Significance of the Prostate Central Gland and Total Gland Volume Ratio in the Diagnosis of Prostate Cancer Patients in the PSA Gray Zone

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Abstract

Objective: To explore the significance of the prostate central gland to total gland volume ratio in the diagnosis of PSA 4-10ng/ml prostate cancer (PCa) patients.

Method: A retrospective analysis was performed on patients who had undergone prostate biopsy in our hospital from July 2015 to December 2020. The anteroposterior, transverse and axial diameters of the prostate and the central prostate gland were measured using multiparametric magnetic resonance imaging (mpMRI). The differences in PSA, f/tPSA, PSAD and PVC/PV between the PCa group and the non-PCa group were compared. ROC curves for PCa and clinically significant PCa (csPCa) diagnosis were drawn according to PSA, f/tPSA, PSAD and PVC/PV respectively. Corresponding PSA was used as the reference standard for comparison.

Results: There was no statistically significant difference in PSA and f/tPSA between the two groups ($P>0.05$), while there were statistically significant differences in PSAD and PVC/PV between the two groups ($P<0.05$). By comparing the AUC values of the ROC curve for any PCa or csPCa, the AUC value of PVC/PV was 0.876 and 0.933, and PSAD was 0.705 and 0.790. This is significantly different from that of the PSA curve ($P<0.05$), whereas f/tPSA was 0.589 and 0.692 showing no significant difference from the PSA curve ($P>0.05$).

Conclusion: Low volume ratio of central prostate gland PVC/PV has a higher incidence of PCa and csPCa, which can be used as an important reference index for the diagnosis of PCa in PSA 4-10 ng/ml patients.

Introduction

In recent years, the incidence and mortality of PCa in China had increased significantly^[1] and PCa has been estimated to account for 21% of all new cancer cases in the US in 2020.^[2] The ability of early diagnosis of PCa is very important. Prostate specific antigen (PSA) is the most important tumor marker of PCa, but when its value is between 4–10 ng/ml, namely the PSA gray zone, the incidence of PCa is only 25%.^[3] Therefore, it is of great significance to study the related factors contributing to prostate biopsy positive rate when the PSA level is in the gray zone. Currently, f/tPSA and PSAD are the most commonly-used related indicators affecting the positive rate of prostate biopsy. However, there are still some problems in the clinical prediction results.^[4] It is commonly considered that benign prostatic hyperplasia (BPH) lesions are mostly located in the central gland, while PCa usually occurs in the peripheral zone of the prostate. We found that patients with PCa and those with BPH have obviously different value of PVC/PV (the volume ratio of central gland to total prostate) showed by mpMRI, which is a new predictor of PCa and BPH. We retrospectively analyzed patients with PSA gray zone who underwent prostate biopsy in our hospital in recent years, and statistically analyzed their PSA, f/t PSA, PSAD and PVC/PV.

The aim of the present study is to evaluate if the new predictor (PVC/PV) can contribute to the diagnosis of PCa for patients with PSA levels in the gray zone.

Patients And Method

1 Patients

1. Patients: 136 patients with PSA between 4-10ng/ml and underwent prostate biopsy from July 2015 to December 2020 in our hospital.
2. Inclusion criteria: (1) PSA between 4-10 ng/ml; (2) No 5 α -reductase inhibitor or other endocrine therapy drugs were taken within 1 year. (3) Patients and their families both provided consent and signed the consent form.
3. Exclusion criteria: (1) have a clear history of PCa; (2) had acute urinary retention or indwelling catheterization within the last 2 weeks; (3) had lower urinary tract surgery or related treatment within the recent 3 months; (4) have urinary tract infection, acute prostatitis or coagulation dysfunction; (5) have a local skin infection, severe infection, abnormal blood coagulation or other diseases which not suitable for invasive examination;(6) patients with severe anal disease or anal diversion;(7) those unable to cooperate with the inspector.

2 Method

All methods were carried out in accordance with relevant guidelines and regulations. All experimental protocols were approved by Ethics committee of Minhang Hospital Affiliated to Fudan University (2019-the certificate-006-01K). PSA, f/tPSA, PSAD and PVC/PV values were collected from all patients.

1.2.1 Determination of fPSA and PSA:

immunofluorescence assay kits (Sorin company, Italy) were used. The detection time was 48 hours after digital rectal examination, cystoscopy, catheterization and so on, and 1 week after prostate massage.

1.2.2 Determination of total prostate volume PV and prostate central gland volume PVC:

all patients underwent a routine clinical prostate mpMRI (1.5T American general motors, Excite HD), and the anteroposterior diameter (cm), left and right diameter (cm) and upper and lower diameter (cm) of the prostate and central gland were measured. Prostate mpMRI acquisition protocol consisted of axial, sagittal and coronal T2-weighted imaging, diffusion-weighted imaging, and dynamic contrast-enhanced imaging. The most commonly-used diffusion-weighted imaging was carried out using five b-values in the range of b50–b2000, while Gadodiamide (Omniscan; GE Healthcare Ireland Limited) was used as an

intravenous contrast agent. Image interpretation was carried out by one of the three fellowship trained radiologists according to PI-RADS-V2.0 recommendations.^[5] The volume of the anterior column gland and the central gland was calculated as $\pi/6 \times \text{anteroposterior diameter} \times \text{left and right diameter} \times \text{upper and lower diameter (ml)}$. PSAD = PSA/ PV.

1.2.3 Standard biopsy:

12 standard biopsy cores + X biopsy (18G, TSK biopsy gun) guided by a B-ultrasound (Esaote, myLab 60, transrectal biplane probe, frequency 3-9MHz) in the lithotomy position, including 1 needle at the apex, middle and bottom of the median sagittal section, and 1 needle at the tip, middle and bottom of the bilateral peripheral zone. For any suspicious parts, 1 more needle was inserted. Pathological specimens were fixed with 10% formaldehyde for biopsy, and a senior pathologist reviewed all prostate biopsy specimens, reporting ISUP-Gleason GG according to the latest recommendations.^[6]

1.3 Statistical methods

SPSS17.0 and STATA14 were used for statistical analysis. Enumeration and measurement data was compared between groups using the chi-square test and the Student's *t*-test. The receiver operating characteristic curve (ROC) was used to analyze and compare the accuracy of PSA, f/tPSA, PSAD and PVc/PV in predicting prostate biopsy results. The area under the ROC curve was compared using the Z test. Associations were considered statistically significant if the *P* value was ≤ 0.05 .

Results

All biopsies were completed successfully. The overall population descriptive characteristics are listed in Table 1. 39 cases of PCa were diagnosed. There were significant differences in PSAD and PVc/PV between the PCa group and the non-PCa group ($P < 0.05$), but there was no significant difference in PSA and f/tPSA between the two groups ($P > 0.05$), as shown in Table 2.

Table 1
Descriptive characteristics of the overall population

Variable	n = 136
Age (years)	70.6 ± 8.7
PSA (ng/mL)	6.63 ± 2.0
DRE, n(%)	105 (77.2%)
Negative	31 (22.8%)
Suspicious	127(93.4%)
Biopsy history, n(%)	9(6.6%)
Biopsy naive	42 (30.9%)
Previous negative biopsy	65 (47.8%)
PI-RADS	29 (21.3%)
1 ~ 2	97(71.3%)
3	25(18.4%)
4 ~ 5	14(10.3%)
Biopsy results	
Negative, n(%)	
GG 1, n(%)	
csPCa, n(%)	
Abbreviations: DRE: digital rectal examination; PI-RADS: prostate Imaging-Reporting and Data System; GG1: Gleason group 1 (3 + 3); csPCa: Gleason group ≥ 2(≥ 3 + 4).	

The ROC curve of PSA, f/tPSA, PSAD and Pvc/PV in the diagnosis of all PCa (Fig. 1) and csPCa (Fig. 2). The AUC values of the ROC curve for each parameter are shown in Table 3 and Table 4.

Table 3
Comparison of AUC values of the ROC curve for each parameter in the diagnosis of all PCa (with PSA group as a control)

parameter	AUC	Σ	95%CI	P value
PSA (ng/ml)	0.529	0.0645	0.426 to 0.631	-
f/tPSA	0.589	0.0662	0.486 to 0.688	0.4819
PSAD(ng/ml/cm ³)	0.705	0.0595	0.605 to 0.793	0.0138*
PVc/PV	0.876	0.0416	0.794 to 0.934	0.0000*
Notes: *P: statistically different;				
Abbreviations: AUC: area under ROC curve;				

Table 4
Comparison of AUC values of the ROC curve for each parameter in the diagnosis of csPCa (with PSA group as a control)

parameter	AUC	Σ	95%CI	P value
PSA (ng/ml)	0.559	0.111	0.444–0.670	-
f/tPSA	0.692	0.0793	0.579–0.790	0.2957
PSAD(ng/ml/cm ³)	0.790	0.0632	0.685–0.873	0.0259*
PVc/PV	0.933	0.0310	0.854–0.977	0.0004*
Notes: *P: statistically different;				
Abbreviations: AUC: area under ROC curve;				

Discussion

There were about 1.27 million new cases of PCa around the world in 2018, which was also the world's second highest incidence of all cancer for men.^[7] Many laboratory and imaging methods are widely used in the early screening of PCa, but the gold standard of diagnosis is prostate biopsy. PSA is not a specific marker of PCa; furthermore, prostatitis, hyperplasia, prostate compression and related endoscopic operation through the prostate would also result in the increase of PSA. Currently, there is still great controversy regarding the performance of a biopsy on patients with PSA levels in the gray zone. Therefore, some other PSA-based indicators such as f/tPSA and PSAD can also be used as indicators for PCa diagnosis. This study revealed that there was no significant difference in the level of PSA between

the PCa group and the non-PCa group, indicating that the specificity of PSA was low when its level is within the gray zone. Previous studies had confirmed the value of f/tPSA in the diagnosis of PSA gray zone PCa,^[8] in which low f/tPSA predicted a high risk of PCa.^[9] However, the value of f/tPSA in the diagnosis of gray zone PCa in East Asia is still very controversial. Huang et al found that the predictive value of f/tPSA in gray zone PCa diagnosis in Chinese people was low,^[10] Jeong et al^[11] reported that f/tPSA did not improve the diagnostic accuracy of PSA gray zone PCa for Korean people aged 50–65 in a prospective multicenter study. A meta-analysis showed that the reasons for heterogeneity regarding the predictive value of f/tPSA included race, age, detection reagents and standards.^[12] In this study, we also found no significant difference in f/tPSA between the two groups. However, considering the small number of cases in this study and the existence of age heterogeneity factors, it is necessary to expand the sample and stratify the age to further verify its diagnostic value.

A destruction of the barrier between the acinar epithelium, ductal epithelium and capillaries in the prostate would also lead to an increase in PSA and per unit volume of PSA. PSAD has been used to distinguish PCa from BPH since 1992.^[13] Ghafoori et al^[14] demonstrated that the accuracy of PSA in predicting PCa was inferior to that of PSAD. The results of our study also showed that the value of PSAD in the diagnosis of PCa for patients with PSA gray zone preceded that of PSA.

The increase of PSA in BPH patients is mainly caused by hyperplasia in the transitional zone of the central gland,^[15] while PSA produced by the peripheral zone is relatively stable. As the incidence location of PCa is often in the peripheral zone, it is less likely to spot hyperplasia in the central gland of the prostate. Research shows^[16, 17] that the PSAD level in the prostate transitional zone of a PCa patient is significantly higher than that in a BPH patient, which means when presented with the same level of PSA, the ratio of transitional zone volume to total volume in patients with PCa was smaller than those with BPH. Since the transitional zone is the main component of the prostate's central gland, this also means that the ratio of central gland volume to total volume is smaller in PCa patients^[18]. Although transrectal ultrasounds are widely used in the measurement of prostate volume, there are obvious limitations such as measurement error and incomplete image preservation.^[19] There are obvious advantages in the measurement of prostate volume when using mpMRI, especially the T2 sequence, which can well distinguish the different zone of prostate.^[20, 21] In order to ensure the stability and accuracy of data used in the study, prostate volume was measured by the same clinician. The PVc/PV value in the PCa group was significantly lower than that of the non-cancer group (Table 2), which confirmed the correlation between PVc/PV value and PCa risk in the PSA gray zone. The AUC value of the ROC curve corresponding to PVc/PV in any PCa and csPCa was 0.876 and 0.933 respectively, which were the highest two values of all parameters tested. In comparison, the AUC value of the PSA group and the f/tPSA group was statistically significant ($P < 0.01$), indicating that PVc/PV could be used as an important predictive parameter for the diagnosis of both PCa and csPCa in the PSA gray zone.

The predictive factors of PSA gray zone PCa include f/tPSA, PSAD, lesion area, age, family history etc. However, there are also a few studies which suggest that the central gland to total prostate volume ratio

(PVc/PV) is a predictive factor. This study suggested that PVc/PV could be a predictor of PCa when PSA is between 4–10 ng/ml. This brings certain clinical application value such as improving the accuracy of PCa and csPCa diagnosis when PSA is in the special gray zone interval, reducing unnecessary prostate biopsies, and thus is worthy of further clinical application. However, the number of cases in this study is small, and further large sample studies to externally validate this finding in a racially diverse population are required to confirm and improve the results.

Declarations

Ethical Approval

Ethical approval to report this case was obtained from Ethics committee of Minhang Hospital Affiliated to Fudan University (2019-the certificate-006-01K).

Consent for publication and availability of data and materials

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient /guardian/ relative of the patient. The findings of the study will be published in peer-reviewed journals and presented at national and international scientific meetings. The data-sets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declaration of Conflicting Interests

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Authors' contributions

Zhui-feng Guo, Cong-hui Han contributed to the conception of the study and formulation of overarching research goals and aims. Zhui-feng Guo, Fan Yang, Xu-wei Lu performed application of statistical to analyze study data; Zhui-feng Guo, Fan Yang contributed to creation and presentation of the published work, specifically writing the initial draft. Zhui-feng Guo, Jia-wen Wu, Chang He Conducted the research and investigation process, specifically performing the data collection.

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Table

Due to technical limitations, table 2 is only available as a download in the Supplemental Files section.

Figures

Figure 1
ROC curve comparing the predictive value of PVc/PV and other parameters in the diagnosis of all PCa.

Figure 2

ROC curve comparing the predictive value of PVc/PV and other parameters in the diagnosis of csPCa.

Supplementary Files

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- [table2.docx](#)