Positive surgical margin is associated with biochemical recurrence risk following radical prostatectomy: a meta-analysis from high-quality retrospective cohort studies

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Abstract

Background and purpose: Although numerous studies have shown that positive surgical margin (PSM) is linked to biochemical recurrence (BCR) in prostate cancer (PCa), the research results have been inconsistent. This study aimed to explore the association between PSM and BCR in patients with PCa following radical prostatectomy (RP).

Materials and methods: In accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), PubMed, EMBASE and Wan Fang databases were searched for eligible studies from inception to November 2017. The Newcastle–Ottawa Scale was used to assess the risk of bias of the included studies. Meta-analysis was performed by using Stata 12.0. Combined hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs) were calculated using random-effects or fixed-effects models.

Results: Ultimately, 41 retrospective cohort studies of high quality that met the eligibility criteria, comprising 37,928 patients (94–3294 per study), were included in this meta-analysis. The results showed that PSM was associated with higher BCR risk in both univariate analysis (pooled HR = 1.56; 95% CI 1.46, 1.66; \( p < 0.001 \)) and multivariate analysis (pooled HR = 1.35; 95% CI 1.27, 1.43; \( p < 0.001 \)). Moreover, no potential publication bias was observed among the included studies in univariate analysis (p-Begg = 0.971) and multivariate analysis (p-Begg = 0.401).

Conclusions: Our meta-analysis demonstrated that PSM is associated with a higher risk of BCR in PCa following RP and could serve as an independent prognostic factor in patients with PCa.

Keywords: Positive surgical margin, Prostate cancer, Radical prostatectomy, Biochemical recurrence, Meta-analysis

Background

Prostate cancer (PCa) is the most diagnosed malignancy and the second leading cause of cancer-related deaths among men in Western countries [1]. Radical prostatectomy (RP) has been shown to have a cancer-specific survival benefit for men with clinically localised PCa [2]. Although many patients are disease-free after surgery, nearly 30% [3] of patients still continue to experience biochemical recurrence (BCR). Defined as a detectable prostate-specific antigen (PSA) level following RP in the absence of clinical progression, BCR is the most common pattern of disease relapse [4]. Patients with BCR have a considerably worse prognosis, often develop metastasis, and can die of the disease [3, 4]. Therefore, identifying prognostic predictors of BCR after RP to assist clinicians in predicting outcomes for decision making is required.

Numerous nomograms including pathological tumour stage [5], Gleason’s score [6], seminal vesicle invasion [7], and lymphatic invasion [8] have been developed to predict subsequent risk of BCR after RP. Unfortunately, because the collective prognostic value of these factors is unsatisfactory, better biomarkers are urgently needed. Positive surgical margin (PSM) is defined as the histological presence of cancer cells at the inked margin on the RP specimen [9]. Although PSM is frequently reported in radical prostatectomy series, their clinical relevance remains uncertain despite extensive investigation. A number of studies have
| Authors            | Year  | Country   | No. of patients | Recruitment period | Age (years) | p-PSA (ng/ml) | Follow-up (months) | Surgical approach |
|--------------------|-------|-----------|-----------------|-------------------|-------------|---------------|--------------------|-------------------|
| Wettstein et al.   | 2017  | Switzerland | 371             | 2008–2015         | Median (range 63 (41–78)) | Median (range 6.79 (0.43–81.4)) | Median (range 28 (1–64)) | NA                |
| Xu et al.          | 2017  | China     | 172             | 2003–2014         | Median (IQR 68 (62–72)) | Median (IQR 16.1 (10.9–28.3)) | Median (IQR 46.4 (33.4–62.4)) | NA                |
| Meyer et al.       | 2017  | Germany   | 903             | 1992–2005         | Median (IQR 63 (59–66)) | Median (IQR 6.4 (4.6–9.0)) | Median (IQR 133 (97–157)) | NA                |
| Gandaglia et al.   | 2017  | Multi-centred | 94              | 2011–2015         | Median (IQR 64.3 (57.1–68.9)) | Median (IQR 9.7 (5.1–17.5)) | Median (IQR 23.5 (18.7–27.3)) | Robot-assisted RP |
| Shangguan et al.   | 2016  | China     | 172             | 2003–2014         | Median (range 68 (62–72)) | Median (range 16.1 (10.9–28.3)) | Median (IQR 46.4 (33.4–62.4)) | Open and laparoscopic RP |
| Zhang et al.       | 2016  | China     | 168             | 2006–2011         | Median (range 69 (53–85)) | Median (range 13.31 (4.59–36.12)) | Median (range 68 (7–98)) | Laparoscopic RP    |
| Simon et al.       | 2016  | Multi-centres | 411             | 2001–2013         | Mean ± SD 61 ± 6.1 | NA | Median 63 | NA |
| Sevcenco et al.    | 2016  | Multi-centres | 7205            | 2000–2011         | Median (IQR 61 (57–66)) | Median (IQR 6 (4–9)) | Median (IQR 27 (19–48)) | NA                |
| Pagano et al.      | 2016  | USA       | 180             | 1990–2011         | Median (range 63.7 (58.8–67.6)) | Median (range 9.1 (6.3–17.1)) | Median (range 26.7 (8.8–66)) | NA                |
| Moschini et al.    | 2016  | USA       | 1011            | 1987–2012         | Median 12.0 | NA | Median 211.2 | NA |
| Mortezavi et al.   | 2016  | Switzerland | 100             | 1999–2007         | Mean ± SD 63.5 ± 6.5 | Mean ± SD 9.6 ± 8.3 | Median (range 126 (60–176)) | Laparoscopic RP |
| Mao et al.         | 2016  | China     | 106             | 2008–2009         | Mean (range 68.1 (48–83)) | Mean (range 25.1 (3.1–104.3)) | Median (range 69 (8–84)) | Laparoscopic RP |
| Whalen et al.      | 2015  | USA       | 609             | 2005–2011         | Mean ± SD 61.2 ± 7.3 | Mean ± SD 6.8 ± 6.3 | Median (range 20.5 (1–80)) | NA                |
| Song et al.        | 2015  | Korea     | 2137            | 1988–2011         | Median (IQR 67 (63–71)) | Median (IQR 6.9 (4.7–11.2)) | Median (range 39.4 (8–1834)) | NA                |
| Reeves et al.      | 2015  | Australia | 1479            | 2005–2012         | Median 62 | NA | Median 14 | NA |
| Hashimoto et al.   | 2015  | Japan     | 837             | 2006–2013         | Median (range 65 (39–78)) | Median (range 6.9 (3–47.4)) | Median (range 20.5 (1.3–91.3)) | Robot-assisted RP |
| Alvin et al.       | 2015  | Singapore | 725             | 2003–2013         | Median (range 62 (37–79)) | Median (range 7.9 (0.79–72.9)) | Mean (range 28.5 (6–116)) | Robot-assisted RP |
| Touijer et al.     | 2014  | USA       | 369             | 1988–2010         | Median (IQR 62 (57–66)) | Median (IQR 8 (5–15)) | Median 48 | NA |
| Ritch et al.       | 2014  | USA       | 979             | 2003–2009         | Median 62 | NA | Median 47 | Open and robot-assisted RP |
| Kang et al.        | 2014  | Korea     | 3034            | 2004–2011         | Mean ± SD 65.9 ± 6.6 | Mean ± SD 11.6 ± 12.2 | Median 47 | NA |
| Fairey et al.      | 2014  | USA       | 229             | 1987–2008         | Median (range 65 (41–83)) | NA | Median (range 174 (2.4–253.2)) | NA |
| Turker et al.      | 2013  | Turkey    | 331             | 1993–2009         | Mean ± SD 62.79 ± 6.4 | Mean ± SD 11.1 ± 10.5 | Mean ± SD 29.7 ± 33.2 | NA |
| Sammon et al.      | 2013  | USA       | 794             | 1993–2010         | Mean ± SD 63.4 ± 8.1 | Mean ± SD 5.6 ± 3.6 | Median (IQR 26.4 (12.2–54.6)) | NA                |
| Chen et al.        | 2013  | China     | 152             | 2004–2011         | NA | NA | Median (range 48 (12–87)) | Laparoscopic RP |
| Sooriakumaran et al.| 2012  | Sweden    | 944             | 2002–2006         | Median (IQR 62.2 (58.2–65.8)) | Median (IQR 6.4 (4.8–9.0)) | Median (IQR 75.6 (67.2–86.4)) | Robot-assisted RP |
| Lu et al.          | 2012  | China     | 894             | 1993–1999         | Median (IQR 62 (57–66)) | Median (IQR 6.0 (4.5–8.6)) | Median (IQR 9.9 (6.1–11.3)) | NA                |
| Iremashvili et al. | 2012  | USA       | 1444            | 2003–2010         | Mean (range) | Mean (range) | Median (range) | NA |

**Table 1** Primary characteristics of the included studies
demonstrated an association between PSM and BCR [5, 10, 11], while others have observed insignificant or even contrary correlations [12–14].

Previously, Yossepowitch [15] systematically reviewed related studies on PSM reporting survival of surgical treatment for patients with PCa. These studies suggested that PSM in PCa should be considered an adverse oncological outcome. Nevertheless, a meta-analysis was not performed because of low-quality evidence and potential risks of bias. A meta-analysis utilises statistical methods to contrast and combine results from multiple studies, increasing the statistical power and reproducibility compared with individual studies [16]. Hence, to obtain the most conclusive results, we conducted a meta-analysis with high-quality retrospective cohort studies to assess the prognostic value of PSM in BCR.

**Methods**

**Literature search**

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive search of the literature in PubMed, EMBASE, and Wan Fang databases up to November 2017 was performed using a combined text and MeSH heading search strategy with the following terms: (“prostate cancer” or “prostate AND neoplasms”) and (“radical prostatectomy”) and (“positive surgical margin”) and (“biochemical recurrence” OR “biochemical failure”). In addition, reference lists in the recent reviews, meta-analysis, and included articles were manually searched to identify related articles. The language of the publications was limited to English and Chinese.

**Inclusion and exclusion criteria**

We defined the inclusion and exclusion criteria for study selection at the initiation of the search. The following inclusion criteria were used: (1) included definitive diagnosis of PCa and PSM assessed by pathologists; (2) all patients underwent RP treatment; (3) BCR after RP was

| Author         | Year | Country | No. of patients | Recruitment period | Age (years) | p-PSA (ng/ml) | Follow-up (months) | Surgical approach |
|---------------|------|---------|----------------|-------------------|-------------|--------------|-------------------|------------------|
| Connolly et al. [48] | 2012 | Australia | 160             | 1988–1997         | 61.3 (56–66.3) | 5.7 (4.5–8.0)  | 43.2 (3–216)      | Open and robot-assisted RP |
| Busch et al. [49] | 2012 | Germany | 1845            | 1999–2007         | 63.1 ± 6.3  | Median (IQR)  | 9.95 (6.0–21.4)  | Robot-assisted RP |
| Berge et al. [50] | 2012 | Norway  | 577             | 2002–2008         | 62.0 ± 5.9  | Median (range) | 26.3 (17.0–42.1) | Laparoscopic RP   |
| Lee et al. [51]  | 2011 | Korea   | 1000            | 2003–2009         | Mean (range) | Median (range) | 7.8 (0.1–261.8)  | Mean NA          |
| Alenda et al. [23] | 2011 | France  | 1248            | 1998–2008         | Mean (range) | Median (range) | 10.9 (0.9–134)   | Median NA         |
| Fukuhara et al. [52] | 2010 | Japan   | 364             | 2000–2009         | Mean (range) | Median (range) | 8.1 (1.7–77.7)   | Median (range) NA |
| Cho et al. [53]  | 2010 | Korea   | 171             | 2005–2009         | Mean (range) | NA            | Mean (range) 23.3 (2–51) | NA               |
| Alkhateeb et al. [26] | 2010 | Canada  | 1268            | 1992–2008         | Mean (range) | Median (range) | 6.2 (0.1–65.9)   | Mean (range) 78.1 (3–192) |
| Jeon et al. [54] | 2009 | Korea   | 237             | 1995–2004         | Mean (range) | Median (range) | 11.5 (0.2–98)    | Median (range) 21.6 (2–88) |
| Schroek et al. [55] | 2008 | USA     | 3194            | 1988–2007         | Median (IQR) | Median (range) | 6.45 (44–86)     | Median (range) 31.2 |
| Pavlovich et al. [56] | 2008 | USA     | 508             | 2001–2005         | Mean (range) | Median (range) | 57.6 ± 6.7       | Median (range) 12 (2–52) |
| Hong et al. [57] | 2008 | Korea   | 372             | 2003–2007         | Mean (range) | Median (range) | 6.2 (37–72)      | Median (range) NA  |
| Cheng et al. [8] | 2005 | Indiana | 504             | 1990–1998         | Mean (range) | NA            | Median (range) 62 (34–80) | NA               |
| Shariat et al. [58] | 2004 | USA     | 630             | 1994–2002         | Median (range) | Mean (range) | 6.1 (0.1–99)     | Median (range) 21.4 (1–101.3) |

*p-PSA* preoperative prostate-specific antigen, SD standard deviation, IQR interquartile range, NA data not applicable
| Author                  | Specimen | Staging system | T stage 1–2/3–4 | SM+ / SM− | No. of BCR (%)   | Definition of BCR                                                                 |
|------------------------|----------|----------------|-----------------|-----------|-----------------|----------------------------------------------------------------------------------|
| Wettstein et al. [35]  | 292 /79  | WHO/ISUP 2016  | 263 /108        | 133 /238  | 49 (13.2%)      | Rising and verified PSA levels > 0.1 ng/ml                                        |
| Xun et al. [6]         | 131 /41  | TNM 2002       | NA              | 62 /110   | 80 (46.5%)      | The date of the first PSA elevated to 0.2 ng/ml                                  |
| Meyer et al. [36]      | 879 /24  | TNM 2002       | 903 /0          | 37 /206   | 137 (15.2%)     | PSA level of ≥ 0.2 ng/ml and rising after RP                                      |
| Gandaglia et al. [37]  | 55 /39   | TNM 2002       | 22 /72          | 30 /64    | 24 (25.5%)      | Two consecutive increases in PSA ≥ 0.2 ng/ml                                     |
| Shangguan et al. [33]  | 131 /41  | NA             | NA              | 62 /110   | NA              | Two consecutive increases in PSA ≥ 0.2 ng/ml                                     |
| Zhang et al. [34]      | 136 /32  | TNM 2012       | NA              | 30 /138   | NA              | First PSA elevated to 0.2 ng/ml                                                  |
| Simon et al. [12]      | 368 /43  | NA             | NA              | 353 /58   | 70 (1.7%)       | Single PSA concentration of > 0.2, two concentrations at 0.2 ng/ml              |
| Sevcenco et al. [38]   | 6645 /560| TNM 2009       | NA              | 6137 /1074| 798 (11.1%)     | Two consecutive increases in PSA ≥ 0.2 ng/ml                                     |
| Pagano et al. [20]     | 90 /90   | TNM 2002       | NA              | 74 /106   | 120 (66.5%)     | Two postoperative PSA values of ≥ 0.2 ng/ml                                      |
| Moschini et al. [39]   | 647 /364 | NA             | NA              | 566 /445  | 697 (69%)       | PSA 0.4 ng/ml or greater                                                        |
| Mortezavi et al. [40]  | 86 /14   | NA             | 79 /21          | 20 /86    | 31 (29.2%)      | Two consecutive increases in PSA ≥ 0.2 ng/ml                                     |
| Whalen et al. [29]     | 516 /93  | TNM 1997       | 435 /174        | 483 /126  | 73 (12%)        | Two consecutive increases in PSA ≥ 0.2 ng/ml                                     |
| Song et al. [42]       | 1722 /415| NA             | NA              | 1899 /248 | 2132 /13,433   | Greater than 0.2 ng/ml                                                          |
| Reeves et al. [43]     | 1306 /142| NA             | 1042 /454       | 390 /1089 | 238 (20.5%)     | Greater than 0.2 ng/ml                                                          |
| Hashimoto et al. [5]   | 634 /373 | WHO 2004       | 677 /160        | 243 /594  | 102 (12.2%)     | Two consecutive increases in PSA ≥ 0.2 ng/ml                                     |
| Alvin et al. [44]      | 663 /58  | TNM 2010       | 497 /228        | 311 /414  | 104 (14%)       | Two consecutive increases in PSA ≥ 0.2 ng/ml                                     |
| Touijer et al. [13]    | 184 /185 | TNM 2010       | 46 /323         | 138 /231  | 201 (54%)       | PSA ≥ 0.1 ng/ml with confirmatory rise                                          |
| Ritch et al. [45]      | 783 /196 | TNM 2002       | 955 /24         | 335 /644  | 317 (32.4%)     | Greater than 0.2 ng/ml                                                          |
| Kang et al. [21]       | 2757 /459| TNM 2009       | 974 /2060       | NA        | NA              | A serum PSA value of 0.4 ng/ml or greater after RP                               |
| Fairey et al. [14]     | 133 /96  | TNM 2002       | 0 /229          | 105 /124  | 83 (36.2%)      | Detectable PSA (ng/ml) followed by two consecutive confirmatory (1988–1994: PSA ≥ 0.3; 1995–2005: PSA ≥ 0.05; 2006–present: PSA ≥ 0.03) |
| Turker et al. [46]     | 167 /164 | TNM 1994       | NA              | 80 /251   | 70 (21%)        | Higher than 0.2 ng/ml on 2 separate measurements 1 month apart                 |
| Sammon et al. [10]     | 760 /34  | AJCC 2002      | 592 /202        | 162 /632  | 107 (13.5%)     | Two consecutive increases in PSA ≥ 0.2 ng/ml                                     |
| Chen et al. [30]       | 109 /43  | NA             | 0 /152          | 27 /125   | 80 (52.6%)      | Two consecutive increases in PSA ≥ 0.2 ng/ml                                     |
| Soonikamuran et al. [11]| 900 /44  | NA             | 651 /230        | 194 /704  | 135 (15.2%)     | Greater than 0.2 ng/ml                                                          |
| Lu et al. [31]         | 796 /98  | TNM 2010       | 703 /191        | 250 /644  | 277 (31%)       | PSA ≥ 0.1 ng/ml with confirmatory rise                                          |
| Iremashvili et al. [47]| 1286 /258| NA             | 479 /965        | 210 (15%) | Greater than 0.2 ng/ml                                     |
| Connolly et al. [48]   | 95 /65   | NA             | 65 /95          | 60 /100   | 88 (55%)        | Greater than 0.2 ng/ml                                                          |
| Busch et al. [49]      | 1538 /307| NA             | 1802 /9         | 537 /1308 | 450 (24.4%)     | PSA ≥ 0.1 ng/ml with confirmatory rise                                          |
| Berge et al. [50]      | 553 /24  | TNM 2002       | 441 /136        | 168 /409  | 91 (16%)        | Two consecutive increases in PSA ≥ 0.2 ng/ml                                     |
| Lee et al. [51]        | 236 /764 | NA             | NA              | 337 /663  | 99 (99%)        | Two consecutive increases in PSA ≥ 0.2 ng/ml                                     |
| Alenda et al. [23]     | 1248 /0  | NA             | NA              | 400 /843  | 176 (16.9%)     | PSA > 0.2 ng/mL                                                                |
| Fukushima et al. [52]  | 332 /32  | TNM 2002       | 275 /89         | 157 /207  | 66 (18.1%)      | Two consecutive increases in PSA ≥ 0.2 ng/ml                                     |
| Cho et al. [53]        | 153 /14  | TNM 2002       | 126 /45         | 58 /109   | 15 (8.8%)       | A serum PSA value of 0.4 ng/ml or greater after RP                               |
| Alkhateeb et al. [26]  | 1159 /109| NA             | 853 /415        | 264 /1004 | NA              | A serum PSA value of 0.4 ng/ml or greater after RP                               |
| Jeon et al. [54]       | 190 /45  | TNM 2002       | 145 /92         | 86 /151   | 67 (28.3%)      | Two consecutive increases in PSA ≥ 0.2 ng/ml                                     |
| Schroek et al. [55]    | 2855 /359| NA             | 1991 /1166      | 982 /2212 | 706 (25.7%)     | Greater than 0.2 ng/ml                                                          |
| Pavlovich et al. [56]  | 494 /14  | TNM 2002       | 416 /92         | 69 /439   | 102 (20%)       | Two consecutive increases in PSA ≥ 0.2 ng/ml                                     |
| Hong et al. [57]       | 361 /11  | TNM 2002       | 371 /0          | 46 /326   | NA              | First value greater than 0.2 ng/ml                                              |
| Cheng et al. [8]       | 410 /94  | TNM 1997       | 348 /156        | 174 /330  | 157 (21.2%)     | Two consecutive increases in PSA ≥ 0.1 ng/ml                                     |
| Shariat et al. [58]    | 565 /65  | TNM 1997       | NA              | 179 /451  | 80 (12.7%)      | First value greater than 0.2 ng/ml                                              |

GS Gleason score, SM+ / SM− surgical margin positive / surgical margin negative, BCR biochemical recurrence, NA data not applicable
defined; (4) the risk of BCR was estimated as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) or the risk could be calculated from the reported data; and (5) published in English or Chinese. The following exclusion criteria were used: (1) letters, reviews, case reports, editorials, and author responses; (2) non-human studies; (3) studies that did not analyse the outcome after PSM and BCR; (4) studies with duplicated patient populations that had been reported in previous publications; or (5) articles contained elements that were inconsistent with the inclusion criteria.

Data extraction and quality assessment

Two investigators (Zhenlei Zha and Hu Zhao) independently extracted the data from all eligible publications. Any differences among evaluators were resolved by discussion with a third investigator (BinWu). The following data were extracted from the included studies using a standardised data collection protocol (Table 1, Table 2): first author’s name, year of publication, country, recruitment period, sample size, patient’s age, preoperative PSA level, Gleason score, pathological stage, positive percentage of PSM and BCR, definition of BCR, follow-up time, and the HRs (95% CIs) of PSM in univariate or multivariate Cox analyses for BCR. The quality of the eligible studies was evaluated according to the Newcastle–Ottawa Scale (NOS), which include three domains (selection of the study population, comparability of the groups, ascertainment of the outcome). We identified articles of “high quality” as those with NOS scores of 6–9, whereas scores of 0–5 were considered to indicate poor quality.

Statistical analyses

All statistical analyses in this meta-analysis were performed by Stata 12.0 software (Stat Corp, College Station, TX, USA). The association between PSM and BCR outcome was presented as summary relative risk estimates (SRREs) and 95% CIs. Heterogeneity between studies was calculated by the chi-square-based Q test and $I^2$. A value of $p < 0.10$ or $I^2 > 50\%$ was considered as statistically significant heterogeneity. A random-effects model was used if heterogeneity was significant, and otherwise, a fixed-effects model was used. Sensitivity analysis was used to estimate the reliability of the pooled

Fig. 1 Flow diagram of the study selection process for this meta-analysis
results via the sequential omission of each study. Sub-
group analysis was performed to check whether the
pooled HR was influenced by the region, publication
year, mean age, sample size, mean preoperative PSA
(p-PSA), median follow-up, and the cut-off value for
BCR. To assess the stability of the combined HR, sensi-
tivity analysis was performed by removing individual
studies from the meta-analysis. Publication bias was
assessed by funnel plots and was statistically determined
by Egger’s linear regression. Statistical significance
was defined as a two-tailed value of \( p < 0.05 \), except for
the heterogeneity tests.

Results

Literature search and study characteristics

The full process of the systematic literature review is
shown in Fig. 1. In accordance with the PRISMA search
strategy, 1048 relevant studies were initially identified.
After carefully reading each article, 780 studies were ex-
cluded for the following reasons: duplicates, letters, or
reviews; or contained no evaluated margin status and
focus on BCR. After the remaining studies (\( n = 268 \))
were reviewed, additional studies were excluded because
certain cohorts were studied more than once or relevant
data were lacking. Forty-one high-quality retrospective
studies comprising 37,928 patients (94–3294 per study)
were ultimately included in the meta-analysis.

The primary characteristics of the included studies are
summarised in Table 1. All studies were published be-
tween 2004 and 2017. Of these, 19 studies were con-
ducted in an Asian country, and 12 were conducted in
North America; the rest were conducted in Europe (7)
or in multiple countries (3). The median follow-up
period of the studies ranged from 14 to 174 months. All
included studies were published in English, except for
two that were in Chinese. Of all of the studies, 8 used
laparoscopic RP, 7 used robot-assisted RP, and 3 used
open RP. BCR was defined using different cut-off values
(0.1 ng/ml, 0.2 ng/ml, 0.4 ng/ml) among the included
studies, and the incidence of BCR after RP ranged from
8.8 to 66.5% according to the reported values (Table 2).

NOS [17] was applied to assess the quality of the in-
cluded studies, and the results showed that all of the
studies were of high quality with an NOS score \( \geq 7 \).
(Additional file 1: Table S1).

Meta-analysis

The forest plots of the meta-analysis in our study demonstr-
ated that PSM was associated with poorer BCR in RP
patients by univariate analysis (random-effects model,
pooled HR = 1.56; 95% CI 1.46, 1.66; \( p < 0.001 \); Fig. 2) and

![Forest plots of the association between PSM and BCR risk in the stratification analysis by univariate model](image-url)
multivariate analysis (random-effects model, pooled HR = 1.35; 95% CI 1.27, 1.43; \( p < 0.001 \); Fig. 3). Given the large heterogeneity between the studies, subgroup analyses were performed by region, publication year, mean age, sample size, mean preoperative PSA (p-PSA), median follow-up, and the cut-off value for BCR. Although no significant modifiers accounting for the inter-study heterogeneity were detected, the results of subgroup analyses were consistent with the primary findings (Table 3).

The sensitivity analysis and publication bias
With a sensitivity analysis, the overall significance did not change when any single study was omitted. The summary relative risk estimate (SRRE) for BCR ranged from 1.52 (95% CI, 1.44–1.62) to 1.58 (95% CI, 1.48–1.68) (Fig. 4a) in univariate analysis and 1.34 (95% CI, 1.26–1.42) to 1.37 (95% CI, 1.29–1.45) (Fig. 4b) in multivariate analysis. These results indicated that the findings were reliable and robust. To test for publication bias, Egger’s linear regression was performed. No significant publication bias was detected between these studies regarding HR of BCR in univariate analysis (\( p_{-\text{Begg}} = 0.971 \); Fig. 5a) and multivariate analysis (\( p_{-\text{Begg}} = 0.401 \); Fig. 5b), respectively.

Discussion
With the increased public awareness and wide use of PSA-based screening, the number of patients diagnosed with PCa annually has been increasing [6]. Because RP provides superior cancer control and functional outcomes, this surgery has become a standard first-line treatment for eligible patients [18]. However, despite various advances in surgical technology, BCR has been reported in approximately 25–35% patients after RP and even more patients with intermediate–high risk [19]. Because BCR reportedly leads to distant metastasis and cancer death [20], it is necessary for men with BCR to undergo salvage radiation or hormonal therapy [11]. Therefore, identifying modifiable factors that affect the progression of BCR may help physicians in the selection of patients who are more likely to benefit from adjuvant multimodal therapy.

A number of nomograms have been developed to predict BCR after RP using either preoperative or postoperative variables [21]. Several clinical and pathologic factors have been included in these models, most of which cannot be altered by the treating physician (preoperative PSA [22], pathological T stage [5], pathological...
Table 3 Overall analyses and subgroup analyses for the included studies

| Analysis specification | No. of studies | Study heterogeneity  | Effects model | Pooled HR (95% CI) | p value |
|------------------------|----------------|----------------------|---------------|--------------------|---------|
|                        |                | $I^2$ (%)            |               |                    |         |
|                        |                | $p_{heterogeneity}$  |               |                    |         |
| Univariate analysis (BCR) |                |                      |               |                    |         |
| Overall                | 25             | 70.9                 | < 0.001       | Random             | 1.56 (1.46,1.66) | < 0.001 |
| Geographical region    |                |                      |               |                    |         |
| Asia                   | 12             | 72.1                 | < 0.001       | Random             | 1.61 (1.43,1.82) | < 0.001 |
| Europe and North America | 12             | 70.8                 | < 0.001       | Random             | 1.50 (1.37,1.65) | < 0.001 |
| Date of publication    |                |                      |               |                    |         |
| ≥ 2014                 | 13             | 81.8                 | < 0.001       | Random             | 1.52 (1.36,1.70) | < 0.001 |
| < 2014                 | 12             | 18.5                 | 0.262         | Fixed              | 1.61 (1.52,1.71) | < 0.001 |
| Mean age (years)       |                |                      |               |                    |         |
| ≥ 64                   | 9              | 84                   | < 0.001       | Random             | 1.62 (1.34,1.97) | < 0.001 |
| < 64                   | 15             | 55.6                 | 0.005         | Random             | 1.54 (1.45,1.64) | < 0.001 |
| Sample size (cases)    |                |                      |               |                    |         |
| ≥ 500                  | 10             | 40.1                 | 0.09          | Random             | 1.61 (1.52,1.70) | < 0.001 |
| < 500                  | 15             | 76.9                 | < 0.001       | Random             | 1.51 (1.33,1.71) | < 0.001 |
| Mean p-PSA (ng/ml)     |                |                      |               |                    |         |
| ≥ 10                   | 7              | 81                   | < 0.001       | Random             | 1.65 (1.38,1.97) | < 0.001 |
| < 10                   | 14             | 58.5                 | 0.003         | Random             | 1.59 (1.48,1.71) | < 0.001 |
| Median follow-up       |                |                      |               |                    |         |
| ≥ 36 months            | 11             | 77.1                 | < 0.001       | Random             | 1.49 (1.33,1.67) | < 0.001 |
| < 36 months            | 14             | 59.8                 | 0.002         | Random             | 1.61 (1.49,1.74) | < 0.001 |
| BCR (ng/ml)            |                |                      |               |                    |         |
| Cutoff value 0.1       | 4              | 0                    | 0.775         | Fixed              | 1.61 (1.49,1.72) | < 0.001 |
| Cutoff value 0.2       | 20             | 72                   | < 0.001       | Random             | 1.58 (1.46,1.70) | < 0.001 |
| Cutoff value 0.4       | 1              | –                    | –             | –                  | –       |
| Multivariate analysis (BCR) |            |                      |               |                    |         |
| Overall                | 32             | 79.2                 | < 0.001       | Random             | 1.35 (1.27,1.43) | < 0.001 |
| Geographical region    |                |                      |               |                    |         |
| Asia                   | 14             | 67                   | < 0.001       | Random             | 1.42 (1.29,1.55) | < 0.001 |
| Europe and North America | 15             | 84.7                 | < 0.001       | Random             | 1.31 (1.19,1.43) | < 0.001 |
| Multi-centred          | 3              | 71.9                 | 0.029         | Random             | 1.33 (1.00,1.78) | 0.053 |
| Date of publication    |                |                      |               |                    |         |
| ≥ 2014                 | 16             | 82.9                 | < 0.001       | Random             | 1.27 (1.17,1.39) | < 0.001 |
| < 2014                 | 16             | 67.2                 | < 0.001       | Random             | 1.44 (1.32,1.56) | < 0.001 |
| Mean age (years)       |                |                      |               |                    |         |
| ≥ 64                   | 8              | 62.5                 | 0.009         | Random             | 1.56 (1.32,1.85) | < 0.001 |
| < 64                   | 22             | 81.5                 | < 0.001       | Random             | 1.33 (1.24,1.43) | < 0.001 |
| Sample size (cases)    |                |                      |               |                    |         |
| ≥ 500                  | 18             | 77.1                 | < 0.001       | Random             | 1.40 (1.32,1.49) | < 0.001 |
| < 500                  | 14             | 76.8                 | < 0.001       | Random             | 1.28 (1.12,1.47) | < 0.001 |
| Mean p-PSA (ng/ml)     |                |                      |               |                    |         |
| ≥ 10                   | 7              | 80.8                 | < 0.001       | Random             | 1.36 (1.22,1.57) | < 0.001 |
| < 10                   | 19             | 79                   | < 0.001       | Random             | 1.35 (1.24,1.48) | < 0.001 |
| Median follow-up       |                |                      |               |                    |         |
The D’Amico risk stratification scheme [20] and Cancer of the Prostate Risk Assessment (CAPRA) score [24] have also been adopted in the urological community to predict the probability of BCR. Although these nomograms have been internationally validated, unfortunately, only a small number of them have predicted the probability of 5-year BCR with more than 70% accuracy [25]. Thus, efforts to improve existing outcome prediction tools for PCa are always encouraged.

PSM is a frequent situation encountered after radical prostatectomy (RP) for localised PCa with an occurrence ranging from 6 to 41% [9, 26, 27]. The incidence of PSM depends on various factors, including tumour biology, patient characteristics, pathological assessment method, and surgical technique [28]. We reported an overall PSM rate of 45.7% (17,339/37,928), which was slightly higher than other large series. Because the goal of surgical procedures is the complete removal of the tumour, the presence of PSM after RP is considered to be an adverse outcome associated with failure of the surgery to cure the PCa. However, the effects of PSM on clinical outcomes and the risk of BCR are still unclear. Several studies concluded that a PSM is an independent factor of BCR in patients with PCa after RP [11, 29–31]. However, not all patients with PSM show recurrence according to other studies [27, 28, 32]. Moreover, several reports showed that the effect of PSMs on prognosis depends on certain clinical and pathological features of the disease [26].

To the best of our knowledge, this study is the most up-to-date and informative meta-analysis on the association between PSM and BCR risk. The results obtained in our meta-analysis are in line with the previous systematic review by Yossepowitch et al. In addition, our study presented a series of advancements in comparison with previous studies. First, we included more eligible studies with high quality. The search by Yossepowitch et al. included studies up to 2013. However, our search included 21 additional studies published from 2014 to 2017, thereby improving the evaluation on the effect and enabling more subgroup analyses. In addition, the studies retrieved for our analysis were not limited to English; two Chinese articles [33, 34] also met the criteria for inclusion.

### Table 3 Overall analyses and subgroup analyses for the included studies (Continued)

| Analysis specification | No. of studies | Study heterogeneity | Effects model | Pooled HR (95% CI) | p value |
|------------------------|----------------|---------------------|---------------|-------------------|---------|
| ≥ 36 months            | 16             | 79.6                | Random        | 1.36 (1.24,1.46)  | < 0.001 |
| < 36 months            | 15             | 79.8                | Random        | 1.34 (1.21,1.47)  | < 0.001 |
| BCR (ng/ml)            |                |                     |               |                   |         |
| Cutoff value 0.1       | 5              | 87.7                | Random        | 1.22 (1.01,1.48)  | 0.044   |
| Cutoff value 0.2       | 23             | 71.3                | Random        | 1.39 (1.30,1.48)  | < 0.001 |
| Cutoff value 0.4       | 4              | 82.2                | Random        | 1.34 (1.15,1.57)  | < 0.001 |

**Fig. 4** Sensitivity analysis of the association between PSM and BCR risk in PCa patients. **a** Univariate analysis mode. **b** Multivariate analysis mode.
Similar to Yossepowitch et al., we identified a significant relationship between PSM and BCR in RP. However, we also found that the pooled result of PSM had a large heterogeneity in both univariate ($I^2 = 70.9\%$) and multivariate ($I^2 = 79.2\%$) analyses. Even though the cut-offs varied among the included studies (0.1 ng/ml, 0.2 ng/ml, 0.4 ng/ml), the subgroup analyses achieved results similar to both univariate and multivariate analyses (Table 3). 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.

However, several limitations of this study should be considered. First and foremost, all included studies were retrospective; therefore, the data extracted from those studies may have led to potential inherent bias. Second, the criteria to determine the presence of PSM in the pathological specimen were inconsistent in the included studies, which may have potentially contributed to heterogeneity. Thus, rigorous morphological criteria should be established to standardise the diagnosis of PSM. Third, substantial heterogeneity was observed in the meta-analysis, and although we used the random-effects model according to heterogeneity, it still existed in our studies. Moreover, from the subgroup analyses, we believed that the heterogeneity was caused by differences in factors such as patient and tumour characteristics. Finally, studies with negative results tend to be unsubmitted or unpublished; grey literature was not included, meaning that language bias may have been present in this study.

Conclusions
In conclusion, this meta-analysis demonstrates that PSM has a detrimental effect on BCR risk in patients with PCa after RP and could therefore be considered to be an independent prognostic factor of BCR. Due to PSM’s excellent feasibility and low cost, this method should be more widely employed for BCR risk stratification and BCR prediction in patients with PCa. Given the inherent limitations of retrospective studies, further research is warranted, preferably with a longer follow-up period, to elucidate the potential role of PSM in influencing BCR risk.

Additional file

Additional file 1: Table S1. Quality assessment of cohort studies included in this meta-analysis. (DOCX 20 kb)

Availability of data and materials
All data generated or analysed during this study are included in this published article (and its supplementary information files).

Authors’ contributions
LZ and BW contributed to the conceptualization. ZZ, HZ, and BW contributed to the literature search. YJ and YJ contributed to the data analysis. ZZ, HZ, and YJ contributed to the writing of the original draft. LZ contributed to the writing and review and editing. All authors read and approved the final manuscript.

Ethics approval and consent to participate
Not applicable.

Consent for publication
I give my consent for information about my relative circle to be published in the World Journal of Surgical Oncology (WJSO-D-18-00097R1, Lijin Zhang). I understand that the information will be published without my relative’s (circle as appropriate) name attached, but that full anonymity cannot be guaranteed. I understand that the text and any pictures or videos published in the article will be freely available on the internet and may be seen by the general public. The pictures, videos, and text may also appear on other websites or in print, may be translated into other languages, or used for commercial purposes. I have been offered the opportunity to read the manuscript.

Competing interests
The authors declare that they have no competing interests.

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