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The influence of prostate volume on pathological outcomes after radical prostatectomy

A single-center retrospective study

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Abstract

Currently, the association between prostate volume (PV) or prostate weight with pathological outcomes in patients with prostate cancer (PCa) is not well understood. This study aimed to explore whether PV can predict the adverse pathological outcomes of PCa patients after radical prostatectomy (RP). A total of 1063 men with confirmed localized PCa who underwent RP at the First Affiliated Hospital of Zhejiang University from January 2014 to April 2019 were retrospectively analyzed. Patients were assigned into small, medium and large groups based on the PV. The analysis of variance, χ^2 test or Student *t* test was performed to compare differences among groups. Univariate and multivariate analyses were performed to identify significant predictors of pathological outcomes upgrading. Among the 1063 cases, approximately 35.0% had an upgrade of postoperative pathology. Compared with the small prostate group, more patients in the large prostate group achieved a Gleason score (GS) 6 and International Society of Urological Pathology (ISUP) grade 1 of postoperative pathological findings, clinical cT_{1c} and cT_{2a} stages and pathological pT_{2a} and pT_{2b} stages; the incidence of positive surgical margins and extraprostatic extension was relatively low (all $P < .001$). In multiple logistic regression, PV served as a significant predictor of any Gleason score upgrading (GSU) (odds ratio [OR] 0.988, 95% confidence interval [CI] 0.978–0.998), major GSU (OR 0.980, 95% CI 0.965–0.995) and any ISUP grade group upgrading (GGU) (OR 0.989, 95% CI 0.979–0.999). This study shows that PV can predict adverse pathological outcomes in PCa patients after radical prostatectomy. Pca patients with smaller prostate volume tend to have the high-grade disease at postoperative pathology as well as pathological outcome upgrading.

Abbreviations: BMI = body mass index, CI = confidence interval, EPE = extraprostatic extension, GGU = grade group upgrading, GS = Gleason score, GSU = Gleason score upgrading, ISUP = International Society of Urological Pathology, OR = odds ratio, PCa = prostate cancer, PSA = prostate-specific antigen, PSAD = prostate-specific antigen density, PSM = positive surgical margins, PV = prostate volume, RP = radical prostatectomy, SVI = seminal vesicle invasion, TRUS = transrectal ultrasound.

Keywords: Chinese cohort, pathological outcome upgrading, prostate cancer, prostate volume, radical prostatectomy

1. Introduction

A recent study published in 2019 indicated that prostate cancer (Pca) is the most common cancer and the second leading cause of cancer mortality among men in the U.S.[1] Currently, radical prostatectomy (RP) is the gold standard treatment for localized PCa that decreases cancer-specific mortality.[2] A

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All the authors had full access to the data in the study and gave final approval of the manuscript. The corresponding author had final responsibility for the decision to submit for publication.

The authors have no conflicts of interest to declare.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

All research involving human participants was approved by the First Affiliated Hospital, Zhejiang University School of Medicine prior to the start of study. Due to the retrospective nature of this study, the requirement for informed consent was waived by the review board of the hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

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Table 1

Patient characteristics.

	Overall	Small prostate group: PV < 30 mL	Medium prostate group: PV 30–80 mL	Large prostate group: PV > 80 mL	*P* value
No. pts (%)	1063 (100.0%)	519 (48.8%)	514 (48.4%)	30 (2.8%)	
Mean ± SD age	67.52 ± 6.48	67.33 ± 6.54	67.96 ± 5.71	69.20 ± 4.27	**.001**
Mean ± SD BMI (kg/m^2)	23.67 ± 3.15	23.26 ± 2.90	23.28 ± 2.52	23.55 ± 2.94	.85
Median ng/mL PSA (IQR)	11.40 (7.53–19.78)	10.64 (7.02–17.25)	12.11 (7.85–22.18)	14.32 (10.90–19.75)	**.001**
PV (cm^3):					
Median (IQR)	30.41 (23.89–40.11)	23.79 (20.20–26.96)	38.90 (34.32–49.04)	92.90 (83.73–104.11)	**.001**
Mean ± SD	34.76 ± 16.69	23.92 ± 4.31	44.87 ± 11.44	93.81 ± 10.96	
PSAD:					
Median (IQR)	0.38 (0.23–0.64)	0.48 (0.31–0.80)	0.31 (0.19–0.52)	0.16 (0.10–0.19)	**.001**
Mean ± SD	0.56 ± 0.65	0.79 ± 0.85	0.40 ± 0.30	0.27 ± 0.41	
No. procedure (%):					
Opened RP	305 (28.7%)	135 (12.7%)	159 (15.0%)	11 (1.0%)	.123
Laparoscopic RP	347 (32.6%)	168 (15.8%)	173 (16.3%)	6 (0.6%)	
Robot-assisted RP	411 (38.7%)	216 (20.3%)	182 (17.1%)	13 (1.2%)	
Surgery yr (%):					
2015	244 (23.0%)	128 (12.0%)	110 (10.3%)	6 (0.6%)	.405
2016	216 (20.3%)	106 (10.0%)	100 (9.4%)	10 (0.9%)	
2017	44 (4.1%)	23 (2.2%)	19 (1.8%)	2 (0.2%)	
2018	236 (22.2%)	113 (10.6%)	116 (10.9%)	7 (0.7%)	
2019	323 (30.4%)	149 (14.0%)	169 (15.9%)	5 (0.5%)	
% Cores positive:					
Median (IQR)	0.38 (0.20–0.50)	0.40 (0.25–0.63)	0.30 (0.20–0.50)	0.16 (0.10–0.41)	**.001**
Mean ± SD	0.41 ± 0.25	0.47 ± 0.24	0.37 ± 0.24	0.26 ± 0.22	
No. biopsy Gleason score (%):					
6	323 (30.4%)	143 (13.5%)	164 (15.4%)	16 (1.5%)	.063
7	492 (46.3%)	254 (23.9%)	230 (21.6%)	8 (0.8%)	
8	182 (17.1%)	87 (8.2%)	91 (8.6%)	4 (0.4%)	
9 or 10	66 (5.9%)	35 (3.3%)	29 (2.7%)	2 (0.2%)	
No. pathological gleason score (%):					
6	156 (14.7%)	53 (5.0%)	92 (8.7%)	11 (1.0%)	**.001**
7	680 (64.0%)	356 (33.5%)	310 (29.2%)	14 (1.3%)	
8	122 (11.5%)	60 (5.6%)	61 (5.7%)	1 (0.1%)	
9 or 10	105 (9.9%)	50 (4.7%)	51 (4.8%)	4 (0.4%)	
No. biopsy ISUP grade (%):					
1	323 (30.4%)	143 (13.5%)	164 (15.4%)	16 (1.5%)	.073
2	298 (28.0%)	155 (14.6%)	140 (13.2%)	3 (0.3%)	
3	197 (18.5%)	99 (9.3%)	93 (8.7%)	5 (0.5%)	
4 or 5	245 (23.0%)	122 (11.5%)519	117 (11.0%)	6 (0.6%)	
No. Pathological ISUP grade (%):					**.001**
1	156 (14.7%)	53 (5.0%)	92 (8.7%)	11 (1.0%)	
2	374 (35.2%)	187 (17.6%)	179 (16.8%)	8 (0.8%)	
3	306 (28.8%)	169 (15.9%)	131 (12.3%)	6 (0.6%)	
4 or 5	227 (21.4%)	110 (10.3%)	112 (10.5%)	5 (0.5%)	
No. Clinical stage (%):					**.001**
cT_{1c}	84 (7.9%)	32 (3.0%)	48 (4.5%)	4 (0.4%)	
cT_{2a}	128 (12.0%)	47 (4.4%)	68 (6.4%)	13 (1.2%)	
cT_{2b}	301 (28.3%)	154 (14.5%)	143 (13.5%)	4 (0.4%)	
cT_{2c}	526 (49.5%)	278 (26.2%)	239 (22.5%)	9 (0.8%)	
cT_{3a}	3 (0.3%)	2 (0.2%)	1 (0.1%)	0 (0.0%)	
cT_{3b}	21 (2.0%)	6 (0.6%)	15 (1.4%)	0 (0.0%)	
No. Pathological stage (%):					**.001**
pT_{1c}	1 (0.1%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	
pT_{2a}	126 (11.9%)	40 (3.8%)	75 (4.6%)	11 (1.0%)	
pT_{2b}	180 (16.9%)	81 (7.6%)	92 (3.3%)	7 (0.7%)	
pT_{2c}	275 (25.9%)	138 (13.0%)	131 (6.0%)	6 (0.6%)	
pT_{3a}	328 (30.9%)	188 (17.7%)	137 (5.2%)	3 (0.3%)	
pT_{3b}	150 (14.1%)	70 (6.6%)	77 (3.4%)	3 (0.3%)	
pT_4	3 (0.3%)	1 (0.1%)	2 (0.1%)	0 (0.0%)	
PSM No. Pts (%)	348 (32.7%)	188 (17.7%)	156 (14.7%)	4 (0.4%)	**.009**
EPE No. Pts (%)	491 (46.2%)	265 (24.9%)	220 (20.7%)	6 (0.6%)	**.001**
SVI No. Pts (%)	154 (14.5%)	71 (6.7%)	80 (7.5%)	3 (0.3%)	.537
LNI No. Pts (%)	44 (4.1%)	19 (1.8%)	2 (0.2%)	2 (0.2%)	.629

Values are presented as number (%) or mean (±SD).

BMI = body mass index, EPE = extraprostatic extension, ISUP = International Society of Urological Pathology, LNI = lymph node involvement, PSA = prostate-specific antigen, PSAD = PSA density, PSM = positive surgical margins, PV = prostate volume, RP = radical prostatectomy, SVI = seminal vesicle invasion.

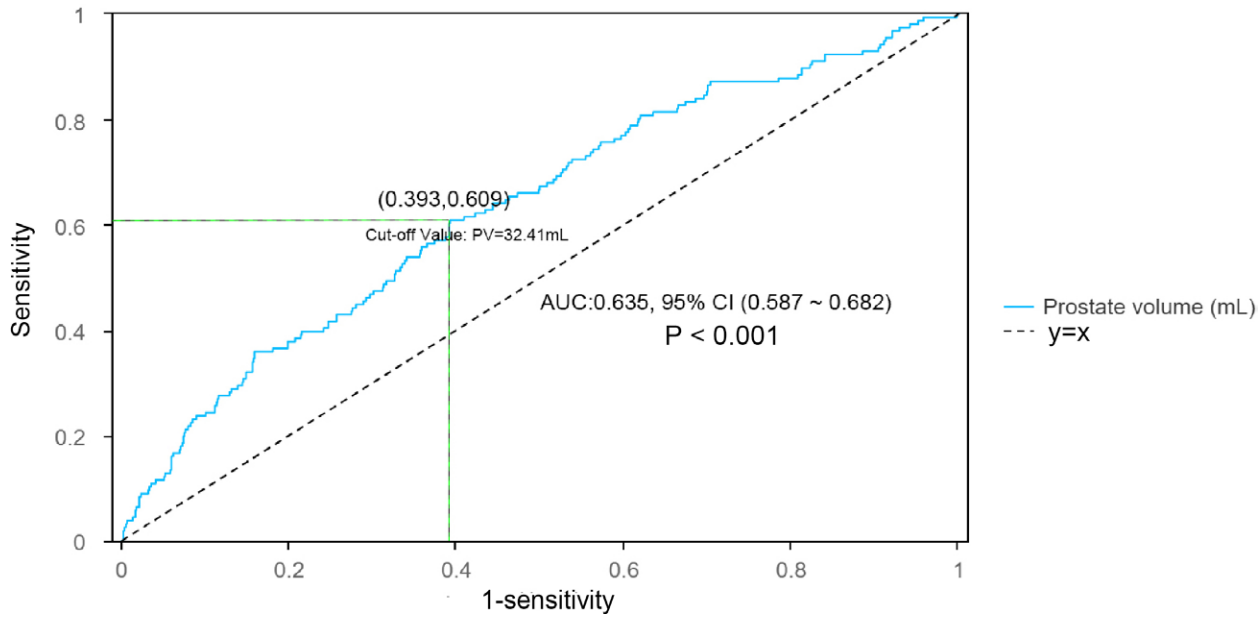

Figure 1. Receiver operating characteristic (ROC) curve predicting the association between prostate volume and low-risk prostate cancer.

prostate biopsy is widely recognized as a clinical gold standard for the diagnosis of PCa. It is a common clinical phenomenon that approximately 30% to 50% of patients with low-risk PCa experienced pathological outcome upgrading in postoperative pathology.[3–5] Therefore, it is imperative to identify factors correlated with pathological outcome updating or adverse pathological outcome among PCa patients. Although evidence from numerous studies has indicated PV may be associated with adverse pathological outcomes in PCa,[6–12] some research has shown that there is no actual relationship between the 2.[13,14]

Therefore, considering the limited studies published in China on this topic, we hypothesized that PV or prostate weight might be a risk factor of adverse pathological outcomes. To test this hypothesis, we investigated the relationship between PV and a range of adverse tumor features in PCa patients treated with RP based on a large cohort of data from an electronic medical record system.

2. Methods

2.1. Patient population and exclusion criteria

The electronic medical record system of the Department of Urology at the First Affiliated Hospital, Zhejiang University School of Medicine was searched under approval by the institutional review board. We retrospectively analyzed 1256 consecutive patients with clinically localized PCa from January 2014 to April 2019. All cases treated with RP at the First Affiliated Hospital of Zhejiang University for this period. Exclusion criteria included the following. Patients who received radiation therapy (59) or neoadjuvant hormonal therapy (24) or chemotherapy (2) before RP; had previously undergone transurethral resection of the prostate (17); used 5a-reductase inhibitors (38) and those with incomplete pathological or clinical information (53). The final analytical cohort comprised of remaining 1063 patients. Potential grade progression between examination procedures appears not to be a problem because most patients who performed biopsy were operated on within 3 months. Clinicopathological information, including age, PV, body mass index (BMI), preoperative serum prostate-specific antigen (PSA) levels, percentage of positive biopsy cores, prostate-specific antigen density (PSAD), biopsy and operative specimen Gleason score (GS), biopsy and surgical specimen International Society of Urological Pathology (ISUP) grade, surgical mode, year of surgery, clinical stage and pathological characteristics, were collected and analyzed from medical records.

2.2. Variable definitions

PV of each patient was measured preoperatively using transrectal ultrasound (TRUS), which is the most commonly applied in PV estimation.[15] PV was measured through taking the widely accepted prolate ellipsoid formula: PV = 0.52 × (length × widt h × height).[16,17] PSAD was obtained by dividing the preoperative serum PSA level by the TRUS-measured PV. The following formula was used to determine the extent of PCa detected by biopsy: cores positive percentage = (number of positive cores/number of cores taken) × 100%.

RP was conducted by open, laparoscopic or robot-assisted techniques. Prostate specimens were processed using same methods and subjected to microscopic examination. All preoperative biopsies, microscopic examinations of the surgical specimen and pathological grading were performed by a urogenital pathologist in our hospital. The clinical staging of PCa patients was assessed by the 8th edition of the American Joint Committee on Cancer staging system.[18] Gleason score, International Society of Urological Pathology (ISUP) grade group and the pathological classification of PCa patients were evaluated in line with the ISUP PCa 5-level grouping method proposed in 2014,[19,20] and were considered important pathologic outcomes. Pathological outcome upgrading, including Gleason score upgrading (GSU) and ISUP grade group upgrading (GGU) were defined as an increase in pathological score from biopsy tissues to the surgical specimen. For further analysis, GSU was subdivided into minor GSU and major GSU.

2.3. Statistical analyses

Patients were assigned into small, medium and large prostate groups depending on different PV. The grouping criteria were: PV < 30 mL, PV ≥ 30 and ≤ 80 mL, and PV > 80 mL, respectively, following the latest European Association of Urology Guidelines.[2] The analysis of variance, χ^2 test or Student *t* test was performed to estimate whether differences among groups

Table 2

Associations of prostate volume with adverse pathologic features at radical prostatectomy as assessed via univariate and multivariable logistic regression models.

	PV on univariate analysis			PV On Multivariate Analysis		
Outcomes	**Estimated parameters**	**95% CI**	***P* value**	**Estimated parameters**	**95% CI**	***P* value**
No. clinical stage (%)						
(ref: cT3b)	0.445	−0.559 to 1.449	.385			
cT1c	0.391	−0.582 to 1.364	.431			
cT2a	−0.670	−1.662 to 0.283	.168			
cT2b	−0.510	−1.442 to 0.423	.284			
cT2c	−0.001	−2.571 to 2.571	1.000			
cT3a						
Biopsy ISUP grade						
group	1.0	−0.063 to 0.670	.104			
(ref: grade 4)	0.304	−0.726 to 0.075	.111			
grade 1	−0.326	−0.699 to 0.186	.257			
grade 2	−0.256					
grade 3						
Pathological ISUP						
grade group	1.0	0.301 to 1.173	**.001**	0.500	0.034 to 0.966	**.036**
(ref: grade 4)	0.737	−0.316 to 0.443	.547	−0.087	−0.483 to 0.309	.667
grade 1	0.064	−0.813 to 0.025	.065	−0.512	−0.941 to −0.083	**.019**
grade 2	−0.394					
grade 3						
Biopsy GS (ref: GS ≥ 9)	1.0					
GS = 6	0.500	−0.134 to 1.134	.122			
GS = 7	−0.101	−0.730 to 0.528	.752			
GS = 8	0.259	−0.415 to 0.933	.451			
Pathological GS (ref:	1.0					
GS ≥ 9)	0.186	0.215 to 1.306	.442			
GS = 6	−0.120	−0.583 to 0.378	.547			
GS = 7	0.357	−0.560 to 0.649	.078			
GS = 8						
PSM negative	0.380	0.074 to 0.685	**.015**	−0.044	−0.503 to 0.415	.850
EPE negative	0.525	0.242 to 0.807	**.001**	0.468	0.034 to 0.902	**.035**
SVI negative	−0.058	−0.445 to 0.329	.769			
LNI negative	−0.341	−0.985 to 0.303	.299			

EPE = extraprostatic extension, GS = Gleason score, ISUP = International Society of Urological Pathology, LNI = lymph node involvement, PSM = positive surgical margins, PV = prostate volume, SVI = seminal vesicle invasion.

were significant. The receiver operating characteristic curve analysis was conducted to predict the association between PV and low-risk PCa. cutoff value was calculated by the area under the curve. Univariate and multivariate analyses were performed using the logistic regression models to identify predictive factors of pathological outcome upgrading. All statistical analyses were conducted using the IBM SPSS 16.0 software (SPSS, Chicago, IL) and a 2-tailed $P < .05$ was considered statistically significant.

3. Results

The characteristics of all 1063 patients are presented in Table 1. The mean age of the patients at the time of surgery was 67.52 (standard deviation (SD) 6.48) years, the mean BMI was 23.67 (SD 3.15) kg/m2, the mean preoperative PV was 34.76 (SD 16.69) mL, the mean preoperative serum PSA level was 11.40 ng/mL and the mean preoperative PSAD was 0.56 (SD 0.65). The mean age of the large prostate group was significantly higher relative to that of the small prostate group (69.20 years v 67.33 years; $P < .001$). Similarly, the small prostate group had lower preoperative PSA levels (10.64 ng/mL v 14.32 ng/mL; $P < .001$). Patients with smaller prostates had higher PSAD and percentage of positive biopsy cores, when compared to large prostate group (0.48 v 0.16 and 40% v 16%; all $P < .001$, respectively). In addition, a significant difference for various clinicopathological PCa features was observed between large and small prostate group. A higher percentage of patients in the large prostate group had Gleason score 6 and ISUP grade 1 in postoperative pathological findings, clinical cT_{1c} and cT_{2a} stages and pathological pT_{2a} and pT_{2b} stages (all $P < .001$). The incidence of PSM and extraprostatic extension (EPE) was lower in the large prostate group compared with that in the small prostate group ($P = .009$ and $P < .001$, respectively). There was no significant difference in the incidence of SVI and lymph node involvement between the 2 groups (Table 1). For the relationship between PV and low-risk PCa, the area under the curve was 0.635 (95% CI 0.587–0.682, $P < .001$) and the cutoff value of PV was 32.41mL, indicating that patients with PV > 32.41 mL had better pathological GS (Fig. 1).

Univariate analyses showed that a large PV was significantly associate with the pathological ISUP grade 1 ($P < .001$) and PSM negative incidence ($P = .015$) in Table 2. After adjusting for age, BMI, PSA level, year of surgery, surgical mode, clinical stage and the percentage of positive biopsy cores, multivariable analyses also showed that a larger PV was linked to pathological ISUP grade 1 ($P = .036$) and EPE negative incidence ($P = .035$) while a smaller PV was linked to pathological ISUP grade 3 ($P = .019$).

Table 3 shows the relationship between adverse pathological outcomes and clinical characteristics of 1063 PCa patients. High-grade PCa patients, including GS 9 or 10 and ISUP grade 4 or 5 were older, had a higher percentage of cores positive, higher preoperative baseline serum PSA, higher PSAD, higher clinical stage and higher incidence of PSM, EPE, SVI and lymph node involvement.

Table 3

Clinical characteristics of 1063 PCa patients performed with RP and univariate comparisons across groups.

	Pathological Gleason Score					Pathological ISUP Grade				
	6	7	8	9 or 10	*P* value	1	2	3	4 or 5	*P* value
No. pts (%)	156 (14.7%)	680 (64.0%)	122 (11.5%)	105 (9.9%)		156 (14.7%)	374 (35.2%)	306 (28.8%)	227 (21.4%)	
Age Mean ± SD	65.54 ± 7.77	67.78 ± 6.15	68.20 ± 6.35	67.99 ± 6.22	**.001**	65.54 ± 7.77	67.52 ± 5.98	68.09 ± 6.342	68.11 ± 6.279	**.001**
BMI Mean ± SD (kg/m2)	23.32 ± 3.10	23.69 ± 3.14	24.22 ± 2.64	23.42 ± 3.72	.095	23.32 ± 3.10	23.89 ± 2.64	23.44 ± 3.64	23.84 ± 3.21	.108
PSA Median	8.58	11.03	14.84	19.23	**.001**	8.58	9.78	14.04	17.16	**.001**
(IQR) ng/ml	(6.80–12.46)	(7.35–18.86)	(9.41–27.46)	(12.56–34.97)		(6.80–12.46)	(6.80–14.78)	(8.48–23.34)	(10.40–30.86)	
PV (cm^3)										
Median	35.62	29.28	30.29	30.87	**.001**	35.62	30.00	28.40	30.77	**.001**
(IQR) (cm^3)	(27.64–51.59)	(23.12–38.44)	(24.60–40.06)	(22.99–39.02)		(27.63–51.59)	(23.15–40.82)	(23.08–37.19)	(24.24–39.91)	
Mean ± SD	42.05 ± 20.66	33.38 ± 15.72	33.64 ± 13.82	34.17 ± 16.70		42.05 ± 20.66	34.17 ± 16.23	32.42 ± 15.03	33.89 ± 15.19	
PSAD:										
Median	0.23	0.38	0.52	0.64	**.001**	0.23	0.33	0.46	0.58	**.001**
(IQR)	(0.17–0.32)	(0.24–0.62)	(0.28–0.96)	(0.39–1.12)		(0.17–0.32)	(0.21–0.52)	(0.31–0.79)	(0.34–0.99)	
Mean ± SD	0.27 ± 0.16	0.53 ± 0.50	0.76 ± 0.82	1.00 ± 1.21		0.27 ± 0.16	0.44 ± 0.33	0.64 ± 0.46	0.87 ± 0.58	
No. procedure										
Opened RP (%)	43 (4%)	188 (17.7%)	31 (2.9%)	43 (4.0%)	.388	43 (4.0%)	102 (9.6%)	86 (8.1%)	74 (7.0%)	.643
Laparoscopic RP	54 (5.1%)	226 (21.3%)	41 (3.9%)	26 (2.4%)		54 (5.1%)	118 (11.1%)	108 (10.2%)	67 (6.3%)	
Robot-assisted	59 (5.6%)	266 (25.0%)	50 (4.7%)	36 (3.4%)		59 (5.6%)	154 (14.5%)	112 (10.5%)	86 (8.1%)	
Surgery year:										
2015	28 (2.6%)	159 (15.0%)	31 (2.9%)	26 (2.4%)	.209	28 (2.6%)	89 (8.4%)	70 (6.6%)	57 (5.4%)	**.030**
2016	38 (3.6%)	124 (11.7%)	32 (3.0%)	22 (2.1%)		38 (3.6%)	77 (7.2%)	47 (4.4%)	54 (5.1%)	
2017	4 (0.4%)	35 (3.3%)	3 (0.3%)	2 (0.2%)		4 (0.4%)	18 (1.7%)	17 (1.6%)	5 (0.5%)	
2018	34 (3.2%)	148 (13.9%)	26 (2.4%)	28 (2.6%)		34 (3.2%)	67 (6.3%)	81 (7.6%)	54 (5.1%)	
2019	52 (4.9%)	214 (20.1%)	30 (2.8%)	27 (2.5%)		52 (4.9%)	123 (11.6%)	91 (8.6%)	57 (5.4%)	
Cores pos: %										
Median (IQR)	0.20 (0.10–0.30)	0.38 (0.20–0.50)	0.46	0.60	**.001**	0.20	0.30	0.40	0.50	**.001**
Mean ± SD	0.24 ± 0.18	0.40 ± 0.24	(0.30–0.63)	(0.38–0.88)		(0.10–0.30)	(0.20–0.50)	(0.25–0.60)	(0.30–0.75)	
			0.47 ± 0.24	0.61 ± 0.28		0.24 ± 0.18	0.36 ± 0.22	0.44 ± 0.25	0.54 ± 0.27	
Clinical stage					**.001**					**.001**
cT1c	36 (3.4%)	45 (4.2%)	3 (0.3%)	0 (0.0%)		36 (3.4%)	29 (2.7%)	16 (1.5%)	3 (0.3%)	
cT2a	43 (4.0%)	73 (6.9%)	8 (0.8%)	4 (0.4%)		43 (4.0%)	51 (4.8%)	22 (2.1%)	12 (1.1%)	
cT2b	33 (3.1%)	199 (18.7%)	44 (4.1%)	25 (2.4%)		33 (3.1%)	103 (9.7%)	96 (9.0%)	69 (6.5%)	
cT2c	43 (4.0%)	357 (33.6%)	60 (5.6%)	66 (6.2%)		43 (4.0%)	189 (17.8%)	168 (15.8%)	126 (11.9%)	
cT3a	0 (0.0%)	1 (0.1%)	0 (0.0%)	2 (0.2%)		0 (0.0%)	0 (0.0%)	1 (0.1%)	2 (0.2%)	
cT3b	1 (0.1%)	5 (0.5%)	7 (0.7%)	8 (0.8%)		1 (0.1%)	2 (0.2%)	3 (0.3%)	15 (1.4%)	
No. PSM (%)	22 (2.1%)	201 (18.9%)	53 (5.0%)	72 (6.8%)	**.001**	22 (2.1%)	100 (9.4%)	101 (9.5%)	125 (11.8%)	**.001**
No. EPE (%)	28 (2.6%)	296 (27.8%)	78 (7.3%)	89 (8.4%)	**.001**	28 (2.6%)	149 (14.0%)	147 (13.8%)	167 (15.7%)	**.001**
No. SVI (%)	1 (0.1%)	76 (7.1%)	23 (2.2%)	54 (5.1%)	**.001**	1 (0.1%)	23 (2.2%)	53 (5.0%)	77 (7.2%)	**.001**
No. LNI (%)	0 (0.0%)	12 (1.1%)	10 (0.9%)	22 (2.1%)	**.001**	0 (0.0%)	3 (0.3%)	9 (0.8%)	32 (3.0%)	**.001**

Values are presented as number (%) or mean (±SD).

BMI = body mass index, CI = confidence interval, EPE = extraprostatic extension, ISUP = International Society of Urological Pathology, LNI = lymph node involvement, PCa = prostate cancer, PSA = prostate-specific antigen, PSAD = PSA density, PSM = positive surgical margins, PV = prostate volume, RP = radical prostatectomy, SVI = seminal vesicle invasion.

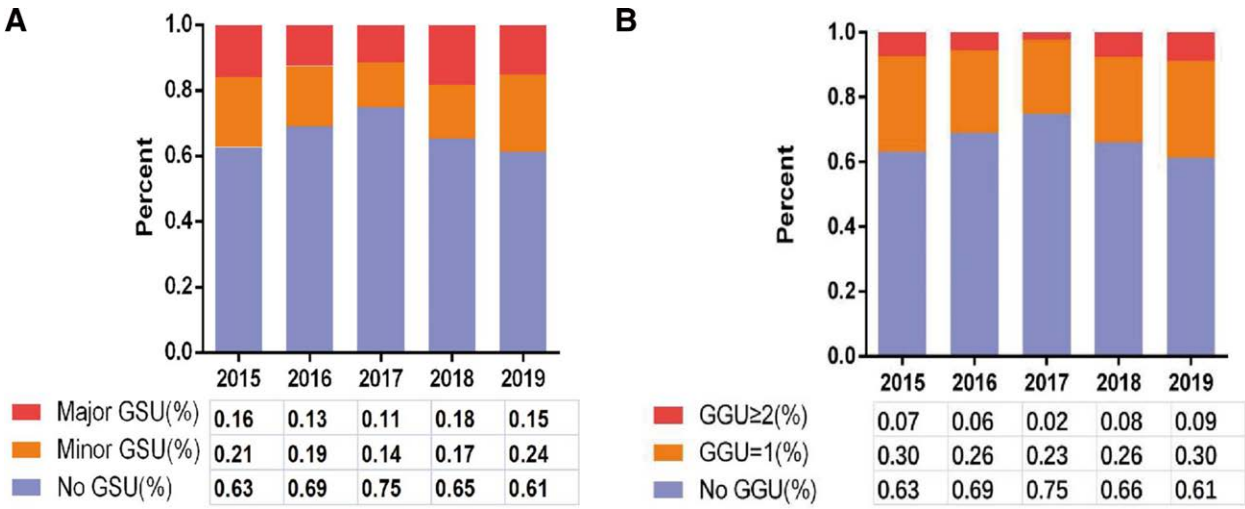

Figure 2. Proportion of Gleason score upgrading (GSU) and ISUP grade group upgrading (GGU) per surgery year is presented by the bar chart.

Table 4

Multivariate logistic regression models to predict any and major GSU, any and GGU ≥ 2.

	Any GSU		Major GSU		Any GGU		GGU ≥ 2	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.017 (0.996–1.038)	.112	1.019 (0.991–1.047)	.181	1.013 (0.993–1.034)	.204	0.984 (0.951–1.019)	.374
BMI (kg/m^2)	1.016 (0.974–1.060)	.453	1.003 (0.949–1.060)	.915	1.018 (0.976–1.062)	.441	1.049 (0.970–1.134)	.235
PSA ng/mL	1.009 (0.995–1.023)	.216	1.010 (0.993–1.027)	.253	1.008 (0.994–1.023)	.239	1.009 (0.986–1.032)	.446
PV (cm^3)	0.988 (0.978–0.998)	**.025**	0.980 (0.965–0.995)	**.011**	0.989 (0.979–0.999)	**.040**	0.992 (0.973–1.012)	.428
PSAD	1.072 (0.709–1.623)	.741	1.031 (0.636–1.673)	.901	1.084 (0.718–1.638)	.701	0.998 (0.498–1.999)	.995
Cores pos %	0.854 (0.404–1.804)	.679	0.896 (0.330–2.431)	.830	0.909 (0.430–1.921)	.802	0.768 (0.209–2.821)	.691
Surgery procedure								
(ref: opened RP)	1.0	.333	1.0	.797	1.0	.472	1.0	.340
Laparoscopic RP	1.177 (0.846–1.636)	.401	1.060 (0.682–1.645)	.710	1.129 (0.812–1.569)	.587	1.335 (0.737–2.419)	.428
Robot-assisted RP	1.147 (0.833–1.580)		1.084 (0.707–1.662)		1.093 (0.793–1.505)		1.266 (0.706–2.269)	
Clinical stage								
(ref: cT1c)	1.0	.764	1.0	.318	1.0	.869	1.0	.872
cT2a	1.093 (0.612–1.951)	.880	0.666 (0.300–1.479)	.943	1.050 (0.588–1.875)	.780	0.907 (0.276–2.980)	.409
cT2b	0.960 (0.560–1.643)	.455	1.025 (0.515–2.041)	.272	0.926 (0.541–1.586)	.417	1.546 (0.550–4.349)	.539
cT2c	0.800 (0.446–1.436)	.999	0.649 (0.300–1.404)	.999	0.785 (0.438–1.408)	.999	1.416 (0.466–4.301)	.999
cT3a	0.000 (0.000-NA)	.767	0.000 (0.000-NA)	.487	0.000 (0.000-NA)	.463	0.000 (0.000-NA)	.804
cT3b	0.850 (0.289–2.497)		0.595 (0.137–2.577)		0.663 (0.220–1.991)		0.746 (0.074–7.520)	

BMI = body mass index, CI = confidence interval, GGU = ISUP grade group upgrading, GSU = Gleason score upgrading, ISUP = International Society of Urological Pathology, OR = odds ratio, PSA = prostate-specific antigen, PSAD = PSA density, PV = prostate volume, RP = radical prostatectomy.

As shown in Figure 2, among the 1063 cases, approximately 35.0% had an upgrade of postoperative pathology, including GSU and GGU. Multivariate logistic regression analysis was further performed to identify the groups most likely to experience an upgrade of pathological outcomes after adjusting for BMI, age, PSA level, surgical mode, year of surgery, percentage of positive biopsy cores and clinical stage (Table 4). As expected, PV remained an important predictor of any GSU (OR 0.988, 95% CI 0.978–0.998), major GSU (OR 0.980, 95% CI 0.965–0.995) and any GGU (OR 0.989, 95% CI 0.979–0.999). Interestingly, patients with PV at the 30th percentile (25.12 mL) were more likely to experience major GSU (Fig. 3).

4. Discussion

In this large single-center cohort study, we demonstrated that the PV of the South Chinese cohort was significantly associated with pathological features. In China, the earliest research on the relationship between PV and histopathology in the northern cohort was in 2012.[21] The study reported that a small prostate was associated with poor histopathological prognosis, which is consistent with our results. The smaller PV was significantly associated with adverse clinicopathological outcomes, including higher clinical stage, higher GS or ISUP grade on postoperative pathological findings and higher incidence of EPE. Conversely, a significant correlation was found between the larger PV and clinicopathological outcomes of early-stage cancer.

Previous studies have explored the association between PV and pathological outcomes. Such studies reported that patients with larger PV (> 80 mL) have favorable pathological outcomes,[22] whereas smaller PV may reflect adverse pathological outcomes and an increased risk of progression after RP.[10]

In the present study, approximately 35.0% of cases were upgraded, which is in line with previous literature reports.[4] PV is still an important predictor of any GGU, any GSU and major GSU, especially at 30% of the PV (25.12 mL). Xu et al reported that PV < 30 mL was an independent risk factor for GSU after RP and in the group that PV < 30 mL, 62.5%

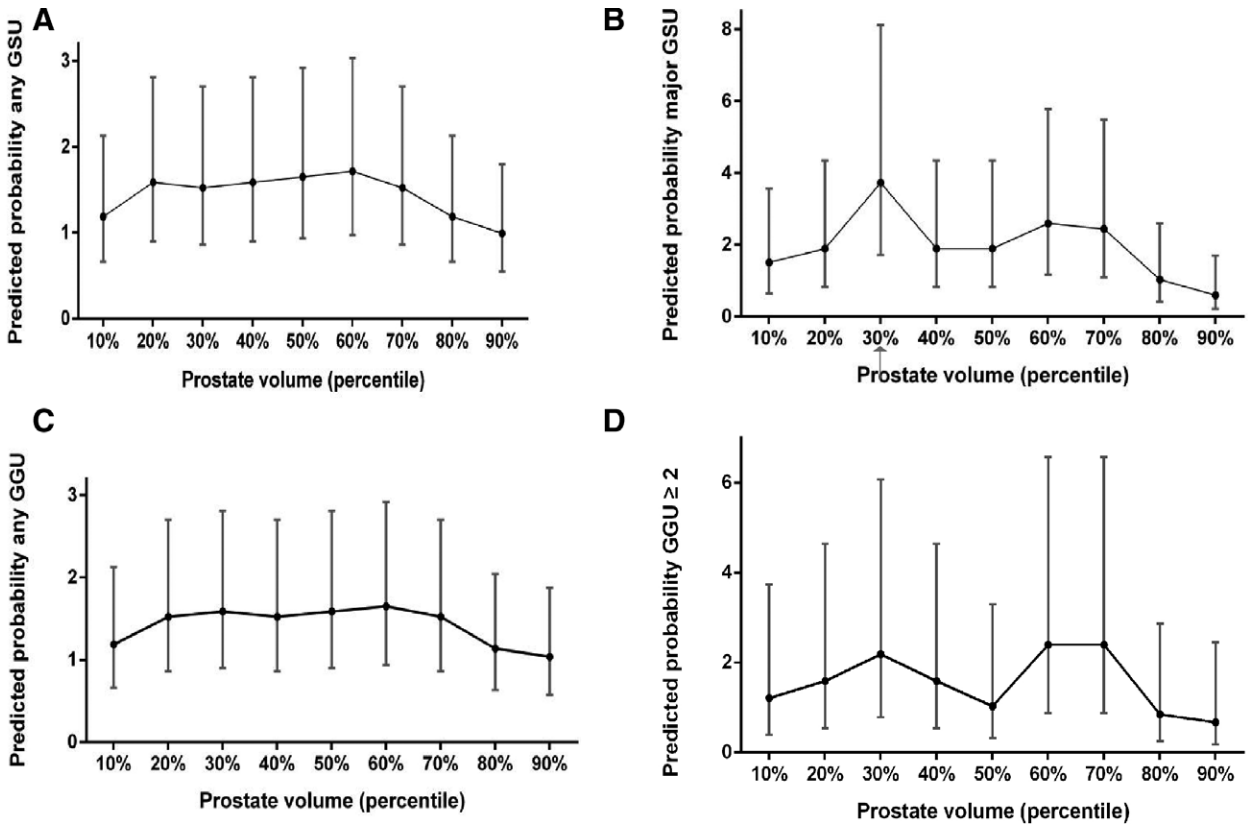

Figure 3. Line chart of prostate volume percentile with predicted GSU and GGU probability presented by OR and 95% CI.

of the cases had performed GSU.[23] Recently, other investigators suggested that smaller prostate was associated with an increased risk of GS upgrading, which could also strongly confirm our findings.[7,8]

The phenomenon that patients in large prostate group had better pathological results in PCa may perhaps be explained by the following 2 propositions. First, the presence of benign tissue in the large prostate may act as a biomolecular barrier to the growth of cancer cells, strangling their ability to grow. Also, it may serve as a physical buffer to prevent the local spread of malignant foci.[24,25] Benign prostate hyperplasia related transition zone enlargement may lead to adequate atrophy, scarring, and apoptosis of epithelial cells in the peripheral zone, significantly reducing the risk of developing prostatic adenocarcinoma in the remaining epithelial glands.[6] Another possibility is the lead-time bias. PSA level is largely influenced by the gland volume and not PCa. The PSA-driven biopsy is on account of PSA elevation from an enlarged gland.[26] This lead-time bias would lead to better pathological results.

Our study shows that men with smaller PV have a higher risk of pathological outcome upgrading. Previous studies have found that low serum testosterone levels were associated with higher grade, advanced stage and higher progression rates in PCa.[27,28] Small gland size may be a sign of lower androgenicity, which may promote the biological aggressiveness of PCa.[26,29] The exact mechanisms underlying this difference may be the change of intraprostatic microenvironment, where low testosterone level increases the density of androgen receptor and facilitates tumor microvessel formation[30,31] or a smaller prostate makes it easier for PCa cells to migrate beyond the prostatic capsule through a shorter distance. However, it is also argued that a significant reduction of androgen level may interfere with the grading of PCa, leading to artificial upgrading without accurately reflecting tumor biology.[32]

Regardless of the mechanisms between PV and pathological outcomes upgrading, this study has broad urological consequences. Identifying pathological outcomes upgrading in a high-risk group may be beneficial in clinical settings. Urologists make treatment decisions according to the patient risk class in which GS or ISUP grade of biopsy is a major component. Better risk assessment models are warranted for early identification of patients who are at high risk for pathological outcome upgrading and may assist clinicians determine whether the patients should receive individualized treatments such as brachytherapy or active surveillance. Therefore, patients with low-risk disease particularly benefit from the prediction of upgrading.

Nonetheless, our study has some limitations. First, because this is a retrospective study, there are inevitably potential selection bias and inaccuracy in data collection. Second, the evaluation of PV was performed only with TRUS, rather than the prostate specimen after RP to measure the prostate weight. This is because the prostate specimen weight in postoperative pathological reports was not recorded. Although the most accurate calculation of PV depends on postoperative measurement, it cannot be evaluated before the operation. Thus, the determination of prognostic role of PV before the operation is more useful for guiding individualized treatments. Third, the electronic medical record did not precisely report the actual situation of enrolled patients. As in other published retrospective studies, it is difficult to avoid the inherent biases of such a design; it is often unclear whether the study subject met the inclusion criteria or exclusion criteria in the true sense. Fourth, the location of tumor lesions and number of tumor lesions might influence the preoperative biopsy pathology outcomes. To minimize this effect, the most experienced sonographers are often assigned to perform prostate biopsy on patients under ultrasound guidance. Fifth, our research did not explore the association between tumor volume or PV and clinical outcomes

such as biochemical recurrence, which requires further study. Finally, as a single-center study in China, sample bias may exist and lead to a lack of representativeness. Therefore, the results may not apply to all patients with PCa. Future large-scale prospective multicenter studies that predict the postoperative pathological grades of the disease using PV and other biopsy parameters as covariate should be conducted to further verify our findings.

5. Conclusion

In conclusion, PV may serve as a useful predictor for adverse pathological parameters. PCa patients with a small volume prostate are more likely to have a high-grade disease at postoperative pathology, as well as PSM and EPE. Conversely, large PV has better pathological results. PCa patients with PV at the 30th percentile (25.12 mL) are at a higher risk of developing major GS upgrading.

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References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69:7–34.
[2] European Association of Urology. European Association of Urology Guidelines. 2020 Edition. Vol presented at the EAU Annual Congress Amsterdam 2020. Arnhem, The Netherlands: European Association of Urology Guidelines Office; 2020.
[3] Epstein JI, Feng Z, Trock BJ, et al. Upgrading and downgrading of prostate cancer from biopsy to radical prostatectomy: incidence and predictive factors using the modified Gleason grading system and factoring in tertiary grades. Eur Urol. 2012;61:1019–24.
[4] Chun FK, Steuber T, Erbersdobler A, et al. Development and internal validation of a nomogram predicting the probability of prostate cancer Gleason sum upgrading between biopsy and radical prostatectomy pathology. Eur Urol. 2006;49:820–6.
[5] Pinthus JH, Witkos M, Fleshner NE, et al. Prostate cancers scored as Gleason 6 on prostate biopsy are frequently Gleason 7 tumors at radical prostatectomy: implication on outcome. J Urol. 2006;176:979–84; discussion 984.
[6] Al-Khalil S, Ibilibor C, Cammack JT, et al. Association of prostate volume with incidence and aggressiveness of prostate cancer. Res Rep Urol. 2016;8:201–5.
[7] Davies JD, Aghazadeh MA, Phillips S, et al. Prostate size as a predictor of gleason score upgrading in patients with low risk prostate cancer. J Urol. 2011;186:2221–7.
[8] Gershman B, Dahl DM, Olumi AF, et al. Smaller prostate gland size and older age predict Gleason score upgrading. Urol Oncol. 2013;31:1033–7.
[9] Hong SK, Poon BY, Sjoberg DD, et al. Prostate size and adverse pathologic features in men undergoing radical prostatectomy. Urology. 2014;84:153–7.
[10] Kwon T, Jeong IG, You D, et al. Effect of prostate size on pathological outcome and biochemical recurrence after radical prostatectomy for prostate cancer: is it correlated with serum testosterone level? BJU Int. 2010;106:633–8.
[11] Newton MR, Phillips S, Chang SS, et al. Smaller prostate size predicts high grade prostate cancer at final pathology. J Urol. 2010;184:930–7.
[12] Sierra PS, Damodaran S, Jarrard D. Clinical and pathologic factors predicting reclassification in active surveillance cohorts. Int Braz J Urol. 2018;44:440–51.
[13] Kulkarni GS, Al-Azab R, Lockwood G, et al. Evidence for a biopsy derived grade artifact among larger prostate glands. J Urol. 2006;175:505–9.
[14] Marks RA, Koch MO, Lopez-Beltran A, et al. The relationship between the extent of surgical margin positivity and prostate specific antigen recurrence in radical prostatectomy specimens. Hum Pathol. 2007;38:1207–11.
[15] Harvey CJ, Pilcher J, Richenberg J, et al. Applications of transrectal ultrasound in prostate cancer. Br J Radiol. 2012;85 Spec No 1:S3–17.
[16] Lee JS, Chung BH. Transrectal ultrasound versus magnetic resonance imaging in the estimation of prostate volume as compared with radical prostatectomy specimens. Urol Int. 2007;78:323–7.
[17] Terris MK, Stamey TA. Determination of prostate volume by transrectal ultrasound. J Urol. 1991;145:984–7.
[18] Paner GP, Stadler WM, Hansel DE, et al. Updates in the eighth edition of the tumor-node-metastasis staging classification for urologic cancers. Eur Urol. 2018;73:560–9.
[19] Epstein JI, Allsbrook WC Jr, Amin MB, et al. The 2005 International Society of Urological Pathology (ISUP) consensus conference on gleason grading of prostatic carcinoma. Am J Surg Pathol. 2005;29:1228–42.
[20] Epstein JI, Egevad L, Amin MB, et al. The 2014 International Society of Urological Pathology (ISUP) consensus conference on gleason grading of prostatic carcinoma: definition of grading patterns and proposal for a new grading system. Am J Surg Pathol. 2016;40:244–52.
[21] Zhang F, Huang Y, Lu M, et al. Effect of prostate volume on histopathological prognosis after laparoscopic radical prostatectomy. Chin J Urol. 2012;33:360–3.
[22] Olsson CA, Lavery HJ, Sebrow D, et al. Does size matter? The significance of prostate size on pathologic and functional outcomes in patients undergoing robotic prostatectomy. Arab J Urol. 2011;9:159–64.
[23] Xu N, Wu YP, Li XD, et al. Risk of upgrading from prostate biopsy to radical prostatectomy pathology: is magnetic resonance imaging-guided biopsy more accurate? J Cancer. 2018;9:3634–9.
[24] Luo J, Duggan DJ, Chen Y, et al. Human prostate cancer and benign prostatic hyperplasia: molecular dissection by gene expression profiling. Cancer Res. 2001;61:4683–8.
[25] Stamey TA, Warrington JA, Caldwell MC, et al. Molecular genetic profiling of Gleason grade 4/5 prostate cancers compared to benign prostatic hyperplasia. J Urol. 2001;166:2171–7.
[26] Freedland SJ, Isaacs WB, Platz EA, et al. Prostate size and risk of high-grade, advanced prostate cancer and biochemical progression after radical prostatectomy: a search database study. J Clin Oncol. 2005;23:7546–54.
[27] Yamamoto S, Yonese J, Kawakami S, et al. Preoperative serum testosterone level as an independent predictor of treatment failure following radical prostatectomy. Eur Urol. 2007;52:696–701.
[28] Massengill JC, Sun L, Moul JW, et al. Pretreatment total testosterone level predicts pathological stage in patients with localized prostate cancer treated with radical prostatectomy. J Urol. 2003;169:1670–5.
[29] Davidson DD, Koch MO, Lin H, et al. Does the size matter?: Prostate weight does not predict PSA recurrence after radical prostatectomy. Am J Clin Pathol. 2010;133:662–8.
[30] Miller LR, Partin AW, Chan DW, et al. Influence of radical prostatectomy on serum hormone levels. J Urol. 1998;160:449–53.
[31] Risbridger GP. Recent progress in our understanding of inhibin in the prostate gland. J Endocrinol. 1998;157:1–4.
[32] Thompson IM, Klein EA, Lippman SM, et al. Prevention of prostate cancer with finasteride: US/European perspective. Eur Urol. 2003;44:650–5.