MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2019; 25: 8836-8842
DOI: 10.12659/MSM.917344

Received: 2019.05.04
Accepted: 2019.08.21
Published: 2019.11.22

Strain Elastography-Targeted Biopsy: Does Prostate Volume Affect Prostate Cancer Detection?

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ACDEF 1 Yi-Cheng Zhu
AF 1 Jun Shan
BCG 1 Yuan Zhang
G 1 Quan Jiang
BD 2 Yong-Bing Wang
B 1 Shu-Hao Deng
F 3 Qing-Hua Qu
C 4 Qing Li

1 Department of Ultrasound, Pudong New Area People's Hospital Affiliated to Shanghai University of Medicine and Health Sciences, Pudong, Shanghai, P.R. China
2 Department of General Surgery, Pudong New Area People's Hospital Affiliated to Shanghai University of Medicine and Health Sciences, Pudong, Shanghai, P.R. China
3 Department of Urology, Pudong New Area People's Hospital Affiliated to Shanghai University of Medicine and Health Sciences, Pudong, Shanghai, P.R. China
4 Department of Pathology, Pudong New Area People's Hospital Affiliated to Shanghai University of Medicine and Health Sciences, Pudong, Shanghai, P.R. China

Corresponding Author: Jun Shan, e-mail: Jun_smd@126.com
Source of support: Funded by Important Weak Subject Construction Project of Pudong Health and Family Planning Commission of Shanghai (Grant No. PWzbr 2017-10)

Background: The present study aimed to assess the correlation between prostate volume and prostate cancer (PCa) detection by strain elastography (SE)-guided targeted biopsy (TB) compared with conventional transrectal ultrasound (TRUS)-guided systematic biopsy (SB).

Material/Methods: This retrospective study enrolled 357 patients suspected to have PCa. All patients received TRUS-guided 10-core SB and SE-guided TB. The sensitivity for PCa detected by SE-guided TB was compared with that by TRUS-guided SB, in combination with prostate biopsy pathology. The correlation between the prostate volume and the detection rate of SE-guided TB was investigated.

Results: PCa was pathologically confirmed in 151 out of 357 patients. The by-patient detection rate of TRUS-guided SB was 72.8% (110/151). Subsequently, a further increase of 6.6% (10/151) in PCa determination was obtained by the SE-guided TB. The sensitivity of SE-guided TB for patients with prostate volume <30 ml, 30–50 ml, 51–80 ml, and >80 ml was 91.7% (44/48), 80.3% (53/66), 70.4% (19/27), and 40.0% (4/10), respectively (p=0.002). For patients with a prostate volume less than 30 ml, SE-guided TB (91.7%) had a higher sensitivity than SB (62.5%) (p<0.007).

Conclusions: SE-guided TB has a higher detection rate of PCa in comparison with TRUS-guided SB. There was also a negative correlation between prostate volume and SE-guided TB. Therefore, use of SE-guided TB may complement use of conventional SB, especially for patients with smaller prostate volume.

MeSH Keywords: Elasticity Imaging Techniques • Image-Guided Biopsy • Prostatic Neoplasms • Ultrasonography

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/917344

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Background

Prostate cancer (PCa) is a commonly diagnosed carcinoma globally. It is the second leading cause of cancer-related death in men, accounting for 7.1% of newly diagnosed cancer cases and 3.8% of total cancer-related mortality [1]. There are 2 commonly used tools for the diagnosis of PCa: serum prostate-specific antigen (PSA) level measurement and physical examination by digital rectal examination (DRE) [2]. However, DRE is limited to palpation of the posterior region of the prostate and is under questioning by researchers regarding its low effectiveness [3]. In 1989, repeated sextant systematic biopsy (SB) was introduced as the criterion standard for determining PCa [4]. However, a few studies demonstrated a relative low true-positive finding by SB [5,6]. The false-negative cases often occurred in non-advanced PCa cells with small nodules, possibly due to the multifocal nature and dispersal growth of PCa cells.

Strain elastography (SE) is considered to be a promising method for generating images of the elastic properties of tissues. Several studies applied this approach for differentiating PCa because of the variations in stiffness between normal and PCa tissues [7,8]. In essence, SE is an extension of the DRE, presenting differences in stiffness of the prostate. A better knowledge of tissue properties and their distribution in the prostate may enable more accurate targeting for tissue acquisition and could eventually improve PCa detection, thus potentially providing more appropriate treatment and therapy. However, studies have indicated that prostate volume can influence the accuracy of SE in detecting PCa [9,10]. For example, multi-artifacts might be generated due to the uneven compression of the gland by the transrectal transducer for patients with large prostate volume [10], which could affect the sensitivity of SE-guided targeted biopsy (TB). Therefore, this retrospective study aimed to evaluate the correlation between prostate volume and PCa detection using SE-guided TB and to compare it with conventional transrectal ultrasound (TRUS)-guided SB.

Material and Methods

Patients selection

This retrospective study was approved by the Ethics Committee of our hospital (approval no. 2018108). Due to the retrospective nature of the work, the requirement to obtain informed consent from the patients was waived. Between January 2017 and March 2018, our center examined 395 consecutive male patients with either palpable abnormalities found at DRE or higher PSA exceeding the normal range (0–4.0 ng/mL). The exclusion criteria were: (a) patients who received previous radiation therapy (n=5); (b) patients who underwent prostate biopsy or surgery (n=24); and (c) patients who underwent hormone therapy (n=9). Finally, a total of 357 patients (mean age 69.44±8.40; range 45–91 years) were included in this study (Figure 1).

Conventional ultrasonography protocol and biopsy

Conventional TRUS and strain elastography (SE) examinations were performed using the same Aplio 500 (Toshiba Medical System Corporation, Tokyo, Japan) device with a convex transducer (5–14 MHz). The patient was required to be placed in the left lateral position. The patient first underwent TRUS examination. The prostate volume was obtained from the examination, and patients were further divided into 4 groups according to the prostate volume (≤30 ml, 30–50 ml, 51–80 ml, and ≥80 ml). A radiologist with 5 years' experience in TRUS performed the

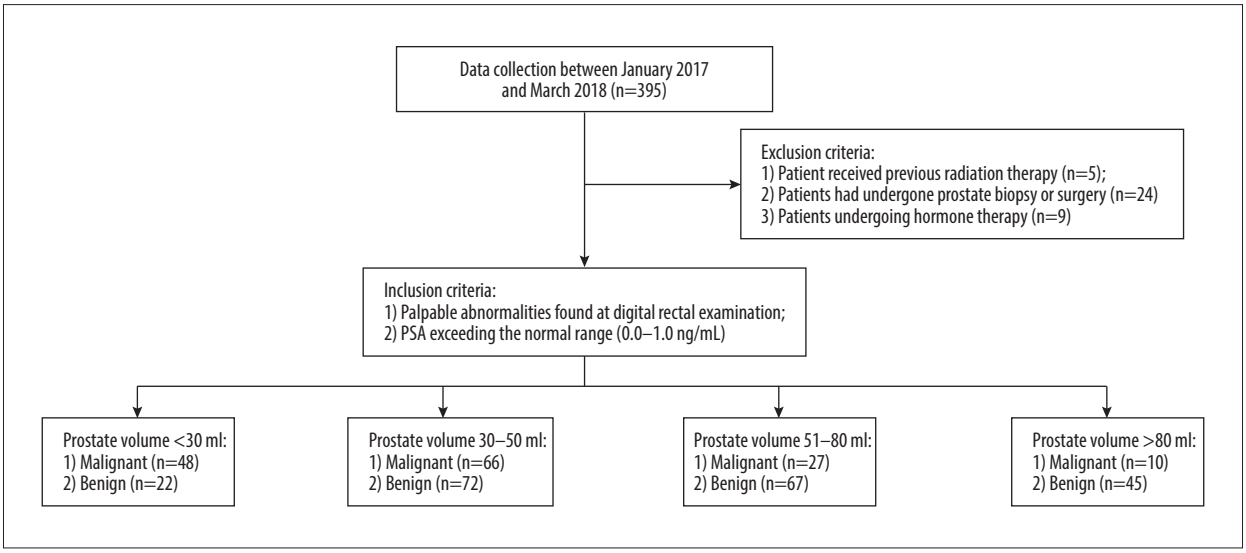

Figure 1. Selection of participants.

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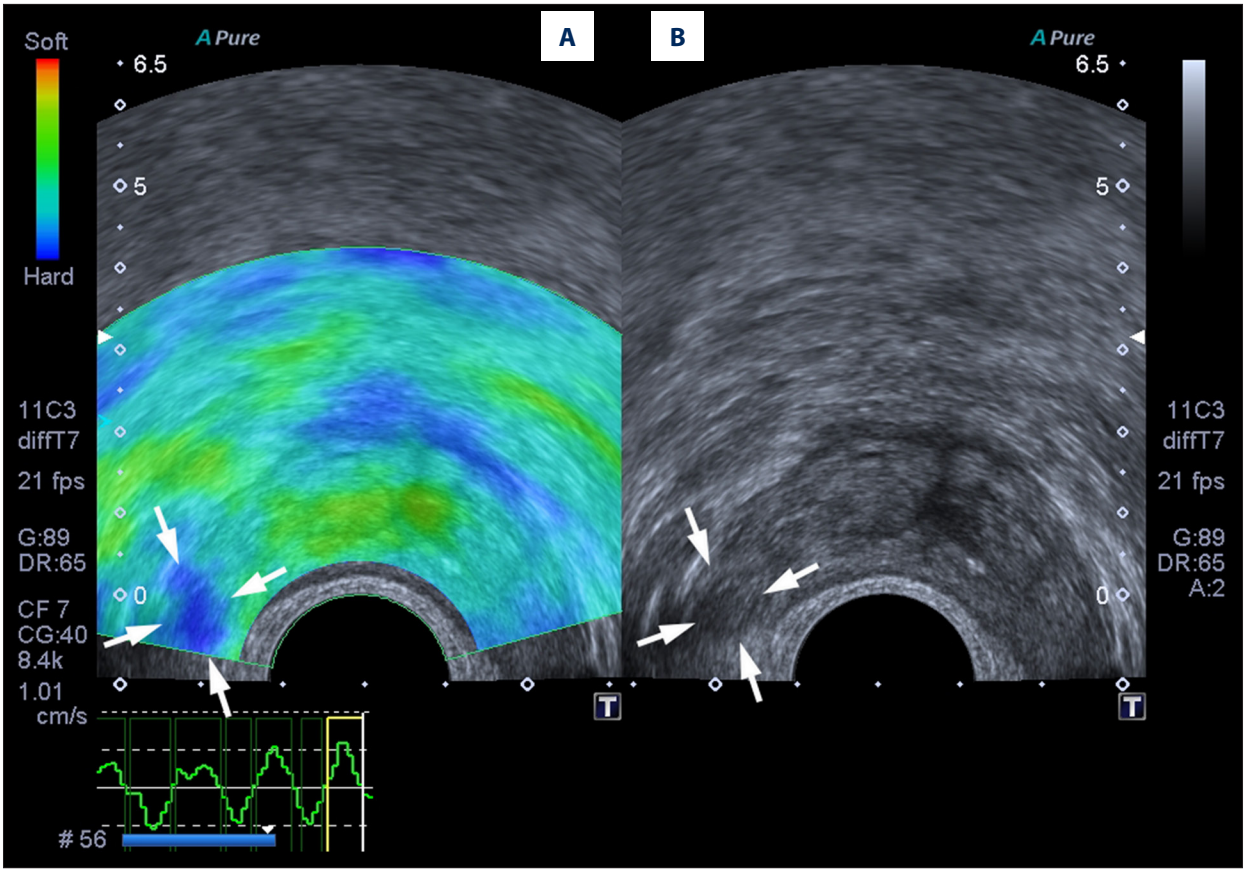

Figure 2. Ultrasound imaging of pathologically confirmed PCa in a 69-year-old male patient with a PSA level of 19.83 ng/ml. Strain elastography showing hard tissue as a blue-colored signal (arrow) (**A**), and B-mode ultrasound showing a low-echoic lesion in the right peripheral area (arrow) (**B**). Biopsy targeted toward the suspicious lesion demonstrated PCa with a Gleason score of 4+3.

TRUS-guided 10-core SB. An 18-gauge needle and automatic biopsy device (Biopty; Bard, Covington, GA) was used to obtain biopsy cores. The biopsy specimens were individually placed in 10% formaldehyde and labeled accordingly. All specimens were assessed by a pathologist with more than 15 years' experience who was blinded to the TRUS results.

Strain elastography protocol and biopsy

SE measurements were obtained after conventional TRUS examination by the same radiologist. The elastography image was obtained by the following procedure. First, the prostate tissue was compressed by moving a transrectal probe from above down. The radiologist repeated the probe movement, applying variations compression ratios until stable and reproducible images were obtained. The stabilized color map image was stored on our internal database system. Dark blue color indicates relatively hard tissue (Figure 2), green indicates average stiffness, while red indicates relatively soft tissue (Figure 3). The SE-guided TB consisted of 2 cores from the 2 most suspicious areas, using the same 18-G biopsy gun. According to Konig's standard, reproducible dark blue areas were defined as suspicious [11].

Statistical analysis

Patients' baseline data (age, PSA, and PSAD) were analyzed using the chi-square (χ^2) test or Fisher's test. The correlation between prostate volume and SE-guided TB was investigated using the chi-square test. The by-patient detection rates of SE-guided TB and TRUS-guided SB were compared using the McNemar test. Data were analyzed with SPSS version 23.0. $P<0.05$ was considered statistically significant.

Results

Study population characteristics

In total, PCa was detected in 151 (42.3%) patients in this study. Of the remaining 200 patients with benign prostatic hyperplasia, 6 had chronic prostatitis. The average PSA of malignant

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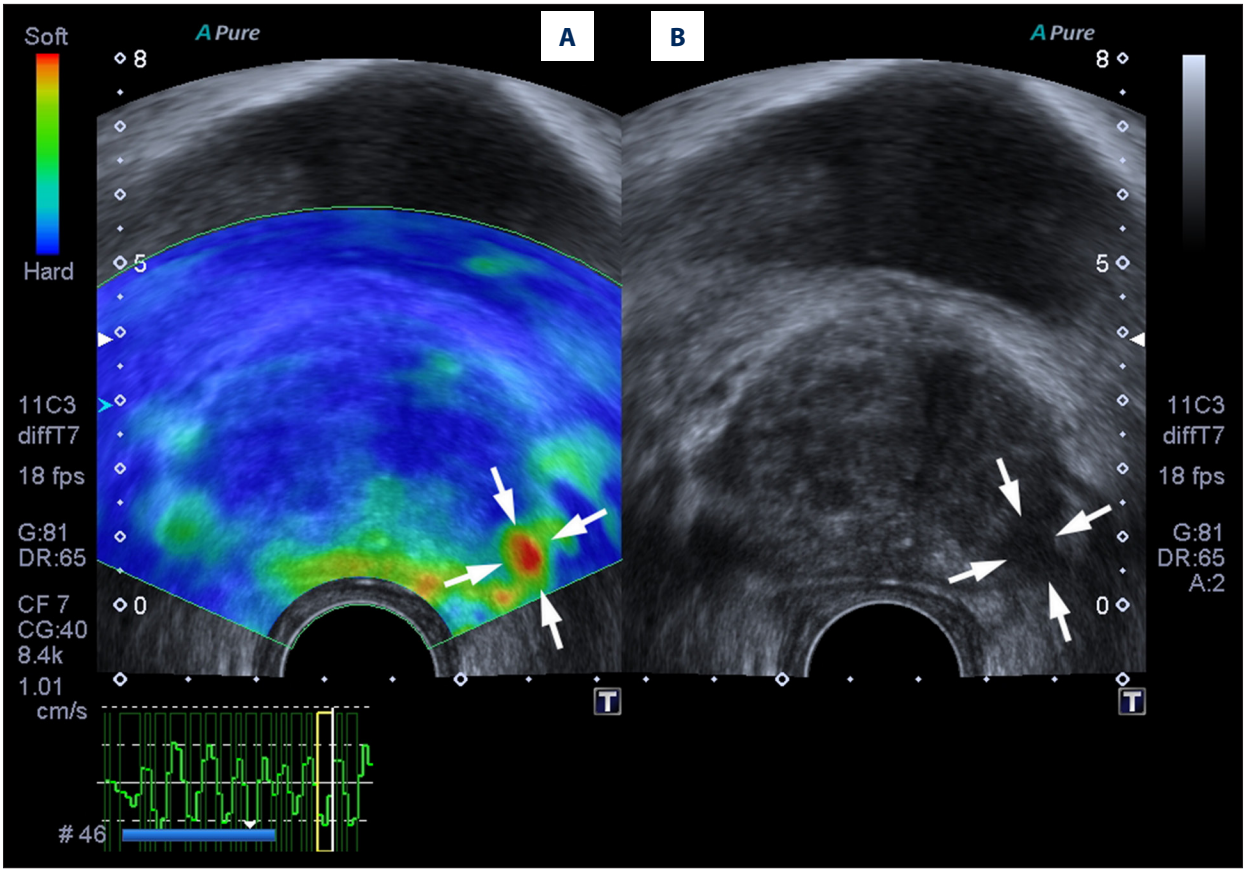

Figure 3. Pathologically confirmed ultrasound images in a 62-year-old male patient with a PSA level of 17.24 ng/ml. Strain elastography showing soft tissue as a red-colored signal (arrow) (**A**), while B-mode ultrasound demonstrated a low-echoic lesion in the left peripheral area (arrow) (**B**). Biopsy targeted toward the suspicious lesion demonstrated chronic prostatitis.

Table 1. Baseline characteristics.

	Benign (n=206)	Malignant (n=151)	p
Age (years)	67.97±8.22	71.44±8.25	<0.001*
PSA (μg/L)	11.26±5.4	14.27±5.80	<0.001*
PSAD (×10³ μg/L$_2$)	0.24±0.19	0.35±0.24	<0.001*
Volume (ml)	47.58±21.85	43.94±13.13	0.069
Gleason score			
5	N/A	15	
6	N/A	26	
7	N/A	46	
8	N/A	39	
9	N/A	25	

PSA – prostate-specific antigen; PSAD – prostate-specific antigen density. * Indicates statistically significant difference.

patients (14.27±5.80) was significantly higher than that of benign patients (11.26±5.4) (p<0.001). No significant difference in prostate volume was found between non-malignant patients and PCa patients (p=0.069) (Table 1).

"By-patient" analysis

Of 357 patients with 379 lesions, SE revealed a 55.7% (211/379) rate of suspicious lesions in 189 patients; 47.0% (71/151)

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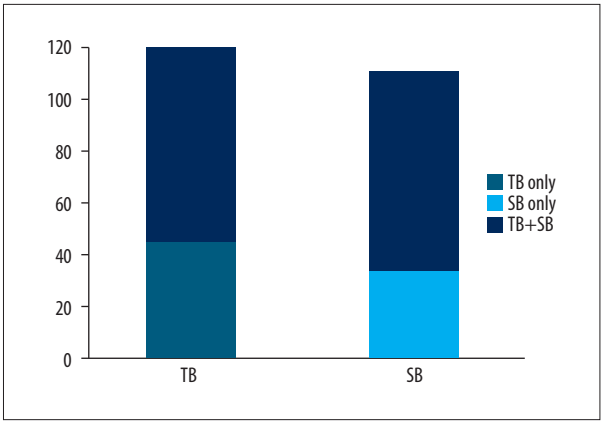

Figure 4. Detection rates of TRUS-guided systematic biopsy and SE-guided targeted biopsy.

of patients with 71 lesions were confirmed by SE-guided TB and SB, while 29.8% (45/151) of patients with 45 lesions and 23.2% (35/151) patients with no suspicious lesions found on SE were solely determined by SE-guided TB and SB, respectively (Figure 4). Even though there was no statistically significant difference between the detection rate for the SE-guided TB (79.5%, 120/151) and for the TRUS-guided SB (72.8%, 110/151) (p=0.314), SE-guided TB increased the detection rate by 6.7% (10/151). Among the 10 PCa patients, 80% had prostate volume less than 50 ml.

"By-core" analysis

Of 357 patients, 189 patients with 211 suspicious lesions on SE (range: 1–2) received SE-guided TB and SB, while the remaining 168 patients with nonsuspicious lesions on SE only received SB. PCa was detected in 277 (7.0%) of 3948 cores, including 134 (3.8%) of 3570 SB-guided TB cores and 143 (37.8%) of 378 SE-guided TB cores. SE-guided TB cores were significantly more likely than SB cores to correctly identify PCa (OR=1.381, P<0.001).

Detection rate of TRUS-guided SB and SE-guided TB in patients with different prostate volumes

We found a negative correlation between prostate volume and the detection rate for SE-guided TB (p=0.002). The sensitivity of SE-guided TB for patients with different prostate volumes was 91.7% (<30 ml: 44/48), 80.3% (30–50 ml: 53/66), 70.4% (51–80 ml: 19/27), and 40.0% (>80 ml: 4/10) (Table 2). The highest sensitivity of TRUS-guided SB was in patients with larger prostate volume (51–80 ml (85.2%, 23/27), followed by patients with medium prostate volume (30–50 ml) (77.3%, 51/66), patients with smaller prostate volume (<30 ml) (62.5%, 30/48), and for patients with prostate volume >80 ml (60.0%, 6/10). SE-guided TB had a higher sensitivity than SB in patients with smaller prostate volume (<30 ml) (p<0.007). However, there was no significant difference between the sensitivity of SE-guided TB and SB for patients with larger prostate volume (30–50 ml, p=0.875; 51–80 ml, p=0.388; >80 ml, p=0.625, respectively).

Discussion

The principles of elastography were first published in 1987 [12], with a later application in PCa detection in 2002 [13]. The ability to visualize tissue stiffness through an elastogram makes ultrasound the most commonly used medical imaging method for differentiating PCa. Several studies confirmed that PCa tissue is typically stiffer than normal prostate tissue [11]. Krouskop et al. demonstrated a significant difference in tissue stiffness between normal and malignant prostate and breast tissue [14]. In 2003, Sperandeo et al. [15] reported a strong

Table 2. Detection rate of SB and SE-guided TB in patients with different prostate volume.

	<30 ml	30–50	51–80	>80 ml	p
Patients	48+22	66+72	27+67	10+45	
Age (years)	70.64±8.48	69.79±8.47	70.20±8.43	65.71±7.19	0.003*
PSA (μg/L)	14.36±6.16	12.14±5.36	11.64±6.04	12.73±5.43	0.028*
PSAD (×10³ μg/L²)	0.49±0.31	0.30±0.18	0.14±0.08	0.14±0.08	<0.001*
Malignancy	31.8% (48/151)	43.7% (66/151)	17.9% (27/151)	6.6% (10/151)	<0.001*
TRUS-guided SB sensitivity	62.5% (30/48)	77.3% (51/66)	85.2% (23/27)	60.0% (6/10)	0.428
SE-guided TB sensitivity	91.7% (44/48)	80.3% (53/66)	70.4% (19/27)	40.0% (4/10)	0.002*

PSA – prostate-specific antigen; PSAD – prostate-specific antigen density; TRUS-guided SB – transrectal ultrasound guided systematic biopsy; SE-guided TB – strain elastography guided targeted biopsy. * Indicates statistically significant difference.

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relationship between nondeformable lesions and PCa, which was also based on the same fact that neoplastic tissue typically is less compressible than benign tissue. In 75% of examined cases, prostate cancer was found in nondeformable lesions. Hoyt et al. further suggested tissue elasticity as a promising biomarker for PCa [16].

Based on the inherent differences in tissue stiffness, SE-guided TB is capable of portraying the anatomical structure of prostate in real time, and therefore differentiating PCa lesions from abnormally indurated nodules. In the first study applying elastography in targeted prostate biopsy [13], Cochlin et al. confirmed an extra 3 patients out of 100 PCa patients by elastography-guided TB. In the present study, we found that patient-based ES-guided TB detected 10 more true-positive case compared with those detected by TRUS-guided SB. Our results confirmed the superior diagnostic performance of ES-guided TB compared to SB. In a core-based study, Aigner et al. [17] demonstrated that the core-based sensitivity for PCa per core was nearly 5 times higher for SE-guided TB compared with TRUS-guided SB. In a a cohort study of 141 patients, Ma et al. demonstrated that the per-core PCa detection rate of real-time elastography-targeted biopsy (44%) was higher than that of SB (30%) [18]. Thus, use of SE-guided TB might decrease the total number of biopsy cores needed, without sacrificing sensitivity.

Gland size may affect elastography results since the prostate compression is formed manually by the force pushed by the operator for achieving stable images. Some researchers have expressed doubt regarding the efficacy of elastography when prostate volume is increasing [19], and the present findings support this hypothesis. The sensitivity of SE-guided TB decreased with increased prostate volume – 91.7% (<30 ml), 80.3% (30–50 ml), 70.4% (51–80 ml), and 40.0% (>80 ml) (p=0.002). The detection rate of PCa for patients with smaller prostate volume (<30 ml) by SE-guided TB (91.7%) was significantly higher than that by TRUS-guided SB (62.5%) (p<0.007). The findings of the present study also agree with several previous studies. Junker et al. [20] compared the real-time elastography and MRI for PCa detection in 61 PCa lesions, showing that the detection rate using elastography for patients with prostate volume >40 m^3 was 42.1%, which was significantly lower than that using MRI (78.9%) (p=0.045), but for patients with volume less than 40 m^3, the detection rate using elastography and MRI was not significantly different (78.6% and 90.5%, respectively) (p=0.227). Brock et al. [21] also pointed out that several factors affected the sensitivity of elastography-guided biopsy in PCa detection, including prostate volume, demonstrating that the higher the sensitivity became, the smaller the prostate volume was. This may be due to the obvious compression and decompression of smaller volumes at the apex.

TB of suspicious lesions on magnetic resonance imaging (MRI) has improved due to technology developments. Either in-bore MRI TB or MRI-TRUS fusion TB demonstrated increased detection rates of significant PCa according to the Epstein criteria [22,23]. However, MRI TB is a costly and time-consuming modality that is not suitable for all patients, especially those having claustrophobia or who have pacemakers. In contrast, SE-guided TB is a cheap and easily accessible solution to determine PCa. In addition, SE-guided TB might be able to improve the detection rate and reduce the number of biopsy cores needed. However, SE-guided TB alone cannot be relied on without taking TRUS into consideration, especially in patients with chronic prostatitis. In these patients, a diffuse increase in the elastic modulus of the prostate tissue was observed; therefore, it was nearly impossible to detect a focus. For this reason, we should also take TRUS images into account when conducting prostate biopsy.

Our study had certain limitations. First, all the ultrasound examinations were conducted by a single radiologist, which led to the lack of inter- and intra-observer variability since, like most ultrasonography examinations, SE is also operator-dependent. For example, the degree of probe pressure on the tissue can directly affect the results. Secondly, we only performed SE examinations on a single US system due to limited resources. Future studies should evaluate the different results generated from different US systems and distinct elastographic methods.

Conclusions

This study evaluated the correlation between prostate volume and strain elastography-guided targeted biopsy. We showed that there was a negative relation between prostate volume and SE-guided TB. In addition, SE-guided TB has a significantly higher positive detection rate than TRUS-guided SB. Therefore, we believe that SE-guided TB could complement TRUS-guided TB, especially for patients with smaller prostate volume.

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