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Original article

Lymphovascular invasion in clear cell renal cell carcinoma—Association with disease-free and cancer-specific survival

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Abstract

Objectives: The objective is to evaluate the effect of lymphovascular invasion (LVI) on disease-free survival (DFS) and cancer-specific survival (CSS) in patients with clinically localized clear cell renal cell carcinoma (ccRCC).

Methods: Patients with ccRCC who were treated surgically in 1997 to 2010 were identified. Retrospective chart review was performed to identify clinical outcomes. Independent pathologic re-review was performed by a single pathologist to confirm LVI status. Pathologic features were correlated with clinical outcomes using Kaplan-Meier and Cox regression analyses.

Results: Four hundred and nineteen patients with nonmetastatic ccRCC comprised the study cohort. Three hundred and thirty-three of these patients had an organ-confined (pT1-2, N any, and M0) disease. LVI was present in 14.3% of all nonmetastatic patients. In all patients with nonmetastatic ccRCC, presence of LVI was correlated with significantly shorter DFS ($P < 0.001$) and CSS ($P = 0.001$) on Kaplan-Meier analysis. In cases of organ-confined, nonmetastatic ccRCC, presence of LVI was a significant predictor of DFS (hazard ratio = 4.0, $P = 0.026$) and CSS (hazard ratio = 12.7, $P = 0.01$) on multivariate analysis. Patients with organ-confined RCC who were LVI positive had similar DFS ($P = 0.957$) and CSS ($P = 0.799$) to patients with locally advanced tumors (pT3-pT4, N any, and M0) on Kaplan-Meier analysis.

Conclusions: The presence of LVI is an independent predictor of both DFS and CSS in organ-confined, nonmetastatic ccRCC. LVI positivity in patients with otherwise pathologically organ-confined ccRCC confers oncologic outcomes similar to those of patients with locally advanced disease. If confirmed by others, future revisions to the tumor-node-metastasis staging system may incorporate LVI status into the prognostic algorithm of patients with RCC.

Keywords: Renal cell carcinoma; Lymphovascular invasion; Clinical outcomes; Survival; Nephrectomy

1. Introduction

There will be an estimated 64,770 new cases of diagnosed kidney cancer and 13,000 deaths in the United States this year [1]. The 2010 American Joint Committee on Cancer (AJCC) staging system for renal cell carcinoma (RCC) uses tumor size, presence of extraparenchymal extension, venous thrombus, and adrenal invasion to estimate oncologic outcomes. Patients with extraparenchymal extension or venous thrombus or both (pT3a-pT4) have a 10-year cancer specific survival (CSS) of 12% to 36% compared with 55% to 96% for organ-confined disease (pT1a-pT2b) [2]. The AJCC staging system has been validated for determination of outcomes, patient counseling, and trial design [2]. There has been conflicting evidence regarding the utility of additional pathologic features not currently taken into account by the 2010 AJCC staging system, such as lymphovascular invasion (LVI), as predictors of oncologic outcomes. Some studies have shown that LVI has an independent prognostic value [3–12] whereas others did not [13–20]. In this study, we aim to investigate the effect of LVI on disease-free survival (DFS) and CSS in a cohort of patients with clear cell RCC (ccRCC) treated at a large, tertiary referral medical center.

2. Methods

After institutional review board approval, retrospective chart reviews were performed for all patients who underwent

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Table 1
Patient and tumor characteristics for nonmetastatic ccRCC ($n = 419$)

	All nonmetastatic (pT1-4) ($n = 419$)	Organ-confined (pT1-2) ($n = 333$)
Age (range)	57.0 (17–85)	55.9 (17–85)
Median follow-up time, months (range)	26 (0–150)	22 (0–150)
Sex, %		
Women	172 (41.1)	139 (41.7)
Men	247 (58.9)	194 (58.3)
Tumor size, cm, (range)	5.1 (0.6–30)	4.3 (0.6–30)
Fuhrman grade, %		
1–2	288 (68.7)	258 (77.5)
3–4		
LVI, %		
Absent	359 (85.7)	312 (93.7)
Present	60 (14.3)	21 (6.3)
Surgical method, %		
Radical nephrectomy	236 (56.3)	153 (45.9)
Partial nephrectomy	183 (43.7)	180 (54.1)
Lymph node dissection		
No	342 (81.6)	294 (88.3)
Yes	77 (18.4)	39 (11.7)
Lymph node positive		
No	411 (98.1)	333 (100)
Yes	8 (1.9)	0 (0)
Surgical margins		
Positive	28 (6.7)	10 (3)
Negative	391 (93.3)	323 (97)
RCC recurrence, %		
No	384 (91.6)	318 (95.5)
Yes	35 (8.4)	15 (4.5)
Cause of death RCC, %		
No	404 (96.4)	327 (98.2)
Yes	15 (3.6)	6 (1.8)

radical or partial nephrectomy for renal tumors from 1997 to 2010. Only the patients with ccRCC were included in the analyses. Patients undergoing cytoreductive nephrectomy with known metastases were excluded. Lymph node status was not considered to be an exclusion criteria due to low number of lymph node positive patients and low percentage of patients who underwent lymph node dissection. Independent pathologic re-review of 3 representative slides from each patient was performed by a single genitourinary pathologist on all specimens to confirm reported pathologic findings and to confirm LVI status. LVI was defined as the presence of the invasion of cancer cells into blood vessels or the lymphatic system (excluding the renal vein and its muscle containing segmental branches and the inferior vena cava), or both. The pathologic stage was defined based on the 2010 AJCC staging system [21]. Grade was defined using the Fuhrman grading system for RCC [22]. Statistical analysis was performed using Chi-square, Kaplan-Meier, and Cox regression models. DFS was defined as the time from date of surgery to the date of diagnosis of recurrence. CSS was defined as the time from date of surgery to the date of death from ccRCC. Patients who were alive or those who died from causes other than ccRCC were censored at the time of their last known follow-up. Statistical analysis was performed with SPSS software (version 20, Chicago, IL).

3. Results

A total of 477 patients with ccRCC treated with partial or radical nephrectomy between 1997 and 2010 were identified. Four hundred and nineteen patients had nonmetastatic disease and were included in the analysis. Three hundred and thirty-three patients were found to have an organ-confined and nonmetastatic disease (pT1a-pT2). Median follow-up for the whole cohort was 23 months (6–150). The LVI was identified in 18.9% of all patients with ccRCC.

Demographic statistics for entire study cohort, nonmetastatic, and organ-confined patients with ccRCC are shown in Table 1. In the whole cohort of patients with nonmetastatic ccRCC, LVI was present in 14.3% of cases and was found to be associated with shorter DFS ($P < 0.001$) and CSS ($P = 0.001$) on Kaplan-Meier analysis. The LVI status broken down by pathologic stage and Fuhrman grade is demonstrated in Table 3. On multivariate analysis controlling for tumor stage and grade, LVI was not found to be an independent predictor of DFS (hazard ratio [HR] 1.7; $P = 0.20$; 95% confidence interval (CI): 0.77–3.6) or CSS (HR 2.7; $P = 0.09$; 95% CI: 0.9–8.4) in all patients with nonmetastatic ccRCC (Table 2). However, in patients with organ-confined (pT1a-pT2b) ccRCC, LVI was present in 6.3% of cases, and was found to be a significant predictor of shorter DFS ($P < 0.001$) and CSS ($P = 0.003$) on Kaplan-Meier analysis (Fig. 1). Moreover, on multivariable analysis controlling for tumor size and grade, LVI was significantly associated with both DFS (HR 4.0; $P = 0.026$; 95% CI: 1.2–13.7) and CSS (HR 12.7; $P = 0.01$; 95% CI: 1.7–92.7) (Table 2). Patients with organ-confined RCC (pT1a-pT2b), who were LVI positive, had similar DFS and CSS to patients with locally advanced tumors (pT3-pT4) (Fig. 2).

4. Discussion

In our cohort of patients with nonmetastatic ccRCC we found LVI to be present in 14.3% of patients. Specifically, prevalence of LVI in organ-confined (pT1-pT2) and locally advanced (pT3-pT4) nonsystemically metastatic RCC was 6.3% and 45.3%, respectively. Our findings are in-line with the 3 largest series in the literature, which document presence of LVI in 19.8% [20], 11% [19], and 5% [10] of 2,078, 641, and 701 cases of ccRCC, respectively. Our findings are further strengthened by the fact that in all cases, presence or absence of LVI was systematically reassessed by a single genitourinary pathologist.