Original Study

Pathologic Predictors of Survival During Lymph Node Dissection for Metastatic Renal-Cell Carcinoma: Results From a Multicenter Collaboration

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Abstract

We report clinical outcomes using multi-institutional data to evaluate oncologic efficacy of lymph node dissection (LND) at the time of cytoreductive nephrectomy. Number of positive lymph nodes was an independent predictor for cancer-specific survival. The performance of lymphadenectomy with standard templates in clinical trials of new systemic therapies could further ascertain prognostic value of LND.

Purpose: To determine the therapeutic value of lymph node dissection (LND) during cytoreductive nephrectomy (CN) and assess predictors of cancer-specific survival (CSS) in metastatic renal-cell carcinoma. **Patients and Methods:** We identified 293 consecutive patients treated with CN at 4 academic institutions from March 2000 to May 2015. LND was performed in 187 patients (63.8%). CSS was estimated by the Kaplan-Meier method for the entire cohort and for a propensity score–matched cohort. Cox proportional hazards regression was used to evaluate CSS in a multivariate model and in an inverse probability weighting–adjusted model for patients who underwent dissection. **Results:** Median follow-up was 12.6 months (interquartile range, 4.47, 30.3), and median survival was 15.9 months. Of the 293 patients, 187 (63.8%) underwent LND. One hundred six patients had nodal involvement (pN+) with a median CSS of 11.3 months (95% confidence interval [CI], 6.6, 15.9) versus 24.2 months (95% confidence interval, 14.1, 34.3) for pN− patients (log-rank $P = .002$). The hazard ratio for LND was 1.325 (95% CI, 1.002, 1.75) for the whole cohort and 1.024 (95% CI, 0.682, 1.537) in the propensity score–matched cohort. Multivariate analysis revealed that number of positive lymph nodes ($P < .001$) was a significant predictor of worse CSS. **Conclusion:** For patients with metastatic renal-cell carcinoma undergoing CN with lymphadenectomy, the number of nodes positive was predictive of survival at short-term follow-up. However, nonstandardized lymphadenectomy only provided prognostic information without therapeutic benefit. Prospective studies with standardized templates are required to further ascertain the therapeutic value of LND.

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Introduction

Approximately one third of patients diagnosed with renal-cell carcinoma (RCC) present with locally advanced or metastatic disease.[1] The benefit of cytoreductive nephrectomy (CN) has been well established since before the arrival of targeted therapies.[2,3] The role of lymph node dissection (LND) for RCC, however, has been

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controversial, with data questioning the advantage of node dissection as a result of its minimal impact on survival while adding time to the procedure and requiring manipulation of the great vessels.[4-6]

With the advent of new systemic therapies, the value of LND has been increasingly discussed in the metastatic RCC (mRCC) population.[7] Although there is evidence that metastasectomy along with CN improves survival, the role of concomitant lymphadenectomy is not yet clear.[8-10] Less information is available regarding histologic predictors of survival found at the time of LND.

Previous studies have evaluated the benefit of LND in the CN setting. One study found survival of patients with regional node involvement (pN+) was identical to that of patients with distant metastatic disease, while 2 other studies found those with node involvement had significantly shorter survival than those without regional disease.[11,12] Furthermore, recent studies have not demonstrated improved outcomes for those undergoing LND during CN, yet pN+ disease is a predictor of more aggressive disease and shorter survival.[4,13,14]

The objectives of this study were to report clinical outcomes using multi-institutional data evaluating the therapeutic benefit of LND at the time of CN and to assess its impact on cancer-specific survival (CSS). In addition, we ascertain CSS on the basis of mRCC risk group classification as well as volume of regional disease based on number of positive lymph nodes (pN+) using propensity score–based analyses to minimize selection bias.

Patients and Methods

Data Source and Study Population

The study was performed after receipt of approval from the local institutional review board at each institution. We retrospectively reviewed medical records of 293 patients from 4 academic centers who sought care between March 2000 and May 2015 with mRCC. None of these patients received presurgical targeted therapies for neoadjuvant purposes before proceeding with CN. Chart review was performed to determine site and volume of metastatic disease at the time of nephrectomy. In general, LNDs were either hilar (with or without extension to pre- and para-aortic nodes for left sided tumors or pre- and paracaval nodes for right-sided tumors) or limited only to enlarged lymph nodes for which invasion was suspected (cN1) on cross-sectional imaging. Extent of dissection was not standardized across institutions and was unavailable for analysis.

Disease Classification and Disease-Specific Variables

Using previously defined prognostic factors as described by Motzer et al,[15] patients were stratified on the basis of the 3-factor Memorial Sloan Kettering Cancer Center (MSKCC) criteria (favorable, intermediate, and poor). Other collected variables included age, Charlson comorbidity index, Karnofsky performance status, estimated blood loss, Fuhrman grade, RCC histology, margin status, presence of tumor necrosis, and sarcomatoid or rhabdoid features. All tissue was examined for the presence of metastases by genitourinary pathologists from each institution according to local institutional procedures. Pathologic stage was assigned according to the 2016 American Joint Committee on Cancer staging manual, 8th edition.

Statistical Analysis

Primary outcome was CSS and was calculated from the date of surgery until death from disease. Patient demographics and clinical characteristics were summarized using descriptive statistics. Univariate analyses were performed by chi-square test and Fisher's exact test for categorical variables, and analysis of variance and Kruskal-Wallis test for numerical variables. Survival was estimated for those with complete follow-up by the Kaplan-Meier method and compared by the log-rank test.

Patients were compared on the basis of LND status, and a propensity score–matched model was developed using variables that were significantly different. The propensity score was calculated using the Logistic procedure in SAS 9.4 software (SAS Institute, Cary, NC) following the radius method described in Baser[16] and further expounded in the proceedings of the SAS User Group.[17,18] The variables included were grade, T stage, number of nodes removed, number of nodes positive, number of metastases, MSKCC category, and use of systemic therapy. We did not use imputation in the analysis and assumed missing data at random. For variables with substantial data missing, we checked to see if there were differences in missing and nonmissing values for variables for the analysis in question (eg, survival outcome).

Using Cox proportional hazards regression, the hazard ratio (HR) for LND was analyzed for the whole cohort and an inverse probability weighting–adjusted cohort to minimize selection bias.[19] Within the sample for LND (n = 187), we performed univariate Cox proportional hazards regression followed by a backward selection multivariate model with a significance level of .10 with CSS as the primary outcome of interest. Statistical analyses were performed by SAS 9.4 software.

Results

Study Cohort Characteristics

Demographic and tumor characteristics for the entire cohort are provided in Table 1. Median age of patients was 61 (interquartile range [IQR], 54.7, 70.3) years with a median follow-up of 12.6 (IQR, 4.47, 30.3) months. Median survival of the entire cohort was 15.9 months. Of the 293 patients, 187 (63.8%) underwent LND. Patients who received LND had tumors with significantly higher Fuhrman grades, more sarcomatoid features, more papillary tumor architecture, and a nonsignificant trend to higher stage (Supplemental Table 1 in the online version). One hundred six patients with pN+ disease were found with a median CSS of 11.3 (95% confidence interval, 6.6, 15.9) versus 24.2 (95% confidence interval, 14.1, 34.3) months for patients with pN− disease (log-rank $P = .002$).

There was no significant difference in age, performance status, intraoperative blood loss, or proportion of bone, brain, liver, or polymetastatic disease. Large intraoperative blood loss was explained by numerous level 3 and 4 thrombus patients requiring complex vascular reconstruction. One hundred ninety-four patients (66.2%) received postoperative systemic therapies, with 42.7% receiving tyrosine kinase inhibitors and the rest receiving chemotherapy, immunotherapy, or combined therapy. Propensity score matching produced 65 pairs with adequate balance between LND and no LND for clinical and pathologic covariates (Supplemental Table 1 in the online version).