Transrectal real-time tissue elastography targeted biopsy coupled with peak strain index improves the detection of clinically important prostate cancer

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Abstract. The focus of the present study was to evaluate transrectal real-time tissue elastography (RTE)-targeted two-core biopsy coupled with peak strain index for the detection of prostate cancer (PCa) and to compare this method with 10-core systematic biopsy. A total of 141 patients were enrolled for evaluation. The diagnostic value of peak strain index was assessed using a receiver operating characteristic curve. The cancer detection rates of the two approaches and corresponding positive cores and Gleason score were compared. The cancer detection rate per core in the RTE-targeted biopsy (44%) was higher compared with that in systematic biopsy (30%). The peak strain index value of PCa was higher compared with that of the benign lesion. PCa was detected with the highest sensitivity (87.5%) and specificity (85.5%) using the threshold value of a peak strain index of ≥5.97 with an area under the curve value of 0.95. When the Gleason score was ≥7, RTE-targeted biopsy coupled with peak strain index detected 95.6% of PCa cases, but 84.4% were detected using systematic biopsy. Peak strain index as a quantitative parameter may improve the differentiation of PCa from benign lesions in the prostate peripheral zone. Transrectal RTE-targeted biopsy coupled with peak strain index may enhance the detection of clinically significant PCa, particularly when combined with systematic biopsy.

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Introduction

Prostate cancer (PCa) is the second most prevalent cause of cancer-associated mortality globally (1). The incidence and mortality of PCa has continually increased within the past decade in China, but remains low compared with Western countries (2). The incidence of PCa in China is predicted to increase further due to diet and lifestyle changes and the aging population (3). Transrectal systematic biopsy is the standard procedure for the detection of PCa. The procedure is invasive and causes discomfort for patients; however, 18 to 47% of cases of PCa may not be detected by this method, whereas a number of clinically insignificant alterations to the prostate may be misdiagnosed as PCa following detection by systematic biopsy (4-7). Therefore, novel methods for the effective and safe detection of clinically significant PCa are required.

PCa tissues may exhibit increased stiffness due to pathological alterations (8). Tissue elasticity has potential as a novel diagnostic factor for PCa (9). Real-time tissue elastography (RTE) is a sonoelastography approach that uses colors to visualize the variations in tissue elasticity or stiffness. In the diagnosis of PCa, the sensitivity and specificity of RTE-targeted biopsy varies from 51.1 to 91.7% and from 62.2 to 86.8%, respectively (10-14). This is as the majority of previous studies use the qualitative threshold 'blue area' for diagnosis, which results in variability between the inter- and intra-observer. However, RTE has not been quantitatively analyzed in targeted biopsies for the detection of PCa.

Strain index is a quantitative parameter for comparing the strain value of two tissues during histological analysis. Zhang *et al* (15) used the peak strain index for classifying benign and suspicious malignant lesions in the peripheral zone of the prostate and yielded higher sensitivity (74.5%) and specificity (83.3%). However, whether peak strain index may aid the diagnosis of clinically significant PCa has yet to be elucidated.

In the present study, the optimal peak strain index in RTE-targeted biopsies was defined for the detection of PCa in Chinese patients, and it was identified that RTE-targeted

biopsy coupled with the peak strain index may improve the detection rate of clinically significant peripheral zone PCa.

Materials and methods

Patients with PCa. Between February 2011 and September 2013, patients with lower urinary tract symptoms were examined for their serum prostate specific antigen (PSA) prior to undergoing a digital rectal examination (DRE) and a transrectal ultrasound (TRUS) at The Second Affiliated Hospital of Soochow University (Jiangsu, China). Patients presenting with an active urinary tract infection or acute urinary retention were excluded from the present study. The following criteria were used to determine the need for a prostate biopsy: a) APSA value of ≥10 ng/ml; b) a PSA value of between 4 and 10 ng/ml, and a free-to-total PSA of <16%; c) DRE or TRUS indicated a prostate nodule. The present study was approved by the Institutional Ethics Committee of The Second Affiliated Hospital of Soochow University and all patients provided written informed consent prior to being enrolled onto the study.

RTE targeted biopsy. A Hitachi EUB-7500HV ultrasound system with a EUP-V53W 7.5-MHz transrectal end-fire probe (Hitachi, Ltd., Tokyo, Japan) was used in the RTE mode. The patient was in the left decubitus position and elastograms were produced by manual compression from the transverse plane and displayed with TRUS images. The pressure and speed induced by manual compression was adjusted by a visual indicator designed to decrease the inter-observer variability. The strain of tissue was classified as soft, moderate and hard according to the colors displayed, in which red signifies high strain (soft), green indicates moderate strain and blue indicates low strain (hard; Fig. 1). Hard lesions that present as blue areas in elastograms were considered to be potential malignant lesions (16). Stable and reproducible elastograms were recorded for further analysis. Regions with calcifications in the prostate are stiff and may affect the elastogram results. However, they are hyperechoic on the TRUS image and were able to be identified and avoided during the biopsy (Fig. 1).

The quantitative parameter peak strain index was calculated using the following formula: Strain ratio (SR) of the surrounding reference tissue (B) that exhibited moderate elasticity (green area) to SR of the peak elasticity (area with the highest level of blue) region (A) (SR_B/SR_A). The smallest size of the region of interest (ROI) in the RTE mode was determined as the standard. A number of sections in the most intense blue areas were measured to determine the highest outstanding peak elasticity.

Two cores were obtained from the hardest area with an 18-gauge biopsy needle. All examinations and targeted biopsies were performed by a single examiner who was blind to the results of the PSA test and other modalities.

Systematic biopsy. Following the RTE-targeted biopsy, a 10-core systematic biopsy that was independent of the RTE and TRUS findings was performed by a different examiner (The Second Affiliated Hospital of Soochow University). A MyLab™90 ultrasound system with an EC-123 7.5-MHz transrectal end-fire probe (EsaoteSpA, Genova, Italy) was used
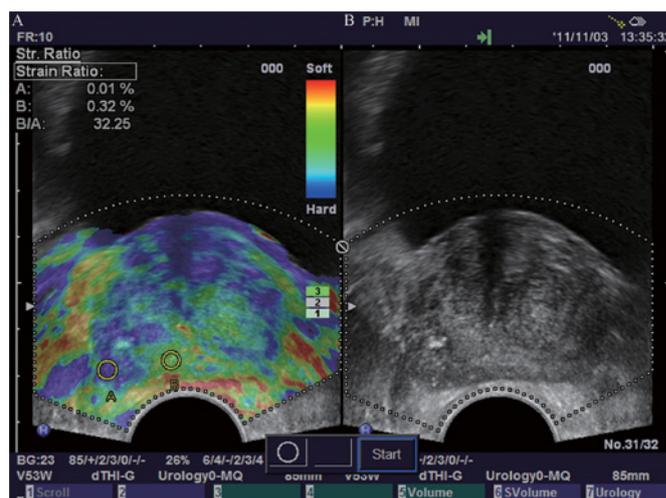

Figure 1. RTE image with the peak strain index. (A) RTE image and (B) TRUS image. The pressure and speed induced by manual compression maybe adjusted using a visual indicator ('3' in the green box). RTE indicates a stiff (blue) area on the right side of the prostate, which may be indicative of prostate cancer. Peak strain index was 32.25 when the local region of peak elasticity (area with the highest level of blue) was selected as ROI_A and the reference tissue was selected as ROI_B. Calcifications on the right side of the prostate were displayed as hyperechoic and maybe identified on the TRUS image. RTE, real-time tissue elastography; TRUS, transrectal ultrasound; ROI, region of interest.
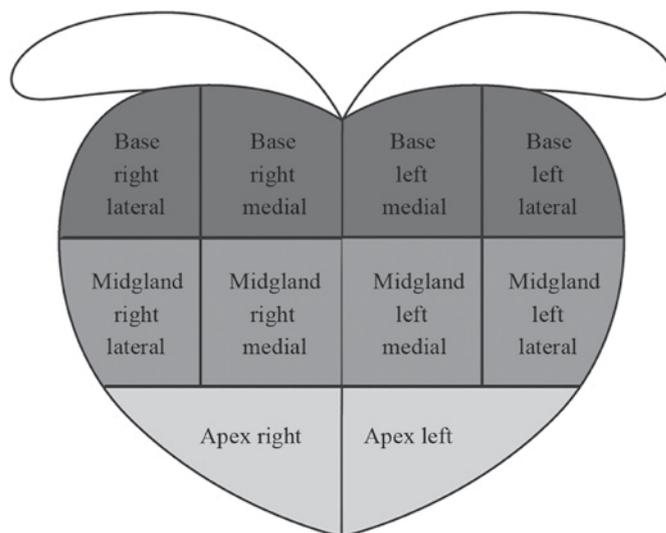

Figure 2. Prostate peripheral zone anatomy. 10 core biopsies were obtained from the base (2 cores), midgland (2 cores) and apex (1 core) from each side of the prostate.

in TRUS mode. The 10 cores included 3 lateral and 2 medial cores in the left and right sides (Fig. 2). All the cores were guided by six dorsal gland sectors: Apex, middle and basement on the left and right sides. The inner gland analysis was not included in the results. The average time of RTE examination and targeted biopsy for each patient was ~10 min.

Pathologic analysis. All cores were marked by identification numbers and analyzed by a senior pathologist (Wuxi Affliated Hospital of Nanjing University of Chinese Medicine) who was blind to the results of the RTE and TRUS.

Table I. Characteristics of patients with benign or malignant prostate lesions.

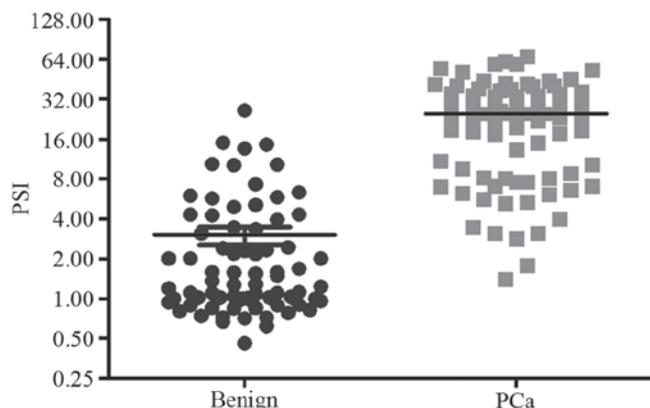| Characteristic	Benign mean (range)	Malignant mean (range)	Overall mean (range)	P-value
Number of patients	69	72	141	
Age, years	70.50 (55-85)	72.60 (49-90)	71.60 (49-90)	0.1422
PSA, ng/ml	10.40 (0.5-47.6)	48.80 (1.1-190)	30.00 (0.5-190)	<0.0001
Prostate volume, ml	51.20 (24.7-178.5)	49.40 (15.8-171)	50.30 (15.8-178.5)	0.1996
Peak strain index	3.02 (0.5-26.3)	24.79 (1.39-66.9)	14.00 (0.5-66.9)	<0.0001

PSA, prostate specific antigen.

Figure 3. Significant difference between the PSI values in the benign lesions and PCa lesions (P<0.0001). Mean value is presented as a black line. PSI, peak strain index; PCa, prostate cancer.

Statistical analysis. Peak strain index comparisons between malignant and benign lesions were analyzed by the student's t-test or Wilcoxon rank sum test. The diagnostic values of peak strain index and PSA were assessed by receiver operating characteristic (ROC) curves. Areas under the ROC curve (AUC) values between the peak strain index and PSA were compared using a χ^2 test. To evaluate the significance of the differences between targeted biopsy and systematic biopsy, McNemar's test was used. The sensitivities of cancer detection for targeted biopsy, systematic biopsy and targeted combined systematic biopsy were compared using a χ^2 test. The association between peak strain index and Gleason scores was compared with Spearman correlation analysis. To compare Gleason scores, the Wilcoxon rank sum test was performed. Values are presented as the mean ± standard deviation. All statistical calculations were performed with SAS software version 9.3 (SAS Institute Inc., Cary, NC, USA). P<0.05 was considered to indicate a statistically significant difference.

Results

PSA and peak strain index value. A total of 141 patients were enrolled for prospective analysis. The average age was 71.6 years (range, 49-90), the mean PSA value was 30 ng/ml (range, 0.5-190) and the average prostate volume was 50.3 ml (range, 15.8-178.5). According to the pathological results, PCa was detected in 51% (72/141) patients. Patient characteristics,

including age and PSA values, are summarized in Table I. The age and prostate volume in each group were similar, whereas the PSA values in the malignant group were significantly higher compared with the benign group (P<0.0001). The ranges of the peak strain index value in malignant and benign lesions of the prostate were 1.39-66.86 and 0.46-26.31 (mean, 24.79 and 3.02, respectively; P<0.0001; Fig. 3).

Characterization of biopsy cores. In 141 patients, 159 suspicious are as detected by RTE were biopsied with 2 cores for each area. The positive incidence of PCa in RTE-targeted biopsy cores was 44% (140/318 cores) and in systematic biopsy was 30.2% (426/1,410 cores). This indicated that the RTE targeted biopsy core had a significantly higher sensitively for detecting PCa (P<0.0001).

The majority of the positive cores in RTE-targeted biopsy were identified in the apex and mid-gland (84% of positive cores). Regarding the apex and mid-gland of the prostate, a higher frequency of positive PCa cores were detected in the right side of the prostate gland. However, using systematic biopsy, an increased number of positive PCa cores were identified in the middle and base of the gland. The distributions of PCa positive cores in the right or left side were similar in these approaches (Table II).

Detection of PCa inpatients using RTE-targeted biopsy and systematic biopsy. Among the 72 patients diagnosed with PCa, 63 cases (87.5%) were detected using RTE-targeted biopsy, 62 cases (86.1%) using systematic biopsy and 53 cases (74%) of PCa were detected by RTE-targeted and systematic biopsy. A total of 10 patients with PCa were detected using RTE-targeted biopsy alone and 9 patients using systematic biopsy alone. The sensitivity for cancer detection was 87.5% for RTE-targeted biopsy and 86.1% for systematic biopsy (P=0.525).

Optimal peak strain index value for the RTE-targeted biopsy. The higher peak strain index values demonstrated a higher sensitivity and specificity for predicting PCa. When the peak strain index was >5.97[AUC=0.95; 95% confidence interval (CI), 0.92-0.98], PCa was predicted with the highest sensitivity (87.5%; 63/72 cases) and specificity (85.5%; 53/69 cases). When the PSA was >10.1 ng/ml (AUC=0.83; 95% CI, 0.76-0.89), the sensitivity and the specificity for detecting PCa were 80% and 72.2%, respectively (Fig. 4).

RTE-targeted biopsy did not diagnose 9 patients with PCa that had a lower peak strain index value (<5.97). The majority

Table II. Number of PCa cores detected by RTE targeted biopsy and systematic biopsy.

Core section	RTE targeted biopsy			Systematic biopsy		
	Right	Left	Overall (%)	Right	Left	Overall (%)
Apex	38	20	58 (41)	44	40	84 (20)
Midgland	38	22	60 (43)	92	87	179 (42)
Base	10	12	22 (16)	85	78	163 (38)
Total	86	54	140	221	205	426

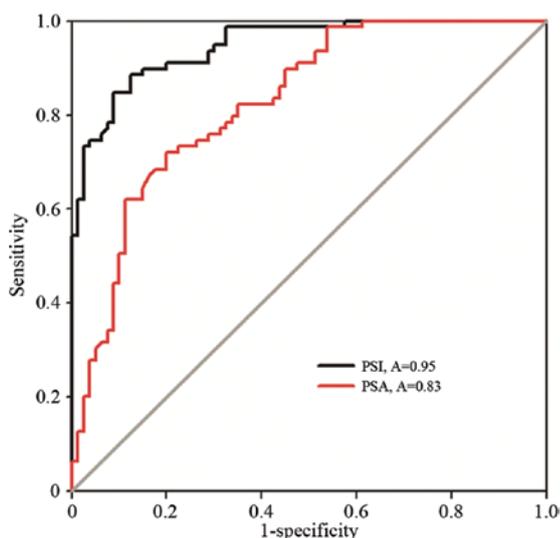PCa, prostate cancer; RTE, real-time tissue elastography.

Figure 4. ROC curve analysis of the differentiation between benign and malignant prostate tissues. The data indicates that AUC values for the PSI were significantly higher compared with the PSA (P=0.0003). The black line indicates the ROC curve for the PSI with an AUC of 0.95 (95% CI, 0.92-0.98). The red line indicates the ROC curve for PSA with an AUC of 0.83 (95% CI, 0.76-0.89). ROC, receiver operating characteristic; AUC, area under the curve; PSA, prostate specific antigen; PSI, peak strain index; A, area; CI, confidence interval.

of these 9 patients had multifocal and diffuse lesions in the prostate with a lower PSA value, lower Gleason score and were at an earlier clinical stage (Table III).

A total of 10 patients with a peak strain index of ≥5.97 were diagnosed as having a benign prostate lesion. Of these 10 cases, 2 cases were benign prostate hyperplasia (BPH), 4 were BPH with chronic inflammation, 2 were granulomatous inflammation and 2 were low-grade prostate intraepithelial neoplasia.

According to the guidelines of the American Urological Association, the European Association of Urology and the Chinese Urological Association, cases of PCa were classified as low, moderate or high risk PCa (17-19) Moderate and high risk PCa (considered to be clinically important) must be treated as early as possible. Higher peak strain index values were associated with clinically significant PCa (r=0.28; P=0.017).

The Gleason scores of the 72 patients diagnosed with PCa were between 5 and 9 and the number that scored 5-6, 7 or 8-9 were 27, 25 and 20, respectively (Table IV). The overall positive incidence for RTE-targeted biopsy and systematic biopsy

were 87.5 and 86.1%, respectively (P=0.525). There was no significant difference in the distribution of Gleason scores between targeted biopsy and systematic biopsy (P=0.539). When the Gleason score was ≥7, RTE targeted biopsy and systematic biopsy detected 95.6 (43/45) and 84.4% (38/45) of PCa cases (Table IV), respectively, and the difference was statistically significant (P=0.0253). Therefore, an RTE-targeted biopsy coupled with a peak strain index of ≥5.97 may be able to detect a higher number of clinically significant cases of PCa compared with systematic biopsy.

Discussion

PCa tissue is stiffer compared with normal prostate tissue (20). A number of previous studies, which applied the qualitative stiffness threshold 'blue area', indicated that RTE-guided biopsy was effective for detecting PCa (4,10,21,22). Nygård *et al* (23) established that the frequency of positive cores was significantly higher in RTE-targeted biopsies compared with standard systematic biopsies. Another previous study indicated that additional patients that were not detected using 10-core biopsies were detected using RTE-targeted four-core biopsy (24). These previous studies suggest that the application of RTE-guided biopsy may be effective in prostate cancer detection and this is concordant with the current study that uses the objective quantitative parameter of stiffness in its approach.

Peak strain index is an objective quantitative parameter that reflects the stiffest region of the PCa tissue and has been established to be effective in distinguishing benign from malignant areas in the breast and thyroid gland (25,26). A previous study demonstrated that the peak strain index in PCa lesions was higher compared with benign lesions with a threshold value of 17.4 (15). In the present study, the threshold value of the peak strain index was lower (5.97 vs. 17.4). The reasons for this variation may be that the methods used for calculating the peak strain index were varied. The size of the ROI was standardized as the smallest area compared with the SR results in other patients in the current study. It was important to select the appropriate site for the reference tissue and to measure SR_B (peak strain index=SR_B/SR_A). Normal tissue is typically present as a green area on the elastogram (27,28), therefore only the green area was selected, and not the blue or red merged areas, as the reference tissue to avoid any effect on ROI calculation.

Table III. Number of patients in each peak strain group and PSA levels, Gleason score and clinical stage.

	Overall	PSA, ng/ml			Gleason score			Clinical stage		
		<10	10-20	>20	≤6	7	≥8	≤T$_{2a}$	T$_{2b}$	≥T$_{2c}$
Peak strain index ≥5.97	63	11	16	36	20	24	19	8	8	47
Peak strain index <5.97	9	3	3	3	7	1	1	1	0	8
Total	72	14	19	39	27	25	20	9	8	55

PSA, prostate specific antigen.

Table IV. Number of patients with PCa and Gleason score distributions in the transrectal RTE targeted biopsy, systematic biopsy and combination groups.

Gleason score	TB	SB	TB+SB
5-6	20	24	27
7	24	21	25
8-9	19	17	20
Total	63	62	72

PCa, prostate cancer; TB, targeted biopsy; SB, systematic biopsy; RTE, real-time tissue electography.

The accuracy of systematic biopsy for detecting PCa varies depending upon the number of cores that are biopsied (29,30). The sensitivity of the 12-core biopsy that adds additional lateral and apical peripheral zone biopsies is only 53% (4). The 18 or 24 core 'saturation biopsy' does not increase the PCa detection rate (31). As the number of cores increase, the potential risk, including pain, bleeding and infection following biopsy, also increase (32,33) RTE-targeted biopsy had a higher sensitivity with fewer biopsy cores compared with the systematic biopsy (16,34).

In the present study, the rate of identifying patients with prostate cancer using RTE-targeted biopsy combined with peak strain index (45%, 63/141 cases) was similar compared with systematic biopsy (44%, 62/141 cases). RTE failed to detect 9 patients with PCa (6%), of which 7 cases (78%) had a Gleason score <7 and 5 cases (56%) had multifocal and diffuse lesions in the prostate gland. The possible hypotheses for the false-negative findings are that low risk PCa may be less stiff, or due to a lack of benign tissue for a reference. Notably, the majority of the false-positive findings were potentially associated with chronic inflammation or BPH with stromal hyperplasia and fibrosis. Junker et al (35) identified that the detection rate of PCa for RTE is dependent on tumor localization and histological type.

The distribution of Gleason scores between RTE-targeted biopsy and systematic biopsy were similar (P=0.539). However, when the peak strain index was ≥5.97, RTE-targeted biopsy detected a higher number of clinically significant PCa cases compared with the systematic biopsy. This suggests that a positive peak strain index may be an independent marker for the detection of moderate and high-risk PCa, which requires timely treatment.

Detection using RTE-targeted biopsy in varying parts of the prostate differs. Pelzer et al (36) indicated that RTE is effective in detecting apex and mid-gland PCa. This is possibly as the size and volume of the base area is too large for the probe to compress adequately. Secondly, the total detection rate of RTE-targeted biopsy on the right side was higher compared with that on the left (61 vs. 39%). Salomon et al (37) theorized that this was due to the use of the left decubitus position during RTE. However, Pelzer et al (36) also demonstrated similar results with patients examined in the lithotomy position.

Magnetic resonance imaging (MRI) is an approach for targeted prostate biopsy. The three techniques of MRI guidance that are available (38,39) are as follows: a) Cognitive targeting (physician performs a TRUS-guided biopsy following a review of the previous prostate MRI revealing a lesion); b) MRI/TRUS fusion (software co-registration of real-time TRUS with stored MRI); c) direct MRI-guided biopsy (in-bore targeting). In-bore targeting is a specific and direct targeting method, but its limitations include a long procedure time, high costs and position difficulties. By contrast, the advantages of RTE targeting combined with peak strain index are obvious. The advantages include: Less time required, cheaper and simpler for the patient to reach the left decubitus position.

The current study has a number of limitations. Firstly, the surrounding media stiffness region (green area) was selected as the reference tissue and chronic inflammatory, low-grade PCa, multifocal and diffuse PCa lesions may also be displayed in green and, therefore, affect the peak strain index value. Secondly, there are artefacts in the elastogram that affect the calculation of the peak strain index, including lateral stiffness artefacts that typically occur in cases of BPH. The examination of the lateral suspicious region following the tilting of the ultrasound probe is effective to identify these artefacts. However, deep stiffness artefacts caused by the increasing depth of ultrasound penetration are challenging to overcome. This may reduce the ability to detect PCa in the transition zone and anterior-localized PCa in enlarged prostates (40). However, Miyagawa et al (41) demonstrated that a higher number of lesions in the anterior prostate were detected using elastography. Junker et al (42) indicated that between RTE and multiparametric MRI, there was no significant difference in the detection of anterior-localized PCa with a prostate volume of <40 cm^3. Thirdly, RTE has intra- and inter-observer variability as elastograms were produced by manual compression and the

pressure and speed induced by manual compression maybe adjusted using a visual indicator. An experienced examiner (performed >500 examinations of patients) is required for performing reliable elastograms used for diagnosis of PCa. Finally, the pathological diagnosis was based on biopsy cores.

To the best of our knowledge, the current study is the first to demonstrate that RTE-targeted biopsy combined with peak strain index may improve the detection rate of clinically significant PCa in the peripheral zone. The present study indicated that the peak strain index may be an effective quantitative parameter in RTE-targeted biopsy.

In conclusion, the results of the present study demonstrated that peak strain index as a quantitative parameter is an independent marker for PCa lesions in the prostate peripheral zone. Transrectal RTE-targeted biopsy combined with peak strain index may enhance the detection of clinically significant PCa with a small number of biopsy cores. RTE-targeted biopsy combined with systematic biopsy may provide an effective approach for the diagnosis of patients with PCa and, particularly, for those with clinically significant prostate cancer.

Acknowledgements

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