Study population	Sample size	Measured outcome	LND	Results
Blom et al. (EORTC 30881) [2]	Prospective, randomized	T1–3	732	CSS	Extended	No benefit
Bekema et al. [23]	Systematic review	cT3–4	605	CSS, OS	Variable	No benefit
Feuerstein et al. [24]	Retrospective	Primary ≥7 cm; pT2–4, N*any*	524	RFS, OS	Variable	No benefit
Gershman et al. [25]	Retrospective	pT*any*,N*any*	1797	CSM, ACM	Variable	No benefit
Herrlinger et al. [26]	Prospective cohort	pT*any*,N*any*	511	OS	Extended	66% vs. 58% 5-year OS
Schafhauser et al. [27]	Retrospective	cT1–4,N*any*	1035	OS	Extended vs. limited vs. none	70% vs. 61% vs. 65% 5-year OS
Whitson et al. [9]	Retrospective	pT*any*,N*any*	9586	CSS	Variable	Improved CSS for pN1
Capitanio et al. [7]	Retrospective	pT*any*,N*any*	1983	CSS, MPFS	Variable	Improved CSS and MPFS for pT2–4,>10 cm, sarcomatoid features
Capitanio et al. [28]	Retrospective	pT4	44	CSS	Variable	Improved CSS with increasing number of nodes removed
Ristau et al. [29]	Secondary analysis of ASSURE (ECOG-ACRIN 2805)	pT*any*,N*any*	1943	CSS, OS	Variable	No benefit

bias. Lack of a formal LND template and a median lymph node yield of 3 (IQR: 1–8) bring into question the quality of LND and adds to the limitations of this study.

Though presence of isolated lymph node involvement at presentation portends poor prognosis with a 5-year MFS and OS of 16% and 25%, respectively, a small subset of these patients may experience an MFS of up to 71% at 1 year [30]. Canfield et al. studied 40 cT1–4 lymph node positive patients who underwent extended LND and observed that patients with only 1 positive node survived significantly longer than those with > 1 positive lymph nodes.

Looking at studies in the metastatic setting (Table 2), there was suggestion that LND along with cytoreductive nephrectomy prior to systemic immunotherapy improved survival. Pantuck et al. demonstrated a 5-month survival advantage for lymph node positive cases who underwent LND [10]. However, a publication from MSKCC failed to show any such benefit. In a cohort consisting of 258 cytoreductive nephrectomies, 69% had undergone LND. The 5-year overall survival was 21% for patients who underwent LND and 31% for patients who did not. No significant difference in survival was found among patients receiving or not receiving LND [31]. The most recent evidence comes from Gershman et al. who studied 305 patients with metastatic RCC and found that LND at the time of cytoreductive nephrectomy did not confer a survival advantage even in those with an increased risk of lymph node positivity [32].

As most of the evidence discussed is retrospective, selection bias and lack of adjustment of confounders makes interpretation of data unreliable. Even after accounting for these drawbacks, contemporary literature does not endorse the use of LND to improve oncological outcomes in RCC. Certain "high risk" subcategories may benefit from an extended LND. However, as outlined even in the EAU guidelines, the supporting evidence is weak and needs validation in future trials.

Extent of LND

A retrospective study looking at the extent of lymphadenectomy showed that systematic, extended LND in cT1–4 RCC was associated with better survival compared to just sampling or lack of LND [27]. Crispen et al. suggested templates for LND based on his study on high-risk patients [8]. However, a major limitation was lack of standardized dissection during the study period. Whitson et al. showed that an increase of 10 lymph nodes in a patient with 1 positive lymph node was associated with a 10% absolute increase in disease-specific survival at 5 years (P = 0.004) [9]. However, this study was criticized for improper handling of

Table 2
Studies assessing therapeutic role of LND in metastatic RCC

Study	Type of study	Study population	Sample size	Measured outcome	LND	Results
Pantuck et al. [10]	Retrospective	pT*any*,N*any*,M1	900	OS	Variable	Improved OS for pN1
Feuerstein et al. [31]	Retrospective	pT*any*,N*any*,M1	258	OS	Variable	No benefit
Gershman et al. [32]	Retrospective	pT*any*,N*any*,M1	305	CSM, ACM	Variable	No benefit

missing data. After appropriate statistical adjustments, the extent of LND was no longer protective [33].

Capitanio et al. also showed that the number of lymph nodes removed had an independent protective effect on metastatic progression-free survival as well as CSS in pT2–4 RCC. The extended LND arm involved removal of nodes surrounding the ipsilateral great vessel and the interaortocaval region from the crus of the diaphragm to the common iliac artery. The mean number of nodes removed was 15. The removal of each node corresponded to a 3%–19% increase in CSS [7].

LND for nodal recurrence

Isolated lymph node recurrence following nephrectomy is rare [5] and salvage LND is challenging and worth the effort only if it improves outcome. In a study done in the pretargeted therapy era, a series from Mayo showed a median CSS of 33.3 months following salvage LND [34]. A retrospective multi-institutional study of 22 patients in this setting seemed to show durable PFS irrespective of histology or original clinical stage [35]. However, most of this cohort had not undergone LND at the time of nephrectomy despite being high risk for lymph node involvement, making interpretation of these results difficult. A more recent multi-institutional effort looking at 50 patients who underwent resection of an isolated nodal recurrence showed 3-year and 5-year PFS of 40.5% and 35.4%, respectively, and better outcomes if recurrence occurred after 1 year of nephrectomy [36].

Complications of LND

Complications associated with LND include injury to major vessels/bleeding, bowel injury/damage to adjacent organs, lymphocele, and chylous ascites [2,37]. However, the EORTC trial failed to show any significant difference in complication rates between the extended LND and no LND arms (26% vs. 22%) [2]. A systematic review of LND in locally advanced RCC too failed to show any difference in adverse events in the LND vs. no LND groups [23]. With the proliferation of minimally invasive surgery, laparoscopic LND though technically challenging, has been shown to be feasible with similar complication rates as open surgery in experienced hands [38].

8. Predictive tools

8.1. Imaging

CT and MRI are ideal tools to diagnose and stage RCC but fall short of accurately predicting lymph node involvement, more so for detecting micrometastasis in normal-sized nodes [39,40]. Association between lymph node size and metastatic involvement was reported to be around 32%–43% even in lymph nodes>1 cm in size [41,42]. A more recent publication has shown that the sensitivity, specificity, and positive and negative predictive values for preoperative CT were 82%, 71%, 56%, and 90%, respectively [43]. In another recent study, maximum lymph node short axis diameter outperformed traditional clinical variables in predicting lymph node involvement with 90% predicted metastatic involvement of lymph nodes > 3 cm [44].

A pilot study using lymphotrophic nanoparticle enhanced MRI evaluating the role of lymph node involvement showed encouraging results with a sensitivity and specificity of 100% and 95.7%, respectively [45], but the sample size studied was small and these results are yet to be validated prospectively.

Clinical studies have confirmed the outstanding ability of cG250 PET (girentuximab PET) in targeting and diagnosing both localized and metastatic clear cell RCC [46], and development of imaging modalities along similar lines may hold the key to accurate identification of even lymph node metastasis in future.

8.2. Clinical predictors and nomograms

As already established, lymph nodal involvement in RCC carries a dismal prognosis. Hence, several preoperative nomograms were developed to try and predict its occurrence and identify those likely to benefit from LND.

Blute et al. [19] identified Fuhrman nuclear grade, tumor size, pathologic stage, sarcomatoid features, and presence of coagulative tumor necrosis as independent predictors of lymph node involvement. These findings were later validated by Crispen et al. [8] in high-risk RCC. However, establishing accurately the adverse histological features preoperatively, on a needle biopsy or even on an intraoperative frozen sample may not always be possible. A preoperative nomogram developed by Capitanio et al. [47] used clinical stage and tumor size to predict lymph node involvement and claimed an accuracy of 87% but lacks external validation. A “truly” preoperative nomogram developed by Babaian et al. [48] including local symptoms, performance status (ECOG), clinical nodal status, and lactate dehydrogenase also managed to achieve very high accuracy but awaits external validation.

Most of these predictive tools are fraught with limitations. Surgeon bias resulting in selection of high-risk cases, absence of a systematic extended LND in study cohorts, and lack of external validation precludes extrapolation of resulting data and clinical use of these nomograms.

8.3. Molecular and genomic biomarkers

Lymph node involvement is an independent predictor of poor survival in RCC even in those with metastatic disease. RCC with predilection for LN spread may represent a

cohort with unique molecular and genomic profiles. Kroeger et at. [49] were able to show that low carbonic anhydrase IX levels and high epithelial vascular endothelial growth factor 2 protein expression was associated with higher rates of lymph node involvement. Loss of chromosome 3p resulted in lower risk.

Identification of key genomic predictors of tumor behavior in RCC is challenging owing to significant intratumoral heterogeneity [50]. Soultati et al. [51] performed multiregion sequencing of clear cell RCC and synchronous lymph node metastasis and found that lymph nodes, unlike the primary, had a largely homogeneous mutational profile consistent with their monoclonal origin. Two primary regions had mutational (BAP1 and LRRK2) and copy number profiles (8q, 12, 1p, 9p, 9q, 10q, 14q, 22q, and 11q) near-identical to those observed in the lymph nodes and completely distinct to the remainder of the primary tumor.

Intratumoral expression of programmed death ligand 1 (PD-L1) in RCC was found to be associated with advanced disease at presentation including lymph node and distant metastasis, resulting in significantly lower overall survival [52]. A systematic review looking at the value of long noncoding RNAs in RCC found that high expression of metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) could be considered a biomarker of the early detection of lymph node metastasis and predictor of poor survival in RCC patients, who likely manifested short overall survival (OS; hazard ratio [HR], 2.97; 95% CI: 1.68−5.28; $P < 0.001$) [53]. Another meta-analysis showed that survivin expression was associated with higher tumor grade (OR = 4.25, 95% CI: 3.04−5.95, $P < 0.001$), advanced tumor stage (OR = 3.83, 95% CI: 2.01−7.3, $P < 0.001$) and lymph node metastasis (OR = 4.19, 95% CI: 2.34−7.52, $P < 0.001$), but had no association with age, sex, or distant metastasis [54].

Identification of accurate biomarkers and their validation in clinical trials will hopefully arm clinicians in future with the ability to identify those likely to benefit from LND and improve outcomes of RCC.

9. Conclusion

LND continues to be the most reliable way to stage the retroperitoneum in RCC. Extended dissection and removal of at least 15 nodes improves accuracy. The only randomized trial looking at the role of LND in RCC failed to show improvement in survival in low-risk disease. Evidence supporting LND in high-risk cases (≥T3, size > 10 cm, sarcomatoid features, etc.) and for isolated nodal recurrence is weak and needs validation. Well-designed, multi-institutional, prospective, randomized trials using a predefined LND template on a clearly defined “high risk” cohort is the need of the hour. Until then, identification of novel molecular and genomic biomarkers may hold the key to identifying patients with RCC who would truly benefit from LND.

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