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The Role of the Virtual Touch Tissue Quantification Technique in Differentiating between Benign Prostatic Hyperplasia and Prostatic Carcinoma

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ABSTRACT

Virtual Touch Tissue Quantification (VTTQ) is a promising new implementation of the acoustic radiation force pulsed ultrasound technique that has gained popularity in recent years. The present study compares the performance of the VTTQ technique in distinguishing between prostate cancer (PCa) and benign prostatic hyperplasia (BPH).

VTTQ was performed on 91 prostate nodular lesions in 72 patients with BPH and suspected PCa prior to a prostate histopathologic examination, while 35 healthy volunteers were included in the study as controls. The mean shear wave velocity (SWV) values of the central and peripheral prostate zone were measured in the healthy volunteers, with the SWV at each nodular lesion quantified through the implementation of an acoustic radiation force impulse (ARFI). The performance of VTTQ in discriminating between PCa and BPH was compared, and the diagnostic value of VTTQ for PCa was evaluated in terms of sensitivity, specificity and cut-off value.

Histopathological examinations detected PCa in 21 of the 91 nodular lesions and BPH in 70. The SWV values (m/s) were significantly higher in prostate cancer than in the BPH and central-peripheral prostate zones (3.85±0.78, 2.29±1.03, 1.65 ±0.95, 1.14±0.56). The mean SWV values of the central-peripheral prostate zones were found to be significantly different from each other. We determined an SWV cut-off value of 3.09 m/s for differentiating between benign and malignant nodules, with a sensitivity and specificity of 90.5% and 80%, respectively.

VTTQ can effectively determine the stiffness of prostate nodular lesions, with significantly higher performance discrimination between PCa and BPH.

Keywords: Prostate cancer; benign prostatic hyperplasia; trans-abdominal ultrasound; virtual touch tissue quantification

Introduction

In a study assessing the incidence and mortality rates of 36 cancer types around the world, PCa was identified as the second most common form of cancer and the fifth most common cause of cancer-related death (1), with an increasing incidence due to improved survival and rapid advances in diagnostic imaging modalities for the detection of tumors (2). Detecting PCa early not only reduces the mortality related to the disease, but also contributes to the prevention of the associated side effects caused by such local symptoms as bleeding, urinary tract obstruction and painful metastasis development (3). The combination of digital rectal examination (DRE) and prostate-specific antigen (PSA) testing has been the standard screening approach for prostate abnormalities for over 30 years. Abnormal or increased PSA levels or abnormal DRE are the main reasons for the performance of trans rectal ultrasonography (TRUS) guided core biopsy. The need to process large numbers of tissue samples and the high negative rate are the major disadvantages of systematic biopsy (4, 5), making targeted biopsy procedures of great importance today. It has been concluded that stromal reactions to invasive cancers are characterized also by high collagen depositions (3), and as such, PCa generally presents as a solid lesion relative to normal prostate tissue that can be palpated with DRE. A PSA cut-off value of <4ng/ml is often used in screening tests for PCa (6). An enlarged prostate (prostate volume >20 mL), and an International Prostate Symptom Score (IPSS) >7 are accepted as important criteria for a diagnosis of benign prostatic hyperplasia (BPH) (7). It has been around 60 years since the first use of ultrasonography

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for the diagnosis of PCa (8), and it has since been suggested that an earlier diagnosis of PCa can be achieved as a result of advances in ultrasonography and the wide spread use of the application (9). Ultrasound is currently the most frequently used imaging modality for the direct visualization of the prostate, being a real-time, low-cost imaging method that does not expose the subject to ionizing radiation. However, in a PCa diagnosis, TRUS is not a sufficiently sensitive and specific test (40-50%)(10-12). In a study of B-mode ultrasound results, only 9–53% of suspected hypoechoic nodules were cancerous (13, 14). PCa usually presents with harder-than-normal prostate tissue, and while the use of trans rectal strain elastography ensures the identification of hard prostatic tissue (15), this technique has some limitations. First, it is operator-dependent; second, it is not possible to apply equal compression to all areas of the gland; third, artifacts may occur due to the displacement of the compression plane; and, fourth, there is a lack of adequate information on quantitative elasticity (5, 16). As another imaging modality, the VTTQ technique is based on the ARFI elastography, the preliminary results of which are encouraging (17, 18). Shear wave elastography is considered to be more objective and reproducible and allows direct assessment of tissue elasticity with the possibility of obtaining quantitative measurements (19, 20) ARFI elastography can thus be considered a non-invasive and effective imaging technology that quantifies the elasticity of tissue using shear-wave velocity technologies (17, 21, 22). There have been few studies in literature investigating the contribution of trans-abdominal ARFI elastography to the diagnosis of BPH and PCa (18, 22).

The present study investigates the effectiveness and contribution of the VTTQ technique to the differentiation of nodular lesions seen in PCa and BPH patients with high PSA levels through measurements of their elasticity.

Materials and Methods

This study was approved by the local ethics committee of our hospital, and signed informed consent forms were obtained from all participants. All consecutive patients who met the inclusion criteria and who were scheduled for prostate biopsy constituted the study group. Patients with higher serum PSA levels (>4 ng/ml) or gradually increasing PSA levels by 0.75 ng/ml/year and/or abnormal DRE (palpable nodular lesions), abnormal trans-abdominal ultrasound findings (lesions diameter ≥10 mm, border forming and space occupying nodules) were also included in the study. The reason why we chose the nodules over 1 cm was to minimize the effect of the contrast and spatial resolution disadvantage of trans-abdominal examination on the study result and to allow optimum elastographic measurement. A total of 72 patients with 97 prostate nodules and a control group of 35 healthy volunteers were included in the study. The healthy volunteers were selected from those with no pathology in clinical (IPSS score<7) and or laboratory finding <4ng/ml PSA value. Patients with bladder cancer, a history of prostate operation, extensive calcified prostate parenchyma, radiotherapy to the pelvic region, presence of diffuse ascites and morbid obesity were excluded from the study. In addition, those with a prostate located >8 cm deeper than the skin were excluded from the study. DRE was performed by a urologist from the department of urology. Prior to rectal palpation, the bladder was evacuated. The patients bent their knees while standing erect and supported their body with their forearms resting on the examination table, and were requested to strain down to facilitate palpation of the prostate. During the DRE, firm irregularities of the prostate and palpable nodules were noted for possible malignancy. All ultrasonographic investigations were performed using an Acuson S2000 ultrasound system (Siemens Solutions, Mountain View, CA, USA) with a convex probe (6 C1, frequency range: 1-4 MHz). Bladder evacuation was requested immediately beforehand. Trans-abdominal B-mode ultrasound imaging was performed with the patient in the neutral supine position on the examination table. After the routine abdominal ultrasound examination, a prostate-oriented evaluation was performed. The characteristics, localization and longest axis dimensions of each nodule were recorded in B-mode imaging and the information was shared with the physicians who performed the biopsy. ARFI measurements (Virtual Touch™ Tissue Quantification package) were made by two radiologists with 4 years of elastography experience, and radiologists interpreted the gray scale and sonoelastography findings in consensus. Elastography was performed by one radiologist (operator) and a second radiologist attended all examinations. The radiologists discussed the findings during and after the examination. All measurements were made in the abdomen module of the convex probe, based on axial images with mild compression, without increasing the intra-abdominal pressure. Consensus was reached in the selection of nodules and the elastography measurement. Prostate tissue and nodules at a distance suitable for measurement were included in the study. Primarily, the VTTQ was implemented with the introductory recognition of a target region of interest (ROI) (box with a fixed dimension of 1×0.5

cm) on conventional ultrasound views. Measurements were made by placing ROIs in different localizations so that the nodules did not overflow, and the values on the right side of the ROI, where the SWVs were calculated and expressed with a quantitative value (m/s), were recorded. A total of four valid SWV measurements were made in two central and two peripheral zones of the prostate in the healthy volunteers. At least three valid measurements were made from the nodules and the average was recorded (figure 1). In the event of invalid measurements, the measurement was repeated and expressed as X.XX m/s. Quantitative measurements of parenchymal elasticity, and the SWV values providing qualitative data were expressed in meters per second (m/s), mean (± SD) and range. Tissue samples were obtained from patients using a simultaneous extended biopsy technique (10-12 quadrants), and the biopsies were performed using a DC-3 Mindray Ultrasound device (model 2009-2010, Shantou, China) using 6 CV1 micro convex transducers with high frequency (5-8 MHz), with the physician being blind to the results of the SWE study. A trans rectal biopsy was performed using an 18G needle, with the goal of obtaining the optimum piece size from each lesion. All specimens were analyzed by a single pathologist with more than 10 years of experience in the evaluation of prostate core biopsy samples, and who was blinded to the imaging results but not to the patient's clinical and biochemical data. A biopsy was considered to be positive (indicating malignancy) when the Gleason score was 6 or higher and the size of the adenocarcinomatous tissue within the biopsy core was 3 mm or larger, while lower Gleason scores and smaller biopsy scores were reported as normal or non-neoplastic prostate histology.

Statistical Analysis: Descriptive statistics of the studied variables (characteristics) were presented as mean, standard deviation, minimum and maximum values. A one-way Analysis of Variance (ANOVA) was used for the comparison of group means of the studied variables. The SWV (m/sn) cut-off values were determined by a ROC analysis. The Kappa coefficient was computed to determine the level of agreement between the VTTQ and the final pathology results, and the intra-observer reliability coefficient was computed for the reliability of the measurements. Statistical significance levels were considered as 5%. IBM SPSS Statistics (Version 22.0. Armonk, NY: IBM Corp.) was used for all statistical computations.

Results

A total of 72 patients with 91 prostate nodules (mean age: 61.47±8.11 years, range: 44–79 years) and a control group of 35 healthy volunteers (mean age: 61.25±7.85 years, range: 48–80 years) were included in the study. Prostate volumes were in the range of 34–146 cm^3, the mean volume range was 60.95 cm^3 and the standard deviation was ±25.84. The longest axis dimensions of the prostate nodules were measured as min:10.9, max:37 mm – mean:17.39 mm, standard deviation±4.51. A histopathological examination of the 91 nodular lesions revealed PCa in 21 and non-neoplastic prostate tissue in the remaining 70 patients.

The minimum, maximum, mean and standard deviation SWV (m/s) values measured from the central prostate zones in the control group were 0.55, 4.4, 1.65 and ±0.95, respectively; and in the peripheral prostate zones, the measurements were 0.51, 3.19, 1.14 and ±0.56, respectively, with a significant difference between the central and peripheral prostate zones. The SWV values of the cancerous nodules were min: 1.87, max: 4.94 and mean 3.85±0.78; while the SWV values of the nodules detected in patients with BPH were min: 0.5, max: 4.55 and mean 2.29±1.03, with a statistically significant difference in the SWV values in patients with cancerous nodules and BPH. In short, there was a statistically significant difference between each of the four groups ($p<0.05$) (figure 2).

As a result of the ROC analysis performed to identify a cut-off value for SWV differentiating the peripheral zone from the PCa nodular lesion, the area under the curve was found to be 0.993±0.006 ($p<0.05$). When 2.57 m/s was selected for the cut off value, the sensitivity and specificity of this value were 95.2% and 97.8%, respectively (figure 3).

The cut-off value discriminating between the BPH and PCa nodular lesions was evaluated with ROC analysis, and the area under curve (AUC), 95% confidence intervals and levels of significance (p) were found as indicated in figure 4. A cut-off SWV value was found to be 3.09 m/s, and the sensitivity and specificity of this value were found 90.5% and 80%, respectively.

We determined a cut-off value for SWV of 3.09 m/s, and a Chi-square test was applied to determine whether SWV is correlated with the optimum pathology discriminating between benign and malignant nodules, revealing a p value of 0.001.

The cut-off value discriminatıng between central zone and PCa nodular lesions was evaluated with a ROC analysis. A cut-off value for SWV of 2.65 m/s was

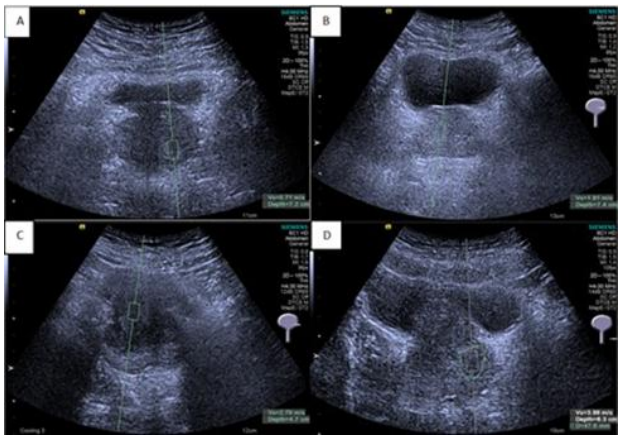

Fig. 1. The Measurement of SWV in The Peripheral Prostate Zone (A), Central Prostate Zone (B), BPH (C) and PCa (D) With VTTQ

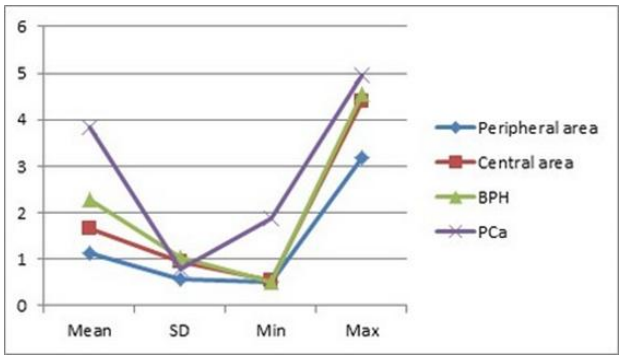

Fig.2. Mean, Minimum, Maximum, and Standard Deviation Values According To Four Groups

identified, with 95.2% sensitivity and 88.6% specificity. When a SWV value of 3.22 m/s was accepted, sensitivity and specificity were 81% and 91.4%, respectively (figure 5).

The Kappa coefficient, identifying the level of agreement between the VTTQ results and the final pathology results, was found to be 55.8%, suggesting a considerable level of agreement between the VTTQ results and the final pathology results. In the VTTQ study, 21 PCa nodules were found when a cut-off point of 3.09 m/s was selected. When determining the performance of the VTTQ for the diagnosis of PCa and BPH, the cut-off value of SWV contributed positively, based on the AUC of the ROC.

The results of an ANOVA, conducted to identify any differences between the SWV measurements of the nodules, are presented in figures 3, 4 and 5. The differences in the mean values obtained as a result of this analysis of variance between nodules were found to be statistically significant ($p<0.01$). A Duncan multiple-comparison test was then applied to detect different nodules, revealing different mean values in two different nodules and the control group values ($p<0.01$). The highest (4.94) and the lowest (1.87) mean values for a malignant nodule were identified,

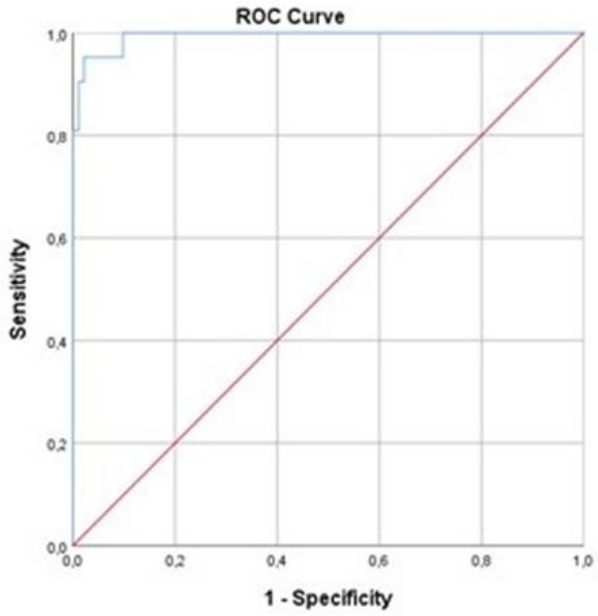

Fig.3. ROC Analysis In Differentiating The Peripheral Zone From The PCa Nodular Lesions

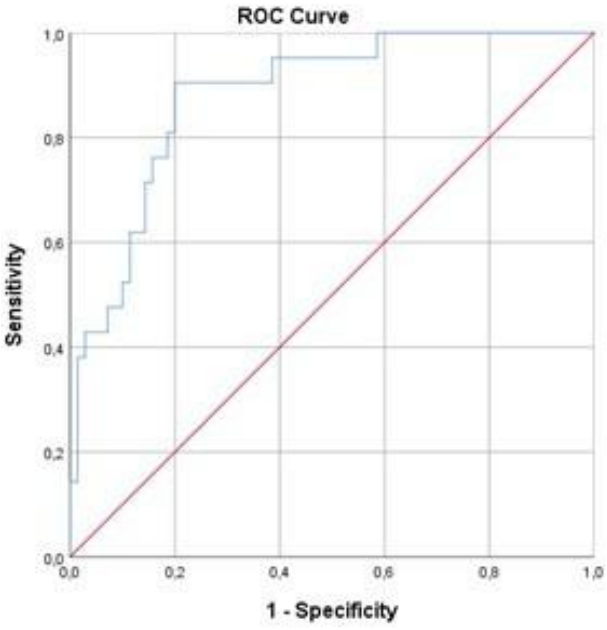

Fig.4. BPH and PCa Nodular Lesions Were Differentiated Using ROC Analysis

along with the mean of the control group for the benign nodule (2.29). The intra-observer agreement was excellent for both the PCa and SWE measurements for both the patient and the control groups, with an intra-observer reliability coefficient of 80%.

Discussion

Changes in prostate stiffness can indicate prostate pathologies. In recent years, with the advances in

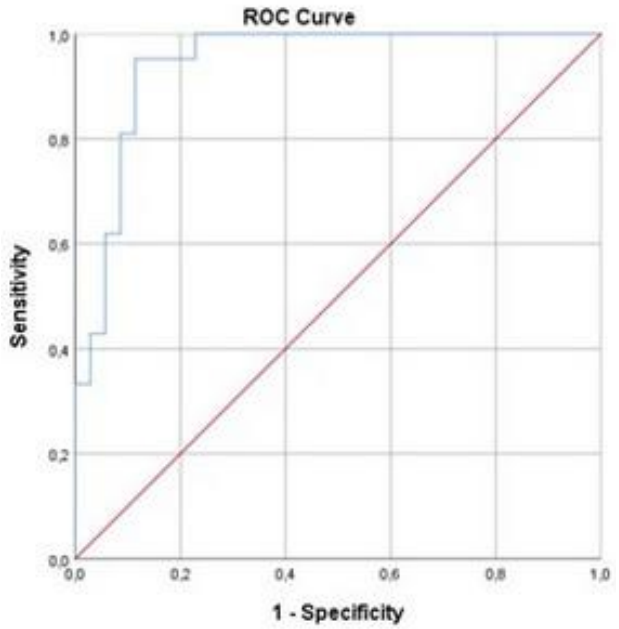

Fig.5. ROC Analysis of The Discrimination Between The Central Zone and PCa Nodular Lesions

imaging technologies, several imaging techniques have emerged that allow the objective analysis of tissue stiffness. Elastography is one such novel real-time imaging technology that can assist in the determination of tissue stiffness (4, 15). ARFI imaging is a new ultrasound imaging modality that is used to evaluate the rigidity of deep tissues based on short-duration acoustic radiation forces that produce localized displacements in a "pushed" ROI, and the SWV, being the speed of a transverse wave propagating perpendicular to the direction of tissue displacement, is an indicative factor of tissue rigidity. Shear-wave velocity can be easily measured using the VTTQ technique without any special preparations or procedures (18, 23, 24), and produces numerical measurements (wave-velocity values) of tissue rigidity at a precise image-based anatomical location (23, 24). SWV can be measured reproducibly in all regions of interest in the peripheral and central zones of the prostate in all patients. To optimize the results, we averaged at least two measurements from zones of intact tissue, and at least three measurements from suspicious nodules. Since there may be differences in SWV values in the central and peripheral regions of the prostate with age, we attempted to keep the ages of the patient and control groups equal. In the study by Zheng et al. investigating the variability of stiffness with age in the inner and outer regions of the prostate via trans-abdominal elastography, no difference was observed in the same age groups (23). In the present study, the mean age of the patient and control groups was around 60 years, and the mean stiffness values of the inner prostate zone were significantly higher than those of the outer prostate zone. Considering that most PCas are located peripherally, this structural feature of prostate tissue offers significant advantages for elastography, especially in the detection of cancerous nodules. In the patient group, measurements were taken only from nodules larger than 1 cm that could be distinguished from the intact parenchyma area, and all nodular lesions detected in PCa and BPH were found to have higher SWV values than those of normal prostate tissue. This finding is similar to the results of previous studies (5, 18, 23). The mean stiffness of nodules with PCa was found to be significantly higher than BPH nodules. Since VTTQ is a non-invasive and easily available technology, it allows the evaluation of prostatic stiffness in a selected prostate zone. As a result, the rigidity of any prostatic nodular lesion can be easily achieved, whether in the peripheral or central zone, based on SWV measurements through an abdominal or perineal approach, and SWV measurements can be repeated using the VTTQ technique. The good reproducibility of VTTQ has been noted in earlier studies (18). Within this context, the changes in prostatic stiffness caused by differences in prostatic tissue components may aid in the diagnosis of PCa and BPH. A comparison of trans-abdominal US, ARFI imaging and trans rectal US reveals VTTQ to be a non-invasive method that provides quantitative data about the SWV and ensures a more objective evaluation of prostatic rigidity. The method is also useful for the characterization of prostatic nodules in selective cases with trans-abdominal examination, and without the need for any preparation in daily practice.

Although VTTQ is a potentially important quantitative analysis diagnostic tool, it has some limitations. The limitations on tissue depth (max. 8 cm) and the fixed box size (1×0.5 cm) of the targeted ROI may hinder the extensive application of this new technology. As a further limitation, all study groups were assessed with only one US system. Besides, not all cancerous tissues were found to be stiff, and not all of the stiff lesions were cancerous (especially benign lesions that experience tissue changes). The most important disadvantage of trans-abdominal ultrasonography is the lower anatomical detail and contrast resolution achieved when compared to trans rectal ultrasonography. To minimize the restrictions, included in the study were lesions with boundary nodular formations larger than 1 cm.

In this study evaluating the utility of VTTQ for the detection of PCa, the approach was identified as an innovative and promising ARFI imaging technique for the quantitative measurement of tissue hardness. This non-invasive procedure can assist in DRE and PSA testing by characterizing space-occupying,

border-forming nodular lesions in the prostate. Our study found that trans-abdominal examinations can be applied safely in patients that meet certain criteria as an alternative to TRUS, which is the currently preferred imaging method for prostate pathologies. It is highly important for patient comfort that elastography, which has proven effectivity in many organs, primarily for the detection of malignant pathologies, be applied to the prostate via a non-invasive method. There is a need for more comprehensive studies that include trans rectal and multiparametric MRI and detailed pathological scoring.

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