

## Elastography in prostate gland imaging and prostate cancer detection

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### Abstract

Transrectal prostate biopsies under ultrasonography guidance remain the gold standard for the detection of prostate cancer (PCa). Transrectal ultrasonography (TRUS), however, has a limited sensitivity in PCa detection. Prostate elastography (TRES) increases the sensitivity of a TRUS examination. Therefore, the aim of this review is to discuss the usefulness of TRES in prostate gland imaging for the diagnosis and management of prostate cancer based on published literature. The advantages of transrectal elastography were analysed in the context of better diagnostic performance provided by this method. TRES provides additional information for the detection and biopsy guidance concerning prostate cancer, enabling a significant reduction in the number of biopsies.

**Keywords:** elastography; prostate cancer; transrectal ultrasonography; biopsy

### Introduction

Prostate cancer (PCa) is one of the most frequent cancers in males and the second highest cause of death after lung cancer in the USA [1]. Risk factors for PCa include age, a positive family history and ethnicity. Black African and Caribbean men have three times higher risk for being diagnosed with PCa and dying from prostate cancer than Caucasian men, whereas Asian men have the lowest risk. Basic diagnostic management for PCa is based on a digital rectal examination (DRE) and prostate-specific

antigen (PSA) testing for the qualification of prostate biopsy that was introduced in the 1980s by Catalona et al [2,3]. The most common form of prostate biopsy is the 12-core systematic biopsy incorporating apical and far-lateral cores. The major morphological difference between normal and malignant prostate tissue is locally increased cohesion that could be identified by DRE and transrectal elastography (TRES) [4]. In this review paper, the current knowledge and value of elastography in the diagnosis of PCa is discussed.

### Greyscale TRUS

TRUS was first developed in the 1970s and became a routine method to detect PCa. Modern transducers typically are end-firing probes scanning at frequencies of 5-10 MHz. The diagnostic resolution of conventional ultrasonography in PCa detection is low. Neoplastic suspected lesions are typically visible as a hypoechoic focal lesion in the peripheral zone, however, their ultrasound morphology is highly variable. Benign lesions such as inflammatory ones may also appear as hypoechoic

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foci making reliable recognition of a tumour suspected lesion particularly difficult. TRUS sensitivity in PCa detection was estimated to be between 17–57% and is highly dependent on the practitioner's experience [5]. TRUS examination of the prostate gland should focus on identification of asymmetry, hypoechogenicity, irregularity of the capsule and the presence of focal lesions [6]. All above features are associated with the suspicion of PCa; however, the images should always be evaluated considering clinical evaluation and level of PSA.

### **Multiparametric ultrasonography**

The combination of ultrasound-based modalities called "multiparametric ultrasound" (mpUS) was developed to improve sensitivity and specificity of US imaging. This combined imaging technic includes dynamic contrast-enhanced ultrasound (DCE-US), colour Doppler ultrasound (CDU), power Doppler ultrasound (PDU), computerized transrectal ultrasound (C-TRUS) and elastography (TRES) [7]. Additional information for grey scale TRUS, such as tissue vascular supply and stiffness may improve targeting of suspected lesions in the prostate. PCa occurrence and progression is associated with volume expansion and compression of the surrounding tissue as well as increased angiogenesis and microvascular density. Using power Doppler ultrasound imaging flow, vessels as small as 1mm can be detected. Sauvani et al [8] in a prospective study on 429 patients showed that cases with PSA <10 ng/ml, normal DRE and TRUS-PDU have a less than a 5% risk of high- to intermediate-risk of cancer, allowing for the reduction of patients requiring prostate biopsies. The vascularization of the prostate can also be assessed with contrast-enhanced US (CEUS). During this examination, gas-filled microbubbles are intravenously administered. The microbubbles have diameters comparable to the morphotic blood elements, enabling them to pass the microvasculature. The enhancement of the ultrasound waves by microbubbles located in various concentrations in tissues enables the differentiation of healthy tissues from pathological ones [9]. Mitterberger et al concluded that the PCa detection rate was significantly higher for the contrast-enhanced colour Doppler ultrasound than grey scale US-guided systematic biopsy in 100 patients [10]. The detection rate for targeted biopsy cores (15.6%) was significantly higher than for systematic biopsy cores (6.8%)  $p < 0.001$  including a reduced number of biopsy cores. Increased angiogenesis was associated with a higher Gleason score and worse prognosis [11,12]. Gao et al compared the diagnostic accuracy of CEUS versus greyscale TRUS with colour Doppler and noticed that CEUS can be character-

ized with higher diagnostic accuracy than diffuse PCa. Detection of diffuse PCa without an obvious focal mass identified in TRUS or clinical examination may help detect patients who do not need a repeat biopsy [13]. Koh et al compared CEUS guided biopsy and sonoelastography guided biopsy. Despite the small cohort, the authors concluded that elastography may improve systematic biopsy results [14].

The above-mentioned techniques in combination with computer algorithms and elastography seem to be promising diagnostic methods for modern PCa detection and are worthy of further development. MpUS might improve sensitivity in the visualization of suspicious lesions compared to grey scale US; however, standardized clinical imaging with validated protocols are necessary to achieve this purpose. Delgado et al drew attention to the low sensitivity, specificity, positive predictive and negative predictive values of grey scale US, PDU and CEUS in the diagnosis of localized PCa. The author compared the diagnostic profitability of randomized biopsy (RB) and targeted biopsy and concluded that randomized biopsy still cannot be excluded from a biopsy strategy plan [15].

### **What does elastography offer?**

Elastography (TRES) was firstly used by Ophir in 1991 as a novel technology that allowed for obtaining real time information regarding the stiffness of imaged tissues [16]. Malignant lesions are substantially more rigid than healthy tissue. Elastography facilitated to recognize these areas and create a digitally processed map of prostate stiffness; an elastogram. This imaging strategy is less subjective than DRE and additionally facilitates the performance of a targeted biopsy for suspected lesions, even those located in the anterior part of the prostate which are not available during palpation. Moreover, the range of the examined area covers the complete volume of the prostate gland [17]. Thanks to TRES, the significance of US examination in PCa diagnosis could rise and TRUS with TRES might become an alternative diagnostic tool to magnetic resonance imaging (MRI) [18]. The major benefit of elastography in urological management is the ability to improve the effectiveness of TRUS guided biopsy [19].

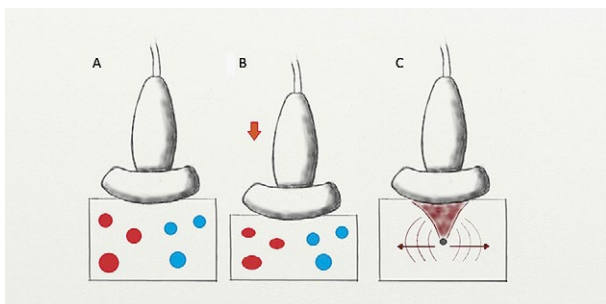
### ***Elastography techniques***

There are two different techniques to obtain an elastography map of the prostate (fig 1). In the first method, the operator exerts manual compression on the tissue with the ultrasound transducer. The image of strain elastography (SE) is thereafter obtained based on the calculation of tissue displacement and strain by quasi-

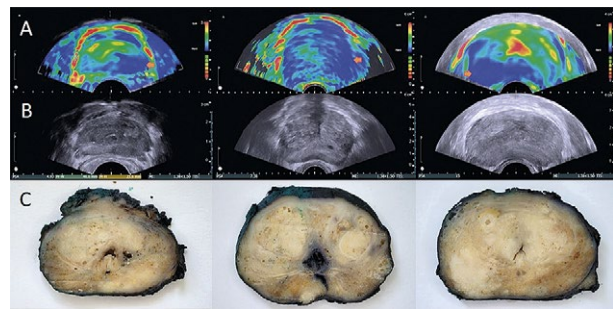
static compression. The second technique - shear wave elastography (SWE) - uses the radiation force of focused ultrasound to remotely create a ‘push’ inside the tissue measuring different shear wave velocities in soft and hard tissues to create a digital map of prostate elasticity. The major advantage of this approach is to demonstrate results as absolute values in kiloPascals or in m/s. Depending on the investigation, cut off values range from 28.5 kPa [20] to 52 kPa [21]. According to EFSUMB guidelines and recommendations for the clinical use of ultrasound elastography, predictive values for malignant lesions should be 35 and 37 kPa [22-24]. WFUMB guidelines state that values greater than 35 kPa are suggestive of a malignancy [25]. The images are recorded and displayed as a colour-coded map of tissue stiffness where blue corresponds to hard tissue and red with soft tissue (fig 2). The quality of the SE greatly depends on the experience of the operator in contrast to SWE. Due to the necessity for manual compression of the transrectal probe during SE, training is required for reproducible results. Heinzelbecker et al concluded that learning plateau in SE might be achieved quickly after training with an expert [26]. There are no studies comparing SWE and SE; however, SWE appears to be easier to perform and does not require manual compression training [27]. On the other hand, shear waves penetrate up to 3-4 cm in patients with large prostates, making full prostate volume assessment impossible [28].

**Elastography when and for who?**

The material obtained during prostate biopsies consist of several cores, which represent only a limited region of the prostate gland [29]. Considering focal development and expansion of PCa, the prostate biopsy results are a weak representative of the actual neoplastic process. Without the adequate visualization of cancer foci, multi-



**Fig 1.** (A, B) Strain elastography evaluates stiffness of tissues thorough its compression (B) assessing the degree of tissue displacement. Greater deformation of soft tissues is observed (red) rather than hard tissues (blue). (C) Shear wave elastography evaluates the elasticity of tissue using transverse-oriented shear waves. The speed of the wave’s propagation is faster in hard tissue than in soft tissue.



**Fig 2.** (A) Elastographic images, (B) transrectal ultrasonography of the prostate glands before the surgical treatment compared with (C) macroscopic image of the prostate gland after radical prostatectomy. The arrows mark suspected lesions (increased stiffness; blue range of colors) in which the cancer was confirmed by pathology examination after surgery. Clearly visible changes in elastography correspond to a certain extent to subtle hypoechogenic changes in ultrasonography and even to macroscopic changes in the macroscopic prostate section image.

ple biopsies might be negative despite the progress of the malignant process [30]. Therefore, the current advances of PCa detection modalities concentrate on improvement of biopsy accuracy using new imaging techniques including elastography. Precisely targeted specimens from the appropriate cancerous foci should reduce the number of cores needed to diagnose. Furthermore, elastography might also decrease the number of biopsies per se and related complications [31]. Carneiro et al showed that a higher number of TRUS biopsy cores (>12) was associated with a higher risk of haemorrhage and perioperative complications during robotic-assisted radical prostatectomy [32]. In these circumstances, the ability to enhance prostate imaging during biopsy is of great clinical importance and consequent development of elastography technology reflects this need.

**The effectiveness of elastography based on available research**

In the past decade, six meta-analyses discussing the application of elastography as a tool for a prostate cancer imaging were published (Table I) [23,33-37]. In all available studies, TRES showed superiority in PCa detection in comparison to standard TRUS. Higher sensitivity as well as the specificity in discrimination between the malignant and healthy tissues were reported.

**Systematic versus targeted biopsy using elastography**

SE was proved to reduce the number of core biopsies necessary for the PCa confirmation and qualification for further treatment [38]. Another observation was increasing diagnosis accuracy with a higher Gleason score PCa. The reliable convergence of TRES images with pathological data obtained after radical prostatectomy might

Table I. Published meta-analyses evaluating the use of elastography in detecting prostate cancer

Author	Number of studies included	Number of patients	Sensitivity	Specificity	Conclusions
Aboumarzouk [23]	16 (10 comparing SE with TRUS biopsy; 6 comparing TRES with RP specimens)	2278	0.71-0.82 (RP as reference) 0.26-0.87 (TRUS biopsy as reference)	0.6-0.95 (RP as reference) 0.17-0.76 (TRUS biopsy as reference)	1. SE may improve prostate cancer detection 2. High accuracy comparing with prostate specimen after RP
Teng [33]	6 (comparing SE with TRUS biopsy)	527	0.62 (0.55-0.68)	0.79 (0.74-0.84)	1. SE is a valuable technique in PCa detection 2. May decrease the number of overall biopsy core or be supplemental to systematic biopsy in future
Zhang [34]	7 (comparing SE with RP specimen)	508	0.72 (0.66-0.88)	0.76 (0.6-0.92)	1. SE may decrease the number of overall biopsy core 2. Valuable in differentiation of cancer from benign prostate lesions
Sang [35]	7 (5 comparing SWE with TRUS biopsy; 2 comparing SWE with RP specimen)	923 + 30	0.844 (0.696-0.927)	0.860 (0.792-0.908)	1. SWE shows high accuracy for the detection of PCa 2. SWE may reduce the number of core biopsies needed for diagnosis
Woo [36]	8 (6 comparing SWE with TRUS biopsy; 2 comparing SE with RP specimen)	1028	0.83 (0.66-0.92)	0.85 (0.78-0.90)	1. SWE shows good performance for the detection of PCa 2. Cutoff value cannot be made because of study heterogeneity
Tu [37]	7 (comparing SE with TRUS biopsy)	1240	0.695	-	1. Not enough evidence that SE-targeted biopsy can outperform systematic biopsy 2. The combination of systematic and SE-targeted biopsy may improve PCa detection

SE – strain elastography; TRUS – transrectal ultrasonography; TRES – transrectal elastography; RP – radical prostatectomy; SWE – shear wave elastography PCa prostate cancer

significantly improve the PCa diagnostic path with using SE. The major limitation, however, is the insufficient standardization of available protocols for the final interpretation of collected results. New prospective studies should shed new light on this issue [39-45].

Sang et al [35] and Woo et al [36] found that SWE showed an excellent PCa detection rate. The lack of consensus regarding the stiffness cut-off values differentiating the malignant and benign tissues made it difficult to standardize SWE guided biopsy. The additional factors that may affect the cut-off values are the imaging plane and location of the examined region within the prostate. Rouvière et al showed different thresholds depending on the imaging plane (axial or sagittal) and the location within the prostate gland. All tissue classes were stiffer on sagittal sections vs axial sections in the transitional zone than in the peripheral zone, and in the median peripheral zone than in the lateral peripheral zone [21].

#### ***Stiffer lesions, higher Gleason values?***

At the time when more attention is paid to diagnosing only significant prostate cancer at the initial stage, it is important to obtain the most reliable biopsy cores [46]. The linear correlation between SE and SWE results and Gleason score of PCa lesions were determined in many studies [47-51]. The size of the lesion (>5 mm) and local advancement of the cancer including infiltration beyond the prostate capsule was defined as major important factors improving SE sensitivity [52]. According to Junker et al, SE detected 9.7% of cancer lesions with a maximum diameter of 0-5 mm, 27% with a maximum diameter of 6-10 mm, 70.6% with a maximum diameter of 11-20 mm and 100% with a maximum diameter of >20 mm [53]. Compression and decompression performed by an examiner might cause artefacts and incorrect assessment of tissue stiffness in SE. On the other hand, controlled compression delivered by balloon inflation proposed by



Tsutsumi et al improved prostate visualisation and led to the reduction of artefacts. However, this technique is not common [54]. Boehm et al found a higher correlation of targeted biopsy Gleason scores predicted with elastography and pathological radical prostatectomy (RP) reporting compared to only using systematic biopsy [55]. SE improved preoperative Gleason score assessment between specimens derived from targeted and systematic biopsy (68.3% vs 56.7 %) and the number of patients undegraded after radical prostatectomy was lower after applying elastosonography. The sensitivity and specificity of systematic biopsy were improved by 31% (94% vs 63 %) and by 10% (92% vs 82%) respectively, after addition of elastography to standard biopsy protocols. Interestingly, Porsch et al unexpectedly showed a poor prediction rate of malignancy by SWE and demonstrated a significant increase in elasticity of benign prostate tissue from the basal to the apical region [56].

#### ***How to interpret the examination?***

The use of elastography still generates difficulties in the interpretation of elastogram. The increased prostate stiffness in benign prostate diseases such as chronic inflammation and fibrosis may be difficult to distinguish from cancer [57]. Reliable conclusions resulting from elastography must be drawn after a full clinical examination and laboratory tests (TPSA, fPSA). The intriguing results were presented by Barr et al. (2012) who showed that patients with elevated PSA levels or abnormal DRE and negative SWE might not require biopsy [28]. This correlation could significantly reduce the negative biopsy rate in PCa detection and on the other hand improve the identification of patients with significant PCa. Xu et al. introduced 5-grading descriptive rating score for diagnosis of PCa with real-time elastosonography. The authors assessed the diagnostic value of SE score depending on the level of the PSA and prostate volume. The sensitivity, specificity and accuracy in the diagnosis of PCa were 68.6%, 69.4% and 69.2%, respectively. High diagnostic values of SE scores were proven in patients with a prostate volume less than 30 ml and PSA level between 4 and 10 ng/ml, which occurs in the largest group of patients [58]. In this context, elastography would be a helpful tool to qualify patients with slightly elevated PSA for biopsy. Unfortunately, many PCa are difficult to be identified in elastography; hence systematic biopsy cannot be omitted [59,60].

#### ***TRES; a new helpful tool in prostate cancer detection***

Imaging data acquired by TRES may reveal cancer lesions that are usually difficult to target in standard ultrasonography and trigger further diagnosis and therapy. Kamoi et al. (2008) compared sensitivity and specific-

ity of power Doppler ultrasonography (PDUS) combined with SE to visualize prostates during a biopsy in 107 patients. The compilation of images gathered by SE with PDUS increased biopsy sensitivity to 78% vs. 50%. Authors underlined that PCa detection rates of biopsy enhanced by PDUS with SE were significantly higher than systematic biopsies alone (50% vs. 15%) [61].

Modern diagnostic tools in PCa management include prostate cancer antigen 3 (PCA3). PCA3 is a gene that expresses in non-coding RNA and it is highly overexpressed in prostate cancer. It was shown to be useful to predict the presence of malignancy. Nygård et al. (2016) combined a real-time elastography with a PCA3 score in 124 patients. This method was showed to identify 96% patients that should undergo further diagnostic workup. Authors concluded that SE helped to avoid about 20% of the prostate biopsies without missing high-risk PCa. The use of SE and the inclusion of PCA3 may reduce the number of prostate biopsies especially in the upper age group, which will undoubtedly reduce the number of potential complications. PCa targeted biopsies will become easier if urologists would obtain reliable real time prostate stiffness maps with a display of suspected cancer regions. The more effective a visualization of malignant areas within the prostate gland is, the more decisive pathological results would be after each biopsy [62].

#### ***Magnetic resonance imaging and elastography***

Multiparametric magnetic resonance imaging (mpMRI) emerged as a key diagnostic tool in PCa detection [63]. The prostate magnetic resonance scale PI-RADS (Prostate Imaging Reporting and Data System) was developed for the most precise tumour staging assessment. It is characterized by good sensitivity and specificity in detecting significant prostate cancers and staging before making a decision about treatment [64]. The recent Prostate MR imaging study (PROMIS) trial showed that (mpMRI) might allow for 27% of patients avoiding a primary biopsy and diagnosis of 5% fewer clinically insignificant cancers. More cases (18%) of clinically significant cancer were detected in comparison to standard systematic TRUS-biopsies [65]. The ability to target suspected lesions in MRI/TRUS fusion biopsies improved its effectiveness. MpMRI/TRUS fusion biopsy was also recommended by the European Association of Urology (EAU) in guidelines as an important tool before a second biopsy. Junker et al. (2014) and Aigner et al. (2011) demonstrated that mpMRI had similar detection rates to SE. In Junker's study, MRI had better sensitivity especially in the transition zone (72.7% vs. 18.2% for SE), anterior part of prostate and in prostates with volumes more than 40ml. SE identified 67.2% of cancer lesions while MRI identifies 86.9% of lesions. Detection of high-risk PCa was high in

both methods 93.8% for MRI vs. 87.5% for SE [66,67]. In another study, Pelzer et al. (2013) showed a better sensitivity of SE especially in dorsal and apical parts of the prostate. Most of the missed tumours were of low volume and low Gleason score [68]. Detection of prostate capsule involvement is a crucial factor for determining further management [69]. In a study performed by Brock et al, MRI/SE fusion improved sensitivity and specificity to 65.9% and 75.3%. Each of the imaging methods has specific advantages in terms of the evaluation of a prostate region. Accordingly, MRI showed a better sensitivity and specificity for the ventral part of a prostate, whereas SE was better in the dorsal and apical parts of a prostate [70]. Brock et al in another study showed that targeted biopsies using a fusion of SE/MRI improved detection of clinically significant PCa in repeat biopsies compared to systematic biopsies (90.6% vs. 73.9%) [71]. Maxeiner et al. used multiparametric ultrasonography including B-mode, power Doppler, strain elastography, and CEUS. Lesions were evaluated by US modalities resulting in a mpUS score. The authors concluded that a mpUS score correlated with PI-RADS in PCa prediction. The mpUS score predicted PCa and PI-RADS score with an overall accuracy of 86% and 80%, respectively [72]. Brock et al. combined the real-time elastography with contrast-enhanced ultrasound. The multiparametric ultrasonography decreased the false-positive value of SE alone from 34.9% to 10.3% and improved the positive predictive value of cancer detection from 65.1% to 89.7% [73]. The fusion of mpMRI and mpUS may improve the results of prostate focal therapy. MRI and ultrasound image fusion using a computer-assisted 3-dimensional transrectal ultrasound biopsy system enable an accuracy with less than 3 mm error for targeting suspected lesions. Convicted diagnosis of focal disease allows for the effective focal treatment [74-76].

### Conclusions

Transrectal elastography (TRES) seems to be a promising imaging method of the prostate which allows for the detection of cancerous tissue. The main goal of urology nowadays is to only detect significant PCa and TRES seems to be an important biopsy qualification tool more available and cheaper than magnetic resonance imaging. Visualization of the lesion in the prostate gland may also increase the accuracy of targeted biopsy and reduce the number of biopsy cores. On the other hand, the current systematic biopsy protocol should not be omitted until we gather more research data documenting the better efficiency of elastography in this field. Future multicentre studies are required to evaluate and compare SE

and SWE in the detection of significant PCa. Combining elastography with other diagnostic methods especially with multiparametric magnetic resonance may be essential to increase sensitivity and specificity in detecting significant PCa.

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