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Prognostic significance of lymphovascular invasion in radical prostatectomy specimens

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Abstract

OBJECTIVES—To determine whether lymphovascular invasion (LVI) in radical prostatectomy (RP) specimens has prognostic significance.

The study examined whether LVI is associated with clinicopathological characteristics and biochemical recurrence (BCR).

PATIENTS AND METHODS—LVI was evaluated based on routine pathology reports on 1298 patients treated with RP for clinically localized prostate cancer between 2004 and 2007.

LVI was defined as the unequivocal presence of tumour cells within an endothelium-lined space.

The association between LVI and clinicopathological features was assessed with univariate logistic regression. Cox regression was used to test the association between LVI and BCR.

RESULTS—LVI was identified in 10% (129/1298) of patients.

The presence of LVI increased with advancing pathological stage: 2% (20/820) in pT2N0 patients, 16% (58/363) in pT3N0 patients and 17% (2/12) in pT4N0 patients; and was highest in patients with pN1 disease (52%; 49/94).

Univariate analysis showed an association between LVI and higher preoperative prostate-specific antigen levels and Gleason scores, and a greater likelihood of extraprostatic extension, seminal vesicle invasion, lymph node metastasis and positive surgical margins (all $P < 0.001$).

With a median follow-up of 27 months, LVI was significantly associated with an increased risk of BCR after RP on univariate ($P < 0.001$) and multivariate analysis (hazard ratio, 1.77; 95% confidence interval, 1.11–2.82; $P = 0.017$).

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CONFLICT OF INTEREST
None declared.

As a result of the relatively short follow-up, the predictive accuracy of the standard clinicopathological features was high (concordance index, 0.880), and inclusion of LVI only marginally improved the predictive accuracy (0.884).

CONCLUSIONS—Although associated with features of aggressive disease and BCR, LVI added minimally to established predictors on short follow-up.

Further study of cohorts with longer follow-up is warranted to help determine its prognostic significance.

Keywords

prostate; prostatic neoplasms; prostatectomy; disease progression; lymphovascular invasion

INTRODUCTION

Predictive models have been developed to identify patients at increased risk for disease recurrence after radical prostatectomy (RP). Accepted clinicopathological factors associated with disease recurrence after RP include serum PSA, Gleason score, pathological stage, lymph node metastasis and status of the surgical margins [1]. Lymphovascular invasion (LVI) is an additional pathological feature that has been receiving attention as a potential risk factor for cancer recurrence, and the College of American Pathologists has recommended reporting whether or not LVI was identified in the RP specimen [2]. It is hypothesized that the presence of LVI could indicate micrometastases as seen in other malignancies, such as urothelial carcinoma [3–5].

Previous retrospective studies report not only differing incidence rates of LVI, but also differing conclusions with respect to its prognostic significance [6–20]. In the present study, data from a large contemporary cohort of patients treated with RP for clinically localized prostate cancer were analyzed to determine whether LVI was associated with either clinicopathological characteristics or biochemical recurrence (BCR), and whether the presence of LVI was more important in patients with organ-confined disease. In addition, the study examined whether a postoperative model (i.e. a nomogram) predicting BCR after RP could be improved by including LVI as a factor.

PATIENTS AND METHODS

PATIENT POPULATION

Between August 2004 and July 2007, 2150 consecutive patients with clinically localized prostate cancer were treated with RP at Memorial Sloan-Kettering Cancer Center. Patients who received neoadjuvant therapy (n = 145) were excluded. The pathology reports of the remaining patients were reviewed. Pathology reports that did not include LVI status (n = 379) or other pathological features (Gleason score, extent of extraprostatic extension, seminal vesicle invasion or lymph node metastasis; n = 328) were also excluded, leaving a total of 1298 patient reports available for univariate analyses of pathological features. Of these, 74 were missing PSA measurements and 75 had no data on BCR, leaving 1149 patient

reports available for multivariate analyses for BCR. Patient data were collected prospectively and entered into an electronic database.

Patients were followed at 3-month intervals for the first year, at 6-month intervals for the next 4 years, and annually thereafter with DRE and serum PSA measurements. BCR was defined as a serum PSA >0.1 ng/mL at least 6 weeks after surgery with a confirmatory rise. Patients who received adjuvant therapy (n = 24) before BCR were not considered to have disease recurrence until they met the same criteria.

PATHOLOGICAL EVALUATION

All RP specimens were uniformly processed and submitted in their entirety. The prostate and seminal vesicles were fixed in 10% neutral formalin overnight after inking the outer surface. The superficial fragments of muscular tissue surrounding the proximal urethra were shaved and the most apical 3 mm was embedded on end after radial sectioning in cone-like fashion, to allow assessment of both the bladder neck and inked apical margins. The seminal vesicles were amputated at their junction with the prostate and submitted separately. Finally, the remaining prostate was serially sectioned from apex to base at 3- to 5-mm intervals and submitted as whole-mount sections for examination. Whole-mount sections of 5 μm thickness were stained with haematoxylin and eosin. Specimens were assigned a Gleason grade and staged according to the 2002 TNM clinical staging system developed by the American Joint Committee on Cancer and the International Union Against Cancer. LVI was defined as the unequivocal presence of tumour cells within an endothelium-lined space (Fig. 1). Because of the difficulty and lack of reproducibility when using routine light microscopy, no attempt was made to differentiate between lymphatic and vascular vessels [17]. LVI was identified based on routine pathology reports and, beginning in August 2004, was a parameter that required a yes or no response on our institutional online synoptic sign-out sheet. A positive surgical margin was defined as presence of tumour cells at the inked margin of the specimen.

STATISTICAL ANALYSIS

Univariate logistic regression was used to evaluate the association between LVI and clinicopathological features (preoperative PSA level and Gleason score, postoperative extraprostatic extension, seminal vesicle invasion, lymph node metastasis and surgical margin status). The probability of freedom from BCR following RP was estimated using Kaplan–Meier methods. Multivariate Cox regression analysis was used to test for the association between LVI and BCR, adjusting for the effects of preoperative PSA and standard pathological features (Gleason score, extraprostatic extension, seminal vesicle invasion, lymph node metastasis and margin status). The present study also explored whether the association between LVI and BCR was different according to pathological stage (≤ pT2 vs > pT2) by including an interaction term between LVI and pathological stage in the multivariate model.

To determine whether the addition of LVI improved the predictive accuracy of a base postoperative nomogram that included preoperative PSA and standard pathological features, the concordance index of the model was calculated with and without the addition of LVI

[21] and bootstrap methods were used to reduce overfit bias, which may inflate the predictive accuracy [22]. $P < 0.05$ (two-sided) was considered statistically significant. Statistical analyses were performed using the Stata 10 software package (StataCorp, College Station, TX, USA).

RESULTS

Table 1 lists the clinical and pathological features that were included in the present evaluation and their associations with LVI in 1298 patients treated with RP for clinically localized prostate cancer. The median patient age was 59 years and the median preoperative serum PSA level was 5.3 ng/mL.

Overall, LVI was identified in 10% (129/1298) of patients. The presence of LVI increased with advancing disease stage: it was found in 2% (20/820) of patients with pT2N0 disease, 16% (58/363) with pT3N0 and 17% (2/12) with pT4N0, and was highest in patients with pN1 disease (52%, 49/94). Patients with LVI were more likely to have pT3 or higher stage disease than those without LVI (81% vs 30%, respectively). On univariate analyses, LVI was associated with higher preoperative PSA, higher pathological Gleason score, extraprostatic extension, seminal vesicle invasion, lymph node metastasis and positive surgical margins (all $P < 0.001$). Some 43% of men with LVI had a Gleason score of ≥8 vs only 4% of men without LVI.

In total, 99 of the 1149 patients included in multivariate analyses experienced BCR, including 41 patients with LVI and 58 without. The median follow-up for patients without BCR was 2.3 years. The 2-year BCR-free probability was 95% (95% CI, 94–96) for men without LVI and 62% (95% CI, 52–71) for those with LVI (Fig. 2).

On univariate analysis, LVI was significantly associated with an increased risk of BCR after RP ($P < 0.001$) and remained significantly associated after adjusting for the effects of preoperative PSA and standard pathological features in multivariate analysis (hazard ratio, HR, 1.77; 95% CI, 1.11–2.82; $P = 0.017$) (Table 2).

In evaluating whether the addition of LVI improved the predictive accuracy of the standard clinicopathological features, it was noted that the standard model's concordance index (0.880) was higher than previously reported [23]. This is likely a result of the short length of follow-up; it is much easier to predict those patients who will experience BCR in the short term (<2 years) than over the long term (>5 years). Given the high predictive accuracy of the base model, the concordance index would not be expected to be substantially improved by the inclusion of any additional variable. The addition of LVI improved the predictive accuracy of the postoperative nomogram only marginally (from 0.880 to 0.884).

There was no evidence to suggest that organ-confined disease status modified the association between LVI and BCR ($P = 0.5$ for interaction term). In a model that included only LVI, lymph node involvement, and an interaction term, the effect of LVI appeared to be stronger without lymph node involvement (HR, 2.75; 95% CI, 1.17–6.43; $P = 0.020$ for interaction term); however, after adjustment for the effects of standard prognostic variables, this association was no longer statistically significant ($P = 0.9$). This is probably a result of

patients with LVI in the subgroup with negative lymph nodes being more likely to have extraprostatic extension or seminal vesicle invasion compared to those without LVI (72% vs 29%).

DISCUSSION

The present study identified LVI in 10% of patients undergoing RP for clinically localized prostate cancer. The reported incidence of LVI is in the range 5–53% (Table 3) [6–20]. Among the 363 patients in our series with pT3N0 disease, the LVI rate was 16%, below the reported rates of 22–35% in previous studies [12,15]. These discrepancies may be attributable to various factors, including specimen handling, differences in patient populations, inter-observer variability and the lack of uniform definitions of LVI. LVI was defined in the present study as the unequivocal presence of tumour cells within an endothelium-lined space. However, to ultimately assess the true prognostic value of LVI, standardized histological criteria and consistent pathological examination are essential.

In the present study, the strong and significant association of LVI with established adverse clinicopathological features was confirmed, including higher preoperative PSA, higher Gleason score, extraprostatic extension, seminal vesicle invasion, lymph node metastasis and positive surgical margins [8,11,14,18]. Although an association with pathological features is interesting, an association with BCR after RP is more important in the management of patients with prostate cancer. LVI was found to be an independent predictor of BCR after RP in a multivariate analysis that controlled for the effects of standard predictors. Infiltration of the vascular and/or lymphatic structures by tumour cells is an important step in tumour dissemination because these pathways enable them to access distant organs. The initial entry of neoplastic cells into the circulation occurs through the local microvascular network, including the lymphatic and/or blood vessels. This premise, together with the strong association of LVI with lymph node metastasis and BCR after apparently effective local treatment, suggests that LVI plays a role in the metastatic process.

The addition of LVI, however, only marginally improved the concordance index (from 0.880 to 0.884) of our postoperative nomogram, and therefore was not clinically meaningful. Because LVI was significantly associated with all other standard prognostic features, its limited clinical usefulness is not unexpected once these features are taken into account. On the other hand, although the small incidence of LVI may limit its statistical value, its real value may be in helping clinical decision-making regarding receiving adjuvant therapy for patients treated with RP.

Previous studies have investigated the predictive value of LVI with conflicting results (Table 3) [6–20]. Although several studies found LVI to be an independent predictor of BCR [6,8–13,15,16,19,20], others did not [7,14,17,18]. Unlike the present study, these studies found that LVI was associated with BCR after RP on univariate, but not multivariate, analysis [14,18]. Loeb *et al*. [14] concluded that the effect of LVI on BCR was mediated through its strong association with other adverse pathological features. Shariat *et al*. [18] also failed to show an independent association between LVI and BCR, but found that LVI was associated with established features of biologically aggressive prostate cancer (e.g.

shorter PSA doubling times after biochemical failure, rapid failure to respond to salvage local radiation therapy and, most remarkably, increased likelihood of early distant metastases and death). According to Shariat *et al*. [18], the association of LVI with early biochemical and clinical disease progression suggests that LVI is a feature of the metastatic process, putting patients at the highest risk for early metastasis and death.

Conversely, May *et al*. [15] found LVI in 10% of 412 patients undergoing RP, and reported an association between LVI and higher preoperative PSA, PSA density, percentage of positive biopsy cores, Gleason score and seminal vesicle invasion. A statistically significant difference in BCR-free probability between patients with and without LVI was also shown [15].

Given these divergent results, the prognostic significance of LVI remains unclear. Although some studies find LVI to be a statistically significant factor in predicting BCR, it may not be useful in improving existing prognostic models. In their 1999 consensus statement, the College of American Pathologists considered LVI a category 3 prognostic factor, meaning that there was insufficient evidence to support its prognostic value [24]. Currently, they consider the assessment of LVI to be clinically important, at the same time recognizing that it has not yet been validated and is not regularly used in patient management [2].

LVI may have differing prognostic significance for specific subgroups of patients with prostate cancer. Patients with pT3N0 tumours have an intermediate risk of disease recurrence after RP compared to patients with organ-confined or lymph node-positive disease. In a cohort of 263 patients with pT3N0 tumours, Herman *et al*. [12] found LVI to be an independent predictor of disease recurrence on multivariate analysis. Similarly, studies by Epstein *et al*. [10] and Yamamoto *et al*. [20] found LVI to be an independent predictor of BCR in patients with pT3aN0 and pT3b tumours. In a study by Babaian *et al*. [6], LVI was associated with BCR in the overall population but not in the pT2 (margin negative or positive) disease subgroups. In the present study, there was no evidence to suggest that the association between LVI and BCR was stronger in either pT2N0 or pT3N0 disease subgroups.

Several limitations of the present study should be acknowledged. We did not quantitate the extent of LVI or determine the location of LVI foci because other investigators have found adverse outcomes even among cases with a limited number of foci [11,12]. As with previous studies, LVI was identified based on routine pathology reports rather than a detailed slide review by a single uropathologist. Another limitation is that the inherent difficulty in determining the presence of LVI at the morphological level is exacerbated when there are significant differences between local pathologists and central pathology review [8,25]. For example, retraction artefacts present in the surrounding stromal tissue can mimic vascular invasion [26,27]. In addition, we did not perform immunohistochemical staining for endothelial markers (e.g. CD31) because this is not recommended for the routine evaluation of LVI. We also did not perform immunohistochemical staining to identify the vessels because heterogeneity in the expression of immunohistochemical markers by different capillary structures renders it impractical for routine clinical use [28,29].

Other potential shortcomings of the present study include not addressing the impact of LVI location (i.e. peritumoural vs intratumoural invasion) [30] or the differential impact of lymphatic vs blood vasculatures on outcomes. In most cases, only capillary structures are recognizable, making it very difficult to distinguish lymphatics from blood vessels. Although fairly reliable vessel identification is possible with haematoxylin and eosin staining, it is of utmost importance that strict morphological criteria are established to standardize and make the diagnosis of LVI reproducible, and consequently allow its recommendation in a clinical setting.

Finally, the present study was performed at a tertiary referral centre and may not be applicable to the general population of patients with prostate cancer. Despite these limitations, we found that LVI was a significant independent predictor of BCR. Its inclusion as an additional pathological feature, however, did not meaningfully improve the accuracy of a postoperative nomogram predicting BCR after RP.

LVI is present in ≈10% of RP specimens taken from patients with clinically localized prostate cancer. Although the inclusion of LVI only marginally improved the predictive accuracy of the concordance index of established clinicopathological variables, it is associated with features of aggressive disease and is an independent predictor of BCR. Longer follow-up is needed to corroborate these results and to determine whether LVI is a useful prognostic indicator in prostate cancer.

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Abbreviations

BCR	biochemical recurrence
HR	hazard ratio
LVI	lymphovascular invasion
RP	radical prostatectomy

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What's known on the subject? and What does the study add?

The reported incidence of lymphovascular invasion (LVI) in radical prostatectomy specimens ranges from 5% to 53%. Although LVI has a strong and significant association with adverse clinicopathologic features, it has almost uniformly not been found to be a predictor of biochemical recurrence (BR) on multivariate analysis.

This study confirms that LVI is associated with features of aggressive disease and is an independent predictor of BCR. Given that LVI may play a role in the metastatic process, it may be useful in clinical decision-making regarding adjuvant therapy for patients treated with RP.

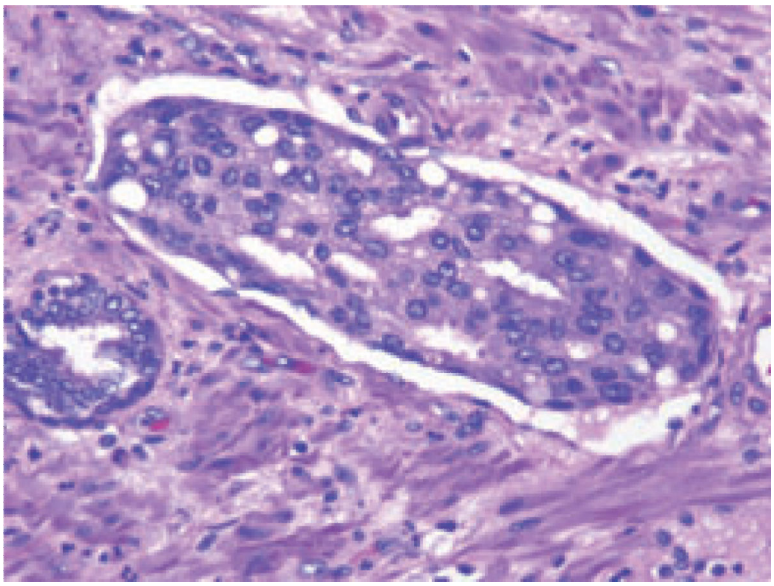

FIG. 1.
Lymphovascular invasion in prostate cancer. Magnification ×200.

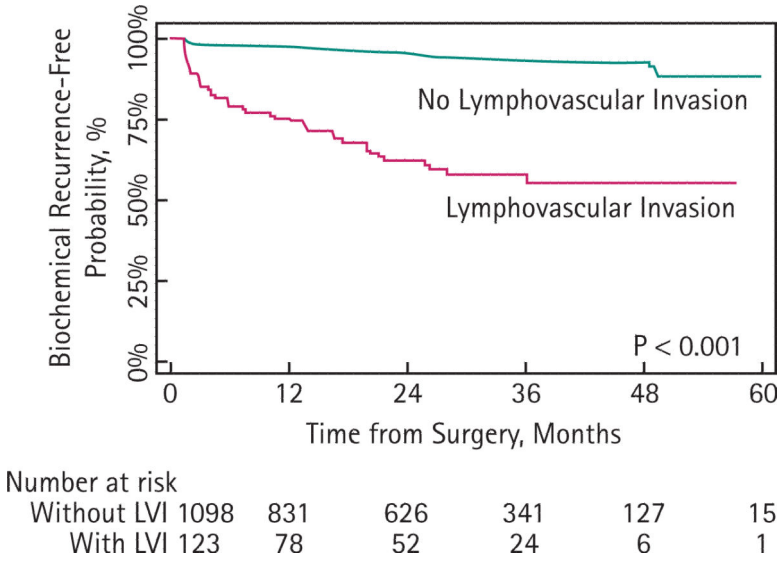

FIG. 2.

Probability of freedom from biochemical recurrence according to the presence or absence of lymphovascular invasion.

TABLE 1

Association between lymphovascular invasion and clinicopathological features in 1298 patients treated with radical prostatectomy for clinically localized disease

Characteristics	Patients (*n*)	Lymphovascular invasion		*P*
		Absent (*n* = 1169)	Present (*n* = 129)	
Age (years), median (IQR)	1298	59 (55–64)	61 (56–66)	NA
Preoperative PSA (ng/mL), median (IQR)*	1224	5.1 (3.7–7.1)	7.3 (4.9–11.3)	<0.001
Gleason score, *n* (%)				<0.001
2–6	320 (25)	314 (27)	6 (5)	
7	874 (67)	806 (69)	68 (53)	
8–10	104 (8)	49 (4)	55 (42)	
Extraprostatic extension, *n* (%)				<0.001
Absent	853 (66)	821 (70)	32 (25)	
Present	445 (34)	348 (30)	97 (75)	
Seminal vesicle invasion, *n* (%)				<0.001
Absent	1208 (93)	1128 (96)	80 (62)	
Present	90 (7)	41 (4)	49 (38)	
Lymph node metastasis, *n* (%)				<0.001
Absent	1204 (93)	1124 (96)	80 (62)	
Present	94 (7)	45 (4)	49 (38)	
Surgical margins, *n* (%)				<0.001
Negative	1127 (87)	1034 (88)	93 (72)	
Positive	171 (13)	135 (12)	36 (28)	

*Missing in 74 patients. IQR, interquartile range; NA, not applicable.

TABLE 2

Multivariate Cox regression analysis of clinicopathological features for the prediction of biochemical recurrence in 1149 patients treated with radical prostatectomy for clinically localized disease

	Hazard ratio	95% CI	*P*
Preoperative PSA	1.02	1.01–1.04	0.004
Lymphovascular invasion	1.77	1.11–2.82	0.017
Gleason score			<0.001
≤6	1.00	Reference	–
7	4.64	1.10–19.55	
≥8	12.35	2.75–55.43	
Extraprostatic extension	3.45	1.91–6.22	<0.001
Seminal vesicle invasion	2.33	1.44–3.75	<0.001
Lymph node metastasis	1.38	0.85–2.23	0.19
Surgical margin positivity	1.98	1.28–3.06	0.002

TABLE 3

Literature review of lymphovascular invasion incidence and prognostic significance for biochemical recurrence in patients treated with radical prostatectomy

References	Surgery (years)	Patients (*n*)	Pathological stage	% LVI	Mean follow-up (months)	BCR predictor
Bahnson *et al.* [7]	1975–1982	55	pT2-3, pN0-1	51	84	No
Salomao *et al.* [17]	1991–1992	210	pT2-3, pN0-1	53	NA	No
McNeal and Yemoto [16]	1984–1991	357	pT2-3, pN0-1	14	NA	Yes
van den Ouden *et al.* [19]	1977–1994	273	pT2-4, pN0-1	12	49 (median)	Yes
Herman *et al.* [12]	1983–1997	263	pT3, pN0	35	36 (median)	Yes
Epstein *et al.* [10]	1984–1994	60	pT3b, pNna	22	NA	Yes
de la Taille *et al.* [9]	1993–1998	241	pT2-4, pNna	12	23	Yes
Babaian *et al.* [6]	1987–1993	265	pT2-3, pN0	NA	48 (minimum)	Yes
Ito *et al.* [13]	1989–1998	82	pT2-3, pN0	46	22	Yes
Ferrari *et al.* [11]	1990–1998	620	pT2-3, pN0-1	18	90	Yes
Shariat *et al.* [18]	1994–2002	630	pT2-3, pN0-1	5	21 (median)	No
Cheng *et al.* [8]	1990–1998	504	pT2-3, pN0-1	21	44	Yes
Loeb *et al.* [14]	1989–2004	1709	pT2-3, pN0-1	7	74	No
May *et al.* [15]	1996–2003	412	pT2-3, pN0	10	53	Yes
Yamamoto *et al.* [20]	1994–2005	94	pT3aN0	28	47 (median)	Yes

BCR, biochemical recurrence; LVI, lymphovascular invasion; NA, not available.