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ORIGINAL ARTICLE

Lymphovascular invasion is a pathological feature related to aggressive cancer behavior and predicts early recurrence in prostate cancer

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Abstract In order to determine the prognostic impact of lymphovascular invasion (LVI) in patients after radical prostatectomy, the retrospective data from our institution has been analyzed. From 1998 to 2010, 117 patients underwent radical prostatectomy. A total of 87 patients were included in this retrospective study. The relationship between LVI and advanced prostate cancer characteristics was evaluated by χ^2 test. The Kaplan-Meier method and meta-analysis were used to describe the impact of LVI invasion upon early biochemical failure after radical prostatectomy. LVI was observed in patients with clinically or pathologically aggressive prostate cancer including patients of higher preoperative risk group, higher preoperative PSA, advanced Gleason grade, and pathological T3 disease. LVI is also associated with early biochemical failure rate both in our report and in the literature. Therefore, LVI is a pathological feature which indicates prognosis correlates with aggressive prostate cancer behavior and results in early biochemical failure after radical prostatectomy.

Introduction

Radical prostatectomy is thought to be a curative treatment for clinically localized prostate cancer. However, 26–68% of patients are still found to have extraprostatic disease even after radical prostatectomy [1–3]. Early biochemical recurrence can be observed in 16–38% of patients, and it is therefore important to identify pathological features predicting aggressive cancer behavior

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[4–6]. Further adjuvant therapy may improve biochemical control and delay cancer progression.

The Gleason score, pathological tumor stage (pT), surgical margins, or the presence of lymph node metastasis are generally classically used as prognostic factors of prostate cancer. Many studies have indicated micro-environmental factors may influence cancer progression [7,8]. Lymphovascular invasion (LVI) is easily identified by pathological review and it has also been reported to be important for prognosis after radical prostatectomy [9–14]. Validation of the relationship between LVI and aggressive prostate cancer behavior with pathological or biochemical results by cohort study is reasonable.

Materials and methods

Patients were retrospectively identified from our institutional database. From 1998 to 2010, 117 patients with clinically localized prostate cancer received retropubic radical prostatectomy at our institution. All patients underwent preoperative staging by abdominal computed tomography (CT) or magnetic resonance imaging (MRI) and bone scan to be sure that the disease was organ-confined. A total of 87 patients with detailed records of preoperative PSA, clinical staging, pathological staging, Gleason score, and LVI were included in this study.

The primary end-point was the association of these variables with biochemical failure, defined as PSA level of more than 0.2 ng/mL during clinical follow-up. Patients were divided into two groups for the study: those who had undergone radical prostatectomy with or without LVI. Each group was further subdivided into low-, intermediate-, and high-risk groups: low-risk group was composed of patients with a PSA level of <10, a Gleason score of ≤ 6, or a T-stage of T2a or lower; intermediate-risk group was composed of patients with a PSA level of 10–20, a Gleason score of 7, or a T-stage of T2b; and the high-risk group included those patients with a PSA level of >20, a Gleason score of ≥ 8, or a T-stage of T2c or higher. Aggressive pathological features, such as Gleason score greater than 7, extraprostatic invasion, and seminal vesicle involvement were also identified in these two groups.

SPSS v.17 software (SAS Institute, Cary, NC, USA) was used for statistical analysis. Correlation between the distribution of these two groups and comparison of preoperative risk group and aggressive pathological features were analyzed by χ^2 test; 5-year biochemical failure incidence was estimated by the Kaplan-Meier method with Log-rank test. The results were statistically significant if $p < 0.05$. Furthermore, meta-analysis was used for review of prognostic impact of LVI in radical prostatectomy specimens.

Results

This retrospective study enrolled 87 patients with clinically localized prostate cancer. Median age was 63 (range from 49 to 83) and median follow-up duration was 40.9 (range from 0.6 to 99.9) months. The detailed characteristics regarding preoperative risk group, advanced Gleason grade, advanced pathological staging such as capsular penetration and seminal vesicle involvement, and 5-year biochemical failure incidence are listed in Table 1.

There were 18 patients with LVI and 69 patients without LVI as determined by pathological review. Comparing both groups, a greater number of patients in the LVI group belonged to preoperative high risk than in the nonLVI group (88.9% and 44.9%, $p = 0.003$). The pathological result showed that preoperative PSA of more than 20 ng/mL (44.4% and 15.9%, $p = 0.009$), Gleason grade of more than 7 (50.0% and 11.6%, $p < 0.001$), capsular penetration (77.8% and 37.7%, $p < 0.002$), and seminal vesicle involvement (55.6% and 10.1%, $p < 0.001$) occurred significantly more frequently in patients with LVI compared with those without LVI.

Regarding oncological outcome, a significantly higher biochemical failure rate was noted in patients with LVI than in those without LVI ($p = 0.012$) (Fig. 1). We reviewed recent studies with detailed reports concerning biochemical failure incidence related to LVI in radical prostatectomy specimens. The risk ratio of biochemical failure increased from 1.64 to 7.66 if LVI was present (Table 2).

Discussion

Several clinical studies have indicated that Gleason grade, capsular penetration, seminal vesicle involvement and

Table 1 Correlation of LVI with clinical and pathological variables.

	LVI(+)($n = 18$)	LVI(−)($n = 69$)	p value
Follow-up (months)	49.8 (5.1–91.8)	34.4 (0.6–99.9)	0.101
Age (year)	61.2 (52–76)	64 (49–83)	0.746
Risk classification			0.003
Low-risk group	1 (5.6%)	7 (10.1%)	
Intermediate-risk group	1 (5.6%)	31 (44.9%)	
High-risk group	16 (88.9%)	31 (44.9%)	
Preoperative PSA>20	8 (44.4%)	11 (15.9%)	0.009
Gleason score >7	9 (50.0%)	8 (11.6%)	<0.001
Capsular invasion	14 (77.8%)	26 (37.7%)	0.002
Seminal vesicle invasion	10 (55.6%)	7 (10.1%)	<0.001
Positive surgical margin	10 (55.6%)	28 (40.5%)	0.185
Nodal positive disease	2 (11.1%)	3 (4.3%)	0.272
5-year biochemical failure	12 (66.7%)	28 (40.5%)	0.012

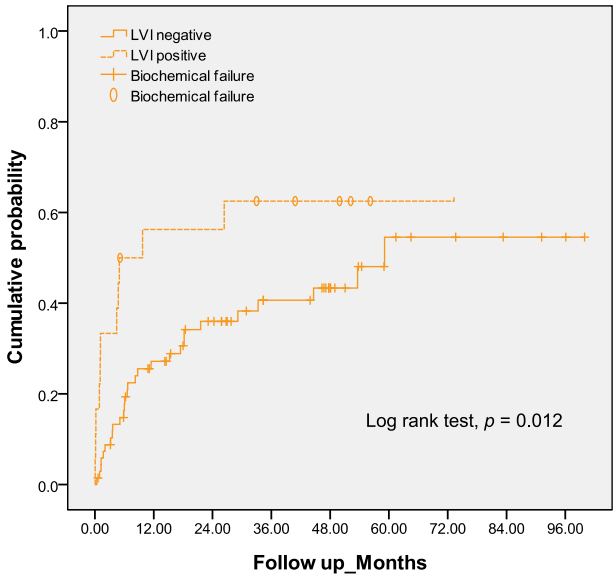


Figure 1. Biochemical failure incidence between LVI and no LVI.

surgical margin status could be used as prognostic predictors [3—6]. Pathologists traditionally examine the microscopic features for the urologist to evaluate whether or not adjuvant therapy is necessary to prevent biochemical disease recurrence. LVI is a well-established prognostic factor in many human malignancies, such as breast cancer, testicular cancer, and renal cell carcinoma. According to the latest guidelines from the Association of Directors of Anatomic and Surgical Pathology, LVI was suggested to be included in the pathological report but currently it is still not recommended for routine use. However, tumor angiogenesis was thought to be associated with cancer invasion and thus distant metastasis. It is reasonable to examine the presence of LVI and possible further correlations between the cancer behavior and oncological outcome. The independently predictive role of LVI has been recently discussed in biochemical failure after radical prostatectomy [9,10]. The aim of this study was to validate the prognostic impact of LVI upon prognosis prediction and discuss the relationship between LVI and prostate cancer behavior.

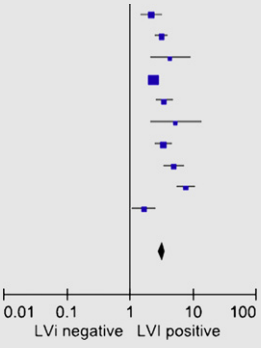
This study showed that the incidence of LVI in radical prostatectomy specimens was 20.7%. The incidence (from 5% to 46%) reported in previous studies varies according to different distribution of preoperative risk group. Patients with LVI tend to have a significant association with higher Gleason grade and preoperative PSA [12,15]. A higher incidence of locally advanced disease related to LVI was also noted in previous studies [10,12,15,16]. In addition, early biochemical recurrence or shorter PSA doubling time could be observed in patients with LVI [17]. Prostate cancer with higher recurrence potential, such as with higher preoperative PSA level, higher Gleason grade, capsular invasion, and seminal vesicle involvement, was found to occur significantly more frequently in patients with LVI in this retrospective study.

The presence of nodal positive disease made no difference in our series. This may have resulted from relatively small patient numbers in the nodal positive group. The duration-related incidence of biochemical failure after radical prostatectomy was significantly higher in patients with LVI. This indicated the importance of identifying LVI in pathological reports, and it may provide a valuable parameter for urologists to arrange further adjuvant therapy.

The possible explanation and current belief for the correlation between LVI and clinically or pathologically aggressive prostate cancer is tumor angiogenesis. LVI could be considered to be a result of aggressive cancer behavior or an enhancing factor which interacts with the tumor. Further demonstration of the molecular pathway is worthy of investigation. For clinical practice, locally advanced disease does not independently cause poor prognosis and it differs according to surgical factors and nodal status [18]. Though the correlation between LVI and locally advanced disease cannot reflect the impact upon biochemical result directly, LVI was reported to be an independent predictor of a poorer biochemical result in recent studies after assessing surgical and histopathological factors with multivariate analysis [9—12]. It may be because possible occult distant metastasis

Table 2 Meta-analysis of literature review about prognostic impact of LVI on prostate cancer.

Study or Subgroup	LVI positive		LVI negative			Risk Ratio	Risk Ratio
	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Herman, 2000	41	91	36	172	14.6%	2.15 [1.49, 3.11]	
de la Taille, 2000	28	30	63	211	9.2%	3.13 [2.49, 3.93]	
Ito, 2003	26	38	7	44	3.8%	4.30 [2.11, 8.77]	
Ferrari, 2004	78	110	153	510	31.8%	2.36 [1.98, 2.83]	
Shariat, 2004	21	32	113	597	6.7%	3.47 [2.57, 4.68]	
Cheng, 2005	11	106	7	353	1.9%	5.23 [2.08, 13.16]	
Loeb, 2006	40	118	159	1591	12.9%	3.39 [2.53, 4.54]	
May, 2007	26	42	47	370	5.6%	4.87 [3.41, 6.97]	
Yee, 2010	49	129	58	1169	6.8%	7.66 [5.48, 10.69]	
Present series	12	18	28	69	6.8%	1.64 [1.06, 2.54]	
Total (95% CI)		**714**		**5086**	**100.0%**	**3.19 [2.88, 3.53]**	
Total events	332		671				



Heterogeneity: $Chi^2 = 58.24$, df = 9 ($P < 0.00001$); $I^2 = 85\%$

Test for overall effect: Z = 22.17 ($P < 0.00001$)

via the lymphatic or vascular systems cannot be actually identified by radical prostatectomy specimens.

The nonsignificance of positive margin status counterbalances the effect of surgical factors between these two groups. The incidence of biochemical failure is still significantly higher in patients with LVI in our series. It is not proven to be an independent predictor by the logistic regression model and thus a larger patient pool is needed for validation of this finding. However, the prognostic significance can still be found under univariate analysis. Therefore, biochemical failure incidences in other studies were reviewed in the English literature from 2000 to 2010. We used the meta-analysis method to identify the hazard ratio of biochemical recurrence in patients with LVI after radical prostatectomy. The average risk ratio of biochemical recurrence within 5 years increased up to 3.19 in patients with LVI as compared to those without LVI. We recommend that LVI should be routinely included in pathological reports due to its prognostic significance.

Several limitations should be considered with regard to this retrospective study. The result is not independently conclusive due to the relatively small series. In addition, the radical prostatectomy was performed by different surgeons and surgical factors may thus interfere with the biochemical result. No further reporting was done concerning the extent in a high power field which may have potential prognostic influence [15]. Specimens were evaluated by different pathologists and the diagnostic criteria of LVI carry subtle differences. Bias correction in a single-center experience with a single surgeon, a single pathologist, and a detailed description of LVI would provide better validation of risk.

Conclusion

Lymphovascular invasion can be observed in a proportion of the radical prostatectomy specimens, especially in high-risk group patients. It is a prognosis predicting pathological feature which correlates with aggressive prostate cancer behavior and results in early biochemical failure after radical prostatectomy.

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