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Lymph node dissection should not be dismissed in case of localized renal cell carcinoma in the presence of larger diseases

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Abstract

Objective: To assess whether even in the group of localized renal cell carcinoma (RCC), some patients might harbor a disease with a predilection for lymph node invasion (LNI) and/or lymph node (LN) progression and might deserve lymph node dissection (LND) at the time of surgery.

Materials and methods: Between 1990 and 2014, 2,010 patients with clinically defined T1-T2N0M0 RCC were treated with nephrectomy and standardized LND at a single tertiary care referral center. The endpoint consists of the presence of LNI and/or nodal progression, defined as the onset of a new clinically detected lymphadenopathy (>10 mm) in the retroperitoneal lymphatic area with associated systemic progression or histological confirmation or both. We tested the association between clinical characteristics and the endpoint of interest. Predictors consisted of age at surgery, clinical tumor size, preoperative hemoglobin, and platelets levels. Multivariable logistic regression model and smoothed Lowess method were used.

Results: LNI was recorded in 14 cases (2.2%). The median follow-up after surgery was 68 months. During the study period, 23 patients (1.1%) experienced LN progression; 91% of those patients experienced LN progression within 3 years after surgery. Combining the 2 endpoints, 36 patients (1.8%) had LNI and/or LN progression. Clinical tumor size was the only independent predictors of LNI and/or LN progression (OR = 1.25). A significant increase of the risk of LNI and/or LN progression was observed in RCC larger than 7 cm (cT2a or higher).

Conclusions: LNI and/or LN progression is a rare entity in patients with localized RCC. Nonetheless, patients with larger tumors might still benefit from LND because of a non-negligible risk of LNI and/or LN progression.

Keywords: Renal cell carcinoma; Kidney cancer; Lymph node invasion; Lymph node progression; Lymph node dissection

1. Introduction

The value of lymph node dissection (LND) at the time of nephrectomy is controversial for patients with renal cell carcinoma (RCC) [1–3]. There is only 1 available randomized controlled trial (RCT) published in 2008—the European Organization for Research and Treatment of Cancer (EORTC) 30881—that observed low rate of lymph node invasion (LNI) and no survival benefit for patients with clinically node-negative nonmetastatic RCC treated with radical nephrectomy (RN) with LND relative to RN alone [4]. In consequence, the use of LND at the time of surgery was progressively abandoned, especially

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within patients with localized kidney cancer [5]. However, if additional risk factors are present, the risk of LNI significantly increases, even in the setting of localized RCC [6–9].

To date, no contemporary surgical series including patients with localized RCC systematically treated with a standardized LND are available, making all previous studies [4,10–12] not applicable in such setting for the presence of a high rate of false-negative cases (namely patients with misdiagnosed LNI for omitted or inadequate LND). Under this light, for the first time we reported detailed information regarding LND and lymph node (LN) progression, which limits, at least partially, the presence of false-negative cases. The objective of the current study was to assess a possible relationship between preoperative characteristics and LNI and/or LN progression. We hypothesized that between localized RCC patients there are some individuals who may harbor a disease with a predilection for LNI and/or LN progression.

2. Materials and methods

2.1. Study population

Between 1990 and 2014, 2,954 patients with RCC treated with nephrectomy at a tertiary care referral center were assessed. For the aim of the study, we exclusively focused on patients with clinical stage T1 or T2 (cT1–T2), without lymphadenopathies (cN0) and without distant metastases (cM0) at diagnosis. Additional exclusions criteria consisted of patients with uncommon or unclassified carcinoma (n = 35), with only 1 functional kidney (n = 65) and with multiple lesions (n = 158). The final population consisted of 2,010 patients with cT1-T2N0M0 RCC treated with partial nephrectomy (n = 968, 48.2%) or RN (n = 1,042, 51.8%).

2.2. Variable definition

Covariates consisted of age at surgery, sex, body mass index, Charlson comorbidity index [13], clinical tumor size (defined as the greatest tumor diameter in centimetres at preoperative imaging), clinical tumor stage (classified as cT1a vs. cT1b vs. cT2a vs. cT2b) [14], preoperative blood tests (hemoglobin and platelets), and tumor side (left vs. right).

Follow-up consisted of a postoperative baseline visit at 3 months after surgery. Subsequently, the minimum follow-up consisted of at least 2 annual visits. All patients included in this study underwent CT scan or abdomen ultrasound plus chest X-ray at 6 months after surgery and then biannually [14].

2.3. Outcomes

The endpoints of interest were 3. First, we assessed the rate of LNI and/or LN progression in patients with localized RCC. LN progression was defined as the presence of a new radiologically detected lymphadenopathy (>10 mm) in the retroperitoneal lymphatic area with associated systemic progression or histological confirmation or both.

Second, we described the differences between clinical and pathological characteristics between patients with LNI and/or LN progression vs. no LNI and no LN progression.

Third, we investigated which clinical characteristics are associated with LNI and/or LN progression that could help the clinicians to preoperatively identify which localized patients might benefit from LND.

2.4. Lymph node dissection

LND was performed based on the clinical judgment of each treating physician, according to preoperative patient and cancer characteristics and intraoperative assessment by direct palpation. When performed, LND included the paracaval, retrocaval, and precaval nodes from the adrenal vein to the level of the inferior mesenteric artery for the right kidney, and the paraaortic and preaortic nodes from the crus of the diaphragm to the inferior mesenteric artery for the left kidney. Interaortocaval nodes were removed according to the clinical judgment of the surgeons. Fat tissue-containing LNs were sent in separate containers per region and fixed in 10% buffered formalin. All blocks were embedded in paraffin, cut at 3 mm, stained with hematoxylin-eosin, and examined by dedicated genitourinary pathologist for the presence of LNI, defined as one or more metastatic LNs.

2.5. Statistical analyses

Statistical analyses consisted of 3 steps. First, medians and interquartile ranges (IQR) or frequencies and proportions were reported for continuous or categorical variables, respectively. Graphical representation of LNI in patients who underwent LND was performed. Moreover, 1-, 2-, 3- and 10-year LN progression was estimated using Kaplan-Meier method. Patients with LNI and/or LN progression were combined to describe differences in clinical and pathological characteristics between LNI and/or LN progression vs. no LNI and no LN progression. Mann-Whitney U test and Chi-square test were used to compare the statistical significance of differences in the distribution of continuous or categorical variables, respectively.

Second, multivariable logistic regression analyses were used to assess the relationship between clinical characteristics and LNI and/or LN progression. Covariates consisted of age at surgery, clinical tumor size, preoperative hemoglobin, and platelets levels.

Third, locally weighted scatter plot smoothing method (Lowess) was used to graphically explore the relationship between clinical tumor size and LNI and/or LN progression, after accounting for age at surgery, preoperative hemoglobin, and platelet levels.