

Review Article

Prognostic roles of extraprostatic extension in evaluating biochemical recurrence after radical prostatectomies: PRISMA-compliant systematic review and meta-analysis

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Abstract: Background: Due to a lack of strong evidence in identifying the relationship between extraprostatic extension (EPE) and risk of biochemical recurrence (BCR) in prostate cancer (PCa) following radical prostatectomies (RP), the current meta-analysis was performed to determine the predictive value of EPE in PCa patients. Methods: According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, a search was performed in PubMed, EMBASE, Web of Science, and China National Knowledge Infrastructure (CNKI) for eligible studies from inception to October 2018. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were used to assess the strength of association. All data were analyzed with statistical software Stata 12.0. Results: Based on inclusion and exclusion criteria, 28 retrospective cohort studies, assessing 38,786 samples, were further analyzed. Results showed that EPE was associated with higher BCR risk, according to both univariate analysis (pooled HR=1.69, 95% CI: 1.55-1.85, $p<0.001$) and multivariate analysis (pooled HR=1.27, 95% CI: 1.19-1.35, $p<0.001$). Subgroup analysis also showed significant results in different groups. Sensitivity analysis indicated that results were robust and steady. Moreover, no potential publication bias was found among included studies, according to univariate analysis (p -Egger's=0.399) and multivariate analysis (p -Egger's=0.718). Conclusion: Present results suggest that the presence of EPE is one of the strongest independent predictors of BCR in patients undergoing RP treatment. Further prospective, multi-centered, and large-sample size cohort studies are warranted to confirm present findings.

Keywords: Extraprostatic extension, prostate cancer, radical prostatectomy, biochemical recurrence, meta-analysis

Introduction

Prostate cancer (PCa) is the most common solid tumor diagnosed among the male population, presenting a major health concern in developed countries [1]. In previous years, significant breakthroughs have been made concerning diagnosis, treatment, and understanding of the genesis of PCa. Although radical prostatectomies (RP) are an effective treatment for clinically localized PCa, biochemical recurrence (BCR) occurs in 15%-40% of patients within 10 years [2, 3]. BCR is an early indication of clinical progression, distant metastases, and mortality, indicating that patients will be treated with a

secondary treatment [4]. Additionally, men with adverse pathological features, including Gleason scores [5] and perineural invasion [6], have up to a 60% risk of developing BCR within 3 years [5-8]. To date, there are no completely accurate diagnostic tools for prediction of BCR progression in PCa. Therefore, many clinicians have searched for new tumor markers, aiming to improve detection rates.

Extraprostatic extension (EPE) is defined as an extension of tumor cells beyond the borders of the prostate, most often recognized as tumor intermingling with periprostatic soft tissue [9]. Traditionally, EPE has long been recognized as

an adverse prognostic feature, in terms of both cancer progression and survival [10]. Consequently, it is included in the TNM staging system, classified as pT3a in the American Joint Committee on Cancer [11]. Moreover, recent guidelines for adjuvant therapy after RP recommend the use of adjuvant radiotherapy for all patients with EPE [12]. However, >50% of cases with isolated EPE do not progress, according to long-term follow-ups [13, 14].

It has been shown that there is certain correlation between EPE and RCR, but a unanimous conclusion has not yet been reached. Therefore, further verification is required. To date, there are no quantitative assessments concerning the association of EPE with BCR in patients following RP. In the present study, a systematic review and meta-analysis was conducted to summarize the relationship between EPE and BCR risk based on all published epidemiological studies.

Materials and methods

Literature search

Following the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [15], a comprehensive search of PubMed, EMBASE, Web of Science, and China National Knowledge Infrastructure (CNKI) databases was conducted to identify relevant studies up to October 2018. The search strategy consisted of the following keywords, in combination with Medical Subject Headings (MeSH) terms and text words: (“prostate cancer” or “prostate AND neoplasms”) and (“radical prostatectomy”) and (“extraprostatic extension”) and (“biochemical recurrence” OR “biochemical failure”). Additional studies were incorporated by scanning reference lists of original studies or recent reviews. Publication language was limited to English and Chinese.

Inclusion and exclusion criteria

Inclusion criteria: (1) All patients were diagnosed with PCa and EPE was assessed by pathologists; (2) PCa patients that underwent RP treatment; (3) BCR after RP was defined; (4) Focused on the relationship between EPE and BCR and provided sufficient data to estimate hazard ratios (HR) using univariate or multivariate analyses with 95% confidence intervals

(95% CI); and (5) Articles published as a full paper in English or Chinese. Exclusion criteria: (1) Case reports, meeting abstracts, reviews, editorials and author responses; (2) Studies failing to provide enough data on the relationship between EPE and PCa; (3) Absence of key information; and (4) Articles containing elements that were inconsistent with inclusion criteria. When publications from the same institution were obtained, only the one with the most detail and/or the most credible information was selected.

Data extraction and quality assessment

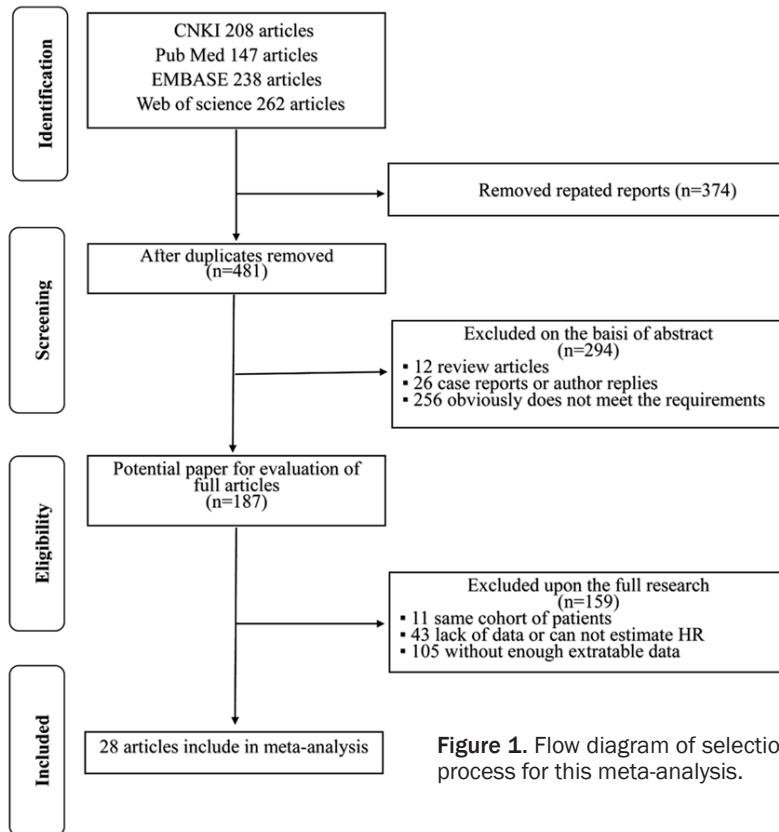
For each included study, data was extracted, independently, with a standardized data collection form by two blind reviewers (Bin Wu and Zhenlei Zha). Any disagreements were addressed by consultation with a third investigator (Hu Zhao). Detailed information was recorded, including first author's name, publication date, country, recruitment period, sample size, median or mean patient age, preoperative prostate specific antigen (PSA) levels, Gleason scores, positive percentage of EPE and BCR, cut-off values for BCR, follow-up duration, and HRs (95% CIs) of PSM, according to univariate or multivariate Cox analyses for BCR.

Quality of eligible studies was evaluated according to the Newcastle-Ottawa Scale (NOS) [16], one of the most useful scales in evaluating the quality of non-randomized studies. Criteria for quality assessment contained 3 domains (selection of the study population, comparability of groups, and ascertainment of outcome). Total quality scores ranged from 0 to 9. High-quality choices were indicated by scores of 6-9, while scores of 0-5 indicated poor quality.

Statistical analyses

Statistical analyses were performed using Stata 12.0 software (Stat Corp, College Station, TX, USA). The relationship between EPE and PCa was examined based on available data. Pooled HRs with 95% confidence intervals (CIs) were utilized to evaluate efficacy. Pooled HR>1 implies a high risk of BCR for patients with EPE. Chi-squared-based Q test and I^2 were used to determine heterogeneity among studies. $P<0.10$ or $I^2>50\%$ indicates statistically significant heterogeneity. A fixed-effects model was used to calculate pooled results when no heteroge-

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neity existed among included studies. Otherwise, a random-effects model was used. Sensitivity analysis was used to estimate the reliability of pooled results by deleting one single study each time, reflecting the impact of the individual to overall. To determine reasons of heterogeneity among studies, subgroup analysis was performed to check whether pooled HRs were influenced by the region, publication year, mean age, sample size, mean preoperative PSA (p-PSA), median follow-ups, and cutoff values for BCR. Publication bias was assessed by funnel plots and Egger's linear regression. A two-sided *P* value less than 0.05 indicates statistical significance.

Results

Literature search and study characteristics

Figure 1 shows the process for identification of eligible studies. Initially, a total of 855 publications were found through an online search of PubMed, EMBASE, Web of Science, and CNKI. A total of 374 duplicate articles were excluded. After carefully reviewing study titles and

abstracts, 294 studies were further excluded because they were letters, reviews, or did not evaluate EPE and BCR. Subsequently, the 187 remaining full-text articles were assessed. A total of 159 studies were then excluded after a full review because they contained insufficient data (148 studies) or consisted of the same patients (11 studies). As a result, a total of 28 articles [7, 17-43], including 38,786 patients (152-7,205 per study), met the inclusion criteria and were included in the final analysis.

Detailed characteristics of these 28 enrolled studies are summarized in **Table 1**. These 28 studies were retrospective cohort studies. All studies were published between 2003 and 2018,

of which 14 were conducted in Asia, 6 in North America, 4 in multi-centers, 3 in Europe, and 1 in Australia. The median follow-up period, in all studies, ranged from 21.4-109 months. Twenty-six were published in English and one was published in Chinese. The cut-off value for BCR (0.1 ng/mL, 0.2 ng/mL, 0.4 ng/mL) in included studies is presented in **Table 1**. Incidence of BCR after RP ranged from 9.9% to 66.5%, according to selected studies. Additionally, the proportion of patients exhibiting EPE in individual studies ranged from 5.0% to 49.0%. Results of quality assessment for included studies are summarized in **Table S1**. Results show that all studies had high levels of methodological quality in this meta-analysis, with NOS scores ≥ 7 .

Meta-analysis

In 17 studies [7, 17-20, 22, 23, 25, 27-29, 34, 35, 39, 41-43], with a total sample size of 17,417 individuals, association between EPE and BCR of PCa patients after RP in a univariate model was reported. A random-effects model was used, revealing a pooled HR=1.69

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Table 1. Main clinicopathological features of eligible studies in this meta-analysis

Author	Year	Country	Sample size	Recruitment period	Age (years)	p-PSA (ng/ml)	Follow-up (months)	Specimen GS <7/≥7	EPE+/EPE-	No. of BCR (%)	Cut-off value for BCR
Murata et al. [7]	2018	Japan	191	2000-2013	Median (range) 70 (41-78)	Median (range) 12.1 (2.5-129.1)	Median (range) 49 (6-164)	10/181	62/129	111 (58%)	0.2 ng/ml
Sato et al. [17]	2017	Japan	1,165	2003-2013	Median 65.5	Median 8.36	Median (range) 39 (15-75)	185/1,010	273/922	286 (23.9%)	0.2 ng/ml
Negishi et al. [18]	2017	Japan	478	1999-2009	NA	NA	Median (range) 90 (60-187.2)	370/106	166/312	113 (23.6%)	0.2 ng/ml
Hong et al. [19]	2016	Korea	1,129	2006-2014	Median (IQR) 62 (57-67)	Median (IQR) 6.3 (4.5-8.9)	Median (IQR) 32 (18.5-53)	34/171	185/20	63 (31.2%)	0.2 ng/ml
Zhang et al. [20]	2016	China	168	2006-2011	Mean (range) 69 (53-85)	Mean 13.31	Mean (range) 68 (7-98)	136/32	41/127	NA	0.2 ng/ml
Simon et al. [21]	2016	Multi-centers	411	2001-2013	Mean ± SD 64±6.1	NA	Median 63	368/43	124/287	70 (17%)	0.2 ng/ml
Sevcenco et al. [22]	2016	Multi-centers	7,205	200-2011	Median (IQR) 61 (57-66)	Median (IQR) 6 (4-9)	Median (IQR) 27 (19-48)	6,645/560	5,261/1,944	798 (11.1%)	0.2 ng/ml
Pagano et al. [23]	2016	USA	180	1990-2011	Mean (range) 63.7 (58.8-67.6)	Median 9.1	Median 26.7	90/90	113/67	120 (66.5%)	0.2 ng/ml
Ohno et al. [24]	2016	Japan	562	2000-2010	Mean ± SD 65.9±6.4	Mean ± SD 10.6±10.1	Mean 54	100/462	181/381	168 (29.9%)	0.1 ng/ml
Maubon et al. [25]	2016	Multi-centers	247	2000-2012	Mean ± SD 62.5±6.2	Mean ± SD 10.9±5.8	Median (range) 49 (20-84)	22/225	247/0	61 (24.7%)	0.2 ng/ml
Jang et al. [26]	2016	Korea	3,092	1992-2014	Median (IQR) 66 (61-70)	Median (IQR) 8 (5.3-13.9)	Median 66	865/2,227	1,488/1,604	899 (29.1%)	0.2 ng/ml
Koo et al. [27]	2015	Korea	516	2005-2009	Mean ± SD 65.6±6.9	Mean ± SD 11.3±10.5	median (IQR) 58.2 (50.2-68.1)	222/391	338/178	156 (30.2%)	0.2 ng/ml
Touijer et al. [28]	2014	USA	369	1988-2010	Median (IQR) 62 (57-66)	Median (IQR) 8 (5-15)	NA	184/185	322/47	201 (54%)	0.1 ng/ml
Ritch et al. [29]	2014	USA	979	2003-2009	Median 62	NA	Median 47	783/196	389/590	317 (32.4%)	0.2 ng/ml
Kang et al. [30]	2014	Korea	2,867	2004-2011	Mean ± SD 65.9±6.6	Mean ± SD 11.6±12.2	Median 47	2,575/459	990/1,877	NA	0.4 ng/ml
Turker et al. [31]	2013	Turkey	331	1993-2009	Mean ± SD 62.7±6.4	Mean ± SD 11.1±10.5	Mean ± SD 29.7±33.2	167/164	122/209	70 (21%)	0.2 ng/ml
Chung et al. [32]	2013	Korea	368	2003-2011	Mean ± SD 63.5±6.7	Mean ± SD 11.1±11.9	Mean ± SD 24.7±15.3	128/240	200/168	54 (21.2%)	0.2 ng/ml
Iremashvili et al. [33]	2012	USA	1,444	1992-2011	Mean (IQR) 61.3 (56-66.3)	Mean (IQR) 5.7 (4.5-8.0)	Median (range) 43.2 (3-216)	1,286/258	235/1,209	210 (15%)	0.2 ng/ml
Busch et al. [34]	2012	Germany	1,845	1999-2007	Mean ± SD 62±5.9	Mean ± SD 8.23±5.68	Median (range) 56 (0-135)	1,538/307	379/1,466	450 (24.4%)	0.1 ng/ml
Yip et al. [35]	2011	Australia	186	1989-1996	Mean (range) 63 (47-75)	Mean (range) 18 (1-191)	Median (range) 109 (13-217)	79/107	134/52	77 (41%)	0.2 ng/ml
Preston et al. [36]	2011	Multi-centers	6,855	1985-2008	NA	NA	Median (IQR) 37.3 (14.9-71.6)	2,326/4,529	4,122/2,611	NA	0.2 ng/ml

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Lee et al. [37]	2011	Korea	1,000	2003-2009	Mean (range) 65.2 (37-82)	Mean (range) 12.5 (0.1-261.8)	Median 37.8	236/764	317/683	99 (9.9%)	0.2 ng/ml
Alenda et al. [38]	2011	France	1,248	1998-2008	Mean (range) 63 (44-78)	Mean (range) 10.9 (0.9-134)	Median 23.4	1,248/0	560/688	176 (16.9%)	0.2 ng/ml
Jeon et al. [39]	2009	Korea	237	1995-2004	Mean (range) 64.5 (44-86)	Mean (range) 11.5 (0.2-98)	Median (range) 21.6 (2-88)	190/45	84/153	67 (28.3%)	0.2 ng/ml
Schroeck et al. [40]	2008	USA	3,194	1988-2007	Median (IQR) 62.6 (57.2-67.9)	Median (IQR) 6.3 (4.5-9.6)	Median 31.2	2,855/359	996/2,198	706 (25.7%)	0.2 ng/ml
Magheli et al. [41]	2007	Germany	1,740	1984-2006	NA	Median 5.2	Median 36	1,189/551	502/1,238	NA	0.2 ng/ml
Shariat et al. [42]	2004	USA	630	1994-2002	Median (range) 60.9 (40-75)	Mean (range) 6.1 (0.1-99)	Median (range) 21.4 (1-101.3)	565/65	57/572	80 (12.7%)	0.2 ng/ml
Satoh et al. [43]	2003	Japan	152	1992-2000	NA	NA	Median (range) 48.2 (1.3-103.3)	49/102	79/73	NA	0.1 ng/ml

p-PSA: preoperative prostate-specific antigen; SD: standard deviation; IQR inter quartile range; NA: data not applicable.

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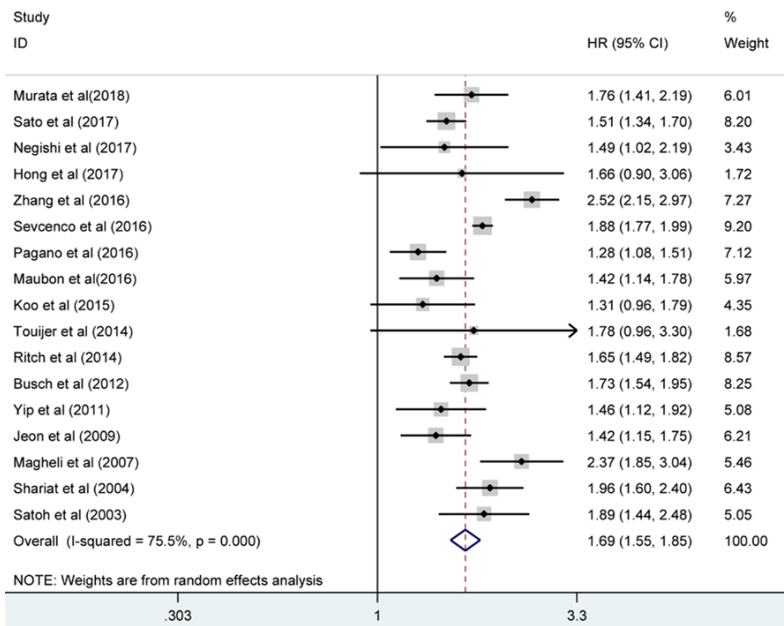


Figure 2. Forest plots concerning association between EPE and BCR risk in univariate analysis.

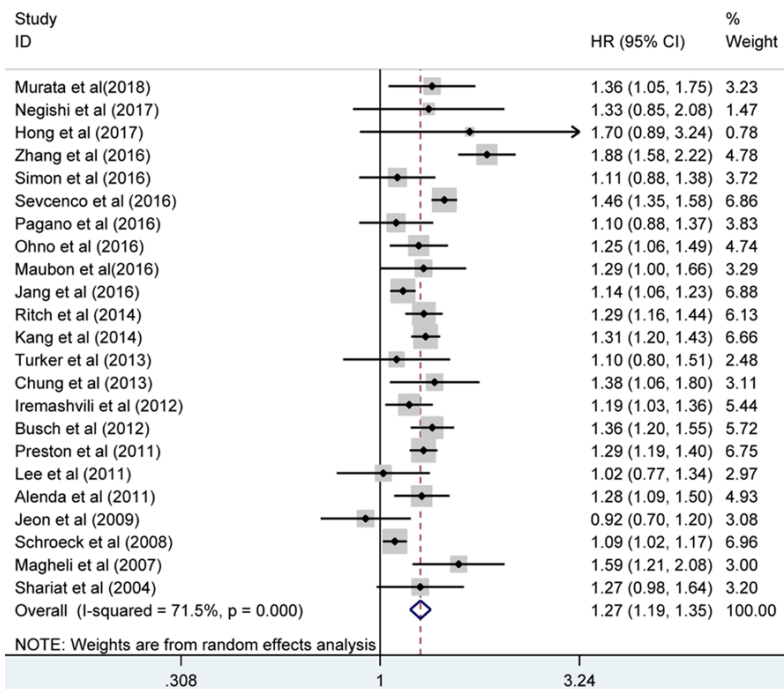


Figure 3. Forest plots concerning association between EPE and BCR risk in multivariate analysis.

(95% CI: 1.55-1.85, $p < 0.001$, **Figure 2**), with significant heterogeneity found (Q statistic, $p < 0.001$; $I^2 = 75.5\%$). Multivariate analysis of BCR risk was reported in 23 studies [7, 18-26,

trim-and-fill method, were similar with original analyses for both univariate (**Figure S1**) and multivariate analysis (**Figure S2**). Sensitivity analysis was conducted to access the stability

29-34, 36-42], enrolling a total of 36,401 PCa patients. A random-effects model was used due to evidence of heterogeneity among studies (Q statistic, $p < 0.001$; $I^2 = 71.5\%$). Significantly higher BCR risk was detected in EPE patients, with a pooled HR=1.27 (95% CI: 1.19-1.35, $p < 0.001$, **Figure 3**).

Subgroup and meta-regression analyses were conducted to explore the source of heterogeneity, according to mean geographical region (Asian vs. Others), date of publication (≥ 2015 vs. < 2015), patient mean age (≥ 63 vs. < 63), sample size (≥ 500 vs. < 500), publication year (≥ 2014 vs. < 2014), p-PSA (≥ 10 vs. < 10), duration of follow-up (≥ 50 months vs. < 50 months), and cut-off values for BCR (0.2 vs. 0.1 or 0.4). Although no significant modifiers accounting for inter-study heterogeneity were detected, results of subgroup analyses are consistent with primary findings (**Table 2**).

Publication bias and sensitivity analysis

Tests for funnel plot asymmetry indicated the absence of publication bias. This was further confirmed by Egger's linear regression in univariate analysis (p-Egger's=0.399, **Figure 4A**) and multivariate analysis (p-Egger's=0.718, **Figure 4B**), respectively. Adjusted estimates, calculated using the

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Table 2. Subgroup and meta-regression analyses for 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	17	75.5	<0.001	Random	1.69 (1.55, 1.85)	<0.001
Geographical region						
Asian	8	78.9	<0.001	Random	1.68 (1.41, 2.02)	<0.001
Others	9	74.9	<0.001	Random	1.69 (1.52, 1.88)	<0.001
Date of publication						
≥2015	9	84.3	<0.001	Random	1.64 (1.41, 1.90)	<0.001
<2015	8	49.5	0.054	Random	1.74 (1.58, 1.92)	<0.001
Mean age (years)						
≥63	7	85.8	<0.001	Random	1.58 (1.30, 1.91)	<0.001
<63	7	41	0.118	Fixed	1.75 (1.62, 1.88)	<0.001
Sample size (cases)						
≥500	8	68.6	0.002	Random	1.74 (1.59, 1.91)	<0.001
<500	9	80.6	<0.001	Random	1.63 (1.36, 1.96)	<0.001
Mean p-PSA (ng/ml)						
≥10	5	85.6	<0.001	Random	1.67 (1.28, 2.18)	<0.001
<10	9	76.9	<0.001	Random	1.69 (1.51, 1.90)	<0.001
Median follow-up						
≥50 months	5	83.4	<0.001	Random	1.70 (1.34, 2.16)	<0.001
<50 months	11	74.8	<0.001	Random	1.67 (1.51, 1.85)	<0.001
BCR (ng/ml)						
Cutoff value 0.2	14	80.0	<0.001	Random	1.68 (1.51, 1.86)	<0.001
Cutoff value 0.1 or 0.4	3	0	0.804	Fixed	1.76 (1.58, 1.95)	<0.001
Multivariate analysis (BCR)						
Overall	23	71.5	<0.001	Random	1.27 (1.19, 1.35)	<0.001
Geographical region						
Asian	12	73.9	<0.001	Random	1.27 (1.13, 1.42)	<0.001
Others	12	71.6	<0.001	Random	1.27 (1.18, 1.36)	<0.001
Date of publication						
≥2015	9	81.5	<0.001	Random	1.32 (1.16, 1.50)	<0.001
<2015	13	59	0.004	Random	1.24 (1.16, 1.32)	<0.001
Mean age (years)						
≥63	11	74.5	<0.001	Random	1.24 (1.12, 1.37)	<0.001
<63	9	76.7	<0.001	Random	1.27 (1.15, 1.40)	<0.001
Sample size (cases)						
≥500	14	71.8	<0.001	Random	1.27 (1.19, 1.35)	<0.001
<500	9	73.5	<0.001	Random	1.26 (1.07, 1.48)	0.006
Mean p-PSA (ng/ml)						
≥10	9	72.4	<0.001	Random	1.28 (1.13, 1.44)	<0.001
<10	10	78.8	<0.001	Random	1.26 (1.15, 1.39)	<0.001
Median follow-up						
≥50 months	6	83.5	<0.001	Random	1.32 (1.13, 1.5)	0.001
<50 months	17	65.9	<0.001	Random	1.25 (1.17, 1.33)	<0.001
BCR (ng/ml)						
Cutoff value 0.2	20	74.6	<0.001	Random	1.26 (1.17, 1.35)	<0.001
Cutoff value 0.1 or 0.4	3	0	0.753	Fixed	1.31 (1.23, 1.40)	<0.001

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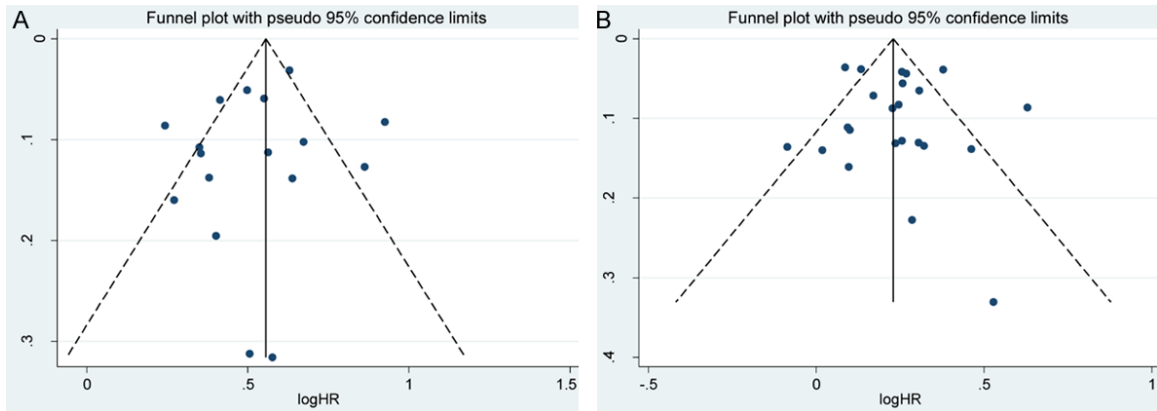


Figure 4. Egger's funnel plot of publication bias in: (A) Univariate analysis mode; (B) Multivariate analysis mode.

of results. Overall results did not alter significantly when any single study was omitted. Pooled HRs and 95% CIs ranged from 1.64 (95% CI, 1.52-1.78) to 1.73 (95% CI, 1.59-1.89) (Figure 5A) in univariate analysis and 1.24 (95% CI, 1.18-1.33) to 1.28 (95% CI, 1.21-1.36) (Figure 5B) in multivariate analysis. Results indicate that present findings are reliable and robust.

Discussion

Although RP has become the most commonly used treatment for patients with localized PCa, with a life expectancy of 10 years [44], nearly half of these patients will develop BCR or subsequent metastasis despite surgical treatments [45]. The most widely studied prognostic factors are total serum prostate-specific antigen (t-PSA) [44], Gleason scores [5], and clinical stage [23], but the specificity and sensitivity of these factors should be challenged. Post-operative PSA can fluctuate up to 20-30%, based on biological and environmental factors [46]. Better methods of identifying patients at increased risk for BCR after RP are necessary.

PCa is currently staged using the 7th edition Union International Control Cancer 2009 Tumor Node Metastasis classification [32]. Accurate staging of prostate cancer patients plays an increasingly important role in choosing between different treatment strategies, including radical prostatectomy, brachytherapy, or external beam radiotherapy. One important distinction is between tumors confined to the prostate pT2 versus pT3a. Patients with pT2 disease have good biochemical and clinical control, while RP for pT3a disease has a 5-year BCR rate between

20% and 70% [47]. Therefore, in making better informed treatment decisions in patients with pT3a disease, a novel risk stratification nomogram should be created.

EPE in the RP specimen has been well-studied. It is a critical part of the pathological tumor staging process. All RP specimens containing EPE have been classified as pathological stage pT3a in the TNM staging system, since 1997, representing about 25% of RP specimens in the current series [25]. EPE found at RP is a risk factor for poor prognosis. It is now suggested as the standard pathological reporting protocol in RP specimens. Adjuvant radiotherapy (RT) is often recommended in patients with pathologically advanced prostate cancer after RP [48]. Although this is an effective adjuvant therapy, it carries a significant risk of toxicity. Urologists may have different views concerning adjuvant therapy, especially in the setting of EPE features [49].

Invasion is widely seen as the first step in metastatic spread, with primary masses spawning pioneer cells, indicating a higher likelihood that cancer has acquired the ability to metastasize [50]. Although it has been well-documented that the spread of prostate cancer beyond the glands is associated with a higher rate of RCR after prostatectomies, it remains unclear whether EPE is an independent contributing factor [51, 52]. In addition, research concerning the connection between EPE and risk of cancer has consistently been a hot topic since the first relevant study was released. Clinical outcomes for patients with EPE are variable. In the study by Epstein et al. [51] and Wheeler et al. [13], 73-82% patients with EPE had a BCR-free sur-

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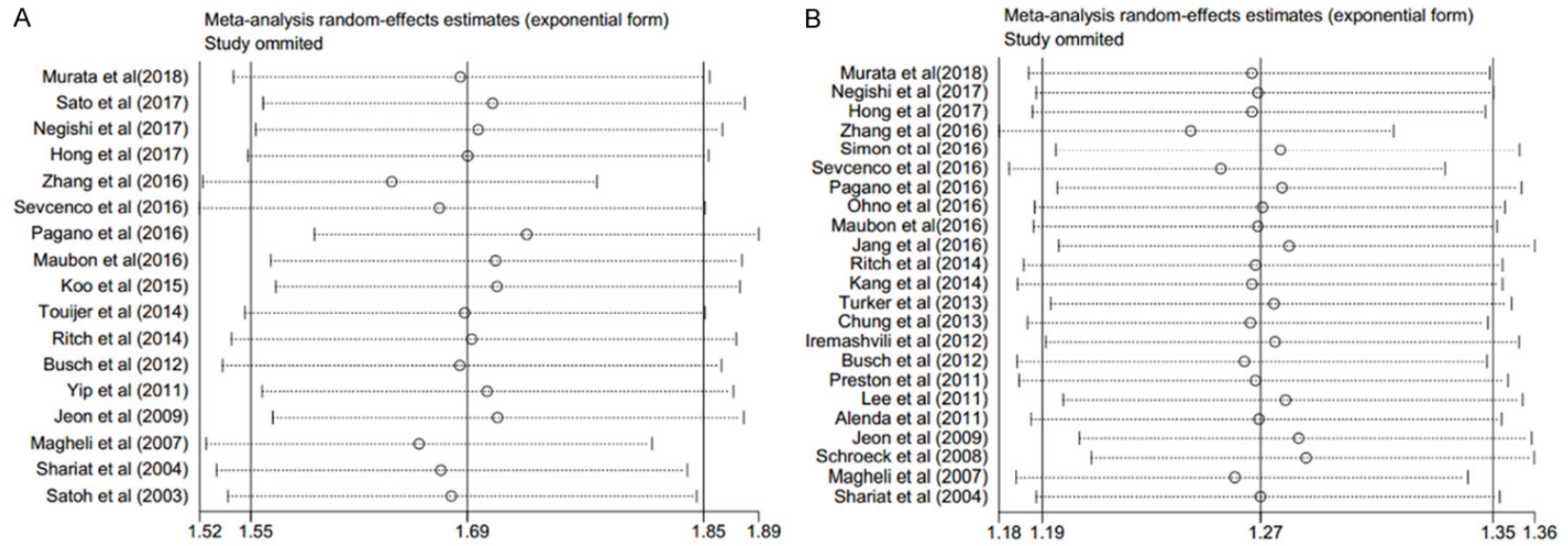


Figure 5. Sensitivity analysis concerning association between EPE and BCR risk in PCa patients. (A) Univariate analysis mode; (B) Multivariate analysis mode.

vival at 5 years after surgery. Danneman et al. [10] confirmed that EPE is an adverse prognostic factor after radical prostatectomies, with a 1.4-fold increased risk of biochemical relapse shown in 194 pT3a patients. Also, Maubon et al. [25] suggested that EPE is an independent predictor of BCR in pT3a PCa patients, according to both univariate and multivariate analysis.

To the best of our knowledge, the current systematic review and meta-analysis is the first study to comprehensively evaluate association between EPE and BCR risk. According to pooled analyses of cohort studies, significant association was found between EPE and BCR, according to both univariate analysis (pooled HR=1.69, $p<0.001$) and multivariate analysis (pooled HR=1.27, $p<0.001$). Present findings were not affected by geographical region, publication year, age, sample size, p-PSA, follow-up duration, and cutoff values for BCR. This study explored potential heterogeneity by conducting meta-regression analyses. Although there were no significant decreases in heterogeneity in the subgroups, potential heterogeneity from these origins could not be excluded. Moreover, the trim-and-fill method further confirmed the robustness of present results. Sensitivity analysis also demonstrated the stability of conclusions in this meta-analysis. In addition, there was no evidence of significant publication bias, according to Egger's tests.

However, there were some limitations to the present study. First, all included studies were retrospective, despite the use of a large sample size. Data extracted from these studies may have led to inherent potential bias. Second, defining and measuring EPE is a challenging task for pathologists. Therefore, the criteria for determining the presence of EPE in pathologic specimens were inconsistent in included studies. This may have contributed to heterogeneity. Third, the evidence grade was compromised by considerable heterogeneity. This may have been caused by various factors, including study design, patient backgrounds, and tumor characteristics. Fourth, studies with negative results tend to be unpublished. Thus, language bias may have occurred in this study.

Conclusion

In summary, the current study was the first meta-analysis to evaluate the clinical value of

EPE in PCa. Results of the present meta-analysis shed light on the association of EPE with BCR risk in RP patients, indicating that it has detrimental effects and may be considered an independent prognostic factor of BCR. Since there were inherent limitations in included retrospective studies, further studies with longer follow-up periods are necessary to confirm present findings.

Disclosure of conflict of interest

None.

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Table S1. Quality assessment of cohort studies included in this meta- analysis

Study	Representative-ness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Control for important factor or additional factor	Outcome assessment	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohort	Total quality scores
Murata et al. [7]	★	★	★	★	★★	★	★	★	9
Sato et al. [17]	★	★	★	★	★	★	★	★	8
Negishi et al. [18]	★	★	★	★	★	★	★	-	7
Hong et al. [19]	★	★	★	★	★★	★	★	★	9
Zhang et al. [20]	★	★	★	★	★★	★	★	★	9
Simon et al. [21]	-	★	★	★	★★	★	★	★	8
Sevcenco et al. [22]	★	★	★	★	★★	★	★	★	9
Pagano et al. [23]	★	★	★	★	★★	★	★	★	9
Ohno et al. [24]	★	★	★	★	★★	★	★	★	9
Maubon et al. [25]	★	★	★	★	★	★	★	-	7
Jang et al. [26]	★	★	★	★	★★	★	★	-	8
Koo et al. [27]	★	★	★	★	★	★	★	★	8
Touijer et al. [28]	★	★	★	★	★★	★	★	★	9
Ritch et al. [29]	★	★	★	★	★	★	★	★	8
Kang et al. [30]	★	★	★	★	★	★	★	★	8
Turker et al. [31]	★	★	★	★	★★	★	★	★	9
Chung et al. [32]	★	★	★	★	★★	★	★	★	9
Iremashvili et al. [33]	★	★	★	★	★	★	★	★	8
Busch et al. [34]	★	★	★	★	★	★	★	★	8
Yip et al. [35]	★	★	★	★	★	★	★	-	7
Preston et al. [36]	★	★	★	★	★	★	★	★	8
Lee et al. [37]	★	★	★	★	★★	★	★	★	9
Alenda et al. [38]	★	★	★	★	★	★	★	★	8
Jeon et al. [39]	★	★	★	★	★	★	★	★	8
Schroeck et al. [40]	★	★	★	★	★★	★	★	★	9
Magheli et al. [41]	★	★	★	★	★★	★	★	★	9
Shariat et al. [42]	★	★	★	★	★	★	★	★	8
Satoh et al. [43]	★	★	★	★	★★	★	★	★	9
Murata et al. [7]	-	★	★	★	★★	★	★	★	8
Sato et al. [17]	★	★	★	★	★★	★	★	★	9

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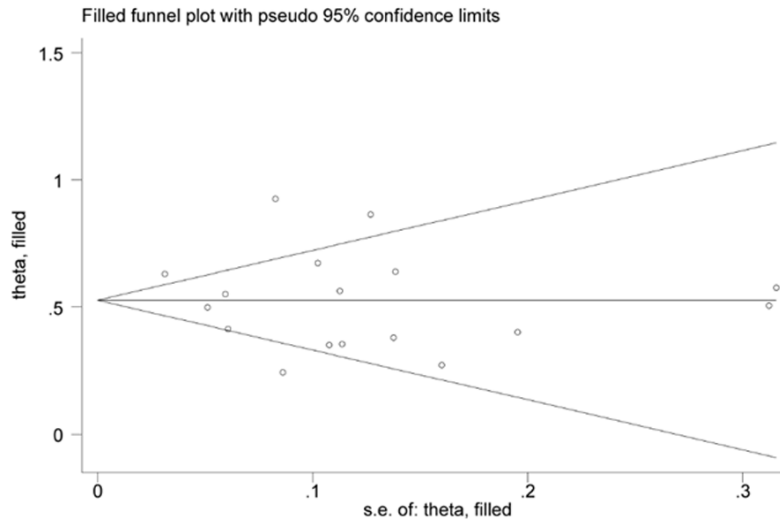


Figure S1. Trim-and-fill analysis in univariate analysis mode.

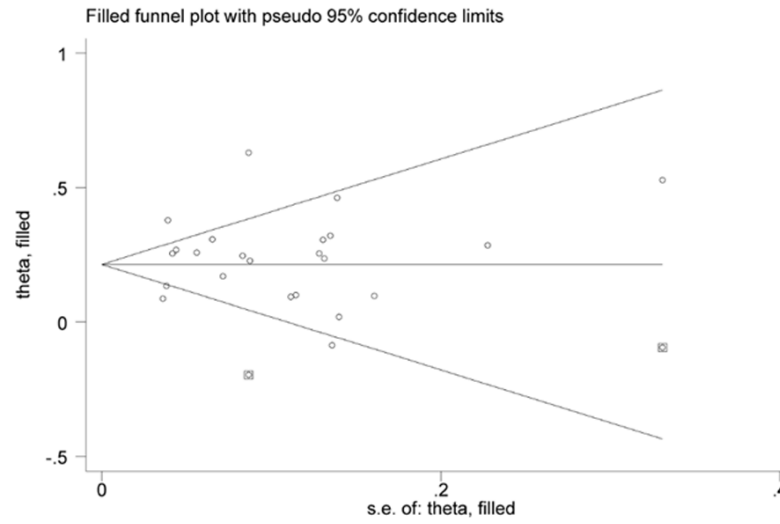


Figure S2. Trim-and-fill analysis in multivariate analysis mode.