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Prostate Disease

# Perineural invasion status, Gleason score and number of positive cores in biopsy pathology are predictors of positive surgical margin following laparoscopic radical prostatectomy

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**This study was designed to define possible preoperative predictors of positive surgical margin after laparoscopic radical prostatectomy. We retrospectively analyzed the records of 296 patients with prostate cancer diagnosed by prostate biopsy, and eventually treated with laparoscopic radical prostatectomy. The prognostic impact of age, prostate volume, preoperative prostate-specific antigen, biopsy Gleason score, maximum percentage tumor per core, number of positive cores, biopsy perineural invasion, capsule invasion on imaging, and tumor laterality on surgical margin was assessed. The overall positive surgical margin rate was 29.1%. Gleason score, number of positive cores, perineural invasion, tumor laterality in the biopsy specimen, and prostate volume significantly correlated with risk of positive surgical margin by univariate analysis ($P < 0.05$). Gleason score (odds ratio [OR] = 2.286, 95% confidence interval [95% CI] = 1.431–3.653, $P = 0.001$), perineural invasion (OR = 4.961, 95% CI = 2.656–9.270, $P < 0.001$), and number of positive cores (OR = 4.403, 95% CI = 1.878–10.325, $P = 0.001$) were independent predictors of positive surgical margin at the multivariable logistic regression analysis. Patients with perineural invasion, higher biopsy Gleason scores and/or a large number of positive cores in biopsy pathology had more possibility of capsule invasion. The positive surgical margin rate in patients with capsule invasion (49.5%) was much higher than that with localized disease (17.8%). In contrast, prostate volume showed a protective effect against positive surgical margin (OR = 0.572, 95% CI = 0.346–0.945, $P = 0.029$). Gleason score, perineural invasion, and number of positive cores in the biopsy specimen were preoperative independent predictors of positive surgical margin after laparoscopic radical prostatectomy while prostate volume was a protective factor against positive surgical margin.**

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**Keywords:** needle biopsy; perineural invasion; positive surgical margin; prostatectomy; prostatic neoplasms

## INTRODUCTION

Prostate cancer is the second most frequently diagnosed cancer and the sixth leading cause of cancer death in men, accounting for 14% of the total new cancer cases and 6% of the total cancer deaths in men (GLOBOCAN 2008).[1] The incidence of prostate cancer in China is lower than in Western countries. However, due to widespread use of serum prostate-specific antigen (PSA) testing and transrectal ultrasound (TRUS)-guided needle biopsy, an increasing number of patients with localized prostate cancer have been diagnosed every year in China (from $1.6 \times 10^{-5}$ in 2002 to $4.3 \times 10^{-5}$ in 2008).[2,3]

Radical prostatectomy (RP) is considered the standard of care for patients with localized prostate cancer.[4] This was traditionally performed by open retropubic RP. During the last decade, minimally invasive surgery (laparoscopic and robot-assisted laparoscopic RP; LRP and RALP, respectively) has become popular worldwide. LRP has already become the gold standard for the treatment of localized prostate cancer in China. However, in Western countries, ~20% of patients who undergo RP have a positive surgical margin (PSM) in the final pathological analysis,[5] which is associated with a higher risk of local recurrence and distant metastasis and may have a direct influence on survival and prognosis.[6–8] The reported PSM rate in China is higher than that in Western countries. Therefore, it is crucial to find preoperative predictors for PSM that can contribute to optimizing surgical treatment of patients with prostate cancer.

In this study, we retrospectively examined 296 patients with prostate cancer who underwent LRP by a single experienced surgeon at our center, to define possible preoperative predictors of PSM.

## PATIENTS AND METHODS

After diagnosis with TRUS-guided needle biopsy, 296 consecutive patients with prostate cancer received LRP by a single surgeon (GHQ) with experience of >200 cases between January 2011 and February

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2015, at our center. Patients who had a previous transurethral resection of the prostate were excluded. All patients had magnetic resonance imaging (MRI) to assess whether extraprostatic extension (EPE) existed before surgery. Bone scan was used to rule out the metastatic bone disease. All patients had good physical performance and a long life expectancy. Informed consent was obtained from each patient after the surgeon reviewed the peer-reviewed data on cancer-specific survival, complication rates, expected convalescence period, and other alternative treatments (external beam radiotherapy or brachytherapy). All patients underwent at least 6 months of follow-up.

Systematic biopsies included 12 cores from separate regions, with six cores from each lobe. All biopsies were performed with an 18 gauge × 2 cm Tru-cut core biopsy needle (Bard, Tempe, AZ, USA) under TRUS guidance. The pathological evaluation focused on Gleason score, percentage of tumor per core, number of positive cores, perineural invasion (PNI), and tumor laterality. PNI was defined as the presence of prostate cancer tracking along or around a nerve within the perineural space.

Laparoscopic prostatectomy was performed under general anesthesia, using a transperitoneal approach described by Hasan and Gill[9] The procedure began with a wide inverted U-shaped incision along the peritoneum of the anterior abdominal wall to drop the bladder posteriorly and enter the Retzius space. The patient was dissected laterally on either side to expose and incise the endopelvic fascia. After ligating the dorsal venous complex, the bladder neck was transected precisely to identify the seminal vesicles and vas deferens, which were completely mobilized bilaterally. Denonvilliers' fascia was incised to enter the prerectal space, and the lateral bladder pedicle controlled on each side. The neurovascular bundles were identified and precisely released using a combination of sharp cold cutting, Hem-o-lok clips, and the harmonic scalpel. The dorsal venous complex was transected, followed by apical dissection and urethral transection. Urethrovesical anastomosis was accomplished by a watertight, double-needle, running suture technique.

All specimens were formalin fixed, coated with India ink, weighed, and serial perpendicular sections were cut. The entire prostate was examined with 2–4 mm interval transactions in a plane perpendicular to the urethra; the apical and basal parts of the prostate were separately sectioned and examined in parallel slices. All specimens were evaluated by one experienced uropathologist and restaged according to the 2010 American Joint Committee on Cancer staging system. Surgical margins were reported as positive when cancer cells reached the inked outer surface of the gland.

All patients received PSA detection and completed self-administered questionnaires concerning their voiding and sexual disorders at 1, 3, 6, 9, and 12 months and every 6 months thereafter postoperatively. Continence was defined as freedom from the use of any form of protection. Potency was defined as the ability to achieve vaginal penetration with or without phosphodiesterase type 5 inhibitors. Biochemical recurrence was defined as any detectable serum PSA (>0.2 ng ml$^{-1}$).

Continuous variables were reported as the median and range. The $\chi^2$ test and Fisher's exact test were used to evaluate the possible statistical correlation between the risk of PSM and several preoperative variables, including age, prostate volume, preoperative serum PSA level, biopsy Gleason score, maximal percentage of tumor per core, number of positive cores, PNI in biopsy, biopsy tumor laterality, and EPE. The correlation between PNI, Gleason score, and number of positive cores and capsular invasion was evaluated with the $\chi^2$ test. Multivariate logistic regression analysis was performed step-wise to estimate the relative importance of the variables in predicting the risk of PSM. SPSS 17.0 statistical software (IBM SPSS, Chicago, IL, USA) was used to analyze the data. Kaplan–Meier curves and log-rank test by GraphPad Prism 6.0 (GraphPad Software, San Diego, CA, USA) were used to compare the risk of developing biochemical recurrence. $P < 0.05$ was considered statistically significant.

## RESULTS

The clinical and biopsy characteristics of 296 patients treated with LRP are listed in **Table 1**. The median age of patients was 70 years (range: 51–80 years), median prebiopsy PSA value was 12.6 ng ml$^{-1}$, and the median prostate volume was 32 ml (range: 10.9–123 ml). Median biopsy Gleason score was 7 (range: 6–10). The median maximum percentage tumor per core was 60% (range: 5%–100%). PNI was present in 85 patients (28.7%). The number of patients with a bilateral tumor finding in biopsy was 150 (50.7%). EPE on MRI was noted in 116 patients (39.2%).

In the final pathological evaluation, 191 patients had pT2 disease, 101 had pT3 disease, and four had pT4 disease. PSM was present in 86 patients (29.1%). PSM rate in patients with pT2, pT3, and pT4 disease was 34/191 (17.8%), 48/101 (47.5%), and 4/4 (100%), respectively. The most common location of PSM was in the apex (54/296 [18.2%]). The PSM rate circumferentially and at the base was 21/296 (7.1%) and 27/296 (9.1%), respectively.

**Table 2** shows the characteristics of PSM based on preoperative clinical and biopsy features. No association was observed in the univariable analysis between PSM and age ($P = 0.565$), PSA ($P = 0.197$), EPE on MRI ($P = 0.295$), and maximum percentage cancer per core ($P = 0.213$). Other parameters (prostate size, biopsy Gleason score, number of positive cores, biopsy PNI, and biopsy tumor laterality) were all significant risk factors of PSM using univariate analysis. Although 52.7% of biopsy-diagnosed unilateral disease was confirmed as bilateral disease in the final pathological report ($P < 0.001$) (**Table 3**), biopsy-determined tumor laterality was still a meaningful predictor of PSM ($P < 0.001$). Multivariate analysis is reported in **Table 4**. Among the five meaningful factors, Gleason score (odds ratio [OR] = 2.286, 95% confidence interval [95% CI] = 1.431–3.653, $P = 0.001$), PNI (OR = 4.961, 95% CI = 2.656–9.270, $P < 0.001$), and number of positive cores (OR = 4.403, 95% CI = 1.878–10.325, $P = 0.001$) in biopsy specimens were predictors of PSM after LRP. In contrast, the volume of prostate gland showed a protective effect against PSM (OR = 0.572, 95% CI = 0.346–0.945, $P = 0.029$). **Table 5** shows the three predictive factors (Gleason score, PNI, and number of positive cores) in biopsy specimens significantly increased the possibility of capsular invasion in the final pathological results ($P < 0.05$).

**Table 1: Characteristics of 296 patients undergoing laparoscopic radical prostatectomy**

| *Variable* | *Value* |
|---|---|
| Age, median (range) (year) | 70 (51–80) |
| Prostate volume, median (range) (ml) | 32 (10.9–123) |
| PSA, median (range) (ng ml$^{-1}$) | 12.6 (2.9–180) |
| Biopsy Gleason score, median (range) | 7 (6–10) |
| Maximum percentage of tumor per core, median (range) (%) | 60 (5–100) |
| Number of positive cores, median (range) | 4 (1–12) |
| Biopsy perineural invasion number, *n* (%) | 85 (28.7) |
| Biopsy bilateral tumor, *n* (%) | 150 (50.7) |
| Extra-prostatic extension on MRI, *n* (%) | 116 (39.2) |
| Pathologic stage, *n* (%) | |
| pT2 | 191 (64.5) |
| pT3 | 101 (34.1) |
| pT4 | 4 (1.4) |

PSA: prostatic-specific antigen; MRI: magnetic resonance imaging

**Table 2: Univariate analysis of clinical and biopsy features for predicting PSM**

| *Variable* | *Number of patients (%)* | *Surgical margin situation (%)* | | *P** |
|---|---|---|---|---|
| | | *Positive* | *Negative* | |
| Patients | 296 | 86 (29.1) | 210 (70.9) | |
| Age (year) | | | | |
| <65 | 68 (23.0) | 23 (26.7) | 45 (21.4) | 0.565 |
| 65–75 | 173 (58.4) | 49 (57.0) | 124 (59.1) | |
| >75 | 55 (18.6) | 14 (16.3) | 41 (19.5) | |
| Prostate volume (ml) | | | | |
| <30 | 138 (46.6) | 50 (58.1) | 88 (41.9) | 0.026 |
| 30–60 | 127 (42.9) | 31 (36.0) | 96 (45.7) | |
| >60 | 31 (10.5) | 5 (5.8) | 26 (12.4) | |
| PSA (ng ml$^{-1}$) | | | | |
| <10 | 90 (30.4) | 23 (26.7) | 67 (31.9) | 0.197 |
| 10–20 | 143 (48.3) | 39 (45.3) | 104 (49.5) | |
| >20 | 63 (21.3) | 24 (27.9) | 39 (18.6) | |
| Biopsy Gleason score | | | | |
| ≤6 (low) | 100 (33.8) | 13 (15.1) | 87 (41.4) | <0.001 |
| 7 (moderate) | 118 (39.9) | 38 (44.2) | 80 (38.1) | |
| ≥8 (high) | 78 (26.3) | 35 (40.7) | 43 (20.5) | |
| Number of positive cores | | | | |
| ≤3 | 123 (41.6) | 17 (19.8) | 106 (50.5) | <0.001 |
| >3 | 173 (58.4) | 69 (80.2) | 104 (49.5) | |
| Maximum tumor per core (%) | | | | |
| <25 | 61 (20.6) | 18 (20.9) | 43 (20.5) | 0.213 |
| 25–50 | 75 (25.3) | 16 (18.6) | 59 (28.1) | |
| >50 | 160 (54.1) | 52 (60.5) | 108 (51.4) | |
| Biopsy perineural invasion | | | | |
| Absent | 211 (71.3) | 36 (41.9) | 175 (83.3) | <0.001 |
| Present | 85 (28.7) | 50 (58.1) | 35 (16.7) | |
| Biopsy tumor laterality | | | | |
| Unilateral | 146 (49.3) | 25 (29.1) | 121 (57.6) | <0.001 |
| Bilateral | 150 (50.7) | 61 (70.9) | 89 (42.4) | |
| Extra-prostatic extension on MRI | | | | |
| Absent | 180 (60.8) | 48 (55.8) | 132 (62.9) | 0.295 |
| Present | 116 (39.2) | 38 (44.2) | 78 (37.1) | |

*Chi-square test and Fisher's exact test, comparing between negative and positive surgical margin situation. *P*<0.05 was considered significant. PSM: positive surgical margin; PSA: prostatic-specific antigen; MRI: magnetic resonance imaging

**Table 3: Consistency of tumor laterality between needle biopsy and radical surgery specimens**

| *Needle biopsy* | *Pathologic specimen* | | *n* | *P** |
|---|---|---|---|---|
| | *Unilateral disease* | *Bilateral disease* | | |
| Unilateral disease (%) | 69 (48.6) | 77 (52.7) | 146 | <0.001 |
| Bilateral disease (%) | 0 (-) | 150 (100) | 150 | |

*Chi-square test and Fisher's exact test, comparing between unilateral and bilateral diseases. *P*<0.05 was considered significant

Overall perioperative complication rate was 10.5%. Minor complications (Clavien grades 1 and 2) occurred in 7.8% of patients. Complications that required intervention (Clavien grade 3a and 3b) occurred in 2.7% of patients. After at least 6 months of follow-up (median: 22 months, range: 6–48 months), the continence rate was 91.6%, and the potency rate in previously potent patients who underwent nerve-sparing surgery was 34.6%. Thirty-six patients were excluded for further analysis of biochemical recurrence owing to loss to follow-up or taking adjuvant therapies. Three-year biochemical recurrence-free survival (RFS) in this study was 72.2% (**Figure 1a**). RFS curves were significantly different between the patients with and without PSM (3-year RFS: 53.6% [PSM$^+$] *vs* 81.5% [PSM$^-$], log-rank test: $P$ <0.001) (**Figure 1b**).

**Table 4: Multivariate analysis of preoperative predictive factors of margin status in patients undergoing laparoscopic radical prostatectomy**

| *Variable* | *OR* | *95% CI* | *P** |
|---|---|---|---|
| Gleason score | 2.286 | 1.431–3.653 | 0.001 |
| Number of positive cores | 4.403 | 1.878–10.325 | <0.001 |
| Perineural invasion | 4.961 | 2.656–9.270 | 0.001 |
| Prostate volume | 0.572 | 0.346–0.945 | 0.029 |

*Multivariate logistic regression analysis was performed step-wise to estimate the relative importance of the variables in predicting the risk of positive surgical margin. *P*<0.05 was considered significant. OR: odds ratio; CI: confidence interval

**Table 5: Correlation between predictive factors in biopsy specimens and capsular invasion in final pathological evaluation**

| | *Intracapsular* | *Extracapsular* | *P** |
|---|---|---|---|
| Perineural invasion | | | |
| Negative | 154 | 57 | <0.001 |
| Positive | 37 | 48 | |
| Gleason score | | | |
| ≤6 (low) | 78 | 22 | 0.001 |
| 7 (moderate) | 72 | 46 | |
| ≥8 (high) | 41 | 37 | |
| Number of positive cores | | | |
| ≤3 | 96 | 27 | <0.001 |
| >3 | 95 | 78 | |

*Chi-square test and Fisher's exact test, comparing between intracapsular and extracapsular diseases. *P*<0.05 was considered significant

## DISCUSSION

PSM status after RP is a well-established prognostic factor of prostate cancer, which is associated with increased biochemical failure and local disease recurrence, as well as the need for secondary treatment. Swindle *et al.*[10] studied 1389 patients treated with RP from 1983 to 2000, and found that PSM was an independent predictor of 10-year tumor progression-free probability. Paulson *et al.*[11] reported that PSM was associated with decreased overall survival. Our study also showed that the 3-year RFS in the PSM$^-$ subgroup was significantly higher than that in the PSM$^+$ group. Owing to refinements in surgical technique and a downward stage migration during the PSA era, there was a decreasing tendency in PSM rate in Western countries recently. Williams *et al.*[12] studied 4247 men diagnosed with prostate cancer who all underwent RP and found that PSM rate decreased from 21.3% in 2004 to 16.6% in 2006. However, the PSM rates of LRP reported in China were still higher than those in Western countries. There are several possible explanations for this phenomenon. To begin with, LRP was popularized much later in China than in Western countries. Rodriguez *et al.*[13] were of the opinion that there was a significant decrease in PSM rate after finishing 200 LRP operations. Therefore, to reduce the effect of the learning curve, the first 200 cases were excluded from the present study. Moreover, many patients were not diagnosed at an early stage because of the poor awareness of the general public of prostate cancer screening in China. In this study, 35.5% of patients had EPE in the final pathological evaluation. Therefore, defining accurate predictors of PSM preoperatively will help us to reduce the PSM rate after RP.

A Gleason score is given to prostate cancer based on its microscopic appearance. A higher Gleason score suggests high tumor aggression

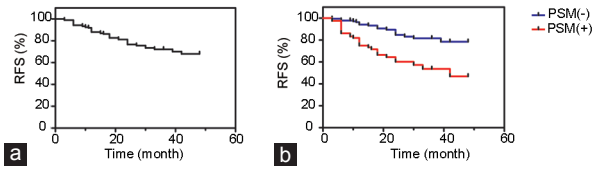


**Figure 1:** Biochemical recurrence-free survival (RFS) curves. (**a**) RFS curve of all patients. (**b**) RFS curves stratified by surgical margin status (log-rank test: $P < 0.001$).

and worse prognosis. When compared with matched surgical specimen grades, biopsy Gleason score grading has a significant rate of downgrading, ranging from 27% to 57%.[14] This discordance is related to the fact that prostate cancer is multifocal, with a heterogeneous population of tumor cells. Although biopsy lacks accuracy in predicting Gleason score in final pathology, Watson *et al.*[15] found that patients with PSM tend to have greater biopsy Gleason scores than those with negative margins. Our study found that the PSM rate was 13.0%, 32.2%, and 44.8% in patients with a Gleason score of ≤6, 7, and ≥8, respectively. Gleason score in biopsy was shown to be a significant predictor of PSM in LRP. Our further analysis showed that patients with higher biopsy Gleason scores had more possibility of capsule invasion, which could interpret the difference of PSM rates above.

The number of positive cores, maximum percentage tumor per core, and tumor laterality can indirectly reflect tumor size.[16] Our univariate analysis indicated that the number of positive cores and tumor laterality were significantly associated with PSM after LRP. Heidenreich *et al.*[17] reported that <50% positive biopsy cores was a significant predictor of organ-confined prostate cancer with negative surgical margins. Tuliao *et al.*[18] showed that the number of preoperative positive biopsy cores is a predictor of PSM after robot-assisted RP, especially in small prostates, which agrees with our study. As for tumor laterality, Bulbul *et al.*[19] reported that a unilateral positive biopsy does not predict unilateral disease and does not reflect the exact volume of the tumor. Our data also confirmed this, so it could not be used as a predictor of tumor distribution or PSM.

PNI is a potential histopathological marker in the prostate needle-biopsy specimen, defined as the tracking of carcinoma around nerves.[20] PNI on needle biopsy may signal an increased likelihood of EPE at the time of prostatectomy.[21] Lee *et al.*[22] found that biopsy PNI was associated with a significantly higher risk of PSM and pathological stage T3 disease. D'Amico *et al.*[23] reported that PNI in biopsy was an independent prognostic factor for prostate cancer recurrence. PNI found in preoperative biopsies, has also been found to be a predictor of metastasis and prostate cancer death in patients treated with dose-escalated radiotherapy.[24] PNI was confirmed as a predictor of PSM after LRP in our study, and with the highest OR value (4.961). Therefore, patients with PNI in biopsy should be paid more attention when doing LRP.

The size of the prostate is associated with oncological outcome.[25] The larger amount of benign tissues in large glands decreases the chances of tumor exposure, whereas tumor in small prostates has a higher possibility of exposure during dissection. Thus, large glands are associated with more difficult procedures but better oncological results.[26] In contrast, small glands are associated with easier surgery but less ideal oncological results.[27,28] Labanaris *et al.*[29] reported that men with smaller prostates had larger tumor volumes, were less organ confined, had more EPE, and experienced more biochemical recurrence. Sooriakumaran *et al.*[30] found that small prostate volume had a higher rate of PSM in patients undergoing RP. The results of multivariate analysis in our study also showed that prostate size was a protective factor against PSM (OR <1).

PSA has been used as a criterion for consideration for prostate biopsy.[31] In addition to diagnosing prostate cancer, preoperative PSA value may be related to PSM. Shelfo *et al.*[32] reported that patients with a PSA value >10 ng ml$^{-1}$ were more likely to have PSM. Liss *et al.*[33] demonstrated that with preoperative PSA >10 ng ml$^{-1}$, the risk of PSM increased nearly 8 times. In our study, there was no significant difference in PSM rate among three subgroups according to PSA values. This might have been attributed to some factors affecting the PSA level: some patients underwent irregular endocrine therapy in other hospitals; some patients may have had prostatitis; some patients experienced long-term indwelling catheterization before biopsy; and PSA detection was not standardized in hospitals from where some patients were referred. Although there was no significant difference, the PSM rate in the subgroup with PSA >20 ng ml$^{-1}$ was 38.1%, which was higher than in the other two subgroups (25.6% in PSA <10 ng ml$^{-1}$ and 27.3% in PSA 10–20 ng ml$^{-1}$). Therefore, we agree that for patients with preoperative PSA >20 ng ml$^{-1}$, PSM should still be fully considered. PSA density is a more significant predictor and cut-off value in terms of PSM compared with PSA.[34] We will include this parameter in our future study.

The overall PSM rate in this study was higher than that of Western countries.[12] A large proportion of our patients had PNI, a high Gleason score, a large number of positive cores in biopsy specimens, and/or high serum PSA, and may have been expected to have more advanced disease. This is reflected in the fact that 35.5% of our patients were found to have T3 or T4 disease. Stratifying patients by pathological stage, the PSM rate in patients with pT2 disease (17.8%) was comparable to the outcomes of studies from Western countries,[35] while the PSM rate in patients with capsule invasion was as high as 49.5%. Therefore, the reason for the high PSM rate in this cohort was largely related to the high proportion of locally advanced disease. The median prostate volume in this study was also smaller than those in the series of Western countries. It is recognized that the relative volume of cancer to prostate volume is higher in small prostates.[29] It may also have partially contributed to the high PSM rate here.

## CONCLUSION

This study suggests patients with PNI, a high Gleason score, and a large number of positive cores in biopsy specimens tend to have EPE in the final pathological evaluation. These three factors are all predictors of PSM after LRP. In contrast, the volume of the prostate gland is a protective factor against PSM.

## AUTHOR CONTRIBUTIONS

RY, KC, and TH collected the data, performed the statistical analysis, and drafted the manuscript. YFZ, HBL, and LFX carried out the pathological evaluation. GTZ, XGL, and HQG conducted the patient care and follow-up. HQG and XGL conceived the study, and participated in its design and coordination, and helped to draft the manuscript. All authors read and approved the final manuscript.

## COMPETING INTERESTS

The authors declare no competing interests.

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