The predictor factors for positive surgical margins in patients of prostate cancer after radical prostatectomy: a systematic review and meta-analysis

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Abstract

Background and objectives The previous studies had demonstrate that positive surgical margins (PSMs) was independent predictive factor for biochemical and oncologic outcome in patients with prostate cancer (PCa). This study aimed to conduct a meta-analysis to identify predictive factors for PSMs after radical prostatectomy (RP). **Methods** We selected eligible studies via electronic database of PubMed, Web of Science and EMBASE from inception to February 2019. The risk factors for PSMs following RP were identified. The pooled estimates of standardized mean differences (SMDs)/ odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. A fixed-effect or random-effect was used to pool the estimates. Subgroup analyses were performed to explore the reasons for heterogeneity. **Results** Twenty two studies including 44,144 patients with PCa were eligible for further analysis. The results showed that PSMs were significantly associated with preoperative PSA(pooled SMD=0.44; 95% CI:0.35–0.54; $P<0.001$), biopsy Gleason Score ($< 6/ \geq 7$) (pooled OR=1.51; 95% CI:1.26–1.81; $P<0.001$), pathological Gleason Score ($< 6/ \geq 7$) (pooled OR= 2.34; 95% CI:2.02–2.71; $P<0.001$), pathological stage (

Background

Prostate cancer (PCa) is the most common type of newly diagnosed malignancy and a leading cause of cancer-related death in males worldwide[1]. With the widely used of the prostate-specific antigen (PSA) screening test, the majority of PCa patients are diagnosed in the early stages[2]. As a result, radical prostatectomy (RP) with bilateral pelvic lymph node dissection has been the gold standard for the treatment of patients with localized PCa[3]. The goal of RP for PCa is complete prostate extirpation, despite the favorable cancer control associated with RP, approximately 25% of all patients experience biochemical recurrence (BCR)[4]. A number of factors have been reported to be associated with BCR after RP, and one adverse risk factor is the presence of positive surgical margins (PSMs).

PSMs is defined as an extension of the cancer cells to the inked cut surface of the RP specimen[5]. Our previous findings have indicate that PSMs are significantly associated with BCR and poor survival outcome after RC[6, 7]. However, no systematic research studies have shown which factors that may affecting the margin of PCa after RC. Conventional parameters for risk estimation of PSMs are mainly based on the following factors, including preoperative PSA (p-PSA), pathological T stage, pathological Gleason Score (GS) and multiple positive biopsy cores[8-11]. However, the prognostic value of these predictive factors is limited. Besides, PSMs may affected by remnant normal tissue and inadequate surgical skill[12]. Therefore, no consensus is reported regarding the above results. For these considerations, a comprehensive meta-analysis and systematic review were necessary to evaluate the predictive factors for PSMs in PCa patients following RP.

Methods

Literature and search strategy

We carried out this meta-analysis in accordance with the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analyses statement (PRISMA)[13]. A comprehensive literature search was conducted of the PubMed, Web of Science, and EMBASE databases. The search strategies were based on the combination of Medical Subject Headings (MeSH) and keywords as follows: 'prsatote cancer', 'radical prostatectomy', 'positive surgical margin', 'clinicopathological' and 'risk factors'. The last search was on February 2019. Meanwhile, to identify other eligible publications, reference lists were also manually screened. The language was restricted to English. Because we did not make clinical research in this study, no ethical approval needed and all analyses were based on previous published literatures.

Selection criteria and data extraction

Papers were included in this meta-analysis if they met the criteria as follows: (1) all patients diagnosis of PCa and PSMs were histopathologically confirmed; (2) treatment was limited to RP; (3) clinicopathological features were analyzed according to surgical margins status, and all studies were comparable study design; (4) standardized mean differences (SMDs)/ odds ratios (ORs) and 95% confidence intervals (CIs) were reported in paper or could be computed from given data; (5) if more than one articles from same cohort were identified, the most comprehensive and largest datasetwasadopted. Accordingly, studies with the following criteria were excluded:(1) case reports, review articles, editorials and non-original articles;(2) papers published not in

English; (3) studies that did not analyze the PSMs and the clinical features; (4) lacking sufficient data to acquire SMDs/ ORs and 95% CIs. The literature search was performed by two investigators independently. Disagreement was resolved by discussion.

Data extraction and quality assessment

Two researchers (ZLZ and WQ) assessed the titles and abstracts of the searched studies, respectively. Any disagreements were reconciled by a third researcher (HZ). The following information was extracted from the included studies: publication information (first author's last name, publication year, country of origin and study design), patients' characteristics (mean age, p-PSA, follow-up time) and PCa outcomes (tumor stage, GS, oncologic outcomes). According to the Newcastle–Ottawa quality assessment scale (NOS)[14], two researchers independently assessed the quality of each study. According to its criteria, the NOS estimates studies based on 3 parts: selection, comparability and outcome assessment. For quality assessment, scores ranged from 0-9, and studies with scores of 6 or more were rated as being of high quality.

Statistical analysis

For this meta-analysis, pooled SMDs/ ORs with 95% CIs were used to describe the relationship between risk factors and PSMs. An OR >1 or SMD > 0 suggested a close relationship for PSMs in patients with PCa. Heterogeneity among studies was evaluated by using Cochran's Q test and Higgins I^2 statistic. If the I^2 value is > 50% or the $P_{heterogeneity}$ is < 0.1, which suggest a statistically significant heterogeneity in the included studies, a random-effects (RE) model was adopted; otherwise, fixed-effects (FE) model was used. To consider potential reason for heterogeneity, subgroup analysis was conducted. To test the stability of the result, we performed the sensitivity analysis by excluding one study in turn. Visual inspection of asymmetry in funnel plots was carried out to assess the potential publication bias. Furthermore, we performed Begg's tests to provide quantitative evidence of publication bias. Those statistical analyses or data syntheses were calculated using STATA version 12.0 (Stata Corporation, College Station, TX, USA). All statistical tests were two sided, and $P < 0.05$ was considered to be statistically significant.

Results

Literature search

A flowchart of the literature selection process is shown in **Figure 1**. The initial search of electronic databases identified 1,284 records according to the searching criteria; after duplicates were removed, 611 papers remained. Four hundred and sixteen papers were then excluded by screening titles and abstracts. Ten 195 full-text articles were further examined and 173 articles were excluded because 18 same cohort of patients and 155 lacking enough data for further research. At last, 22 articles [8, 15-35] published between 2009 and 2018 were included in this meta-analysis.

Features of included studies

Summary of major characteristics of these studies are shown in **Table 1** and **Table 2**. All the studies were of retrospective study design. The sample size ranged from 144 to 12,515, and a total of 44,144 patients were included. A total of 10,457 PCa patients with PSMs were included in our study, which accounts for 23.7% of all patients. Geographically, 8 studies were conducted in North America, 6 in Asian, 5 in Europe, 2 in Australia and 1 in Multi-center. All patients had received RP as primary treatment for PCa. According to NOS quality assessment, all studies in this study were categorized as of high quality. (**Supplementary Table S1**)

Meta-Analysis

The pooled results from the included studies indicated that PSMs were associated with pathological GS (< 6/ ≥7) (RE model, pooled OR= 2.34; 95% CI:2.02–2.71; $P<0.001$, **Figure 2**), pathological stage (<T2/ ≥T2) (RE model, pooled OR=4.68; 95% CI:3.90–5.61; $P<0.001$, **Figure 3**), biopsy GS (< 6/ ≥7) (RE model, pooled OR=1.51; 95% CI:1.26–1.86; $P<0.001$, **Figure 4**), p-PSA (FE model, pooled SMD=0.44; 95% CI:0.35–0.54; $P<0.001$, **Figure 5a**), positive lymph node (PLN) (RE model, pooled OR=3.12; 95% CI:1.94–5.01; $P<0.001$, **Figure 5b**), extraprostatic extension (EPE) (RE model, pooled OR=4.86; 95% CI:3.11–7.51; $P<0.001$, **Figure 5c**) and seminal vesicle invasion(SVI) (RE model, pooled OR=3.56; 95% CI:2.26–5.62; $P<0.001$, **Figure 5d**).

The results of meta-analysis for PSMs showed that no significant associations were found in age (RE model, pooled SMD=-0.01; 95%CI:-0.07–0.04; P=0.754,**Figure 6a**), nerve sparing (RE model, pooled OR=0.94; 95% CI: 0.68–1.29; P=0.705,**Figure 6b**), body mass index(BMI) (FE model, pooled SMD=0.06; 95%CI: -0.03–0.15; P=0.173,**Figure 6c**) and prostate volume (RE model, pooled SMD=-0.28; 95% CI: -0.62–0.05; P=0.444,**Figure 6d**).

Subgroup analysis

Considering that no significant heterogeneity in p-PSA and BMI, besides, the number of studies that evaluated EPE, SVI and prostate volume was relatively small, we only conducted subgroup analysis for biopsy GS, pathological GS, pathological stage, PLN, age and nerve sparing (**Table 3**). The subgroup analyses were conducted according to geographical region (Asian vs. non-Asian), year of publication (≥ 2014 vs. < 2014), No. of patients (≥ 1000 vs. < 1000) and median follow-up (≥ 70 months vs. < 70 months). The results of subgroup analysis are roughly same as the overall results. Besides, the heterogeneity decreased significantly in some subgroup analysis, such as geographical region in Asian, year of publication < 2014 and No. of patients < 1000 cases.

Sensitivity analysisTo validate the reliability of our results, sensitivity analysis was performed. As is shown in **Supplementary Figure S1**, the combined ORs for biopsy GS ranged from 1.44 (95% CI: 1.20 -1.75) to 1.59 (95% CI: 1.34-1.89) (**Supplementary Figure S1a**), for pathological GS ranged from 2.21 (95% CI: 1.94-2.51) to 2.41 (95% CI: 2.08-2.79) (**Supplementary Figure S1b**), for pathological stage ranged from 4.47 (95% CI: 3.74 – 5.35) to 2.85 (95% CI: 4.04-5.83) (**Supplementary Figure S1c**), for PLN ranged from 2.71 (95% CI: 1.59 -4.65) to 3.83 (95% CI: 2.54-5.77) (**Supplementary Figure S1d**) and for nerve sparing ranged from 0.84 (95% CI: 0.62-1.14) to 1.05 (95% CI: 0.79 -1.39) (**Supplementary Figure S1e**). The pooled SMD for p-PSA ranged from 0.42 (95% CI: 0.33 - 0.52) to 0.47 (95% CI: 0.37-0.58) (**Supplementary Figure S2a**), for age ranged from -0.04 (95% CI: -0.12 - 0.05) to 0.00 (95% CI: -0.09-0.11) (**Supplementary Figure S2b**). These data suggesting the results were statistically robust. Because the number of the included studies for BMI, EPE, SVI and prostate volume were small, the sensitivity analysis were not valuable.**Publication bias**

The shape of funnel plots did not reveal any evidence of asymmetry (**Figure 7**). The statistical results of Begg's test still did not show publication bias for biopsy GS (p- Begg = 0.593, **Figure 7a**), pathological GS (p- Begg = 0.772, **Figure 7b**), pathological stage (p- Begg = 0.435, **Figure 7c**), p-PSA (p- Begg = 0.519, **Figure 7d**), PLN (p- Begg = 0.658, **Figure 7e**), EPE (p- Begg = 0.694, **Figure 7f**), SVI (p- Begg = 0.688, **Figure 7g**), age (p- Begg = 0.990, **Figure 7h**) and nerve sparing (p- Begg = 0.456, **Figure 7i**). For the number of studies in prostate volume and BMI were limited, the publication bias were not assessed.

Discussion

PSMs is unfavorable pathological features, which suggests an incomplete tumor resection and confer a poorer cancer control after RP[33]. It was reported that PSMs presented in 11 – 38% of patients who treated by RP and patients with PSMs have a higher risk of BCR compared with those with a negative surgical margins (NSMs)[36]. A multi-institutional review in 2009 conducted by Yossepowitch et al.[37] concluded that PSMs in RP specimens may considered as an adverse outcome following RP. Consistent with these findings, our recent studies[6, 7] demonstrated the adverse effect of PSMs on both BCR and cancer-specific survival through systematic review and meta-analysis. However, not all patients with PSMs have poor tumor outcomes, some patients with localized PCa will occur tumor progression even in the NSMs. PSMs is the factor which may be modified by surgical technique. It seems that surgeon's experience play an important role in the decreased incidence of PSMs[38]. Considerable efforts have been devoted to identifying factors that can predict PSMs and clinical outcome following RP, such as the p-PSA[39], positive biopsy cores[10] and Clinical stage[31]. The conclusion of several published studies indicated that several unfavorable pathological features may associated PSMs. However, inconsistent results have also been demonstrated in the published studies. Besides, for patient with an adverse features of PSMs, prediction parameters that are currently available for PSMs may not reliably. A retrospective study conducted by Boorjian et al.[32] found that increased p-PSA and BMI, higher pathological stage/ GS and greater tumor volume were significantly associated with PSMs risk. Likewise, Ficarra et al.[35] found a association between PSMs and biopsy GS, pathologic stage and GS and EPE, however, no correlation was founded between PSMs and p-PSA. Hashimoto et al.[24] found only prostate-specific antigen density and prostate volume are independent predictors of PSMs after robot-assisted RP based on the data from 244 Japanese patients. Moreover, Yuksel et al.[40] consider

that positive biopsy number, pathologic stage and GS, SVI and EPE as predicted factors for PSMs after robot assist RP. Meanwhile, no correlation was founded for p-PSA, biopsy GS, PNI and PLN. The inconsistent results of the above studies may due to small sample size, single-center design and inhomogeneous population. To the best of our knowledge, no studies have systematic addressed the preoperative predictive factors for PSMs after RP. In the present study, we identified 22 studies involving 44,144 patients, and the PSMs rate was 23.7%, which is comparable to previous reports. The meta-analysis showed that p-PSA, biopsy GS ($< 6/ \geq 7$), pathological GS ($< 6/ \geq 7$), pathological stage ($< T2/ \geq T2$), PLN, EPE and SVI have statistically significant association with PSMs. Moreover, the pooled OR/SMD of the results suggested that age, BMI, prostate volume and nerve sparing were not independent prognostic factors for PSMs in patients after RP. Subgroup analyses revealed similar result despite different geographical region, publication year, sample sizes and median follow-up. Further sensitivity analysis and publication bias test were also taken, and the overall results showed that our data were stable and reliable. This is the first comprehensive study to investigate the pathological features of PSMs and predictive factors for PSMs in patients treated with RP, and the results of this analysis are meaningful. Two strengths of this study are as follows: First, large sample size of PCa patients from different geographic areas were include, and the findings in our study may more robust than those of individual study. Second, a summary OR/SMD were conducted to compare the difference between PSMs and NSMs in PCa patients categorized by several confounders. Therefore, our findings could provide solid evidence for prognostic factors in PCa patients with PSMs. Nevertheless, the present study has some limitations that should be acknowledged. First, all the studies were retrospectively performed. Second, a substantial heterogeneity was detected, while sensitivity analysis and subgroup analysis failed to identify the potential heterogeneity. Third, the number of included studies were limited in publication bias, subgroup and sensitivity analyses, which could lead to unpersuasive conclusions. Finally, all articles are in English, which could cause publication bias, although no bias was detected in the present study.

Conclusions

The meta-analysis demonstrates that p-PSA, biopsy GS, pathological GS, pathological stage, PLN, EPE and SVI were independent factors for predicting PSMs after RP, and a combination of these factors might be useful for predicting PSMs in patients with PCa undergoing RP. Considering the limitation of the present analysis, it is necessary to conduct more large-scale and well-designed studies to validate our results in the future.

Abbreviations

PCa: renal cell cancer; PSMs: positive surgical margins; NSMs: negative surgical margins; RP: radical prostatectomy; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; NOS: Newcastle Ottawa scale; ORs: odds ratios; SMD: standard mean differences; CIs: corresponding confidence intervals; p-PSA: preoperative PSA; GS: Gleason Score; PLN: positive lymph node; EPE: extraprostatic extension; SVI: seminal vesicle invasion; BMI: body mass index; RE: random-effects; FE: fixed-effects.

Declarations

Ethics approval and consent to participate

Not applicable

Consent to publish

I give my consent for information about my relative circle to be published in BMC cancer. 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.

Availability of materials and data

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

Authors' Contributions

Conceptualization: Lijin Zhang Literature search: Zhenlei Zha, Wei Qu Data analysis: Hu Zhao, Jun Yuan, Yejun Feng. Writing – original draft: Lijin Zhang, Bin Wu Writing – review and editing: Bin Wu All authors approved the final manuscript.

Ethical statements

Not applicable

Disclosure of potential conflicts of interest We declare that there have no potential competing interests in this research. **Human participants and/or animals Informed consent** This article does not contain any studies with human participants or animals performed by any of the authors. **Funding** No funding was received for our study.

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Tables

Table 1. The basic characteristics of all studies included in this meta-analysis

Author	Year	Country	Recruitment period	No. of patients		Age (years)		Pre-PSA		Follow-up (months)	
				PSMs	NSMs	PSMs	NSMs	PSMs	NSMs	PSMs	NSMs
Herforth et al[15]	2018	USA	1988-2015	1,902	2,063	Median (IQR) 62 (58-66)	Median (IQR) 63(58-67)	Median (IQR) 7.5 (5.2-12)	Median (IQR) 5.9(4.4-8.5)	Median (IQR) 93(53-152)	Median (IQR) 105(63-147)
Tatsugami et al[16]	2017	Japan	2009-2013	594	1,794	Mean $\pm$ SD 64.9 $\pm$ 6.2	Mean $\pm$ SD 65.3 $\pm$ 6.2	Median (range) 6.6 (1.8-57.1)	Median (range) 7.7 (3.0-69.8)	Median (range) 9 (1-83)	Median (range) 9 (1-83)
Seo et al[8]	2017	Korea	2008-2014	50	94	Mean $\pm$ SD 64.6 $\pm$ 6.5	Mean $\pm$ SD 67.3 $\pm$ 6.7	Mean $\pm$ SD 16.3 $\pm$ 11.4	Mean $\pm$ SD 10.5 $\pm$ 6.7	Mean $\pm$ SD 55.4 $\pm$ 3.9	Mean $\pm$ SD 64.1 $\pm$ 2.0
Meyer et al[17]	2017	USA	1992-2005	118	785	Median (IQR) 63 (60-67)	Median (IQR) 63(58-66)	Median (IQR) 6(4.3-9.0)	Median (IQR) 6.4(4.6-8.9)	Median (IQR) 132(86-145)	Median (IQR) 133(99-157)
Abdollah et al[18]	2016	MC	2002-2013	1,045	11,470	Median (IQR) 62 (56-67)	Median (IQR) 61 (55-56)	Median (IQR) 6.2 (4.7-9.6)	Median (IQR) 5.2 (4.1-7.2)	Median 39	Median 39
Whalen et al[19]	2015	USA	2005-2011	126	453	Mean $\pm$ SD 61.0 $\pm$ 7.7	Mean $\pm$ SD 61.3 $\pm$ 7.0	Mean $\pm$ SD 9.2 $\pm$ 8.6	Mean $\pm$ SD 6.1 $\pm$ 5.4	Median (range) 20.5 (1-80)	Median (range) 20.5 (1-80)
Retèl et al[20]	2014	Switzerland	1990-2008	479	775	Mean $\pm$ SD 63.4 $\pm$ 6.0	Mean $\pm$ SD 62.9 $\pm$ 6.5	NA	NA	Median (range) 73.2 (2-120)	Median (range) 73.2 (2-120)
Rouanne et al[21]	2014	France	1988-2001	108	295	Median (range) 66 (47-77)	Median (range) 66 (46-81)	Median (range) 10 (2-158)	Median (range) 10 (0.5-134)	Median (range) 139 (126-231)	Median (range) 147 (134-251)
Sammon et al[22]	2013	USA	1993-2010	162	632	Mean $\pm$ SD 63.1 $\pm$ 8.9	Mean $\pm$ SD 63.5 $\pm$ 7.8	Mean $\pm$ SD 6.9 $\pm$ 4.6	Mean $\pm$ SD 5.3 $\pm$ 3.3	Median (IQR) 54(27-84)	Median (IQR) 54(27-84)
Lee et al[23]	2013	Korea	2005-2011	167	200	Mean $\pm$ SD 67.9 $\pm$ 5.7	Mean $\pm$ SD 67.8 $\pm$ 5.3	Mean $\pm$ SD 11.2 $\pm$ 10.4	Mean $\pm$ SD 8.4 $\pm$ 6.4	NA	NA
Hashimoto et al[24]	2013	Japan	2006-2011	54	190	Mean $\pm$ SD 64.8 $\pm$ 5.7	Mean $\pm$ SD 64.0 $\pm$ 6.8	Mean $\pm$ SD 12.5 $\pm$ 12.6	Mean $\pm$ SD 9.3 $\pm$ 7.3	NA	NA
Abdollah et al[25]	2013	Italy	1998-2010	305	1,198	Median (range) 64.6 (40.5-81.1)	Median (range) 64.8 (42.3-82.2)	Median (range) 6.6 (1-74.1)	Median (range) 6.2(0.2-47.8)	Mean 122.5	Mean 122.5
Savdie et al[26]	2012	Australia	1997-2003	285	655	Median (range) 61.7 (46.4-81)	Median (range) 61.2 (42.2-77.4)	Median (range) 8.7 (2-63)	Median (range) 7.5 (0.4-84)	Median (range) 82 (5-146)	Median (range) 82 (5-146)

Lu et al[27]	2012	China	1993-1999	250	544	Median (IQR) 62 (57-66)	Median (IQR) 62(52-66)	Median (IQR) 6.2 (4.5-9.3)	Median (IQR) 5.9(4.5-8.0)	Median (IQR) 115.2 (72-132)	Median (IQR) 120(78-135.6)
Karavitakis et al[28]	2012	UK	2007-2009	31	64	Mean 62.9	Mean 61.3	Mean 13.9	Mean 10.9	NA	NA
Corcoran et al[29]	2012	Australia	1995-2010	370	1,144	Median (range) 61.5 (40.2-79.8)	Median (range) 61.5 (40.2-79.8)	Mean $\pm$ SD 7.8 $\pm$ 6.6	Mean $\pm$ SD 7.8 $\pm$ 6.6	Median (range) 22.2 (0.8-181)	Median (range) 22.2 (0.8-181)
Li et al[30]	2011	China	2000-2009	57	92	Mean $\pm$ SD 70.2 $\pm$ 6.3	Mean $\pm$ SD 69.0 $\pm$ 6.0	Mean $\pm$ SD 13.4 $\pm$ 17.6	Mean $\pm$ SD 8.0 $\pm$ 5.8	Mean $\pm$ SD 46.8 $\pm$ 27.8	Mean $\pm$ SD 46.8 $\pm$ 27.8
Coelho et al[31]	2010	USA	2008-2009	101	775	Median (IQR) 62 (56-66)	Median (IQR) 61(56-66)	Median (IQR) 5 (3.9-6.9)	Median (IQR) 4.9(3.8-6.6)	NA	NA
Boorjian et al[32]	2010	USA	1990-2006	3,651	8,078	Median (IQR) 64 (59-69)	Median (IQR) 63(57-68)	Median (IQR) 8.1 (5.4-14.1)	Median (IQR) 5.9(4.1-8.7)	Median (IQR) 98.4 (52.8-145.2)	Median (IQR) 98.4 (52.8-145.2)
Alkhateeb et al[33]	2010	Canada	1992-2008	264	1,004	Mean $\pm$ SD 62 $\pm$ 6.6	Mean $\pm$ SD 62 $\pm$ 6.6	Mean (range) 7.7 (0.1-65.9)	Mean (range) 7.7 (0.1-65.9)	Mean (range) 78.1 (3-192)	Mean (range) 78.1 (3-192)
Shikanov et al[34]	2009	USA	2003-2008	243	1,155	Median (IQR) 59 (54-65)	Median (IQR) 60(55-65)	Median (IQR) 5.6 (4.4-8.1)	Median (IQR) 5.1(4.1-7.1)	Median (IQR) 12.3 (6.3-18.9)	Median (IQR) 12.3(6.3-20.1)
Ficarra et al[35]	2009	Italy	2005-2008	95	227	Mean 61.4	Mean 61.4	NA	NA	Median 14	Median 14
SD: standard deviation; NA: data not applicable; MC: Muti-centers; PSMs: positive surgical margins; NSMs: negative surgical margins.											

Table 2. The main pathological characteristics of all studies included in this meta-analysis

Author	Staging system	Grading system	Biopsy GS < 6/ ≥7		Pathological GS < 6/ ≥7		Pathological stage 1-2/ 3-4	
			PSMs	NSMs	PSMs	NSMs	PSMs	NSMs
Herforth et al[15]	NA	Gleason score	NA	NA	1,902/0	2,063/0	1,249/653	1,567/496
Tatsugami et al[16]	NA	Gleason score	172/422	1,200/594	46/548	276/1,518	539/55	62/594
Seo et al[8]	TNM	Gleason score	14/36	40/54	NA	NA	NA	NA
Meyer et al[17]	TNM	Gleason score	98/20	625/120	69/49	510/275	NA	NA
Abdollah et al[18]	TNM	Gleason score	436/891	1,726/2,237	138/1,198	1,167/2,796	373/954	2,883/1,080
Whalen et al[19]	TNM	Gleason score	7/119	99/354	30/96	214/239	51/75	365/88
Retèl et al[20]	TNM	Gleason score	NA	NA	224/255	502/273	239/240	629/146
Rouanne et al[21]	TNM	Gleason score	81/27	233/62	49/59	181/114	35/73	224/71
Sammon et al[22]	TNM	Gleason score	NA	NA	67/95	525/107	47/115	298/334
Lee et al[23]	TNM	Gleason score	NA	NA	30/136	69/131	88/79	169/31
Hashimoto et al[24]	NA	Gleason score	18/36	63/127	NA	NA	NA	NA
Abdollah et al[25]	TNM	Gleason score	NA	NA	115/190	635/563	256/49	1,115/83
Savdie et al[26]	TNM	Gleason score	NA	NA	75/210	241/414	105/180	438/217
Lu et al[27]	TNM	Gleason score	NA	NA	80/170	293/251	161/89	468/76
Karavitakis et al[28]	TNM	Gleason score	18/13	43/21	7/21	22/43	14/17	45/19
Corcoran et al[29]	TNM	Gleason score	NA	NA	47/323	290/854	182/188	924/220
Li et al[30]	TNM	Gleason score	NA	NA	NA	NA	NA	NA
Coelho et al[31]	TNM	Gleason score	56/45	453/322	21/80	310/463	43/58	669/106
Boorjian et al[32]	TNM	Gleason score	1,905/1,125	5,372/1,621	1,806/1,839	5,719/2,328	2,072/1,579	6,767/1,289
Alkhateeb et al[33]	TNM	Gleason score	NA	NA	42/222	310/694	116/148	737/267
Shikanov et al[34]	TNM	Gleason score	118/125	727/428	73/170	592/563	120/123	980/175
Ficarra et al[35]	TNM	Gleason score	67/28	187/40	26/69	112/115	21/74	177/50
NA: data not applicable; PSMs: positive surgical margins; NSMs: negative surgical margins; GS: Gleason Score.								

Table 3. Summary and subgroup results for PSMs and clinicopathological features in PCa patients.

Analysis specification	No. of studies	Study heterogeneity		Effects model	Pooled OR/SMD(95% CI)	P-Value
		I ² (%)	P _{heterogeneity}			
BMI						
Overall	2	0	0.347	Fixed	0.06[-0.03,0.15]	0.173
p-PSA						
Overall	6	0	0.656	Fixed	0.44[0.35,0.54]	<0.001
EPE						
Overall	4	81.9	0.001	Random	4.86[3.11,7.57]	<0.001
SVI						
Overall	3	57.9	0.093	Random	3.56[2.26,5.62]	<0.001
Prostate volume						
Overall	3	76.3	0.015	Random	-0.28[-0.62,0.05]	0.097
Age						
Overall	8	38.2	0.125	Fixed	-0.01[-0.07,0.04]	0.656
Geographical region						
Asian	5	49.6	0.094	Random	-0.04[-0.12,0.03]	0.268
non-Asian	3	1.8	0.361	Fixed	0.02[-0.06,0.11]	0.572
Year of publication						
≥ 2014	4	65.2	0.035	Random	-0.05[-0.18,0.08]	0.447
< 2014	4	0	0.543	Fixed	0.02[-0.09,0.14]	0.675
No. of patients						
≥ 1000	2	72.8	0.055	Random	-0.01[-0.08,0.06]	0.846
< 1000	6	34.0	0.182	Fixed	-0.02[-0.12,0.07]	0.630
Median follow-up						
≥ 70 months	1	-	-	-	-	-
< 70 months	5	35.6	0.184	Fixed	-0.06[-0.13,0.01]	0.095
Biopsy GS (< 6/ ≥7)						
Overall	12	75.0	<0.001	Random	1.51[1.26,1.81]	<0.001
Geographical region						
Asian	3	0	0.409	Fixed	1.23[1.02,1.48]	0.031
non-Asian	8	72.1	0.001	Random	1.60[1.23,2.08]	<0.001
Year of publication						
≥ 2014	6	74.0	0.002	Random	1.45[1.09,1.92]	0.010
< 2014	6	53.0	0.059	Random	1.63[1.31,2.03]	<0.001
No. of patients						
≥ 1000	4	85.4	<0.001	Random	1.62[1.32,1.99]	<0.001
< 1000	8	61.4	0.011	Random	1.44[1.02,2.03]	0.036
Median follow-up						
≥ 70 months	3	85.6	0.001	Random	1.30[0.73,2.31]	0.367
< 70 months	6	67.5	0.009	Random	1.70[1.35,2.13]	<0.001
P- GS (< 6/ ≥7)						
Overall	19	81.8	<0.001	Random	2.34[2.02,2.71]	<0.001
Geographical region						
Asian	3	0	0.838	Fixed	2.34[1.90,2.87]	<0.001
non-Asian	15	81.8	<0.001	Random	2.26[1.91,2.66]	<0.001
Year of publication						
≥ 2014	7	88.1	<0.001	Random	2.13[1.60,2.85]	<0.001
< 2014	12	73.5	<0.001	Random	2.48[2.08,2.95]	<0.001
No. of patients						
≥ 1000	9	84.3	<0.001	Random	2.29[1.93,2.71]	<0.001
< 1000	10	81.2	<0.001	Random	2.40[1.75,3.30]	<0.001
Median follow-up						
≥ 70 months	9	79.5	<0.001	Random	1.96[1.66,2.32]	<0.001
< 70 months	7	80.4	<0.001	Random	3.03[2.28,4.01]	<0.001
Stage (< T2/ ≥T2)						
Overall	18	85.0	<0.001	Random	4.68[3.90,5.61]	<0.001
Geographical region						
Asian	4	1.9	0.383	Fixed	3.48[2.79,4.36]	<0.001
non-Asian	13	82.2	<0.001	Random	4.81[3.92,5.90]	<0.001
Year of publication						
≥ 2014	6	80.2	<0.001	Random	4.99[3.66,6.79]	<0.001
< 2014	12	82.5	<0.001	Random	4.53[3.64,5.64]	<0.001
No. of patients						
≥ 1000	8	88.6	<0.001	Random	4.17[3.35,5.21]	<0.001
< 1000	10	81.9	<0.001	Random	5.34[3.71,7.69]	<0.001
Median follow-up						
≥ 70 months	7	75.8	0.066	Random	4.24[3.42,5.26]	<0.001
< 70 months	8	87.6	<0.001	Random	4.34[3.11,6.06]	<0.001

Nerve sparing						
Overall	6	78.3	<0.001	Random	0.94[0.68,1.29]	0.705
Geographical region						
Asian	2	0	0.838	Fixed	1.04[0.87,1.24]	0.666
non-Asian	4	79.7	0.002	Random	0.92[0.56,1.51]	0.749
Year of publication						
≥ 2014	3	90.3	<0.001	Random	1.00[0.62,1.63]	0.992
< 2014	3	20.6	0.284	Fixed	0.87[0.60,1.25]	0.452
No. of patients						
≥ 1000	3	86.0	0.001	Random	0.77[0.52,1.14]	0.185
< 1000	3	20.0	0.287	Fixed	1.29[0.88,1.90]	0.189
Median follow-up						
≥ 70 months	2	91.7	0.001	Random	1.05[0.36,3.05]	0.933
< 70 months	3	43.7	0.169	Fixed	0.95[0.70,1.28]	0.721
PLN						
Overall	5	75.5	0.003	Random	3.12[1.94,5.01]	<0.001
Geographical region						
Asian	-	-	-	-	-	-
non-Asian	4	80.5	0.001	Random	3.08[1.46,6.48]	0.003
Year of publication						
≥ 2014	4	80.0	0.002	Random	3.40[2.04,5.66]	<0.001
< 2014	-	-	-	-	-	-
No. of patients						
≥ 1000	2	53.6	0.142	Random	3.86[2.55,5.82]	<0.001
< 1000	3	72.0	0.028	Random	2.52[1.06,5.99]	0.037
Median follow-up						
≥ 70 months	3	82.8	0.003	Random	2.49[1.07,5.79]	0.033
< 70 months	2	47.5	0.168	Fixed	3.97[2.21,7.12]	<0.001

Supplemental Figure Legends

Supplementary Figure S1. Sensitivity analysis (pooled ORs) of the association between the predictive factors and PSMs risk. (S1a) biopsy GS; (S1b) pathological GS; (S1c) pathological stage; (S1d) PLN and (S1e) nerve sparing.

Supplementary Figure S2. Sensitivity analysis (pooled SMDs) of the association between the predictive factors and PSMs risk. (S2a) p-PSA; (S2b) age.

Figures

Figure 1

Flowchart of the literature review process for the selection of eligible literatures.

Figure 2

Forest plot for the association between pathological GS and PSMs risk.

Figure 3

Forest plot reflecting the association between pathological stage and PSMs.

Figure 4

Forest plot assessing the correlation of biopsy GS and PSMs.

Figure 5

Forest plots of studies evaluating the prognostic factors for p-PSA (5a), PLN (5b), EPE (5c) and SVI (5d) with PSMs risk.

Figure 6

Forest plots of studies evaluating the association of PSMs and clinicopathological features in PCa patients. age(6a), nerve sparing (6b), BMI(6c) and prostate volume (6d).

Figure 7

Funnel plot and Begg test for publication bias. (7a) biopsy Gleason Score, (7b) pathological GS, (7c) pathological stage, (7d) p-PSA, (7e) PLN, (7f) EPE, (7g) SVI, (7h) age and (7i) nerve sparing.

Supplementary Files

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