

Original Article

Transrectal real-time elastography-guided transperineal prostate biopsy as an improved tool for prostate cancer diagnosis

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Received February 1, 2015; Accepted April 3, 2015; Epub April 15, 2015; Published April 30, 2015

Abstract: Objectives: The aim of this study is to determine the utility of transrectal real-time elastography (TRTE)-guided prostate biopsies in patients subjected to transrectal ultrasound (TRUS)-guided transperineal prostate biopsies. Materials and methods: A total of 108 consecutive patients suspicious for prostate cancer (PCa) with elevated serum prostate specific antigen (PSA) level > 4 µg/L or abnormal findings on digital rectal examination (DRE) were enrolled in this study. All patients were sequentially underwent 10-cores systematic biopsy and TRTE-guided targeted biopsy. The detection rate of the TRTE-guided targeted biopsy was compared with that of the TRUS-guided 10-cores systematic biopsy, in combination with prostate biopsy pathology. Results: 38 cases among 108 suspicious patients were diagnosed as PCa using the TRUS-guided 10-cores systematic biopsy with a detection rate of 35.2%. Subsequently, a further increase of 13.9% (15/108, $P = 0.039$) in PCa detection was obtained by the TRTE-guided targeted biopsy. The overall detection rate for PCa was 49.1% (53/108). A total of 1296 cores were sampled among the 108 patients, including 1080 cores for the 10-cores systematic biopsy and 216 cores for the TRTE-guided targeted biopsy cores. The positive rate of the TRTE-guided targeted biopsy was significantly higher than that of the TRUS-guided 10-cores systematic biopsy (50.9% versus 14.1%, $P < 0.0001$). Conclusions: TRTE-guided targeted biopsy could be used as a complement to significantly improve the detection rate for PCa in clinical setting.

Keywords: Transrectal real-time elastography (TRTE), prostate cancer (PCa), biopsy, detection rate

Introduction

Prostate cancer (PCa) is the most common cancer in men in the western world and is the second leading cause of cancer death in the United States [1]. The American Cancer Society estimates 233,000 new cases of PCa and 29,480 cases of death related to PCa in the US for the year 2014 [1]. It's expected that this will result in a further increase in the incidence in the next few years with an increasingly ageing population at greater risk of prostate cancer [1, 2].

Early detection is the key to successful PCa treatment. For many years, the diagnosis of PCa is based on prostate-specific antigen (PSA) testing, digital rectal examination (DRE) and transrectal ultrasound (TRUS)-guided biopsy. PSA-based screening commonly results in biopsy in patient with serum PSA levels of > 4.0

µg/L with a detection rate of 30-35% for PCa [3]. To further increase the detection rate, repeated PSA screening and biopsy for suspicious patients at six to 12 months, which incur both increased costs and delays in diagnosis [4]. DRE is of very low detection rate, not able to detect cancer in up to 80% of cases [5]. Systematic biopsy for PCa diagnosis may miss cancers in up to 35% of cases [6, 7]. TRUS-guided biopsy is the standard method for PCa diagnosis in patients with elevated PSA level or abnormal DRE. However, approximately 50% of PCa is not visible by TRUS using conventional gray-scale imaging [8], since PCa tissue typically appears hypoechoic but can appear as echogenic or isoechoic [9, 10]. The low sensitivity and specificity of TRUS for PCa detection make it insufficient tool for PCa screening, though it is a useful tool to guide biopsy [11].

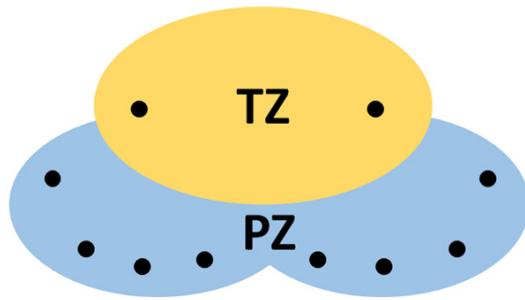


Figure 1. Sketch map of the 10 core-systematic transperineal biopsy. TZ: transitional zone; PZ: peripheral zone.

Other imaging approaches including color Doppler imaging and magnetic resonance imaging (MRI) have been introduced to improve the gray-scale limitations [12-14]. Color Doppler imaging has been proposed to supplement TRUS to improve PCa detection. But color Doppler-guided needle biopsy do not substantially improve the detection rate of PCa [15]. MRI is a promising method, but this method remains expensive and not always available [16]. Therefore, an improved imaging modality for PCa detection using targeted biopsies is needed.

Ultrasound elastography is a new technique developed in recent years. This technique measures the elastic properties of the prostate gland by visualizing the differences in tissue strain produced by freehand compression [17]. The principle of ultrasound elastography is based on the different displacement between hard tissue and soft tissue induced by tissue deformation when a controlled compression is applied to: hard tissue will deform to a smaller displacement while a softer tissue will have a larger displacement [18]. Based on the difference of tissue elasticity between malignant and normal tissue, prostate biopsy using transrectal real-time elastography (TRTE) is commonly used in combination with conventional B-mode imaging [18, 19]. Using TRTE and conventional B-mode imaging, real-time elastograms are obtained throughout the prostate during the ultrasound procedure, and investigator is able to discriminate hard from soft tissue regions within the prostate [20, 21].

The goal of this study was to assess the value of elastography for localizing PCa in a selected, larger cohort of patients scheduled for radical

prostatectomy (RP) by comparing results of the elastogram with PCa foci in whole-mount sections. In addition it was of interest to see whether elastography is feasible in daily routine.

Materials and methods

Patients

Between December 2012 and July 2014, a total of 108 consecutive patients with unusually increased serum prostate specific antigen (PSA) level and/or abnormal digital rectal examination (DRE) from Shanghai Jiao Tong University Affiliated Sixth People's Hospital and Shanghai Children's Hospital Affiliated to Shanghai Jiao Tong University in Shanghai, China were subjected to transrectal ultrasound-guided transperineal prostate biopsies. The age range of the patients was between 54 and 91 years (mean patient age 71.6 ± 8.5). Serum PSA level of these PCa suspected patients ranged from 1.24 to 43.1 $\mu\text{g/L}$ with an average of $12.8 \pm 9.5 \mu\text{g/L}$.

Transrectal real-time elastography (TRTE)

The TRTE was conducted, by a radiologist with 5 years of experience in sonoelastography, in lithotomy position using a transrectal intracavitary ultrasound transducer EUP-V53u: 5-10 MHz; 10R/200° radius angle/length) with HI VISION™ Preirus™ ultrasound system (Hitachi Medical, Tokyo, Japan) in the RTE-mode of the machine (EZU-TE3 or EZU-TE5). Images were produced 1 day before surgery by freehand compression of the intracavitary probe. Image interpretation was carried out under B-mode. Gray-scale images were excluded. Suspicious areas for PC were frozen and stored to the hard disk.

All the images were reviewed by the radiologist who did the original examinations and she was blinded to patient identification, clinical history, other imaging results and pathological findings. The scoring system described by Kamoi et al was used to score the elastograms of lesions from 1 to 5 [19].

Transperineal prostate biopsies

All transperineal prostate biopsies were performed by two attending urologists on an outpatient basis. Patients received a Fleet enema and 500 mg ciprofloxacin before the procedure

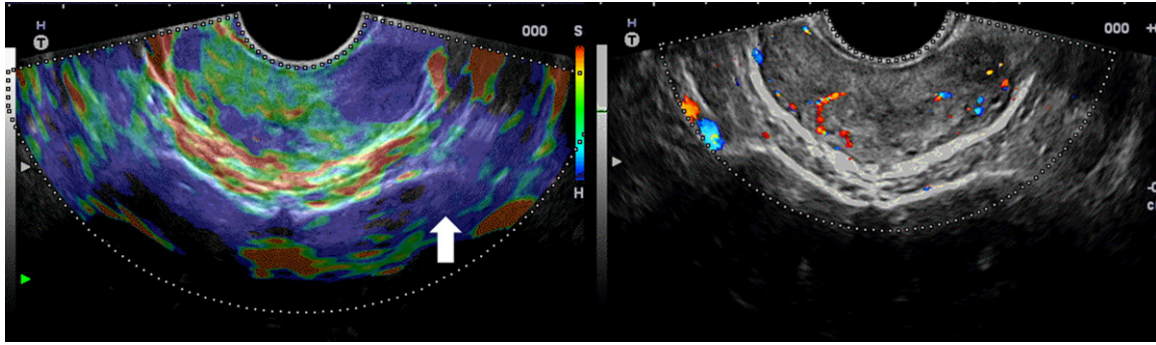


Figure 2. Standard of elastography for diagnosis of PCa in this study. Abnormally indurated nodule with long diameter > 5 mm (white arrow) indicated PCa.

Table 1. Characteristics of 108 PCa suspected patients

Group	Case	Age (years, $\bar{x} \pm s$)	DRE (%)	PSA ($\mu\text{g/L}$, $\bar{x} \pm s$)	Prostate size (ml, $\bar{x} \pm s$)	PSAD (μL^2 , $\bar{x} \pm s$)
PCa	53	73.0 \pm 7.5	22 (41.5%)	14.5 \pm 9.8	41.1 \pm 19.2	0.45 \pm 0.42
non-PCa	55	70.3 \pm 9.4	13 (23.6%)	11.2 \pm 9.0	63.1 \pm 27.7	0.20 \pm 0.17
t/χ^2 value		1.625	3.936	1.839	4.778	4.054
P value		0.106	0.047	0.069	0	0

PCa: prostate cancer; DRE: digital rectal examination; PSA: prostate specific antigen; PSAD: prostate specific antigen density.

with instructions to continue the antibiotic every 12 hours times 5 thereafter.

All patients were examined in the bilateral decubitus position with the same probes used by real-time elastography above. The prostate was examined in both axial and sagittal views, the gland volume was determined with the prolate ellipsoid method, and biopsies were performed using a spring-loaded biopsy gun needle with an 18-gauge needle. All patients underwent combined elastography-targeted and transperineal 10-cores systematic biopsy. The transperineal 10-cores systematic biopsy included the paramedian, center, lateral, anterolateral of the peripheral zone and the transition zone in both sides of the prostate (**Figure 1**). Additional 2-3 cores by targeted biopsy were conducted for the abnormally indurated nodules. Prostate needle biopsies were fixed using 10% formaldehyde for further pathological diagnosis.

Pathological diagnosis

All samples obtained were sent for pathological diagnosis, and were analyzed by specialized prostate pathologists with at least 5 years of experience. Pathological results were classified into PCa (with Gleason score), benign prostate hyperplasia (BPH), chronic prostatitis and prostatic intraepithelial neoplasia (PIN).

Statistical analysis

All data were analyzed by SPSS16.0 and expressed as $\bar{x} \pm s$. The mean was compared by t test or by analysis of variance. Sample was compared by χ^2 test, and $P < 0.05$ was considered statistically significant.

Results

TRTE diagnosis standard

When prostate tissue was compressed or decompressed by freehand compression, back-scattered ultrasound signals underwent displacement, softer tissue was displaced more than harder tissue, therefore, making the discrimination between different tissue types possible [17]. Visual results could be made using color-coded maps and real-time images (**Figure 2**). If harder tissue, in a form of repeated induration zone with the long diameter of > 5 mm in the prostate, is found, the patient is confirmed to be PCa [18].

In this study, all suspected patients confirmed to be PCa had abnormally indurated nodules, with the long diameter of > 5 mm. These results were up to the diagnosis standard set by König et al [18], as illustrated by the sonoelastography assay of a PCa patient (PSA: 14.03 $\mu\text{g/L}$) (**Figure 2**).

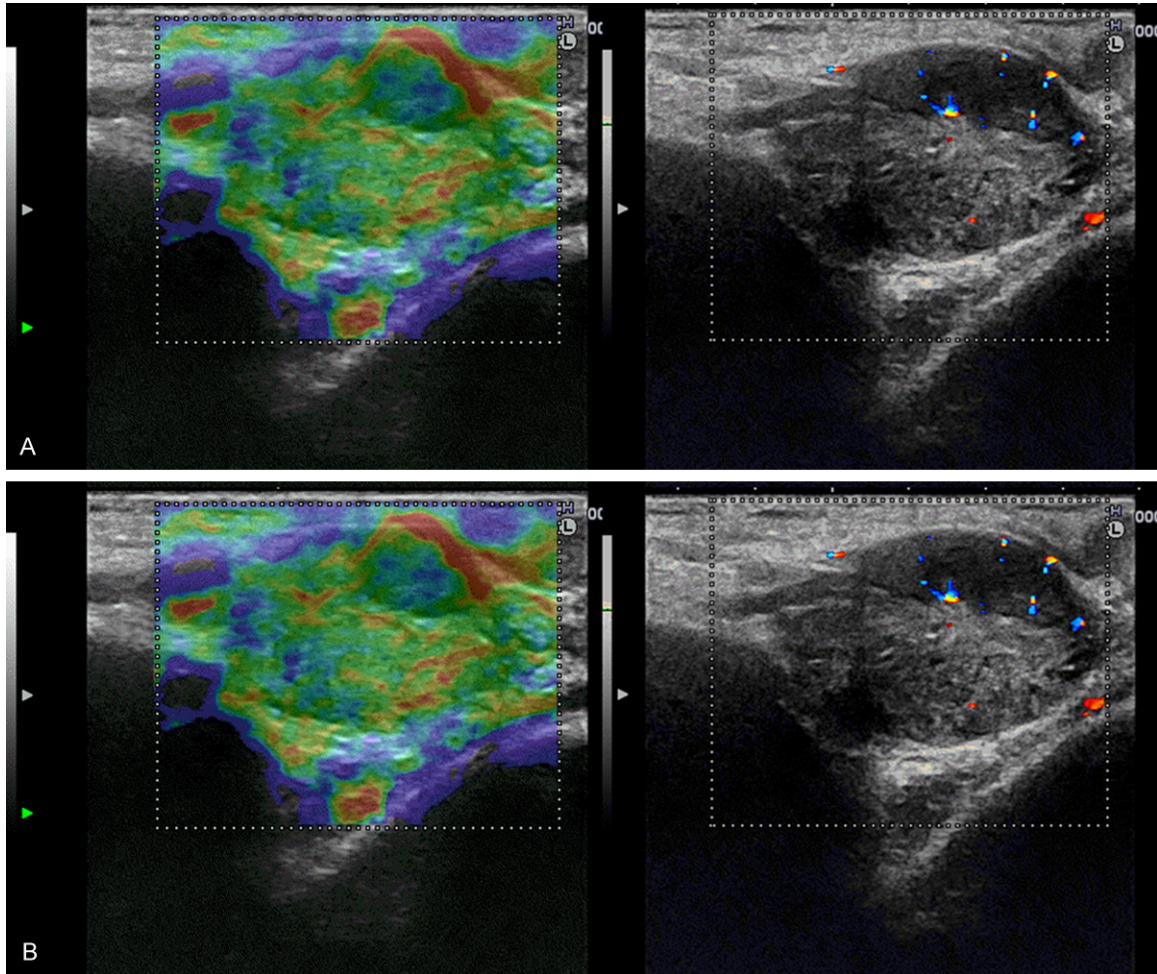


Figure 3. Illustration of PCa and chronic prostatitis. A. A PCa patient with PSA level of 18.37 µg/mL was diagnosed by TRTE-guided targeted biopsy (Gleason score: 5 + 5); B. Patient of chronic prostatitis with PSA level of 13.8 µg/mL had a Gleason score of 2 in the right peripheral zone.

Pathological detection

Pathological diagnosis revealed that among the 108 PCa suspected patients, 53 (49.1%) patients were confirmed to be PCa patients; 30 (27.8%) benign prostate hyperplasia (BPH); 22 (20.4%) BPH plus chronic prostatitis; and 3 (2.8%) BPH plus PIN by transrectal prostatic biopsy (**Table 1; Figure 3**).

Detection rate of this study

15 (28.3%, 15/53) cases of the 53 PCa patients were confirmed solely by TRTE-guided targeted biopsy; 12 (22.6%, 12/53) solely by systematic biopsy; and 26 (49.1%, 26/53) simultaneously by the TRTE-guided targeted and systematic biopsies. The detection rate of the TRTE-guided targeted and systematic biop-

sies was 35.2% (38/108) and 38.0% (41/108), respectively (**Table 2**). Though no significant difference was found between these two biopsies ($\chi^2 = 0.180$, $P = 0.672$), TRTE-guided targeted biopsies for the abnormal indurated nodules could increase the detection rate to 13.9% (15/108) ($\chi^2 = 4.273$, $P = 0.039$) (**Figure 4**). The overall detection of this study was 49.1% (53/108).

Comparison of the TRTE-guided targeted biopsy and systematic biopsy

Totally 1296 cores were analyzed by systematic and TRTE-guided targeted biopsies. TRTE found 74 suspicious cases among the 108 patients, and 216 cores of TRTE-guided targeted biopsies were conducted. Pathological diagnosis showed that up to 50.9% positive rate

Table 2. Characteristics of biopsy positive patients

Group	Positive case	Age (years, $\bar{X} \pm s$)	DRE (%)	PSA ($\mu\text{g/L}$, $\bar{X} \pm s$)	Prostate size (ml, $\bar{X} \pm s$)	PSAD (μL^2 , $\bar{X} \pm s$)	Gleason score
Targeted biopsy	15	73.4 \pm 7.3	5 (33.3%)	10.0 \pm 6.9	37.6 \pm 18.3	0.33 \pm 0.37	6.6 \pm 0.7
Systematic biopsy	12	74.4 \pm 7.3	3 (25.0%)	12.8 \pm 8.2	57.0 \pm 23.1	0.29 \pm 0.27	6.3 \pm 0.5
Targeted & systematic biopsy	26	72.1 \pm 7.8	14 (53.8%)	17.9 \pm 10.9	35.8 \pm 13.1	0.58 \pm 0.46	7.1 \pm 0.9
t/ χ^2 value		0.428	3.39	3.663	6.472	3.009	4.823
P value		0.654	0.184	0.033	0.003	0.058	0.012

PCa: prostate cancer; DRE: digital rectal examination; PSA: prostate specific antigen; PSAD: prostate specific antigen density.

(110/216) by pathological diagnosis was obtained; while a much lower positive rate (14.1%, 152 cores) from 1080 cores was obtained by systematic biopsies. Therefore, the total positive rate of this study was 20.2% (262/1296). TRTE-guided targeted biopsy could elevate the detection rate as stony induration in the peripheral zone were only detected by TRTE-guided targeted biopsy but not the 10-cores systematic biopsy (**Figure 4**). Obviously, the positive rate of TRTE-guided targeted biopsy was significantly higher than that of the 10-cores systematic biopsy ($\chi^2 = 94.128$, $P = 0.0001$).

Discussion

Early, the repeated sextant systematic prostatic biopsy proposed by Hodge et al [22] was the gold standard for PCa diagnosis. However, due to the multifocal and dispersal growth characteristics of PCa cells, especially non-advanced PCa cells with small lesions, the repeated sextant systematic biopsy has a high incidence of false-negative biopsies [23, 24]. In order to increase the detection rate and reduce unnecessary repeated biopsies, extended 10 to 14-cores prostate biopsies were proposed, which have been the mainstream for prostatic biopsy [25, 26]. Therefore, in this study we used 10-cores systematic prostate biopsy, which detected the paramedian, center, lateral, anterolateral of the peripheral zone and the transition zone in both sides of the prostate (**Figure 1**). In the 53 PCa positive cases confirmed by pathological diagnosis, approximately 71.70% (38/53) detection rate was obtained by the 10-cores systematic prostate biopsy (**Table 2**). But, approximately 28.30% incidence of false-negative biopsies remains.

Using imaging method to aid the prostate biopsy for PCa diagnosis can further increase the detection rate for PCa simultaneously reduce

repeated biopsies. Therefore, imageology-aided prostate biopsy has gained more and more attention recently. Transrectal ultrasound (TRUS)-guided prostate biopsy has been widely used in PCa diagnosis [27]. Though PCa is classically described as hypoechoic by TRUS [28], the low sensitivity and specificity of conventional grey-scale ultrasonography hinder its practical value, since many cancers confirmed by biopsy are not visible by TRUS; while many hypoechoic areas found by TRUS do not prove to be malignant by biopsy [12, 29, 30].

In comparison with TRUS, TRTE is more sensitive and specific. Typically, PCa tissue is stiffer than the adjacent normal prostate tissue. Therefore, the strain of PCa tissue induced by compression is smaller than stiffer than that of the adjacent normal prostate tissue [18]. Based on the difference of tissue elasticity between malignant and normal tissue, targeted biopsy guided by TRTE and conventional B-mode imaging could easily display the anatomical structure of prostate in real time, and thus find the PCa lesion from morphology (abnormally indurated nodules) in PCa tissue (**Figure 2**). Although up to 1080 cores were conducted in this study by the 10-cores systematic biopsy, 5 times of the TRTE-guided targeted biopsy, the positive rate of this systematic biopsy was significantly lower ($P < 0.0001$) than that of the TRTE-guided targeted biopsy (14.1% Vs. 50.9%). Furthermore, TRTE-guided targeted biopsy could find abnormally indurated nodules not detected by the 10-cores systematic biopsy (**Figure 4**). Significant increase ($P = 0.039$) of detection rate was obtained by TRTE-guided targeted biopsy. Therefore this technique contributed to enhance PCa detection.

The 12 positive cases only confirmed by the 10-cores systematic prostate biopsy were characterized by relatively large prostate gland, Gleason score < 7 (**Table 2**), which indicated

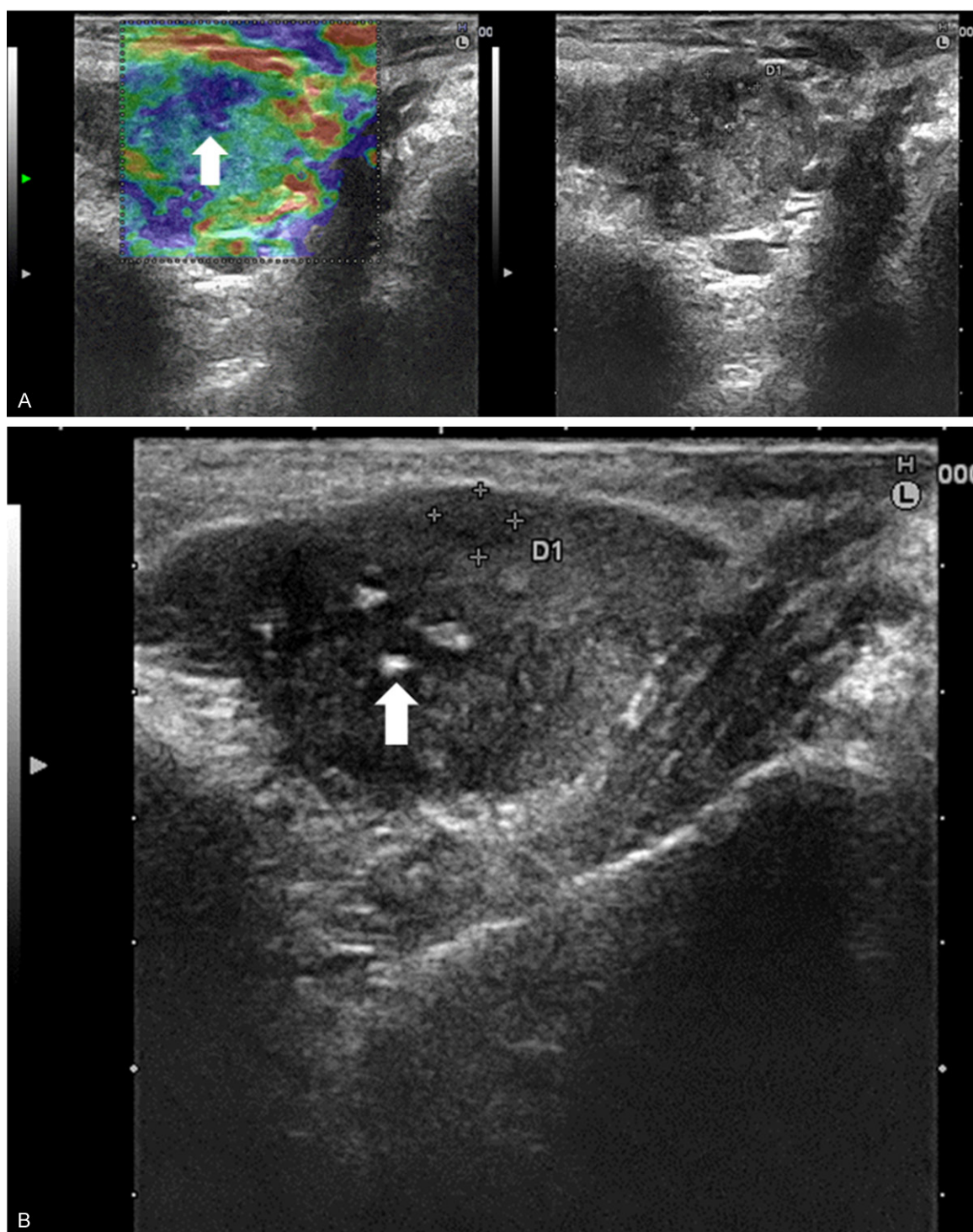


Figure 4. TRTE-guided targeted biopsy of a PCa patient (PSA: 14.22 $\mu\text{g/L}$). A. Stony induration was detected in the junction between the left peripheral zone (white arrow), which was not detected by transperineal 10-cores systematic biopsy; B. This abnormally indurated nodule was confirmed by TRTE-guided targeted biopsy (white arrow), Gleason score: 4 + 3.

that it's difficult for TRTE to discriminate BPH from PCa. TRTE should be interpreted in combination with the conventional B-mode image at

the same time, because stiffer tissue such as BPH and chronic prostatitis can lead to pathologic elastograms [18, 19]. Examiner can easily

recognize prostatolithiasis on B-mode image; however, the discrimination of PCa lesions from hyperplastic nodules or chronic prostatitis is still challenging. At present, up to 24.1-51.0% incidence of false negative of TRTE necessitates the systematic prostate biopsy for small PCa lesions such as non-advanced PCa lesions in BPH tissue [11, 31]. Currently, no other ultrasound techniques can clearly discriminate PCa lesions from these benign conditions. The combination of TRTE-guided targeted biopsy and 10-cores systematic biopsy may be the mainstream to reduce the incidence of false negative for PCa diagnosis.

Conclusion

TRTE is a noninvasive, simple, economic and feasible technique for PCa diagnosis. Through detecting suspicious lesions by TRTE, targeted prostate biopsy can significantly increase the detection rate of PCa. The TRTE-guided targeted biopsy has significantly higher positive rate than conventional systematic biopsy. Therefore we believe that TRTE-guided targeted biopsy can complement conventional systematic biopsy. To further enhance the positive rate, the combination of TRTE-guide targeted biopsy and 10-cores systematic biopsy is recommended for the diagnosis of prostatic diseases.

Acknowledgements

This project was supported by the Shanghai Committee of Science and Technology, China (Grant 12ZR1425600 and 14411965200).

Disclosure of conflict of interest

None.

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