ORIGINAL RESEARCH
Urooncology

Doi: 10.4274/jus.galenos.2024.2024-2-4
J Urol Surg 2024;11(3):164-172

Correlation of Transrectal Ultrasonography Guided Prostate Biopsy Gleason Score Results with Prostate Volume in Patients with Prostate Specific Antigen Level Between 2.5-10 ng/mL

Coşkun Bostancı, Kazım Erdem

T.C. Ministry of Health, Karabük Training and Research Hospital, Clinic of Urology, Karabük, Turkiye

What's known on the subject? and What does the study add?

To investigate the correlation between prostate volume and Gleason score results obtained by systematic transrectal prostate biopsy in patients with a prostate-specific antigen value between 2.5 and 10 ng/mL.

Abstract

Objective: To investigate the correlation between prostate volume (PV) and Gleason score (GS) results obtained by systematic transrectal prostate biopsy in patients with a prostate-specific antigen value between 2.5 and 10 ng/mL.

Materials and Methods: A total of 904 patients who underwent transrectal prostate biopsy at our institution were divided into four groups based on PV calculated by transrectal ultrasonography. Group 1 had a PV ≤35 cc, group 2 had a PV ranging from 36 to 55 cc, group 3 had a PV between 56 and 75 cc, and group 4 had a PV >75 cc. Subgroups were based on biopsy-proven prostate carcinoma patients within each group in the same PV intervals, and prostate cancer detection rates and GSs were calculated for each group and subgroup.

Results: The prostate cancer detection rate was 78.5% in group 1 and decreased to 17.2% in group 4. GS ≥8 also decreased from 16.4% in group 1 to 2.5% in group 4. However, there was no statistically significant difference between GS ≥8 in the subgroups, with the results of 20.9% in group 1a and 15% in group 4a.

Conclusion: Our study results suggest an inverse relationship between PV and cancer detection rates. Although GS ≤6 rates in biopsy-proven prostate carcinoma patients increased and GS of 7 decreased in larger prostates, it was not obvious in patients with GS ≥8. Further prospective studies with large volumes of patients are required to confirm our results.

Keywords: General urology, pathology, urooncology

Introduction

Prostate cancer (PCa) and benign prostate hyperplasia (BPH) are two of the most frequently diagnosed urological diseases affecting aging men, and transrectal ultrasound-guided prostate biopsy (TRUS-PB) remains the commonly applied diagnostic procedure to detect them (1,2).

Although diagnostic multiparametric prostate magnetic resonance imaging (mpMRI) before biopsy has increased over the past decade and assisted biopsy indication in patients with suspicious lesions on mpMRI, the same is not valid for patients without lesions on mpMRI. Current guidelines recommend targeted and systematic biopsy for patients with suspicious lesions on mpMRI, but there is no consensus on patients with negative mpMRI (3). In addition, no suspicious lesion was detected in up to 30% of patients who underwent pre-biopsy mpMRI (4). Therefore, in cases where mpMRI cannot be performed, or the results are negative, classical biopsy parameters are still needed.

Correspondence: Coşkun Bostancı MD, T.C. Ministry of Health, Karabük Training and Research Hospital, Clinic of Urology, Karabük, Turkiye
Phone: +90 532 736 39 57 **E-mail:** coskunbostanci@hotmail.com **ORCID-ID:** orcid.org/0000-0002-4493-8653
Received: 16.02.2024 **Accepted:** 05.05.2024

Cite this article as: Bostancı C, Erdem K. Correlation of Transrectal Ultrasonography Guided Prostate Biopsy Gleason Score Results with Prostate Volume in Patients with Prostate Specific Antigen Level Between 2.5-10 ng/mL. J Urol Surg. 2024;11(3):164-172.

Traditionally, elevated levels of prostate-specific antigen (PSA) and abnormal digital rectal examination (DRE) were the sole parameters for deciding on a biopsy, given that TRUS-PB was conveniently performed in outpatient clinics. But PSA and DRE tests have limited ability to detect PCa, leading to overdiagnosis and overtreatment (5). For that reason, various PSA-dependent measures have been studied to improve the detection rate of PCa while minimizing the number of unnecessary biopsies. These variables include the free-to-total PSA ratio (f/t PSA), PSA velocity, PSA density (PSAD), age-referenced PSA, and transition zone PSAD (6,7). However, several studies have highlighted a significant inverse correlation between prostate volume (PV) and PCa. Clinical studies have demonstrated that patients diagnosed with PCa typically demonstrate comparatively lower PV than those diagnosed with BPH (8,9).

The Gleason score (GS) remains the essential grading system for evaluating PCa, and it plays a crucial role in determining the prognosis and treatment options for patients diagnosed with PCa (10). In addition, studies have shown that for patients with larger prostates, needle biopsy and radical prostatectomy (RP) pathology results have not only yielded lower detection rates of PCa but also resulted in more favorable GS results (11-13).

In this study, we aimed to determine the correlation between PV and PCa detection rate and the correlation of GS with PV in which TRUS-PB pathology results were taken as a reference point in patients with a PSA level between 2.5 and 10 ng/mL. Second aim was to compare diagnostic value of PV to other classical parameters and eligible cut-off value of PV in predicting PCa.

Materials and Methods

The study was conducted in line with the principles of the Declaration of Helsinki and the local ethics committee accepted this single-center retrospective study conducted between January 2016 and October 2023 (Local Ethics Committee of Karabük University, approval number: 2024/1633, date: 07.02.2024), we reviewed the medical records of 1337 patients undergoing TRUS-PB at our tertiary hospital between January 2016 and October 2023. The biopsy criteria included abnormal DRE, PSA ≥4 ng/mL, previous suspicious pathology, and suspicious lesions on mp-MRI. Following a comprehensive evaluation, 307 patients with PSA levels outside 2.5-10 ng/mL, 13 patients with fewer than 10 cores, 91 with atypical small acinar proliferation (ASAP) pathology, 11 with high-grade prostatic intraepithelial neoplasia results, and 11 with a known PCa diagnosis were eliminated. The final study comprised 904 eligible patients meeting all criteria.

TRUS-PB was performed in the same outpatient room with the same ultrasonography equipment and an automatic single-use 18 gauge- 24 cm biopsy needle with local anesthesia in the left decubital position.

The pathology doctors at our hospital evaluated the pathology results. Prostate intraepithelial neoplasia and BPH results were accepted as BPH, whereas GS ≥6 (stated by the International Society of Urological Pathology) was taken as PCa (14).

The study evaluated parameters of patient's age, PSA, free PSA (f PSA), PV measured by TRUS, f/t PSA ratio, PSAD, number of biopsy cores, patients with previous negative pathology (PNB) results, DRE results, biopsy pathology result, number of cores taken, and GSs. Although 455 patients had pre-biopsy mp-MRI, the PV measured by TRUS according to the ellipsoid formula (height × width × length × 0.52) was used for all patients for standardization.

According to the PV values, the patients were divided into four groups. Group 1 (PV ≤35 cc, 140 patients), group 2 (PV 36-55 cc, 287 patients), group 3 (PV 56-75 cc, 245 patients), and group 4 (PV ≥76 cc, 232 patients). Main pathological results and GS results were evaluated for each group. Then, within each main group, additional four subgroups were created for patients who were diagnosed with PCa through TRUS-PB, and the GS results were compared within each subgroup. These subgroups were group 1a (110 PCa patients, PV ≤35 cc), group 2a (112 PCa patients, PV=36-55 cc), group 3a (49 PCa patients, PV=56-75 cc), and group 4a (40 PCa patients, PV ≥76 cc). For our second aim we conducted receiver operating characteristic (ROC) curve analysis to determine the optimal cut-off value of PV for predicting PCa and compared its diagnostic value with other parameters.

Statistical Analysis

The suitability of numerical variables for normal distribution was tested with the Shapiro-Wilk test. Kruskal-Wallis and Dunn tests compared non-normally distributed variables in the four groups. Relationships between categorical variables were tested using the chi-square test, and multiple comparisons were tested using the Bonferroni test. Factors affecting PCa were tested by univariate and multivariate binary logistic regression analysis. ROC curve analysis was used to calculate and compare the area under the curve (AUC) of the variables. The analyses used the SPSS 22.0 Windows version package program and the MedCalc 19.7.1 version package program. $P<0.05$ was considered significant.

Results

Table 1 provides a concise overview of the parameters and pathological results of the 904 patients who were divided into four groups depending on PV. The mean age, PSA level, PV, PSAD, and f/t PSA ratio were 65.3 years, 6.3 ng/mL, 64.9 cc, 0.12 ng/mL/cc, and 0.23, respectively. Seven hundred and ninety-six patients (88.0%) had a primer biopsy, while 108 (11.9%) had a

PNB. The overall PCa detection rate was 34.4%, with a mean of 12.1 biopsy cores.

Group 4 had a higher age than group 2 and group 3. PSA levels were lower in group 1 and group 2 than in groups 3 and 4. PSA was lower in group 1 compared to all other groups. Similarly, f/t PSA was lower in group 1 and group 2 than in other groups. PSAD was lower in group 4 compared to all other groups. Anormal DRE was higher in group 1 and group 2 than group 3 and group 4. PNB was higher in group 3 and group 4 compared to group 1 and group 2. The PCa detection rates for groups one through 4 is 78.6%, 39%, 20%, and 17.2%, respectively. Detailed statistical analysis were shown in Supplementary Table 1, and Figure 1 demonstrates the distribution of BPH, PCa, GS ≤6, GS=7 and GS ≥8 according to groups.

When we compared patients with biopsy-proven PCa across subgroups, the percentage of low-grade PCA (GS ≤6) increased progressively from 27.2% in group 1a to 55.1% in group 1c (p=0.004) and further to 62.5% in group 1d (p=0.001). For patients with GS 7 (considered high-grade PCa), the percentage decreased from 51.8% in group 1a to 22.5% in group 4b (p=0.008). However, no statistically significant difference was observed between the subgroups when comparing the results for GS ≥8 (Table 2 and Figure 2).

Our second aim was to compare the diagnostic value of PV, which demonstrated the second-highest AUC in ROC analysis, following PSAD. The parameter AUC rankings, from highest to lowest, are PSAD (0.797), PV (0.757), f/t PSA (0.742), abnormal DRE (0.696), age (0.609), PSA (0.608), and PNB (0.552) (Supplementary Table 2).

Using the Youden J index to evaluate PV, it was found that a value of ≤49 cc resulted in a sensitivity of 63.6% and a specificity of 80.1%. Based on this cutoff, the detection rate of PCa was 62.6% (198/316). Further classification according to the GS showed that for PV ≤49 cc, GS ≤6 accounted for 18.9% (60/316), GS=7 for 30.3% (96/316), and GS ≥8 for 13.2% (42/316) (Supplementary Table 3).

Discussion

Our study results demonstrated that patients with a PSA value of 2.5-10 ng/mL have a 78.5% PCa detection rate when their PV ≤35 cc, whereas that rate drops to 17.2% in patients with a PV >75 cc. These results were similar to those of previous studies in which PV inversely correlates with the incidence of PCa; as PV increases, the detection rate of PCa decreases (8-13). The reference pathology used in these studies was obtained by TRUS-PB, targeted MRI-fusion, or RP. In two studies similar to ours, where PV was measured via TRUS and biopsies were taken with TRUS-PB, the PCa rate was calculated as 65% when PV <38 cc (15) and 66% when PV <35 cc (16). The same studies calculated the PCa rate as 20% when PV >72 cc and 40% when PV >65 cc. In other studies, in which RP pathology results were taken as a reference, Briganti et al. (13) found a direct correlation between PV and high-grade PCa when PV <45 cc but an inverse correlation when PV >45 cc. Meanwhile, Freedland et al. (17), demonstrated inverse relationship between PV and high-grade PCa when PV <20 cc, compared to PV ≥100 cc. Similarly, in a study by Kassouf et al. (18), the incidence of low-grade PCa was reported to be 17.9% in patients with a PV <25 cc compared to 45.3% in those with a PV >50 cc (p<0.01).

Some authors hypothesize that the low incidence of PCa in large prostates is due to sampling error. However, a study conducted by Elkhoury et al. (19) found that cancer detection rates are inversely related to PV despite the performance of both targeted and systematic biopsies. Specifically, the study

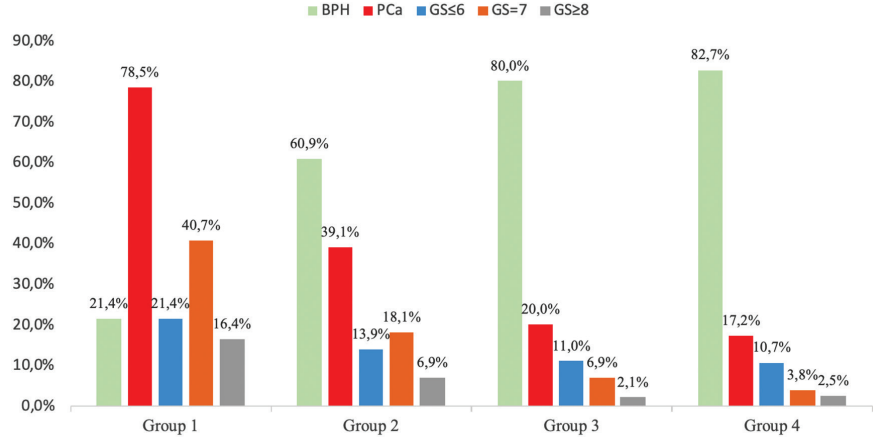


Figure 1. Classification of biopsy pathology results according to groups. Group 1; 140 patients with prostate volume ≤35 cc. Group 2; 287 patients with prostate volume between 36-55 cc. Group 3; 245 patients with prostate volume between 56-75 cc. Group 4; 232 patients with prostate volume ≥76 cc

BPH: Benign prostate hyperplasia, GS: Gleason score, PCa: Prostate carcinoma

Table 1. Main characteristics of groups

	Overall	Group 1	Group 2	Group 3	Group 4	p<0.05
No of patients	904 (100)	140 (15.5)	287 (31.7)	245 (27.1)	232 (25.7)	
Age mean, SD	65.3±6.6	65.29±7.39	64.37±6.91	65.22±6.32	66.56±5.77	0.005†
PSA mean, SD	6.38±1.89	6.16±2.19	5.99±1.72	6.51±1.75	6.87±1.91	0.001†
f PSA mean, SD	1.46±0.75	0.93±0.5	1.21±0.52	1.61±0.64	1.94±0.87	0.001†
f/t PSA mean, SD	0.23±0.1	0.16±0.08	0.21±0.09	0.25±0.08	0.28±0.11	0.001†
PSAD mean, SD	0.12±0.07	0.22±0.09	0.13±0.04	0.1±0.03	0.06±0.02	0.001†
Anormal DRE n, (%)	329 (36.4)	89 (63.6)	119 (41.5)	58 (23.7)	63 (27.2)	0.001ǂ
PNB n, (%)	108 (11.9)	5 (3.6)	25 (8.7)	41 (16.7)	37 (15.9)	0.001ǂ
No. of cores mean, SD	12.12±0.64	12.09±0.66	12.18±0.74	12.09±0.49	12.08±0.64	0.265†
GS results						
GS ≤6 n, (%)	122 (13.4)	30 (21.4)	40 (13.9)	27 (11)	25 (10.7)	0.001ǂ
GS=7 n, (%)	135 (14.9)	57 (40.7)	52 (18.1)	17 (6.9)	9 (3.8)	0.001ǂ
GS ≥8 n, (%)	54 (5.9)	23 (16.4)	20 (6.9)	5 (2.0)	6 (2.5)	0.001ǂ
Main pathology results						
BPH n, (%)	593 (65.6)	30 (21.4)	175 (61)	196 (80)	192 (82.8)	0.001ǂ
PCa n, (%)	311 (34.4)	110 (78.6)	112 (39)	49 (20)	40 (17.2)	0.001ǂ

†: Kruskal Wallis and Dunn tests, ǂ: Chi-square test, BPH: Benign prostate hyperplasia, DRE: Digital rectal examination, f PSA: Free prostate specific antigene, f/t PSA: Free total prostate specific antigene ratio, GS: Gleason score, PCa: Prostate carcinoma, PNB: Previous negative biopsy, PSA: Prostate specific antigene, PSAD: Prostate specific antigene density, PV: Prostate volume, SD: Standard deviation, Group 1; 140 patients with prostate volume ≤35 cc. Group 2; 287 patients with prostate volume between 36-55 cc. Group 3; 245 patients with prostate volume between 56-75 cc. Group 4; 232 patients with prostate volume ≥76 cc

Table 2. The classification of GS in patients with biopsy-proven prostate carcinoma according to subgroups

GS results	Group 1a (PV ≤35 cc)	Group 2a (PV = 36-55 cc)	Group 3a (PV= 56-75 cc)	Group 4a (PV ≥76 cc)	p<0.001
No. of patients	110	112	49	40	
GS ≤6, n, (%)	30 (27.2)	40 (35.7)	27 (55.1)	25 (62.5)	Group1a vs. Group 1c p=0.004* Group 1a vs. Group 1d p=0.001* Group 1b vs. Group 1d p=0.020*
GS=7, n, (%)	57 (51.8)	52 (46.4)	17 (34.6)	9 (22.5)	Group 1a vs. Group 1d p=0.008* Group 1b vs. Group 1d p=0.020*
GS ≥8 n, (%)	23 (20.9)	20 (17.8)	5 (10.2)	6 (15)	No statistical difference

*: The chi-square test and Bonferroni test, GS: Gleason score, PCa: Prostate carcinoma, PV: Prostate volume, Group 1a, 110 PCa patients with PV ≤35 cc; Group 2a, 112 PCa patients with PV=36-55 cc; Group 3a, 49 PCa patients with PV=56-75 cc; Group 4a, 40 PCa patients with PV ≥76 cc

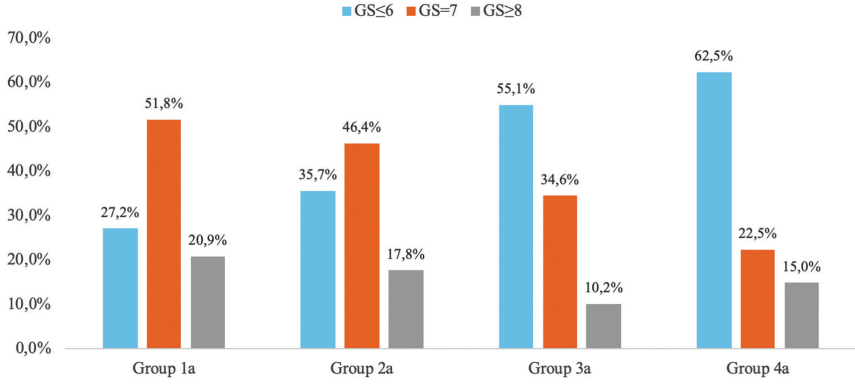


Figure 2. The classification of GS results in patients with biopsy-proven PCa according to subgroups. Group 1a, 110 PCa patients in PV ≤35 cc; group 2a, 112 PCa patients in PV=36-55 cc; group 3a, 49 PCa patients in PV= 56-75 cc; group 4a, 40 PCa patients in PV ≥76 cc

GS: Gleason score, PCa: Prostate carcinoma, PV: Prostate volume

revealed that 77% of men with low volumes (20-30 cc) had PCa, whereas only 42% of men with high volumes (60-100 cc) had PCa. Notably, no significant difference was found between the biopsy methods employed. Another study supporting it demonstrated that the MRI fusion biopsy technique detected 77% of PCa cases in PV <30 cc. However, this detection rate decreased to 34% for PV >55 cc (20). Finally, a meta-analysis in which the correlations between PV and MRI fusion prostate biopsy samples were analyzed also indicated that PCa reduces as PV increases, as demonstrated by prior TRUS biopsy-based research (21).

In contrast, Kulkarni et al. (12) conducted a study to compare biopsy and RP pathology results with PV, which differed from other studies findings. Based on the biopsy results, the study showed an inverse relationship between PV and high-grade PCA. However, the same relationship could not be observed between the RP pathology results, which were taken as a reference point. Karakiewicz et al. (22) also examined the biopsy yield in 10 cc gland-volume intervals in another study. They discovered that cancer detection decreased in larger glands using a traditional sextant biopsy approach, but there were no differences in Gleason grade among the gland-volume intervals.

In our study, we also studied patients with biopsy-proven PCa, subgrouping them on the basis of the same PV intervals, and no statistically significant difference was observed among subgroups with a GS ≥8. This finding aligns with a study by Kassaouf et al. (18), where biopsy pathology results were used as a reference. Specifically, the GS ≥8-10 rate was 13% for PV <25 cc and 11% for PV >50 cc with no statistically significant difference. However, a statistically significant difference was observed when comparing results concerning RP pathology. In another study, in which mpMRI fusion biopsy was used, the PCa detection rate decreased from 71.1% to 30.4% (PV <40 cc vs PV >116 cc), whereas the rate of PCa patients with GS ≥8 was not changed according to PV groups (23).

Two primary theories suggest an inverse correlation between PCa and PV. The first theory posits the hormonal theory that lower levels of dihydrotestosterone in small prostates may lead to the development of high-grade PCa (17). The second theory pertains to the mechanical impact of enlarged prostate tissue in the transitional zone. Histological studies have demonstrated that BPH growth in the transitional zone of larger prostate exerts mechanical pressure on the peripheral zone, where 80% of PCa originates. This pressure can result in glandular tissue atrophy and scarring in the peripheral zone, leading to thickening of the prostate capsule. Histological studies have shown that the thickness of the prostate capsule, gland atrophy, and scarring of glandular epithelial cells in the peripheral zone are positively associated with PV (24,25).

Our study also prioritized parameters for PCa detection. In the ROC curve analysis, PSAD showed the highest AUC value (0.797), followed by PV (0.757) and f/t PSA (0.742). However, PSAD and f/t PSA depended on the PSA level, which had a second-to-last AUC value of 0.608. It is worth noting that PSA levels can increase in various conditions, BPH (26), and f PSA is accused of being unstable (27), whereas PV emerged as a more stable predictor of PCa. In addition, PSAD appeared to be more valuable in only small- and medium-sized prostates (28).

Study Limitations

Our study has two main limitations. First, the study was conducted retrospectively in a single center with a relatively small number of patients. Therefore, the results should be interpreted cautiously due to the limited number of patients with biopsy-proven PCa results. Second, we used transrectal prostate biopsy pathology reports as the basis for the study. However, it is known that 30-40% of these pathologies are upgraded after pathological examination of the RP material.

Conclusion

Our study results suggest an inverse relationship between PV and PCa detection rates. Although, in biopsy-proven PCa patients, the GS ≤6 rate increased and the GS=7 rate decreased in larger prostates, it was not clearly observed in patients with GS ≥8. However, this needs to be confirmed by conducting additional prospective studies with a considerable number of patients.

Ethics

Ethics Committee Approval: The study was conducted in line with the principles of the Declaration of Helsinki and the local ethics committee accepted this single-center retrospective study conducted between January 2016 and October 2023 (Local Ethics Committee of Karabük University, approval number: 2024/1633, date: 07.02.2024).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: C.B., K.E., Concept: C.B., K.E., Design: C.B., K.E., Data Collection or Processing: C.B., K.E., Analysis or Interpretation: C.B., K.E., Literature Search: C.B., K.E., Writing: C.B., K.E.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that they have no relevant financial.

References

1. Frost JM, Smith LA, Sharma P, de Riese WT. Possible clinical implications of peripheral zone changes depending on prostate size. Int Urol Nephrol. 2019;51:1721-1726. [Crossref]
2. Orbe Villota PM, Leiva Centeno JA, Lugones J, Minuzzi PG, Varea SM. Comparison between the European Randomized Study for Screening of Prostate Cancer (ERSPC) and Prostate Biopsy Collaborative Group (PBCG) risk calculators: Prediction of clinically significant Prostate Cancer risk in a cohort of patients from Argentina. Actas Urol Esp (Engl Ed). 2024;48:210-217. [Crossref]
3. EAU Guidelines on Prostate Cancer – Uroweb. In: Uroweb – European Association of Urology. https://uroweb.org/guidelines/prostate-cancer. Accessed 14 Apr 2023. [Crossref]
4. Pagniez MA, Kasivisvanathan V, Puech P, Drumez E, Villers A, Olivier J. Predictive Factors of Missed Clinically Significant Prostate Cancers in Men with Negative Magnetic Resonance Imaging: A Systematic Review and Meta-Analysis. J Urol. 2020;204:24-32. [Crossref]
5. Fenton JJ, Weyrich MS, Durbin S, Liu Y, Bang H, Melnikow J. Prostate-Specific Antigen-Based Screening for Prostate Cancer: Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2018;319:1914-1931. [Crossref]
6. Gann PH, Ma J, Catalona WJ, Stampfer MJ. Strategies combining total and percent free prostate specific antigen for detecting prostate cancer: a prospective evaluation. J Urol. 2002;167:2427-2434. [Crossref]
7. Sun L, Moul JW, Hotaling JM, Rampersaud E, Dahm P, Robertson C, Fitzsimons N, Albala D, Polascik TJ. Prostate-specific antigen (PSA) and PSA velocity for prostate cancer detection in men aged <50 years. BJU Int. 2007;99:753-757. [Crossref]
8. Moolupuri A, Camacho J, de Riese WT. Association between prostate size and the incidence of prostate cancer: a meta-analysis and review for urologists and clinicians. Int Urol Nephrol. 2021;53:1955-1961. [Crossref]
9. Yamashiro JR, de Riese WTW. Any Correlation Between Prostate Volume and Incidence of Prostate Cancer: A Review of Reported Data for the Last Thirty Years. Res Rep Urol. 2021;13:749-757. [Crossref]
10. Pinthus JH, Witkos M, Fleshner NE, Sweet J, Evans A, Jewett MA, Krahn M, Alibhai S, Trachtenberg J. Prostate cancers scored as Gleason 6 on prostate biopsy are frequently Gleason 7 tumors at radical prostatectomy: implication on outcome. J Urol. 2006;176:979-984; discussion 984. [Crossref]
11. Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, Lieber MM, Cespedes RD, Atkins JN, Lippman SM, Carlin SM, Ryan A, Szczepanek CM, Crowley JJ, Coltman CA Jr. The influence of finasteride on the development of prostate cancer. N Engl J Med. 2003;349:215-224. [Crossref]
12. Kulkarni GS, Al-Azab R, Lockwood G, Toi A, Evans A, Trachtenberg J, Jewett MA, Finelli A, Fleshner NE. Evidence for a biopsy derived grade artifact among larger prostate glands. J Urol. 2006;175:505-509. [Crossref]
13. Briganti A, Chun FK, Suardi N, Gallina A, Walz J, Graefen M, Shariat S, Ebersdobler A, Rigatti P, Perrotte P, Saad F, Montorsi F, Huland H, Karakiewicz PI. Prostate volume and adverse prostate cancer features: fact not artifact. Eur J Cancer. 2007;43:2669-2677. [Crossref]
14. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA; Grading Committee. 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;40:244-252. [Crossref]
15. Al-Azab R, Toi A, Lockwood G, Kulkarni GS, Fleshner N. Prostate volume is strongest predictor of cancer diagnosis at transrectal ultrasound-guided prostate biopsy with prostate-specific antigen values between 2.0 and 9.0 ng/mL. Urology. 2007;69:103-107. [Crossref]
16. Al-Khalil S, Ibilibor C, Cammack JT, de Riese W. Association of prostate volume with incidence and aggressiveness of prostate cancer. Res Rep Urol. 2016;8:201-205. [Crossref]
17. Freedland SJ, Isaacs WB, Platz EA, Terris MK, Aronson WJ, Amling CL, Presti JC Jr, Kane CJ. Prostate size and risk of high-grade, advanced prostate cancer and biochemical progression after radical prostatectomy: a search database study. J Clin Oncol. 2005;23:7546-7554. [Crossref]
18. Kassouf W, Nakanishi H, Ochiai A, Babaian KN, Troncoso P, Babaian RJ. Effect of prostate volume on tumor grade in patients undergoing radical prostatectomy in the era of extended prostatic biopsies. J Urol. 2007;178:111-114. [Crossref]
19. Elkhoury FF, Felker ER, Kwan L, Sisk AE, Delfin M, Natarajan S, Marks LS. Comparison of Targeted vs Systematic Prostate Biopsy in Men Who Are Biopsy Naive: The Prospective Assessment of Image Registration in the Diagnosis of Prostate Cancer (PAIREDCAP) Study. JAMA Surg. 2019;154:811-818. [Crossref]
20. de Gorski A, Rouprêt M, Peyronnet B, Le Cossec C, Granger B, Comperat E, Cussenot O, Renard-Penna R, Mozer P. Accuracy of Magnetic Resonance Imaging/Ultrasound Fusion Targeted Biopsies to Diagnose Clinically Significant Prostate Cancer in Enlarged Compared to Smaller Prostates. J Urol. 2015;194:669-673. [Crossref]
21. Knight AS, Sharma P, de Riese WTW. MRI determined prostate volume and the incidence of prostate cancer on MRI-fusion biopsy: a systemic review of reported data for the last 20 years. Int Urol Nephrol. 2022;54:3047-3054. [Crossref]
22. Karakiewicz PI, Bazinet M, Aprikian AG, Trudel C, Aronson S, Nachabé M, Péloquint F, Dessureault J, Goyal MS, Bégin LR, Elhilali MM. Outcome of sextant biopsy according to gland volume. Urology. 1997;49:55-59. [Crossref]
23. Walton Diaz A, Hoang AN, Turkbey B, Hong CW, Truong H, Sterling T, Rais-Bahrami S, Siddiqui MM, Stamatakis L, Vourganti S, Nix J, Logan J, Harris C, Weintraub M, Chua C, Merino MJ, Choyke P, Wood BJ, Pinto PA. Can magnetic resonance-ultrasound fusion biopsy improve cancer detection in enlarged prostates? J Urol. 2013;190:2020-2025. [Crossref]
24. Weaver PE, Smith LA, Sharma P, Keesari R, Al Mekdash H, de Riese WT. Quantitative measurements of prostate capsule and gland density and their correlation to prostate size: possible clinical implications in prostate cancer. Int Urol Nephrol. 2020;52:1829-1837. [Crossref]
25. Guzman JA, Sharma P, Smith LA, Buie JD, de Riese WT. Histological changes of the peripheral zone in small and large prostates and possible clinical implications. Res Rep Urol. 2019;11:77-81. [Crossref]
26. Shigemura K, Arakawa S, Yamanaka K, Yasui N, Matsubara S, Iwamoto T, Kataoka N, Yuien K, Fujisawa M. Potential predictive factors of positive prostate biopsy in the Japanese population. Int Urol Nephrol. 2008;40:91-96. [Crossref]
27. Huang Y, Li ZZ, Huang YL, Song HJ, Wang YJ. Value of free/total prostate-specific antigen (f/t PSA) ratios for prostate cancer detection in patients with total serum prostate-specific antigen between 4 and 10ng/mL: A meta-analysis. Medicine (Baltimore). 2018;97:e0249. [Crossref]
28. Omri N, Kamil M, Alexander K, Alexander K, Edmond S, Ariel Z, David K, Gilad AE, Azik H. Association between PSA density and pathologically significant prostate cancer: The impact of prostate volume. Prostate. 2020;80:1444-1449. [Crossref]

Supplementary Table 1. Detailed statistical analysis for pathological results between groups (a), for parameters (b)

a) Detailed statistical analysis for pathological results between groups

Group 1 (A)		Groups				
		Group 2	Group 3	Group 4	p-value	
		(B)	(C)	(D)		
GS results	≤ 6	C (p=0.034) D (p=0.030)				Group 1 to Group 3 p=0.034* Group 1 to Group 4 p=0.030
	=7	B (p=0.001) C (p=0.001) D (p=0.001)	C (p=0.001) D (p=0.001)			Group 1 to Group 2 p=0.001* Group 1 to Group 3 p=0.001* Group 1 to Group 4 p=0.001* Group 2 to Group 3 p=0.001* Group 2 to Group 4 p=0,001*
	≥ 8	B (p=0.014) C (p=0.001) D (p=0.001)	C (p=0.045)			Group 1 to Group 2 p=0.001* Group 1 to Group 3 p=0.001* Group 1 to Group 4 p=0.001* Group 2 to Group 3 p=0.001*
Main pathology results	BPH		A (p=0.001)	A (p=0.001) B (p=0.001)	A (p=0.001) B (p=0.001)	Group 1 to Group 2 p=0.001* Group 1 to Group 3 p=0.001* Group 1 to Group 4 p=0.001*
	PCa	B (p=0.001) C (p=0.001) D (p=0.001)	C (p=0.001) D (p=0.001)			Group 1 to Group 2 p=0.001* Group 1 to Group 3 p=0.001* Group 1 to Group 4 p=0.001*

* The chi-square test and Bonferroni test, GS: Gleason score, BPH: Benign prostate hyperplasia, PCa: Prostate carcinoma

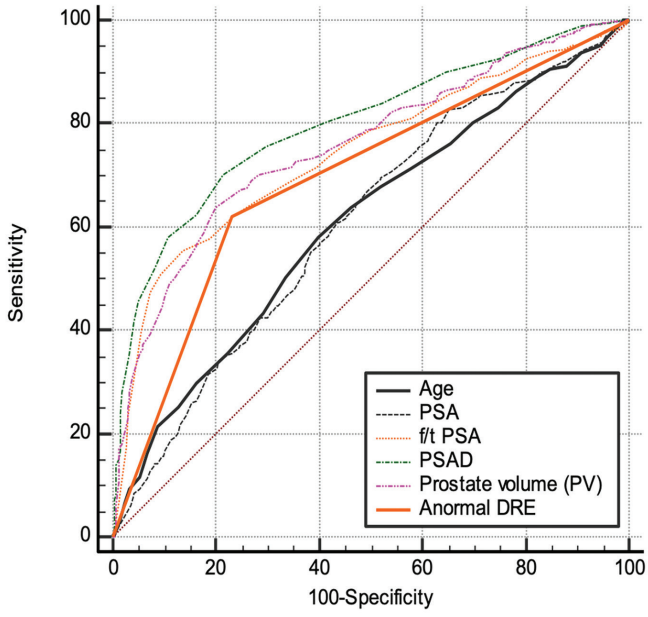
b) Detailed statistical analysis for parameters between groups

Age	p-value	PSA	p-value	f PSA	p-value
Group 2-Group 3	0.139	Group 2-Group 1	0.515	Group 1-Group 2	0.001*
Group 2-Group 1	0.120	Group 2-Group 3	0.001*	Group 1-Group 3	0.001*
Group 2-Group 4	0.001*	Group 2-Group 4	0.001*	Group 1-Group 4	0.001*
Group 3-Group 1	0.765	Group 1-Group 3	0.029*	Group 2-Group 3	0.001*
Group 3-Group 4	0.044*	Group 1-Group 4	0.001*	Group 2-Group 4	0.001*
Group 1-Group 4	0.153	Group 3-Group 4	0.081	Group 3-Group 4	0.001*

f/t PSA	p-value	PSAD	p-value
Group 1-Group 2	0.001*	Group 4-Group 3	0.001*
Group 1-Group 3	0.001*	Group 4-Group 2	0.001*
Group 1-Group 4	0.001*	Group 4-Group 1	0.001*
Group 2-Group 3	0.001*	Group 3-Group 2	0.001*
Group 2-Group 4	0.001*	Group 3-Group 1	0.001*
Group 3-Group 4	0.003*	Group 2-Group 1	0.001*

*The chi-square test and Bonferroni test, f PSA: Free prostate specific antigene, f/t PSA: Free total prostate specific antigene ratio, GS: Gleason score, PCa: Prostate carcinoma, PSA: Prostate specific antigene, PSAD: Prostate specific antigene density

Supplementary Table 2. ROC curve analysis and AUC values of parameters including age, PSA, f/t PSA, PSAD, PV and anormal DRE for risk factors of PCa (a), for parameters including age, PSA, f/t PSA, PSAD, PV and PNB (b)

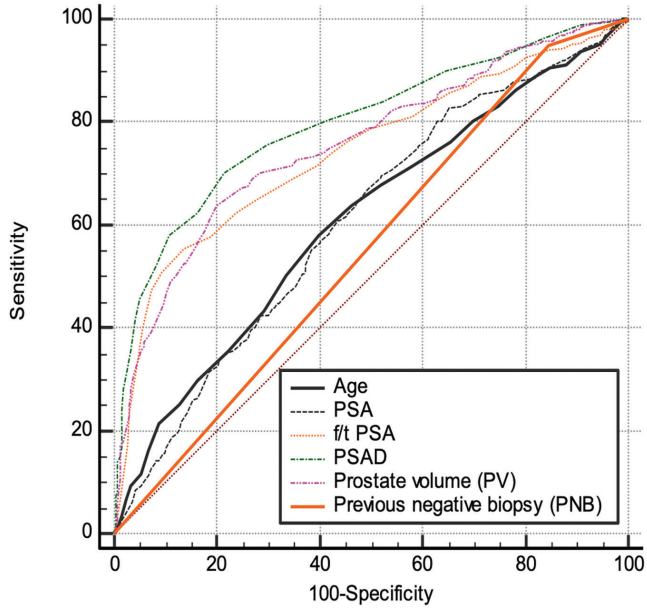


PSA: prostate specific antigene, f/t PSA: Free total prostate specific antigene ratio, PSAD: Prostate specific antigene density, PV: Prostate volume, DRE: Digital rectal examination

Variables	AUC	SE[a]	95% CI[b]
Age	0.609	0.0200	0.576 to 0.641
PSA	0.608	0.0196	0.576 to 0.640
f/t PSA	0.742	0.0185	0.712 to 0.770
PSAD	0.797	0.0165	0.770 to 0.823
Prostate volume	0.757	0.0176	0.727 to 0.784
Anormal DRE	0.696	0.0190	0.664 to 0.725

[a] Hanley & McNeil, 1982, [b] Binomial exact, AUC: Area under the curve, SE: Standard error, CI: Confidence interval, PSA: prostate specific antigene, f/t PSA: Free total prostate specific antigene ratio, PSAD: Prostate specific antigene density, DRE: Digital rectal examination

a) For parameters including age, PSA, f/t PSA, PSAD, PV and PNB



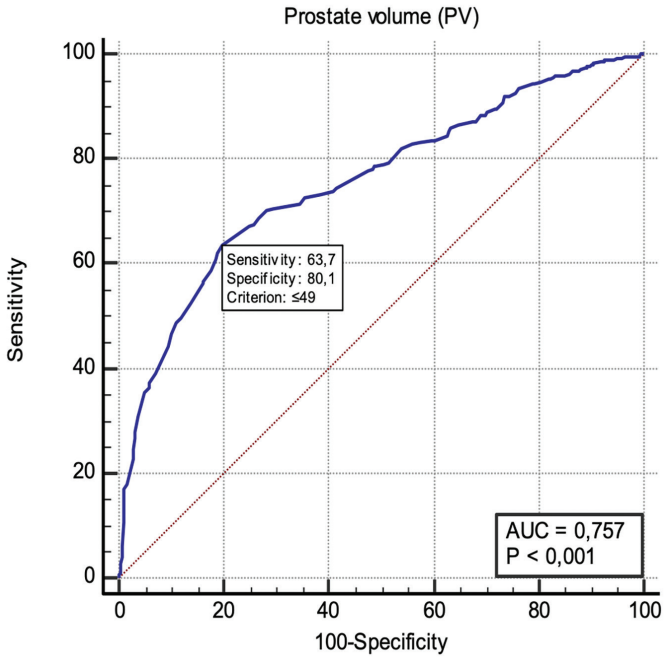
PSA: Prostate specific antigene, f/t PSA: Free total prostate specific antigene ratio, PSAD: Prostate specific antigene density, PNB: Previous negative biopsy

Variables	AUC	SE[a]	95% CI[b]
Age	0.609	0.0200	0.576 to 0.641
PSA	0.608	0.0196	0.576 to 0.640
f/t PSA	0.742	0.0185	0.712 to 0.770
PSAD	0.797	0.0165	0.770 to 0.823
Prostate volume	0.757	0.0176	0.727 to 0.784
Previous negative biopsy	0.552	0.0196	0.519 to 0.585

[a]Hanley & McNeil, 1982, [b]Binomial exact, AUC: Area under the curve, SE: Standard error, CI: Confidence interval, PSA: prostate specific antigene, f/t PSA: Free total prostate specific antigene ratio, PSAD: Prostate specific antigene density, DRE: Digital rectal examination

Supplementary Table 3. AUC value of prostate volume with sensitivity and specificity for prostate carcinoma (a), pathology results according to prostate volume cut-off value of ≤49 cc

a)



Area under the ROC curve (AUC)	0.757
Standard error[a]	0.0176
95% confidence interval[b]	0.727 to 0.784
Z statistic	14.584
Significance level P (area=0.5)	<0.0001

Youden index J	0.4377
Associated criterion	≤49
Sensitivity	63.67
Specificity	80.10

Criterion	Sensitivity	95% CI	Specificity	95% CI
≤49	63.67	58.0-69.0	80.10	76.7-83.2
CI: Confidence interval				

b)

Pathology results	PV ≤49 cc
No. of patients	316
GS ≤6 n, (%)	60 (18.9)
GS=7 n, (%)	96 (30.3)
GS ≥8 n, (%)	42 (13.2)
BPH n, (%)	118 (37.3)
PCa n, (%)	198 (62.6)
PV: Prostate volume, GS: Glason score, BPH: Benign prostate hyperplasia, PCa: Prostate carcinoma	