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Peripheral Zone Sonographic Changes of the Prostate

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ABSTRACT

INTRODUCTION: The aim of the investigation was to identify the diagnostic importance of peripheral zone sonographic findings in correlation with total prostatic specific antigen (tPSA) and pathological findings.

METHODS: Between January 2005 and January 2007, the transrectal biopsy records of 407 patients were reviewed for different prostatic indications. Echogenicity, calcific, and cystic changes of the peripheral zone were correlated with tPSA, total volume of the gland, digital rectal exam (DRE), and pathological findings.

RESULTS: The patients were divided into 3 groups (A, B, and C) according to tPSA: <4 ng/mL (n = 19), 4-10 ng/mL (n = 159), and >10 ng/mL (n = 229), respectively. Heterogenicity was detected in 59.9% of cases and was higher when tPSA increased. Heterogenicity was found in the malignant biopsies of 78.7% of the patients (sensitivity = 78.78%; specificity = 44.6%). Calcific changes were found in 52% (n = 90) of group C ($P < .05$). Calcification was demonstrated in 41.4% (n=41) of malignant findings, but group comparisons were not statistically significant (sensitivity = 41.4%; specificity = 55.5%). Cystic changes were detected in 7.1% (n = 7) of malignant findings, but group comparisons were not statistically significant (sensitivity = 7.1%; specificity = 9.1%). However, 10.3% (n = 23) of patients with cystic peripheral zonal changes had high but not statistically significant PSA.

CONCLUSIONS: Heterogenicity of the peripheral zone is correlated with malignant pathology (positive predictor value = 31.9%) and high tPSA. Whenever a peripheral zone calcific change in prostatic sonography occurs, the urologist should suspect an increase of tPSA but without characteristic indicator of malignant anticipations (positive predictor value = 23.03%). Cystic changes in the peripheral zone are not specific findings and do not reflect any changes in tPSA or prostatic pathology.

KEYWORDS: Transrectal ultrasound; Echogenicity; Prostate calcification; Prostate cystic changes.

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INTRODUCTION

Transrectal prostatic ultrasonography (TRUS) has become a widely utilized procedure since its popularization by Watanabe and associates in 1971 [1]. Anatomic definition from ultrasound examination depends upon the varying degrees to which different tissues reflect and transmit sound waves [2]. In the normal prostate, the central and peripheral zone tend to appear as isoechoic regions, while the transition zone appears as a slightly hypoechoic area [3].

Sonographic details of prostatic tissue, especially in the peripheral zone, were considered a marker for suspicious areas that might be biopsied later for pathological analysis. In

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original study

Table 1. Patient Group Characteristics and Probability of Group Differences
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Variable		Group A (n = 19)	Group B (n = 159)	Group C (n = 229)	P
Age Mean (SD)		65.7 (7.3)	64.3 (7.8)	67.6 (8.4)	.569
Total Gland Volume Mean (SD)		56.2 (2.93)	61.4 (3.1)	69 (3.34)	.503
DRE	Benign Feeling	13	111	104	.0001
	Hard	6	48	125	

1986, Lee et al defined the hypoechoic peripheral zone lesion as the most common area for ultrasonographic appearance of prostate cancer [4]. However, as many as 24% to 39% of prostatic cancers may be isoechoic [5-7] and some cancers may have a mixed or hyperechoic appearance [8]. In addition, various disease processes such as benign prostatic hyperplasia (BPH), prostatitis, and prostatic infarcts may appear as hypoechoic lesions [9]. In 1989, Lee et al found that 32.5% of hypoechoic lesions are cancerous, with the positive predictive value ranging from 19% in the transition zone to 41% in the peripheral zone [10].

Other sonographic prostatic findings such as calcific and cystic changes might appear during TRUS and their clinical importance is warranted. Few articles discuss this issue in English literature.

The aim of the present investigation was to highlight the clinical and diagnostic importance of sonographic details in relation to pathological findings and total prostatic specific antigen (tPSA).

METHODS

Between January 2005 and January 2007, the TRUS evaluations of 407 patients who had been biopsied for different prostatic indications were reviewed. The patients had no past history of prostatic biopsies or intervention. None of the patients were irradiated or received any hormonal medications.

All patients had transrectal prostatic ultrasound examination done in sagittal and axial planes, with men in the lithotomy position. Sextant core biopsies were taken as described by Hodge et al [11], using an 18 G needle driven by a spring-loaded gun. The TRUS machine (B&K Medical Panther, model 2002) was used for prostate scanning and TRUS guided biopsy.

Analysis of transrectal sonographic data included peripheral zonal echogenicity (homogenous or heterogenous) and the presence or absence of calcific and cystic changes. Cysts appeared as anechoic, smooth-walled, spherical structures that increased through enhancement. The calcific changes were described as hyperechoic focus ≤ 5 mm in width, with posterior acoustic shadow.

The corresponding serum tPSA and digital rectal examination (DRE) were retrieved. Correlations with pathological prostatic biopsies were done using the sextant core technique.

Positive predictor value (PPV) was defined as total positive/total positive + false positive cases; negative predictor value (NPV) was defined as total negative/false + true negative cases. The collected data were processed by statistical tests using SPSS version 11. Statistical analysis of the means of continuous variables was performed using Student's *t* (paired and unpaired, when appropriate). Analysis of the significance of categorical variables was performed using the Chi-square test. Statistical significance was defined as $P < .05$.

RESULTS

The mean age was 66.15 years (range 43-86 years). Patients were classified according to tPSA into group A: tPSA < 4 ng/mL, n = 19 (4.8 %); group B: tPSA 4-10 ng/mL, n = 159 cases (38.9 %); and group C: tPSA > 10 ng/mL, n = 229 cases (56.3 %). Table 1 contains the mean age, total gland volume and DRE results (*benign feeling* and *hard*) for each group. Group comparisons across the age, total gland volume, and DRE variables revealed significant differences only for *hard feeling* DRE (P < .05). *Hard feeling* was found in 54.6% of group C.

The relationship between the 3 patients groups on echogenicity and prostatic pathology results is shown in Table 2 and Table 3.

Table 2. Relationship between Echogenicity and tPSA; Probability of Group Differences
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Echogenicity (n)	Group A n (%)	Group B n (%)	Group C n (%)	*P*
Homogenous (155)	5 (3.2)	81 (52.3)	69 (44.5)	.0005
Heterogonous (244)	9 (3.4)	78 (31.9)	158 (64.7)	

Table 3. Relationship Between DRE and Sonographic Changes; Probability of Group Differences
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DRE		Benign Feeling			Hard Feeling			*P*
PSA Groups		A n (%)	B n (%)	C n (%)	A n (%)	B n (%)	C n (%)	
Echogenicity (n = 399)	Homogenous (n = 155)	5 (4.1)	71 (57.7)	47 (38.2)	---	10 (31.3)	22 (68.8)	.007
	Heterogenous (n = 244)	5 (4.7)	45 (42.5)	56 (52.8)	4 (2.9)	33 (23.7)	101 (73.4)	.004
Calcification (n = 407)	Negative (n = 229)	9 (7.2)	56 (44.8)	60 (48)	4 (3.8)	27 (26)	73 (70.2)	.0001
	Positive (n = 178)	3 (2.9)	55 (53.9)	44 (43.1)	2 (2.7)	23 (30.2)	51 (67.1)	.018
Cystic Changes (n = 396)	Negative (n = 361)	11 (5.4)	102 (50)	91 (44.6)	6 (3.8)	42 (26.8)	109 (69.4)	.0001
	Positive (n = 35)	2 (8.3)	9 (37.5)	13 (54.2)	---	1 (9.1)	10 (90.9)	.131

Echogenicity of the peripheral prostatic zone was homogenous in 155 cases (mean tPSA = 14.5 ng/mL; SD = 1.2), while a heterogenous echopattern was observed in 244 cases (mean tPSA = 22.7 ng/mL; SD = 1.4); there were missing data for 8 cases.

The homogenous echopatteren does not exclude the possibility of prostatic malignancy, especially with high tPSA. In contrast, 48.3% (n = 118) of heterogenous peripheral echopattern had benign hyperplasia. Heterogenicity of the prostate was usually associated with malignant prostatic pathological finding, especially with higher tPSA. As shown in Table 3, the heterogenicity of the peripheral zone was associated with the prostate becoming hard in 57% (n = 134) of patients with tPSA > 4 ng/mL. The comparison between DRE and sonographic changes showed a statistically significant difference between groups (*P* = .004).

Table 4 contains the total volume of the gland and its relationship to prostatic changes The total volume of the gland was not significantly correlated with the changes of tPSA and the echogenicity of the gland. Sensitivity of heterogenicity to detect the malignant pathology was 78.78%; specificity was 44.6%. However, the PPV of the heterogenous echopattern to

Table 4. Relationship Between Total Volume of the Gland and Sonographic Changes; Probability of Group Differences. doi: 10.3834/uij.1944-5784.2009.06.05t4

		Total Prostatic Gland Volume			*P*
PSA Groups		A Mean (SD)	B Mean (SD)	C Mean (SD)	
Echogenicity (n = 399)	Homogenous	43.2 (1.64)	58 (3)	67.4 (3.37)	.289
	Heterogenous	60.8 (3.8)	65.7 (3)	68.1 (3.2)	.679
Calcification (n = 400)	Negative (n = 222)	66.3 (1.2)			.065
	Positive (n = 178)	63.2 (2.2)			
Cystic Changes (n = 396)	Negative (n = 361)	65.14 (1.6)			.834
	Positive (n = 35)	66.3 (4.5)			

Table 5. Pathology, Echogenicity, and tPSA; Probability of Group Differences
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Variable		Group A n (%)	Group B n (%)	Group C n (%)	P
Homogenous (n = 155)	Benign (n = 98)	1 (1)	62 (63.3)	34 (35.7)	.0005
	Malignant (n = 21)	---	3 (14.3)	18 (85.7)	
	Prostatitis (n = 29)	1 (3.4)	14 (48.3)	14 (48.3)	
	Low PIN (n = 3)	---	2 (66.7)	1 (33.3)	
	High PIN (n = 4)	2 (50)	---	2 (50)	
Heterogenous (n = 244)	Benign (n = 118)	7 (5.9)	53 (44.9)	58 (49.2)	.0005
	Malignant (n = 78)	2 (2.6)	9 (11.5)	67 (85.9)	
	Prostatitis (n = 46)	---	15 (32.6)	31 (67.4)	
	High PIN (n = 2)	---	1 (50)	1 (50)	

detect malignant pathology was 31.9%; the NPV was 86.45%. With further analysis of sensitivity in correlation with the tPSA, the authors noticed that sensitivity increased for the groups with higher tPSA (75% for group B; 78.8% for group C). PPVs were 11.5% and 42.6% for groups B and C, respectively. The sensitivity of heterogenous echopatten to detect prostatitis was 61.3%; specificity = 38.8%; PPV = 9.8%; NPV = 81.29%. None of the group x variable comparisons in Table 4 indicated significant differences.

The correlations between the pathology and peripheral prostatic zonal findings are shown in Table 5 and Table 6. Table 5 contains a summary of the pathology, echogenicity, and tPSA. Calcific changes were detected in 43.7% (n = 178). Heterogenicity was detected in 78.8% (n = 78) of malignant prostatic biopsies and 54.6% (n = 118) of benign prostatic biopsy; 70.7% (n = 46) showed prostatitic pathological results. The correlation between the pathology and different pathological changes was statistically significant ($P < .05$). However, pathological evidence was not correlated with presence or absence of calcification or the cystic changes.

Hard prostatic feelings were detected in 42.6% (n = 76). The comparison of pathology, echogenicity, and tPSA was significantly different across groups ($P < .05$). The mean age of the group with calcification was 65.4 years (SD = 8). The total volume of the gland was not significantly correlated with the presence of calcific changes. Calcific changes were associated with tPSA > 4 ng/mL ($P = .053$). The presence of calcification was detected in tPSA (mean = 16.9 ng/mL; SD = 1.3). Figure 1 represents the correlation between the 3 patient groups and the presence or absence of calcification: 53.3% of patients with prostatic calcification (n = 95) were in group B, and 43.8% (n = 78) were in group C.

The diagnostic probability of the presence or absence of calcification in prostatic sonography is shown in Table 6. The presence of calcification in the peripheral zone was associated with malignant prostatic biopsy in 41.4% (n=41); a majority of them were in groups B and C. The anticipation of nonbenign pathology was warranted in 46.6% (n = 83) of patients with higher tPSA (> 4 ng/mL) if associated with sonographic calcification ($P = .013$). Sensitivity of prostatic calcification was 41.4%; specificity = 55.5%; PPV = 23.03%; NPV = 25.3% for associated malignancy. When the authors analyzed the calcific changes with prostatitis, the sensitivity = 46.66%; specificity = 56.9%; PPV = 19.6%; and NPV = 35.72%.

The cystic changes of the peripheral zones were detected in 8.6% (n = 35) of total cases; the mean age was 67.7 years (SD =

Table 6. Pathology Versus Calcification and Cystic Changes: Cross Tabulation; Probability of Variable Differences
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Pathology of Sextant Core Biopsy		Number of Cases for Each Pathology						P
		Atypical Acinar	Benign	Malignant	Prostatitis	Low PIN	High PIN	
Calcification (n = 400)	Negative (n = 222)	2	126	58	40	---	3	.264
	Positive (n = 178)	---	95	41	35	3	4	
Cystic Changes (n = 396)	Negative (n = 361)	2	200	92	69	3	6	.933
	Positive (n = 35)	---	21	7	6	---	1	

1.8). The mean total gland volume was 66.3 cc (SD =4.5); 31.4% (n = 11) of those patients had a hard prostatic feeling (*P* = 0.131). The mean tPSA of the cystic group was 21.2 ng/mL (SD = 3.7). As shown in Table 6, there was no significant relationship between cystic changes and the pathological findings.

Figure 2 represents the correlation between patient groups and tPSA and cystic changes. Although the 67.6% of patients with cystic changes (n = 23) had a tPSA > 10 ng/mL, the comparison was not statistically significant. Sensitivity and specificity of cystic changes towards malignant pathology was 7.1% and 9.1%, respectively (PPV = 20%; NPV = 24.7%.

A power analysis was not calculated. Therefore, there is a possibility that some of the statistical comparisons showed statistically significant differences due to chance.

DISCUSSION

Although B-mode ultrasonography may have a low specificity and sensitivity for cancer detection, it is the velocity and angle of the ultrasound signal that are affected by tissue density and abrupt versus gradual changes in tissue density [12]. Such variations cause deviation of the signal. The variations include shadowing because of intense reflectors (eg, calcifications or air), and are increased through enhancement exhibited with fluid-filled structures such as cysts [12].

Figure 1. The Correlation of Patient Groups According to tPSA and Calcifications (*P* = .053)
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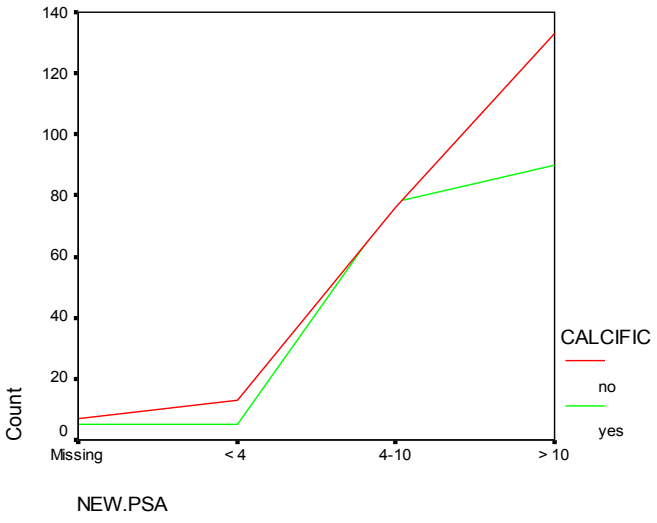


Figure 2. The Correlation of Patient Groups According to tPSA and Cystic Changes (*P* = .384)
doi: 10.3834/uij.1944-5784.2009.06.05f2

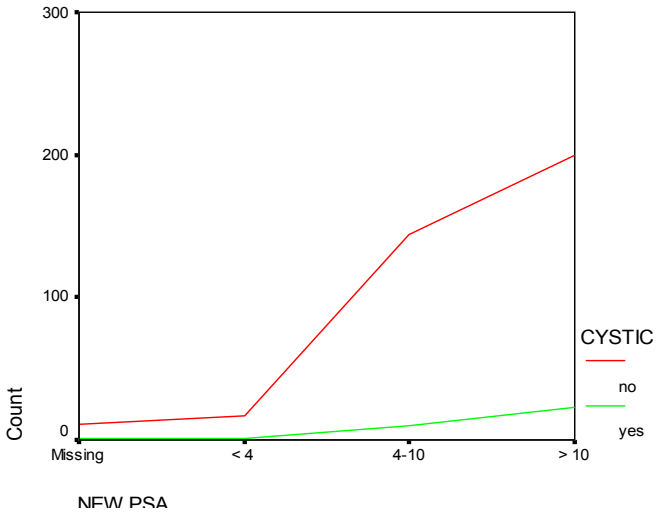


Figure 3. Prostatic Heterogeous Echopattern (Axial and Sagittal TRUS Views).
doi: 10.3834/uij.1944-5784.2009.06.05f3

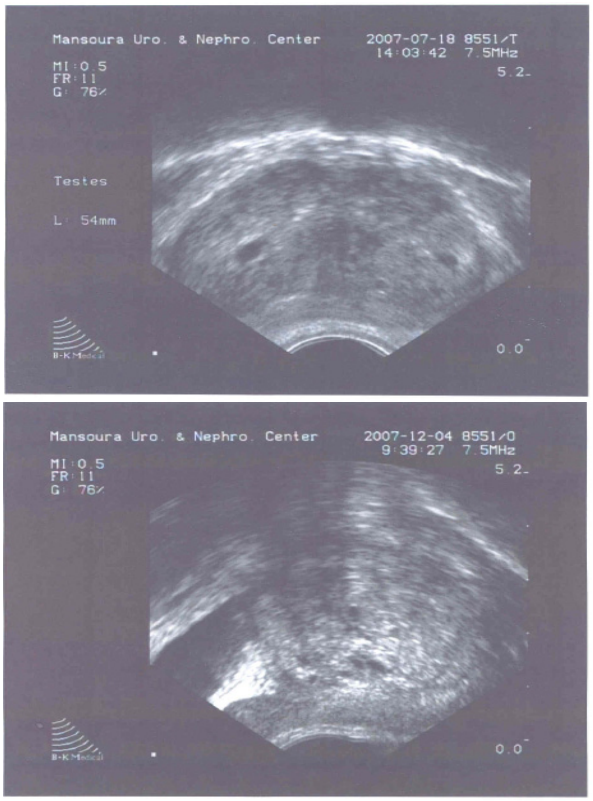
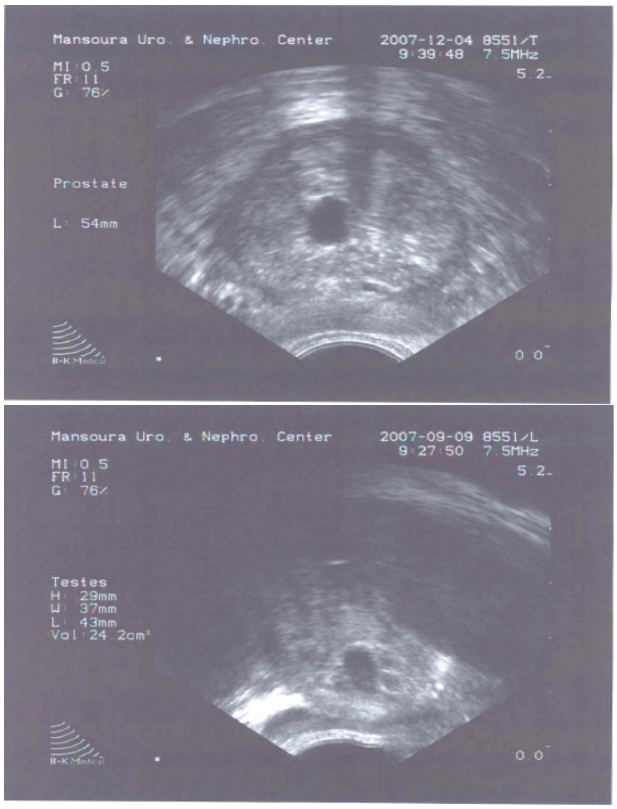


Figure 4. A Prostatic Cyst (Axial and Sagittal TRUS Views)
doi: 10.3834/uij.1944-5784.2009.06.05f4



Many urologists still depend on B-mode TRUS. The urologist should be aware of density changes, especially when detected at the peripheral zone. Thus, a corresponding clinical significance and malignant correlation should be defined.
The boundary between the transitional and the peripheral zones, or the surgical capsule, is normally a hypoechoic convex line. With increasing BPH, this boundary becomes less convex. This margin is often peppered with hyperechoic corpora amylacea; when more calcified and densely packed these deposits interrupt the sound waves, causing posterior shadowing that obscures the transition zone [13,14]. Such calcifications have been correlated with a history of prostatitis but are often seen in healthy men with no history of prostatic inflammation [15].

The peripheral zonal heterogeneity (Figure 3) and hypoechogenicity are likely due to variations in the stroma and glands composition. This hypoechogenicity is not specific and can also be exhibited by inflammation, atrophy, hyperplasia, and even normal prostate tissue [11]. At least 80% of transition zone malignancies are isoechoic, as are 30% to 50% of peripheral zone tumors [17].

Peripheral prostatic cysts (Figure 4) appear as anechoic, smooth-walled, spherical structures that are increased through enhancement. The ultrasound waves move rapidly, without reflection, through the cyst fluid and then abruptly strike the opposite wall of the cyst [13,14].

Abnormal sonographic changes could explain the abnormal DRE. Approximately 70% of palpable prostatic nodules [11] and more than 50% of nonpalpable cancers are hypoechoic [16,17].

In the present study, nonhomogenous peripheral zonal echopatteren of the prostate was associated with significantly higher tPSA than the homogenous echopattern. Approximately 79% of malignant diagnosed cases had heterogenous prostatic echopattern and the number of cases increased significantly with higher tPSA. In spite of the higher tPSA of the nonhomogenous

Figure 5. Prostatic Calcifications (Axial TRUS View)
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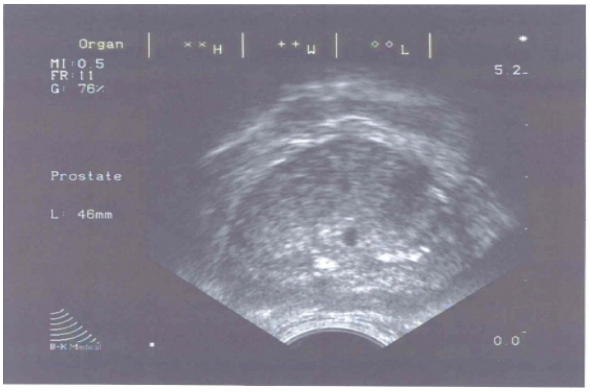

group, the possibility of benign hyperplasia was established in 48.3% of heterogenous cases. The heterogenicity led to changes of prostatic consistency, which might feel hard in 57% of cases especially when accompanied by higher tPSA. The sensitivity of malignant detection with heterogenous echopattern increased with higher tPSA.

Small multiple calcifications are incidental ultrasound findings in the prostate and represent a result of age rather than a pathologic entity [18]. Although Moore [19] reports corpora amylacea even in fetal prostate at 7 months [19], Lee et al [20] found that patient age, prostate volume, and serum PSA were not significantly different in men with or without prostatic calculi.

Older studies have failed to detect a causal relationship between infection and subsequent inflammation with prostatic lithiasis, attributing the inflammatory changes to lipid-rich secretions of the glands or secondary complications of calculi [20-23]. In another study, the authors emphasized that it was impossible to correlate morphology of prostatic calcifications with pathologic conditions; there are no specific symptoms clearly connected with calcification even though the inflammation is often associated with calcifications [24]. Other investigators demonstrated that echogenic foci can be seen within predominantly hypoechoic tumor nodules. Coarse bright echoes, usually at the periphery of the gland, suggest calcifications in benign prostate glands. Tumor calcifications and intraluminal prostatic crystalloid deposits were located more centrally and had a finer stippled sonographic appearance [25].

In the present study, the calcific changes shown in Figure 5 were associated with hard prostate, and accompanied by tPSA > 4 ng/mL (P = .053). Calcification of the prostate could not be added to the sonographic feature of any specific pathology. The nonbenign pathology (eg, prostatitis, prostatic malignancy) might be associated with calcification and will be more evident in cases with tPSA > 4 ng/mL (P = .013). Results of the present study failed to show a strong correlation between prostatic calcification and prostatitis (sensitivity = 46.6%; PPV = 19.6%). A detailed description of calcification is beyond the limits of the present prospective study.

Few articles discuss the clinical importance of cystic degenerative changes in the prostate from sonographic findings. Most of the cystic changes could be identified as being of prostate origin, Wolffian duct origin, or Müllerian duct origin by their sonographic appearance and location. In a Japanese study of 30 patients using ultrasound to diagnose cystic lesions, most patients were asymptomatic. However, 8 of the 30 men with a complaint of hematospermia had a sonographic finding of cystic changes in the prostate (3 patients) or ejaculatory ducts (5 patients). It has been suggested that inflammation and allergic reaction are related to hematospermia; however, their mechanism remains unclear. Soh et al [26] suggest that cystic changes in the ejaculatory duct contribute to hematospermia.

The results of the present study demonstrate that cystic changes were uncommon sonographic details (8.6% of N), associated with tPSA > 10 ng/mL and not differing significantly across groups. Additionally, cystic changes did not affect the prostatic consistency or reflect a specific pathological entity.

In recent literature, Al-Azab et al [27] concluded that the smaller prostatic volume with PSA of 2-9 ng/mL was the best predictor of tumor detection. In the present study the authors recognized a linear relationship between volume and PSA among the patients (see Table 1).

Authors of the previous literature did not specifically correlate the clinical and diagnostic importance of sonographic changes with pathological feature, elevation of serum tPSA, or impact on the changes of prostatic feeling. The present study addressed those comparisons on a large sample of patients.

CONCLUSIONS

The prostatic heterogenous echopattern was associated with hard prostatic consistency and elevated serum tPSA. Moreover, the pathological finding of malignant glandular changes were more frequent than prostatitis and benign prostatic hyperplasia (sensitivity = 78.78%; PPV = 31.9%). The sensitivity of heterogenous echopattern was evident in higher tPSA.

Prostatic calcification was not a pathgnomonic feature for specific pathologic entity. The calcific changes were higher in patients with tPSA > 4 ng/mL.

Cystic changes were not a marker for pathologic prostatic disease. The cystic changes did not alter the tPSA significantly more than in noncystic prostatic cases. They were not associated with changes in prostatic consistency. Therefore, peripheral calcification and cystic changes should not be considered a signal for a specific pathology.

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