Prevalence of Prostatic Calcification Subtypes and Association With Prostate Cancer

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OBJECTIVE To evaluate the prevalence and to classify prostatic calcification on transrectal ultrasonography (TRUS) and correlate the findings with histology.

METHODS A prospective, blinded study of men undergoing TRUS and prostatic biopsy was designed. A standardized reproducible technique was used with a BK 7.5- to 12.5-MHz multiplanar probe. Representative images of the calcification in the sagittal and transverse planes were captured. Blind analysis by an experienced observer was performed. TRUS findings were categorized using a novel classification and correlated with histologic data.

RESULTS A total of 274 patients (58.8%) had prostate cancer, 88 patients (18.9%) inflammation, and 104 patients (22.3%) had benign pathology. Interface calcification was present in 42.3% of patients. Peripheral or transitional zone calcification was unusual (6.8% and 9.0%, respectively). Of the peripheral zone calcification group patients, 78.1% had cancer on histology examination ($P = .020$).

CONCLUSION Prevalence and characteristics of prostatic calcification have been described using this novel and practical classification. Although interface calcification is common and not associated with any particular pathology, peripheral zone calcification appears to be strongly associated with prostate cancer. UROLOGY 85: 178–181, 2015. © 2015 Elsevier Inc.

Prostatic calcification is commonly observed while performing transrectal ultrasonography (TRUS), yet its significance is poorly understood. TRUS-guided biopsy of the prostate currently remains the standard procedure for the diagnosis of prostate cancer (CaP), although the scan is primarily used to guide systematic biopsies rather than to identify pathology.

An initial step in the formation of prostatic calcification is desquamated acinar cells accumulating to form corpora amylacea.[1-3] A variation in density of the matrix of the corpora produces a laminated structure. The deposition of hydroxyapatite crystallites in corpora amylacea leads to the formation of corporal calculi. Further growth and mineralization of corpora calculi leads to the development of the more clinically identifiable prostatic calculi.[1,4]

Prostatic inflammation, calcification, and lower urinary tract symptoms (LUTS) have been implicated in the pathogenesis of CaP.[3,5-8] Prostate inflammation is also associated with benign hyperplasia of prostate as well as CaP.[9-14] Calcification in prostate is also considered relevant in chronic pelvic pain syndrome, prostatitis, and CaP.[15-17] Epidemiologic studies have found significant association between prostatitis and CaP.[5]

Most CaPs arise in the peripheral zone, whereas the transition zones are the location for development of benign prostatic hyperplasia; therefore, zonal calcification may be important. However, it is not clear whether an isolated focus of calcification increases the risk of CaP in that focus or whether the presence of calcification increases the risk of CaP overall.

In the present study, we classified and analyzed prevalence of prostatic calcification during TRUS and correlated results with histologic findings.

METHODS

Study Design

This was a prospective, blinded study of 500 men who underwent TRUS biopsy of the prostate for suspected CaP. The indications for biopsy included high prostate-specific antigen (PSA) level and/or abnormal feeling prostate or patients diagnosed with CaP on active surveillance. Patients were recruited after full informed consent at a single urology unit in the United

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Kingdom, and biopsies were performed by a total of 6 urologists in the unit following a set protocol.

Sample Size Calculation

In men undergoing prostate biopsy at our institution, there is a positive cancer detection rate of 40%. Therefore, a power calculation based on a chi-square test with the conventional 5% significance level, for an approximate sample size of 200 patients with cancer and 300 patients without cancer, resulted in a power of 80% to detect a significant association between calcification and cancer if the difference in prevalence of calcification was at least 13%.

Methods

After informed consent, participants were given 2 validated questionnaires: International Prostate Symptom Score (IPSS) and National Institute of Health (NIH) Prostatitis Symptom Index. IPSS scores are categorized as mild (0-7), moderate (8-19), and severe (20-35). NIH Prostatitis Symptom Index questionnaire consists of 9 questions divided into 3 sections: pain, urinary symptoms, and impact on quality of life, which are used to derive mild (0-9), moderate (10-18), and severe (19-31) symptom scores.

All patients had urine analysis and a PSA test. Our standard protocol for an initial TRUS-guided prostate biopsy was performed using standard, reproducible technique including 6 peripheral biopsies from each lobe with the BK Medical Flex Focus 500 ultrasound system (Analogic Corporation, Peabody, MA) using 7.5-12 MHz multiplanar probe; according to the study protocol, we use a strategic standard protocol[18] which does not specifically include targeting calcification. Images of the prostate were saved at 3 defined regions: (1) at maximum prostate transverse diameter; (2) at maximum prostate sagittal diameter; and (3) transverse and sagittal points where the PCalc under evaluation was the most accurately defined (hyperechoic and cast shadow). These images were printed and blindly analyzed by an experienced urologist. Calcification was classified according to zonal distribution into transitional, interface, and peripheral, as well as unilateral or bilateral (Table 1). Interobserver variability study was performed by an independent observer.

Data Collection and analysis

A pro forma was used to record data, including the IPSS questionnaire, NIH prostatitis symptom index, urine analysis, PSA level, and the detailed histologic report of the biopsy specimen. Relevant information was collated into the spreadsheet database.

Analysis of all these parameters was conducted using multiple logistic regression analysis. Chi-square tests were used to compare zones and sides as categorical predictors. In addition, tests for linear trend were performed for ordered categorical predictors. The distributions of NIH index scores, IPSS scores, and PSA level were skewed and not normally distributed; thus, nonparametric Kruskal-Wallis and Mann-Whitney *U* tests were used. No adjustments were made for multiple testing. All analyses were performed using SPSS, version 15 (IBM).

RESULTS

Baseline Characteristics

Of 500 men, 476 were included for analysis (age range, 46-88 years; median age, 67.0 years; standard deviation, 7.7 years). Of the remaining 24 men, 15 could not tolerate TRUS and biopsies under local anesthesia, and TRUS images were inadequate for analysis in 9 cases. Four hundred seventy-seven men were undergoing prostate biopsies for the first time, and 23 men had biopsies performed as part of active surveillance.

PSA level ranged from 0.4 to 4284.0 mcg/L (median, 8.95mcg/L), and prostate volume measured by TRUS ranged from 15.5 cm^3 to 182.0 cm^3 (median, 45.9 cm^3). Table 2 summarizes baseline characteristics of the study sample.

Based on histology, 274 patients (58.8%) had CaP, 88 patients (18.9%) had inflammation, and 104 (22.3%) had benign pathology (Table 3). Of 274 patients

Table 1. Collins classification

Zone	Unilateral/Bilateral	Score
None	—	0
Interface (IZ)	Unilateral	1
Interface (IZ)	Bilateral	2
Transitional (TZ)	Unilateral	3
Transitional (TZ)	Bilateral	4
Peripheral (PZ)	Unilateral	5
Peripheral (PZ)	Bilateral	6

IZ, Interface Zone calcification; PZ, Peripheral Zone calcification; TZ, Transitional Zone calcification.

Table 2. Patients' baseline characteristics

Characteristic	Age (y)	PSA (mcg/L)	Prostate TRUS Volume (cm^3)
Number of patients	476	476	463
Median	67.0	8.95	45.90
Mean	67.5	—	—
Standard deviation	7.7	—	—
Minimum	46	0.4	15.5
Maximum	88	4284.0	182.0

TRUS, transrectal ultrasonography.

Table 3. Distribution of histology

Histology	Frequency	Percent
Total number of patients	466	100.0
Benign	104	22.3
Inflammation	88	18.9
Cancer right lobe	38	8.2
Cancer left lobe	37	7.9
Cancer bilateral	145	31.1
Cancer right lobe/inflammation left lobe	28	6.0
Cancer left lobe/inflammation right lobe	26	5.6

Table 4. Distribution of prostatic calcification

Calcification Zone	Frequency	Percent
Total number of patients	468	100.0
None	196	41.9
Interface	198	42.3
Transitional	42	9.0
Peripheral	32	6.8