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The value of transperineal apical prostate biopsy in predicting urethral/apical margin status after radical prostatectomy

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Abstract

Purpose: To investigate potential preoperative predictors of urethral or apical positive surgical margin (PSM) and the value of apical prostate biopsy in predicting urethral/apical margin status after radical prostatectomy (RP).

Methods: A total of 531 patients who underwent RP during 2010 to 2017 at West China Hospital were enrolled in this retrospective study. Preoperative and postoperative factors including age, BMI, PSA, clinical T stage and biopsy Gleason score were analyzed. Univariate analysis and logistic regression were used to find out the potential predictive factors for PSM. Two logistic regression models were built to evaluate the role of apical prostate biopsy in predicting urethral/apical margin status.

Results: The overall PSM rate was about 30.1% (160/531) and 97 of them were reported urethral/apical PSM. The incidence of urethral or apical PSM in patients with positive cores in the apical prostate was higher than those without (23.0% vs 9.9%, $P < .001$). We further found that the multivariable model with positive apical prostate biopsy could significantly increase the predictive value of urethral or apical PSM status (AUC: 0.744 vs 0.783, $P = .016$). Our analysis also showed that neo-adjuvant hormone therapy was an independent protective factor for urethral or apical PSM in patients with positive apical prostate biopsy, but not all patients.

Conclusion: This study revealed the necessity of apical prostate biopsy to predict the risk of apical or urethral PSM. In clinical practice, neo-adjuvant hormone therapy should be given when patients with positive apical prostate biopsy to reduce the presence of PSM, especially patients with high/very high risk prostate cancer.

Abbreviations: ADT = androgen-deprivation therapy, AUC = area under curve, BMI = body mass index, cT = clinical T stage, NCCN = National Comprehensive Cancer Network, NHT = neo-adjuvant hormone therapy, PCa = prostate cancer, PSA = prostate-specific antigen, PSM = positive surgical margin, PZP = peripheral zone of prostate, ROC = receiver operating characteristic curve, RP = radical prostatectomy.

Keywords: apical prostate, positive surgical margin, predictive model, prostate cancer, transperineal prostate biopsy

1. Introduction

Prostate cancer (PCa) is a prevalent solid tumor and seriously threaten the health of elderly men in Western and Asian countries.[1,2] Radical prostatectomy (RP) is considered one of the standard treatments for patients with localized PCa.[3–5] Many clinical and pathological factors could affect the progression and prognosis of patients after RP, including Gleason score, prostate-specific antigen (PSA), TNM stage, and so on.[6] Unfortunately, the high occurrence of positive surgical margin (PSM) after RP is always associated with an increased risk of biochemical recurrence.[7–9] Along with laparoscopic and robot-assisted laparoscopic RP are skillfully used, the incidence of PSM is decreased, especially in high and very high risk groups.[10]

Several studies showed that some clinical and histopathologic factors were correlated with the margin status after RP.[6] Serum PSA level, the ratio of positive biopsy needles, Gleason score, clinical T stage, tumor volume and the experience of surgeon have been consistently associated with the margin status after RP.[11–13] The location of tumor in different prostate zone might also influence the status of surgical margin.[14] However, these factors could not fully predict the occurrence of PSM. Therefore, it is critical to find out more accurate preoperative predictors to evaluate the incidence of PSM and to take some measures to minimize it.

By evaluating preoperative variables of 531 consecutive patients who underwent RP, this study was to investigate the

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relationship between a new potential predictive model (focused on transperineal apical prostate biopsy) and the status of urethral or apical margin in the real world, and to find out more rational treatment strategies to reduce PSM occurrence.

2. Methods

After institutional review board approval, we reviewed our PCa database and screened patients undergone RP at West China hospital between January 2009 and December 2017. We excluded patients who had incomplete preoperative biopsy or postoperative pathologic information, mainly those did not undergo an extensive prostate biopsy in our hospital. Finally, a total of 531 patients were included in this retrospective study. All patients were clarified into different risk groups according to National Comprehensive Cancer Network (NCCN) guideline (PSA, Gleason score and T stage). Patients with high/very high risk according to NCCN guideline were advised to receive neo-adjuvant hormone therapy (NHT, mainly androgen-deprivation therapy) before surgery about 3 to 6 months. The baseline demographic information of patients, including age, body mass index (BMI), baseline PSA level, prostate volume, clinical T stage (cT), Gleason score, PSM and prostate biopsy related information were reviewed and reported.

2.1. Prostate biopsy technique

Transperineal prostate biopsy was performed with an 18 gauge × 2 cm Tru-cut core biopsy needle (Bard, Tempe, AZ, USA) under transrectal ultrasound guidance. Ten (left/right 1–5) cores in the peripheral zone of prostate (PZP); 2 (left/right 6) cores in the apical region of prostate (punctured from peripheral zone to transitional zone) (Fig. 1). Gleason grading system was used to evaluate samples from prostate biopsy,[15] number of positive cores and tumor location were also reported.

2.2. Surgical technique and pathologic evaluation of prostate specimens

The surgical procedures were performed by 3 different surgeons (WQ, LX and ZH). 117 (22.1%) patients accepted open RP, 176 (33.1%) patients underwent laparoscopy RP and 238 (44.8%) patients underwent robot-assisted laparoscopic RP.

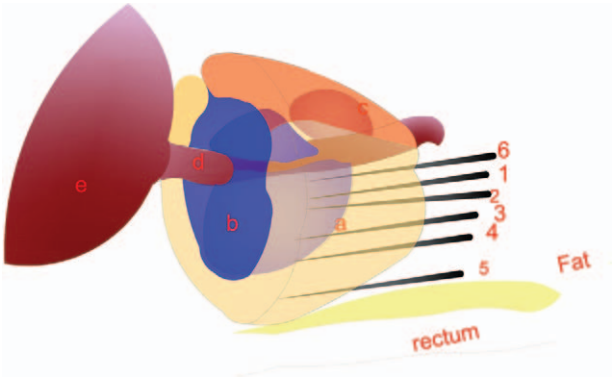

Figure 1. Schematic diagram of transrectal ultrasound-guided transperineal prostate biopsy in different zones. A: peripheral zone of prostate; B: transitional zone of prostate; C: fibrous matrix zone of prostate; D: urethral; E: bladder 1–5th cores: biopsy cores in the right/left peripheral zone of prostate 6th core: biopsy cores in the right/left apical region of prostate (punctured from the peripheral to transitional zone).

Pathologic processing of specimens followed a standardized regimen that did not change substantially over time. The margins of prostate specimens were inked in black, and tissues were fixed overnight in formalin. Prostatic tissue was sectioned according to the standardized protocol: each tissue section was firstly labeled according to its location. The prostatic tissue was subsequently serially sectioned at 5-mm intervals from the apical to the base. Each slice was further sectioned into 4 pieces labeled individually according to their exact location on the slides.

All margin statuses were independently evaluated by two senior pathologists (CN and GJ), including apical, urethral and basal margins.[15] PSM was defined as the unequivocal presence of tumor at the inked margin of the prostate specimens. "Quasi-contact" or "close-by" margins were regarded as negative.

2.3. Statistical analysis

X^2 test and logistic regression were used to identify potential predictive factors for PSM. The total cohort was split into the training (N = 372, 70%) and the validation cohort (N = 359, 30%). The training cohort was used for the multivariate analysis and the model building, while the validation of the models was conducted using the validation cohort. Two logistic regression models were initially built, one using preoperative factors only and another using biopsy cores in the apical zone of the prostate and preoperative variables combined. Preoperative factors entered the 2 models were serum PSA, clinical T stage and biopsy Gleason score. Receiver operating characteristic curve (ROC) was used to test the discrimination ability of the models.

Finally, univariate analysis and logistic regression were used to find out the potential predictive factors for the PSM after RP. A 2-sided $P < .05$ was considered statistically significant. All statistical analyses were performed using SPSS v.22.0 (SPSS Inc, Chicago, IL).

3. Results

Patients' basic characters were shown in Table 1. The overall PSM rate was about 30.1% (160/531). The distributions of these PSMs in different locations were 35.0% (56/160) in the apical margin, 31.9% (51/160) in the urethral margin and 18.1% (29/160) in basal prostate, respectively. Our results also showed that the incidence of urethral or apical PSM in patients with positive cores in apical prostate was higher than those without positive cores in apical prostate (23.0% vs 9.9%, $P < .001$). We also found a significant difference in PSM incidences between patients with low/intermediate risk prostate cancer (14.1%) and patients with high/very high risk prostate cancer (39.2%) ($P < .001$).

3.1. The predictive value of clinical and biopsy features for urethral or apical positive surgical margin in all patients and in patients with high/very high risk prostate cancer

Age, BMI, PSA, prostate volume, Gleason score, cT stage, and NHT were enrolled in the univariable and multivariable analysis. Other important factors, including positive biopsy cores (>9), positive cores in PZP and apical prostate were also analyzed. Before analyzing, the relationship between positive biopsy cores (>9) and the total prostate cancer detection of all patients was found by area under curve (AUC).[16]

Table 1

Characteristics of all patients, patients with apical prostate biopsy (+) and patients with apical prostate biopsy (−).

	All (n, %)	Training Cohort (n, %)	Validation Cohort (n, %)	*P* value*	Apical prostate biopsy (+) (n, %)	Apical prostate biopsy (-) (n, %)
Age (yr)						
≥70	184 (34.7)	129 (34.7)	55 (34.6)	.985	117 (34.5)	67 (34.9)
<70	347 (65.3)	243 (65.3)	104 (65.4)		222 (65.5)	125 (65.1)
BMI (kg/m^2)	23.1±2.56	22.5±2.16	24.3±1.96	.943	23.5±3.07	22.8±2.71
PSA (ng/ml)						
≤20	325 (61.2)	229 (61.6)	96 (60.4)	.798	192 (56.6)	133 (69.3)
>20	206 (38.8)	143 (38.4)	63 (39.6)		147 (43.4)	59 (30.7)
Prostate volume (ml)						
<20	62 (11.7)	43 (11.6)	19 (11.9)	.584	45 (13.3)	17 (8.9)
20-60	410 (77.2)	291 (78.2)	119 (74.8)		262 (77.3)	148 (77.1)
>60	59 (11.1)	38 (10.2)	21 (13.2)		32 (9.4)	27 (14.1)
Grade group						
1	92 (19.3)	65 (17.5)	27 (17.0)	.555	37 (10.9)	55 (28.6)
2	167 (30.5)	122 (32.8)	45 (28.3)		106 (31.3)	61 (31.8)
3	124 (23.5)	81 (21.8)	43 (27.0)		85 (25.1)	39 (20.3)
4	56 (10.5)	42 (11.3)	14 (8.8)		36 (10.6)	20 (10.4)
5	92 (16.3)	62 (16.7)	30 (18.9)		75 (22.1)	17 (8.9)
T stage						
T2	214 (40.3)	152 (40.9)	62 (39.0)	.868	124 (36.6)	90 (46.9)
T3a	208 (39.2)	143 (38.4)	65 (40.9)		140 (41.3)	68 (35.4)
T3b,4	109 (20.5)	77 (20.7)	32 (20.1)		75 (22.1)	34 (17.7)
Neo-adjuvant therapy						
+	57 (10.7)	43 (11.6)	14 (8.8)	.348	40 (11.8)	17 (8.9)
−	474 (89.3)	329 (88.4)	145 (91.2)		299 (88.2)	175 (91.1)
Positive biopsy cores>9						
+	112 (23.0)	86 (23.1)	36 (22.6)	.905	112 (33.0)	10 (5.2)
−	409 (77.0)	286 (76.9)	123 (77.4)		227 (67.0)	182 (94.8)
Apical PSM						
+	56 (10.5)	37 (9.9)	19 (11.9)	.491	46 (13.6)	10 (5.2)
−	475 (89.5)	335 (90.1)	140 (88.1)		293 (86.4)	182 (94.8)
Urethral PSM						
+	51 (9.6)	41 (11.0)	10 (6.3)	.090	41 (12.1)	10 (5.2)
−	480 (90.4)	331 (89.0)	149 (93.7)		298 (87.9)	182 (94.8)
Urethral or apical PSM						
+	97 (18.3)	72 (19.4)	25 (15.7)	.321	78 (23.0)	19 (9.9)
−	434 (81.7)	300 (80.6)	134 (84.3)		261 (73.0)	173 (90.1)
PSM in basilar part						
+	29 (5.5)	22 (5.9)	7 (4.4)	.483	28 (8.3)	1 (0.5)
−	502 (94.5)	350 (94.1)	152 (95.6)		311 (91.7)	191 (99.5)
All PSM						
+	160 (30.1)	109 (29.3)	51 (32.1)	.523	133 (39.2)	27 (14.1)
−	371 (69.9)	263 (70.7)	108 (67.9)		206 (60.8)	165 (85.9)
NCCN risk group						
Low	7 (1.3)	5 (1.3)	2 (1.3)	.607	3 (0.9)	4 (2.1)
Intermediate	125 (23.5)	92 (24.7)	33 (20.8)		69 (20.4)	56 (29.1)
High/very high	399 (75.2)	275 (73.9)	124 (78.0)		267 (78.7)	132 (68.8)

BMI = body mass index, NCCN = National Comprehensive Cancer Network, PSA = prostate-specific antigen, PSM = positive surgical margin.
* Comparison between those in the training and the validation cohort.

As shown in supplemental tables (Tables S1 and S2, http://links.lww.com/MD/D300), no significant association was observed in the univariable analysis between urethral or apical PSM and age, BMI, NHT and positive cores in PZP. But in the multivariable analysis (Tables 2 and 3), cT stage and biopsy Grade group (according to Gleason grading system) were significant predictive factors of PSM both in all patients and in patients with high/very high risk prostate cancer. These results suggested that PSA, Grade group, cT stage and "apical prostate biopsy (+)" were valuable predictors for the status of urethral or apical PSM both in all patients and in patients with high/very high risk prostate cancer.

3.2. Models to predict the possibility of urethral or apical positive surgical margin in all patients and in patients with high/very high risk prostate cancer

The whole patients were split into the training (N=372, 70%) and the validation cohort (N=359, 30%). The training cohort was used for the multivariate analysis and the model building,

Table 2

Multivariate analysis of the relationship between clinical and biopsy features and urethral or apical positive surgical margin in total group.

	Training cohort (N = 372)		Apical prostate biopsy (+) (N = 236)		Apical prostate biopsy (-) (N = 136)	
	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
PSA (≤20 ng/ml vs >20 ng/ml)	1.28 (0.68–2.44)	.446	1.27 (0.61–2.62)	.520	–	–
Grade group (1–5)						
1 vs 2	1.42 (0.41–4.86)	.578	0.91 (0.21–3.93)	.896	2.82 (0.28–28.32)	.379
1 vs 3	1.82 (0.52–6.31)	.348	1.38 (0.32–6.01)	.671	2.99 (0.26–34.82)	.383
1 vs 4	1.43 (1.35–5.91)	.019	0.84 (0.15–4.61)	.837	5.50 (0.44–67.96)	.184
1 vs 5	3.67 (1.02–13.23)	.047	3.02 (0.66–13.82)	.155	7.04 (0.55–90.00)	.133
T stage (T2 vs T3a vs T3b, T4)						
T2 vs T3a	1.48 (0.69–3.17)	.314	2.59 (1.05–6.35)	.038	–	–
T2 vs T3b, T4	4.25 (1.83–9.91)	.001	5.74 (2.07–15.95)	.001	–	–
Positive biopsy cores (>9)	1.28 (0.64–2.57)	.493	1.45 (0.67–3.11)	.343	1.51 (0.14–15.88)	.734
Neo-adjuvant therapy	–	–	0.33 (0.11–0.95)	.046		
Apical prostate biopsy (+)	3.50 (1.59–7.68)	.002	–	–	–	–

CI = Confidence interval, OR = odds ratio, PSA = prostate-specific antigen.

while the validation of the models is conducted using the validation cohort. Baseline factors were perfectly balanced between cases in the two cohorts (Table 1). To investigate the predictive value of positive cores in the apical prostate biopsy in all patients, 2 models were built and compared by logistic regression analysis (with or without "positive apical prostate biopsy"). We found that the addition of "apical prostate biopsy (+)" to a standard multivariable model, including PSA, Gleason score, cT stage, could significantly increase the predictive value of urethral or apical PSM (AUC: 0.783 vs 0.744, $P = .016$) (Table 4 and Fig. 2). According to this model, the risk of urethral or apical PSM in patients with positive apical prostate biopsy was 3.78 times higher than that in patients without positive apical prostate biopsy. It suggested that "apical prostate biopsy (+)" was an independent factor to predict the possibility of urethral or apical PSM in all patients and its incidence might be higher when patients with a positive core in apical prostate than those without a positive core in apical prostate.

To further investigate which factors could predict the urethral or apical PSM status in patients with high/very high risk prostate cancer, another 2 models were also built and compared by logistic regression analysis (with or without "positive apical prostate biopsy"). We found that, as the model for all patients, the model with "apical prostate biopsy (+)" could significantly increase the predictive value of urethral or apical PSM (AUC: 0.795 vs 0.743, $P = .009$) (Table 5 and Fig. 3). It was observed that the risk of urethral or apical PSM in patients with "positive apical prostate biopsy" was 4.88 times higher than that in patients without "positive apical prostate biopsy" in high/very high risk prostate cancer. This suggested that "apical prostate biopsy (+)" was also an independent factor to predict the possibility of urethral or apical PSM in patients with high/very high risk prostate cancer and its incidence would be higher when the patients with a positive core in apical prostate than those without.

3.3. The predictive value of clinical and biopsy features for urethral or apical positive surgical margin in patients with positive core in apical prostate

To investigate which factors could influence the status of urethral or apical PSM in patients with positive core in apical prostate, univariable and multivariate analysis were performed in the subgroups. Besides PSA, Gleason score, cT stage and positive biopsy cores (>9), the association was observed between NHT and urethral or apical PSM in "apical prostate biopsy (+)" subgroup (Table S1, http://links.lww.com/MD/D300 and Table 2). The analysis showed that NHT was an independent

Table 3

Multivariate analysis of clinical and biopsy features in patients with high/very high risk prostate cancer.

	Training cohort (n = 275)		Apical prostate biopsy (+) (n = 183)		Apical prostate biopsy (-) (n = 92)	
	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
PSA (≤20 ng/ml vs >20 ng/ml)	1.49 (0.74–3.02)	.268	1.48 (0.68–3.21)	.326	–	–
Grade group (1–5)						
1 vs 2	1.26 (0.23–6.97)	.789	1.95 (0.19–19.57)	.570	0.38 (0.02–6.70)	.511
1 vs 3	1.35 (0.24–7.46)	.730	2.43 (0.24–24.37)	.451	0.46 (0.03–8.17)	.600
1 vs 4	1.40 (1.23–8.50)	.035	1.88 (0.17–21.04)	.609	1.55 (0.12–20.29)	.739
1 vs 5	3.29 (1.06–17.76)	.043	6.67 (0.68–64.93)	.102	1.97 (0.15–26.78)	.609
T stage (T2 vs T3a vs T3b, T4)						
T2 vs T3a	2.37 (0.78–7.22)	.130	3.91 (1.00–15.20)	.049	–	–
T2 vs T3b, T4	6.78 (2.21–20.79)	.001	9.75 (2.50–37.96)	.001	–	–
Positive biopsy cores (>9)	1.22 (0.58–2.57)	.605	–	–	1.75 (0.16–19.77)	.651
Neo-adjuvant therapy	–	–	0.36 (1.11–1.17)	.039	–	–
Apical prostate biopsy (+)	4.55 (1.80–11.50)	.001	–	–	–	–

CI = confidence interval, OR = odds ratio, PSA = prostate-specific antigen.

Table 4

Models of preoperative predictive factors of urethral or apical surgical margin status in total group.

Validation cohort (N = 159)	Model without apical prostate biopsy (+)		Model with apical prostate biopsy (+)		
	OR (95%CI)	*P*	Beta-value	OR (95%CI)	*P*
PSA (≤20 ng/ml vs >20 ng/ml)	1.48 (0.79–2.75)	.217	0.268	1.31 (0.69–2.47)	.409
Grade group (1–5)					
2 vs 1	1.93 (0.58–6.41)	.282	0.375	1.45 (0.43–4.98)	.550
3 vs 1	2.44 (0.72–8.25)	.151	0.647	1.91 (0.55–6.58)	.306
4 vs 1	2.01 (1.51–7.83)	.015	0.443	1.56 (1.39–6.29)	.033
5 vs 1	5.75 (1.69–19.61)	.005	1.387	4.00 (1.14–14.07)	.030
T stage (T2 vs T3a vs T3b, T4)					
T3a vs T2	1.50 (0.71–3.17)	.289	0.396	1.49 (0.69–3.18)	.307
T3b, T4 vs T2	4.09 (1.85–9.04)	.000	1.521	4.58 (2.02–10.38)	.000
Apical prostate biopsy (+)	–	–	1.329	3.78 (1.77–8.05)	.001
PA	0.744	–		0.783	.016

CI = confidence interval, OR = odds ratio, PSA = prostate-specific antigen.

The logistic regression equation is established based on the beta-value: logit (p) = −3.764 + 0.268 (if PSA > 20ng/mL) + 0.375 (if Grade Group = 2) + 0.647 (if Grade Group = 3) + 0.443 (if Grade Group=3) + 1.387 (if Grade Group = 4) + 0.396 (if T stage=T3a) + 1.521 (if T stage = T3b or T4) + 1.329 (if Apical prostate biopsy +).

The probability (*P*) of a patient to have urethral or apical surgical margin is $\frac{1}{1+\exp[-\text{logit}(p)]}$.

protective factor for urethral or apical PSM in "apical prostate biopsy (+)" subgroup and these patients should be given androgen deprivation therapy before RP. However, NHT could not influence the presence of urethral or apical PSM in the total group and the "apical prostate biopsy (−)" subgroup (Table S1, http://links.lww.com/MD/D300 and Table 2).

To further investigate which factors could influence the status of urethral or apical PSM in high/very high risk prostate cancer patients with "apical prostate biopsy (+)", univariable and multivariate analysis were also performed in this subgroup. The association was also observed between NHT and urethral or apical PSM, besides PSA, Gleason score, cT stage and positive biopsy cores (>9) (Table S2, http://links.lww.com/MD/D300 and Table 3). However, no influence of NHT was observed in the total group and the "apical prostate biopsy (−)" subgroup with high/very high risk prostate cancer. These analyses showed that NHT should be an independent protective factor for urethral or apical PSM in "apical prostate biopsy (+)" patients with high/very high risk prostate cancer and these patients should receive androgen deprivation therapy before RP.

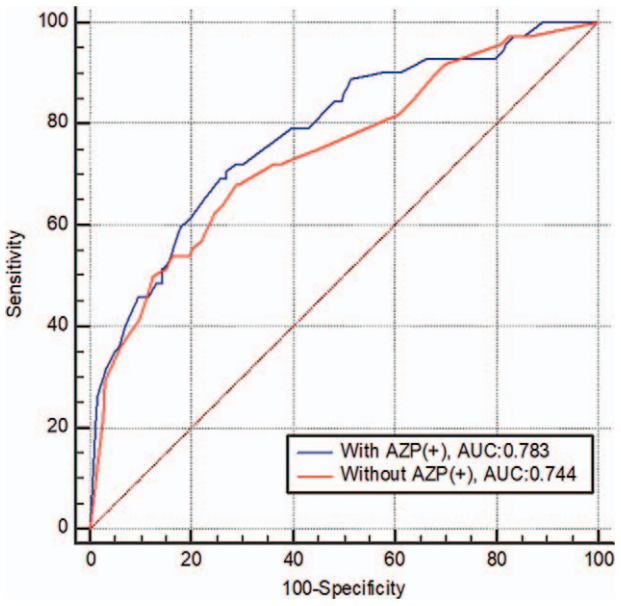

Figure 2. Models to predict the possibility of urethral or apical positive surgical margin in all patients. Addition of apical prostate biopsy (+) to a standard multivariable model, including PSA, Gleason score, cT stage, could significantly increase the predictive value of urethral or apical PSM (*P* = .016).

4. Discussion

To our knowledge, this is the first study to investigate the relationship between the location of prostate biopsy and PSM, and this is the first one to explore the value of positive core in apical prostate to predict urethral/apical PSM. Because a significant difference of PSM incidence is observed between patients with low/intermediate risk prostate cancer and patients with high/very high risk prostate cancer, the subgroup of patients with high/very high risk prostate cancer have been closely focused in our study. This study suggests that the positive biopsy cores in apical prostate are dominant determinant for urethral or apical PSM and could significantly increase the value of the model to predict PSM. What is more, neo-adjuvant hormone therapy could obviously reduce the risk of urethral or apical PSM in patients with positive biopsy cores in apical prostate, especially high/very high risk prostate cancer.

PSM status after RP is a well-established prognostic factor for prostate cancer, which is associated with increased biochemical or local disease recurrence, as well as the need for secondary treatment.[7,8,17–20] Therefore, the status of surgical margins is one of the most important features to be evaluated in any innovative surgical treatment proposed for prostate cancer. Several models have been previously developed to predict PSM and risk of disease recurrence after RP based on preoperative variables.[6,21–23] These models are generally based on preoperative Gleason score, serum PSA, and T stage, which are the most common factors to assess an individual patient's risk of extraprostatic disease and to predict potential PSM.[24]

Even though PSA, Gleason score and T stage can help us to estimate the possibility of PSM,[23] the presence of cancer in apical prostate can significantly improve the prediction accuracy of urethral or apical PSM according to our study. This suggested that we should pay more attention to those patients with positive

Table 5

Models of preoperative predictive factors of urethral or apical surgical margin status in patients with high/very high risk prostate cancer.

Validation cohort (N = 124)	Model without apical prostate biopsy (+)		Model with apical prostate biopsy (+)		
	OR (95%CI)	*P*	Beta-value	OR (95%CI)	*P*
PSA (≤20 ng/ml vs >20 ng/ml)	1.80 (0.91–3.56)	.093	0.413	1.51 (0.75–3.05)	.249
Grade group (1–5)					
1 vs 2	1.83 (0.35–9.54)	.475	0.270	1.31 (0.24–7.23)	.757
1 vs 3	1.80 (0.34–9.35)	.487	0.359	1.43 (0.26–7.84)	.679
1 vs 4	2.03 (1.36–11.49)	.022	0.416	1.52 (1.25–9.03)	.028
1 vs 5	5.31 (1.06–26.51)	.042	1.278	3.59 (1.68–18.85)	.031
T stage (T2 vs T3a vs T3b, T4)					
T3a vs T2	2.61 (0.88–7.76)	.085	0.865	2.37 (0.78–7.24)	.128
T3b, T4 vs T2	6.80 (2.33–19.82)	.000	1.976	7.22 (2.41–21.62)	.000
Apical prostate biopsy (+)	–	–	1.585	4.88 (2.00–11.89)	.000
PA	0.743	–		0.795	.009

CI = confidence interval, OR = odds ratio, PSA = prostate-specific antigen.

The logistic regression equation is established based on the beta-value: logit (p) = −4.369 + 0.413 (if PSA > 20ng/mL) + 0.270 (if Grade Group=2) + 0.359 (if Grade Group = 3) + 0.416 (if Grade Group = 3) + 1.278 (if Grade Group = 4) + 0.865 (if T stage = T3a) + 1.976 (if T stage = T3b or T4) + 1.585 (if Apical prostate biopsy+).

The probability (*P*) of a patient to have urethral or apical surgical margin is $\frac{1}{1+\exp[-\text{logit}(p)]}$.

biopsy core in the apical part of prostate. What is more, the surgical experience of urologists could also have a direct impact on the margin status. A survey study reported that the risk of positive surgical margin after RP was related with surgeon's experience with >100 cases.[13] Another study found a significant reduction of PSM related to surgeon's experience in pT2 patients, but not in pT3 patients.[25] The surgeon's experience should be considered as a potential factor of positive surgical margins.

To prevent urinary incontinence and erectile dysfunction, urologic surgeons always prioritize the preservation of neurovascular bundle and urethral as much as possible.[26] Thus, it is important to balance the contradiction between the execution of wide surgical excision of periprostatic tissue and the risk of PSM occurrence and dysfunction. In our study, we considered the tissue in the apical part of prostate and surrounded urethral by prostate biopsy. After pathological evaluation, we could know whether there was tumor in apical prostate. Some surgeons are attempting to evaluate the margin status in RP specimens by intraoperative pathology consultation. Several studies have shown the potential benefits of frozen section assessment not only when positive margins are suspected, but also when requested routinely at specific prostatic sites where positive margins are often seen (e.g., urethral stump next to the apex).[27–29] However, because of the difficulty in diagnosing prostatic adenocarcinoma on frozen section assessment specimens, there are risks of false positive and false negative surgical margins.[27,29] Additionally, in some of the cases, especially with extensive tumor, positive surgical margins could be identified on RP specimens at the sites where frozen section assessment was not carried out.[30] Thus, there is currently no clear consensus as to patient selection, as well as the appropriate site of margin tissue and the number of the specimens sampled for frozen section consultation.

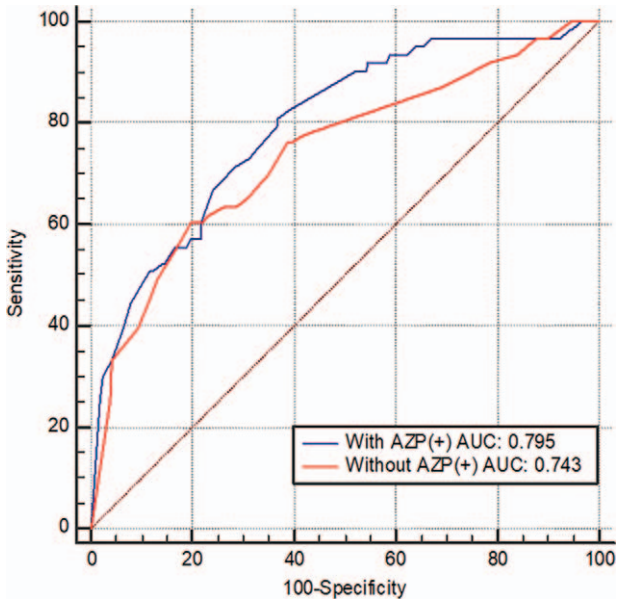

Figure 3. Models to predict the possibility of urethral or apical positive surgical margin in patients with high/very high risk of prostate cancer. As the model for all patients, the addition of apical prostate biopsy (+) to a standard multivariable model, including PSA, Gleason score, cT stage, significantly increase the predictive value of urethral or apical PSM (*P* = .009).

Neo-adjuvant hormone therapy including androgen-deprivation therapy (ADT) and androgen blockade, before radical radiotherapy or radical prostatectomy, has been utilized in multimodal treatment in patients with intermediate to high/very high risk PCa.[31] NHT is recommended for high/very high-risk groups to shrink prostate volume before RP, thereby reducing tissue injury during operation and leading to a safer and more thorough treatment.[31] In patients receiving NHT before RP, pathological down-staging and PSM rates are significantly improved in some patients.[32] However, there is still no preferable biomarker for identifying prostate cancer patients who are suitable for neoadjuvant ADT. Patients whether should be given NHT before RP or not, always dependent his Gleason score, PSA and clinical T stage.[33] Age, as well as serum testosterone levels before treatment, might be other possible biomarkers to identify candidates suitable for neoadjuvant ADT.[34] In our study, it is interesting that NHT could reduce the urethral or apical PSM rate in all patients and in patients with high/very high risk PCa, especially in those with positive biopsy cores in apical prostate. This suggested that "apical prostate biopsy (+)" patients with high/very high risk PCa should be given neo-adjuvant therapy before RP to reduce the incidence of apical/urethral PSM.

There are some limitations and bias in this retrospective study. Even though a large sample of patients underwent RP have been analyzed, the overall incidence of PSMs in our series was proportionally higher than other reports, and the percentage of low/intermediate risk prostate cancer was too lower. In addition, only urethral or apical PSM has been analyzed in our study, the established model was consequently not feasible for other PSMs. And other factors, such as the number of PSMs, the percentage of cancer involving each core and multi-parametric magnetic resonance imaging, have not been evaluated. Neo-adjuvant therapy was mainly given according to PSA, Gleason score or T stage before the operation in this retrospective study; however, only a few patients with high/very high risk would like to receive neo-adjuvant ADT in the clinical practice. Whether NHT still works in reducing PSM based on cancer detection status in apical prostate needs further research.

5. Conclusion

As the first study to investigate the association between biopsy cores in apical prostate and apical or urethral margin status, it demonstrates the value of apical prostate biopsy in predicting urethral or apical PSM. It is necessary to get cores by a transperineal apical prostate biopsy to predict the possibility of apical or urethral PSM after radical prostatectomy. And neo-adjuvant hormone therapy should be given when patients with a positive core in apical prostate to reduce the presence of PSM, especially patients with high/very high risk prostate cancer. Of course, further prospective researches are needed to further verify our topic.

Author contributions

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