Prognostic impact of lymphovascular invasion in radical prostatectomy specimens

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OBJECTIVE

To estimate the prognostic value of lymphovascular invasion (LVI) in patients with node-negative prostate cancer treated by radical prostatectomy (RP).

PATIENTS AND METHODS

In all, 412 patients with prostatic adenocarcinoma who had RP and pN0 status were analysed for all established standard pathological factors and LVI. The influence of these pathological findings on biochemical failure was evaluated by multivariate analysis with the Cox model. The mean (range) follow-up was 52.5 (10–116) months.

RESULTS

LVI was identified in 42 patients (10.2%) and significantly associated with a high preoperative prostate-specific antigen (PSA) level, a high PSA density, high percentage of positive biopsy cores, high Gleason score, and seminal vesicle invasion. Of the 42 patients with LVI, 33 (79%) had a Gleason score of ≥7 and 27 (64%) had pathological stage pT3. The 5-year biochemical-free survival was 87.3% for patients with no LVI and 38.3% with LVI on the RP specimen ($P < 0.001$). By multivariate analysis, LVI and Gleason score were independent predictors of biochemical failure.

CONCLUSION

These results show that in addition to the Gleason score, only LVI is strongly correlated with biochemical failure after RP. These findings support the routine evaluation of LVI status in RP specimens and provide the option for its incorporation into nomograms predictive of oncological outcome.

KEYWORDS

prostate cancer, prostatectomy, biochemical failure, lymphovascular invasion

INTRODUCTION

Radical prostatectomy (RP) is an efficient therapy for prostate cancer, especially when the tumour is organ-confined. Despite current staging methods, 26–68% of patients are found to have extraprostatic disease after RP [1–3]. As 16–38% of patients will have biochemical failure during a 5-year follow-up it is essential to characterize the pathological features of RP specimens that might predict a high risk of biochemical failure and progression, to recommend adjuvant therapy [4–6]. Classically, most investigators consider prognostic factors to be directly related to a given tumour. Examples include histological subtype, Gleason score, pathological tumour stage (pT), surgical margins, or the presence of lymph node metastasis. More detailed histopathological features add to prognostic precision. These integrate tumour volume, tumour proliferation, and molecular factors such as HER-2/neu receptor status, cell cycle-associated proteins (p21, p27, p53, BCL-2), and cellular adhesion molecules (CD44, e-cadherin) [7–11].

Lymphatic and vascular invasion are among the histological variables in RP specimens that the Association of Directors of Anatomic and Surgical Pathology and the College of American Pathologists (CAP) recommend are reported [12,13]. Few studies to date have assessed the rate and the prognostic impact of lymphovascular invasion (LVI). The reported incidence rates of LVI differ widely, at 5–53% [14–25]. Although there is general agreement that LVI is a significant predictor of disease progression in univariate analysis of RP series, not all studies have found independent significance of LVI in multivariate analysis.

The current study was undertaken to determine the predictive value of clinical factors, including PSA, percentage positive biopsy cores, and other pathological variables, specifically Gleason score, seminal vesicle involvement (SVI), surgical margin status (SMS), extraprostatic extension, and LVI for the prognosis of biochemical failure in patients treated by RP. To clarify the significance of LVI for biochemical failure in surgical RP specimens, we evaluated only those patients who were node-negative (pN0) and who received no neoadjuvant or adjuvant hormonal or radiation treatment.

The exclusion of patients with node-positive disease from the study was based on the following considerations. First, lymph node metastasis is already a well established predictor of disease progression in patients undergoing RP. Second, in a preliminary analysis of our data most of the patients who had RP during the same period and who were node-positive also had LVI in the prostate, so that the finding of prostatic LVI in node-positive patients would not give additional information likely to influence clinical decision making. Third, most patients who were node-positive also had signs indicating a high risk of locally advanced disease, and thus had either received neoadjuvant hormonal treatment or as an adjuvant because of their pN+ status. For these reasons, all node-positive patients were excluded from this specific analysis.

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PATIENTS AND METHODS

We analysed all patients undergoing retropubic RP at two teaching hospitals in Berlin, Germany between January 1996 and May 2003; 528 patients with prostatic adenocarcinoma who had had no hormonal therapy and/or radiation therapy before or after RP were evaluated. Patients without pelvic lymphadenectomy (78) and patients with positive lymph node status (38) were excluded from the analysis. This left a study group of 412 patients in whom the LVI in RP specimens was determined as a matter of routine. Furthermore, possible or certain systemic disease could be excluded through exploration of the regional lymph nodes, verifying the pN0 status. The mean (SEM, median) number of lymph nodes per patient removed at RP was 10.8 (0.24, 11). The operative surgeon assigned the clinical stage according to the 1997 revision (Fifth edition) of the TNM classification system. In all, 162 patients had no suspicion on DRE (39.3%, T1c), 243 had palpable or ultrasonographically visible lesions confined to the prostate (59.0%, T2), and seven were classified as T3 (1.7%, tumour extended through the prostatic capsule and/or were involved in the SVs). The serum level of PSA was assayed by immunoassay (AxSYM, Abbott Diagnostics Division, Abbott Park, IL, USA, analytic sensitivity 0.04 ng/mL). The mean (SEM, range) PSA level before RP was 12.1 (0.54, 0.1–151) ng/mL and the patient age was 63.7 (0.28, 44–79) years. The percentage of positive biopsy cores was defined as (number of positive biopsy cores/total number of biopsy cores) × 100.

All RP specimens were evaluated in a standard manner. After eliminating the apical and bladder neck margins, specimens were sectioned transversely at 4-mm intervals from the apex to the base. The SV were evaluated at the intersection where they enter the prostate gland. Whole-mount sections 5 μm thick were stained with haematoxylin and eosin (H&E). All cases were evaluated by one pathologist (V.L.). Tumour location, Gleason score (as primary and secondary tumour grading), the presence and location of extraprostatic extension, SVI and SMS were documented. Additionally to apical and bladder neck margins, the positive anterior, lateral, posterior and posterolateral SMs were defined as tumour in direct contact with the indicated inked surface of the prostate in sections. All pelvic lymph nodes were counted and inspected for the presence of metastatic disease. We excluded patients with pelvic lymph node metastases, and those without lymphadenectomy. For pathological staging the 1997 TNM system (Fifth edition) was used.

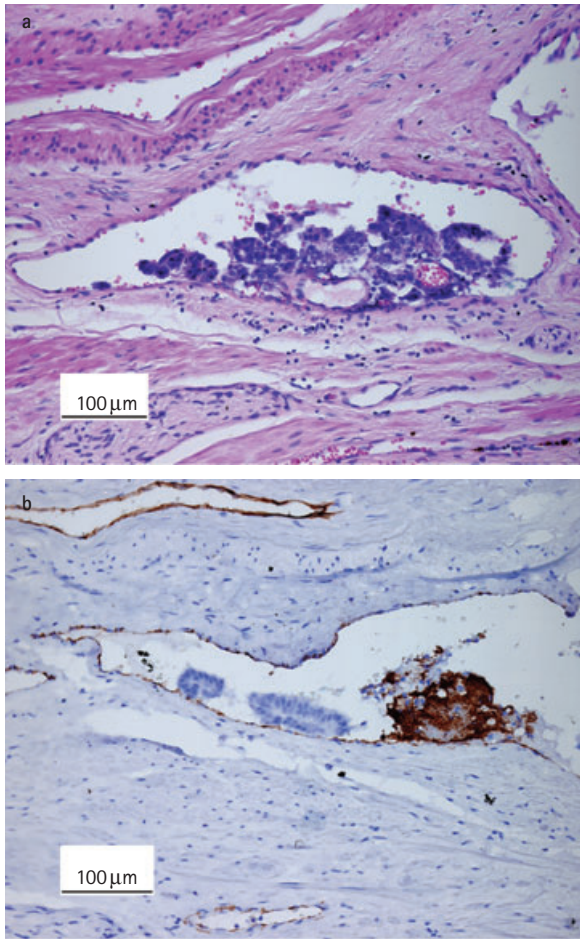

FIG. 1.
***a**, Unequivocal LVI with tumour cells adhering to the vascular wall (H&E, original × 200); and **b**, in deeper sections the lining of the lumen is identified as endothelium by immunoreactivity for CD31 (immunoperoxidase stain, original × 200).*

All patients had LVI analysed, assessed from H&E-stained sections, in agreement with the specified criteria [20–25]. LVI was defined as the unequivocal existence of tumour cells in an endothelium-lined space with no underlying muscular walls (Fig. 1a). Equivocal cases and tumour cells that simply encroached on a microvascular lumen were considered negative and a perivascular reaction was not required. Care was taken to exclude retraction artefacts, pseudoemboli, tumour within prostatic ducts, and tumour within perineural spaces. No effort was made to distinguish between lymphatic vessels and vascular vessels, because of the difficulty and lack of reproducibility when using routine light microscopy. All cases with vascular invasion foci identified on routine stains were confirmed for the presence of endothelium using antibody to CD31 (Clone CJ70A, Dako, Copenhagen, Denmark). CD31 immunostaining was done using the avidin-biotin peroxidase complex method on paraffin-embedded, zinc formalin-fixed tissue (Fig. 1b).

The mean (SEM, range) clinical follow-up was 52.5 (1.18, 10–116) months. The serum levels of PSA were determined at 3-month intervals after RP for the first year and at 6-month intervals thereafter. Biochemical failure was classified as a constant or increasing PSA level of >0.2 ng/mL on two or more occasions.

The results are presented as the mean (SEM). Analyses between groups were compared using the Mann–Whitney *U*-test for continuous variables and Fisher's exact and chi-square tests for categorical variables. The correlation of various clinical and pathological variables with LVI was calculated using Spearman's correlation statistics (two-tailed, r with range: −1 and +1). For

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TABLE 1 Correlation of LVI with clinical and pathological variables of 412 patients who had RP for lymph-node negative prostate cancer

Variables	N (%) patients	LVI, n (%)		P
		Absent	Present	
Clinical stage				0.811
T1c	162 (39.3)	144 (89)	18 (11)	
T2	243 (59.0)	220 (91)	23 (9)	
T3	7 (1.7)	6 (86)	1 (14)	
Gleason score (RP)				<0.001
2–4	11 (2.7)	11 (100)	0	
5–6	232 (56.3)	223 (96)	9 (4)	
7	131 (31.8)	108 (82)	23 (18)	
8–10	38 (9.2)	28 (74)	10 (26)	
Pathological staging				<0.001
pT2	299 (72.6)	284 (95)	15 (5)	
pT3a	60 (14.5)	50 (83)	10 (17)	
pT3b	53 (12.9)	36 (68)	17 (32)	
SMS				0.926
Negative	326 (79.1)	293 (90)	33 (10)	
Positive	86 (20.9)	77 (89)	9 (11)	
Mean (range):				
Age at RP, years	63.7 (44–79)	63.6 (44–79)	64.7 (53–76)	0.261
Serum PSA, ng/mL	12.1 (0.1–151)	10.9 (0.1–51)	22.6 (6.4–151)	<0.001
PSA density, ng/mL^2	0.46 (0.01–10)	0.42 (0.01–3.3)	0.88 (0.02–10)	<0.001
% positive biopsy cores	47.0 (10–100)	45.2 (10–100)	62.3 (10–100)	0.001

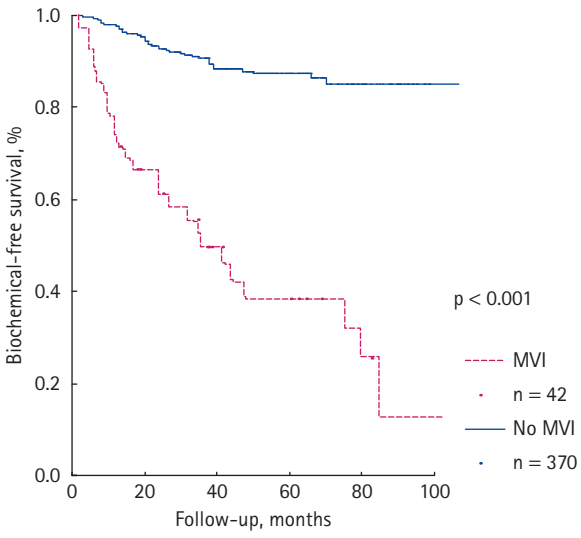

FIG. 2. Probabilities of PSA progression-free survival in 412 patients who had RP for prostate cancer, according to LVI.

survival analyses all variables were organized in a dichotomised manner. Biochemical recurrence-free survival (BRFS) rates were calculated using the Kaplan–Meier method and differences assessed with the log-rank test. For multivariate analysis the Cox proportional-hazard regression was used; $P \leq 0.05$ was taken to indicate statistical significance.

RESULTS

LVI was identified in 10.2% of patients (42 of 412); Table 1 shows the clinical and pathological characteristics of the study group, and correlations with LVI. Of the 412 patients treated by RP, 113 (27%) had pathological T3 tumours. The rate of SVI and positive SMs in all patients were 12.9% and 20.9%, respectively. Notably, 45% had serum PSA level of >10 ng/mL and 41% of all patients had high-grade tumours (Gleason sum grade ≥7).

There was a significant correlation between LVI and a PSA level of >20 ng/mL before RP ($P < 0.001$, $r = 0.228$), PSA density >0.75 ng/mL^2 ($P = 0.002$, $r = 0.153$), a percentage of positive biopsy cores >80% ($P < 0.001$; $r = 0.194$), Gleason score ≥7 (4 + 3) ($P < 0.001$, $r = 0.239$), and the existence of SVI ($P < 0.001$, $r = 0.278$). There was no association between LVI and clinical stage ≥T2 ($P = 0.621$, $r = -0.024$), positive SMs ($P = 0.926$, $r = 0.005$), and patient age at surgery ($P = 0.261$, $r = 0.055$). Of the 42 patients with LVI, 33 (79%) had a Gleason score of ≥7 and 27 (64%) had pathological stage pT3.

Of all patients, 16.5% (68 of 412) had biochemical progression during the follow-up. The overall BRFS rates were 95.1%, 89.4%, 86.4% and 82.2% at 1, 2, 3 and 5 years, respectively. The BRFS after 1, 3 and 5 years were 97.6%, 90.6% and 87.3% for patients without LVI, vs 73.8%, 49.7% and 38.3% with LVI in the RP specimen (log-rank test, $P < 0.001$; Fig. 2 and Table 2).

In the multivariate Cox proportional hazard model analysis only the high-risk combination of LVI ($P < 0.001$, hazard ratio 4.39) and Gleason score ≥7 (4 + 3) ($P < 0.001$, hazard ratio 3.51) were independent predictors of biochemical failure (Table 3).

For further analysis, subgroups of organ-confined prostate carcinoma (299 men) were formed which were exclusively orientated on Gleason score and LVI. Patients with a Gleason score of ≤7 (3 + 4) and no LVI (group 1, 257 men) had a BRFS rate of 91.6% after 5 years; those with a Gleason score of ≥7 (4 + 3) or LVI (group 2, 36 men) had a BRFS rate after 5 years of 58.7%. All six patients who had both a Gleason score ≥7 (4 + 3) and LVI in the RP specimen (group 3) were in PSA progression after ≤42 months ($P < 0001$; Fig. 3). For the whole study group (including patients with pT3 disease), the BRFS rates after 5 years in

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groups 1 (315 men), 2 (78 men) and 3 (19 men) were 91.4%, 58.5% and 29.3%, respectively ($P < 0.001$).

DISCUSSION

Several clinical and pathological variables, e.g. serum PSA level before RP, tumour stage, SMS and Gleason score, have been shown to be unfailing predictors of disease progression in patients with prostate cancer [1–7]. Debate continues on the significance of LVI for predicting cancer progression. Currently the Association of Directors of Anatomic and Surgical Pathology view the reporting of vascular and/or lymphatic invasion as optional for RP specimens [12]. The CAP did not directly address LVI in their 2006 consensus statement for prognostic factors in prostate cancer after RP [13]. Because tumour angiogenesis is thought to simplify the invasion of tumour cells into vascular spaces secondary to highly permeable and discontinuous endothelial basement membranes, the assessment of microvessel density is related to vascular invasion [20]. CAP considers the assessment of LVI as clinically important but not yet validated or regularly used in patient management [13].

In the present study LVI was detected in 10.2% of all patients having node-negative disease. Almost all previous studies reported a higher percentage of patients with LVI (5–53%, Table 4, [14–25]). This discrepancy in the LVI rate in different studies has various causes. Apart from the different histopathological composition of specimens, different definitions of LVI, variations of interobserver interpretation and different ranges of tumour stages in the studies are responsible for this large variance in the LVI rate in the reported investigations. For estimates of LVI to be useful clinically, the criteria that define LVI must be standardized. The criteria used here define LVI in prostate cancer as the unequivocal presence of tumour cells in simple endothelial-lined spaces surrounded by normal stroma tissue, with a smooth discrete luminal border of the tumour mass. Using these criteria, most studies report LVI rates of 5–22% [16,17,19,20,23–25]. The study of Herman *et al.* [18], which used the same definition of LVI and documented an LVI rate of 35%, evaluated only patients with pT3 tumours. Considering only the pT3 tumours in the present study, the LVI rate would increase to 24% (27 of 113). This also

Factors investigated	N (%)	5-year BRFS, %	P
Preoperative PSA, ng/mL			
≤20	364 (88.3)	84.5	0.002
>20	48 (11.7)	66.3	
PSA density, ng/mL^2			
≤0.75	351 (85.2)	84.7	0.002
>0.75	61 (14.8)	68.5	
Positive biopsy cores, %			
≤80	337 (81.8)	84.5	<0.001
>80	75 (18.2)	72.3	
Pathological stage			
Negative SVI	359 (87.1)	85.4	<0.001
Positive SVI	53 (12.9)	61.6	
Gleason score (RP):			
≤7 (3 + 4)	338 (82.0)	88.1	<0.001
≥7 (4 + 3)	74 (18.0)	55.7	
SMS			
Negative	326 (79.1)	82.9	0.434
Positive	86 (20.9)	79.5	
LVI			
Absent	370 (89.8)	87.3	<0.001
Present	42 (10.2)	38.3	

TABLE 2 Univariate 5-year BRFS analysis of different clinical and pathological high-risk combinations of progression

TABLE 3 Multivariate Cox regression analysis of the risk of PSA failure in patients with prostate cancer after RP

Risk combination	N (%)	Hazard ratio (95% CI)	P
Preoperative PSA >20 ng/mL	48 (11.7)	0.96 (0.48–1.93)	0.918
Gleason score ≥7 (4 + 3)	74 (18.0)	3.51 (2.06–6.00)	<0.001
SVI	53 (12.9)	1.10 (0.58–2.10)	0.766
PSA density >0,75 ng/mL^2	61 (14.8)	1.35 (0.70–2.60)	0.363
Positive biopsy cores >80%	75 (18.2)	1.24 (0.68–2.24)	0.471
LVI	42 (10.2)	4.39 (2.47–7.80)	<0.001

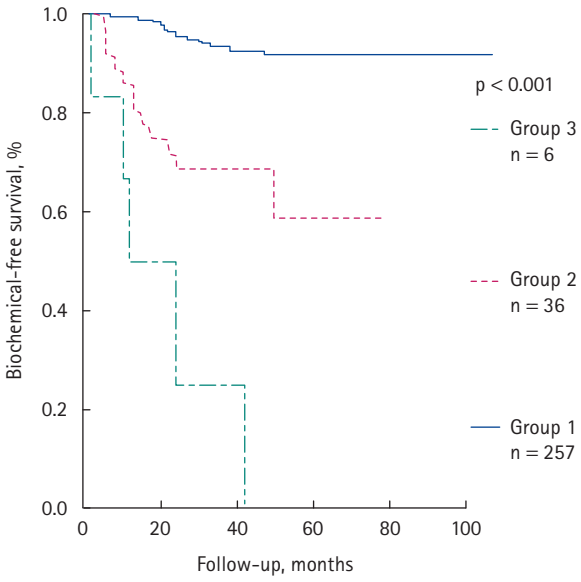

FIG. 3. Probabilities of PSA progression-free survival in 299 patients who had RP for organ-confined prostate cancer (pathological stage T2) according to three risk groups (group 1 Gleason score ≥7 (4 + 3) + no LVI; group 2 Gleason score ≥7 (4 + 3) or LVI; group 3 Gleason score ≥7 (4 + 3) and LVI.

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TABLE 4 A comprehensive review of previous reports for the prognostic impact of microvascular invasion in prostate cancer

Pathological stage	Number of patients	Mean follow-up, months	MVI, %	Outcome	Reference
pT2-3, pN0-1	55	84	51	Not independent predictor of disease progression	[14]
pT2-4, pN0-1	210	na	53	Correlated with established poor prognostic factors	[15]
pT2-4, pN0-1	357	na	14	Independent predictor of biochemical progression	[16]
pT2-4, pN0-1	273	49 (median)	12	Independent predictor of biochemical and clinical progression and cancer-specific survival	[17]
pT3, pN0	263	36 (median)	35	Independent predictor of disease progression	[18]
pT3b, pNna	60	na	22	Independent predictor of disease progression	[19]
pT2-3, pNna	241	23	12	Independent predictor of biochemical progression	[20]
pT2-3, pN0	265	48 (minimum)	na	Independent predictor of biochemical progression	[21]
pT2-3, pN0	82	22	46	Independent predictor of biochemical progression	[22]
pT2-4, pN0-1	620	90	18	Independent predictor of disease progression	[23]
pT2-4, pN0-1	630	21 (median)	5	Not independent predictor of biochemical progression	[24]
pT2-3, pN0-1	504	44	21	Independent predictor of biochemical progression and cancer specific death	[25]
pT2-3, pN0	412	53	10	Independent predictor of biochemical progression	Present

na, not available.

shows the dependency of the LVI rate on the composition of tumour stages of the evaluated patient groups. In the present study, LVI correlated with other important factors and was an independent prognostic factor for biochemical failure in addition to Gleason score in multivariate analysis. The result of RP for organ-confined disease is indeed excellent, but some patients with organ-confined disease develop biochemical failure. These patients might have had microscopic metastasis before RP and LVI might be related to disease progression in the less advanced stage. Whereas patients with organ-confined tumours, Gleason score ≤(3 + 4) and no LVI have a high 5-year BRFS rate of 92%, all patients with Gleason score ≥(4 + 3) and LVI will fail by 42 months and are likely to need adjuvant therapy.

Apart from the study of Shariat *et al.* [24] all other studies which used the definition of LVI as given above considered LVI to be an independent predictor of biochemical failure (Table 4) [16–21,23,25]. There are several possible explanations for the differences in results reported by Shariat *et al.* [24] and the current study. In the study of Shariat *et al.* the pathology was investigated by several staff pathologists, which could potentially introduce significant interobserver variability. In the present study, all RP specimens were examined by one pathologist (V.L.), thus eliminating the possibility of inter-examiner variability. This factor might also account for the relatively low incidence of LVI in patients reported by Shariat *et al.* (5%). A major strength of the present study is the relatively long follow-up of 53 months; the study of Shariat *et al.* had a much shorter follow-up (median 21 months, range 1–101). The other study that denied the independent impact of LVI on biochemical progression was by Bahnson *et al.* [14]; they distinguished between invasion of vascular and/or lymphatic vessels and defined invasion as the presence of tumour in the lumen, in the venous channel or in the cellular reaction around or in the lymphatic. This might be a possible reason why their results differed from the present. Moreover, their study included few patients (55). Table 4 list the results of all relevant studies.

However, the present study has several potential limitations. The RPs were done by several surgeons at two academic institutions; although there was no apparent association between surgeon and outcome it is possible that different surgical techniques might have affected the outcome. The specimens were assessed by one pathologist, which although enhancing the uniformity of assessment of LVI and other variables, might limit the general applicability of our findings. Finally, the pathological analysis was conducted on 4-mm, serially sectioned specimens, which might differ from the methods used in other institutions. Additional research is needed to assess whether community-based pathology assessments and quantification of LVI provide similar prognostication.

In conclusion, our findings indicate that LVI in prostate cancer has a positive correlation with SVI, pathological stage, Gleason score, preoperative PSA level, PSA density and percentage positive biopsy cores. On multivariate analysis LVI and Gleason score ≥7 (4 + 3) were independent high-risk factors for biochemical failure. The analysis of LVI should be considered as a routine in the evaluation of RP specimens. LVI as a pathological variable might help the clinician to classify patients with a higher risk of tumour relapse and then be used in postoperative nomograms with other histological variables to identify patients who might benefit from adjuvant therapies.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **LVI**, lymphovascular invasion; **H&E**, haematoxylin and eosin; **RP**, radical prostatectomy; **CAP**, College of American Pathologists; **SV(I)**, seminal vesicle (involvement); **SM(S)**, surgical margin (status); **BRFS**, biochemical recurrence-free survival.

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