Systematic Review

Clinicopathological Significances of Positive Surgical Resection Margin after Radical Prostatectomy for Prostatic Cancers: A Meta-Analysis

Minseok Kim 1,†, Daeseon Yoo 2,†, Jungsoo Pyo 3 and Wonjin Cho 1,*

1 Department of Urology, Chosun University Hospital, Chosun University School of Medicine, Gwangju 61453, Korea
2 Department of Urology, Daejeon Eulji University Hospital, Eulji University School of Medicine, Daejeon 35233, Korea
3 Department of Pathology, Uijeongbu Eulji University Hospital, Eulji University School of Medicine, Uijeongbu 11759, Korea
* Correspondence: uro2097@gmail.com; Tel.: +82-62-220-3210
† These authors contributed equally to this work.

Abstract: Background and Objectives: This study aims to elucidate the positive rate and the clinicopathological significance of surgical margin after radical prostatectomy (RP) through a meta-analysis. Materials and Methods: This meta-analysis finally used 59 studies, including the information about the positive surgical margin (PSM) and those clinicopathological significances after RP. The subgroup analysis for the estimated rates of PSM was evaluated based on types of surgery, grade groups, and pathological tumor (pT) stages. We compared the clinicopathological correlations between positive and negative surgical margins (NSM). Results: The estimated PSM rate was 25.3% after RP (95% confidence interval [CI] 21.9–29.0%). The PSM rates were 26.0% (95% CI 21.5–31.1%) and 28.0% (95% CI 20.2–37.5%) in robot-assisted RP and nerve-sparing RP, respectively. The PSM rate was significantly higher in high-grade groups than in low-grade groups. In addition, the higher pT stage subgroup had a high PSM rate compared to the lower pT stage subgroups. Patients with PSM showed significantly high PSA levels, frequent lymphovascular invasion, lymph node metastasis, and extraprostatic extension. Biochemical recurrences (BCRs) were 28.5% (95% CI 21.4–36.9%) and 11.8% (95% CI 20.2–37.5%) in robot-assisted RP and nerve-sparing RP, respectively. The PSM rate was significantly higher in high-grade groups than in low-grade groups. In addition, the higher pT stage subgroup had a high PSM rate compared to the lower pT stage subgroups. Patients with PSM showed significantly high PSA levels, frequent lymphovascular invasion, lymph node metastasis, and extraprostatic extension. Biochemical recurrences (BCRs) were 28.5% (95% CI 21.4–36.9%) and 11.8% (95% CI 21.4–36.9%) in high and low-grade subgroups, respectively. Patients with PSM showed worse BCR-free survival than those with NSM (hazard ratio 2.368, 95% CI 2.043–2.744%). Conclusions: Our results showed that PSM was significantly correlated with worse clinicopathological characteristics and biochemical recurrence-free survival. Among the results in preoperative evaluations, grade group and tumor stage are useful for the prediction of PSM.

Keywords: biochemical recurrence; meta-analysis; prostatic cancer; surgical margin

1. Introduction

Prostate cancer was the most diagnosed cancer in men, and it was reported as the fourth most diagnosed cancer in the entire population [1]. Radical prostatectomy (RP) is one of the most effective and most used treatment methods for patients with localized prostate cancer. The surgical techniques have been developed from open RP in the 20th century to laparoscopic surgery and robotic surgery in recent decades [2,3]. There was no statistically significant difference in surgical, oncological, and functional results between these surgical techniques [4]. Despite advances in surgical procedures, 30% of patients undergoing RP still experience biochemical recurrence (BCR) [5]. In addition, in some cases in 20–30% of prostatic cancers progress to metastatic cancer and die [6]. A positive surgical margin (PSM) means that cancer cells are found at the surgical margin in the pathologic specimen after RP. The neurovascular bundle, bladder neck, and distal urethral sphincter
are preserved to maintain urinary continence and erectile function, increasing the risk of PSM [7]. It has been reported that the operator’s surgical skills affect PSM or BCR in open or laparoscopic RP, but a recent large scale retrospective study showed that the surgical learning curve had no effect in robot-assisted radical prostatectomy [8,9]. The rate of PSM after RP was reported to occur at about 11 to 38% [10]. Previous studies have reported on the impacting factors causing BCR after RP, and among them, several studies have been published on the relevance of PSM. Although several studies have shown that patients with PSM after RP have a worse prognosis than those without PSM [11], some discrepancies in the clinicopathological significance of PSM are present. PSM is associated with BCR, prostate cancer survival rate, and distant metastasis [12,13]. However, some studies have reported that PSM is not significantly related to the patient’s oncological prognosis [14] and Dev, Harveer S., et al. reported that the length of PSM and apical PSM were related to BCR [15].

We performed this study to elucidate the positive rate and the clinicopathological significance of surgical margin after RP through a meta-analysis. In addition, a subgroup analysis, based on types of surgery, grade groups, and pathological tumor (pT) stages, was conducted in the present study.

2. Materials and Methods

2.1. Published Study Search and Selection Criteria

The literature search was performed using the PubMed and MEDLINE databases through 30 June 2020. The search was performed using the following keywords: “(prostate or prostatic) and (cancer or adenocarcinoma)” and “(radical prostatectomy)” and “(positive surgical margin).” The titles and abstracts of searched articles were primarily screened for exclusion. PICO (population, intervention, comparator, outcomes) was defined as, (1) population: patients with prostatic cancer; (2) intervention: RP; (3) comparator: the presence of PSM; and (4) outcomes: the rate of PSM and BCR-free survival. Literature or systematic review articles were also screened to find additional eligible studies. The inclusion and exclusion criteria were as follows: (1) studies for PSM after RP were included, and (2) non-original articles, such as case reports or review articles were excluded.

2.2. Data Extraction

For the meta-analysis, data were extracted in the eligible studies as follows [7,16–73]: the first author’s name, study location, study year, type of surgery, number of patients analyzed, patients’ age, prostate-specific antigen (PSA), and rates of lymphovascular invasion, perineural invasion, lymph node metastasis, and extraprostatic extension. In addition, biochemical-free recurrence and survival rate by the positivity of surgical margins were extracted from eligible studies. For the quantitative aggregation of survival results, the correlation between PSM and survival rate was analyzed according to the hazard ratio (HR), using one of three methods. In studies not reporting the HR or its confidence interval (CI), these variables were calculated from the presented data using the HR point estimate, log-rank statistic or its p-value, and the O-E statistic (the difference between the number of observed and expected events) or its variance. If those data were unavailable, the HR was estimated using the total number of events, the number of patients at risk in each group, and the log-rank statistic or its p-value. Finally, if the only useful data were in the form of graphical representations of survival distributions, survival rates were extracted at specified times to reconstruct the HR estimate and its variance under the assumption that patients were censored at a constant rate during the time intervals. The published survival curves were evaluated independently by two authors to reduce variability. The HRs were then combined into an overall HR using Peto’s method [74].

2.3. Statistical Analyses

To perform a meta-analysis, the Comprehensive Meta-Analysis software package was used (Biostat, Englewood, NJ, USA). The PSM rates after RP were investigated from overall
cases. The PSM rates based on types of surgery were obtained and calculated through subgroup analysis. In addition, the estimated rates of PSM according to grade group and pT stages were investigated. We compared various characteristics, including age, PSA, lymphovascular invasion, perineural invasion, lymph node metastasis, extraprostatic extension, and biochemical recurrence between patients with PSM and NSM. In this meta-analysis, among fixed and random effect models, interpretation was made using the values of a random-effects model. Heterogeneity between eligible studies was assessed using Q and I² statistics and presented using p-values. In addition, the sensitivity analysis was conducted to assess the heterogeneity of eligible studies and the impact of each study on the combined effect. Statistical significances between subgroups were evaluated through a meta-regression test. To consider the publication bias, Egger’s test was used. If significant publication bias was found, the fail-safe N and trim-fill tests were performed to confirm the degree of publication bias. p-value < 0.05 was considered significant.

3. Results
3.1. Selection and Characteristics of Studies

A total of 436 studies were identified in the database, searching for the meta-analysis. Finally, 59 studies were selected according to the inclusion and exclusion criteria. Among the searched studies, 300 studies were excluded due to a lack of sufficient information. In addition, 75 reports were excluded due to being articles in a language other than English (n = 39) and non-original articles (n = 36). Two remaining reports were excluded as they focused on other diseases (Figure 1). The characteristics of the eligible studies are shown in Table 1.

![Flow chart](Figure 1. Flow chart.)
Table 1. Main characteristics of the eligible studies.

| Location      | Operation       | No of Patients | Location | Operation  | No of Patients |
|---------------|-----------------|----------------|----------|------------|----------------|
|               |                 |                | Total PSM Total PSM |                |                |
| Albisinni 2018 [16] | Belgium | Mixed          | 539 127 | Poon 2000 | USA | Non-robot | 220 64 |
| Bianco 2003 [18] | USA | Non-robot      | 4073 257 | Porcaro 2018 | Italy | Mixed | 476 327 |
| Cangiano 1999 [19] | USA | Non-robot | 319 127 | Foulakis 2006 | Germany | Non-robot | 182 31 |
| Cannon 2005 [20] | USA | Non-robot | 402 257 | Preisser 2019 (a) | Germany | Mixed | 8770 579 |
| Ceylan 2016 [21] | Turkey | Non-robot | 130 93 | Preston 2015 | Canada | Mixed | 6120 848 |
| Dae 2019 [22] | China | Mixed | 531 160 | Rabbani 1998 | USA | Non-robot | 241 85 |
| Eastham 2007 [23] | USA | Non-robot | 25 64 | Rosen 1992 | USA | Non-robot | 144 33 |
| Furubayashi 2014 [24] | Japan | ND | 275 56 | Sachdeva 2017 | UK | Mixed | 592 181 |
| Ginzburg 2012 [25] | USA | Robot-assisted | 1595 316 | Salomon 2003 | USA | Non-robot | 371 66 |
| Holleman 2020 [28] | Netherlands | ND | 835 284 | Soulier 2001 | France | Non-robot | 212 71 |
| Jo 2017 [29] | Korea | Robot-assisted | 815 270 | Stephens 1997 | USA | Non-robot | 53 7 |
| Jones 1990 [30] | Canada | Non-robot | 199 92 | Takahara 2019 | Japan | Robot-assisted | 230 52 |
| Kang 2017 [31] | Korea | ND | 1600 760 | Tan 1993 | Puerto Rico | Mixed | 45,426 4522 |
| Keller 2019 [7] | Switzerland | Robot-assisted | 973 315 | Tatsugami 2017 | Japan | Robot-assisted | 3469 916 |
| Kim 2018 [32] | Korea | Mixed | 461 50 | Tian 2019 | China | Non-robot | 418 142 |
| Keizumi 2018 [33] | Japan | Mixed | 450 64 | Trabulsi 2009 | USA | Robot-assisted | 240 38 |
| Konety 2004 [34] | Korea | Non-robot | 33 8 | van den Ouden 1993 | Netherlands | Non-robot | 172 56 |
| Lee 2016 [35] | Korea | ND | 1733 473 | Villers 2000 | USA | ND | 400 111 |
| Menard 2006 [36] | France | Non-robot | 640 180 | Vis 2006 | Netherlands | ND | 281 66 |
| Meyer 2017 [37] | Germany | ND | 903 118 | Wolaysek 2018 | ND | Mixed | 107 29 |
| Mitsuzuka 2013 [38] | Japan | Non-robot | 1268 307 | Ward 2004 | USA | ND | 7268 2103 |
| Miyake 2011 [39] | Japan | Non-robot | 172 14 | Weldon 1995 | USA | Non-robot | 200 85 |
| Pak 2019 [40] | Korea | ND | 2013 484 | Wu 2019 | USA | ND | 2796 476 |
| Palisaar 2005 [41] | Germany | ND | 1343 264 | Yamada 2020 | Japan | Robot-assisted | 614 144 |
| Park 2003 [42] | USA | Non-robot | 221 43 | Yu 2018 | Korea | Mixed | 3224 461 |
| Park 2018 [43] | Korea | Mixed | 546 179 | Yuksel 2017 | Turkey | Mixed | 140 46 |
| Partin 1993 [44] | USA | Non-robot | 107 50 |                   |                |                |

No, number; PSM, positive surgical margin. * included duplicated patients [7,16–44].

3.2. The Positive Surgical Margin Rates after Radical Prostatectomy

The PSM rates ranged from 6.2 to 71.5% in the eligible studies. The estimated rate of PSM after RP was 25.3% (95% CI 21.9–29.0%) (Table 2). The robot-assisted RP subgroup showed 26.0% (95% CI 21.5–31.1%) the PSM rate. The PSM rates were 28.0% (95% CI 20.2–37.5%) and 30.1% (95% CI 26.8–33.6%) in nerve-sparing and non-nerve-sparing subgroups, respectively. Cases with the intraoperative frozen section showed 19.3% (95% CI 12.2–29.1%). However, the PSM rate of cases without the intraoperative frozen section was 29.5% (95% CI 23.4–36.3%).

Table 2. The estimated rates of positive surgical margin after radical prostatectomy in prostatic cancers.

| Number of Subsets | Fixed Effect [95% CI, %] | Heterogeneity Test [p-Value] | Random Effect [95% CI, %] | Egger's Test [p-Value] | Meta-Regression Test [p-Value] |
|-------------------|--------------------------|-----------------------------|---------------------------|------------------------|-------------------------------|
| Overall           | 20.2 [19.9, 20.5]        | <0.001                      | 25.3 [21.9, 29.0]         | 0.005                  | 0.688 *                      |
| Robot-assisted    | 26.9 [26.1, 27.7]        | <0.001                      | 26.0 [21.5, 31.1]         | 0.726                  | -                             |
| Others            | 26.5 [25.6, 27.4]        | <0.001                      | 27.2 [22.2, 32.7]         | 0.471                  | -                             |
| Nerve-sparing     | 24.5 [23.7, 25.2]        | <0.001                      | 28.0 [20.2, 37.5]         | 0.661                  | 0.580 †                      |
| Non-nerve-sparing | 29.4 [28.4, 30.3]        | <0.001                      | 30.1 [26.6, 33.6]         | 0.753                  | -                             |
| Intraoperative frozen | 19.1 [14.7, 24.5] | 0.087                      | 19.3 [12.2, 26.9]         | 0.577                  | -                             |
| Non-intraoperative frozen | 29.5 [23.4, 36.3] | 1.000                      | 29.5 [23.4, 36.3]         | -                      | -                             |

CI: confidence interval. * Comparison between robot-assisted and other radical prostatectomy. † Comparison between nerve-sparing and non-nerve-sparing radical prostatectomy.

PSM rates were 10.0% (95% CI 6.8–14.6%), 17.6% (95% CI 9.3–30.8%), 24.1% (95% CI 11.9–42.8%), 21.6% (95% CI 19.7–38.8%), and 36.2% (95% CI 11.3–71.7%) in grade groups 1, 2, 3, 4, and 5, respectively (Table 3). In a subgroup analysis based on pT stage, PSM rates were 13.5% (95% CI 10.2–17.7%), 41.4% (95% CI 33.4–49.8%), and 65.1% (95% CI 32.6–87.8%) in pT2, pT3, and pT3 stages, respectively. The multifocality of PSM was estimated at 30.9% (95% CI 22.9–40.1%). The apical PSM rate was 28.9% (95% CI 23.1–35.5%) after RP.
Table 3. Detailed analysis of the estimated rates of positive surgical margin after radical prostatectomy in prostatic cancers.

| Number of Subsets | Fixed Effect [95% CI, %] | Heterogeneity Test [p-Value] | Random Effect [95% CI, %] | Egger's Test [p-Value] | Meta-Regression Test [p-Value] |
|-------------------|---------------------------|------------------------------|---------------------------|-----------------------|------------------------------|
| Grade group       |                           |                              |                           |                       |                              |
| GG1 (Gleason score ≤ 6) | 10 | 8.2 [7.8, 8.6] | <0.001 | 10.0 [6.8, 14.6] | 0.535 | Ref. |
| GG2 (Gleason score 3 + 4) | 7  | 17.4 [16.1, 18.8] | <0.001 | 17.6 [9.3, 30.8] | 0.918 | 0.100 |
| GG3 (Gleason score 4 + 3) | 6  | 22.7 [20.3, 25.3] | <0.001 | 24.1 [11.9, 42.8] | 0.995 | **0.010** |
| GG4/5 (Gleason score ≥8) | 8  | 15.5 [14.4, 16.6] | <0.001 | 26.8 [16.8, 40.1] | 0.078 | **0.001** |
| GG4 (Gleason score 8) | 4  | 13.0 [11.8, 14.3] | <0.001 | 21.6 [10.7, 36.8] | 0.230 | 0.036 |
| GG5 (Gleason score 9/10) | 4  | 17.5 [15.0, 20.2] | <0.001 | 36.2 [11.3, 71.7] | 0.307 |                              |
| pT stage          |                           |                              |                           |                       |                              |
| pT2               | 17 | 13.8 [13.2, 14.5] | <0.001 | 13.5 [10.2, 17.7] | 0.991 | Ref. |
| pT3               | 15 | 34.5 [33.2, 35.7] | <0.001 | 41.4 [33.4, 49.8] | 0.119 | <0.001 |
| pT4               | 3  | 65.1 [32.6, 87.8] | 0.561 | 65.1 [32.6, 87.8] | 0.064 | 0.002 |
| Multifocal PSM rate | 10 | 29.0 [27.3, 30.8] | <0.001 | 30.9 [22.9, 40.1] | 0.370 |                              |
| Apical PSM rate   | 11 | 25.0 [238.0, 263.0] | <0.001 | 289 [231.0, 355.0] | 0.173 |                              |

CI: confidence interval; PSM: positive surgical margin; Ref: reference.

3.3. Comparison of Clinicopathological Characteristics between PSM and NSM

Next, the clinicopathological characteristics were compared between PSM and NSM. The mean PSA levels of PSM and NSM were 9.190 (95% CI 8.284–10.095) and 7.360 (95% CI 6.927–7.793), respectively (Table 4). There was a significant difference in mean PSA level between PSM and NSM (p < 0.001 in a meta-regression test). In addition, the lymphovascular invasion was significantly higher in the PSM subgroup than in the NSM subgroup (36.8%, 95% CI 29.4–45.0% vs. 25.6%, 95% CI 23.1–28.3%). Rates of lymph node metastasis were 9.7% (95% CI 5.9–15.6%) and 2.3% (95% CI 1.1–4.7%) in PSM and NSM subgroups, respectively. Extraprostatic extension was more frequently found in the PSM subgroup than in the NSM subgroup (63.9%, 95% CI 52.0–74.3% vs. 23.2%, 95% CI 15.0–34.1%; p < 0.001 in a meta-regression test). However, there was no significant difference in the patient’s age and perineural invasion between PSM and NSM.

Table 4. Comparisons of clinicopathological parameters between positive and negative surgical margins after radical prostatectomy in prostatic cancers.

| Number of Subsets | Fixed Effect [95% CI, %] | Heterogeneity Test [p-Value] | Random Effect [95% CI, %] | Egger’s Test [p-Value] | Meta-Regression Test [p-Value] |
|-------------------|---------------------------|------------------------------|---------------------------|-----------------------|------------------------------|
| Age (years)       |                           |                              |                           |                       |                              |
| PSM               | 12 | 64.427 [64.341, 64.514] | <0.001 | 64.291 [63.149, 65.432] | 0.787 | 0.970 |
| NSM               | 9  | 63.492 [63.459, 63.523] | <0.001 | 64.273 [63.081, 65.465] | 0.416 |                              |
| PSA (ng/mL)       | 10 | 8.368 [8.312, 8.425] | <0.001 | 9.190 [8.284, 10.095] | 0.234 | <0.001 |
| NSM               | 8  | 6.867 [6.853, 8.881] | <0.001 | 7.360 [6.927, 7.793] | 0.424 |                              |
| Lymphovascular invasion (%) | 2  | 36.8 [29.4, 45.0] | 0.470 | 36.8 [29.4, 45.0] | - | 0.005 |
| PSM               | 2  | 25.6 [21.6, 28.3] | 0.710 | 25.6 [23.1, 28.3] | - | 0.005 |
| NSM               | 2  | 25.6 [21.6, 28.3] | 0.710 | 25.6 [23.1, 28.3] | - | 0.005 |
| Perineural invasion (%) | 2  | 24.5 [17.0, 33.9] | <0.001 | 41.2 [6.7, 83.7] | 0.483 | 0.997 |
| PSM               | 2  | 27.6 [20.8, 35.7] | <0.001 | 41.7 [4.5, 91.5] | - | 0.005 |
| NSM               | 2  | 27.6 [20.8, 35.7] | <0.001 | 41.7 [4.5, 91.5] | - | 0.005 |
| Lymph node metastasis (%) | 6  | 9.1 [7.4, 11.3] | 0.001 | 9.7 [5.9, 15.6] | 0.745 | <0.001 |
| PSM               | 6  | 3.8 [3.2, 4.6] | <0.001 | 2.3 [1.1, 4.7] | 0.168 |                              |
| NSM               | 6  | 3.8 [3.2, 4.6] | <0.001 | 2.3 [1.1, 4.7] | 0.168 |                              |
| Extraprostatic extension (%) | 3  | 61.7 [57.5, 65.7] | 0.009 | 63.9 [52.0, 74.3] | 0.413 | <0.001 |
| PSM               | 3  | 26.6 [25.0, 28.3] | <0.001 | 23.2 [15.0, 34.1] | 0.620 | <0.001 |
| NSM               | 3  | 26.6 [25.0, 28.3] | <0.001 | 23.2 [15.0, 34.1] | 0.620 | <0.001 |

CI: confidence interval; PSM: positive surgical margin; NSM: negative surgical margin.
3.4. Comparison of Biochemical Recurrence and Biochemical Recurrence-Free Survival between PSM and NSM

Rates of biochemical recurrence (BCR) were 28.5% (95% CI 21.4–36.9%) and 11.8% (95% CI 8.1–16.9%) in the PSM and NSM subgroups, respectively. There was a significant difference in BCR between the PSM and NSM subgroups ($p < 0.001$ in a meta-regression test). Comparing BCR-free survival, the PSM subgroup had a worse BCR-free survival rate than the NSM subgroup (hazard ratio 2.368, 95% CI 2.043–2.744; Figure 2).

![Figure 2. Forest plot for BCR-free survival between PSM and NSM.](image)

### Table 4. Comparisons of clinicopathological parameters between positive and negative surgical margins

| Study name          | Subgroup within study | Statistics for each study | Hazard ratio and 95% CI |
|---------------------|-----------------------|---------------------------|-------------------------|
| Furubayashi 2014    | PSM vs. NSM           | **3.329, 1.735, 6.047**   | **0.000**               |
| Golabeck 2014       | PSM vs. NSM           | **4.115, 2.306, 7.067**   | **0.000**               |
| Hashine 2012        | PSM vs. NSM           | **3.313, 2.314, 4.744**   | **0.000**               |
| Jo 2017             | Apical PSM vs. NSM    | **1.951, 1.300, 1.947**   | **0.000**               |
| Kang 2017           | PSM vs. NSM           | **2.125, 1.775, 2.544**   | **0.000**               |
| Keifer 2019         | mPSM vs. NSM          | **4.500, 3.787, 7.266**   | **0.000**               |
| Keifer 2019         | uPSM vs. NSM          | **2.500, 1.822, 3.853**   | **0.000**               |
| Kim 2016            | PSM vs. NSM           | **3.607, 1.863, 7.728**   | **0.001**               |
| Lee 2016            | PSM vs. NSM           | **1.224, 0.695, 2.158**   | **0.000**               |
| Lee 2016            | mPSM vs. NSM          | **2.362, 1.823, 3.437**   | **0.000**               |
| Lee 2016            | PSM vs. NSM           | **2.811, 2.000, 3.836**   | **0.000**               |
| Meyer 2017          | PSM vs. NSM           | **2.450, 1.847, 3.344**   | **0.000**               |
| Mitsuoka 2015       | PSM vs. NSM           | **2.420, 1.793, 3.267**   | **0.000**               |
| Pak 2019            | PSM vs. NSM           | **2.306, 1.864, 2.818**   | **0.000**               |
| Palisaar 2005       | PSM vs. NSM           | **1.400, 1.073, 1.726**   | **0.013**               |
| Presser 2019        | PSM vs. NSM           | **2.490, 1.821, 3.162**   | **0.000**               |
| Sachdeva 2017       | PSM vs. NSM           | **1.669, 0.890, 3.160**   | **0.000**               |
| Takahara 2019       | PSM vs. NSM           | **2.330, 1.912, 2.946**   | **0.000**               |
| Vis 2008            | PSM vs. NSM           | **4.231, 2.150, 9.285**   | **0.000**               |
| Ward 2004           | PSM vs. NSM           | **1.560, 1.399, 1.739**   | **0.000**               |

4. Discussion

RP is the most common treatment option for localized prostatic cancers [75,76]. Microscopic examination of the RP specimen is performed for the entire prostate, including Gleason’s score, tumor extension, and surgical resection margin. After RP specimens, the presence of PSM is an important factor in predicting BCR and BCR-free survival [7,24,27,29,31,32,35,37,38,40,41,48,53,59,66,68]. However, in localized prostate cancer with PSM, the management after RP remains controversial [62]. If PSM is highly suggestive in the preoperative evaluation, it will be useful in establishing a treatment strategy and a postoperative follow-up. Previous studies have reported the correlation between PSM and clinicopathological characteristics by evaluating patients who underwent RP [7,16–73]. However, the conclusive information from the individual study is not fully understood. The present study is a meta-analysis to investigate the correlation between PSM and clinicopathological characteristics and BCR-free survival after RP.

In the previous studies, the PSM rate after RP had a wide range and was approximately 20% [62]. Radiologic examination may be the most effective tool for predicting PSM among preoperative evaluations. However, the prediction of PSM in preoperative evaluations is limited in daily practice. In the present meta-analysis, the estimated PSM rate was 25.3% (95% CI 21.9–29.0%). This estimation resulted from simple integration. PSM was correlated with pT stage [77], BMI [78], serum PSA level [79], cancer percentage in biopsy specimens [80,81], prostate weight [82], and tumor volume [83]. In pathologic examination, the Gleason score is evaluated for the overall tumor, regardless of the tumor portion at PSM. So, the interpretation of the correlation between the grade group and PSM can be limited. Coelho et al. [84] suggested that the clinical stage was the only independent factor for predicting PSM. Although previous studies have reported the predicting factors of PSM, the integrative evaluation is limited by various populations and surgical methods.
Therefore, a meta-analysis is more appropriate for obtaining detailed information. In addition, to obtain the detailed information, an additional subgroup analysis was needed. As expected, the PSM rate was significantly correlated with the higher grade group and pT stage in the present meta-analysis.

In the present study, clinicopathological characteristics were compared between patients with PSM and NSM. Patients with PSM had more frequent lymphovascular invasion than those with NSM. In addition, the rate of lymph node metastasis was significantly higher in the PSM subgroup than in the NSM subgroup. In cases with PSM, a precise microscopic examination is needed to detect the lymphovascular invasion because of hidden lymph nodes and distant metastasis. In addition, the comparison of BCR and BCR-free survival between PSM with and without lymphovascular invasion is needed. Porten et al. reported that tumor volume was associated with PSM [85]. Since tumor volume is associated with PSA level, the evaluation for the difference in PSA is needed. Patients with PSM had higher PSA levels than those with NSM (9.190 vs. 7.360). However, there were no significant differences in age and perineural invasion between PSM and NSM subgroups. These factors, age, and perineural invasion, are included in the characteristics of prostate cancer.

In eligible studies, BCR rates ranged from 10.7 to 46.0% in PC with PSM [21,24,28,29,37,38,53,67,73]. BCR was significantly correlated with the Gleason score, preoperative PSA, and pathologic stage [75]. BCR was significantly higher in cases with PSM than in cases with NSM (28.5 vs. 11.8%). In addition, patients with PSM showed a worse BCR-free survival than those with NSM (HR 2.368, 95% CI 2.043–2.744). Some report that there was no correlation between PSM and cancer-specific survival in long-term follow-up [86,87]. Chapin et al. reported that tumor location was not associated with BCR [75]. In our results, PSM at the apex was detected in 28.9% of overall PSM. However, the PSM rate could not be obtained by other tumor locations due to insufficient information. Further evaluation is needed on the impact of tumor location on BCR and BCR survival.

Recently, the application of robot-assisted RP has been increased in localized prostatic cancers. Previous studies have reported that PSM rates were low in robot-assisted RP specimens [62]. Robot-assisted RP showed a slightly low PSM rate compared to other RPs. However, there was no significant difference in PSM rate in a meta-regression test ($p = 0.688$). Nerve-sparing surgery can be applied to diminish complications after RP. However, because the neurovascular bundles are anatomically located adjacent to the prostate, the possibility of increasing PSM is present [56]. In the previous systematic review and meta-analysis, nerve-sparing surgery was not correlated with an increased risk of PSM in patients with pT2 tumors [88]. Interestingly, the risk of PSM increased in the pT3 stage with nerve-sparing surgery [88]. In the present study, the PSM rate was lower in the subgroup with nerve-sparing RP than in the subgroup without nerve-sparing RP (28.0 vs. 30.1%). This is probably because the non-nerve-sparing subgroup is more likely to have worse oncological factors such as tumor burden or high PSA levels, compared to the nerve-sparing subgroup. Therefore, despite the difference in the surgical method, it is believed that the PSM rate was lower in the nerve-sparing subgroup. We additionally performed a detailed analysis of the impact of the nerve-sparing technique on PSM based on the pT stage. However, unlike the previous study, there was no significant difference in PSM rate by application of the nerve-sparing technique in the same pT stage (data not shown). Theoretically, the impact of the intraoperative frozen section on reducing PSM rate is important. The rate of PSM was lower in the subgroup with the intraoperative frozen section than in the subgroup without the intraoperative frozen section (19.3 vs. 29.5%). However, a meta-regression test could not be performed due to an insufficient number of studies. Although the surgical resection margin is actually negative, PSM is detected by loss or cauterization of periprostatic tissue in the pathological examination. In addition, tumor locations, including lateral locations, can be considered.

This study has some limitations. First, the impact of the length of PSM could not be investigated due to insufficient information. The evaluation of the length of involved
PSM is recommended in the pathological examination for RP specimens [89]. Second, an additional analysis for the correlation with tumor multifocality, location, and volume is needed.

5. Conclusions

PSM was significantly correlated with frequent lymphovascular invasion, lymph node metastasis, BCR, and BCR-free survival. Patients with higher grade group and pT stage showed frequent PSM. Grade group and tumor stage in preoperative evaluations can be useful for predicting PSM. In addition, evaluating PSM will help establish a careful strategy for RP and postoperative follow-up observation.

Author Contributions: Conceptualization, M.K., D.Y. and W.C.; methodology, J.P.; software, J.P.; validation, M.K., D.Y., J.P. and W.C.; formal analysis, J.P. and W.C.; investigation, M.K., D.Y. and W.C.; resources, M.K. and D.Y.; data curation M.K. and D.Y.; writing—original draft preparation, M.K. and D.Y.; writing—review and editing, W.C.; visualization, J.P.; supervision, W.C.; project administration, W.C.; funding acquisition, W.C. All authors have read and agreed to the published version of the manuscript.

Funding: This study was supported by research funds from Chosun University, 2021.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The datasets generated during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest: The authors declare that they have no conflict of interest.

References

1. Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R.L.; Torre, L.A.; Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA A Cancer J. Clin. 2018, 68, 394–424. [CrossRef] [PubMed]
2. Binder, J.; Kramer, W. Robotically-assisted laparoscopic radical prostatectomy. BJU Int. 2001, 87, 408–410. [CrossRef] [PubMed]
3. Schuessler, W.W.; Schulam, P.G.; Clayman, R.V.; Kavoussi, L.R. Laparoscopic radical prostatectomy: Initial short-term experience. Urology 1997, 50, 854–857. [CrossRef]
4. De Carlo, F.; Celestino, F.; Verri, C.; Masedu, F.; Liberati, E.; Di Stasi, S.M. Retropubic, laparoscopic, and robot-assisted radical prostatectomy: Surgical, oncological, and functional outcomes: A systematic review. Urol. Int. 2014, 93, 373–383. [CrossRef]
5. Isbarn, H.; Wanner, M.; Salomon, G.; Steuber, T.; Schlomm, T.; Köllermann, J.; Sauter, G.; Haese, A.; Heinzer, H.; Huland, H. Long-term data on the survival of patients with prostate cancer treated with radical prostatectomy in the prostate-specific antigen era. BJU Int. 2010, 106, 37–43. [CrossRef]
6. Loeb, S.; Feng, Z.; Ross, A.; Trock, B.J.; Humphreys, E.B.; Walsh, P.C. Can we stop prostate specific antigen testing 10 years after radical prostatectomy? J. Urol. 2011, 186, 500–505. [CrossRef]
7. Keller, E.X.; Bachofner, J.; Britschgi, A.J.; Saba, K.; Mortezavi, A.; Kaufmann, B.; Fankhauser, C.D.; Wild, P.; Sulser, T.; Hermanns, T. Prognostic value of unifocal and multifocal positive surgical margins in a large series of robot-assisted radical prostatectomy for prostate cancer. World J. Urol. 2019, 37, 1837–1844. [CrossRef]
8. Bravi, C.A.; Dell’Oglio, P.; Mazzone, E.; Moschovas, M.C.; Falagario, U.; Piazza, P.; Scarcella, S.; Bednarz, C.; Sarchi, L.; Tapper, S. The surgical learning curve for biochemical recurrence after robot-assisted radical prostatectomy. Eur. Urol. Oncol. 2022. [CrossRef]
9. Bravi, C.A.; Tin, A.; Vertosick, E.; Mazzone, E.; Martini, A.; Dell’Oglio, P.; Stabile, A.; Gandaglia, G.; Fossati, N.; Suardi, N. The impact of experience on the risk of surgical margins and biochemical recurrence after robot-assisted radical prostatectomy: A learning curve study. J. Urol. 2019, 202, 108–113. [CrossRef]
10. Yossepowitch, O.; Bjartell, A.; Eastham, J.A.; Graefen, M.; Guillonneau, B.D.; Karakiewicz, P.I.; Montironi, R.; Montorsi, F. Positive surgical margins in radical prostatectomy: Outlining the problem and its long-term consequences. Eur. Urol. 2009, 55, 87–99. [CrossRef]
11. Hashimoto, T.; Yoshioka, K.; Horiguchi, Y.; Inoue, R.; Yoshio, O.; Nakashima, J.; Tachibana, M. Clinical effect of a positive surgical margin without extraprostatic extension after robot-assisted radical prostatectomy. In Urologic Oncology: Seminars and Original Investigations; Elsevier: Amsterdam, The Netherlands, 2015; Volume 503, pp. 503.e1–503.e6.
12. Chalfin, H.J.; Dinizo, M.; Trock, B.J.; Feng, Z.; Partin, A.W.; Walsh, P.C.; Humphreys, E.; Han, M. Impact of surgical margin status on prostate-cancer-specific mortality. BJU Int. 2012, 110, 1684–1689. [CrossRef]
13. Sammon, J.D.; Trinh, Q.-D.; Sukumaran, S.; Ravi, P.; Friedman, A.; Sun, M.; Schmitges, J.; Jeldres, C.; Jeong, W.; Mander, N. Risk factors for biochemical recurrence following radical perineal prostatectomy in a large contemporary series: A detailed assessment of margin extent and location. In Urologic Oncology: Seminars and Original Investigations; Elsevier: Amsterdam, The Netherlands, 2013; pp. 1470–1476. [CrossRef]

14. Mithal, P.; Howard, L.E.; Aronson, W.J.; Terris, M.K.; Cooperberg, M.R.; Kane, C.J.; Amling, C.; Freedland, S.J. Positive surgical margins in radical prostatectomy patients do not predict long-term oncological outcomes: Results from the Shared Equal Access Regional Cancer Hospital (SEARCH) cohort. BJU Int. 2016, 117, 244–248. [CrossRef]

15. Dev, H.S.; Wiklund, P.; Patel, V.; Parashar, D.; Palmer, K.; Nyberg, T.; Skarecky, D.; Neal, D.E.; Ahlerring, T.; Soorjakumaran, P. Surgical margin length and location affect recurrence rates after robotic prostatectomy. In Urologic Oncology: Seminars and Original Investigations; Elsevier: Amsterdam, The Netherlands, 2015; Volume 109, pp. 109.e7–109.e13.

16. Albisini, S.; Grosman, J.; Aoum, F.; Quackels, T.; Feltier, A.; Van Velthoven, R.; Roumeguère, T. Exploring positive surgical margins after minimally invasive radical prostatectomy: Does body habitus really make a difference? Prog. Urol. 2018, 28, 434–441. [CrossRef]

17. Aminsharifi, A.; Schulman, A.; Howard, L.E.; Tay, K.J.; Amling, C.L.; Aronson, W.J.; Cooperberg, M.R.; Kane, C.J.; Terris, M.K.; Freedland, S.J.; et al. Influence of African American race on the association between preoperative biopsy grade group and adverse histopathologic features of radical prostatectomy. Cancer 2019, 125, 3025–3032. [CrossRef] [PubMed]

18. Bianco, F.J.; Grignon, D.J.; Sakr, W.A.; Shekarziz, B.; Upadhyay, J.; Dornelles, E.; Pontes, J.E. Radical prostatectomy with bladder neck preservation: Impact of a positive margin. Eur. Urol. 2003, 43, 461–466. [CrossRef]

19. Cangiano, T.G.; Litwin, M.S.; Naitoh, J.; Dorey, F.; deKernion, J.B. Intraoperative frozen section monitoring of nerve sparing radical retropubic prostatectomy. J. Urol. 1999, 162 Pt 1, 655–658. [CrossRef]

20. Cannon, G.M., Jr.; Pound, C.R.; Landsittel, D.P.; Bastacky, S.I.; Dhir, R.; Becich, M.J.; Nelson, J.B. Perineural invasion in prostate cancer biopsies is not associated with higher rates of positive surgical margins. Prostate 2005, 63, 336–340. [CrossRef]

21. Ceylan, C.; Tonyali, S.; Keles, I. Impact of positive surgical margin on biochemical recurrence following radical prostatectomy in locally advanced prostate cancer. Kaohsiung J. Med. Sci. 2016, 32, 514–517. [CrossRef]

22. Dai, J.; Zhang, X.; Zhao, J.; Sun, G.; Chen, J.; Liu, J.; Tao, R.; Zeng, H.; Shen, P. The value of transperineal apical prostate biopsy in predicting urethral/apical margin status after radical prostatectomy. Medicine 2019, 98, e17633. [CrossRef]

23. Eastham, J.A.; Kuroiwa, K.; Ohori, M.; Serio, A.M.; Gorbonos, A.; Maru, N.; Vickers, A.J.; Slawin, K.M.; Wheeler, T.M.; Reuter, V.E.; et al. Prognostic significance of location of positive margins in radical prostatectomy specimens. Urology 2007, 70, 965–969. [CrossRef]

24. Furubayashi, N.; Negishi, T.; Hirata, Y.; Taguchi, K.; Shimokawa, M.; Nakamura, M. Positive resection margins may not reflect the true margin in patients undergoing radical prostatectomy. Oncol. Lett. 2014, 8, 2237–2242. [CrossRef] [PubMed]

25. Ginzburg, S.; Nevers, T.; Staff, I.; Tortora, J.; Champagne, A.; Kesler, S.S.; Laudone, V.P.; Wagner, J.R. Prostate cancer biochemical recurrence rates after robotic-assisted laparoscopic radical prostatectomy. JSLS 2012, 16, 443–450. [CrossRef] [PubMed]

26. Golabek, T.; Jaskulska, J.; Jarecki, P.; Dudek, P.; Szopiński, T.; Chłosta, P. Laparoscopic radical prostatectomy with bladder neck preservation: Positive surgical margin and urinary continence status. Wideochir Inne Technol. Maloinwazyjne 2014, 9, 362–370. [CrossRef] [PubMed]

27. Hashine, K.; Ueno, Y.; Shinomori, K.; Ninomiya, I.; Teramoto, N.; Yamashita, N. Correlation between cancer location and oncological outcome after radical prostatectomy. Int. J. Urol. 2012, 19, 855–860. [CrossRef]

28. Hollemans, E.; Verhoef, E.I.; Bangma, C.H.; Rietbergen, J.; Helleman, J.; Roobol, M.J.; van Leenders, G.J.L.H. Prostate carcinoma patients: A single institutional analysis. Jpn. J. Clin. Oncol. 2014, 44, 191–197. [CrossRef]

29. Jo, J.K.; Hong, S.K.; Byun, S.S.; Zargar, H.; Autorino, R.; Lee, S.E. Positive surgical margin in robot-assisted radical prostatectomy: Correlation with pathology findings and risk of biochemical recurrence. Minerva. Urol. Nefrol. 2017, 69, 493–500. [CrossRef]

30. Jones, C.E. Resection margin status in radical retropubic prostatectomy specimens: Relationship to type of operation, tumor size, tumor grade and local tumor extension. J. Urol. 1990, 144, 89–93. [CrossRef]

31. Kang, Y.J.; Kim, H.S.; Jang, W.S.; Kwon, J.K.; Yoon, C.Y.; Lee, J.Y.; Cho, K.S.; Ham, W.S.; Choi, Y.D. Impact of lymphovascular invasion on lymph node metastasis for patients undergoing radical prostatectomy with negative resection margin. BMC Cancer 2017, 17, 321. [CrossRef]

32. Kim, A.; Kim, M.; Jeong, S.U.; Song, C.; Cho, Y.M.; Ro, J.Y.; Ahn, H. Level of invasion into fibromuscular band is an independent factor for positive surgical margin and biochemical recurrence in men with organ confined prostate cancer. BMC Urol. 2018, 18, 7. [CrossRef]

33. Koizumi, A.; Narita, S.; Nara, T.; Takayama, K.; Kanda, S.; Numakura, K.; Tsuruta, H.; Maeno, A.; Huang, M.; Saito, M.; et al. Incidence and location of positive surgical margin among open, laparoscopic and robot-assisted radical prostatectomy in prostate cancer patients: A single institutional analysis. Jpn. J. Clin. Oncol. 2018, 48, 765–770. [CrossRef]

34. Koney, B.R.; Eastham, J.A.; Reuter, V.E.; Scardino, P.T.; Donat, S.M.; Dalbagni, G.; Russo, P.; Herr, H.W.; Schwartz, L.; Kantoff, P.W.; et al. Feasibility of radical prostatectomy after neoadjuvant chemohormonal therapy for patients with high risk or locally advanced prostate cancer: Results of a phase I/II study. J. Urol. 2004, 171 Pt 1, 709–713. [CrossRef]

35. Lee, S.; Kim, K.B.; Jo, J.K.; Ho, J.N.; Oh, J.J.; Jeong, S.J.; Hong, S.K.; Byun, S.S.; Choe, G.; Lee, S.E. Prognostic value of focal positive surgical margins after radical prostatectomy. Clin. Genitourin. Cancer 2016, 14, e313-9. [CrossRef]
58. Stephenson, R.A.; Middleton, R.G.; Abbott, T.M. Wide excision (nonnerve sparing) radical retropubic prostatectomy using an initial perirectal dissection. J. Urol. 1997, 157, 251–255. [CrossRef]
59. Takahara, K.; Sumitomo, M.; Fukaya, K.; Jyoudai, T.; Nishino, M.; Hikichi, M.; Zennami, K.; Nukaya, T.; Ichino, M.; Fukami, N.; et al. Clinical and oncological outcomes of robot-assisted radical prostatectomy with nerve sparing vs. non-nerve sparing for high-risk prostate cancer cases. Oncol. Lett. 2019, 18, 3896–3902. [CrossRef] [PubMed]
60. Tan, W.S.; Krimphove, M.J.; Cole, A.P.; Marchese, M.; Berg, S.; Lipsitz, S.R.; Läppenberg, B.; Nabi, J.; Abdollah, F.; Choueiri, T.K.; et al. Variation in positive surgical margin status after radical prostatectomy for T2 prostate cancer. Clin. Genitourin. Cancer 2019, 17, e1060–e1068. [CrossRef] [PubMed]
61. Tatsugami, K.; Yoshioka, K.; Shiroki, R.; Eto, M.; Yoshino, Y.; Tozawa, K.; Fukasawa, S.; Fujisawa, M.; Takenaka, A.; Nasu, Y.; et al. Japanese society of endourology. Reality of nerve sparing and surgical margins in surgeons’ early experience with robot-assisted radical prostatectomy in Japan. Int. J. Urol. 2017, 24, 191–196. [CrossRef]
62. Tian, X.J.; Wang, Z.L.; Li, G.; Cao, S.J.; Cui, H.R.; Li, Z.H.; Liu, Z.; Li, B.L.; Ma, L.L.; Zhuang, S.R.; et al. Development and validation of a preoperative nomogram for predicting positive surgical margins after laparoscopic radical prostatectomy. Chin. Med. J. 2019, 132, 928–934. [CrossRef]
63. Trabulsi, E.J.; Linden, R.A.; Gomella, L.G.; McGinnis, D.E.; Strup, S.E.; Lallas, C.D. The addition of robotic surgery to an established laparoscopic radical prostatectomy program: Effect on positive surgical margins. Can. J. Urol. 2008, 15, 3994–3999.
64. van den Ouden, D.; Bentvelsen, F.M.; Boevé, E.R.; Schröder, F.H. Positive margins after radical prostatectomy: Correlation with local recurrence and distant progression. Br. J. Urol. 1993, 72, 489–494. [CrossRef]
65. Villers, A.; Stamey, T.A.; Yemoto, C.; Rischmann, P.; McNeal, J.E. Modified extraperitoneal radical retropubic prostatectomy technique decreases frequency of positive surgical margins in T2 cancers >2 cm3. Eur. Urol. 2000, 38, 64–73. [CrossRef] [PubMed]
66. Vis, A.N.; Schröder, F.H.; van der Kwast, T.H. The actual value of the surgical margin status as a predictor of disease progression in men with early prostate cancer. Eur. Urol. 2006, 50, 258–265. [CrossRef] [PubMed]
67. Volavšek, M.; Blanca, A.; Montironi, R.; Cheng, L.; Raspollini, M.R.; Vau, N.; Fonseca, J.; Pierconti, F.; Lopez-Beltran, A. Digital versus light microscopy assessment of surgical margin status after radical prostatectomy. Virchows Arch. 2018, 472, 451–460. [CrossRef] [PubMed]
68. Ward, J.F.; Zincke, H.; Bergstralh, E.J.; Slezak, J.M.; Myers, R.P.; Blute, M.L. The impact of surgical approach (nerve bundle preservation vs wide local excision) on surgical margins and biochemical recurrence following radical prostatectomy. J. Urol. 2004, 172 Pt 1, 1328–1332.
69. Weldon, V.E.; Tavel, F.R.; Neuwirth, H.; Cohen, R. Patterns of positive specimen margins and detectable prostate specific antigen after radical perineal prostatectomy. J. Urol. 1995, 153, 1565–1569. [CrossRef]
70. Wu, S.; Lin, S.X.; Wirth, G.J.; Lu, M.; Lu, J.; Subtelny, A.O.; Wang, Z.; Dahl, D.M.; Olumi, A.F.; Wu, C.L. Impact of Multifocality and Multilocation of Positive Surgical Margin After Radical Prostatectomy on Predicting Oncological Outcome. Clin. Genitourin Cancer 2019, 17, e44–e52. [CrossRef]
71. Yamada, Y.; Teshima, T.; Fujimura, T.; Sato, Y.; Nakamura, M.; Niimi, A.; Kimura, N.; Kakutani, S.; Kawai, T.; Yamada, D.; et al. Comparison of perioperative outcomes in elderly (age ≥75 years) vs. younger men undergoing robot-assisted radical prostatectomy. PLoS ONE. 2020, 15, e0234113. [CrossRef]
72. Yu, Y.D.; Lee, M.; Hong, S.K.; Byun, S.S.; Lee, S.E.; Lee, S. Impact of variations in prostatic apex shape on apical margin positive rate after radical prostatectomy: Robot-assisted laparoscopic radical prostatectomy vs. open radical prostatectomy. J. Endourol. 2018, 32, 46–53. [CrossRef]
73. Yüksel, M.; Karamik, K.; Anl, H.; Ismailoglu, E.; Ates, M.; Savas, M. Factors affecting surgical margin positivity in robotic assisted radical prostatectomy. Arch. Ital. Urol. Androl. 2017, 89, 71–74. [CrossRef]
74. Yusuf, S.; Peto, R.; Lewis, J.; Collins, R.; Sleight, P. Beta blockade during and after myocardial infarction: An overview of the randomized trials. Prog. Cardiovasc. Dis. 1985, 27, 335–371. [CrossRef]
75. Lee, W.; Lim, B.; Kyung, Y.S.; Kim, C.S. Impact of positive surgical margin on biochemical recurrence in localized prostate cancer. Prostate International 2021, 9, 151–156. [CrossRef]
76. Cooperberg, M.; Broering, J.M.; Litwin, M.; Lubeck, D.P.; Mehta, S.S.; Henning, J.M.; Carroll, P.R. The contemporary management of prostate cancer in the United States: Lessons from the cancer of the prostate strategic urologic research endeavor (CapSURE), a national disease registry. J. Urol. 2004, 171, 1393–1401. [CrossRef]
77. Novara, G.; Ficarra, V.; Mocellin, S.; Ahmed, T.E.; Carroll, P.R.; Graefen, M.; Guazzoni, G.; Menon, M.; Patel, V.R.; Shariat, S.F.; et al. Systematic review and meta-analysis of studies reporting oncologic outcome after robot-assisted radical prostatectomy. Eur. Urol. 2012, 62, 382–404. [CrossRef]
78. Wiltz, A.L.; Shikanov, S.; Eggner, S.E.; Katz, M.H.; Thong, A.E.; Steinberg, G.D.; Shalhav, A.L.; Zagaja, G.P.; Zorn, K.C. Robotic radical prostatectomy in overweight and obese patients: Oncological and validated-functional outcomes. Urology 2009, 73, 316–322. [CrossRef]
79. Liss, M.; Osann, K.; Ornstein, D. Positive surgical margins during robotic radical prostatectomy: A contemporary analysis of risk factors. BJU Int. 2008, 102, 603–608. [CrossRef]
80. Cheng, L.; Slezak, J.; Bergstralh, E.J.; Myers, R.P.; Zincke, H.; Bostwick, D.G. Preoperative prediction of surgical margin status in patients with prostate cancer treated by radical prostatectomy. J. Clin. Oncol. 2000, 18, 2862–2868. [CrossRef]
81. Tuliao, P.H.; Koo, K.C.; Komninos, C.; Chang, C.H.; Choi, Y.D.; Chung, B.H.; Hong, S.J.; Rha, K.H. Number of positive preoperative biopsy cores is a predictor of positive surgical margins (PSM) in small prostates after robot-assisted radical prostatectomy (RARP). BJU Int. 2015, 116, 897–904. [CrossRef]

82. Marchetti, P.E.; Shikanov, S.; Razmoria, A.A.; Zagaja, G.P.; Shalhav, A.L. Impact of prostate weight on probability of positive surgical margins in patients with low-risk prostate cancer after robotic-assisted laparoscopic radical prostatectomy. Urology 2011, 77, 677–681. [CrossRef]

83. Secin, F.P.; Serio, A.; Bianco, F.J.; Karanikolas, N.T.; Kuroiwa, K.; Vickers, A.; Touijer, K.; Guillonneau, B. Preoperative and intraoperative risk factors for side-specific positive surgical margins in laparoscopic radical prostatectomy for prostate cancer. Eur. Urol. 2007, 51, 764–771. [CrossRef]

84. Coelho, R.F.; Chauhan, S.; Orvieto, M.A.; Palmer, K.J.; Rocco, B.; Patel, V.R. Predictive factors for positive surgical margins and their locations after robot-assisted laparoscopic radical prostatectomy. Eur. Urol. 2010, 57, 1022–1029. [CrossRef] [PubMed]

85. Porten, S.P.; Cooperberg, M.R.; Carroll, P.R. The independent value of tumour volume in a contemporary cohort of men treated with radical prostatectomy for clinically localized disease. BJU Int. 2010, 105, 472–475. [CrossRef] [PubMed]

86. Yossepowitch, O.; Briganti, A.; Eastham, J.A.; Epstein, J.; Graefen, M.; Montironi, R.; Touijer, K. Positive surgical margins after radical prostatectomy: A systematic review and contemporary update. Eur. Urol. 2014, 65, 303–313. [CrossRef] [PubMed]

87. Bolla, M.; van Poppel, H.; Tombal, B.; Vekemans, K.; Da Pozzo, L.; De Reijke, T.M.; Verbaeys, A.; Bosset, J.-F.; Van Velthoven, R.; Colombel, M. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: Long-term results of a randomized controlled trial (EORTC trial 22911). Lancet 2012, 380, 2018–2027. [CrossRef]

88. Nguyen, L.N.; Head, L.; Witiuk, K.; Punjani, N.; Mallick, R.; Crossen, S.; Fergusson, D.A.; Cagiannos, I.; Lavallée, L.T.; Morash, C.; et al. The risks and benefits of cavernous neurovascular bundle sparing during radical prostatectomy: A systematic review and meta-analysis. J. Urol. 2017, 198, 760–769. [CrossRef]

89. Srigley, J.R.; Allan, R.; Amin, M.B.; Chang, S.S.; Brett, D.; Epstein, J.I.; Grignon, D.J.; Humphrey, P.A.; McKiernan, J.M.; Pettus, J.; et al. Protocol for the Examination of Specimens from Patients with Carcinoma of the Prostate Gland. Arch. Pathol. Lab. Med. 2009, 133, 1568–1576. [CrossRef]