The prognostic value of lymphovascular invasion in radical prostatectomy: a systematic review and meta-analysis

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INTRODUCTION
Prostate cancer (PCa) is the second most common cancer and the sixth leading cause of cancer-related death in Caucasian men, and there were estimated 238 590 new PCa cases and 29 720 deaths from PCa in the United States in 2014.1 With advances in the minimally invasive technologies, radical prostatectomy (RP) as the standard treatment has made great progress in improving perioperative outcomes. Nevertheless, early biochemical recurrence (BCR) occurred in approximately 20% patients undergoing RP,2,3 in whom the 5-year metastasis rate was as high as 30%–44%.4 Thus, it is imperative for clinicians to identify risk factors of post-RP BCR, and provide advisable indexes for adjuvant therapies including external beam radiotherapy (EBRT), intensity-modulated radiotherapy, and androgen deprivation therapy.

To date, although some potential biomarkers including Lymphovascular Invasion (LVI) have been added to the pathological reports of PCa patients who underwent prostatectomy, their impact on prognosis such as BCR has not been sufficiently evaluated.5 LVI has been documented as a poor prognostic factor in many solid tumors.5,6 Some authors have demonstrated an association between the presence of LVI in prostatectomy specimens and BCR. Although the College of American Pathologists (CAP) suggested that LVI should be reported in the routine examination of RP specimens in the 2010 consensus statement, there is a lack of convincing evidence to support its prognostic value.7 Therefore, we conducted a systematic review of current publications to assess the prognostic value of LVI in BCR, and a meta-analysis was performed for the extracted data that could be merged.

MATERIALS AND METHODS

Literature search
We search Electronic databases including PubMed, Web of Science and the Cochrane Library for published studies that analyzed the prognostic value of LVI in PCa up to May 31, 2014. The following Medical Subject Headings terms and free texts were used: “lymphovascular,” “microvascular,” “vascular,” “vessel,” “invasion,” “prostate,” “prostatic,” “cancer,” “carcinoma,” “neoplasm,” “tumor,” and “mass.” The searching strategies and results are shown in Table 1. In addition, a full manual search from the reference list of each identified article was performed.

Study selection
We defined the inclusion and exclusion criteria at the initiation of the search. Studies were included when they met the following
criteria: (1) studies that included definitive diagnosis of PCa; (2) studies that assessed LVI in RP specimens involving lymphatic or vascular invasion for which no attempt was made to differentiate them; (3) studies that chose RP as the only treatment; (4) studies that investigated the relationship between LVI and patient pathological outcomes or the correlation between LVI with preoperative prostate specific antigen (PSA) and pathological parameters; and (5) studies that offered a hazard ratio (HR) and 95% confidence interval (CI) directly or rendered the data that could be used to calculate HR and 95% CI. The exclusion criteria were: (1) review articles, letters to the editor, commentaries, or case reports; (2) studies that duplicated patient populations that had been reported in previous publications; and (3) studies on PCa cell lines or animal models.

The whole process was monitored by two reviewers (YH and HH) independently. Discrepancies between the reviewers were resolved by a consensus meeting with three senior investigators (YG, YH, and XGC) who made the final decision regarding inclusion or exclusion of the study.

Data extraction

The following specified data were gathered from each eligible study: (1) main characteristics including the author, country, publication year, institution, recruitment period, study design, pathology stain method, definition of LVI, definition of BCR, the number of patients, median age at operation, the number of pelvic lymph node dissection (PLND), neoadjuvant (neo), androgen deprivation therapy (ADT), external beam radiotherapy (EBRT), and median follow-up time (Supplementary Table 1); (2) Tumor-Node-Metastasis (TNM) stage characteristics, Gleason score, and correlation between LVI and preoperative PSA and pathological parameters (Supplementary Table 2); (3) HR of LVI in univariate or multivariate Cox analyses, Co-factors, and the conclusion of each study concerning whether LVI was an independent predictor (Supplementary Table 3).

Statistical analysis

The primary objective of this review was to determine differences in survival outcomes between patients with negative LVI and positive LVI. HR and 95% CI were collected from each study if they were not directly reported, and the HR was estimated according to the method reported by Tierney et al.1 The overall pooled HR was estimated by calculating the weighted average of the log-HRs and their 95% CI from each study. An observed HR >1 implied a poor survival outcome for patients with positive LVI. The impact of LVI on the outcome was considered as an independent predictor if the 95% CI did not overlap with 1 and $P < 0.05$. Subgroup analysis was performed to check whether the pooled HR was influenced by the region and number of patients, pathologic N stage, median follow-up, analysis results, definition of BCR, staining method, and staging system. In order to assess the stability of the combined HR, sensitivity analysis was performed by removing one study. The heterogeneity of the combined HR was evaluated using the Chi-square ($\chi^2$ test) and inconsistency (I² test). Meta-analysis used the fixed-effect model, when $P \geq 0.1$ and $I^2 \leq 50\%$, which indicated a moderate heterogeneity between studies, whereas when $P < 0.1$ or $I^2 > 50\%$, which indicated large heterogeneity, the random-effect model was applied. In addition, publication bias was evaluated by Egger’s linear regression and Begg’s rank correlation.

The secondary objective of this review was to study the relationship between the pathological parameters of PCA and LVI. The data of pathological stage were divided as low-stage (pT2) group and high stage (pT3-4) group. Gleason scores were categorized as low Gleason score (GS <7) and high Gleason score (GS ≥7). The RR of the high stage or high Gleason score along with the corresponding 95% CI was calculated by meta-analysis. In addition, the extracapsular extension (ECE), seminal vesicle involvement (SVI), and pathological node (pN) were directly divided as positive and negative. RR and CI of positive components were analyzed. Stata (Version 12.0; Stata Corp, College station, TX, USA) was used for all statistical analyses.

RESULTS

A total of 25 studies were selected for the systematic review and meta-analysis (Figure 1). With regard to the primary objective, survival outcomes with negative LVI and positive LVI were evaluated. Some studies revealed that LVI was an independent predictor in cancer-specific survival (CSS), distant metastasis (DM), progression-free survival (PFS), overall survival (OS), and these details are shown in Supplementary Table 3, however, the data for CSS, DM, PFS, OS were not available in any study. Nevertheless, 21 studies provided the BCR data, and the meta-analysis showed that positive LVI was correlated with poorer BCR in RP patients (HR = 2.05, 95% CI, 1.64–2.56, $P < 0.00001$) (Figure 2). Test of Cochrane Q ($\chi^2 = 47.39, P = 0.001$) and inconsistency test ($I^2 = 57.8\%$) could not exclude a significant heterogeneity. Given the large heterogeneity between the studies, subgroup analysis was performed, and the results are shown in Supplementary Table 4. In sensitivity analysis, one-way sensitivity analysis was carried out to exclude a single study and calculated the pooled HR for remaining studies, and omission of each study did not have a significant impact on the merged value of HR. Allowing for publication bias, Begg’s funnel plot was performed, and no significant
publication bias was detected between these studies regarding HR of BCR with \( P = 0.112 \). In addition, Egger’s test (\( P = 0.207 \)) demonstrated a similar result (Figure 3).

The secondary objective was to assess the relationship between LVI and higher pathological tumor stages (> pT3 stage), higher Gleason score (> GS = 7), positive pN, ECE, and SVI. Ten studies provided data on the number of higher pT stage in the positive LVI groups and negative LVI groups, and the pooled RR was 1.90 (95% CI, 1.73–2.08; \( Z = 13.45, P < 0.00001 \)) with a moderate heterogeneity (\( P = 0.054 \) for heterogeneity; \( I^2 = 46.1\% \)) (Figure 4a). Similarly, the data of other pathological parameters were extracted from eligible studies, and we found that LVI was significantly correlated with higher GS (pooled RR, 1.30; 95% CI, 1.23–1.39; \( Z = 8.55, P < 0.00001 \)) with a moderate heterogeneity (\( P = 0.019 \) for heterogeneity; \( I^2 = 47.1\% \)) (Figure 4b), positive pN status (pooled RR, 5.67; 95% CI, 3.14–10.24; \( Z = 5.74, P < 0.00001 \)) with a large heterogeneity (\( P < 0.00001 \) for heterogeneity test; \( F = 72.8\% \)) (Figure 4c), ECE (pooled RR, 1.72; 95% CI, 1.46–2.02; \( Z = 6.50, P < 0.00001 \)) with a large heterogeneity (\( P < 0.00001 \) for heterogeneity test; \( F = 73.6\% \)) (Figure 4d) and SVI (pooled RR, 3.36; 95% CI, 2.41–4.70; \( Z = 7.11, P < 0.00001 \)) (Figure 4e) despite a large heterogeneity among studies (\( P < 0.00001 \) for heterogeneity test; \( F = 81.9\% \)).

**DISCUSSION**

Lymphovascular invasion is defined as the presence of a tumor within an endothelial-lined space, which most probably links with the hematogenous spread of tumor cells. Tumor cells first infiltrate into lymphatic and/or vascular vessels, and then disseminate, which is a much more common phenomenon in malignant tumors including PCA.43 In addition, LVI is a significant prognostic factor in bladder, upper urinary tract urothelial and lung cancers, which has been confirmed in several systematic review studies.41–43 As regards to liver and testicular tumors, LVI has been added to the TNM staging system, in terms of improved tumor staging.44–46 Although the prognostic value of LVI in PCA patients after RP has been appraised by a number of studies, the results remain controversial.

The results obtained in our meta-analysis are in line with those in a previous System Review by Ng et al.”46 In addition, our study presented a series of advancements in comparison with the previous studies. First, we included more eligible studies with large sample sizes. The Ng’s search time was ended in 2009. However, we added 8 extra studies including 2825 patients from 2009 to 2014, thus providing more exact evaluation on the effect and enabling more authentic subgroup analyses.

Second, although the same result was obtained in Ng’s study reporting a significant relationship between LVI and BCR in RP, we found that the pooled result of LVI had a large heterogeneity (\( F = 57.8\% \)) by meta-analysis, and so we conducted a subgroup analysis. Meanwhile, the sensitivity analysis of our study revealed that the omission of each study did not have a significant impact on the merged value of HR. In contrast, Ng et al.”46 only assessed the quality of publications and no other analysis on the reliability of the result was done.

In our subgroup analyses of the region, sample size, pN status, follow-up time, negative/positive result of LVI, PSA level definition of BCR and staining method, we found a significant correlation between LVI and staining method, we found a significant correlation between LVI and poor BCR. Notably, in large sample groups with the number of patients larger than 500, the pooled HR was 1.58 (1.28–1.95). In the short-term follow-up group with the follow-up duration <24 months, we also found that LVI could serve as a predictor in early BCR and be used in Nomogram for predicting BCR.47 Although only one study43 revealed that the addition of LVI only marginally improved the predictive accuracy (from 0.880 to 0.884). In addition, LVI was correlated with higher pT stages, higher GS, positive pN status, ECE, and SVI, indicating that the presence of LVI in PCa may predict the higher risk of progression with poor BCR, PFS, CSS, DM, and OS, and some previous studies13,20,22,23 may support this possibility though we do not have available data to further analysis.

**Figure 2:** Forest plots of hazard ratios with the random-effects model for lymphovascular invasion in patients with prostate cancer (biochemical recurrence-free probability).
There are some limitations in our meta-analysis. The first is the problem of heterogeneity due to relevant baseline patient characteristics of each study. Although we took into account the heterogeneity in our meta-analysis using the random-effects model, the conclusion drawn in this study should be considered prudently. Second, as some of the studies were unable to provide data available to calculate HRs of BCR, we could not merge their results, although publication bias evaluation of BCR showed no significant difference and sensitivity analysis confirmed the prognostic value of LVI. In addition, as only few included studies covered survival outcomes such as PFS, CSS, DM, and OS, we were unable to perform a meta-analysis for the lack of data available to calculate HR and 95% CI directly or indirectly. Finally, most studies were retrospective, and only two studies included in our meta-analysis were prospective. Therefore, more prospective multicenter trials are required to confirm the conclusion.

In addition to these study limitations, it is usually difficult to completely exclude subjective bias among pathologists in clinical practice.

Figure 3: Begg’s Funnel plots for publication bias test. Assessment of potential publication bias in studies of lymphovascular invasion in patients with prostate cancer (biochemical recurrence-free probability).

Figure 4: Forest plots of RR’s for the Association of LVI with (a) higher pathological tumor stages (>pT3 stage); (b) higher Gleason score (>GS = 7); (c) pathological node (pN); (d) extracapsular extension (ECE); (e) seminal vesicle involvement (SVI). RR: risk ratio.
practice. Knowing that the surrounding stromal tissue can mimic vascular invasion that cannot be easily be recognized, experts have reached agreement that the report of LVI is only in unequivocal cases. With regard to staining method, hematoxylin and eosin (HE) is the most commonly used examination for LVI. However, some included studies incorporated immunohistochemical analysis, and this added measure may increase the detection rate of LVI. But as there are still controversies over the use of immunohistochemical analysis, it is not used routinely in clinical practice. What’s more, in most studies, tumor cells invasion in lymphatic vessels and vascular vessels were combined as LVI and no effort was made to distinguish between them. One reason for this is the difficulty that there is lack of reproducibility when using routine light microscopy, and previous studies have not fully evaluated the clinical values to assess the survival outcomes of prostate cancer in terms of distinguishing vascular invasion from lymphatic invasion.

CONCLUSION
Our meta-analysis indicates that LVI has a detrimental effect on the BCR-Free probability, and clinicopathological features in RP specimens and, therefore, could be considered as an independent prognostic factor of BCR. It could also be used to predict BCR patients who need further adjuvant therapies.

AUTHOR CONTRIBUTIONS
Y Huang reviewed articles, analyzed data, and drafted the manuscript; HH and XWP reviewed articles, analyzed data, and revised the manuscript critically; HH participated in as the third reviewer and drafting the manuscript; JC and Y Hong participated in data analyzing and revised the manuscript; JQY and LL participated in its design and helped to draft the manuscript; DFX supervised the project and revised manuscript; XGC and YG conceived of the study, participated and revised the manuscript; XGC and YG conceived of the study, participated and revised the manuscript; HH participated in as the third reviewer and revising manuscript; JQY and LL participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS
The authors declare that they have no competing interests.

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Supplementary information is linked to the online version of the paper on the Asian Journal of Andrology website.

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| Study | Country | Year | Institution | Recruitment period | Study design | Pathology stain method | Definition of LVI | Number of patients | Median age at operation, range (year) | PLND | Neo | ADT | EBRT | Median follow-up, range (months) |
|-------|---------|------|-------------|-------------------|-------------|------------------------|-----------------|------------------|-------------------------------------|------|-----|-----|------|-----------------------------|
| Yee et al. | USA | 2010 | Memorial Sloan-Kettering Cancer Center | 2004–2007 Prospective | HE | Yes | PSA ≥ 0.1 | 1298 | 59, NA | 1298 | 0 | 24 | NA | 27, NA |
| Lee et al. | Korea | 2010 | Pusan National University Hospital | 1999–2010 Retrospective | HE | Yes | PSA ≥ 0.2 | 361 | 69.0 ± 6.8, 49–94 | NA | 0 | NA | 42.4 ± 33.6, 6.5–141.6 |
| Cho et al. | Korea | 2010 | Korea Nation Cancer Center | 2005–2009 Retrospective | NA | No | PSA ≥ 0.4 | 167 | 64.4, 49–80 | NA | 0 | NA | 23.3–51 |
| Jeon et al. | Korea | 2009 | Seoul National University Hospital | 1995–2004 Retrospective | NA | Yes | PSA ≥ 0.2 | 237 | 64.5, 44–86 | 135 | 18 | 30 | 41.4, 1–141.4 |
| Whittimore et al. | USA | 2008 | Wilford Hall Medical Center | 1988–2003 Retrospective | NA | No | PSA ≥ 0.2 | 214 | NA | NA | 0 | 0 | NA | NA |
| Yamamoto et al. | Japan | 2008 | Cancer Institute Hospital, Tokyo | 1994–2005 Retrospective | HE | Yes | PSA ≥ 0.2 | 94 | 68, 52–76 | 94 | 0 | NA | 47.4, 9.1–146.8 |
| May et al. | Germany | 2006 | Carl-Thiem Hospital Vivantes-Clinic Am Urban | 1996–2003 Retrospective | IHC (CD31)/HE | Yes | PSA ≥ 0.2 | 412 | 63.7, 44–79 | 412 | 0 | 0 | NA | 52.5–10–116 |
| Hofer et al. | Germany | 2005 | University of Ulm Hospital | 1986–2002 Retrospective | NA | Yes | PSA ≥ 0.4 | 201 | 64, 48–78 | 201 | 0 | 201 | NA | 41, 1–151 |
| Antunes et al. | Brazil | 2006 | Syrian Lebanese Hospital | 1993–2000 Retrospective | NA | No | PSA ≥ 0.4 | 428 | 62.8, 40–83 | NA | 0 | 0 | NA | 53.9 ± 20.1, NA |
| Loeb et al. | USA | 2006 | Washington University School of Medicine North Western University Feinberg School of Medicine | 1989–2002 Retrospective | HE | Yes | PSA ≥ 0.2 | 1709 | NA | NA | NA | NA | NA | 34, 1–122 |
| Brooks et al. | USA | 2006 | Walter Reed Army Medical Center National Naval Medical Center | 1991–2001 Retrospective | NA | No | PSA ≥ 0.2 | 160 | NA | 160 | NA | NA | 32 | 99.6, NA |
| Cheng et al. | USA | 2005 | Indiana University Hospital | 1990–1998 Retrospective | NA | Yes | PSA ≥ 0.1 | 504 | 62, NA | 504 | 0 | NA | 44, 1.5–144 |
| Shariat et al. | USA | 2004 | University of Texas South Western Medical Center | 1994–2002 Retrospective | HE | Yes | PSA ≥ 0.2 | 630 | 60.9, 40–75 | 630 | NA | NA | NA | 43.9, 4–100 |
| Ito et al. | Japan | 2002 | Keio University School of Medicine | 1989–1998 Retrospective | HE | Yes | PSA ≥ 0.2 | 82 | 66.5 ± 0.5, 56–74 | 82 | 0 | 0 | 0 | 21.7 ± 1.9, 9–84.2 |
| de la Taille et al. | USA | 1999 | Columbia-Presbyterian Medical Center | 1993–1998 Retrospective | HE | Yes | PSA ≥ 0.2 | 241 | 62, 42–77 | NA | NA | NA | 22.9, 6–77.6 |
| van den Ouden et al. | Netherlands | 1997 | Erasmus University and Academic Hospital | 1977–1994 Retrospective | HE | Yes | PSA ≥ 0.1 | 273 | 63.8, 45–75 | 273 | NA | NA | 49, 1–206 |
| Leng et al. | Korea | 2013 | Veterans Health Service Medical Center | 2005–2010 Retrospective | NA | No | PSA ≥ 0.2 | 166 | NA | NA | 167 | 0 | 0 | 33.7 ± 18.7, NA |
| Chromecki et al. | USA | 2011 | Weil Cornell Medical College | 2011 Retrospective | NA | No | PSA ≥ 0.2 | 232 | 62.6, NA | 232 | 0 | 0 | 69.0, 4.3–113.4 |
| Quinn et al. | Australia | 2001 | St. Vincent’s Hospital Campus | 1986–1999 Retrospective | NA | Yes | PSA ≥ 0.4 | 732 | 62.1, 40.7–76.7 | 724 | 83 | NA | 41.1, 1.0–167.7 |
| Huang et al. | China | 2007 | Kaohsiung Medical University Kaohsiung Veterans General Hospital | 2000–2005 Prospective | NA | No | PSA ≥ 0.2 | 126 | NA | NA | NA | NA | NA | NA |
| Jung et al. | Korea | 2011 | Yonsei University College of Medicine | 2005–2009 Retrospective | NA | Yes | PSA ≥ 0.2 | 407 | 63.24, 38–82 | 407 | 0 | 0 | 0 | 18.43, 6–50 |
| Ferrari et al. | USA | 2004 | Stanford University Medical Center | 1984–1999 Retrospective | HE | Yes | PSA ≥ 0.1 | 620 | 64.5, 42–78 | 614 | 0 | NA | 90, 24–216 |
| Luo et al. | China | 2012 | Kaohsiung Chang Gung Memorial Hospital | 1998–2010 Retrospective | NA | No | PSA ≥ 0.2 | 87 | 63, 49–83 | NA | NA | NA | 40.9, 0.6–99.9 |
| Herman et al. | USA | 2000 | Memorial Sloan-Kettering Cancer Center | 1983–1997 Retrospective | HE | Yes | PSA ≥ 0.4 | 263 | 64, NA | 263 | 8 | NA | 36, 1–158 |
| Baydar et al. | Turkey | 2007 | Hacettepe University, School of Medicine | 1992–2001 Retrospective | IHC (CD31)/HE | Yes | PSA ≥ 0.2 | 71 | 62, 48–75 | 69 | 0 | NA | 54, 4–145 |

BOR: biochemical recurrence; PSA: prostate specific antigen; EBRT: external beam radiotherapy; RP: radical prostatectomy; ADT: androgen deprivation therapy; PLND: pelvic lymph node dissection; Neo: neoadjuvant; HE: hematoxylin and eosin; IHC: immunohistochemistry; NA: not available; LV: lymphovascular invasion
**Supplementary Table 2: The TNM stage characteristics and correlations between LVI and preoperative PSA and pathological parameters**

| Study               | TNM stages and GS characteristics (staging system) | Number (% of positive LVI) | Preoperative PSA (ng/mL) | pT stage ≥pT3/total | ECE Positive/total | SVI Positive/total | GS ≥7 GS/total | pN stage pN+/total |
|---------------------|----------------------------------------------------|----------------------------|--------------------------|---------------------|--------------------|---------------------|----------------|------------------|
| Yee et al.          | pT2-4, pNO-1 GS (<7, 7, >7) (2002 AJCC)            | 129/1298 (9.9)             | 7.3 (4.9–11.3)           | 5.1 (3.7–7.1)       | <0.001             | NA                  | NA             | NA               |
| Lee et al.          | pT2-4, pNO-1 GS (<7, 7, >7) (2002 AJCC)            | 40/361 (11.1)              | NA                       | NA                  | NA                 | NA                  | NA             | NA               |
| Cho et al.          | pT2-3, pNx GS (<7, 7, >7) (2002 AJCC)              | 16/167 (9.6)               | NA                       | NA                  | NA                 | NA                  | NA             | NA               |
| Jeon et al.         | pT2-3, pNO-1 GS (<7, 7, >7) (2002 AJCC)            | 41/237 (17.3)              | 16.4 (2.7–98.0)          | 10.5 (0.2–86.6)     | 0.002              | 30/41 (74.4)       | 62/196         | 26/41 (58.2)     |
| Whitemore et al.    | pT2-4, pNO-1 GS (7) (2002 AJCC)                    | 12/214 (5.6)               | NA                       | NA                  | NA                 | NA                  | NA             | NA               |
| Yamamoto et al.     | pT3a, pNO GS (<7, 7, >7) (1997 AJCC)               | 26/64 (27.7)               | 12.8 (3.5–59.0)          | 8.55 (0.5–75.0)     | 0.022              | 26/26 (94.4)       | NA             | 0/26 (0.0)       |
| May et al.          | pT2-3b, pNO GS (<7, 7, >7) (1997 AJCC)             | 42/412 (10.2)              | 22.6 (6.4–151)           | 10.9 (0.1–51)       | <0.001             | 27/42 (64.3)       | 86/370         | NA               |
| Hofer et al.        | pTx, pNO GS (<7, 7, >7) (2002 AJCC)                | 29/116 (25.0)              | NA                       | NA                  | NA                 | NA                  | NA             | NA               |
| Antunes et al.      | pT2-3, pNO GS (<7, 7, >7) (1992 AJCC)              | 47/428 (11.0)              | 10.6 (8.6–13.1)          | 8 (7.5–8.5)         | 0.004              | 24/47 (88.2)       | 95/381         | 43/47 (98.9)     |
| Loeb et al.         | pTx, pNO-1 GS (<7, 7, >7) (NA)                     | 118/1109 (6.9)             | 5.8                      | 4.5                | <0.0001            | 78/118 (67.1)      | 346/1573       | 55/115 (47.5)   |
| Brooks et al.       | pTx, pNO-1 GS (<7, 7, >7) (NA)                     | 18/160 (11.3)              | 10.9 (4.7–40.7)          | 17.7 (1.3–21.7)     | 0.44               | NA                  | NA             | 13/18 (72.2)    |
| Cheng et al.        | pT2-2, pNO-1 GS (<7, 7, >7) (1997 AJCC)            | 106/504 (21.0)             | NA                       | NA                  | NA                 | 73/106 (70.3)      | 83/398         | 63/106 (59.7)   |
| Shariat et al.      | pTx, pNO-1 GS (<7, 7, >7) (1997 AJCC)              | 32/630 (5.1)               | 7.8 (4.0–99.0)           | 6.0 (0.1–52.0)      | 0.04               | NA                  | NA             | 26/32 (80.9)    |
| Ito et al.          | pT2-3, pNO GS (<7, 7, >7) (1992 AJCC)              | 38/82 (46.3)               | NA                       | NA                  | NA                 | NA                  | NA             | NA               |
| de la Taille et al. | pT2-3, pNO-1 GS (<7, 7, >7) (NA)                   | 21/241 (12.4)              | NA                       | NA                  | NA                 | 20/30 (66.7)       | 56/211         | 21/30 (78.6)    |
| van den Ouden et al.| pT2-4, pNO-1 GS (<7, 7, >7) (1992 AJCC)            | 33/273 (12.1)              | NA                       | NA                  | NA                 | 32/33 (155/240)    | 30/33         | 14/240 (57.1)   |
| Leng et al.         | pT2-4, pNO-1 GS (7) (2010 AJCC)                     | 40/166 (24.1)              | NA                       | NA                  | NA                 | NA                  | NA             | NA               |
| Chromecki et al.    | pTx, pNO-1 GS (<7, 7, >7) (NA)                     | 8/102 (7.8)                | NA                       | NA                  | NA                 | NA                  | NA             | NA               |
| Quinn et al.        | pT2-4, pNO-1 GS (<7, 7, >7) (1992 AJCC)            | 38/731 (5.2)               | NA                       | NA                  | NA                 | NA                  | NA             | NA               |
| Huang et al.        | pT2-4, pNO-1 GS (<7, 7, >7) (1992 AJCC)            | 17/111 (15.3)              | NA                       | NA                  | NA                 | NA                  | NA             | NA               |
| Jung et al.         | pT2-3, pNO-1 GS (<7, 7, >7) (2002 AJCC)            | 27/407 (6.6)               | 12.83 (2.40–30.78)       | 9.83 (1.76–83.23)   | 0.075              | 17/27 (62.9)       | 108/380        | 50/380 (50.0)   |
| Ferrari et al.      | pTx, pNO-1 GS (<7, 7, >7) (NA)                     | 110/620 (17.7)             | NA                       | NA                  | NA                 | 70/110 (63.6)      | 14/9/509       | 31/109 (31.0)   |
| Luo et al.          | pTx, pNO-1 GS (<7, 7, >7) (NA)                     | 18/87 (20.7)               | NA                       | NA                  | NA                 | 14/18              | 26/69         | 10/18 (57.1)    |
| Herman et al.       | pT3, pNO GS (<7, 7, >7) (NA)                       | 91/172 (52.9)              | NA                       | NA                  | NA                 | 63/91              | 97/172         | 37/91 (39.2)    |
| Baydar et al.       | pT2-3, pNO-1 GS (<7, 7, >7) (NA)                   | 11/71 (15.5)               | NA                       | NA                  | NA                 | 11/11              | 36/60          | 7/11 (63.6)     |

*A P value represent a statistically difference. TNM: tumor-node-metastasis; ECE: extracapsular extension; SVI: seminal vesicle involvement; LVI: lymphovascular invasion; PSA: prostate-specific antigen; pT: pathological tumor; pN: pathological node; AJCC: American Joint Committee on Cancer and the International Union Against Cancer; GS: Gleason score; NA: not available*
**Supplementary Table 3: Estimation of the HR**

| Study                  | Survival analysis | HR estimation or P | Co-factors                                                                 | LVI independent predictor? |
|------------------------|-------------------|-------------------|---------------------------------------------------------------------------|----------------------------|
| Yee et al.24           | BCR               | HR (95% CI): 1.77 | Pre-PSA, ECE, SVI, GS, SM, LNI                                            | Yes                        |
| Lee et al.22           | BCR               | HR (95% CI): 1.086| GS, pT stage, SM, TV, Primary-Gleason grade, secondary-Gleason grade, Number of positive lymph nodes, nadir PAS | No                         |
| Yee et al.24           | CSS               | *P=0.533          | NA                                                                         | No                         |
| Cho et al.31           | BCR               | HR (95% CI): 2.683| Pre-PSA, biopsy GS, GS, SM, ECE, SVI, Bcl-2 expression                     | No                         |
| Jeon et al.30          | BCR               | HR (95% CI): 1.08 | Pre-PSA, ECE, SVI, GS, SM, PNI                                            | No                         |
| Whittemore et al.28    | BCR               | HR (95% CI): 2.49 | >pT2 stage, pre-PSA, SM, PNI, LNI, percentage cancer (tumor burden)       | Yes                        |
| Yamamoto et al.29      | BCR               | HR (95% CI): 1.64 | Pre-PSA, biopsy GS, GS, SM, clinical stage                                 | Yes                        |
| May et al.26           | BCR               | HR (95% CI): 4.39 | Pre-PSA, GS, SVI, PSA density, positive biopsy cores                      | Yes                        |
| Hofer et al.23         | BCR               | HR (95% CI): 1.9  | Gleason grade 4/5, nuclear grade 3                                        | Yes                        |
| Antunes et al.21       | BCR               | HR (95% CI): 1.78 | Pre-PSA, ECE, SM, clinical stage, present of positive biopsy cores        | Yes                        |
| Loeb et al.24          | BCR               | HR (95% CI): 1.5  | GS, SVI, SM, ECE, LNI                                                     | No                         |
| Brooks et al.22        | BCR               | HR (95% CI): 5.47 | Pre-PSA, SM, LNI, ECE, SVI, GS, PNI, Undetectable PSA after RP, pre-RP PSA level | Yes                        |
| Cheng et al.20         | BCR               | HR (95% CI): 1.6  | pT stage, GS, SM                                                          | Yes                        |
| Shariat et al.19       | CSS               | *P=0.001          | NA                                                                        | Yes                        |
| Ito et al.17           | BCR               | HR (95% CI): 4.39 | GS, ECE, SM, SVI, PNI                                                     | Yes                        |
| de la Taille et al.14  | BCR               | HR (95% CI): 7.15 | pT3 stage, pre-PSA, GS, SM                                                | Yes                        |
| van den Ouden et al.13 | BCR               | HR (95% CI): 2.3  | ECE, grade 3, positive lateral margin                                       | Yes                        |
| OS                     | *P=0.02           | NA                | NA                                                                        | Yes                        |
| DM                     | *P=0.001          | NA                | NA                                                                        | Yes                        |
| Leng et al.27          | BCR               | HR (95% CI): 0.75 | >pT2 stage, PSA density, TV, SM, PNI                                       | No                         |
| Chomecki et al.25      | BCR               | HR (95% CI): 7.435| pT stage, pre-PSA, LNI, ECE, SVI, GS, SM, abnormal IMP3                    | Yes                        |
| Quinn et al.16         | BCR               | HR (95% CI): 1.37 | pT stage, pre-PSA, GS, SVI, LNI, PNI, SM, year of RP, adjuvant therapy (excluding indefinite hormonal therapy) | No                         |
| Huang et al.25         | BCR               | HR (95% CI): 3.51 | Pre-PSA, GS, PNI, SM, age, tumor multifocality, HGPIN                     | No                         |
| Jung et al.23          | BCR               | HR (95% CI): 1.839| Pre-PSA, SVI, GS, SM, ECE, LNI, PNI, HGPIN                               | No                         |
| Luo et al.36           | BCR               | NA                | NA                                                                        | Yes                        |
| Baydar et al.27        | BCR               | NA                | NA                                                                        | Yes                        |
| Ferrari et al.18       | BCR               | NA                | NA                                                                        | Yes                        |
| Herman et al.15        | BCR               | NA                | NA                                                                        | Yes                        |

*A P value was determined by the log rank test. BCR: biochemical recurrence-free survival; GS: Gleason score; ECE: extracapsular extension; SVI: seminal vesicle invasion; LNI: lymph node invasion; SM: surgical margins; TV: tumor volume; PNI: perineural invasion; PSA: prostate-specific antigen; IMP3: insulin-like growth factor III mRNA binding protein 3; HGPIN: high-grade prostatic intraepithelial neoplasia; XRCC1: X-ray repair cross-complementing protein-1; PTL0: pertumoral lymphatic vessel density; RP: radical prostatectomy; P-XRT: postprostatectomy radiotherapy; RT: radiotherapy; PFS: progression-free survival; DM: distant metastases; OS: over survival; CSS: cancer specific survival; HR: hazard ratio; NA: not available; LVI: lymphovascular invasion; CI: confidence interval; PAS: periodic acid-Schiff.
### Supplementary Table 4: Subgroup analysis of biochemical recurrence-free survival

| Region          | Number of included articles | Number of cases | Pooled HR (95% CI) | ES         | Heterogeneity P (het) | Publication bias          |
|-----------------|----------------------------|----------------|--------------------|------------|-----------------------|---------------------------|
|                 |                            |                |                    |            |                       | Begg’s P | Egger’s P |
| Asian           | 8                          | 1625           | 1.479 (1.139–1.921) | Fix, (inverse variance) | Z=2.94 | P=0.003 | 32.2 | 0.171 | 0.108 | 0.405 |
| Other           | 13                         | 6818           | 2.322 (1.771–3.043) | Random, (inverse variance) | Z=6.10 | P=0.001 | 62.9 | 0.001 | 0.035 | 0.058 |
| Number of patients |                            |                |                    |            |                       |             |         |
| <200            | 8                          | 998            | 2.590 (1.539–4.360) | Fix, (inverse variance) | Z=3.58 | P=0.000 | 69.2 | 0.002 | 0.386 | 0.209 |
| 200–500         | 8                          | 2771           | 2.219 (1.454–3.387) | Random, (inverse variance) | Z=3.69 | P=0.000 | 63.7 | 0.007 | 0.902 | 0.757 |
| >500            | 5                          | 4872           | 1.582 (1.281–1.953) | Fix, (inverse variance) | Z=4.27 | P=0.000 | 0.0  | 0.963 | -     | -     |
| Pathologic N stage |                            |                |                    |            |                       |             |         |
| pN−             | 4                          | 1016           | 2.493 (1.471–4.224) | Random, (inverse variance) | Z=3.39 | P=0.001 | 69.1 | 0.021 | -     | -     |
| pN+             | 1                          | 116            | 1.9 (1.1–3.5)       | NA         | NA                    | NA          | NA      |
| Median follow-up |                            |                |                    |            |                       |             |         |
| ≤24 months      | 4                          | 897            | 3.645 (2.091–6.353) | Fix, (inverse variance) | Z=4.56 | P=0.000 | 19.0 | 0.295 | -     | -     |
| 24–36 months    | 3                          | 3173           | 1.442 (1.059–1.965) | Fix, (inverse variance) | Z=2.32 | P=0.020 | 43.5 | 0.170 | -     | -     |
| >36 months      | 12                         | 4048           | 2.031 (1.536–2.685) | Random, (inverse variance) | Z=4.97 | P=0.000 | 64.3 | 0.001 | 0.902 | 0.511 |
| LVI independent predictor? |               |                |                    |            |                       |             |         |
| No              | 9                          | 4519           | 1.374 (1.088–1.734) | Fix, (inverse variance) | Z=2.67 | P=0.008 | 0.0  | 0.598 | 0.536 | 0.496 |
| Yes             | 12                         | 3924           | 2.618 (1.953–3.509) | Random, (inverse variance) | Z=6.44 | P=0.000 | 63.3 | 0.002 | 0.019 | 0.038 |
| Definition of BCR |                            |                |                    |            |                       |             |         |
| PSA ≥0.1        | 3                          | 2075           | 1.765 (1.353–2.301) | Fix, (inverse variance) | Z=4.19 | P=0.000 | 0.0  | 0.623 | -     | -     |
| PSA ≥0.2        | 14                         | 4926           | 2.311 (1.610–3.318) | Random, (inverse variance) | Z=4.54 | P=0.000 | 70.2 | 0.000 | 0.902 | 0.544 |
| PSA ≥0.4        | 4                          | 1442           | 1.691 (1.252–2.285) | Fix, (inverse variance) | Z=3.43 | P=0.001 | 0.0  | 0.733 | -     | -     |
| Stain method    |                            |                |                    |            |                       |             |         |
| HE              | 9                          | 5192           | 1.776 (1.483–2.128) | Fix, (inverse variance) | Z=6.23 | P=0.000 | 35.9 | 0.131 | 0.386 | 0.117 |
| IHC and HE      | 1                          | 412            | 4.39 (2.47–7.8)     | NA         | NA                    | NA          | NA      |

PSA: prostate-specific antigen; BCR: biochemical recurrences; HE: hematoxylin and eosin; IHC: immunohistochemistry; HR: hazard ratio; CI: confidence interval; LVI: lymphovascular invasion; ES: effect size; NA: not available