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Are Hypoechoic Lesions on Transrectal Ultrasonography a Marker for Clinically Significant Prostate Cancer?

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Purpose: To investigate the relationship of transrectal ultrasound (TRUS) findings with the pathological characteristics of prostate cancer (PCa).

Materials and Methods: The study was conducted retrospectively by analyzing the data for 970 patients who underwent prostate biopsies. Gleason scores and other clinical variables were compared between PCa patients with and without hypoechoic lesions on TRUS.

Results: Of the 970 patients, PCa was diagnosed in 291 (30%). Of these, high-grade PCa (Gleason score of 7 or more) was diagnosed in 190 (65%). The cancer detection rate was higher in patients with hypoechoic lesions (43.9%) than in those without hypoechoic lesions (21.4%, $p < 0.001$). High-grade PCa was detected more often in patients with hypoechoic lesions than in those without hypoechoic lesions ($p < 0.001$). Independent predictors for high-grade PCa by logistic regression analysis included hypoechoic lesions on TRUS and abnormal digital rectal examination findings.

Conclusions: Patients with PCa who had hypoechoic lesions on TRUS had more aggressive pathological disease than did those without lesions. Therefore, hypoechoic lesions on TRUS could be a marker for clinically significant PCa.

Keywords: *Clinical marker; Prostate neoplasms; Ultrasonography*

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INTRODUCTION

Since Watanabe et al. [1] initially applied imaging methods in the prostate, the value of transrectal ultrasound (TRUS) for the detection and evaluation of prostate cancer (PCa) has been reported [2,3]. Although the efficacy of screening for PCa is under continuous debate [4,5], the advent of TRUS has improved visualization of prostate lesions. Hypoechoic lesions found during TRUS, as well as high levels of serum prostate-specific antigen (PSA) and abnormal digital rectal examination (DRE) findings, are the typical findings considered to be suspicious for PCa, and TRUS-guided prostate biopsy is generally recommended. There has been some controversy over TRUS owing to its low specificity and sensitivity; hence, new methods and imaging techniques are being intensely explored by investigators [6-9]. However, as previously reported in many studies, TRUS-guided biopsy is a widely practiced method for histological diagnosis in men with suspected PCa [10,11].

Although TRUS has significantly improved the diagnostic rate, the correlation between findings on TRUS and clinically significant PCa is incompletely understood. The aim of this study was to investigate the relationship of TRUS findings with the pathological characteristics of PCa.

MATERIALS AND METHODS

A total of 996 patients who had lesions suspected of being PCa (with a PSA level ≥ 4.0 ng/mL, a palpable nodule upon

TABLE 1. Clinical characteristics of the study Cohort and differences between the groups by transrectal ultrasonographic findings

Variable	All cases (n=970)	Normal TRUS (n=599)	Abnormal TRUS (n=371)	p-value
Age (y)	65.9±8.95	64.7±9.22	67.8±8.15	<0.001
Nodule on DRE	215 (22.2)	68 (11.4)	147 (39.6)	<0.001
PSA (ng/mL)	6.66 (4.48–11.85)	5.87 (4.19–9.14)	9.20 (5.24–26.44)	0.004
Prostate volume (cm^3)	39.0 (28.6–52.7)	40.3 (29.0–54.7)	36.9 (28.0–50.0)	0.243
Transitional zone volume (cm^3)	17.5 (10.9–27.6)	18.2 (11.0–28.9)	16.9 (10.8–26.2)	0.030
PSAD (ng/mL/cm^3)	0.17 (0.10–0.32)	0.14 (0.10–0.24)	0.25 (0.13–0.71)	0.002
PSAD-TZ (ng/mL/cm^3)	0.38 (0.21–0.84)	0.32 (0.19–0.58)	0.57 (0.28–1.92)	0.003
Patients with PCa	291 (30.0)	128 (21.4)	163 (43.9)	<0.001
Gleason score				<0.001
≤6	101	60	41	
7	46	21	25	
≥8	144	47	97	

Values are presented as mean±standard deviation, number (%) or median (interquartile range).
TRUS, transrectal ultrasound; DRE, digital rectal examination; PSA, prostate-specific antigen; PSAD, PSA density; PSAD-TZ, PSAD of transition zone volume; PCa, prostate cancer.

DRE, or a hypoechoic lesion upon TRUS) underwent TRUS-guided prostate biopsy between January 2004 and December 2010. Men were excluded from the analysis if they had previously undergone prostate biopsy, had received a prior diagnosis of PCa, or had undergone prostate surgery or radiation treatment. A total of 970 men met the criteria and constituted the study cohort. According to the approval of the Institutional Review Board of the hospital (IRB No. GR10070-001), the clinical data were collected retrospectively. Informed consent was exempted by the board.

The methods of TRUS-guided biopsy were as follows. The rectum was cleaned with 10% povidone iodine and prophylactic antibiotics were administered before the TRUS-guided biopsy. All biopsies were performed with an automatic 18-gauge biopsy needle (Bard Urological Division, Covington, GA, USA) in conjunction with a Hawk 2102EXL medical ultrasound scanner (BK Medical A/S, Herlev, Denmark). TRUS was performed by using a 7.5-MHz biplane or multiplaner probe. Specimens of 10 cores were taken from the prostate of patients with suspected PCa. The biopsy specimens were examined for the presence of cancer and were categorized by Gleason score by a pathologist.

The positive predictive value of hypoechoic lesions on TRUS for PCa was calculated. The Gleason score was compared between PCa patients with or without hypoechoic lesions. The factors we evaluated for the risk of high-grade PCa included age, abnormal DRE result, PSA, prostate volume, transitional zone (TZ) volume, PSA density (PSAD), PSAD of the TZ (PSAD-TZ), and hypoechoic lesion on TRUS.

Continuous variables were expressed as either the mean±standard deviation or the median (interquartile range). Categorical variables were reported as the number of occurrences and frequency. Student t-test and the Pearson chi-square test were used for statistical comparisons of continuous and categorical variables, respectively. Simple and multiple logistic regressions with a backward variable selection procedure were performed to identify independent predictors of high-grade PCa. All statistical outcomes were presented as the odds ratio and the 95% confidence interval based on a two-sided test using SPSS 12.0 (SPSS Inc., Chicago, IL, USA). We regarded a p-value <0.05 as statistically significant.

RESULTS

Among the 970 patients, PCa was diagnosed in 291 (30%). PCa was detected in 163 patients among 371 patients who had hypoechoic lesions on TRUS (positive predictive value, 43.9%), which was higher than the cancer detection rate in patients without hypoechoic lesions (21.4%, $p<0.001$). Of the 163 patients with PCa who had hypoechoic lesions, 122 patients had a Gleason score of 7 or more. Of 128 patients with PCa who did not have hypoechoic lesions, 68 men had a Gleason score of 7 or more ($p\leq0.001$). The detailed results of the patients' characteristics and pathologic findings of PCa are described in Table 1.

A comparison was made among the 291 patients in whom PCa was diagnosed according to Gleason scores (Table 2). There were more patients with hypoechoic findings on TRUS among the patients with a Gleason score of 7 or more than among those with lower Gleason scores ($p<0.001$). Patients with high-grade PCa also had higher ages, more abnormal DRE findings, and higher levels of PSA, PSAD, and PSAD-TZ ($p<0.05$).

Logistic regression analysis was also performed among the 291 patients. In the simple logistic regression analysis, age, abnormal DRE findings, PSA, prostate volume, TZ volume, PSAD, PSAD-TZ, and hypoechoic lesions on TRUS were significant factors for high-grade PCa (Gleason score ≥7, Table 3). In the multiple logistic regression analysis, abnormal DRE findings and hypoechoic lesions on TRUS were identified as significant factors.

The numbers of biopsied men with a PSA level <4 ng/mL, normal DRE findings, and a hypoechoic lesion on TRUS

TABLE 2. Clinical characteristics of patients with prostate cancer according to Gleason score

Variable	Gleason score≤6 (n=101)	Gleason score≥7 (n=190)	p-value
Age (y)	66.5±7.61	69.6±7.98	0.001
Nodule on DRE	30 (29.7)	102 (53.7)	<0.001
PSA (ng/mL)	7.31 (5.31–14.3)	30.4 (11.1–99.4)	0.004
Prostate volume (cm^3)	31.2 (25.3–43.7)	34.7 (25.5–49.6)	0.317
Transitional zone volume (cm^3)	13.3 (9.17–20.9)	15.4 (9.70–22.8)	0.371
PSAD (ng/mL/cm^3)	0.24 (0.16–0.43)	0.93 (0.35–2.37)	<0.001
PSAD-TZ (ng/mL/cm^3)	0.57 (0.35–1.17)	2.19 (0.82–5.20)	<0.001
Hypoechoic lesion on TRUS	41 (40.6)	122 (64.2)	<0.001

Values are presented as mean±standard deviation, number (%) or median (interquartile range).
DRE, digital rectal examination; PSA, prostate-specific antigen; PSAD, PSA density; PSAD-TZ, PSAD of transition zone volume; TRUS, transrectal ultrasound.

TABLE 3. Simple and multiple logistic regression model analyzing the predictors of high-grade prostate cancer (Gleason score ≥7) in 291 patients

Variable	Simple logistic regression			Multiple logistic regression		
	OR	95% CI	p-value	OR	95% CI	p-value
Age	1.07	1.05–1.09	<0.001			
Nodule on DRE	6.84	4.83–9.69	<0.001	3.63	2.34–5.64	<0.001
PSA	1.03	1.02–1.04	<0.001			
Prostate volume	0.99	0.98–1.00	0.005			
Transitional zone volume	0.98	0.97–0.99	0.002			
PSAD	6.98	4.73–10.31	<0.001			
PSAD-TZ	2.05	1.78–2.37	<0.001			
Hypoechoic lesion on TRUS	3.83	2.74–5.33	<0.001	1.56	1.02–2.40	0.042

OR, odds ratio; CI, confidence interval; DRE, digital rectal examination; PSA, prostate-specific antigen; PSAD, PSA density; PSAD-TZ, PSAD of transition zone volume; TRUS, transrectal ultrasound.

were 37. Among them, only one case with PCa with a Gleason score of 6 was diagnosed.

DISCUSSION

The incidence of PCa has been rapidly increasing and this phenomenon is currently a major health issue worldwide. Because early detection of PCa has been a primary concern in the last several decades, various studies of PCa screening have been performed [11-13]. However, although previous studies of PCa screening have demonstrated the improvements in PCa diagnosis, overdiagnosis of clinically insignificant PCa is considered to be the major problem causing increased costs and burden. Recent PCa studies have focused on the current issues in identifying clinically significant PCa [14-16].

In our study, patients with PCa who had hypoechoic lesions on TRUS had more aggressive pathological disease than did those who did not have hypoechoic lesions. Other studies have also reported methods for predicting aggressive forms of PCa. Newton et al. [17] concluded that prostate volume is inversely associated with high-grade PCa as well as extraprostatic extension and positive surgical margins. We also identified small prostate volume and small TZ volume of the prostate as significant risk factors for high-grade PCa in the simple logistic regression analysis; however, they were not significant by multiple logistic regression analysis. Another study suggested that the results of contrast-enhanced sonography with micro flow imaging are associated with the aggressiveness of PCa [18].

The significant majority of PCa originates from the peripheral zone. Hence, all hypoechoic lesions within the peripheral zone should be noted and included in the biopsy material. However, lack of a hypoechoic area does not preclude proceeding with biopsy, because 40% of cancers are isoechoic or hyperechoic on TRUS [19]. There has been controversy about the advantages and drawbacks of TRUS. TRUS biopsies are presently the method of choice for determining PCa [20-22]. However, Flanigan et al. [23] mentioned the limited accuracy of TRUS in identifying and localizing PCa. Chang et al. [24] reported that 55% to 60% of all small hypoechoic lesions in the posterior prostate ultimately prove to be benign and, therefore, refinement of the ultrasound criteria for identifying the lesions to which immediate attention should be paid is necessary. Ellis et al. [25] reported that performing biopsy of only hypoechoic sectors would have misdiagnosed 24.6% of the patients with PCa and that only 6.3% of patients with normal DRE results and a PSA level of less than 4.0 ng/mL demonstrated

PCa on biopsy.

In the present study, more than half of the patients with hypoechoic lesions on TRUS did not have PCa and 2.7% of patients with normal DRE results and PSA levels of less than 4.0 ng/mL were diagnosed as having PCa on biopsy. Babaian et al. [26] suggested the relationship of PSA levels to other detection techniques and to the finding of cancer. In that analysis, PCa that was diagnosed by TRUS alone was least likely to be cancer (positive predictive values, 5.4%). Therefore, the present study demonstrates that TRUS may not be a screening method for PCa and that hypoechoic lesions on TRUS do not guarantee the presence of PCa. However, once PCa exists in the prostate, hypoechoic lesions on TRUS could imply its pathological aggressiveness.

Several studies have shown that abnormal DRE findings are related with more progressive forms of PCa. Okotie et al. [27] found that a substantial proportion of PCa detected by DRE at PSA levels less than 4 ng/mL has features associated with clinically aggressive tumors and concluded that DRE is useful in diagnosing biologically aggressive PCa and provides important prognostic information. According to Gosselaar et al. [28,29], men who had an abnormal DRE result would have a high chance of detection of aggressive PCa (Gleason score >7), indicating that an abnormal DRE finding is associated with clinically significant PCa. The findings of our study were consistent with these previous studies.

CONCLUSIONS

PCa was detected in about half of patients with hypoechoic lesions on TRUS. Patients with PCa who had hypoechoic lesions on TRUS had more aggressive pathological disease than did those who did not have hypoechoic lesions. Therefore, hypoechoic lesions on TRUS can be a marker for clinically significant PCa.

Although the widespread use of screening methods has led to increased diagnosis of PCa, the issue of overdiagnosis has been raised recently. Additional studies are required for determining the pathological features and the clinical significance of PCa. With the rapid advent of new technologies, combining new strategies and guidelines will be suggested to improve the quality of PCa evaluation.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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