The Role of Lymphadenectomy in Patients with Advanced Renal Cell Carcinoma

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KEYWORDS

• Renal cell carcinoma • Lymph node dissection • Template • Indications • Survival • Outcomes

KEY POINTS

- Lymph node dissection serves an important staging role by providing pathologic lymph node stage, which has been independently associated with survival in nonmetastatic and metastatic renal cell carcinoma.
- Lymph node dissection does not seem to provide a survival benefit for nonmetastatic or metastatic renal cell carcinoma, even in patients at increased risk for lymph node metastases.
- Most patients with clinically isolated lymph node involvement develop systemic progression within the first year after surgery, although a small subset demonstrates long-term recurrence-free survival.
- Lymph node dissection is not associated with an increased risk of perioperative morbidity when performed in experienced centers.

INTRODUCTION AND HISTORICAL PERSPECTIVE

Lymph node dissection (LND) plays a central role in the management of urologic malignancies. However, its role in the management of renal cell carcinoma (RCC) has been controversial.[1–4] Although LND provides indisputable pathologic nodal staging, its impact on survival has been uncertain. The attribution of a potential survival benefit to LND can be traced back to Robson's seminal description of radical nephrectomy in 1969, wherein the authors suggested that the improved survival of patients in that series, compared to contemporaneous reports, was due in part to the performance of a thorough lympadenectomy.[5]

Since then, a number of observational studies have similarly suggested improved survival with LND.[6–8] However, the only randomized trial to examine this question, EORTC 30881, reported no survival benefit upon its publication in 2009.[9] Despite criticism that the trial enrolled overwhelmingly low-risk patients, and that LND may still benefit those at higher risk of lymph node metastases, more recent investigations have not supported a therapeutic benefit to LND, even in locally advanced or metastatic RCC.[1,10–15] Still, LND provides valuable prognostic data, and as such may have a role for improved staging.

In this article, we review the contemporary role of LND in the management of locally advanced and metastatic RCC. We critically evaluate the available evidence base to address several important clinical questions, including the indications for LND, optimal LND templates, staging role, survival benefit, and morbidity.

LYMPH NODE DISSECTION TEMPLATES

To examine the role of LND, it is essential to first define the templates and techniques for LND. In

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contrast with retroperitoneal LND for testicular cancer[16] or pelvic LND for prostate cancer,[17] there is no standardized, universally accepted template or templates for performing LND for RCC.[18–20] However, several principles for LND can be inferred based on both anatomic and clinical studies.[21–23]

The anatomic basis for retroperitoneal lymphatic drainage has been described in several anatomic studies.[21] Such studies demonstrate renal lymphatic drainage into the retroperitoneal lymph nodes, with side-specific preferential drainage of the right kidney into the hilar, pre-caval, and interaortocaval lymph nodes, whereas the left kidney drains into the hilar, para-aortic, and interaortocaval lymph nodes.[21] However, drainage patterns vary tremendously, and direct communication of the efferent lymphatics to the thoracic duct have also been described. Further complicating these heterogeneous drainage patterns, direct lymphovenous communications to the renal vein and vena cava have been reported, likewise bypassing the retroperitoneal lymph nodes altogether.[21]

More recently, an in vivo study using sentinel lymph node mapping with single photon emission computed tomography reinforced the unpredictable lymphatic drainage pattern of RCC and the potential for bypassing the retroperitoneal lymph nodes.[22] In that study, 35% of patients were found to have sentinel lymphatic drainage outside the locoregional retroperitoneal template, including 20% for whom sentinel nodes were supradiaphragmatic.[22] Such data reinforce the overarching concept that lymphatic drainage for RCC does not follow a uniform, step-wise drainage pattern, an understanding that has important implications for the role of lymphadenectomy.

Few clinical studies have examined the optimal template for LND. In a seminal study, Crispen and colleagues[23] characterized patterns of lymphatic spread in 169 patients at high risk for lymph node metastases. They reported the notable observation that there were no skip metastases to the contralateral lymph nodes without involvement of the interaortocaval lymph nodes: for right-sided tumors, there was no involvement of para-aortic lymph nodes without interaortocaval involvement; and for left-sided tumors, there was no involvement of para-caval lymph nodes without interaortocaval involvement (**Fig. 1**). Based on these observations, the authors recommended that patients without clinical lymphadenopathy undergo removal of the lymph nodes surrounding the ipsilateral great vessel to the interaortocaval lymph nodes, from the crus of the diaphragm to the common iliac arteries; if the interaortocaval lymph nodes are positive, then a full bilateral dissection should be performed.[23]

Furthermore, there are data to support the logical concept that a more extensive LND is associated with better staging accuracy. For instance, Terrone and colleagues[24] noted that a more extensive lymphadenectomy was associated with increased detection of lymph node metastases, suggesting at least 13 lymph nodes be removed for adequate staging. Several other studies have also suggested that a more extended LND may be associated with improved survival, although these findings must be reconciled within the overall body of evidence suggesting no benefit to LND (discussed in detail elsewhere in this article).[7,25]

STAGING ROLE OF LYMPH NODE DISSECTION

Radiographic staging has poor performance for the identification of lymph node metastases from RCC.[26–29] Although the classical 1-cm size threshold for radiographically enlarged lymph nodes is quite specific for the diagnosis of metastatic disease in other urologic malignancies such as prostate or bladder cancers, radiographic lymphadenopathy has poor specificity in RCC.[29] For instance, in a seminal study by Studer and colleagues,[29] the authors reported that only 42% of patients with radiographically enlarged lymph nodes on computed tomography harbored pathologically confirmed RCC, while 58% of these patients were found to have only inflammatory changes. A more recent investigation reinforced these findings, reporting that there was an approximately linear relationship between lymph node short axis diameter and the risk of pN1 disease.[30] In that study, the risk of lymph node metastases ranged from approximately 29% for 1.0 cm short axis diameter to 90% at 3.0 cm.[30] Conversely, cross-sectional imaging is relatively good for excluding lymph node metastases; for instance, only 4.4% of patients with cN0 disease in the EORTC 30881 trial had occult lymph node metastases,[9] similar to the 3.1% false-negative rate for computed tomography in the study by Studer and colleagues.[29]

Given the poor performance of radiographic imaging for the identification of lymph node metastases, several groups have developed predictive models for pN1 disease.[1] For instance, Blute and colleagues[23,31] reported that tumor size greater than 10 cm, stage pT3/T4, nuclear grade 3 to 4, and presence of coagulative tumor necrosis or sarcomatoid differentiation were associated with pN1 disease, validating these findings in a prospective investigation. Other groups have developed nomograms to predict the risk of pN1

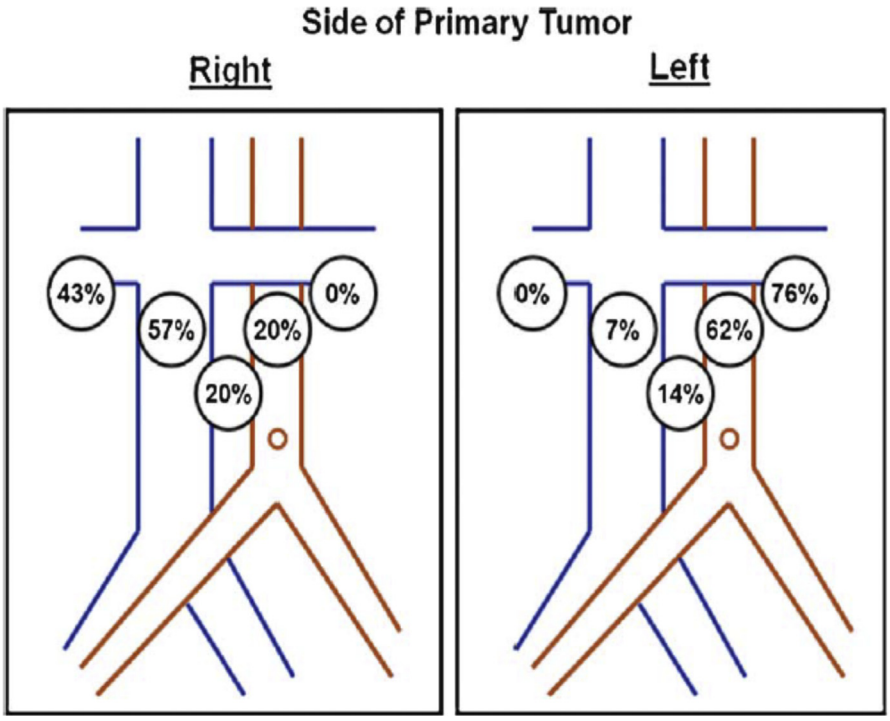

Fig. 1. Location of positive lymph nodes based on side of primary tumor. Reported percentage represents frequency of involved location in patients with lymph node–positive disease. (*From* Crispen PL, Breau RH, Allmer C, et al. Lymph node dissection at the time of radical nephrectomy for high-risk clear cell renal cell carcinoma: indications and recommendations for surgical templates. Eur Urol. 2011;59(1):18-23; with permission.)

disease, identifying similar clinicopathologic features as being associated with lymph node metastases.[32–34]

Despite the availability of clinical risk prediction models to identify patients with pN1 disease, there is no substitute for pathologic lymph node staging. Indeed, LND serves as the gold standard in establishing nodal stage. Accordingly, it provides actionable data to improve prognostication and guide postoperative management. For instance, it may identify patients for consideration of adjuvant systemic therapy after surgery, enrollment into clinical trials, or the use of more intensive surveillance imaging.[1]

Nodal stage provides valuable prognostic information.[1] Multiple studies have reported that, even when adjusting for other clinicopathologic features, both clinical nodal (cN) stage and pathologic nodal (pN) stage are independently associated with survival.[1,11,35–37] Remarkably, nodal stage remains prognostic even in the setting of metastatic RCC. Although it may seem logical that the presence of distant metastatic disease should drive prognosis regardless of the presence of nodal metastases, several studies have reported that lymph node metastases are associated with more aggressive tumor biology, even in the M1 setting.[12,37] For instance, pN1 tumors have an increased incidence of higher pT stage, coagulative tumor necrosis, and sarcomatoid differentiation.[12,37] These findings may explain why lymph node metastases carry an adverse prognosis, even in the setting of metastatic RCC.

SURVIVAL BENEFIT OF LYMPH NODE DISSECTION IN M0 RENAL CELL CARCINOMA

The question of whether LND confers a survival benefit has generated interest for more than 50 years, dating back to the original description of radical nephrectomy by Robson and coworkers.[5] However, although a number of studies have examined this topic,[6–8] there were few high-quality data to inform clinical practice until recent years. The highest level of evidence has been provided by the only randomized trial to examine LND in RCC, EORTC 30881.[9] In that study, 772 patients with cT1 to 3 cN0 cM0 RCC were randomized to radical nephrectomy with LND or radical nephrectomy alone. At a median follow-up of 12.6 years, there was no statistically significant difference in any oncologic end point examined, including

disease progression or death.[9] It is important to underscore that the study population had a low incidence of lymph node metastases of only 4.0%.

More recently conducted observational studies, as well as a meta-analysis of such studies, have similarly reported no survival benefit in M0 patients at average risk of lymph node metastases (**Fig. 2**).[1,10,13,14] In a meta-analysis of EORTC 30881 and 3 observational studies with multivariable statistical adjustment, the pooled hazard ratio for the association of LND with survival was 1.02 and not statistically significant (95% confidence interval, 0.92–1.12). Thus, both randomized and high-quality observational data agree that LND does not confer a survival benefit in average-risk patients with clinically localized, node-negative (cN0) RCC.

Because removal of benign lymph nodes cannot be expected to improve survival, it is logical to examine whether LND may confer a survival advantage in patients at higher risk of lymph node metastases. Support for this concept was provided by an older observational study, in which the authors reported improved survival for cN1 patients who underwent LND compared with patients who did not.[6] However, methodologic limitations in that study (eg, multivariable adjustment limited to only 5 variables) limit causal inference from these results.

Several more recent studies have also examined the survival benefit of LND in higher risk patients. In one institutional study of 1797 patients with M0 RCC, the authors examined two high-risk patient subsets: patients with cN1 RCC and patients stratified by predicted probability of pN1 disease ranging from ≥10% to ≥50%.[13] In both high-risk subsets, LND was not associated with a decreased risk of distant metastases, cancer-specific mortality, or all-cause mortality. In another study in which the authors conducted a secondary analysis of the ASSURE (ECOG-ACRIN 2805) trial, there was no difference in disease-free or overall survival.[14] Notably, this was a high-risk population by design, because the trial enrolled patients with grade 3 to 4 pT1b N0, pT2 to 4 N0, or pTany N+ RCC, and is reflected in a pN+ rate of 23.4%. In a third study, in which the authors conducted a secondary analysis of EORTC 30881, examining patients with cT3 tumors, there was no statistically significant difference in overall survival.[15] It is worth noting that, even when considering a seemingly higher risk cohort of patients with cT3 tumors, the rate of lymph node metastases was still only 6.3%.[15] Taken together, these studies suggest that there is no survival benefit to LND in cN1 RCC or in otherwise high-risk patients for lymph node metastases.

These discrepancies between the underlying biologic plausibility for a survival benefit to LND and the lack thereof in published studies may be reconciled by considering the anatomic basis for lymphatic drainage in RCC, as well as the tumor characteristics of lymph node positive disease. As discussed elsewhere in this article, renal

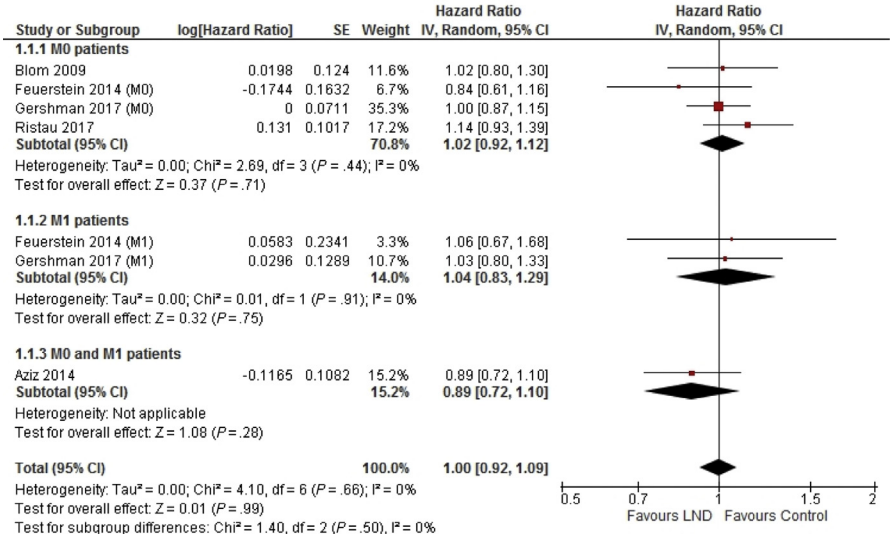

Fig. 2. Forest plot for meta-analysis of the association of LND with oncologic outcomes among patients with M0 and M1 disease. (*From* Bhindi B, Wallis CJD, Boorjian SA, et al. The role of lymph node dissection in the management of renal cell carcinoma: a systematic review and meta-analysis. *BJU international.* 2018;121(5):684-698; with permission.)

lymphatic drainage may frequently bypass retroperitoneal lymph nodes, with early hematogeneous dissemination from direct lymphovenous communications or nonretroperitoneal sentinel lymphatic drainage.[21,22] Moreover, the presence of lymph node metastases is associated with more aggressive tumor biology, such as higher pT stage, coagulative tumor necrosis, and sarcomatoid differentiation.[12,37]

SURVIVAL BENEFIT OF LYMPH NODE DISSECTION IN M1 RENAL CELL CARCINOMA

The underlying biologic plausibility for a survival benefit to LND in the metastatic setting borrows from cytoreductive principles in kidney cancer. For instance, two randomized trials conducted in the immunotherapy era demonstrated that, in properly selected patients, cytoreductive nephrectomy followed by interferon-alpha was associated with improved survival compared with interferon-alpha alone.[38,39] Such trials support the hypothesis that cytoreductive surgery may decrease the tumor burden, alleviate tumor-mediated immunosuppression, and improve the response to systemic therapy.

Few high-quality studies have examined the survival benefit of LND in M1 RCC.[1] In one institutional analysis of 305 patients who underwent cytoreductive nephrectomy, including 62% with concomitant LND, LND was not associated with a difference in cancer-specific or all-cause mortality.[12] Moreover, there was no survival benefit to LND, even among patients with cN1 RCC or across increasing probability thresholds for pN1 disease, ranging from 20% to 80%. In another study of 258 patients undergoing cytoreductive nephrectomy, including 69% who underwent LND, there was no difference in overall survival.[11]

Despite the underlying biologic plausibility discussed elsewhere in this article, the lack of a survival benefit to LND in the metastatic setting likely reflects the finding that lymph node–positive disease is more often associated with aggressive disease biology. Several studies have noted an increased incidence of higher pT stage, coagulative tumor necrosis, and sarcomatoid differentiation in the setting of pN1 disease.[12,37] More aggressive biology, even in the presence of metastatic disease, may therefore confer a worse prognosis with rapid systemic progression, obviating the potential benefits of cytoreduction. Moreover, this biology may also explain the observation that nodal stage is independently associated with a worse prognosis, even in the presence of distant metastatic disease.[1]

RENAL CELL CARCINOMA WITH ISOLATED LYMPH NODE METASTASES (pN1 M0 RENAL CELL CARCINOMA)

The natural history of RCC with isolated lymph node metastases not only represents the outcomes of an advanced disease state but, more importantly, provides a unique case study to examine the potential survival benefit of LND. That is, in the nonmetastatic setting, patients with isolated lymph node metastases represent the specific population who may benefit from therapeutic LND, because resection of all sites of nodal metastases should render cure in the setting of otherwise nonmetastatic RCC. To this end, several groups have described the natural history of pN1 M0 RCC.

In the largest single-institution series on the topic of 138 patients with pN1 M0 RCC, the authors reported 5-year metastasis-free survival of only 16%.[40] Moreover, the median time to the development of metastases was only 4.2 months. The authors also identified clinicopathologic features associated with the development of metastases and mortality, which included markers of aggressive disease biology, such as coagulative tumor necrosis, sarcomatoid differentiation, and pT4 stage.[40] In another study of 68 patients with pN1 M0 RCC, only 22.1% were disease free at a median of 43.5 months, and distant recurrence developed within 4 months postoperatively in 51% of patients.[41] Other studies have reported similar oncologic outcomes for pN1 M0 RCC, with 5-year cancer-specific survivals ranging from 22% to 74% and overall survivals from 17% to 53%.[1]

These observations suggest that the overwhelming majority of patients with clinically isolated lymph node metastases harbor occult systemic disease, with rapid progression after surgery. Interestingly, the anatomic basis for the lymphatic drainage of the kidney may explain such behavior. As discussed elsewhere in this article, anatomic mapping studies demonstrate several mechanisms for early hematogeneous dissemination, bypassing the retroperitoneal lymph nodes, including direct communication of efferent lymphatics to the thoracic duct, and direct lymphovenous communications to the renal vein and vena cava.[21]

Still, a small subset of patients demonstrates durable long-term survival.[1] Such patients are more likely to harbor less aggressive tumors. In 1 study, long-term survivors had tumors with lower pT stage and grade, and a lesser incidence of adverse pathologic features.[40] Nonetheless, for the majority of patients, it seems that lymphotropic

RCC tends to reflect an aggressive tumor biology, which portends an ominous prognosis.

MORBIDITY OF LYMPH NODE DISSECTION

In the absence of high-quality data to support a survival benefit, the role of LND is predominantly limited to disease staging. However, if such a role is to be tenable in the management of advanced and/or metastatic RCC, LND cannot be associated with substantial incremental morbidity. To this end, several studies reinforce that, in experienced centers, LND is not associated with increased perioperative morbidity.

In the only randomized data on the topic, EORTC 30881 reported that the performance of LND was not associated with an increase in complications.[9] In that trial, the overall complication rate was 26% for patients undergoing LND compared with 22% for radical nephrectomy alone. Observational studies reinforce these findings. In a secondary analysis of the ASSURE trial, the overall complication rates were 14.2% for LND compared with 13.4% for no LND.[14] In another study, LND was not significantly associated with an increased risk of Clavien grade 3 or higher complications in either M0 or M1 RCC.[42]

SUMMARY

LND does not appear to provide a survival benefit for advanced, nonmetastatic, or metastatic RCC, even in patients at increased risk for lymph node metastases. However, LND serves an important staging role in the management of advanced and metastatic RCC by providing pathologic lymph node stage. LND is not associated with increased perioperative morbidity when performed in experienced centers, which would support a predominantly staging role.

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