Evaluating Incidence, Location, and Predictors of Positive Surgical Margin Among Chinese Men Undergoing Robot-Assisted Radical Prostatectomy

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Abstract
Purpose: To evaluate the incidence and locations of positive surgical margin (PSM) among Chinese men undergoing RARP and identify the preoperative predictors for PSM.

Methods: We retrospectively identified 393 patients who underwent RARP according to inclusion criteria by single surgeon in our hospital. PSM was defined as the presence of cancer adjacent to inked surface of the specimen and categorized into four groups based on locations: apex, posterolateral, base, and multifocal. Logistic regression analysis was performed to identify the predictors of overall and location-specific PSM.

Results: The overall PSM rate was 133/393 (34%). The PSM rates for pT2, pT3, and pT4 stage were 63/278 (23%), 50/89 (56%), and 20/26 (77%), respectively. The estimated rates for apical, posterolateral, basal, and multifocal PSM were 8%, 4%, 7%, and 14%, respectively. In univariate analysis, overall PSM related to tPSA, f/tPSA, percentage of positive needles, and Gleason score. Multifocal PSM correlated with smoking history, drinking history, tPSA, f/tPSA, percentage of positive needles, and Gleason score. In multivariate analysis, percentage of positive needles reminded the only independent predictor for overall (OR = 10.5, 95% CI: 2.58–44.4) and basal PSM (OR = 24.0, 95% CI: 3.22–179.4). The f/tPSA (OR = 2.59, 95% CI: 2.18–5.71) and percentage of positive needles (OR = 31.0, 95% CI: 3.17–303) were independent risk factors for multifocal PSM.

Conclusion: The multifocal sites were the most common location of positive surgical margin, followed by apical and basal sites among Chinese patients undergoing RARP. The percentage of positive needles was an independent predictor for overall, basal, and multifocal PSM.

Keywords
prostate cancer, robot, radical prostatectomy, positive surgical margin

Introduction
Prostate cancer (PCa) is the second most diagnosed cancer among men, and the fifth leading cause of cancer death among men worldwide, with over one million cases and 358,989 deaths in 2018.1,2 Although the incidence of PCa in China is significantly lower than that of the United States and Europe, it has been progressively rising due to the aging population.
changes in diet, and widespread implementation of health examination in recent decades.²,³ Radical prostatectomy (RP) is the standard therapy for clinically localized PCa, and a part of potential multi-model therapy for locally advanced disease.⁵ Robotic prostatectomy (RARP) has been routinely performed for RP in developed countries and is now a new choice for most PCa cases in China. With the advantages of enhanced vision and 7 of freedom, RARP is supported to provide efficient oncological control and good functional results.⁶ Despite advances in surgical techniques and methodologies, positive surgical margin (PSM) is still inevitable and remains an independent factor of biochemical recurrence, local recurrence, and distant metastasis.⁷ Systematic review showed that PSM rates varied from 6.5 to 32%, and the stage-specific rates were 4–23% for pT2, 29–50% for pT3, and 40–75% for pT4 among European and American population undergoing RARP.⁸

In the past decade, several studies have correlated preoperative factors with surgical margin status after RARP.⁹⁻¹¹ However, most studies were based on cohorts of European or American people, and the knowledge about the Chinese population is limited. In our study, we aimed to evaluate the incidence and locations of PSM among Chinese population following RARP and identify the predictive factors associated with PSM stratified by locations. This study will be helpful to improve counseling of PSM and provide guidance for clinically decisions, preoperatively and intraoperatively.

Material and Methods

Study Population

This retrospective study was approved by the Ethics Review Board of the First Affiliated Hospital of Zhengzhou University (IRB No. 2021-KY-0118-002), and a waiver of informed consent was obtained. Between October 2014 and December 2019, a total of 425 men underwent RARP through transperineal approach by a single surgeon (X. P. Z) in our institution. The 32 patients with incomplete clinical data were excluded from the study, leaving 393 cases available for analysis.

The RARP was performed by transperineal approach using the DaVinci system. Limited (obturator) or standard (obturator and external iliac) pelvic lymph node dissection was usually performed among patients with low-risk or intermediate-risk PCa.⁵ And extended (obturator, external iliac, and internal iliac) pelvic lymph node dissection was usually performed among patients with suspected lymph node invasion by MRI¹² and/or high-risk PCa.⁵,¹³ Nerve sparing procedure was cautiously performed using interfascial or intrafascial techniques¹⁴ based on clinical stage (≤T2b), Gleason score (GS ≤7), tPSA ≤10ng/mL, erectile function, and patients’ request. Additionally, we adopted the reelpipe approach for hemostasis and protecting nerve.¹⁵ PSM, defined as cancer cells involving the inked surface of the specimen, was categorized into four groups according to the following locations: apex, posterolateral, base, and multifocal sites.¹⁶

Clinical Parameters Collection

The preoperative parameters including age at surgery, history of smoking, drinking, abdominal surgery and TURP, comorbidities such as hypertension and diabetes mellitus, serum tPSA and tPSA level before biopsy, prostate volume before biopsy, Gleason score determined by biopsy, number and percentage of positive cores in preoperative biopsy, surgical margin status, location of PSM, pathological stage of the cancer, and neoadjuvant ADT were extracted from clinical records. Prostate volume (PV) was measured by 3.0-T MRI system (Siemens, Germany) or ultrasonography scanner (BK Medical, Denmark) using the exact prostate ellipsoid formula.¹⁷ All patients underwent transrectal ultrasound-guided systematic 12-point biopsy according to the same protocol by the same surgeon. If suspected malignant nodules by MRI and/or ultrasound, additional 1–5 needles were performed in regions with cognitive MRI-TRUS fusion and/or abnormal ultrasound echoes.¹⁸ Pathological evaluation of biopsy cores and postoperative specimens were done according to the standards of International Society of Urological Pathology (ISUP).

Statistical Analysis

We described the profile of age, history of smoking, drinking, abdominal surgery and TURP, comorbidities, PSA derivatives, prostate volume, and pathological parameters of enrolled participants by surgical margin status. The overall PSM rate was calculated by dividing the number of patients with PSM by the number of enrolled patients. The location-specific PSM rate was estimated using the following formula: location-specific PSM rate ≈ the number of patients with location-specific PSM /the number of patients with location-available PSM * the overall PSM rate. Student’s t test or ANOVA was used to analyze continuous data. The Mann–Whitney U test or Kruskal–Wallis H test was used to analyze ranked data. The χ² test or Fisher’s exact test was used to analyze categorical data. Bonferroni correction was used for multiple comparisons. Logistic regression analysis was performed to identify predictors for PSM. All tests were two sided with significant level set at .05. All data cleaning and analysis were conducted using R statistical software (version 4.0.2).

Results

Overall and Location-Specific PSM Rates

Between October 2014 and December 2019, 393 (92%) of the total of 425 patients with RARP met study inclusion criteria. The overall PSM rate was 133/393 (34%). In the final pathological evaluation, 278 (71%) patients had pT2 stage, 89
(23%) patients had pT3 stage, and 26 (7%) patients had pT4 stage (Table 1). The PSM rates for pT2, pT3, and pT4 disease were 63/278 (23%), 50/89 (56%), and 20/26 (77%), respectively. Among patients with PSM, 67 (50%) had a solitary PSM, including 29 (18%) with apical PSM, 15 (11%) with posterolateral PSM, 23 (17%) with basal PSM, and 49 (37%) had multiple positive sites. The PSM site was not available among 17 patients (13%). The estimated apical, posterolateral, basal, solitary, and multifocal PSM rates were 8%, 4%, 7%, 20%, and 14%, respectively.

**Clinicopathological Characteristics of Patients by Surgical Margin Status**

The clinicopathological characteristics by status of surgical margin were summarized in Table 1. Patients with PSM had a

| Parameter | Overall (n = 393) | Surgical Margin Status | P Value |
|-----------|------------------|------------------------|---------|
|           |                  | Negative (n = 260) | Positive (n = 133) |         |
| Age (years) | 67 (63–72) | 67 (63–72) | 68 (63–73) | .993 |
| Smoking history (n, %) | | | |
| No | 270 (69) | 180 (69) | 90 (68) | .841 |
| Yes | 123 (31) | 80 (31) | 43 (32) | |
| Drinking history (n, %) | | | |
| No | 322 (82) | 215 (83) | 107 (80) | .683 |
| Yes | 71 (18) | 45 (17) | 26 (20) | |
| Hypertension (n, %) | | | |
| No | 265 (67) | 180 (69) | 85 (64) | .341 |
| Yes | 128 (33) | 80 (31) | 48 (36) | |
| Diabetes mellitus (n, %) | | | |
| No | 330 (84) | 223 (86) | 107 (89) | .225 |
| Yes | 63 (16) | 37 (14) | 26 (20) | |
| Abdominal surgery (n, %) | | | |
| No | 323 (82) | 211 (81) | 112 (84) | .542 |
| Yes | 70 (18) | 49 (29) | 21 (16) | |
| TURP (n, %) | | | |
| No | 295 (75) | 190 (73) | 105 (79) | .250 |
| Yes | 98 (25) | 70 (27) | 28 (21) | |
| tPSA (ng/ml) | 26.8 (13.5–65.3) | 25.3 (12.4–60.0) | 40.7 (16.2–91.9) | .017 |
| f/tPSA | .12 (.08–.17) | .11 (.07–.16) | .14 (.10–.19) | .007 |
| PSAD (ng/ml²) | .34 (20–65) | .36 (20–69) | .32 (21–64) | .747 |
| Prostate volume (ml) | 81 (55–125) | 74 (52–112) | 88 (66–135) | .078 |
| % of positive needles | .59 (.25–1.00) | .59 (.25–1.00) | 1.00 (.62–1.00) | <.001 |
| Gleason score (n, %) | | | |
| ≤3+3 | 88 (22) | 72 (28) | 16 (12) | <.001 |
| 3+4 | 57 (15) | 41 (16) | 16 (12) | |
| 4+3 | 97 (25) | 64 (25) | 33 (25) | |
| ≥4+4 | 151 (38) | 83 (32) | 68 (51) | |
| Risk category | | | |
| low-risk | 53 (13) | 51 (20) | 2 (2) | <.001 |
| intermediate-risk | 132 (34) | 99 (38) | 33 (27) | |
| High-risk | 208 (53) | 110 (42) | 98 (74) | |
| Pathological T stage (n, %) | | | |
| T2 | 278 (71) | 215 (83) | 63 (47) | <.001 |
| T3 | 89 (23) | 39 (15) | 50 (38) | |
| T4 | 26 (7) | 6 (2) | 20 (15) | |
| Nerve-sparing (n, %) | | | |
| No | 366 (93) | 236 (91) | 130 (97) | .018 |
| Yes | 27 (7) | 24 (9) | 4 (3) | |

Abbreviations: PSM, positive surgical; TURP, transurethral resection of the prostate; tPSA, total prostate-specific antigen; fPSA, free prostate-specific antigen; f/tPSA, fPSA / tPSA; PSAD, prostate-specific antigen density; NA, not applicable.
higher serum tPSA (40.7 vs 25.3, P = .017), f/tPSA (.14 vs .11, P = .007), percentages of positive needles (1.00 vs .59, P < .001), Gleason score (P < .001), and pathological T stage (P < .001), but a lower percentage of nerve-sparing (3% vs 9%, P = .007), percentages of positive needles (OR = 2.43, 95% CI: 1.37–4.35) were significant predictors for apical and posterolateral PSM (Supplementary Table 2).

On multivariate analysis, percentages of positive needles reminded the only independent predictor for overall (OR = 2.90, 95% CI: 1.22–6.88) and percentages of positive needles (OR = 3.11, 95% CI: 1.22–8.13) were significantly independent risk factors of multiple positive sites (Supplementary Table 3).

**Discussion**

In our study, we evaluated the incidence and locations of PSM among Chinese patients undergoing RARP, and comprehensively identified the preoperative predictors for PSM stratified by locations. The incidences for overall, apical, posterolateral, basal, and multifocal PSM were 34%, 8%, 4%, 6%, and 13%, respectively. The PSM rates for pT1, pT2, and pT3 stage were 23%, 56%, and 77%, respectively. The percentage of positive needles reminded the only independent predictor for overall and basal PSM. The f/tPSA and percentage of positive needles were significantly independent risk factors of multifocal PSM.

In our study, the overall PSM rate was 34%, which was comparable with the reported PSM rates among Chinese (29–42%)19,21 and Korean (25–34%) population.22 However, the overall PSM rate was higher than that (mean: 15%, range: 6.5–32%) among Western population.23 Additionally, the PSM...
rates stratified by pathological stage were also higher among Chinese population (18–23% for pT2 stage, 44–50% for pT3 stage, and 59–100% for pT4 stage), compared with European and American population (9% for pT2 stage, 37% for pT3 stage, and 50% for pT4 stage). This may suggest that Chinese population has a higher PSM rate after adjusting for the pathological stage. Some study found that race was largely independent of adverse pathological features including extracapsular extension, seminal vesicle invasion, and PSM after radical prostatectomy. The underlying causes of higher PSM rates among Chinese population, including tumor biology, biological process, biological process, smoking-related tumor DNA methylation promoting aggression of PCa, and increased plasma levels of testosterone involved in PCa development and progression.

The present study was subject to several imitations. First, this study was a single center study and limited by its retrospective design. Second, even though the total number of patients included in this study was satisfactory, the subgroup analysis by PSM location was not feasible and/or underpowered. Third, no central review of pathological results was performed in our study, which may lead to classification errors. However, all the pathological specimens were examined by the pathologists in the same institution according to the same protocol. Therefore, the pathological bias was minimal in our study.

Conclusions

The PSM rate was higher among Chinese population undergoing RARP, compared to Western population. The multifocal sites were the most common location of PSM, followed by apical and basal sites among Chinese patients undergoing RARP. The percentage of positive needles was a strong predictor for overall, basal, and multifocal PSM. The f/tPSA and percentage of positive needles were significantly independent risk factors of multifocal PSM. This study will be helpful to improve counseling of PSM and provide guidance for clinically decisions, such as neoadjuvant therapy, nervesparing, or modified surgical method, preoperatively and intraoperatively.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The research was supported by the Henan Medical Science and Technology Project (grant no. LHGJ20190181 and LHGJ20200334).

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the First Affiliated Hospital of Zhengzhou University, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This retrospective study was approved by the Institutional Ethics Review Board, and a waiver of informed consent was obtained.

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References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015; 65(2): 87-108.

2. International Agency for Research on Cancer. Global Cancer Observatory; 2020 [cited 2021 3 May]. Available from: http://gco.iarc.fr/.

3. Center MM, Jemal A, Lortet-Tieulent J, et al. International variation in prostate cancer incidence and mortality rates. Eur Urol. 2012; 61(6): 1079-1092.

4. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. CA Cancer J Clin. 2016; 66(2): 115-132.

5. European Association of Urology. EAU Guidelines on Prostate Cancer: 2020 [cited 2020 8 May]. Available from: https://uroweb.org/guideline/prostate-cancer/.

6. Cakmak S, Canda AE, Atmaca AF, Altinova S, Balbay MD. Does type 2 diabetes mellitus have an impact on postoperative early, mid-term and late-term urinary continence after robot-assisted radical prostatectomy? J Endourol. 2019; 33(3): 201-206.

7. Keller EX, Bachofner J, Britschgi AJ, et al. Prognostic value of unifocal and multifocal positive surgical margins in a large series of robot-assisted radical prostatectomy for prostate cancer. World Journal of Urology. 2019; 37(9): 1837-1844.

8. Yossepowitch O, Briganti A, Eastham JA, et al. Positive surgical margins after radical prostatectomy: a systematic review and contemporary update. Eur Urol. 2014; 65(2): 303-313.

9. Coelho RF, Chauhan S, Orvieto MA, Palmer KJ, Rocco B, Patel VR. Predictive factors for positive surgical margins and their locations after robot-assisted laparoscopic radical prostatectomy. Eur Urol. 2010; 57(6): 1022-1029.

10. Stephenson AJ, Wood DP, Kattan MW, et al. Location, extent and number of positive surgical margins do not improve accuracy of predicting prostate cancer recurrence after radical prostatectomy. J Urol. 2009; 182(4): 1357-1363.

11. Kang SG, Schatloff O, Haidar AM, et al. Overall rate, location, and predictive factors for positive surgical margins after robot-assisted laparoscopic radical prostatectomy for high-risk prostate cancer. Asian Journal of Andrology. 2016; 18(1): 123-128.

12. Hou Y, Bao M-L, Wu C-J, Zhang J, Zhang Y-D, Shi H-B. A machine learning-assisted decision-support model to better identify patients with prostate cancer requiring an extended pelvic lymph node dissection. BJU International. 2019; 124(6): 972-983.

13. Fossati N, Willemsen PM, Van den Broeck T, et al. The benefits and harms of different extents of lymph node dissection during radical prostatectomy for prostate cancer: a systematic review. Eur Urol. 2017; 72(1): 84-109.

14. Stolzenburg JU, Kallidonis P, Do M, et al. A comparison of outcomes for interfascial and intrafascial nerve-sparing radical prostatectomy. Urology. 2010; 76(3): 743-748.

15. Zhang X, Zhu Z, Wang S, Tao J, Yu S, Fan Y. Reelpipe approach for nerve sparing during robot-assisted radical prostatectomy. J Mod Urol. 2021; 26(1): 1-4.

16. Patel VR, Coelho RF, Rocco B, et al. Positive surgical margins after robotic assisted radical prostatectomy: a multi-institutional study. J Urol. 2011; 186(2): 511-516.

17. Christie DRH, Sharpley CF. How accurately can prostate gland imaging measure the prostate gland volume? results of a systematic review. Prostate Dis. 2019; 2019: 6932572.

18. Liu J, Dong B, Qu W, et al. Using clinical parameters to predict prostate cancer and reduce the unnecessary biopsy among patients with PSA in the gray zone. Sci Rep. 2020; 10(1): 5157.

19. Tian XJ, Wang ZL, Li G, et al. Development and validation of a preoperative nomogram for predicting positive surgical margins after laparoscopic radical prostatectomy. Chinese medical journal. 2019; 132(8): 928-934.

20. Yang R, Cao K, Han T, et al. Perineural invasion status, Gleason score and number of positive cores in biopsy pathology are predictors of positive surgical margin following laparoscopic radical prostatectomy. Asian Journal of Andrology. 2017; 19(4): 468-472.

21. Xu B, Luo C, Zhang Q, Jin J. Preoperative factors of the P.R.O.S.T.A.T.E. scores: a novel predictive tool for the risk of positive surgical margin after radical prostatectomy. J Cancer Res Clin Oncol. 2017; 143(4): 687-692.

22. Choo MS, Cho SY, Jeong CW, et al. Predictors of positive surgical margins and their location in Korean men undergoing radical prostatectomy. Int J Urol. 2014; 21(9): 894-898.

23. Novara G, Ficarra V, Mocellin S, et al. Systematic review and meta-analysis of studies reporting oncologic outcome after robot-assisted radical prostatectomy. Eur Urol. 2012; 62(3): 382-404.

24. Aminsharifi A, Schulman A, Howard LE, 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(17): 3025-3032.

25. Rabbani F, Yunis LH, Vora K, et al. Impact of ethnicity on surgical margins at radical prostatectomy. BJU International. 2009; 104(7): 904-908.

26. Tuliao PH, Koo KC, Komminos C, et al. Number of positive preoperative biopsy cores is a predictor of positive surgical margins (PSM) in small prostate after robot-assisted radical prostatectomy (RARP). BJU International. 2015; 116(6): 897-904.

27. Sato N, Shiota M, Shiga KI, et al. Smoking effect on oncological outcome among men with prostate cancer after radical prostatectomy. Jpn J Clin Oncol. 2017; 47(5): 453-457.

28. Darcey E, Boyle T. Tobacco smoking and survival after a prostate cancer diagnosis: a systematic review and meta-analysis. Cancer Treatment Reviews. 2018; 70: 30-40.

29. Zhao J, Stockwell T, Roemer A, Chikritzhs T. Is alcohol consumption a risk factor for prostate cancer? A systematic review and meta-analysis. BMC Cancer. 2016; 16(1): 845.

30. Kenfield SA, Stampfer MJ, Chan JM, Giovannucci E. Smoking and prostate cancer survival and recurrence. J Am Med Assoc. 2011; 305(24): 2548-2555.