## Original Article
# Perineural invasion is an independent predictor of biochemical recurrence of prostate cancer after local treatment: a meta-analysis

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Abstract: Controversy still existed regarding the role of perineural invasion (PNI) in prostate cancer. The present meta-analysis aimed to investigate the association between PNI and biochemical recurrence (BCR) of prostate cancer after local treatment. A systematic search of Medline, Embase and CENTRAL was performed for eligible studies. Pooled estimates of hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) were acquired by using the generic inverse variance method. Subgroup analyses were performed by the method treating prostate cancer including radical prostatectomy (RP) and radiotherapy (RT) as well as the specimens which were acquired from RP and biopsy. A total of 12 studies incorporating 5188 patients were included in the meta-analysis. Overall, PNI was significantly associated with BCR (HR 1.59, 95% CI 1.37-1.84). Similarly, a significant correlation between PNI and BCR was also found in RP series (HR 1.51, 95% CI 1.25-1.83) and RT series (HR 1.70, 95% CI 1.35-2.13). PNI predicted BCR of prostate cancer in both RP (HR 1.51, 95% CI 1.23-1.85) and biopsy specimens (HR 1.68, 95% CI 1.36-2.09). PNI was demonstrated to be associated with higher risk for BCR of prostate cancer after local treatment. Therefore, PNI should be considered when assessing the risk of BCR in prostate cancer, thereby to achieve the best treatment.

Keywords: Perineural invasion, biochemical recurrence, prostate cancer, local treatment

## Introduction

In the USA, prostate cancer is the most commonly diagnosed tumor in men, with 233000 new cases and 29480 cancer-specific deaths estimated for year 2014 [1]. Radical prostatectomy (RP) and radiation therapy (RT) are alternative standard treatment modalities for localized prostate cancer [2], and both of them has shown excellent cancer-specific survival. However, 9.7%-38% of patients will experience biochemical recurrence (BCR) after local treatment (RP or RT) [3-5], these patients with BCR often need salvage therapy. Previous studies demonstrated that pretreatment prostate-specific antigen (PSA) level, Gleason score, clinical T stage and extraprostatic extension (EPE) were independent predictors of BCR of prostate cancer after treatment [6-8], therefore, these clinicopathological parameters had been routinely reported. Several studies reported that perineural invasion (PNI, defined as cancer tracking along or around a nerve within the perineural space) was significantly associated with EPE [9, 10], and thus may be with BCR of prostate cancer [11, 12]. According to the College of American Pathologists' consensus statement [13], PNI is a potential prognostic factor in prostate cancer, it seems to be considered when assessed the risk of BCR. PNI can be evaluated in biopsy specimen or RP specimen, and it is present in 17%-75% of prostate cancer patients [14-16]. Whether PNI is an independent predictor of BCR of prostate cancer is still debatable [11, 12, 14-16]. Thus, the present meta-analysis aimed to explore the association between PNI and BCR of prostate cancer, which could help to assess BCR risk of prostate cancer after local treatment and determining further beneficial treatment.
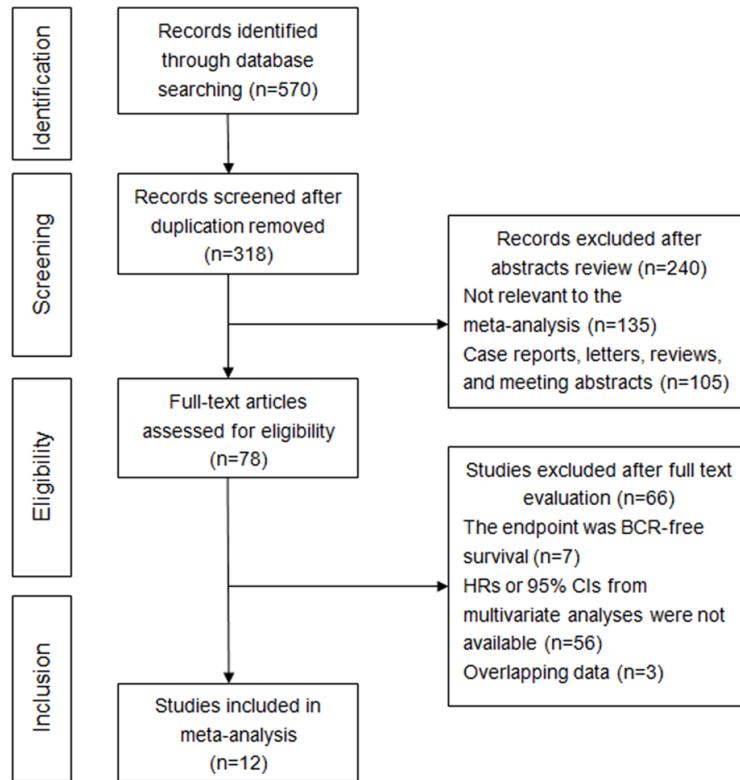
**Figure 1.** The flow diagram of the study selection process.

**Materials and methods**

*Search strategy*

An electronic search of Medline, Embase and CENTRAL for all relevant studies was conducted, with the last search run on January 19, 2015. The search terms were as follows: perineural and (recurrence OR relapse OR PSA failure OR biochemical failure OR PSA progression OR biochemical progression) and (prostate cancer OR prostate carcinoma OR prostatic cancer OR prostatic carcinoma). Studies only in English language were included.

*Selection criteria*

The inclusion criteria was as follows: studies that (a) reported the association of PNI with BCR of prostate cancer after treatment (e.g. RP or RT); (b) provided hazard ratios (HRs) from multivariate analyses using Cox proportional hazards regression model and their corresponding 95% confidence intervals (CIs). Case reports, letters, reviews and conference abstracts and irrelevant studies were excluded. Studies including patients with metastatic

prostate cancer were also excluded. For studies that reported results based on overlapping data, only the study with the largest sample size was included.

*Study selection*

All titles and abstracts of relevant articles through databases search were screened after duplicates removed; case reports, letters, review articles, conference abstracts, and irrelevant records were excluded. Then, we screened the full texts of these identified relevant articles and evaluated the eligibility of studies for inclusion. The references of included studies and relevant reviews were also examined for additional relevant studies.

*Data extraction and study quality assessment*

Two authors (P.X. and Y.M.) extracted data from eligible studies independently. The following characteristics were extracted: first author, year of publication, country, study design, population characteristics, the prevalence of BCR, definition of BCR, follow-up period, the rate of PNI, HRs with their corresponding 95% CIs and covariates in multivariate analyses. As all eligible studies were nonrandomized studies, the quality of these studies were assessed by using the Newcastle-Ottawa scale (ranged from 0 to 9 stars) [17]. Any disagreement was resolved by discussion.

*Data analyses*

Cumulative effects of PNI were evaluated by using the generic inverse variance method. Between-study heterogeneity was estimated using both Cochran Q test and $I^2$ statistics. If there was significant between-study heterogeneity (P<0.10 for Q test or $I^2$ statistics >50%), a random-effects model was used to combine the data, otherwise a fixed-effects model would be chose [18]. Subgroup analyses were performed according to primary treatment method for prostate cancer (RP versus RT) and speci-

**Table 1.** The characteristics and quality assessment of eligible studies

| Studies | Country | Treatment | No. of patients | Age, years | No. of BCR (%) | Median/ mean follow-up, mo | Definition of BCR | No. of patients with PNI (%) | Specimens evaluated for PNI | Clinical stage | Adjusted for | Quality assessment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Jeon et al (2009) [18] | Korea | RP | 237 | Median 64.5 | 67 (28.3%) | 21.8/- | two consecutive PSA >0.2 ng/ml | 100 (42.0%) | RP specimens | T1-3 | 2, 4, 7, 8, 9, 10 | 7 |
| Kumano et al (2009) [19] | Japan | RP | 267 | Mean 68.3 | 30 (12.7%) | 40/- | PSA persistently >0.2 ng/ml | 165 (61.8%) | RP specimens | T1-2 | 1, 2, 4, 6, 11, 20, 21, 22 | 7 |
| Loeb et al (2010) [20] | USA | RP | 1256 | Mean 56 | 57 (4.5%) | -/34 | PSA >0.2 ng/ml | 188 (15%) | Biopsy specimens | T1-3 | 2, 3, 5, 23 | 8 |
| Jung et al (2011) [21] | Korea | RP | 407 | Mean 63.2 | 45 (11.1%) | 18.4/- | two consecutive PSA >0.2 ng/ml | 170 (41.8%) | RP specimens | T1-3 | 2, 4, 7, 8, 9, 11 | 7 |
| Tanaka et al (2011) [22] | Japan | RP + 50.4% with neoadjuvant/ adjuvant therapy | 468 | Mean 67.5 | 171 (36.5%) | -/53 | PSA ≥0.2 ng/ml | 226 (48.3%) | RP specimens | T1-3 | 2, 4, 12 | 6 |
| Somford et al (2012) [23] | The Netherlands | RP | 249 | Mean 63.8 | 102 (41%) | 40/- | PSA ≥0.2 ng/ml | - | RP specimens | pT2-3 | 2, 4, 6, 16 | 6 |
| Andersen et al (2014) [24] | Norway | RP | 535 | Median 62 | 170 (31.8%) | 89/- | two consecutive PSA ≥0.4 ng/ml | 134 (25.0%) | RP specimens | pT2-3 | 2, 4, 6, 17, 18 | 7 |
| Copp et al (2005) [25] | USA | BT + ADT + EBRT | 91 | Median 69.1 | 16 (17.6%) | 45/- | PSA nadir + ≥2 ng/ml | 17 (18.7%) | Biopsy specimens | T1-3 | 2, 3, 5, 12, 19 | 7 |
| Yu et al (2011) [26] | USA | EBRT + 67.4% with ADT | 586 | Mean 68 | 161 (27.5%) | 68/- | PSA nadir + ≥2 ng/ml | 112 (19.1%) | Biopsy specimens | T1-4 | 2, 3, 5, 13, 14 | 7 |
| Feng et al (2011) [27] | USA | EBRT + 40% with ADT | 651 | Median 69.4 | - | 62.2/- | PSA nadir + 2 ng/ml | 220 (33.8%) | Biopsy specimens | T1-4 | 2, 5, 13 | 7 |
| Bouchaert et al (2012) [28] | France | EBRT | 238 | Median 71 | 72 (30.3%) | 48/- | PSA nadir + 2 ng/ml | 57 (23.9%) | Biopsy specimens | T1-3 | 2, 3, 5, 24 | 7 |
| Schreiber et al (2014) [29] | USA | EBRT + 30.5% with ADT | 203 | Median 70 | 33 (16.3%) | 42/- | PSA nadir + 2 ng/ml, or salvage therapy | 37 (18.2%) | Biopsy specimens | - | 1, 2, 5, 13, 15 | 7 |

PSA: prostate-specific antigen. Adjusted for: 1, age; 2, pretreatment PSA level; 3, clinical stage; 4, pathological Gleason score; 5, biopsy Gleason score; 6, pathological stage; 7, extraprostatic extension; 8, seminal vesicle invasion; 9, surgical margin status; 10, lymphovascular invasion; 11, lymph node invasion; 12, percent of positive biopsy cores; 13, androgen deprivation therapy; 14, radiation dose; 15, race; 16, number of positive surgical margin; 17, apical positive surgical margin; 18, non-apical positive surgical margin; 19, high risk group; 20, capsular incision; 21, microvenous invasion; 22, surgical procedure; 23, nerve-sparing technique; 24, DNA protein kinase, catalytic subunits. pT: Pathological stage.

| Study or Subgroup | log[Hazard Ratio] | SE | Weight | Hazard Ratio IV. Fixed, 95% CI | Year |
|---|---|---|---|---|---|
| Copp 2005 | 0.515 | 0.577 | 1.7% | 1.67 [0.54, 5.19] | 2005 |
| Yu 2007 | 0.451 | 0.2 | 14.0% | 1.57 [1.06, 2.32] | 2007 |
| Kumano 2009 | 0.658 | 0.446 | 2.8% | 1.93 [0.81, 4.63] | 2009 |
| Jeon 2009 | 0.723 | 0.286 | 6.9% | 2.06 [1.18, 3.61] | 2009 |
| Loeb 2010 | 0.445 | 0.303 | 6.1% | 1.56 [0.86, 2.83] | 2010 |
| Tanaka 2011 | 0.421 | 0.209 | 12.8% | 1.52 [1.01, 2.29] | 2011 |
| Jung 2011 | 0.524 | 0.345 | 4.7% | 1.69 [0.86, 3.32] | 2011 |
| Feng 2011 | 0.531 | 0.177 | 17.9% | 1.70 [1.20, 2.41] | 2011 |
| Somford 2012 | 0.199 | 0.275 | 7.4% | 1.22 [0.71, 2.09] | 2012 |
| Bouchaert 2012 | 0.334 | 0.353 | 4.5% | 1.40 [0.70, 2.79] | 2012 |
| Schreiber 2014 | 1.078 | 0.393 | 3.6% | 2.94 [1.36, 6.35] | 2014 |
| Andersen 2014 | 0.3 | 0.179 | 17.5% | 1.35 [0.95, 1.92] | 2014 |
| **Total (95% CI)** | | | **100.0%** | **1.59 [1.37, 1.84]** | |

Heterogeneity: Chi² = 5.59, df = 11 (P = 0.90); I² = 0%
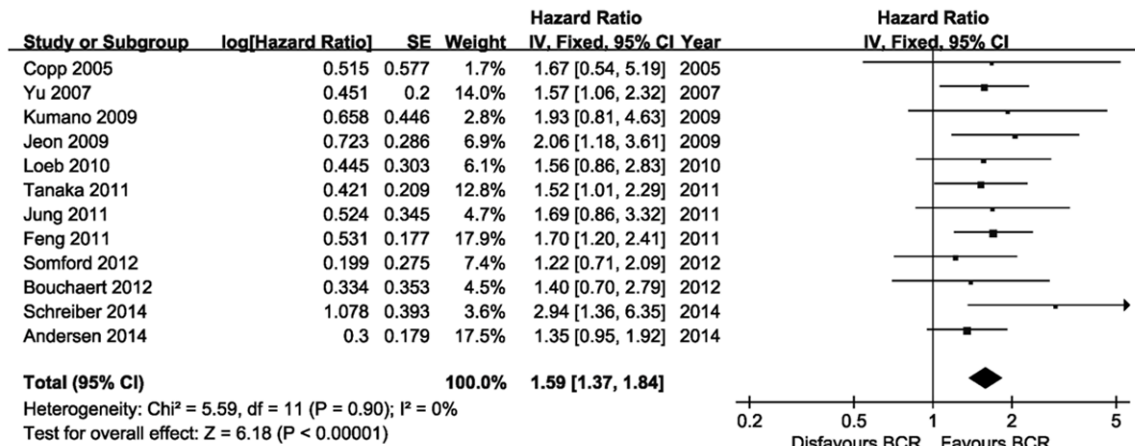Test for overall effect: Z = 6.18 (P < 0.00001)

**Figure 2.** Forest plot of PNI and BCR risk of prostate cancer.

mens evaluated for PNI (RP specimens versus biopsy specimens). The potential publication bias was assessed the visual inspection of symmetry of the funnel plot. We performed sensitivity analysis by removing the study with the largest weight and subsequently pooling the remaining studies. This meta-analysis was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [19]. All statistical analyses were performed with RevMan 5.3 software and two-sided *P* values of 0.05 were considered statistically significant.

## Result

### Characteristics of eligible studies

A total of 12 studies [20-31] recruiting 5188 patients were included in our meta-analysis. The flow chart of selection process was showed in **Figure 1**. Only 1 study was prospective cohort [22], the others were retrospective studies. Besides, 7 studies primarily treated with RP [20-26], 4 studies primarily treated with external beam radiotherapy (EBRT) [28-31], while 1 study is focused on trimodality therapy-androgen deprivation (ADT) + EBRT + brachytherapy (BT) [27]. Moreover, one study based on RP series reported that 50.4% of the patients received neoadjuvant and/or adjuvant therapy [24]. Three studies in which patients were primarily treated with EBRT reported that 30.5%-67.4% of patients received ADT [28, 29, 31]. There were 6 studies that evaluated the presence of PNI in RP specimens [20, 21, 23-26],

while 6 studies evaluated it in biopsy specimens [22, 28-31]. The incidence of BCR after local treatment ranged from 4.5% to 41.0%, while the percentage of positive PNI ranged from 15.0% to 61.8% in our study. All included studies were adjusted for various covariates, such as pretreatment PSA level, clinical stage, and Gleason score. Characteristics and quality assessments of included studies were listed in **Table 1**.

### Data synthesis and subgroup analysis

Overall, PNI was associated with 1.6-fold higher risk of BCR of prostate cancer after local treatment (HR 1.59, 95% CI: 1.37-1.84; P<0.01, I² = 0%, **Figure 2**). Subgroup analyses according to primary treatment modality and specimen in which PNI was evaluated were performed. A significant correlation between PNI and BCR was noted in RP (HR 1.51, 95% CI: 1.25-1.83; P<0.01, I² = 0%) and RT (with or without ADT) group (HR 1.70, 95% CI: 1.35-2.13; P<0.01, I² = 0%). Besides, PNI was a significant predictor of BCR in RP specimens after RP (HR 1.51, 95% CI: 1.23-1.85; P<0.01, I² = 0%). Consistently, PNI had 1.7-fold higher risk for BCR of prostate cancer after local treatment in biopsy specimens (HR 1.68, 95% CI: 1.36-2.09; P<0.01, I² = 0%).

### Sensitivity and publication bias analysis

When excluding the study with the largest weight (17.9%) [29], the pooled result remained robust (HR 1.56, 95% CI: 1.33-1.84), Visual inspection of the symmetry of funnel plot did
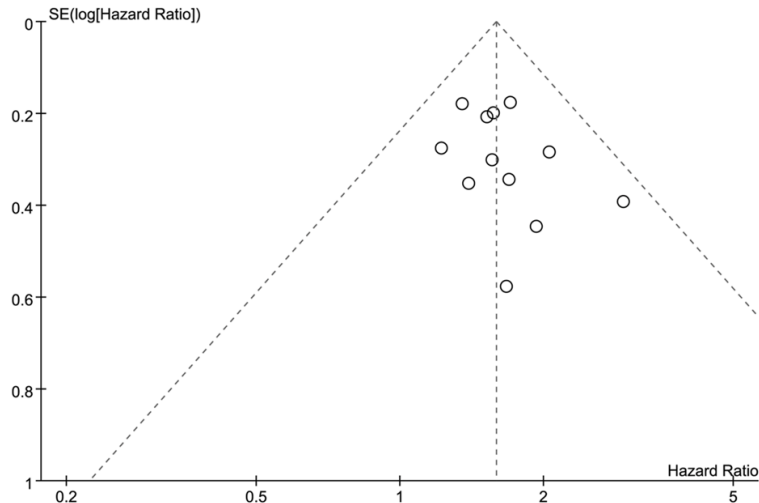
**Figure 3.** The funnel plot.

not reveal obvious publication bias in our meta-analysis (**Figure 3**).

## Discussion

Controversy existed regarding the prognostic value of PNI on BCR of prostate cancer. Hence, we performed the present meta-analysis to investigate the relationship between PNI and BCR of prostate cancer. The present study revealed that PNI was an independent predictor of BCR of prostate cancer after local therapy. Besides, a significant correlation between PNI and BCR in patients primarily treated with RP and RT was also noted. Consistently, PNI was also associated with higher risk for BCR in RP specimens and biopsy specimens.

In 2007, Harnden et al. [32], in a systematic descriptive review, attempted to explore the impact of PNI in biopsy on BCR and clinical recurrence of prostate cancer. They concluded that PNI was a predictor of prostate cancer recurrence, and immediate treatment rather than watchful waiting might be more appropriate for patients with localized prostate cancer and PNI. However, the conclusion of the study was not based on strong statistical evidence.

Evidence from basic research showed that PNI in prostate cancer resulted in inhibition of apoptosis and increased proliferation in the cancer cells in the perineural location, which subsequently increased the risk of local recurrence [33, 34]. Moreover, several previous studies had showed that PNI was significantly associated with EPE and positive surgical margin (PSM) [9, 10, 35, 36], while both EPE and PSM were predictors of BCR of prostate cancer [9, 22, 37] and had been applied in the CAPRA-S score which was used for risk stratification after RP [38]. What stated above may collectively explain the prognostic value of PNI.

Furthermore, several nomograms and predictors, like CAPRA score and D'Amico risk-group classification, have been used for prostate cancer risk stratification [39, 40]. Since our study demonstrated that PNI was a predictive factor of BCR of prostate cancer, it seemed to be considered when defining the risk groups of localized prostate cancer, thereby achieving beneficial treatment strategy. D'Amico et al. [41] reported that resection of the neurovascular bundle on the side of prostate with PNI in biopsy may decrease the positive surgical margin rate and improve outcome for patients with low risk prostate cancer. Therefore, PNI in biopsy and some other pathological parameters (Gleason score and tumor volume) on biopsy should be considered when planning nerve-sparing RP [42, 43]. In addition, considering the high risk of EPE and PSM, patients with PNI should discuss with their doctors receive RT after RP. Similarly, as patients primarily treated with RT may benefit from ADT [28, 31], a combination of RT and ADT will be more appropriate for patients with PNI.

This was the first meta-analysis focus on the association between PNI and BCR of prostate cancer. Owing to the strict eligibility criteria, applying of the PRISMA guidelines and the relatively large number of patients, our study provided reasonable evidence for the prognostic value of PNI. On the other hand, some limitations of the meta-analysis should be noted. Firstly, since only published studies were included in the meta-analysis, publication bias might occur, though the funnel plot showed no apparent publication bias. Secondly, most of these included studies were retrospective observational studies, which might lead to bias,

although we used HRs from multivariate analyses to account for the latent source of bias. Further researches are needed to confirm the significant correlation of PNI with BCR of prostate cancer.

Overall, our meta-analysis demonstrated that PNI was an independent predictor of BCR of prostate cancer after local treatment which should be routinely included in the pathology report and predictive element. Therefore, Patients with localized prostate cancer and PNI should be immediately treated. Besides, PNI should be considered when assessing BCR risk of prostate cancer, thereby helping to decide on the best treatment.

## Disclosure of conflict of interest

None.

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