Value of ultrasound elastography in the diagnosis and management of prostate carcinoma

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Abstract

The aim of the paper is to review and illustrate the role of sonoelastography in the diagnostic and therapeutic approach of prostate cancer. The examination technique and normal appearance are presented. The paper describes and illustrates the appearance of prostate cancer and suggested diagnostic scores. Artifacts, causes for false results and limitations are discussed and also illustrated. The diagnostic influence of intraprostatic tumor location, tumor volume and Gleason score are presented. The paper also reviews the statistical diagnostic value of the method, the relation to prostate biopsy and magnetic resonance assessment. In the end, potential uses and future developments of the method are mentioned.

Keywords: ultrasonography, elastography, prostate cancer.

Rezumat

Scopul lucrării este de a trece în revistă şi ilustra rolul elastografiei ultrasonore în abordarea diagnostică şi terapeutică a cancerului de prostată. Sunt prezentate considerații asupra tehnicii de examinare şi a aspectului normal al prostatei. Sunt descrise şi ilustrate aspectele observate în cancerul de prostată şi scorurile diagnostice. Lucrarea ilustrează artefactele, cauzele de rezultate false şi limitările metodei. Sunt discutate influențele diagnostice ale localizării intraprostatice, a volumului tumoral şi scorului Gleason. De asemenea, este trecută în revistă valoarea diagnostică statistică a metodei, relația cu puncția bioptica a prostatei şi cu examinarea prin rezonanță magnetică. În final sunt prezentate direcții potențiale de dezvoltare şi aplicare a metodei.

Cuvinte cheie: ultrasonografie, elastografie, cancer prostatic

Ultrasound elastography was developed in the early nineties as an alternative ultrasonographic technique able to visualize tissue stiffness. The method was originally described by Ophir et al [1]. The sonoelastographic (SEG) difference between normal and tumor prostate tissue was also described as early as 1998 [2]. Description of the clinical use of SEG for diagnosing prostate carcinoma (PrCa) dates back to the year 2000 [3]. Preliminary studies published as early as 2002 demonstrated that SEG is capable of detecting more PrCa cases than other ultrasonographic techniques [4]. The principle of PrCa detection with SEG relies on the fact that tumor tissue has a greater stiffness than surrounding normal prostate. Based on this premise, the method is expected to supplement some of the other ultrasound techniques' lack of sensitivity in diagnosing PrCa. The aim of this paper is to review and illustrate the current status of SEG in prostate disease diagnosis.

Examination technique

Commercially available SEG relies on manual transmitted vibration into tissues followed by analysis and reconstruction of relative displacement of reflectors along the US information line. More information on the physical principles and overall clinical usefulness of SEG is available in reviews our group published in this journal [5,6]. The endorectal transducers used are either endfire or biplane in construction. Different manufacturers have
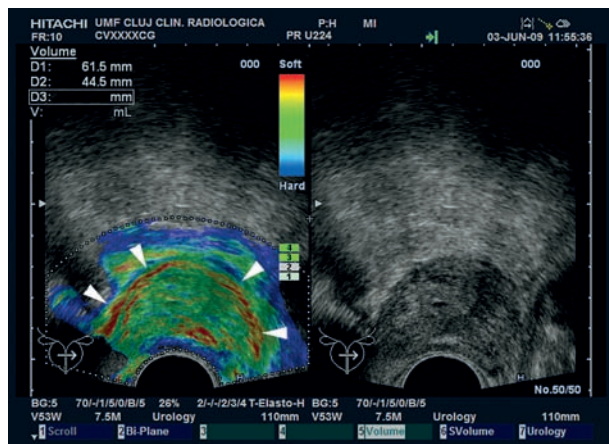
slightly different approaches to the technique, including the color coding of tissue stiffness.

In order to minimize the subjectivity induced by manual vibration, automated balloon inflation and deflation around the transducer tip was developed. This method induces tissue movement that replaces manual vibration and was shown to produce dynamic stable and repeatable images [7].
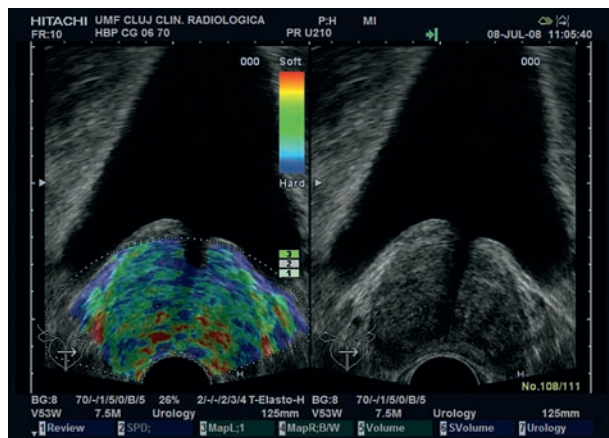
More recently, however, prostate elastography was also achieved with acoustic radiation force imaging (ARFI), a commercially available technology where no external mechanical vibration is needed [8].

Elastographic appearance

On SEG, the normal prostate displays a homogenous strain, the entire gland being evenly colored in green.

Quite often, a red rim of elastic periprostatic fatty tissue is seen (fig 1). Larger prostates, normal or with benign prostatic hyperplasia, may exhibit a heterogeneous appearance with a symmetric mosaic or striated pattern consisting of a mixture of green and blue (fig 2). The larger the prostate and the greater the distance from the transducer, the more prominent the heterogeneity will be. Central, periurethral tissue encompassing the sphincter may appear stiffer than the rest of the gland, inducing a central blue nucleus (fig 3).

Carcinoma is supposed to be stiffer than the surrounding tissue. The original diagnostic criteria, introduced by Konig et al [9] are:
- stiff lesion
- reproducible after tilting the transducer
- diameter of at least 5 mm (fig 4).

Fig 1. Normal sonoelastographic appearance of the prostate. Sonoelastographic image (left) and corresponding gray scale image (right). Note the evenly distributed mid-range stiffness of the parenchyma (green) as opposed to gray scale inhomogeneity. Periprostatic fatty tissue appears as a rim of increased elasticity (red, arrowheads) around the gland.
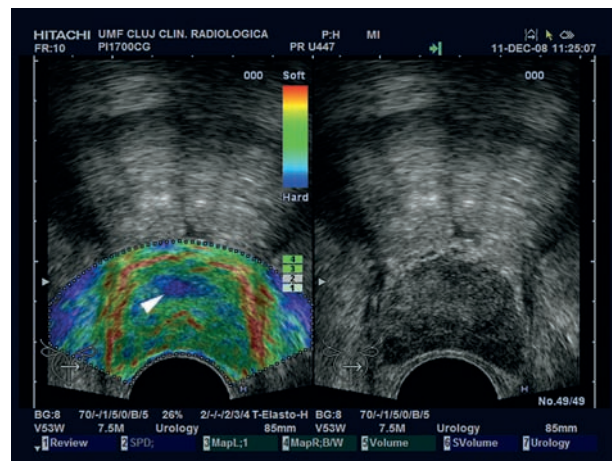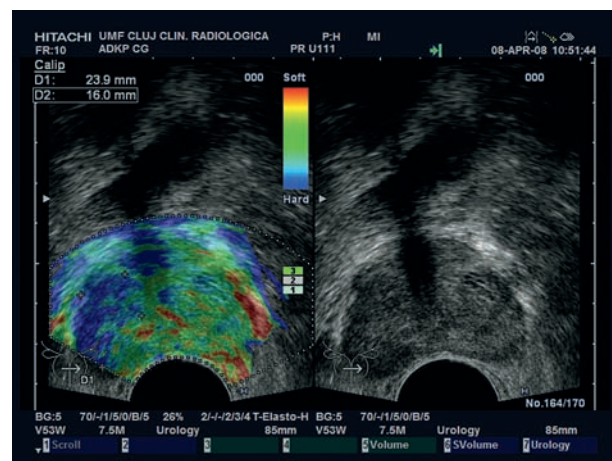

Fig 2. Large prostate with striated elastographic pattern of the base.

Fig 3. Periurethral stiff nucleus (arrowhead) in the center of the prostate

Fig 4. Typical sonoelastographic appearance of prostate carcinoma: asymmetric peripheral stiff nodule of the right lobe, measuring more than 1 cm in every dimension.

These criteria were later refined by Pallwein et al [10,11] who suggested a three step scoring system (table I) (fig 5).

In order to assess the SEG appearance of the prostate, Kamoi et al [12] proposed a subjective scoring system that takes into account both the grayscale appearance and the stiffness displayed by elastography (table II) (fig 6).

The key point in this scale is represented by the relationship between a hypoechoic lesion and a stiff prostatic area. Lesions scaled 3 and above are highly suggestive for malignancy [12].

Extracapsular spread of malignancy is suggested by the interruption of the periprostatic soft rim (fig 7) while increased vesicular stiffness indicates seminal vesicle involvement [13].

Artifacts

The main artifact in prostate elastography, although

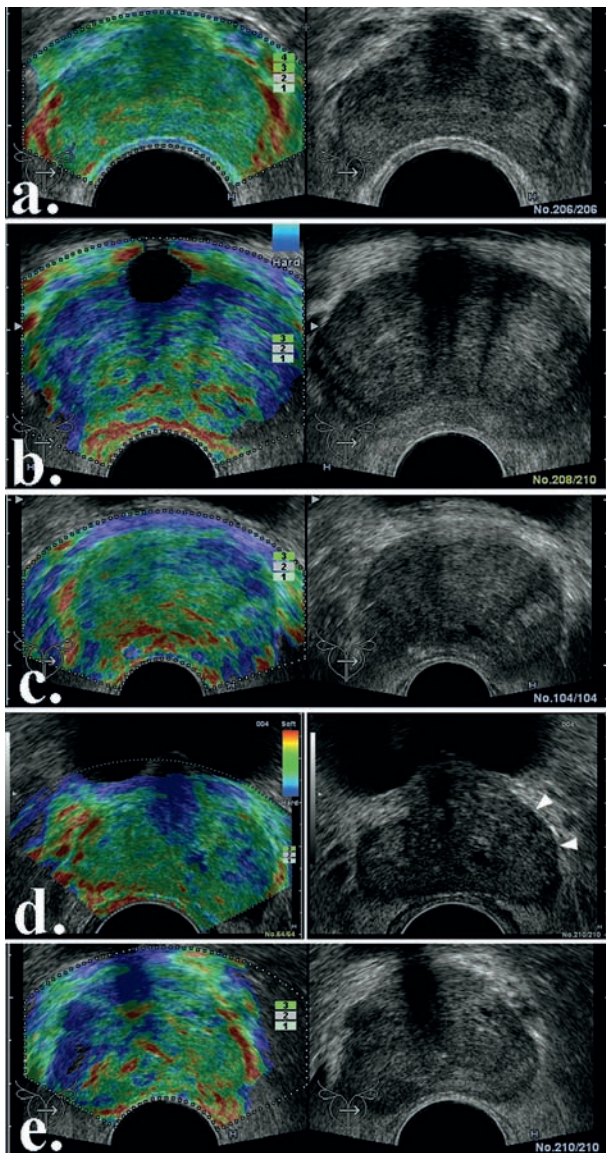Table I. Sonoelastographic scoring system – adapted after Pallwein et al [10,11]

Score	Description	% of patients presenting cancer
1	Evenly distributed, uniform stiffness	2.3 – 11.9
2	Inhomogeneous increase of stiffness, alternating blue and green, each blue dot with diameter < 5 mm, reproducible after tilting the transducer (indeterminate)	26.4 – 28.8
3	Focal increase in stiffness – almost homogenous asymmetric focal area, diameter > 5 mm, reproducible after tilting the transducer (suspicious)	68 – 82.4

Table II. Sonoelastographic scoring system – adapted after Kamoi et al [12]

Score	Description	significance
1	homogeneous strain, the entire gland evenly shaded in green	normal
2	symmetric heterogeneous strain, the gland shows a symmetrical mosaic pattern of green and blue	probably normal
3	focal asymmetric lesion without strain not related to hypoechoic lesion, the focal asymmetric lesion in blue	indeterminate
4	strain at the periphery of the hypoechoic lesion with sparing of the center of the lesion, the peripheral part of lesion in green and the central part in blue	probably carcinoma
5	no strain in the entire hypoechoic lesion or in the surrounding area, the entire lesion in blue	definitely carcinoma
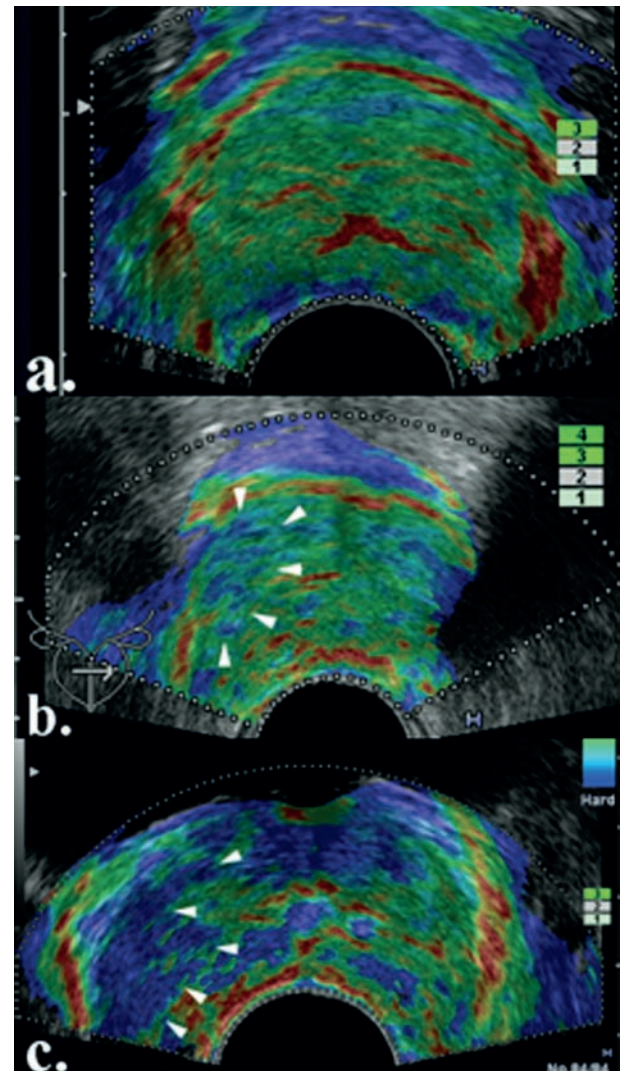
**Fig 5.** Sonoelastographic scoring system proposed by Pallwein [11]: a) Score 1 - uniform stiffness of the whole gland; b) Score 2 - inhomogeneous increase of stiffness, alternating blue and green, each blue dot with diameter < 5 mm, in the right lobe (outlined by arrowheads); c) Score 3 - Focal increase in stiffness – almost homogenous asymmetric focal area, diameter > 5 mm, in the right lobe (outlined by arrowheads).

Fig 6. Sonoelastographic scoring system proposed by Kamoi [12]: a) score 1 – normal - homogeneous strain, the entire gland evenly shaded in green; b) score 2 – probably normal - symmetric heterogeneous strain, the gland shows a symmetrical mosaic pattern of green and blue; c) score 3 - indeterminate - focal asymmetric stiff lesion not related to hypoechoic area, the focal asymmetric lesion in blue, in the left lobe; d) score 4 - probably carcinoma - hypoechoic lesion (bulging the contour of the left lobe, arrowheads) with stiffness in the center of the lesion and strain at the periphery; the peripheral part of lesion in green and the central part in blue; e) score 5 - definitely carcinoma - stiffness in the entire hypoechoic lesion in the right lobe and in the surrounding area, the entire lesion in blue.
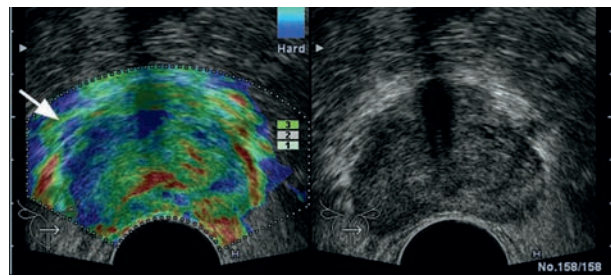
Fig 7. Capsular breach with extracapsular spread suggested by interruption of the periprostatic soft rim and extension of stiffness outside the gland.
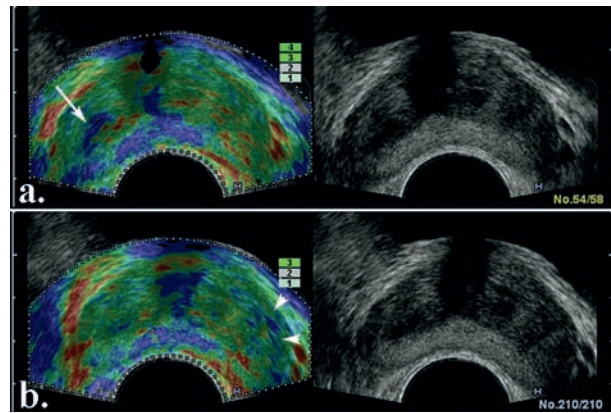
Fig 8. Tilting artifact: a) midline compression. Note the apparent stiff area in the right lobe (arrow) and the homogenous strain pattern of the left lobe; b) slight probe tilting to the right. No change in grayscale appearance. The "stiff" area in the right lobe disappears while a "stiffer" area appears in the left lobe (arrowheads). Both "lesions" are artifactual.

mentioned rather as a technical prerequisite, is related to probe tilting. As most of the transducers used are the end-fire type, the pressure applied is uneven, most of it being directed along the axis of the probe, to the central part of the prostate, while the lateral parts of the gland only receive a derivative of the movement vector. This engenders less displacement in the lateral parts of the image and, as a consequence, a stiffer appearance, with more blue areas. It is the reason why a stiff lesion needs to be reproducible after probe tilting (fig 8).

Slippage out of the examination plane may be encountered in up to 32% of cases during manually induced vibration but in only 1% of cases when using automated balloon inflation [7]

False results and limitations

False results, both positive and negative, may occur during SEG for prostate cancer, with a sizeable influence

on sensitivity and specificity [14]. Prostate volume above 80 cc or a large transitional zone place part of the prostate out of the range of SEG. Large calcification in the peripheral gland as a consequence of prostatitis or focal stiffness changes subsequent to transurethral resection induce hard areas in the parenchyma. Multifocal tumors with individual focus diameter less than 3-5 mm are difficult to depict. Very large tumors, involving the whole gland, do not produce focal stiff areas. The examination is difficult to perform in patients who cannot relax the pelvic floor.

On the other hand, positive elastography with negative biopsy has been reported in benign hypertrophy patients [15].

Well differentiated adenocarcinoma resembles normal parenchyma and cannot be obviated with SEG. Chronic prostatitis and BPH, due to their inherent stiffness, may mimic carcinoma on SEG. "Hardness" artifacts appear in BPH and in the lateral parts of the gland. Repeat exami-

nation with transducer tilting may cancel lateral artifacts but distance artifacts remain and finally alter the diagnostic value of the method [13]. The majority of false positive results are associated with chronic inflammation and atrophy in the basal area of the gland [16].

Some of the causes of false results in SEG of prostate cancer are summarized in table III and depicted in figures 9–13.

The main *limitations* of the method are related to variability induced by manual operation of the probe and examiner experience. The effect of these limitations

Table III. Causes for false positive and false negative sonoelastographic results for prostate carcinoma

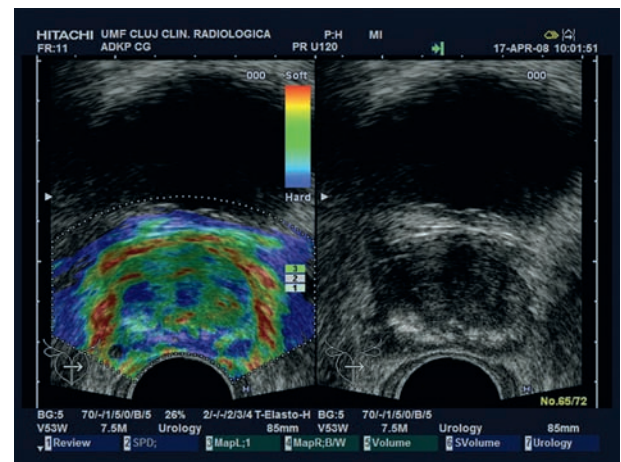| False positive	False negative
Prostatitis	
Calcification	Soft carcinoma
Attenuation	Small tumor
Distance	Very large tumor - diffuse
Hard nodule in BPH	Tilting
Periurethral central zone	Distance
Tilting	
Striated appearance of the base	

Fig 10. Effect of calcifications. Stiffness cannot be assessed behind the heavy calcifications in the transitional gland.
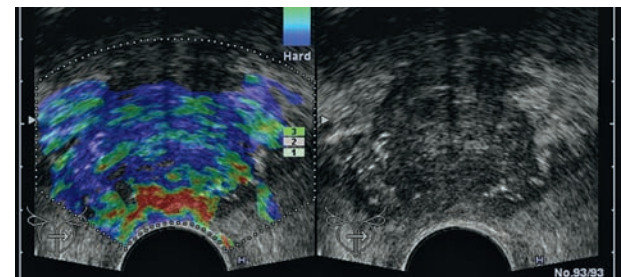
Fig 11. Complete prostate involvement by carcinoma. The whole gland appears stiff, with no focal hard area.

Fig 9. Effect of gland size on SEG of the prostate: in this very large benign hyperplasia, most of the basal part appears stiff due to distance from transducer and difficulty to transmit vibration.

Fig 12. False positive in benign prostatic hyperplasia. The stiff appearing nodule in the right lobe was not confirmed to be malignant at repeat biopsy.

Fig 13. False negative SEG for prostate carcinoma: a) small tumor (arrows) with no elasticity difference from surrounding tissue; b) large, well differentiated carcinoma (arrowheads) with almost no focal stiffness change.
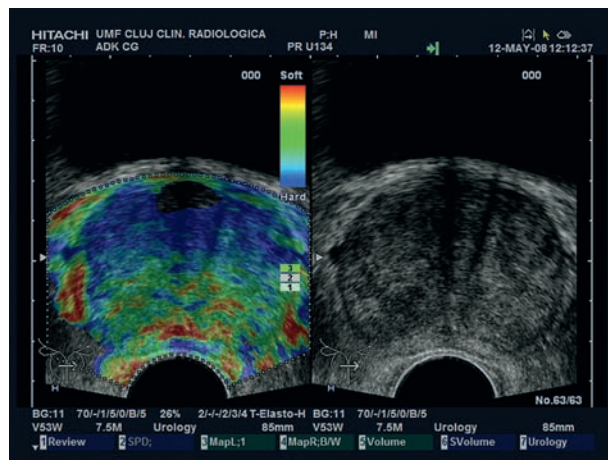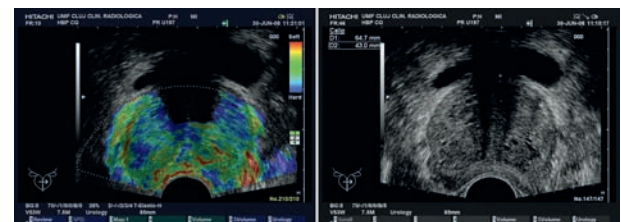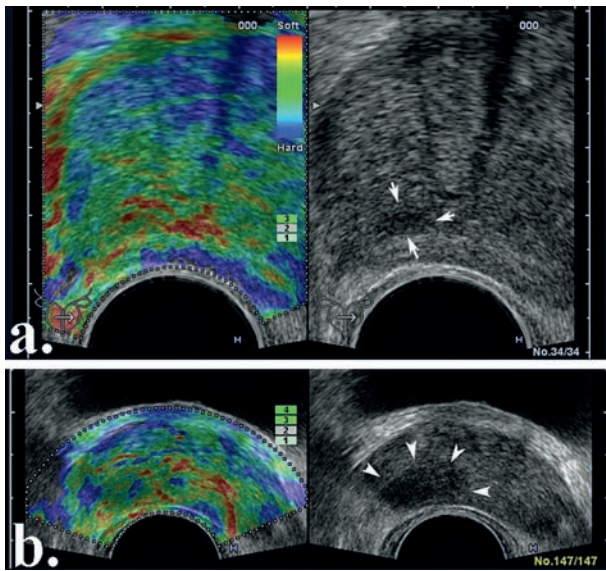
may be reduced by using automated balloon pulsation and verifying the accuracy of vibration on the automated scale some machines are provided with. The use of strain ratio for diagnostic purposes has not been satisfactorily studied, yet [13].

The effect of the learning curve of SEG cannot be underestimated [17,18].

Intraprostatic tumor location, volume and Gleason score

Several studies have shown that intraprostatic tumor location influences the SEG detection rate [7,13,19-20]. For tumors located in the apex of the gland, sensitivity ranges between 79-89%, while at the base and the posterior part of the gland, reported sensitivities are between 60-76%. It does not matter whether automated balloon inflation is used or not, anterior tumors are detected to a greater extent than the posterior ones. Specificity for detecting apical tumors ranges between 68 – 93%.

Small tumors, with a volume less than 1 ml, are detected in a proportion of 72.7%, while 100% of the tumors larger than 5 ml are seen with SEG [21].

There is also a linear relationship between the SEG detection rate and Gleason score [21]. Approximately 74% of the tumors with a Gleason score of 9-10 are detected by SEG while for scores 5-6 the detection rate drops to 60% [7].

Diagnostic value

A number of studies assessed the value of SEG in the diagnosis of PrCa, using either prostate needle biopsy or radical prostatectomy as a golden standard. The results of these studies are summarized in table IV.

All published studies to date ascertain that SEG increases sensitivity and, depending on study design, specificity of ultrasound imaging diagnosis of prostate cancer.

The study conducted by our group showed higher SEG sensitivity for patients with PSA < 10 ng/ml (80%), patient age above 70 years (87.5%) and patients with 10-12 core biopsy (75%) [18].

Guiding puncture

The main advantage of SEG appears to be the improved results of biopsy guidance. Whereas systematic biopsy detected 76.9% of cancers, SEG guided biopsy detected 88.8%, 91% or even 93% of cancers in a preliminary study [10,11,24]. It appears obvious that SEG guidance improves prostate cancer detection as it has a 2.9 to 4.7 times higher detection rate than systematic biopsy [10,13,25,26]. Elastography has the potential to reduce the number of biopsy samples necessary to diagnose carcinoma as it detects more cancer foci than systematic biopsy with less than half the sample numbers [13,25].

Biopsy guidance by means of SEG detects more cancers than biopsy guided by means of grayscale or power Doppler appearance [24]. Moreover, detection rate of biopsy guided by SEG associated with power Doppler is higher than biopsy guided by SEG or power Doppler alone [12]. Although (grayscale, power, SEG) guided biopsy has more chances to produce positive fragments, more than 50% of cancer positive sites (sextant biopsy) have no sonographically detectable change associated [27].

The one study stating that SEG does not improve prostate cancer detection rate, used a prototype machine with a different approach to sonoelastography [28].

Comparison to magnetic resonance assessment of the prostate

Both sensitivity and specificity of SEG are higher than 1.5T T2 weighted images for the detection of morphologic changes associated with carcinoma [29]. When automated balloon pulsation is used, SEG related SE and SP are higher than both T2 and dynamic contrast enhanced MR images [23]. Another study found an equal diagnostic value of SEG and 3T MR imaging of the pros-

Table IV. Diagnostic value of sonoelastography for prostate cancer diagnosis.

Reference	SE	SP	PPV	NPV	Ac	Notes	Reference standard
Pelzer A et al [22] 2010	89.8	78.5				For the identification of the existence of tumor	Radical prostatectomy
	60.5	78.3				For identifying the presence of the tumor in a certain quadrant	Radical prostatectomy
Miyagawa T et al [15] 2009	72.6						Needle biopsy
	89.5%					SEG combined with grayscale	Needle biopsy
Sumura M et al [23] 2010	71.9	85.8				Manual vibration	Needle biopsy
	85.8	97.7				Automated balloon vibration	Needle biopsy
Kamoi et al [12] 2008	68	81			76	For cutoff 3 on a 5 degree subjective scale presented in table 2.	Needle biopsy
	78					SEG + power Doppler	Needle biopsy
Salomon G et al [19] 2008	75.4	76.6	87.8	59	76		Radical prostatectomy
Pallwein L et al [13] 2008	88					Pilot study	Needle biopsy
	86	72				For the whole gland	Needle biopsy
	79	85-93				For outer gland areas, highest at the apex	Needle biopsy
Pallwein L et al [17] 2007	80					Preliminary experience, detects at least one tumor focus in each tumor containing gland	Needle biopsy
Giurgiu C et al [18] 2010	70.6	67.9	57	79		Pilot study	Needle biopsy
	82.3					Association of either grayscale or color Doppler to SEG	Needle biopsy
	88.2					Association of both grayscale and color Doppler to SEG	Needle biopsy

tate, with obvious higher costs and duration associated with MR [22]. However, associating SEG and endorectal coil MR to define suspicious areas increases the success rate of prostate biopsy [13].

Other applications and future prospects

Elastography has been used to obviate HIFU induced lesions in the prostate as soft areas, SEG being useful both in the location of the lesions and in the control of therapy efficiency [30].

The development of three dimensional SEG acquisition techniques offers the prospect of lesion recognition and analysis according to their appearance [31, 32]. Newly introduced shear wave elasticity imaging of the prostate offers another field of research and potential improvement [33].

Closing remarks

Sonoelastography definitely improves the detection of prostate cancer. This assertion is especially validated when SEG is used to guide biopsy. Associating SEG with either grayscale or power Doppler US further increases the diagnostic sensitivity. Tumor size and cellularity both influence the SEG appearance. Far from being perfect, SEG is impeded by operator dependency of manually induced vibration and probe tilting as well as by various manufacturer approaches to elasticity imaging. Furthermore, even the golden standard used is disputable, since needle biopsy of the prostate does not detect all of the tumors or tumor foci.

Although not validated for clinical use yet, sonoelastography represents a valuable addition to the diagnostic armamentarium, reviving prostate ultrasonography and

reopening competition with MR, to the benefit of the patient.

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