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Standard TRUS guided prostate biopsy Vs new multiparametric approach using transrectal SE and CEUS. A randomized controlled study.

Tutor:
Prof.ssa Teresa Pellegrino

Valutatori:
Prof. Michele Danzi
Prof. Pietro Muto

Candidato :
Dr. Francesco Forchia

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Introduction

Prostate cancer (PCA) has the highest incidence rate and is the second highest cause of cancer death in men in Western countries. It is the second most frequent malignant tumor in males worldwide [1-3]. With improvements in prostate-specific antigen (PSA) screening, diagnostic techniques and prolonged life expectancy, the incidence and prevalence of PCA have increased steadily in the last decade [4-5]. It is reported that more than 500,000 patients per year undergo prostate biopsy in the United States [6]. Current guidelines support systematic sampling with 10 to 12 biopsy cores, which has a significantly higher cancer detection rate than sextant biopsies [7-9]. Nevertheless, the conventional biopsy protocol on the one hand misses significant PCA in a large percentage of patients and, on the other hand, detects many insignificant PCAs that do not require immediate treatment, resulting in overdiagnosis and overtreatment [10]. The estimated overdetection rate for prostate biopsy ranges from 27% to 56% [11]. Methods for detection of PCA include PSA screening, digital rectal examination (DRE) and diagnostic imaging techniques such as ultrasound (US) and magnetic resonance imaging (MRI). PCA is generally a stiff lesion compared with normal prostate tissue and can be detected on DRE. However, DRE is subjective and operator dependent, and its sensitivity is questionable for deep or small lesions [12,13]. It has limited accuracy for staging disease and locating the different foci [14], which are two factors mandatory for planning primary therapy. Despite the low specificity of PSA testing and the low sensitivity

of systematic biopsy (SB), these techniques remain the standard of care for PCA diagnosis, mainly because of their widespread availability and low cost [1, 15-17]. Ultrasound is the most common imaging method for direct visualization of the prostate because it is real time, does not involve ionizing radiation and is low in cost. However, transrectal ultrasound (TRUS) is not highly sensitive or specific (40% - 50%) in the diagnosis of PCA because suspicious hypo-echoic areas represent cancer in only 9% - 53% of cases with B-mode technique [18-21]. Nearly 58% of PCAs are multifocal and progress along the capsule of the prostate and may not appear as well-defined nodules like other malignant tumors. Therefore, it is difficult to detect lesions accurately using conventional imaging technology [22]. Meanwhile, color Doppler and power Doppler imaging do not substantially improve the diagnostic accuracy [18,21]. Pathologic results obtained by TRUS-guided SB remain the mainstay in confirming or ruling out PCA [21]. Prostate biopsy also allows estimation of the aggressiveness of PCA (Gleason score, invasion of capsule or neurovascular bundles) [11]. Because of the inaccuracy of TRUS and the limitations of SB, improved imaging for the detection, localization and staging of PCA is needed. As cancerous tissue in the prostate has a higher stiffness compared with benign tissue, an imaging technique able to assess tissue stiffness would be useful in the diagnosis of PCA. PCA tissue becomes stiffer than the surrounding healthy prostate tissue because of the following changes: an increase in cellular density and microvascularization, destruction of the glandular architecture [23] and triggering of wound repair. This process is characterized by stromal reaction [23, 24] and

collagen deposition surrounding the cancer [25]. Deposition of collagen increases significantly with Gleason grade [26, 27] and is linked to a significant reduction in the acinar area in the PCA stroma. All of these changes contribute to the increased stiffness of tissue affected by PCA [28]. At present, two US lastography techniques have been developed for image the prostate in clinic practice: strain elastography (SE) and shear wave elastography (SWE). US elastography improves both prostate lesion characterization and PCA detection; in particular, this approach can be extremely useful in the detection of prostate lesions, disclosing lesions on the elasticity map that are not visible on conventional TRUS imaging (iso-echoic lesions) or other imaging modalities such as on the other hand, detects many insignificant PCAs that do not require immediate treatment, resulting in overdiagnosis and overtreatment [10].

TRANSRECTAL STRAIN ELASTOGRAPHY

Transrectal SE assesses the differences in tissue strain produced by freehand manual compression, with stiffer tissues having less strain. Transrectal SE represents the distribution of strain and helps differentiate benign from malignant tissue [22]. As a novel biomechanical technique, transrectal SE is an improvement over conventional ultrasonic imaging, with better diagnostic value for PCA. Transrectal prostate SE is based on the analysis of tissue deformation generated by inducing an external mechanical stress (slight compressions and decompressions of the tissue by the transrectal transducer itself). The deformation needs to be uniform in intensity throughout the gland [29;30]. A speckle comparison, before and after compression, yields a color-coded map of local tissue deformation or strain, called the elastogram. Tissue stiffness is estimated by visualizing the differences in strain between adjacent regions. The stiffness color scale is automatically distributed from the lowest to the highest strain found in the image plane and displayed as an overlay on the B-mode image. Stiff tissues exhibit reduced strain, whereas soft tissues have higher strain (distortion). A quality index may help ensure appropriate frequency and applied pressure of the manual compressions. Recently, the guidelines and recommendations of the European Federation of Societies for Ultrasound in Medicine and Biology Guidelines [31] and the Japan Society of Ultrasonics in Medicine (JSUM) [32] have assessed the clinical use of ultrasound elastography. These documents are intended to form a reference and to guide

clinical users in a practical way. The guidelines also give practical advice on its use and interpretation [31;33].

Procedure

No specific preparation is required for transrectal SE, which is conducted after a complete, high-quality TRUS examination in the transverse and sagittal planes. The examination includes measuring the prostate volume, identifying suspicious areas in the gland and analyzing the periprostatic space (including the seminal vesicles). The same transrectal probe is used for both conventional US and SE. Awater-filled balloon may be placed between the transducer and the rectal wall to improve the homogeneity of the deformation [34]. The patient lies in the left lateral position with bended knees and hip flexion or in the lithotomy position.

A cover is placed on the transducer using a moderate amount of coupling gel, and the transducer is slowly inserted into the rectum. The prostate capsule, symmetry, abnormal echogenicity patterns, especially hypo-echoic lesions, calcification and boundary are observed initially on conventional US. The prostate volume is measured and recorded. The entire gland is evaluated from the apex to the base or vice versa, including the seminal vesicles and periprostatic tissues. Color or power Doppler can then be performed if required. After conventional imaging, SE is performed. The elastogram is displayed over the B-mode image in a color-coded scale. Various color-coded scales can be used. Most systems have an indicator (quality index) displayed in real time that allows the user to determine if the

degree of compression/release is appropriate. The frequency of the small compressions/release should remain constant to generate a continuous series of images. The quality index helps ensure appropriate frequency and pressure of the compression/release. Transrectal SE images are obtained in the transverse plane at up to 30 frames per second. The focus should be placed in the far field of the region of interest (ROI). The ROI should cover the entire prostate gland and the surrounding tissues, but avoid the bladder. Semi-quantitative stiffness information can be derived by measuring the strain ratio between two ROIs (usually one considered as the reference normal prostate tissue and the other as the abnormal area). The amount of compression/release needed for most systems is less than 2%. With use of the quality index for the process of compression/release, the pressure and direction of manual vibration are adjusted until stable, repeatable images (prostatic capsule is clear, smooth and symmetrical bilaterally, unless there is capsular extension of the tumor), with the pressure indicator bar displaying good quality are obtained. The images and or clips are stored in the system for further analysis. By stepwise scanning of the prostate from base to apex, strain elastography allows detection of stiff regions and provides stiffness comparisons between lesions and the adjacent prostate tissue. Several different applications of SE of the prostate have been reported, including (i) characterization of abnormal regions detected on B-mode US, color Doppler US and/or power Doppler US, or MRI/multiparametric (mp) MRI,

detection of lesions not seen with any imaging technique; (ii) staging of PCA; and (iii) biopsy targeting.

Contrast Enhanced UltraSound

Comparisons between systematic and CEUS-targeted biopsies have shown that the targeted approach detects more cancers with a lower number of biopsy cores. CEUS has also been shown to detect cancers with higher Gleason scores compared with the systematic approach, which seems to improve prostate cancer grading. This article will discuss the value of CEUS in the imaging of prostate cancer. Newly developed US contrast agents enable improved detection of low-volume blood flow by increasing the signal-to-noise ratio. [35] Therefore, US contrast agents allow for a more complete delineation of the neovascular anatomy by enhancing the signal strength from small vessels (i.e. neovessels). Furthermore, these agents can be used to time the transit of an injected bolus. Unlike radiographic contrast media, which diffuse into the tissue and may obscure smaller vessels, microbubble echo-enhancing agents are confined to the vascular lumen, where they persist until they dissolve. US contrast agents are made of gas bubbles small enough to cross through capillary beds. [36] They have two main important acoustic properties: first, they are many times more reflective than blood, thus improving flow detection; and second, their vibrations generate higher harmonics to a much greater degree than surrounding tissues. The half-life of contrast agents is dependent on bubble construction. Bubbles can be free or encapsulated in soft or hard shells. The duration of enhancement after injection may last from a few seconds to many minutes, depending on the bubble type.

Bree at al. demonstrated the potential use of contrast-enhanced colour Doppler to enhance the diagnostic yield in a group of 17 patients with normal greyscale transrectal US and elevated PSA values. Correlation of biopsy sites with colour Doppler US abnormalities revealed a sensitivity of 54%, a specificity of 78%, a positive predictive value (PPV) of 61% and a negative predictive value (NPV) of 72% for the detection of prostate cancer. Three of the cases with a positive contrast-enhanced biopsy site had negative transrectal US random biopsy within the previous year. [37]

Frauscher et al. examined the use of contrast-enhanced colour Doppler US in 72 patients identified by PSA screening in a previous study. Using a quantitative scale to characterise the degree of vascularity, the technique had a sensitivity of 53%, specificity of 72% and PPV of 70% in distinguishing prostate cancer from benign lesion. [38] Previous studies reported the value of contrast-enhanced colour Doppler in a prospective study in 2305 and 380 male screening volunteers,6 and found that targeted biopsies based on contrastenhanced colour Doppler detected as many cancers as systematic biopsies, with less than half the number of biopsy cores.

Bogers et al. evaluated contrast-enhanced 3D transrectal ultrasound imaging of the prostate vasculature with power Doppler. 3D power Doppler images were obtained before and after intravenous (IV) administration of 2.5g Levovist™ (Schering, Berlin). Subsequently, random and/or directed transrectal US (TRUS)-guided biopsies were performed. Prostate vasculature was judged with respect to symmetry and vessel

distribution. Eighteen patients with a suspicion of prostate cancer because of either an elevated PSA (greater than 4.0ng/ml; Tandem-R-assay) or an abnormal DRE were included in the study. Prostate cancer was detected in 13 patients. Vascular anatomy was judged abnormal in unenhanced images in six cases, of which five proved malignant. Enhanced images were considered suspicious for malignancy in 12 cases, including one benign and 11 malignant biopsy results. Sensitivity of enhanced images was 85% (specificity 80%) compared with 38% for unenhanced images (specificity 80%) and 77% for conventional greyscale TRUS (specificity 60%). Among six patients who showed no B mode abnormalities, vascular patterns were judged abnormal in four cases, of which three were malignant. Based on these findings they concluded that contrast-enhanced 3D power Doppler angiography is feasible in patients with suspicion of prostate cancer who are scheduled for prostate biopsies.[38]

Aim of the study

Several promising imaging techniques to identify cancer lesions and detect various histological growth patterns of Prostate Cancer are under investigation [39]. Compared to benign prostate tissue, multifocal cancer development is associated with histopathological loss of benign glandular architecture, increased cellular density and altered microvasculature [40;41] . Transrectal SE visualizes differences in prostate tissue strain [42]. Due to a high rate of false-positive results, especially in areas of former prostatitis or benign hyperplastic nodules, specificity to detect PC remains variable at 71.5% to 76.6% [43, 44]. Based on the hypothesis that histo-architectural changes in PC development induce hemodynamic changes, perfusion based imaging techniques have been developed and added to current imaging methods to possibly improve cancer detection [45;46]. CEUS enables the visualization of prostate areas with abnormal vascularity [39]. Adding this information to current gray scale and Transrectal SE imaging methods might improve the visualization and detection of PC. We prospectively assessed whether a combined approach of transrectal SE and CEUS in a multiparametric setting might improve cancer visualization before RP. The detection rate by this multiparametric technique, was compared with our personal PC detection ratewith a standard prostate biopsy TRUS guided.

Material and methods

Between November 2013 and September 2016, 100 consecutive patients with biopsy proven PC scheduled for RP were prospectively examined by a single investigator using a multiparametric ultrasound approach. All men underwent prostate biopsy more than 4 weeks before examination. Patients showing signs of prostatitis within 4 weeks before examination were excluded from study. No patient received androgen deprivation therapy. Each patient provided informed consent. Patients underwent multiparametric transrectal ultrasound using a HI VISION™ Preirus™ ultrasound device with a V53W transrectal end fire probe (Hitachi Medical, Tokyo, Japan) 1 day before surgery. Standardized transrectal SE was performed with the patient in the left lateral position. Areas of decreased elasticity, were considered suspicious for PC according to the malignancy criteria previously described by Konig et al [47]. The localization of each suspicious area was assigned to the corresponding prostate sector. A compression scale was used to standardize investigator movements. Imaging was saved on video files. The largest cancer suspicious area during transrectal SE was defined as the TL and used for analysis during contrast enhanced imaging. To assess microvessel architecture in the transrectal SE determined TL, 5 ml contrast agent (25 mg SonoVue® in 5 ml 0.9% sodium chloride) were administered via an antecubital vein of the right arm as a single bolus injection, followed by 10 ml 0.9% sodium chloride. The contrast agent contains microbubbles consisting of a phospholipid shell filled

with sulfur hexafluoride gas. The low diameter (2 to 8 m) enables the microbubbles to pass the pulmonary circulation and remain intravascular for several minutes. To visualize the circulation of bubbles in microvessels we used a specific ultrasound mode with a low mechanical index of 0.14. CEUS was initiated when the contrast agent was injected. A video file was recorded to monitor perfusion behavior in the TL with time. We examined 3 perfusion patterns (normoperfusion, hypoperfusion and hyperperfusion) of the TL compared to those of adjacent tissue. After surgery prostatectomy specimens were color inked, formalin fixed and cut into 4 mm transverse whole mount slides. Subsequently, 4 paraffin embedded tissue sections were obtained from each slide and stained with hematoxylin and eosin according to the Stanford protocol (48). After microscopic examination malignant areas on whole mount slides were outlined and recorded for analysis. The TL previously documented by transrectal SE underwent detailed examination by a dedicated uropathologist on the corresponding whole mount slide. If cancer was histopathologically confirmed, the maximum dimension of the lesion was measured and the predominant Gleason pattern was recorded. We calculated the sensitivity, specificity, and negative and positive predictive values of transrectal SE to detect tumor foci by prostate sector. CEUS perfusion patterns were grouped as normal (hypoperfused) or suspicious (hyperperfused) to estimate the accuracy of PC detection in each defined TL. To analyze the frequency of PC areas in the 3 groups during CEUS we used the chi-square test with significance considered at $p \leq 0.05$.

Correlation between the CEUS perfusion pattern and the predominant Gleason score of the TL was evaluated with the Mann-Whitney U test. Data from our PC detection rate with Standard prostate biopsy TRUS guided, obtained analyzing the prostate biopsy performed by a single operator from November 2013 to September 2016, were compared with the detection rate of the multiparametric ultrasound approach. SPSS® version 19 was used for statistical analysis.

Results

A total of 100 patients (mean age 64.5 ± 8.5) were prospectively examined with musculoskeletal ultrasound and underwent RP. Mean prostate specific antigen was 11.1 ±3.4 ng/ml and mean prostate volume was 45.4 ± 5.6 ml. A cancer suspicious palpable mass was assessed by digital rectal examination in 50 of 100 patients. Mean histopathological tumor volume was 4.12 ± 2.7 cm^3 (range 0.26 to 43.5). Histopathological analysis of RP specimen whole mount sections showed Gleason score 3+4 and 4+3 in 46% and 26% of cases, respectively. Complete analysis of prostate sectors could be accomplished in 86 of 100 patients. Of the patients 14 were excluded from study because whole mount slides could not be accurately matched with the corresponding imaging TL due to fixation artifacts or slide disruption. A total of 1.032 prostate sectors (12 per patient) were assessed. PC was histopathologically verified in 621 sectors with the highest frequency in the mid gland (39%), followed by the apical region (31%) and prostate base (30%). PC was more frequently detected in dorsal (57%) than in ventral (43%) parts of the gland. Systematic evaluation using transrectal SE correctly identified cancer in all prostate sectors with overall 49% sensitivity and 74% specificity. Sensitivity was lower in ventral areas (30% to 35%) compared to dorsal areas (32% to 89%). It was most accurate at the apex of the prostate gland (89%). In each prostate the largest radiographic cancer suspicious area during transrectal SE was defined as the TL. Maximum median diameter of the TL measured during transrectal SE was 14.3 mm

(range 5.1 to 43.7). The TL was subsequently monitored using CEUS contrast perfusion patterns. Mean examination time, including transrectal SE and CEUS, was 5.3 minutes (range 2 to 15). Of 86 TLs 58 (67%) showed a suspicious perfusion pattern, 31 (36%) showed hypoperfusion and 27 (31%) showed hyperperfused tissue. Normoperfusion was found in 28 of identified TLs (33%). PC was histopathologically verified in 56 of 86 TLs (65%) with a maximum median diameter of 15 mm (range 2 to 40). Of these 56 histopathological PC positive TLs CEUS revealed suspicious perfusion patterns in 52 (93%). Hypoperfusion and hyperperfusion were identified in 27 (48%) and in 25 TLs (45%), respectively. Only 4 normoperfused TLs (7%) on CEUS showed histopathologically malignant tissue. When comparing normoperfused TLs vs suspiciously perfused (hypoperfused or hyperperfused) TLs to detect histopathologically proven cancer, statistical analysis revealed statistically significant differences ($p \leq 0.001$). Using transrectal SE alone showed a false-positive result in 30 of 86 TLs (35%). Adding CEUS to RTE decreased the false-positive result to 6 of 58 TLs (10%). In other words, if the transrectal SE positive TL showed a suspicious perfusion pattern, the likelihood of correctly detecting histopathological PC was 90%. Due to the finding that cancer more likely showed abnormal perfusion patterns than benign lesions on transrectal SE, we investigated whether the Gleason score in the defined area might correlate with hypoperfusion or hyperperfusion. In each group of TLs with suspicious perfusion patterns Gleason 4 was predominant. However, the predominant Gleason score in the TL did not

significantly correlate with the perfusion pattern during CEUS ($p \leq 0.12$). Histopathological examination of the 4 TLs considered normoperfused revealed Gleason 3 in 2 (50%) and Gleason 4 in 2 (50%). The maximum diameter of these lesions was 2, 3, 17 and 26 mm, respectively.

The detection rate of our standard prostate biopsy TRUS guided performed by a single operator was 71%.

Discussion

To our knowledge this is the second prospective study combining transrectal SE and CEUS in a multiparametric imaging approach to investigate PC in patients before RP. In the defined TL transrectal SE alone identified histopathological PC infiltration with a positive predictive value of 65%. Adding CEUS to visualize microvessel perfusion patterns improved the positive predictive value to correctly identify cancer to 90%. Based on the low sensitivity and accuracy of gray scale ultrasound alone, various imaging techniques have been introduced to optimize PC visualization. Since its first introduction in 1991 by Ophir et al, transrectal SE has been established at various urological centers of excellence to provide an additional tool to improve PC detection [42]. Several groups have investigated the accuracy of transrectal SE correlated with biopsy results to detect PC [49]. Despite promising results in regard to using this imaging technique with biopsy results, sensitivity and specificity did not attain levels that would enable safe visualization of lesions in the gland preoperatively. Thus, to determine the true sensitivity or specificity of transrectal SE a correlation with thin sectioned whole mount prostatectomy specimens is obligatory [41]. Studies investigating a correlation with whole mount slides showed variable 57% to 100% sensitivity [50]. Salomon et al investigated 109 patients and reported overall 75.4% sensitivity and 76.7% specificity for cancer detection [44]. Tsutsumi et al reported 57% to 94% variable sensitivity depending on lesion anatomical location

according to the sextant scheme used in that study [51]. They postulated higher sensitivity in the ventral than in the dorsal parts of the gland. Other studies revealed better transrectal SE accuracy for the apex of the prostate compared to the base [52]. In an earlier study in 229 patients we evaluated the staging ability of transrectal SE [43]. Sensitivity was 51% and specificity was 72%. In addition, we identified extracapsular extension of PC with 38% sensitivity and 96% specificity.

In addition to the limitation of a known learning curve to apply transrectal SE, this technique is associated with a high number of false-positive results, especially in areas of former prostatitis, which can lead to the fibrosis of benign prostate hyperplasia (49,53,54). Due to the limitations of transrectal SE alone we, as already did Brock et al [55], hypothesized that adding CEUS might improve the distinction of benign from malignant areas by visualizing perfusion patterns resulting from cancer impacted changes to the microvessel architecture. Since the initial report in 1993 of increased capillary density of prostatic carcinoma by Bigler et al [45] several groups have found that microvessel density is significantly higher in cancer than in benign tissue [56, 57]. Sedelaar et al noted that CEUS enhanced areas had 1.93 times higher microvessel density than nonenhanced areas in the prostatectomy specimen [58]. Matsumoto et al evaluated 50 patients before RP using a bolus injection of contrast agent [59]. They identified at least 1 tumor focus in 62% of cases when counting the areas of increased contrast enhancement, and reported 30.8% sensitivity for CEUS. Halpern et al observed an improved sensitivity of 42% in 12 patients with

biopsy proven PC [60]. Sano et al expanded the definition of CEUS malignancy according to the theory that various histopathological cancer types can coexist in a single patient [61]. Evaluation of 13 patients before RP revealed variable behavior of contrast enhancement. Consistent with the findings of Sano et al, we observed suspicious perfusion (hypoperfusion or hyperperfusion) of cancer. In cases of suspicious hypoperfusion or hyperperfusion the examined TL showed histopathological PC in 52 of 58 cases (89.6%). Using a multiparametric targeted biopsy approach Aigner et al observed that the overall 59.4% PC detection rate (70 of 133 cases) was superior to that of a systematic approach [62]. Combining transrectal SE and CEUS in our study significantly decreased the false-positive results of transrectal SE alone from 34.9% to 10.3% and thereby improved the positive predictive value to 89.7% to correctly identify histopathologically confirmed PC in defined TLs. Although there was a trend toward higher Gleason patterns in hyperperfused TLs in our study, statistical analysis did not attain significance to assign a Gleason score to a hypoperfused or hyperperfused imaging pattern. In addition to the limitations associated with a pilot study, hematoxylin and eosin stained whole mount slides were histopathologically evaluated by a dedicated uropathologist but microvessel density using immunohistological markers was not assessed. The segmentation into 12 prostate sectors applied in our study carries the risk of inaccurate documentation of PC. To date no standard consensus for ultrasound PC evaluation has been recommended. However, using a segmentation system with

additional sectors (e.g. recommendations for magnetic resonance imaging of an optimal requirement of 27 regions) might enhance reporting accuracy [63]. Evaluation of transrectal SE combined with CEUS in our exploratory study was limited to defined TLs according to the design of our protocol because screening the whole prostate using CEUS is associated with the difficulty of accurately visualizing the whole gland in a short time. Contrast enhanced perfusion to detect suspicious areas depends on the time after the contrast agent is administered and Aigner et al observed optimal detection in the first 15 to 20 seconds after injection [64]. Consistent with their findings, we noted the best visualization of suspicious contrast enhancement patterns within the first 20 seconds after infusion. Repeat intravenous injections of contrast agent or specific techniques that enable reperfusion, such as the replenishment technique, might improve the evaluation of multiple cross sections [61]. The evaluation of CEUS behavior might be affected by patient position, which could have an influence on prostatic blood flow [65]. Therefore, the supine position may affect the outcome of CEUS in future examinations. The results of our study highlight the possible use of combining various imaging techniques, such as gray scale ultrasound, transrectal SE and perfusion imaging, in a multiparametric approach to improve and optimize prostate cancer detection and visualization. Nevertheless, this integrated approach, despite demonstrated an overall detection rate higher than our standard biopsy detection rate, was too expensive, and required an intricate diagnostic process.

Conclusions

In our study we demonstrated that adding the dimension of perfusion imaging using a combined approach of transrectal SE and CEUS resulted in a significant decrease in false-positive results and improved the positive predictive value of correctly identifying histopathological cancer, but, the cost of the imaging, the increase in the time and in the complexity of the diagnostic process, did not support the availment of this method, especially if compared with the our detection rate with standard TRUS guided biopsy.

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