Role of Lymphadenectomy for Patients Undergoing Radical Nephrectomy for Renal Cell Carcinoma

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The potential benefits of a lymph node dissection (LND) include more accurate staging, decreased local recurrence rates, and improved survival. However, only limited data support the potential benefits of routine, extensive LND for renal cell carcinoma (RCC). Because of lack of data, no clear practice standard has been established about whether to perform LND and, if so, to what extent. The value of LND for RCC is only relevant if the pattern of lymphatic spread is predictable, which it is not. However, although little evidence supports the value of LND for RCC, it is probable that an occasional patient will have very early metastasis confined to the area of the primary and secondary major lymphatic flow medially and perhaps will benefit therapeutically. In this case, a limited LND is supportable. No information currently available strongly supports the value of a more extensive and potentially more morbid LND for either staging or therapeutic value. Extensive investigation is necessary in order to establish LND as a standard component of RCC surgery.
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Key words: Lymphadenectomy • Renal cell carcinoma • Lymph node dissection

Extensive and meticulous lymphadenectomy for any tumor is designed for either or both of 2 purposes: accurate staging and effective therapy. Although both goals are certainly laudatory, one has to examine them in the light of the specific tumor. Most important is the likelihood of accomplishing either effective staging or effective therapy. To a large extent, this depends on the lymphatic drainage

pattern of the organ involved and the mode of spread of the specific tumor. Although lymphatic draining of renal cell carcinoma (RCC) usually follows general rules, numerous alternate pathways exist. Moreover, RCC frequently has blood-borne metastasis in the absence of lymph spread. For these reasons, only 2 tumors allow us as urologists to enthusiastically embrace and support routine lymph node dissection (LND): cancer of the penis and cancer of the testis. However, recognizing the facts as they exist and the data as we now have them, one still has to make a clinical decision regarding how and when to perform LND. In this point-counterpoint discussion, we describe the potential benefits and risks of LND for RCC and ultimately outline what we do in our own practice.

Standard treatment of RCC, as described by Robson and colleagues in 1969,[1] includes radical nephrectomy as well as removal of "the para-aortic and para-caval lymph nodes from the bifurcation of the aorta to the crus of the diaphragm." The potential benefits of a lymph node dissection (LND) include more accurate staging, decreased local recurrence rates, and improved survival. However, only limited data support these potential benefits for routine, extensive LND for RCC. Because of lack of data, no clear practice standard has been established about whether to perform LND and, if so, to what extent.

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The incidence of positive nodes following a LND for RCC varies depending on the stage of the primary tumor. Therefore, the potential benefits of LND also vary depending on primary tumor stage. Thus, to completely discern whether LND should be a standard component of RCC surgery, one must look on a stage-for-stage basis. However, prior to this, several issues must be addressed, including a discussion of any possible side effects related to LND and a more detailed examination of the lymphatic drainage of the kidneys.

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Morbidity

The potential benefits of LND must be weighed against its risks. The risks of LND include, but are not limited to, bowel damage, chylous ascites, bleeding, and even death.[2-4] However, in general, the added morbidity related to LND is slight.[5-7] In a prospective, randomized study of radical nephrectomy with or without LND (EORTC Protocol 30881), there was no significant increased morbidity associated with LND.[8] The incidence of blood loss greater than 1 L was slightly higher among patients treated with LND (10% vs 7%), although this did not reach statistical significance. Similar findings of increased blood loss that did not reach statistical significance for patients treated with LND has been seen in other series.[7] Extended LND slightly increases surgical time relative to no LND. However, this is a minor drawback and should not be factored into the equation of whether to perform an LND.

Patterns of Lymphatic Spread

The value of LND for RCC is only relevant if the pattern of lymphatic spread is predictable. In a classic study in 1935, Parker[9] outlined the lymphatic drainage from the normal non–tumor-bearing kidney. After coalescing along the various major and minor vascular channels, the lymphatics course along the main renal vessels in the hilum. On the right, they can go to right paracaval nodes or, more commonly, into the interaortocaval region. On the left, they are often found in the hilum or in the left para-aortic region. If these were the only modes of lymphatic drainage of tumors, lymphadenectomy would be much more beneficial. However, it has also been demonstrated that numerous lymphatics course in Gerota's fascia and the perinephric fat and may spread along various routes, including diaphragmatic branches, various parasitized vessels, and along the cava into the thoracic region. In addition, single lymph node involvement has been found distally along the great vessels, presumably coursing from lymphatics along either aberrant accessory vessels or the ureter.

Clinical data supporting this lack of specificity of primary drainage to the para-aortic and/or paracaval nodes are abundant. Johnsen and Hellsten[10] performed an autopsy study of 554 subjects in whom RCC was unknown until autopsy and found 80 cases with lymph node involvement. Of these 80 subjects, only 21 (26%) had positive nodes in the para-aortic and/or paracaval nodes only. Moreover, only 5 (6%) of the 80 subjects had no additional sites

of metastasis. Thus, the overall unpredictable pattern of lymph node spread and low incidence of lymph node–only metastases puts into serious question the potential therapeutic value of routine LND for RCC.

LND for Staging

One of the potential benefits of LND for RCC is improved pathologic staging. Recognizing the presence of lymph node involvement can be helpful. First, it can guide the planning of future follow-up of the patient. Second, on rare occasions, patients have resectable local recurrence in the lymph nodes. Third, this information will be important for new adjuvant trials being developed. However, the current lack of proven benefit for adjuvant treatment in patients with high-risk, completely resected RCC[11,12] makes the benefit of improved staging less clear.

To understand the role of LND in improved staging, one must look at the risk of lymph node involvement. Among all patients, the overall risk of lymph node metastasis is approximately 20%. However, the risk of lymph node involvement varies greatly depending on primary tumor stage and size, renal vein involvement, presence of metastases, and extent of LND dissection performed.[7,13-16] Patients with clinically localized disease have a relatively low incidence (2%-9%) of nodal involvement,[8,16-19] whereas the incidence of nodal involvement in patients with metastatic disease or renal vein involvement is as high as 45%.[15,20] Not surprisingly, Terrone and colleagues,[16] in a retrospective study, found that the incidence of positive nodes significantly depended on the number of nodes removed. For patients with fewer than 13 nodes removed, the incidence of positive nodes was 10%, compared with 21% for patients with 13 or more nodes removed.

Improved staging is most relevant in identifying the patient with apparent early-stage disease who has pathologically malignant lymph node involvement. However, the majority (58%-95%) of patients with lymph node involvement have associated synchronous metastatic disease.[7,10,14,21] Thus, the likelihood of identifying a patient with lymph node–only involvement is low, and it is difficult to justify routine LND for all patients in order to identify those few rare patients.

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The one value that LND may have for staging is in the patient with enlarged lymph nodes on preoperative imaging. Studer and colleagues[22] studied this patient population and found that, although axial computed tomography scans were highly sensitive (95%) for detecting enlarged nodes, many of these nodes did not contain cancer. Indeed, among 43 patients with enlarged lymph nodes (1.0-2.2 cm), 58% had enlargement due to inflammatory changes and/or follicular hyperplasia. Thus, fewer than half of patients with moderately enlarged nodes actually have lymph node metastasis. Therefore, a strong argument can be made that, for the patient with no evidence of metastatic disease and enlarged lymph nodes on preoperative imaging, an LND may prove valuable for staging. However, it should again be noted that no adjuvant therapy has been shown to reduce mortality for high-risk patients with completely resected RCC.

LND to Prevent Local Recurrence

Another potential benefit of LND is a reduction in local recurrence. One possible source for local recurrence may be unresected tumor-bearing lymph nodes. However, other sources exist, including the adrenal gland when adrenal-sparing surgery is performed and the kidney when nephron-sparing surgery is performed. A recent series from UCLA found the local recurrence rate to be less than 1% whether an LND was performed or not.[7] Similarly, data from the nephron-sparing literature demonstrate that the incidence of local recurrence following partial nephrectomy, for which LND is rarely performed, is generally less than 3%.[23,24] Thus, given the low overall rate of local recurrence, it is difficult to justify routine LND in order to reduce the risk of local recurrence.

LND to Improve Survival

Over 20 years ago, it was stated that "the impact of regional lymphadenectomy on survival of patients with renal carcinoma is difficult to quantify."[25] Although various studies have sought to address this issue, the ultimate conclusion remains that the impact of LND on survival is unclear. The patient with lymph node involvement who can potentially be cured by LND is one who has very early lymph node metastasis and no metastatic disease. As discussed above, approximately 20% of patients present with lymph node involvement, of whom approximately two thirds will also have metastatic disease.[7] Thus, only 5% to 10% of patients have lymph node–only metastasis and would potentially benefit from an extended LND. However, 5-year survival among men with positive lymph nodes following an extensive LND, which

would include all patients who were theoretically cured by LND, is 20% to 50%.[1,14,19,26] Assuming the most optimistic estimate of 50% survival, a maximum of 2% to 5% of patients undergoing nephrectomy for RCC could be cured by an extensive LND who would not be cured without it.

To examine the impact of LND on survival requires a prospective, randomized study. Only 1 such study has been performed: EORTC protocol 30881.[8] This study evaluated patients with non-metastatic RCC who underwent radical nephrectomy with or without LND from the crus of the diaphragm to the bifurcation of the aorta. After a median 5-year follow-up, there were no differences in progression or survival between patients who had an LND and those who did not. The authors note that the overall 5-year survival was high (82%) and longer follow-up is needed.

While the long-term results of this prospective study are accruing, we can look at the results of several retrospective studies that examined the impact of LND on survival.[5,6,17,18,27] A number of the studies found no difference in survival between patients who had no or limited LND versus those who had extended LND for all stages of RCC.[6,17,18] Other studies found no difference in survival for low-risk patients but demonstrated a survival benefit for high-risk patients and/or patients with metastatic disease treated with LND.[7,27] Specifically, Peters and Brown[27] demonstrated an 18% improvement in 5-year survival for patients with stage C disease treated with LND. However, important data regarding the number and extent of lymph node positivity were missing from this article. Moreover, improvements in imaging since publication of this study (1980) would allow the preoperative identification of patients with nodal disease who would be most likely to benefit from LND. Other studies that demonstrated a survival advantage for LND suffer from similar limitations.[5,28,29]

One particular study, by Herrlinger and colleagues,[5] deserves a special mention. In this retrospective, nonrandomized study, the authors found improved survival with LND for patients with stage pT1-3a (Robson stage I and II) disease but not for those with Robson stage III (pT3b, N0-3, M0) disease. Specifically, for patients with pT1-T2, N0 tumors, the authors found a 26% improvement in 10-year survival among patients treated with systematic LND relative to facultative LND. It is difficult to accept this dramatic improvement in survival in light of the fact that the difference in incidence of nodal involvement between the 2 groups was 8%. One possible explanation reflects an understaging among men not treated with LND, in that men treated with LND and found to have nodal metastasis were considered as Robson stage III. Thus, in only examining patients with Robson stages I and II (no nodal metastasis), the authors are comparing the survival of patients with clinically negative nodes (no LND) to patients with pathologically negative nodes (plus LND). As expected, a subset of patients with clinically negative nodes will have positive nodes at the time of LND and, therefore, be upstaged. This unfair comparison between clinical and pathologic staging must be kept in mind when interpreting the results of retrospective series.

Several recent studies have shed light on the value of LND for patients with both nodal and disseminated metastasis. Studies from both UCLA and the National Institutes of Health found that, among patients with metastatic disease, the simultaneous occurrence of nodal metastasis imparts a worse prognosis.[30,31] However, in a separate study from UCLA, Pantuck and colleagues[7] found that, among patients with metastatic disease, there was a significant survival advantage for patients who were also treated with LND at the time of cytoreductive nephrectomy. As a

Main Points

- The potential benefits of a lymph node dissection (LND) include more accurate staging, decreased local recurrence rates, and improved survival. However, only limited data support these potential benefits for routine, extensive LND for renal cell carcinoma (RCC).
- The likelihood of identifying a patient with lymph node–only involvement is low, and it is difficult to justify routine LND for all patients in order to identify those few rare patients.
- Given the low overall rate of local recurrence, it is difficult to justify routine LND in order to reduce the risk of local recurrence.
- The patient with lymph node involvement who can potentially be cured by LND is one who has very early lymph node metastasis and no metastatic disease.
- No information currently available supports the value of a more extensive and potentially more morbid LND for either staging or therapeutic value. If future studies define an adjuvant therapy protocol that results in improved survival, the issue of when and how to perform an LND will need to be revisited.

possible mechanism for this improved survival, the authors found that patients with metastatic disease treated with LND had improved responses to immunotherapy. Although this retrospective study is intriguing, further prospective studies are needed to confirm these findings.

Conclusion

Although little evidence supports the value of LND for RCC, occasionally, a patient may have very early metastasis confined to the area of the primary and secondary major lymphatic flow medially and perhaps benefit therapeutically. For these reasons, one of us (JBD) routinely performs a limited LND. Patients with tumors on the right side undergo removal of all the tissue to the right and behind the vena cava as well as the interaortocaval lymph nodes. The superior extent is the renal hilum and the distal extent is the approximate level of the inferior epigastric artery. On the left side, the superior and inferior limits are the same. However, the LND is confined to the left paraaortic lymph nodes. This adds little time or risk to the surgery and provides important staging information. However, no information currently available supports the value of a more extensive and potentially more morbid LND for either staging or therapeutic value. If future studies define an adjuvant therapy protocol that results in improved survival, the issue of when and how to perform an LND will need to be revisited. ■

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