

The impact of lymphovascular invasion in patients with prostate cancer following radical prostatectomy and its association with their clinicopathological features

An updated PRISMA-compliant systematic review and meta-analysis

Wei Jiang, MS^a, Lijin Zhang, MS^{b,*}, Bin Wu, BS^b, Zhenlei Zha, MS^b, Hu Zhao, PhD^b, Yuan Jun, BS^b, Yuefang Jiang, BS^b

Abstract

Objective: Numerous studies have shown that lymphovascular invasion (LVI) is linked to biochemical recurrence (BCR) in prostate cancer (PCa) patients following radical prostatectomy (RP). However, the actual clinicopathological impacts of LVI remain unclear. Thus, we performed a meta-analysis to evaluate the pathologic and prognostic impacts of LVI in PCa patients.

Methods: Following the guidance of the PRISMA statement, relevant studies were collected systematically from the PubMed, EMBASE, and Web of Science databases to identify relevant studies published before June 2018. The hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated to investigate the association of LVI with BCR and clinicopathological features.

Results: A total of 20 studies including 25,570 patients (106–6678 per study) with PCa were incorporated into this meta-analysis. Overall pooled analysis suggested that LVI was associated with a higher BCR risk both in univariate (pooled HR=1.50, 95% CI: 1.34–1.68, $P < .001$) and multivariate analyses (pooled HR=1.25, 95% CI: 1.17–1.34, $P < .001$). In addition, LVI was closely correlated with extraprostatic extension (yes vs no: OR = 4.23, 95% CI: 1.86–9.61, $P < .001$), pathological GS (≥ 7 vs < 7 : OR = 5.46, 95% CI: 2.25–13.27, $P < .001$), lymph node metastases (yes vs no: OR = 18.56, 95% CI: 7.82–44.06, $P < .001$), higher pathological stage ($\geq T3$ vs $< T2$: OR = 6.75, 95% CI: 5.46–8.36, $P < .001$), positive surgical margin (positive vs negative: OR = 2.42, 95% CI: 1.57–3.72, $P < .001$) and seminal vesicle invasion (yes vs no: OR = 5.72, 95% CI: 2.45–13.36, $P < .001$).

Conclusions: This study suggests that LVI in histopathology is associated with a higher risk of BCR and advanced clinicopathological features in PCa patients and could serve as a poor prognostic factor in patients who underwent RP.

Abbreviations: BCR = biochemical recurrence, CIs = confidence intervals, EPE = extraprostatic extension, HRs = hazard ratios, LNM = lymph node metastases, LVI = lymphovascular invasion, NOS = Newcastle–Ottawa scale, ORs = odds ratios, PCa = prostate cancer, PSA = prostate-specific antigen, PSM = positive surgical margin, RP = radical prostatectomy, SVI = seminal vesicle invasion.

Keywords: biochemical recurrence, lymphovascular invasion, meta-analysis, prostate cancer, radical prostatectomy

Editor: Giuseppe Lucarelli.

BW, ZZ, and HZ contributed equally to this work.

All data generated or analyzed during this study are included in this published article (and its Supplementary Information files).

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

^a Department of Urology, Taizhou People's Hospital, The Fifth Affiliated Hospital of Medical School of Nantong University, Taizhou, ^b Department of Urology, Affiliated Jiang-yin Hospital of the Southeast University Medical College, Jiang-yin, Jiangsu Province, China.

* Correspondence: Lijin Zhang, Department of Urology, Affiliated Jiangyin Hospital of the Southeast University Medical College, 163 Shoushan Road, Jiangyin 214400, Jiangsu Province, China (e-mail: stzlj913729553@163.com).

Copyright © 2018 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Medicine (2018) 97:49(e13537)

Received: 13 August 2018 / Accepted: 12 November 2018

<http://dx.doi.org/10.1097/MD.0000000000013537>

1. Introduction

Prostate cancer (PCa) is the second most prevalent cancer in people aged ≥ 50 years and poses a substantial burden on the healthcare system all over the world.^[1] With superior cancer control and functional outcomes, radical prostatectomy (RP) has become the gold standard treatment for localized PCa.^[2] However, approximately 40% of patients who undergo RP will experience biochemical recurrence (BCR),^[3] which is defined as an elevation in prostate-specific antigen (PSA) levels. BCR after RP is often assumed to represent clinical progression or distant metastases, indicating that the patients will need to be treated with secondary treatment.^[4,5]

The traditional risk factors for BCR rely on known clinical and pathologic variables, including extraprostatic extension (EPE),^[6] seminal vesicle invasion (SVI),^[7] lymph node metastases (LNM)^[8] and positive surgical margin (PSM).^[9] However, the outcomes of surgically treated patients with adverse local pathologic features are not invariably poor,^[10] as not every patient suffers eventual cancer recurrence, and the consistent use of adjuvant radiotherapy could lead to considerable

overtreatment. Consequently, research on the identification and evaluation of new prognostic predictors could help urologists precisely assess PCa risk, recurrence, and prognosis in the clinic.

Lymphovascular invasion (LVI) is defined as the presence of tumor cells in an endothelium-lined space. According to the International Society of Urological Pathology (ISUP) recommendation, LVI is part of the standard examination of RP specimens,^[11] and the reported incidence rates of LVI differ widely from 5% to 53% in patients who have undergone RP.^[12] Although there is general agreement that LVI is a significant predictor of BCR in univariate analyses of RP samples, not all studies have found LVI to be independently significant in multivariate analyses.^[13–15]

Therefore, to further clarify the prognostic and clinicopathological value of LVI in PCa, we performed this meta-analysis based on published studies to evaluate whether the presence of LVI has a prognostic impact on BCR both in univariate and multivariate analyses.

2. Materials and methods

2.1. Literature search

This study was carried out in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).^[16] A comprehensive online search of the literature in the PubMed, EMBASE, and Web of Science databases up to June, 2018 was performed using the following keywords

(“prostate cancer” or “prostate and neoplasms”) and (“radical prostatectomy”) and (“lymphovascular invasion”) and (“biochemical recurrence” or “biochemical failure”). In addition, we checked potentially relevant publications by examining the reference lists in the recent reviews, meta-analyses, and cited articles to identify related articles. Only publications written in English with available full text were included in this meta-analysis. Because the studies included in this meta-analysis have been published, no ethical approval was required.

2.2. Inclusion and exclusion criteria

Studies included in the meta-analysis must meet all of the following criteria:

- (1) articles published as full papers in English;
- (2) all patients were diagnosed with PCa, and LVI was assessed by pathologists;
- (3) studies excluded patients who received RP treatment;
- (4) BCR after RP was defined in all studies; and
- (5) the association between LVI and BCR was reported, and sufficient published data were available for estimating hazard ratios (HRs) from univariate or multivariate analyses with 95% confidence intervals (CIs).

Accordingly, the exclusion criteria were as follows:

- (1) reviews, letters, case reports, editorials, and author responses;
- (2) studies without sufficient data;
- (3) studies that did not analyze the correlation between LVI and the BCR rate of PCa; and
- (4) articles that contained elements that were inconsistent with the inclusion criteria.

If more than 1 article from the same cohort was identified, only the most recent and informative 1 was included.

2.3. Data extraction and quality assessment

Data were independently abstracted by 2 investigators (Zhenlei Zha and Hu Zhao) using a standard protocol and data collection form in accordance with PRISMA. Any controversy was resolved by discussion with and rereading by the third investigator (Bin Wu). The following data were extracted from the included studies: the first author’s name, publication year and country, recruitment period, sample size, age of patients, preoperative PSA level, Gleason score (GS), pathological staging, definition of LVI and BCR, the number of patients with LVI and BCR, median time to follow-up, and the HRs of LVI in univariate and multivariate Cox analyses.

The quality of the eligible studies was evaluated according to the Newcastle–Ottawa Scale (NOS)^[17] guidelines, which contains 3 main areas:

- (1) selection of the study population;
- (2) comparability of the groups; and
- (3) ascertainment of the outcome.

The total score ranges from 0 to 9, and the studies with scores of 6 or more were deemed of high quality, whereas scores of 0 to 5 were considered to indicate poor quality.

2.4. Statistical analyses

Stata 12.0 software (Stat Corp, College Station, TX) was used to perform the meta-analysis. The estimated effects of the LVI and BCR risk were calculated using HRs and 95% CIs. Heterogeneity was analysed by the Chi-square-based Q test and I^2 . $P < .10$ or $I^2 > 50\%$ was considered statistically significant heterogeneity. A fixed model (FE) and random effect model (RE) were used according to the I^2 value of heterogeneity. Sensitivity analysis was used to validate the reliability of the outcomes via the sequential omission of individual studies from the meta-analysis. Subgroup analysis was performed to check whether the heterogeneity was influenced by the geographical region, date of publication, mean age, sample size, mean preoperative PSA (p-PSA), median follow-up or the different cutoff values for BCR. Funnel plots and Egger linear regression were used to explore whether any publication bias existed. Statistical significance was defined as $P < .05$ in a 2-tailed test.

To determine the significance of LVI in pathological diagnosis, we also studied the associations between LVI and the clinicopathological features of PCa. Dichotomous variables were calculated by odds ratios (ORs) and pooled OR with 95% CI. Information about EPE (yes vs no), pathological GS (≥ 7 vs < 7), LNM (yes vs no), pathological stage ($\geq T3$ vs $< T2$), surgical margin (positive vs negative) and SVI (yes vs no) were dichotomized. The event numbers were obtained from the original studies, and the ORs and 95% CIs were calculated.

3. Results

3.1. Literature search and study characteristics

The study search process used in this study is shown in Figure 1. A total of 219 potentially relevant studies were identified through systematic literature searches. After title and/or abstract screening, 150 studies were excluded because they were duplicates, reviews, case reports, or association between LVI and BCR was not evaluated. After the remaining studies ($n = 69$) were reviewed, 49 studies were excluded by the inclusion criteria: 39 due to the absence of HRs and/or enough extractable data,

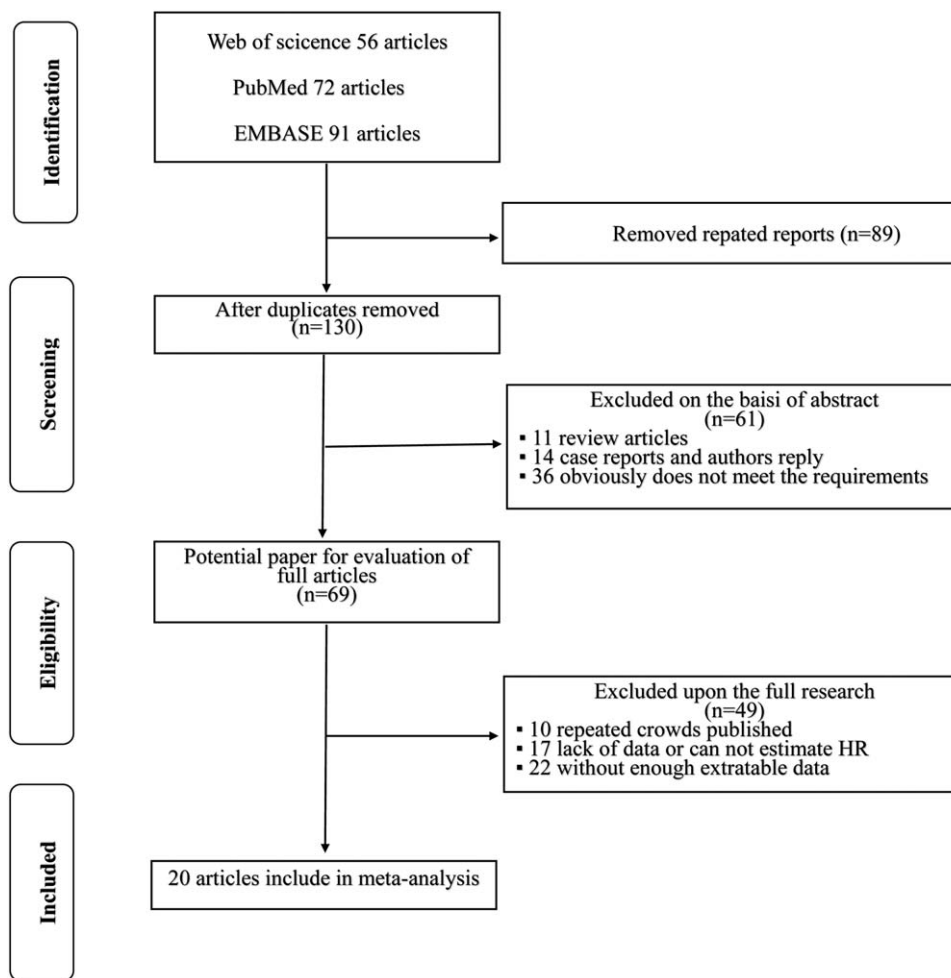


Figure 1. Flow diagram of the literature search and selection process.

and 10 were repeated cohort publications. Finally, 20 retrospective studies^[9,13–15,18–33] involving 25,570 patients were included in the study.

The main characteristics and clinicopathological outcomes in the included studies are summarized in Tables 1 and 2. All studies were published between 2004 and 2017, of which 10 studies were conducted in Asia, 6 in North America, 2 in Germany, and 2 in multiple centers. The median or mean follow-up of patients ranged from 18.4 to 69.8 years. In regard to the prognostic value of LVI in PCa, 3 articles only reported univariate analysis, 6 articles only reported multivariate analysis, and 11 both reported univariate and multivariate analyses. The incidence of BCR after RP ranged from 7.6% to 34.5% in the studies. The cutoff value for BCR in these included studies was slightly different, with 17 studies using 0.2 ng.mL⁻¹, 2 studies using 0.1 ng.mL⁻¹, and 1 study using 0.4 ng.mL⁻¹. The results of the methodological assessment by NOS ranged from scores of 7 to 9, indicating that all of the studies in our meta-analysis had high levels of methodological quality. (Supplementary Table S1, <http://links.lww.com/MD/C681>)

3.2. Meta-analysis results

The forest plots of the meta-analysis in our study demonstrated that LVI was associated with a higher BCR risk in univariate (RE

model, pooled HR=1.50, 95% CI: 1.34–1.68, $P<.001$, Fig. 2) and multivariate (RE model, pooled HR=1.25, 95% CI: 1.17, 1.34, $P<.001$, Fig. 3) analyses. Due to the heterogeneity, we performed the subgroup analyses presented in Table 3 by stratifying the combined data according to the region (Asia vs No-Asia/Multicentre), publication year (≥ 2015 vs <2015), mean patient age (≥ 65 vs <65), sample size (≥ 500 vs <500), mean p-PSA level (≥ 10 vs <10), median follow-up time (≥ 30 vs <30) and the cutoff value for BCR (0.2 ng.mL⁻¹ vs 0.1 ng.mL⁻¹ or 0.4 ng.mL⁻¹). The results showed that significant association between LVI and BCR based on Multicentre and mean p-PSA levels ≥ 10 ng.mL⁻¹ in the univariate analysis. In the multivariate analysis, the subgroup analysis showed a significant association with BCR based on Asia region, mean age ≥ 65 , sample size ≥ 500 , mean p-PSA levels <10 ng.mL⁻¹ and 0.1 ng.mL⁻¹ or 0.4 ng.mL⁻¹ cut-off values.

As shown in Table 4, patients with LVI were at a higher risk of having EPE (yes vs no: OR=4.23, 95% CI: 1.86–9.61, $P<.001$, Supplementary Figure S1A, <http://links.lww.com/MD/C681>), pathological GS (≥ 7 vs <7 : OR=5.46, 95% CI: 2.25–13.27, $P<.001$, Supplementary Figure S1B, <http://links.lww.com/MD/C681>), LNM (yes vs no: OR=18.56, 95% CI: 7.82–44.06, $P<.001$, Supplementary Figure S1C, <http://links.lww.com/MD/C681>), higher pathological stage ($\geq T3$ vs $<T2$: OR=6.75, 95% CI: 5.46–8.36, $P<.001$, Supplementary Figure S1D, <http://links.lww.com/MD/C681>).

Table 1

Main characteristics of the eligible studies.

Author	Year	Country	Sample size	Recruitment period	Age (years)	p-PSA level (ng.mL-1)	Follow-up time (months)	NOS score
Song et al ^[9]	2017	Korea	795	2006–2014	Mean ± SD 66.3 ± 6.6	Mean ± SD 13.7 ± 12.3	Median (range) 58.8(2.9–172.3)	9
Fujimura et al ^[18]	2017	Japan	908	2005–2016	Median 67	Median 7.7	NA	7
Sevcenco et al ^[19]	2016	Multicentre	7,205	2000–2011	median (IQR) 61 (57–66)	median (IQR) 6 (4–9)	median (IQR) 27 (19–48)	9
Pagano et al ^[20]	2016	USA	180	1990–2011	Mean (range) 63.7 (58.8–67.6)	Mean (range) 9.1 (6.3–17.1)	Mean (range) 26.7 (8.8–66)	9
Mao et al ^[21]	2016	China	106	2008–2009	Mean (range) 68.1(48–83)	Mean (range) 25.1(3.1–104.3)	median (IQR) 69 (8–84)	8
Kang et al ^[22]	2016	Korea	2,034	2003–2014	Mean (range) 67(62–71)	Mean (range) 7.4(4.93–12.03)	median (IQR) 48 (25–74)	9
Fajkovic et al ^[23]	2016	Multicentre	6,678	2000–2011	median (IQR) 61 (57–66)	median (IQR) 6 (4–9)	median (IQR) 28 (21–44)	9
Karl et al ^[24]	2015	Germany	946	1994–2013	Median (range) 64(40–79)	NA	Mean 48	9
You et al ^[25]	2014	Korea	397	2000–2009	Mean ± SD 64.7 ± 6.3	Mean ± SD 14.2 ± 713.2	NA	8
Chromecki et al ^[26]	2012	USA	232	NA	Median 62.6	Median 7.7	median (IQR) 69.8 (40.1–99.5)	8
Jung et al ^[28]	2011	Korea	407	2005–2009	Mean (range) 63.2(38–82)	Mean (range) 10(2.8–83.2)	Median (range) 18.4(6–50)	9
Yee et al ^[27]	2011	USA	1298	2004–2007	Median 59	Median 5.3	Median 27	8
Lee et al ^[29]	2010	Korea	361	1999–2010	Mean ± SD 69 ± 6.8	Mean ± SD 15.6 ± 18.6	Mean (range) 42.4(6.5–141.6)	8
Cho et al ^[30]	2010	Korea	171	2005–2009	Mean (range) 64.4(49–80)	NA	Mean (range) 23.3(2–51)	9
Jeon et al ^[31]	2009	Korea	237	1995–2004	Mean (range) 64.5(44–86)	Mean (range) 11.5(0.2–98)	Mean (range) 41.1(1–141.4)	9
Yamamoto et al ^[32]	2008	Japan	360	1994–2005	median (IQR) 68 (52–76)	median (IQR) 28 (21–44)	median (IQR) 47.4 (9.1–146.8)	8
May et al ^[13]	2007	Germany	412	1996–2003	mean (IQR) 63.7 (44–79)	mean (IQR) 12.1(0.1–151)	mean (IQR) 52.5 (10–116)	8
Loeb et al ^[14]	2006	USA	1,709	1989–2004	NA	NA	NA	7
Cheng et al ^[33]	2005	USA	504	1990–1998	Median (range) 63(34–80)	NA	Mean (range) 44(15–144)	8
Shariat et al ^[15]	2004	USA	630	1994–2002	Mean ± SD 60.4 ± 6.7	Mean ± SD 8.1 ± 8	Median (range) 21.4(1–101.3)	9

IQR = interquartile range, NA = data not applicable, p-PSA = preoperative prostate-specific antigen, SD = standard deviation.

lww.com/MD/C681), PSM (positive vs negative: OR = 2.42, 95% CI: 1.57–3.72, $P < .001$, Supplementary Figure S1E, <http://links.lww.com/MD/C681>) and SVI (yes vs no: OR = 5.72, 95% CI: 2.45–13.36, $P < .001$, Supplementary Figure S1F, <http://links.lww.com/MD/C681>). Some significant interstudy heterogeneity was observed in EPE, pathological GS, LNM, PSM, and SVI but analyses of pathological stage did not exhibit significant heterogeneity.

3.3. The sensitivity analysis and publication bias

The overall significance did not change when any single study was omitted. Sensitivity analysis showed that the pooled HR for BCR ranged from 1.44 (95% CI, 1.30–1.59) to 1.53 (95% CI, 1.35–1.72) (Fig. 4A) in univariate analysis and from 1.22 (95% CI, 1.15–1.30) to 1.26 (95% CI, 1.17–1.35) (Fig. 4B) in multivariate analysis. These results indicated that the findings were reliable and robust. The funnel plots of the studies were symmetrical, and Egger’s linear regression was performed. No significant publication bias was detected between these studies by univariate

(p-Egger = 0.167, Fig. 5A) or multivariate analysis (p-Egger = 0.583, Fig. 5B).

4. Discussion

In the current treatment paradigm, BCR after RP serves as a trigger point for further treatment,^[34] and identifying effective predictors of BCR after the surgical operation to determine whether treatment is required is a main challenge in PCA research. Patients at high risk of BCR after RP can be offered adjuvant radiation therapy or androgen deprivation treatment.^[35] Early risk stratification for BCR among the heterogeneous patients undergoing RP could help physicians select patients who are more likely to benefit from adjuvant multimodal therapy. Several nomograms for prognostication of BCR after RP have been proposed.^[9,20,30] However, their validated prognostic accuracies are not yet optimal. A novel biomarker may provide a better understanding of an individual’s tumor and improve the risk stratification of the patient population treated with RP.

Table 2
Tumour characteristics of the eligible studies.

Author	Specimen GS < 7/≥7	Staging system	T stage 1-2/3-4	LVI+/LVI-	No. of patients with BCR (%)	Definition of BCR
Song et al et al ^[9]	87/708	NA	0/795	156/639	274 (34.5%)	2 consecutive increases in the PSA level ≥ 0.2 ng/mL
Fujimura et al ^[18]	345/562	NA	224/683	282/625	157 (17.3%)	2 consecutive increases in the PSA level ≥ 0.2 ng/mL
Sevcenco et al ^[19]	2165/5040	AJCC 2009	NA	6299	798 (11.1%)	2 consecutive increases in the PSA level ≥ 0.2 ng/mL
Pagano et al ^[20]	90/90	NA	0/180	75/105	120 (66.5%)	2 consecutive increases in the PSA level ≥ 0.2 ng/mL
Mao et al ^[21]	47/59	AJCC 2002	63/43	17/89	31 (29.2%)	2 consecutive increases in the PSA level ≥ 0.2 ng/mL
Kang et al ^[22]	308/1726	AJCC 2009	1481/553	252/1782	300 (14.7%)	2 consecutive increases in the PSA level ≥ 0.2 ng/mL
Fajkovic et al ^[23]	2,197/4,469	AJCC 2009	NA	767/5,911	689 (10.3%)	2 consecutive increases in the PSA level ≥ 0.2 ng/mL
Karl et al ^[24]	367/579	AJCC 2009	956/0	47/899	243 (25.4%)	2 consecutive increases in the PSA level ≥ 0.2 ng/mL
You et al ^[25]	32/365	AJCC 2002	0/397	74/323	199 (50.1%)	2 postoperative PSA values ≥ 0.2 ng/mL
Chromecki et al ^[26]	102/128	NA	NA	22/210	47 (20.3%)	2 postoperative PSA values ≥ 0.2 ng/mL
Jung et al ^[28]	160/247	AJCC 2002	282/125	27/380	45 (11.1%)	2 consecutive increases in the PSA level ≥ 0.2 ng/mL
Yee et al ^[27]	320/978	TNM 2002	NA	129/1169	99 (7.6%)	a serum PSA level > 0.1 ng/mL at least 6 weeks after surgery with a confirmatory rise
Lee et al ^[29]	191/170	TNM 2002	253/108	40/321	83 (23%)	2 consecutive increases in the PSA level ≥ 0.2 ng/mL
Cho et al ^[30]	NA	AJCC 2002	126/45	16/151	15 (8.8%)	postoperative serum PSA level of at least 0.4 ng/mL
Jeon et al ^[31]	52/183	TNM 2002	145/92	41/194	67 (28.3%)	2 consecutive increases in the PSA level ≥ 0.2 ng/mL
Yamamoto et al ^[32]	29/365	TNM 1997	86/8	26/68	26 (27.7%)	2 consecutive increases in the PSA level ≥ 0.2 ng/mL
May et al ^[13]	243/169	TNM 1997	299/113	42/370	68 (16.5%)	2 consecutive increases in the PSA level ≥ 0.2 ng/mL
Loeb et al ^[14]	543/1,166	NA	NA	118/1,591	149 (11%)	2 consecutive increases in the PSA level ≥ 0.2 ng/mL
Cheng et al ^[33]	182/322	AJCC 1997	348/156	108/504	157 (31.2%)	consecutively increased postoperative serum PSA level (0.1 ng/mL)
Shariat et al ^[15]	256/374	AJCC 1997	630/0	32/598	80 (13%)	2 consecutive increases in the PSA level ≥ 0.2 ng/mL

BCR = biochemical recurrence, GS = Gleason score, NA = data not applicable.

Tumour metastasis is a complex process in which cancer cells obtain the ability to leave the primary tumor site via the lymphatic system and/or the bloodstream.^[36] LVI, as a detailed pathological finding, has been identified as an independent predictor of disease recurrence after curative treatment in multiple cancer types, including bladder cancer,^[37] gastric cancer,^[38] colorectal cancer,^[39] and PCa. Some authors suggest that the presence of LVI in PCa is associated with adverse oncological outcomes and higher recurrence rates,^[2,3] whereas others argue that LVI is not an independent predictor for prognosis.^[14,15,28] Ng et al^[40] suggested that there is insufficient evidence to recommend the routine use of LVI for clinical prognostication in a review article. A possible reason for the differences may arise from study design, sample size, source of the controls, or geographical region. All of these factors contribute to the limited statistical power in the published studies.

In 2016, Huang et al^[41] attempted to explore the impact of LVI on the BCR-free probability in a meta-analysis. They concluded that LVI may be a predictor of the BCR-free probability in PCa patients. However, given the confused definition of LVI in the study by Huang et al, the conclusion of the study was not based on strong statistical evidence. In addition, the calculation method for pooled HRs and 95% CIs in the study by Huang et al was

inappropriate. Compared to the results of a univariate analysis, the data from a multivariate analysis is more accurate, as it accounts for confounding factors.^[42] Therefore, it is inappropriate to put the data, which were extracted from 2 different analysis models, in a single forest plot in the meta-analysis. In addition, our study presented more studies in comparison with the study by Huang et al. As the search time reported in the meta-analyses from Huang et al ended in 2014, we added 9 extra studies with high quality from 2014 to 2017, thus providing more exact data evaluation for the pooled HRs and enabling more subgroup analyses. In addition, as we included more studies assessing the associations between LVI and the risk of BCR, our meta-analysis provides more reliable conclusions that reveal real associations compared with the study by Huang et al.

In the present study, among the 25,570 patients with PCa after RP, BCR was identified in 3647 (14.3%) patients. This meta-analysis supports that LVI was a strong independent predictor of BCR both in univariate (pooled HR = 1.50, *P* < .001) and multivariate (pooled HR = 1.25, *P* < .001) analyses. In the multivariate analysis, the subgroup analyses suggested that the associations were significant in the subgroups with an Asia region, mean age ≥ 65, sample size ≥ 500, mean p-PSA levels < 10 ng.mL-1 and 0.1 ng.mL-1 or 0.4 ng.mL-1 cut-off values. Besides,

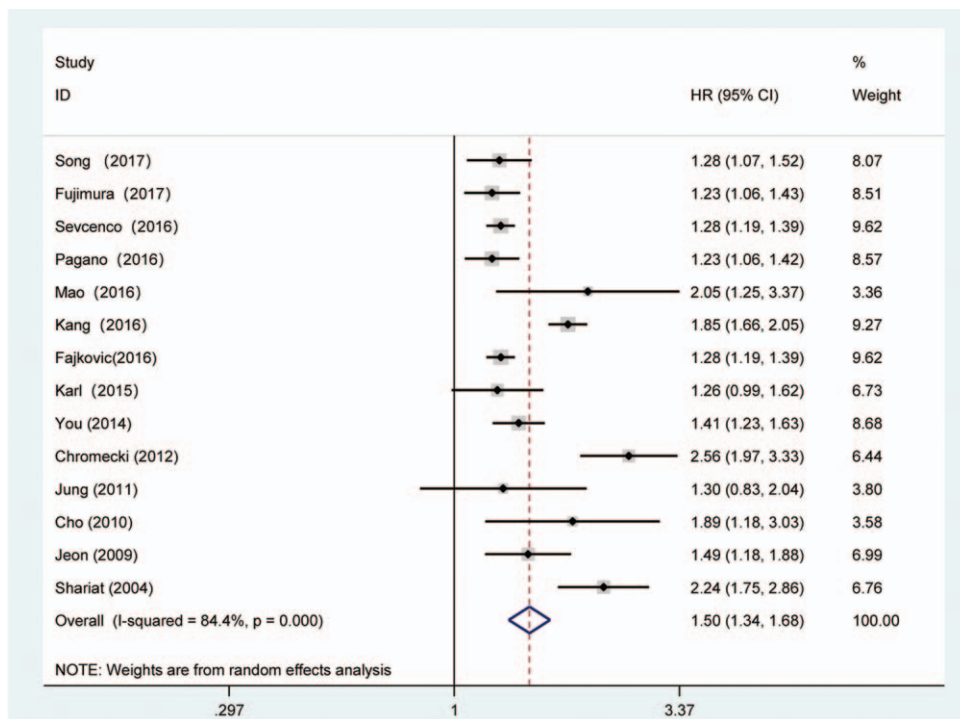


Figure 2. Forest plot and meta-analysis of studies evaluating the association between LVI and the BCR risk among men who underwent radical prostatectomy in univariate analysis mode. BCR=biochemical recurrence, LVI=lymphovascular invasion.

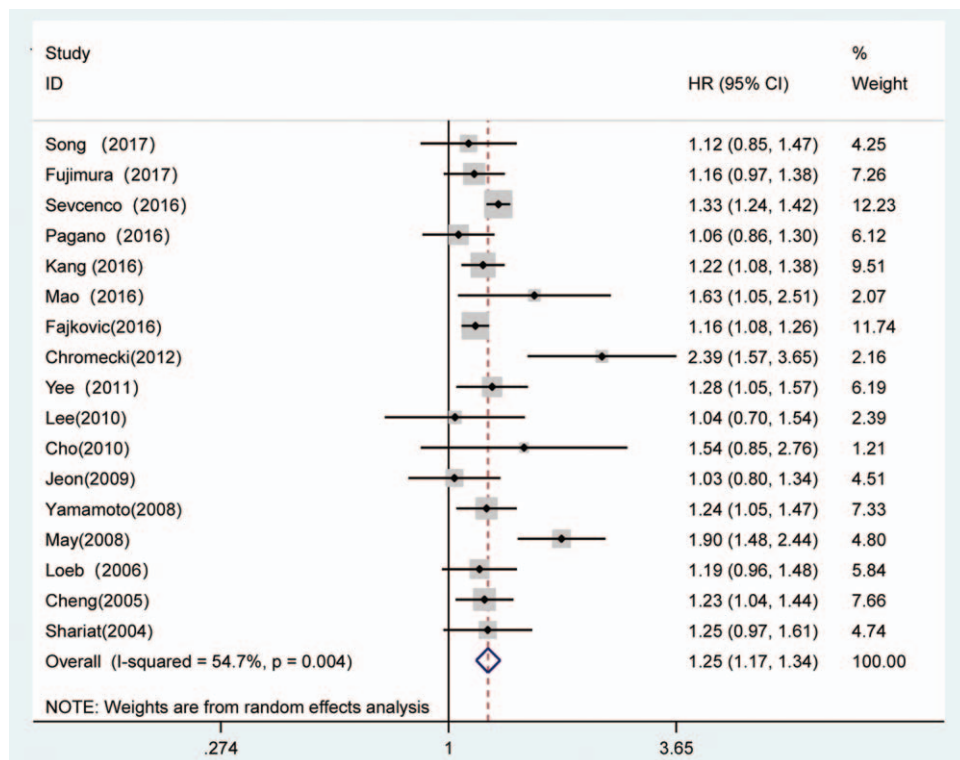


Figure 3. Forest plot and meta-analysis of studies evaluating the association between LVI and the BCR risk among men who underwent radical prostatectomy in multivariate analysis mode. BCR=biochemical recurrence, LVI=lymphovascular invasion.

Table 3
Summary and subgroup analyses for the eligible studies.

Analysis specification	No. of studies	Study heterogeneity		Effects model	Pooled HR (95% CI)	P value
		I ² (%)	P _{heterogeneity}			
Univariate analysis (BCR)						
Overall	14	84.4	<.001	Random	1.50 (1.34,1.68)	<.001
Geographical region						
Asia	8	75.8	<.001	Random	1.49 (1.28,1.73)	<.001
No- Asia	4	91.5	<.001	Random	1.71 (1.18,2.49)	.005
Multicentre	2	0	1.00	Fixed	1.28 (1.22,1.36)	<.001
Date of publication						
≥2015	8	84.3	<.001	Random	1.36 (1.21,1.54)	<.001
<2015	6	78.6	<.001	Random	1.77 (1.40,2.23)	<.001
Mean age (years)						
≥65	3	85	.001	Random	1.64 (1.21,2.21)	.001
<65	6	73.1	.002	Random	1.53 (1.27,1.84)	<.001
Sample size (cases)						
≥500	7	89.2	.09	Random	1.61 (1.52,1.70)	<.001
<500	7	77.4	<.001	Random	1.51 (1.33,1.71)	<.001
Mean p-PSA level (ng.mL-1)						
≥10	5	0	.433	Fixed	1.40 (1.27,1.54)	<.001
<10	3	92.3	<.001	Random	1.70 (1.23,2.35)	.001
Median follow-up						
≥30 months	5	92.3	<.001	Random	1.69 (1.32,2.16)	<.001
<30 months	3	88.9	<.001	Random	1.56 (1.05,2.33)	.030
Multivariate analysis (BCR)						
Overall	17	54.7	.004	Random	1.25 (1.17,1.34)	<.001
Geographical region						
Asia	8	0	.67	Fixed	1.19 (1.11,1.29)	<.001
No- Asia	7	72.7	.001	Random	1.36 (1.15,1.60)	<.001
Multicentre	2	84.1	.012	Random	1.25 (1.10,1.42)	.001
Date of publication						
≥2015	7	48	.073	Random	1.21 (1.13,1.30)	<.001
<2015	10	60.6	.007	Random	1.32 (1.16,1.50)	<.001
Mean age (years)						
≥65	4	0	.581	Fixed	1.19 (1.09,1.31)	<.001
<65	5	74.8	.003	Random	1.29 (1.01,1.65)	.045
Sample size (cases)						
≥500	7	25	.238	Fixed	1.23 (1.16,1.30)	<.001
<500	10	66.6	<.001	Random	1.33 (1.15,1.54)	<.001
Mean p-PSA level (ng.mL-1)						
≥10	5	73.7	.004	Random	1.30 (0.99,1.70)	.058
<10	3	0	.469	Fixed	1.18 (1.07,1.30)	.001
Median follow-up						
≥30 months	5	64.2	.025	Random	1.35 (1.13,1.62)	.001
<30 months	4	52.7	.096	Random	1.25 (1.15,1.36)	<.001
BCR value (ng.mL-1)						
cutoff value 0.2	15	59.8	.003	Random	1.25 (1.16,1.34)	<.001
cutoff value 0.1 or 0.4	2	0	.568	Fixed	1.31 (1.08,1.58)	.006

Table 4
Meta-analysis of the associations between LVI and the clinicopathological features of PCa patients.

Variables	Studies	Pooled OR	95% CI	P value	Model	Heterogeneity I ² (%)	P value
EPE (yes vs no)	7	4.23	1.86–9.61	.001	RE	96.6	<.001
Pathological GS (≥7 vs <7)	9	5.46	2.25–13.27	<.001	RE	91.6	<.001
LNM (yes vs no)	6	18.56	7.82–44.06	<.001	RE	71.8	.003
Pathological stage (≥T3 vs <T2)	5	6.75	5.46–8.36	<.001	FE	36.2	.18
Surgical margin (positive vs negative)	10	2.42	1.57–3.72	<.001	RE	88.9	<.001
SVI (yes vs no)	7	5.72	2.45–13.36	<.001	RE	95	<.001

EPE=extraprostatic extension, LNM=lymph node metastases, SVI=seminal vesicle invasion.

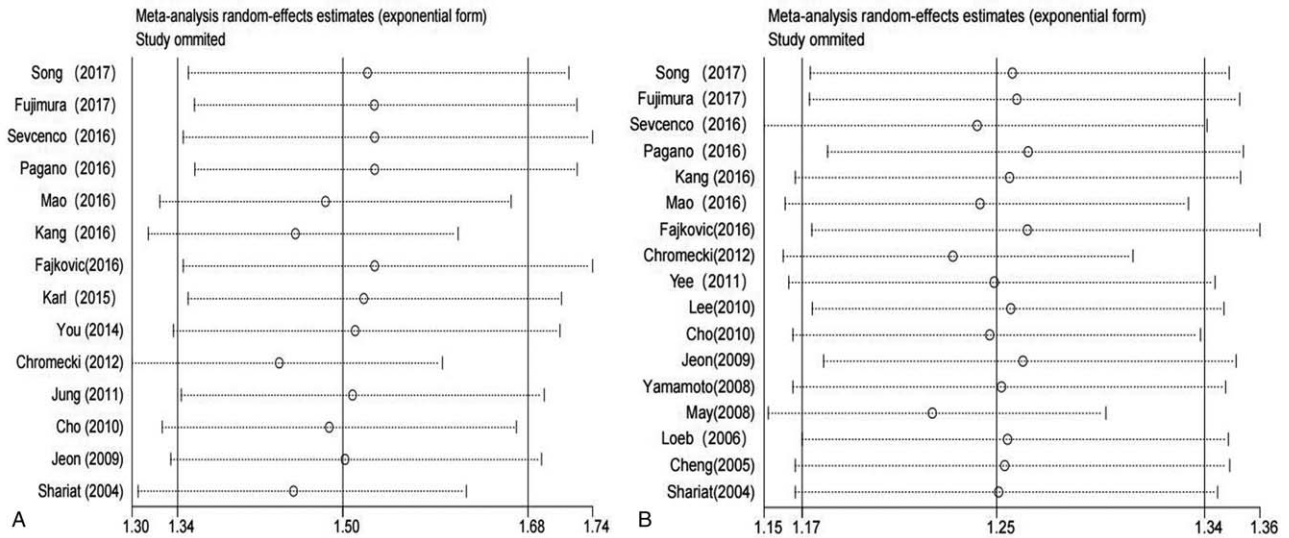


Figure 4. Sensitivity analysis of the association between LVI and the BCR risk in PCa patients. (A) Univariate analysis mode and (B) multivariate analysis mode. BCR = biochemical recurrence, LVI = lymphovascular invasion, PCa = prostate cancer.

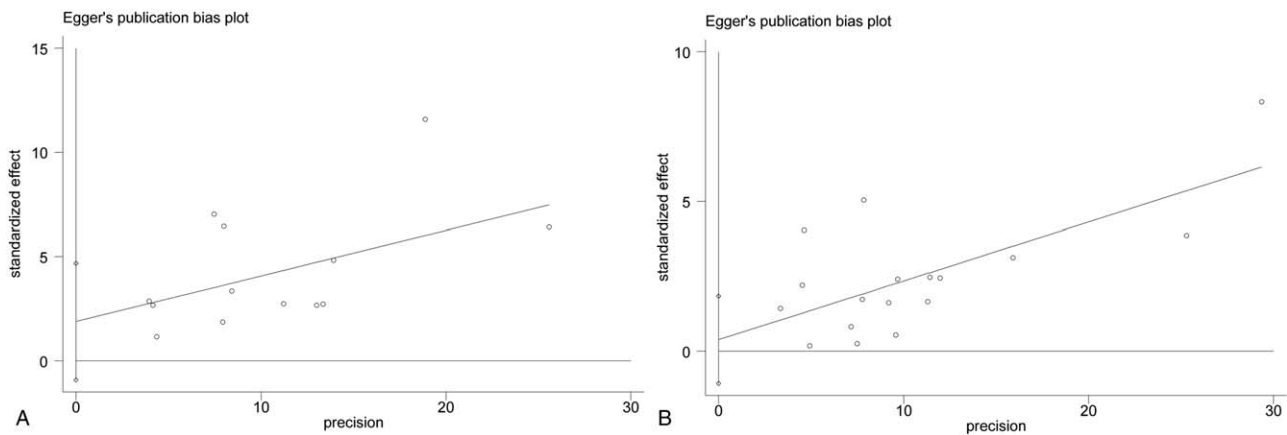


Figure 5. Funnel plots and Egger's tests for the evaluation of potential publication bias. (A) Univariate analysis mode and (B) multivariate analysis mode.

the association was also present in the subgroup with Multicentre and mean p-PSA levels ≥ 10 ng.mL⁻¹ in univariate analysis. In addition, our results also suggested that PCa patients with LVI were likely to have a higher GS and pathological stage, PSMs, EPE, SVI, and LNM. The correlation between LVI and these factors revealed that LVI has the potential to be adopted as a dichotomous biomarker. The sensitivity analyses indicated that the findings were reliable and robust. In addition, there was no evidence of significant publication bias in these analyses according to Egger linear regression. Taken together, the current evidence suggests that LVI plays a pivotal role in cancer progression.

As a meta-analysis, the present study allows us to obtain a better understanding of the clinicopathological role of LVI in PCa patients. However, certain limitations in the meta-analysis should draw our attention as well. The first of which is its retrospective nature, despite the use of a large sample size. Second, we only included published studies written in English, which may cause selection bias. Third, although uniform criteria were used to select eligible studies, inherent differences among the studies still

existed. Fourth, substantial heterogeneity was observed in the meta-analysis, and the heterogeneity was probably caused by differences in factors, such as the characteristics of the patients and variation in the cutoff values for BCR. Therefore, we should design randomized, controlled studies to provide more evidence of the prognostic importance of LVI in PCa patients.

5. Conclusions

In summary, although certain limitations exist, the results of the present study provide strong evidence that LVI was associated with a more aggressive tumor phenotype and could be regarded as a poor prognosis indicator for BCR in patients with PCa. These findings indicated that LVI expression is a potentially novel clinical prognostic factor in identifying individuals at an increased risk for BCR progression.

Author contributions

Conceptualization: Wei Jiang, Lijin Zhang, Bin Wu.
Data analysis: Jun Yuan, Yuefang Jiang.

Data curation: Lijin Zhang, Zhenlei Zha, Hu Zhao, Yuan Jun.
Literature search: Zhenlei Zha, Hu Zhao, Bin Wu.
Software: Yuefang Jiang.
Writing – original draft: Wei Jiang, Lijin Zhang.
Writing – review & editing: Bin Wu, Lijin Zhang.
 all authors approved the final manuscript.

References

- [1] Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA: Cancer J Clin* 2017;67:7–30.
- [2] Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol* 2017;71:618–29.
- [3] Boorjian SA, Eastham JA, Graefen M, et al. A critical analysis of the long-term impact of radical prostatectomy on cancer control and function outcomes. *Eur Urol* 2012;61:664–75.
- [4] Shanguan X, Dong B, Wang Y, et al. Management of prostate cancer patients with locally adverse pathologic features after radical prostatectomy: feasibility of active surveillance for cases with Gleason grade 3 + 4=7. *J Cancer Res Clin Oncol* 2017;143:123–9.
- [5] Fossati N, Karnes RJ, Boorjian SA, et al. Long-term impact of adjuvant versus early salvage radiation therapy in pt3n0 prostate cancer patients treated with radical prostatectomy: results from a multi-institutional series. *Eur Urol* 2017;71:886–93.
- [6] Lin S, Zhang Q, Li P, et al. Prediction of extraprostatic extension in patients with clinically organ-confined prostate cancer. *Urol Int* 2014;92:282–8.
- [7] Kristiansen A, Drevin L, Delahunt B, et al. Prognostic significance and biopsy characteristics of prostate cancer with seminal vesicle invasion on radical prostatectomy: a nationwide population-based study. *Pathology* 2017;49:715–20.
- [8] Porpiglia F, Manfredi M, Mele F, et al. Indication to pelvic lymph nodes dissection for prostate cancer: the role of multiparametric magnetic resonance imaging when the risk of lymph nodes invasion according to Briganti updated nomogram is <5. *Prostate Cancer Prostatic Dis* 2018;21:85–91.
- [9] Song W, Lee DH, Jeon HG, et al. Impact of Gleason score on biochemical recurrence in patients with pT3aN0/Nx prostate cancer with positive surgical margins: a multicenter study from the Prostate Cancer Research Committee. *J Cancer Res Clin Oncol* 2017;143:2393–400.
- [10] Negishi T, Kuroiwa K, Hori Y, et al. Predictive factors of late biochemical recurrence after radical prostatectomy. *Jpn J Clin Oncol* 2017;47:233–8.
- [11] Magi-Galluzzi C, Evans AJ, Delahunt B, et al. International Society of Urological Pathology (ISUP) consensus conference on handling and staging of radical prostatectomy specimens. Working group 3: extraprostatic extension, lymphovascular invasion and locally advanced disease. *Mod Pathol Off J US Canadian Acad Pathol Inc* 2011;24:26–38.
- [12] Fajkovic H, Mathieu R, Lucca I, et al. Validation of lymphovascular invasion is an independent prognostic factor for biochemical recurrence after radical prostatectomy. *Urol Oncol* 2016;34:233.e1–6.
- [13] May M, Kaufmann O, Hammermann F, et al. Prognostic impact of lymphovascular invasion in radical prostatectomy specimens. *BJU Int* 2007;99:539–44.
- [14] Loeb S, Roehl KA, Yu X, et al. Lymphovascular invasion in radical prostatectomy specimens: prediction of adverse pathologic features and biochemical progression. *Urology* 2006;68:99–103.
- [15] Shariat SF, Khoddami SM, Saboorian H, et al. Lymphovascular invasion is a pathological feature of biologically aggressive disease in patients treated with radical prostatectomy. *J Urol* 2004;171:1122–7.
- [16] Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol* 2009;62:e1–34.
- [17] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603–5.
- [18] Fujimura T, Fukuhara H, Taguchi S, et al. Robot-assisted radical prostatectomy significantly reduced biochemical recurrence compared to retro pubic radical prostatectomy. *BMC Cancer* 2017;17:454.
- [19] Sevcenco B, Mathieu R, Baltzer P, et al. The prognostic role of preoperative serum C-reactive protein in predicting the biochemical recurrence in patients treated with radical prostatectomy. *Prostate Cancer Prostatic Dis* 2016;19:163–7.
- [20] Pagano MJ, Whalen MJ, Paulucci DJ, et al. Predictors of biochemical recurrence in pT3b prostate cancer after radical prostatectomy without adjuvant radiotherapy. *Prostate* 2016;76:226–34.
- [21] Mao Y, Li K, Lu L, et al. Overexpression of Cdc20 in clinically localized prostate cancer: Relation to high Gleason score and biochemical recurrence after laparoscopic radical prostatectomy. *Cancer Biomark* 2016;16:351–8.
- [22] Kang M, Oh JJ, Lee S, et al. Perineural invasion and lymphovascular invasion are associated with increased risk of biochemical recurrence in patients undergoing radical prostatectomy. *Ann Surg Oncol* 2016;23:2699–706.
- [23] Fajkovic H, Mathieu R, Lucca I, et al. Validation of lymphovascular invasion is an independent prognostic factor for biochemical recurrence after radical prostatectomy. *Urol Oncol* 2016;34:233.e231–6.
- [24] Karl A, Buchner A, Tympner C, et al. The natural course of pT2 prostate cancer with positive surgical margin: predicting biochemical recurrence. *World J Urol* 2015;33:973–9.
- [25] You D, Jeong IG, Song C, et al. High percent tumor volume predicts biochemical recurrence after radical prostatectomy in pathological stage T3a prostate cancer with a negative surgical margin. *Int J Urol* 2014;21:484–9.
- [26] Chromceki TF, Cha EK, Pummer K, et al. Prognostic value of insulin-like growth factor II mRNA binding protein 3 in patients treated with radical prostatectomy. *BJU Int* 2012;110:63–8.
- [27] Yee DS, Shariat SF, Lowrance WT, et al. Prognostic significance of lymphovascular invasion in radical prostatectomy specimens. *BJU Int* 2011;108:502–7.
- [28] Jung JH, Lee JW, Arkoncel FR, et al. Significance of perineural invasion, lymphovascular invasion, and high-grade prostatic intraepithelial neoplasia in robot-assisted laparoscopic radical prostatectomy. *Ann Surg Oncol* 2011;18:3828–32.
- [29] Lee JT, Lee S, Yun CJ, et al. Prediction of perineural invasion and its prognostic value in patients with prostate cancer. *Korean J Urol* 2010;51:745–51.
- [30] Cho IC, Chung HS, Cho KS, et al. Bcl-2 as a predictive factor for biochemical recurrence after radical prostatectomy: an interim analysis. *Cancer Res Treat* 2010;42:157–62.
- [31] Jeon HG, Bae J, Yi JS, et al. Perineural invasion is a prognostic factor for biochemical failure after radical prostatectomy. *Int J Urol* 2009;16:682–6.
- [32] Yamamoto S, Kawakami S, Yonese J, et al. Lymphovascular invasion is an independent predictor of prostate-specific antigen failure after radical prostatectomy in patients with pT3aN0 prostate cancer. *Int J Urol* 2008;15:895–9.
- [33] Cheng L, Jones TD, Lin H, et al. Lymphovascular invasion is an independent prognostic factor in prostatic adenocarcinoma. *J Urol* 2005;174:2181–5.
- [34] Couture F, Tholomier C, Zorn KC. Prostate cancer biochemical recurrence after salvage radiotherapy: first look into risk stratification and prognosis. *BJU Int* 2018;121:320–1.
- [35] Fryczkowski M, Bryniarski P, Szczebara M, et al. The impact of adjuvant therapy in patients with biochemical recurrence on prostate cancer progression and mortality five years after radical prostatectomy. *Central Eur J Urol* 2011;64:218–22.
- [36] Xu N, Chen HJ, Chen SH, et al. Upregulation of Talin-1 expression associates with advanced pathological features and predicts lymph node metastases and biochemical recurrence of prostate cancer. *Medicine* 2016;95:e4326.
- [37] Lotan Y, Gupta A, Shariat SF, et al. Lymphovascular invasion is independently associated with overall survival, cause-specific survival, and local and distant recurrence in patients with negative lymph nodes at radical cystectomy. *J Clin Oncol* 2005;23:6533–9.
- [38] Kim SJ, Choi CW, Kang DH, et al. Preoperative predictors of beyond endoscopic submucosal dissection indication or lymphovascular invasion in endoscopic resection for early gastric cancer. *Surg Endosc* 2018;32:2948–57.
- [39] Mohajeri G, Mohajeri MR, Afshar-Moghaddam N, et al. The significance of clinicopathological aspects of tumor for the detection of liver micrometastasis in patients with colorectal cancer. *J Res Med Sci* 2014;19:410–3.
- [40] Ng J, Mahmud A, Bass B, et al. Prognostic significance of lymphovascular invasion in radical prostatectomy specimens. *BJU Int* 2012;110:1507–14.
- [41] Huang Y, Huang H, Pan XW, et al. The prognostic value of lymphovascular invasion in radical prostatectomy: a systematic review and meta-analysis. *Asian J Androl* 2016;18:780–5.
- [42] Moraes LE, Kebreab E, Strathe AB, et al. Multivariate and univariate analysis of energy balance data from lactating dairy cows. *J Dairy Sci* 2015;98:4012–29.