Postprint of a Meta-Analysis of Risk Factors for Positive Surgical Margins after Radical Prostatectomy in Chinese Populations

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Date: 2022-08-12T00:00:00+00:00

Abstract

Objective: To investigate the risk factors for positive surgical margins after radical prostatectomy in the Chinese population, to provide a reference for prevention and control efforts. Methods: A computerized search was conducted in PubMed, EMbase, The Cochrane Library, Web of Science, CNKI, WanFang Data, CBM, and VIP databases to collect relevant literature on risk factors for positive surgical margins after radical prostatectomy, with the search period spanning from database inception to March 1, 2022. Stata 16 software was used to perform meta-analysis on data from included studies. Results: A total of 21 case-control studies were ultimately included, comprising 6782 patients, of whom 2028 had positive surgical margins. Meta-analysis results showed that preoperative PSA (OR=1.77, 95%CI: 1.18～2.65) , percentage of positive biopsy cores(OR=1.83, 95%CI: 1.35～2.47) , number of positive biopsy cores (OR=2.17, 95%CI:0.98～4.8), biopsy Gleason score(OR=2.14, 95%CI:1.67～2.74), perineural invasion on biopsy (OR=5.83, 95%CI:2.05～16.59) , preoperative clinical T stage (OR=2.17, 95%CI:1.06～4.42) , postoperative pathological T stage (OR=4.30, 95%CI: 2.43～7.63) , and postoperative Gleason score (OR= 2.33, 95%CI:1.80～3.01) were risk factors for positive surgical margins after radical prostatectomy. Subgroup analysis by surgical approach showed that for laparoscopic radical prostatectomy, preoperative PSA (OR=1.47, 95%CI: 0.42～5.09) , number of positive biopsy cores (OR=2.17, 95%CI:0.98～4.80) , preoperative clinical T stage (OR=4.57, 95%CI:2.57～8.12) , postoperative pathological T stage (OR=4.80, 95%CI: 2.20～10.48) , and postoperative Gleason score (OR=2.46, 95%CI:1.57～3.86) were risk factors for positive surgical margins; for robot-assisted laparoscopic radical prostatectomy, risk factors for positive surgical margins were preoperative PSA (OR=2.17, 95%CI:1.60～2.94) and preoperative clinical T stage (OR=1.19, 95%CI: 0.52～2.74) . Conclusion: Positive surgical margins after radical prostatectomy involves multiple preoperative and postoperative factors,

which should be identified early in clinical practice, and intervention measures should be taken to prevent tumor recurrence and progression.

Full Text

Preamble

Risk Factors for Positive Surgical Margin After Radical Prostatectomy in Chinese Population: A Meta-Analysis

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Funding: Gansu Provincial Science and Technology Program (Key R&D Program) (Grant No. 21YF5FA016)
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Abstract

Objective: To investigate the risk factors for positive surgical margin (PSM) after radical prostatectomy (RP) in Chinese populations and provide evidence for clinical prevention and management.

Methods: We systematically searched PubMed, EMbase, The Cochrane Library, Web of Science, CNKI, WanFang Data, CBM, and VIP databases for relevant literature on risk factors for PSM after RP from inception to March 1, 2022. Meta-analysis was performed using Stata 16 software.

Results: Twenty-one case-control studies involving 6,782 patients were included, of whom 2,028 had positive surgical margins. Meta-analysis revealed that preoperative PSA (OR=1.77, 95%CI: 1.18-2.65), percentage of positive biopsy cores (OR=1.83, 95%CI: 1.35-2.47), number of positive biopsy cores (OR=2.17, 95%CI: 0.98-4.80), biopsy Gleason score (OR=2.14, 95%CI: 1.67-2.74), perineural invasion on biopsy (OR=5.83, 95%CI: 2.05-16.59), preoperative clinical T stage (OR=2.17, 95%CI: 1.06-4.42), postoperative pathological T stage (OR=4.30, 95%CI: 2.43-7.63), and postoperative Gleason score (OR=2.33, 95%CI: 1.80-3.01) were significant risk factors for PSM after RP. Subgroup analysis by surgical approach showed that for laparoscopic radical prostatectomy (LRP), risk factors included preoperative PSA (OR=1.47, 95%CI: 0.42-5.09), number of positive biopsy cores (OR=2.17, 95%CI: 0.98-4.80), preoperative clinical T stage (OR=4.57, 95%CI: 2.57-8.12), postoperative pathologi-

cal T stage (OR=4.80, 95%CI: 2.20-10.48), and postoperative Gleason score (OR=2.46, 95%CI: 1.57-3.86). For robot-assisted laparoscopic radical prostatectomy (RARP), risk factors were preoperative PSA (OR=2.17, 95%CI: 1.60-2.94) and preoperative clinical T stage (OR=1.19, 95%CI: 0.52-2.74).

Conclusion: Positive surgical margin after radical prostatectomy involves multiple preoperative and postoperative factors that should be identified early in clinical practice to enable timely interventions for preventing tumor recurrence and progression.

Keywords: Prostatic Neoplasms; Radical Prostatectomy; Positive Surgical Margin; Risk Factors; Meta-Analysis

Introduction

Prostate cancer is one of the most common malignant tumors of the male genitourinary system. According to 2020 global cancer statistics, its incidence and mortality rank second and fifth, respectively, among all male malignancies worldwide [1]. In recent years, with population aging, improved living conditions, and advances in medical care, the incidence of prostate cancer in China has shown a significant upward trend, posing a serious threat to men' s health [2]. Radical prostatectomy (RP) remains the primary treatment for localized prostate cancer; however, some patients develop positive surgical margins (PSM) on pathological specimens. Studies have identified PSM as a high-risk indicator for postoperative biochemical recurrence (BCR) and a significant predictor of poor prognosis [3,4]. Therefore, investigating the risk factors for PSM is crucial for reducing adverse prognostic outcomes.

Currently, numerous studies have examined risk factors for PSM in Chinese populations, but no consensus has been reached. To address this gap, we conducted a meta-analysis to systematically evaluate the risk factors for PSM after RP in Chinese populations, aiming to provide evidence-based guidance for clinical treatment and prognosis assessment.

1. Materials and Methods

1.1 Literature Search Strategy

We systematically searched PubMed, EMbase, The Cochrane Library, Web of Science, CNKI, WanFang Data, CBM, and VIP databases for relevant literature published from inception to March 1, 2022. Additionally, we manually reviewed the reference lists of included studies to identify supplementary articles. Chinese search terms included: radical prostatectomy, radical prostatectomy, positive margin, positive surgical margin, risk factors, and influencing factors. English search terms included: radical prostatectomy, prostatectomy, positive surgical margin, and risk factors. We combined Medical Subject Headings (MeSH) with

free-text terms in our search strategy. The detailed search strategy for each database is provided in Appendix 1.

1.2 Inclusion and Exclusion Criteria

Inclusion Criteria: (1) Study design: case-control studies; (2) Study population: Chinese patients who underwent radical prostatectomy, with the case group comprising patients with PSM and the control group comprising patients with negative surgical margins; (3) Outcome measure: positive surgical margin after RP.

Exclusion Criteria: (1) Reviews, meta-analyses, case reports, or animal studies; (2) Non-Chinese or non-English publications; (3) Duplicate publications; (4) Studies with incomplete or unusable data; (5) Studies of non-Chinese populations.

1.3 Literature Screening and Data Extraction

Two investigators independently screened literature, extracted data, and cross-checked results. Any discrepancies were resolved through consultation with a third reviewer. Screening involved initial review of titles and abstracts to exclude obviously irrelevant studies, followed by full-text review for final inclusion. Extracted data included: first author, publication year, study region, sample size, surgical approach, outcome measures, and key elements for bias risk assessment.

1.4 Quality Assessment of Included Studies

Two investigators independently assessed the risk of bias using the Newcastle-Ottawa Scale (NOS), which evaluates three domains: selection of exposed and unexposed cohorts, comparability of cohorts, and outcome assessment. Studies scoring $ $5 points out of a maximum of 9 were considered high-quality.

1.5 Statistical Analysis

We performed meta-analysis using Stata 16 software. For dichotomous data, odds ratios (OR) were used as effect measures, while for continuous data, mean differences (MD) were employed. Heterogeneity among studies was assessed using the ^{2} test (with α=0.1) and I^2 statistic. In the absence of significant heterogeneity, a fixed-effects model was applied; otherwise, a random-effects model was used after exploring sources of heterogeneity. The significance level for meta-analysis was set at α=0.05. Sensitivity analysis was conducted by sequentially removing individual studies to examine the impact on the pooled effect size.

2. Results

2.1 Literature Search Results

The initial search yielded 6,178 potentially relevant articles. After systematic screening, 21 case-control studies [5-25] involving 6,782 patients were included, of whom 2,028 had positive surgical margins. The literature screening process is illustrated in [Figure 1: see original paper]. The basic characteristics and quality assessment of included studies are summarized in .

Figure 1 Flow chart of literature screening
Note: The specific databases and number of retrieved articles were as follows: CNKI (n=117), VIP (n=20), WanFang Data (n=163), CBM (n=106), PubMed (n=1,159), EMbase (n=1,707), The Cochrane Library (n=233), and Web of Science (n=2,673).

Table 1 Basic characteristics and risk of bias assessment of included studies
Note: RARP = robot-assisted laparoscopic radical prostatectomy; LRP = laparoscopic radical prostatectomy; ORP = open radical prostatectomy; -= surgical approach not specified. Risk factors: 1 = preoperative PSA; 2 = percentage of positive biopsy cores; 3 = number of positive biopsy cores; 4 = biopsy Gleason score; 5 = preoperative clinical T stage; 6 = perineural invasion on biopsy; 7 = prostate transverse diameter; 8 = PI-RADS score; 9 = LMR (lymphocyte-to-monocyte ratio); 10 = open surgery (vs. LRP); 11 = high risk; 12 = postoperative Gleason score; 13 = postoperative pathological T stage; 14 = extracapsular extension; 15 = tumor volume; 16 = pathological perineural invasion; 17 = pelvic lymph node invasion; 18 = prostate volume; 19 = neoadjuvant therapy for T3 stage.

2.2 Meta-Analysis Results

The meta-analysis identified the following risk factors for PSM after RP in Chinese populations: preoperative PSA, percentage of positive biopsy cores, number of positive biopsy cores, biopsy Gleason score, perineural invasion on biopsy, preoperative clinical T stage, postoperative pathological T stage, and postoperative Gleason score. Detailed results are presented in , with forest plots shown in [Figure 2: see original paper].

Table 2 Meta-analysis of risk factors for PSM after RP in Chinese population

Figure 2 Forest plots of associations between risk factors and PSM after RP in Chinese population
Note: A: preoperative PSA; B: percentage of positive biopsy cores; C: number of positive biopsy cores; D: biopsy Gleason score; E: perineural invasion on biopsy; F: preoperative clinical T stage; G: postoperative pathological T stage; H: postoperative Gleason score.

2.2.1 Subgroup Analysis Subgroup analysis by surgical approach revealed different risk factor profiles. For laparoscopic radical prostatectomy (LRP),

significant risk factors included preoperative PSA (OR=1.47, 95%CI: 0.42-5.09), number of positive biopsy cores (OR=2.17, 95%CI: 0.98-4.80), preoperative clinical T stage (OR=4.57, 95%CI: 2.57-8.12), postoperative pathological T stage (OR=4.80, 95%CI: 2.20-10.48), and postoperative Gleason score (OR=2.46, 95%CI: 1.57-3.86). For robot-assisted laparoscopic radical prostatectomy (RARP), risk factors were preoperative PSA (OR=2.17, 95%CI: 1.60-2.94) and preoperative clinical T stage (OR=1.19, 95%CI: 0.52-2.74). Results are detailed in .

Table 3 Subgroup analysis of different risk factors by surgical approach

2.3 Sensitivity Analysis

We compared results from fixed-effects and random-effects models, which showed similar pooled effect sizes, indicating robust findings (see). For risk factors with substantial heterogeneity (I^2 \$ $50^{\{2\}=0, P=0.625)withapooledORof2.31(95}\{2\}=8.4^{\{2\}=49.3}\{2\}=0, P=0.451)withapooledORof1.95(95\hat{}\{2\}$=39.0%, P=0.146) with a pooled OR of 3.77 (95%CI: 2.58-5.51).

Table 4 Sensitivity analysis of risk factors for PSM after RP in Chinese population

2.4 Publication Bias Assessment

Funnel plot analysis was performed for risk factors with sufficient studies (preoperative PSA, preoperative clinical T stage, postoperative pathological T stage, and postoperative Gleason score), showing generally symmetrical distributions. Egger' s test for the two most frequently studied risk factors (preoperative PSA and postoperative pathological T stage) revealed P<0.05, suggesting potential publication bias, likely related to the limited number of studies for each risk factor.

3. Discussion

Recent cancer statistics in China indicate that prostate cancer has become one of the fastest-growing malignancies in terms of both incidence and mortality among Chinese men [2]. Therefore, prevention and treatment of prostate cancer are crucial for reducing disease burden. Positive surgical margin after RP significantly impacts surgical outcomes, and early identification of risk factors —given their multifactorial nature spanning preoperative and postoperative domains—can substantially improve recurrence and progression outcomes.

This meta-analysis integrated 21 studies on risk factors for PSM after RP in Chinese populations. Our findings demonstrate that risk factors include preoperative PSA, percentage of positive biopsy cores, number of positive biopsy cores, biopsy Gleason score, perineural invasion on biopsy, preoperative clinical T stage, postoperative pathological T stage, and postoperative Gleason score.

PSA is a kallikrein-like serine protease composed of 237 amino acid residues, secreted by prostate acinar and ductal epithelial cells. Under normal conditions, most PSA is excreted with semen, with only a small amount entering the circulation. Prostate inflammation or cancer can disrupt the prostate barrier, leading to increased PSA release into the bloodstream [26]. Studies have shown that PSA levels exceeding 10 ng/ml significantly increase PSM risk, consistent with our findings [27]. Additionally, PSA levels correlate with outcomes of salvage radiotherapy and antiandrogen therapy after prostatectomy [28]. As the only widely recognized biomarker for prostate cancer diagnosis, PSA plays a critical role in prevention and treatment [29].

The number and percentage of positive biopsy cores are important indicators for predicting prostate volume and indirectly reflect tumor size. More positive biopsy cores suggest larger tumor volume and higher likelihood of PSM. Tuliao et al. [30] reported that in small prostates, the number of positive biopsy cores better predicts PSM. While the percentage of positive cores may have greater clinical value by adjusting for total biopsy cores [15], our results showed a larger effect size for absolute number of positive cores, possibly due to the limited number of included studies for each factor.

Perineural invasion (PNI) on biopsy is a histopathological marker indicating that cancer cells may extend beyond the surgical margin [31]. A meta-analysis evaluating PNI on prostate biopsy as a predictor of PSM after RP confirmed this association [32], consistent with our findings.

Both preoperative clinical and postoperative pathological T stages were identified as risk factors, aligning with most included studies. Higher T stage indicates tumor extension beyond the prostate capsule, increasing surgical difficulty and PSM risk. Wang et al. [24] reported that preoperative clinical stages T3a and T3b conferred PSM risks of 5.116 (95%CI: 1.014–25.802, P=0.048) and 9.194 (95%CI: 1.798–47.017, P=0.008), respectively. Similarly, Gong et al. [33] found higher postoperative pathological stage correlated with increased PSM risk.

The Gleason score is a widely used histological grading system for prostate cancer with important diagnostic, prognostic, and predictive value. Higher Gleason scores indicate worse prognosis and greater PSM likelihood. Liang et al. [34] found that postoperative Gleason score >7 conferred a 4-fold higher PSM risk (95%CI: 1.911–8.849, P=0.001) compared to $ $7, and was an independent predictor of biochemical recurrence (HR=1.920, 95%CI: 1.384–2.665, P=0.001).

Subgroup analysis by surgical approach revealed different risk factor profiles, with preoperative PSA and clinical T stage being common risk factors for both LRP and RARP, highlighting the importance of preoperative factors in prostate cancer prognosis. Given that many Chinese patients are diagnosed at advanced stages, enhanced screening and early diagnosis are essential for PSM prevention.

This study has several limitations: (1) Some included studies had relatively low quality scores, potentially introducing unavoidable bias; (2) Certain risk factors were examined in only a few studies, and funnel plot analysis suggested possible

selection bias, which may affect result accuracy; (3) As all included studies were case-control designs, various biases inherent to this study design cannot be eliminated. Future multicenter, large-scale prospective studies are needed to further clarify risk factors for PSM after RP.

In conclusion, preoperative PSA, percentage of positive biopsy cores, number of positive biopsy cores, biopsy Gleason score, perineural invasion on biopsy, preoperative clinical T stage, postoperative pathological T stage, and postoperative Gleason score are significant risk factors for PSM after RP in Chinese populations. Patients undergoing RP require careful risk assessment and appropriate interventions to reduce PSM rates, decrease biochemical recurrence, and improve quality of life.

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Appendix 1: Search Strategy (Example for PubMed)

#1 ("Prostatectomy" [Title/Abstract] OR "Prostatectomies" [Title/Abstract] OR "suprapubic prostatectomy" [Title/Abstract] OR "suprapubic prostatectomies" [Title/Abstract] OR "retropubic prostatectomy" [Title/Abstract] OR "retropubic prostatectomies" [Title/Abstract] OR "radical prostatectomy" [Title/Abstract] OR (("radical" [All Fields] OR "radical's" [All Fields] OR "radicals" [All Fields]) AND ("resect" [All Fields] OR "resectability" [All Fields] OR "resectable" [All Fields] OR "resectates" [All Fields] OR "resected" [All Fields] OR "resecting" [All Fields] OR "Resection" [All Fields] OR "resectional" [All Fields] OR "resectioned" [All Fields] OR "resectioning" [All Fields] OR "resections" [All Fields] OR "resective" [All Fields] OR "resects" [All Fields]) AND "prostate cancer" [Title/Abstract]))

#2 ("positive margin" [Title/Abstract] OR "positive excision margins" [Title/Abstract] OR "margins of excision" [Title/Abstract] OR "excision margin" [Title/Abstract] OR "excision margins" [Title/Abstract] OR "resection margin" [Title/Abstract] OR "resection margins" [Title/Abstract] OR "surgical margins" [Title/Abstract] OR "surgical margin" [Title/Abstract] OR "positive surgical margins" [Title/Abstract] OR "positive surgical margin" [Title/Abstract] OR "negative surgical margins" [Title/Abstract] OR "negative surgical margin" [Title/Abstract] OR "tumor free margins" [Title/Abstract] OR "tumor free margin" [Title/Abstract])

#3 ("Risk factors" [Title/Abstract] OR "social risk factors" [Title/Abstract] OR "social risk factor" [Title/Abstract] OR "health correlates" [Title/Abstract] OR "population at risk" [Title/Abstract] OR "populations at risk" [Title/Abstract] OR "risk scores" [Title/Abstract] OR "risk score" [Title/Abstract] OR "risk factor scores" [Title/Abstract] OR "risk factor score" [Title/Abstract] OR "dangerous factor" [Title/Abstract] OR "hazardous factors" [Title/Abstract] OR "risky factors" [Title/Abstract] OR "risks factors" [Title/Abstract] OR "Risk-factors" [Title/Abstract] OR "danger factor" [Title/Abstract] OR "hazard factors" [Title/Abstract] OR "Factor" [Title/Abstract] OR "Factors" [Title/Abstract] OR "elements" [Title/Abstract] OR "element" [Title/Abstract])

#4 #1 AND #2 AND #3

Note: Figure translations are in progress. See original paper for figures.