



Is nodal disease burden relevant in patients with renal cell carcinoma and lymph node invasion?

Francisco Rodriguez-Covarrubias

Department of Urology, Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico

Correspondence to: Francisco Rodriguez-Covarrubias, MD. Department of Urology, Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico. Email: frodriguez.covarrubias@gmail.com.

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Lymph node (LN) metastases confer poor prognosis in the vast majority of malignancies and renal cell carcinoma (RCC) is not an exception. Previously, we and other groups have demonstrated that LN invasion is associated with decreased survival in patients with locally advanced RCC (1). In a recent publication, Yu and colleagues analyzed an institutional database of 912 patients with stage III RCC. They found that the outcome of those having nodal involvement was significantly worse than those without nodal involvement and similar to patients with stage IV RCC (2). Ten-year overall survival (OS) described by prior series ranges between 15% and 26% (3,4). However, the results of such series are based on retrospective analysis evaluating the presence or absence of LN metastases as a dichotomic prognostic factor instead of considering the number of positive LN affected by tumor (nodal disease burden).

In addition, despite some efforts, the exact role of LN dissection (LND) in RCC has not been completely clarified. In the only prospective randomized trial assessing LND in patients undergoing nephrectomy for RCC, Blom and colleagues found no survival advantage for lymphadenectomy along with radical nephrectomy (5). Unfortunately, since these investigators included 70.9% of patients with clinical stages T1–T2 kidney tumors in whom LND would not be necessary, their findings do not rule out the chance that LND for high-risk tumors (i.e., stage cT3 or higher) may be of therapeutic value. Accordingly, in a

secondary analysis of a prospective trial assessing the role of lymphadenectomy in patients with high risk completely resected RCC who were randomized to receive adjuvant sunitinib, sorafenib or placebo, Ristau and coworkers found no association between LND and OS at a median follow-up of 67.9 months (6). Interestingly, in this study lymphadenectomy was associated with worse disease-free survival, particularly in patients with pN+ disease who received sunitinib.

Therefore, the impact of LN metastases—including the number of positive LN affected by disease—and the role of LND—and its extent—in patients with high-risk non-metastatic RCC is still controversial. In this regard, recently Zareba and Russo (7) evaluated the prognostic significance of nodal disease burden in 3,656 patients from the U.S. National Cancer Data Base with lymphatic metastases from RCC. These authors found that collecting duct/medullary or unspecified histological subtype conferred worse OS. High grade, tumor necrosis, pathological stage and positive surgical margins were independent predictors of all-cause mortality (ACM). After adjusting for patient, tumor and facility characteristics, an association between higher number of positive LN removed and ACM was confirmed (HR 1.06 per 1 positive LN; 95% CI: 1.04–1.07, $P < 0.001$), with similar findings across tumor histologies, grade and pathological stages, being stronger in those individuals classified as cN0 in comparison to cN1 ($P_{interaction} = 0.028$). Higher negative LN counts were associated with better outcomes. The number

of positive LN removed in comparison to negative ones had also an impact on OS, showing that adjusted 2-year OS probabilities for patients with 1 positive LN removed out of 10 were 64% while for those with 10 positive LN out of 10 were 38%. When positive and negative LN counts were replaced by LN density, a statistical significant association with ACM was confirmed with higher proportion of positive LN (HR 1.04 per 10% increase, 95% CI: 1.02–1.05, $P < 0.001$). Based on their findings, these authors suggest that patients at high risk of harboring LN metastases could benefit from an extended LND, irrespective of the own therapeutic value of LND.

Previously, Marchioni and colleagues analyzed 25,357 RCC patients within the Surveillance, Epidemiology, and End Results (SEER) database of whom 24.8% underwent LND and 17.1% had positive LN (8). They found worse survival with higher number of positive nodes, particularly in pT3 patients and a protective effect on cancer-specific mortality (CSM) from the number of removed nodes in the entire cohort. Although they did not specifically analyze the concept of LN density, they found that the number of positive nodes increased de rate of CSM. In line with this investigation, Tilki and coworkers retrospectively analyzed a multicenter cohort of RCC patients with tumor thrombus managed with surgery to assess the clinical benefit of lymphadenectomy (9). They found that the number of positive nodes as well as LN density were strong prognostic indicators of cancer-specific survival, supporting the evidence showing the negative impact of LN metastases.

Despite heterogeneity of factors analyzed and endpoints evaluated, there is no doubt that LN invasion portends poor prognosis in RCC patients. Although the number of positive LN appears to be relevant, uncertainty remains regarding the exact benefit of LND as well as its extension. LN density has demonstrated to be an accurate prognostic factor in patients with pN+ bladder cancer in whom extended LND is the standard of care (10). Applying the concept of LN density to RCC may be useful to elucidate the exact role of nodal involvement as well as the prognostic and/or potentially therapeutic role of LND. Therefore, this represents an area of opportunity for a prospective trial comparing no LND *vs.* standardized template LND in cT2-3 RCC patients with OS as primary endpoint and CSM as secondary endpoint.

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Footnote

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