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Original article

Validation of lymphovascular invasion is an independent prognostic factor for biochemical recurrence after radical prostatectomy

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Abstract

Objective: To validate the impact of lymphovascular invasion (LVI) on biochemical recurrence (BCR) in patients treated with radical prostatectomy (RP) in a large multiinstitutional cohort.

Material and methods: Retrospective data from 6,678 patients treated with a RP and bilateral lymphadenectomy for prostate cancer (PC) from 8 centers were collected. The primary endpoint was BCR.

Results: Overall, 767 patients (11.5%) had LVI. Patients with LVI had significantly higher Gleason scores ($P = 0.01$). After a median follow-up of 28 months (interquartile range: 21–44), patients with LVI had a 1.66 fold increased risk of BCR ($P < 0.001$). The 1-, 2- and 5-year biochemical recurrence-free survival probabilities for LVI vs. no LVI were 94% vs. 97%, 91% vs. 94%, and 76% vs. 84%, respectively. On multivariable analysis that adjusted for the effects of established prognostic factors, LVI was an independent predictor of BCR (hazard ratio $= 1.42$, $P < 0.001$). Adding LVI to a multivariable base model increased the discrimination by a small but significant margin (+0.2%, $P = 0.0005$). In subgroup analyses, LVI remained an independent predictor for BCR in patients with worse pathological features.

Conclusions: About 10% of patients with localized PC have LVI on their RP specimen. We confirm that LVI is associated with features of biologic aggressive PC such as high Gleason grade and BCR after RP. Adverse further studies with strict definitions of LVI and longer follow-up periods are needed to determine the prognostic and predictive utility of LVI in the management of PC.

Keywords: Localized prostate cancer; Biochemical recurrence; Lymphovascular invasion; Radical prostatectomy

1. Introduction

Although radical prostatectomy (RP) results in long-term local disease control, approximately 20% to 30% of patients experience a biochemical recurrence (BCR), which is

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detected by a rise in serum prostate-specific antigen (PSA) levels after RP. The association of certain clinicopathological features such as Gleason score, pathological stage, and lymph node metastasis with BCR has been previously described [1,2], and understanding how these factors affect prognosis is paramount in guiding treatment. Over the past decade, pathological lymphovascular invasion (LVI) has been identified as an independent predictor of disease recurrence after curative treatment for multiple cancer types, including prostate cancer (PC) [3–7].

Previous retrospective studies have reported conflicting results regarding the role of LVI for predicting BCR [8–14,5,7,6]. In their consensus conference on handling and staging of RP specimens in 2009, the International Society of Urological Pathology (ISUP), considered the reporting of microscopic LVI part of the standard pathologic evaluation for RP specimens [15]. Despite this, a recent review suggested that there is insufficient evidence to recommend the routine use of LVI for clinical prognostication [16].

In this present study, we analyzed data from a large multiinstitutional contemporary cohort of patients undergoing RP for clinically localized PC to determine the association of LVI with BCR and whether addition of LVI status would help us better prognosticate PCA outcomes after RP.

2. Patients and methods

2.1. Patient selection and data collection

Data was collected in retrospective fashion from 8 institutions worldwide. All participating sites provided Institutional Review Board approval and the necessary data sharing agreements before the initiation of the study. A central computerized databank was generated for data collection. The initial cohort was composed of 7,427 patients treated with a RP and bilateral standard pelvic lymph node dissection for clinically localized PC between 2000 and 2011. Patients who received preoperative radiotherapy, hormone therapy or chemotherapy before, with positive lymph nodes, and missing data on surgical margin status, preoperative prostate-specific PSA and RP Gleason score were excluded. A total of 6,678 patients were included in the final dataset. No patient had evidence of distant metastasis at the time of surgery.

2.2. Pathological specimens

Surgical specimens were processed according to standard pathologic procedures by according to international standards [17]. The entire prostate was submitted for pathological evaluation. All cases were reviewed by 1 pathologist at each institution to confirm Gleason grading according to the most recent ISUP classification and LVI. LVI was defined as the presence of tumor cells within an endothelium-lined space. Pathologic stage was assessed according to the 2009 American Joint Committee on Cancer (AJCC) TNM staging system. Samples with tumor cells in contact with the inked surface of the prostatectomy specimens were considered as having a positive pathological margin.

2.3. Follow-up

Patient follow-up was institution- and physician-dependent. Most patients were followed quarterly within the first year, semiannually in the second year and annually thereafter with a digital rectal examination and PSA. BCR was defined as a PSA >0.2 ng/ml by 2 subsequent measurements. No patient underwent adjuvant hormonal therapy or radiotherapy.

2.4. Statistical analysis

Categorical variables are presented as numbers and percentages, and continuous variables as median and interquartile range. Group differences in categorical variables and continuous variables were analyzed with χ^2 tests and Kruskal-Wallis tests, respectively. The endpoint of this study was BCR-free survival, which was calculated from the date of RP to BCR or last follow-up, respectively. The Kaplan-Meier method was used to estimate BCR-free survival. Survivor functions were compared using log-rank tests. Uni- and multivariable estimates were obtained from Cox regression models as hazard ratios and 95% CI. Discrimination of multivariable models was evaluated with the concordance (C) index. Discrimination between models was compared with likelihood ratio tests. Statistical testing was 2-sided and a $P < 0.05$ was considered statistically significant. Analyses were all conducted with STATA 12 (College Station, TX).

3. Results

3.1. Cohort characteristics

Of the 6,678 patients, 767 (11.5%) showed LVI at RP. Among the 1,702 patients with pT3 disease, 213 (12.5%) had LVI. Clinical and pathological characteristics are listed in Table 1. The LVI group showed significantly higher Gleason scores ($P = 0.01$). Preoperative PSA levels and the frequencies of extracapsular extension, seminal vesicle invasion, and positive margins were similarly distributed between the 2 groups. Patients with LVI tended to be older than those without ($P = 0.054$).

3.2. Association between LVI and BCR

After a median follow-up of 28 months (interquartile range: 21–44), 689 (10.3%) patients demonstrated BCR.