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Ultrasound elastography of the prostate: State of the art

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Abstract Prostate cancer is the cancer exhibiting the highest incidence rate and it appears as the second cause of cancer death in men, after lung cancer. Prostate cancer is difficult to detect, and the treatment efficacy remains limited despite the increase use of biological tests (prostate-specific antigen [PSA] dosage), the development of new imaging modalities, and the use of invasive procedures such as biopsy. Ultrasound elastography is a novel imaging technique capable of mapping tissue stiffness of the prostate. It is known that prostatic cancer tissue is often harder than healthy tissue (information used by digital rectal examination [DRE]). Two elastography techniques have been developed based on different principles: first, quasi-static (or strain) technique, and second, shear wave technique. The tissue stiffness information provided by US elastography should improve the detection of prostate cancer and provide guidance for biopsy. Prostate elastography provides high sensitivity for detecting prostate cancer and shows high negative predictive values, ensuring that few cancers will be missed. US elastography should become an additional method of imaging the prostate, complementing the conventional transrectal ultrasound and MRI. This technique requires significant training (especially for quasi-static elastography) to become familiar with acquisition process, acquisition technique, characteristics and limitations, and to achieve correct diagnoses.

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Prostate cancer is a public health issue, because it is the cancer with the highest incidence rate and the second cause of cancer death in men, the first cause being lung cancer. There were around 790,000 cases in the United States in 2012, and 241,740 new cases [1]. These figures are slightly higher than those for breast cancer for the same year. In France, the

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number of new cases is estimated to be 71,000 in 2011 with a significant increasing rate (+8.5% every year between 2000 and 2005). This is a result of combined ageing of the population, improvement in diagnostic techniques and increased use of prostatic specific antigen (PSA) dosage [2]. The number of new cases is around 3.3 times higher than that of colorectal cancer, while the number of deaths related to prostate cancer is estimated to be 8700 in 2011, almost identical to that of colorectal cancer (9200 deaths). Despite improvement in diagnosis due to imaging techniques progress and better treatment efficacy, the specific mortality rate is only falling slightly, but this fall is constant (−2.5% per year for the period 2000–2005). There is no systematic screening. Individual screening relies on annual digital rectal examination (DRE) and PSA dosage. Detection and characterization of prostate nodules using ultrasound or MRI remain difficult to carry out [3].

Prostate cancer screening

Prostate cancer systematic screening is challenged again following the publication of recent recommendations by the French National Authority for Health (HAS) [2]. The aim of systematic screening is to detect a clinically significant cancer in healthy men to identify a curable lesion at an early stage, thereby improving the prognosis of the disease. Its benefits must be greater than its drawbacks, which include complications related to treatment (urinary incontinence, impotence, radiation cystitis or proctitis), to diagnostic methods (hematuria/rectorrhagia/retention/post-biopsy prostatitis, complications due to MRI and administration of contrast agents, PSA false positives), to diagnostic psychological impact and finally to false positives of MRI examinations or PSA dosage. The limits of screening stem from the lack of an effective and simple test to pinpoint men with a risk of cancer high enough to justify continuing the diagnostic procedure with more aggressive tests. Screening may concern either an entire population based on age (systematic screening), or a target population considered to be at high risk. Screening is considered to be organized when it concerns an entire population actively recruited, or individual when the population is recruited when treatment is sought. In France, just like in the United States or in United Kingdom, there is no systematic screening, because of the lack of proof that specific death rate can be reduced [2]. We cannot, however, rule out the role played by extending individual screening through combining PSA dosage to DRE in the recent fall in specific death rate.

However, individual screening for prostate cancer may be offered to men over 50 without a predisposition, after disclosing the benefits and risks to the patient. For high-risk patients (first degree family history, Afro-American patients), screening may even start earlier, at age 40.

Individual screening for prostate cancer is based on DRE and PSA dosage. However, increase of PSA is not specific of prostate cancer and can be related to prostatic hyperplasia, acute and chronic prostatitis, or prostate trauma (caused by cystoscopy, resection, and biopsies). Moreover, there are

significant prostate cancers with PSA levels lower than the threshold of 4 ng/ml.

Prostate cancer diagnosis

Prostate cancer may be suspected if PSA level is abnormal or increasing, or if DRE is abnormal. Further tests are then carried out, which in most cases mean an ultrasound-guided transrectal biopsy. Prostate biopsy also allows estimating the tumor volume (number and spatial dispersion of the positive cores, length of the tumor in each positive sample) and its aggressiveness (Gleason score, invasion of the capsule or the neurovascular bundles) [4].

However, this approach has several limitations. PSA screening leads to a substantial number of unnecessary biopsies in patients with no cancer or with indolent cancer that do not need immediate treatment, with an estimated over-detection rate ranging from 27 to 56% [4]. The false negative rate of prostate biopsy varies from 17 to 21%, in patients with a negative first series of biopsies [5,6]. Many urologists are now facing a dilemma when patients present with an abnormal level of PSA and negative biopsies: when should one stop and when should one continue carrying out biopsies [7]? Finally, although PSA levels and biopsy results are correlated with the clinical stage, tumour volume and histologic tumour grade, the information provided is limited for predicting the tumour mass and its aggressiveness in each patient.

The increase in the number of core biopsies (saturation biopsies up to 40) improves PC detection and offers a better estimation of the tumor volume and Gleason score [8,9], but has many limitations including increased cost and morbidity, and over diagnosis and overtreatment of microscopic tumor foci [10,11]; saturation biopsies cannot really rule out PC [8,9].

MRI recently provided interesting results in terms of detecting and locating tumors [11–15]. Multi-parametric MRI (MP-MRI), combining T2-weighted imaging and functional sequences has become a major modality for tumor detection and staging [11–15], particularly in candidates to radical prostatectomy, with areas under the ROC curve over 0.9 [16–19]. However, MRI performance varies depending on which combination of positive features is selected for cancer diagnosis between T2-weighted sequence, diffusion sequence (including ADC calculation), dynamic contrast-enhanced sequence and sometimes spectro-MRI [20,21]. If the sensitivity of MP-MRI is high, its specificity remains low especially because it is affected by the increased vascularity of the normal inner gland and coexisting benign prostate hyperplastic nodules. Also while its sensitivity is high for large and high Gleason grade prostate cancers, its remains low for the detection of small lesions of limited Gleason score (≤ 6) [22] and there is little information to help distinguish between aggressive and indolent tumors [23]. Quantitative approaches, in particular with diffusion and dynamic contrast-enhanced sequences, could probably help to standardize the interpretation of images and to define thresholds for distinguishing aggressive tumors [24]. In addition, it is difficult to decide on the best way to combine the results of these various approaches, especially when they are discordant [24,25]. This latter issue underlines the lack of

reproducibility in the interpretation of MP-MRI data from one radiologist to another.

Conventional TRUS B-mode imaging has limited sensitivity and specificity in between 40 to 50% for PC detection, and is not significantly improved by the use of Colour/Power Doppler [26–28]. Contrast-Enhanced Ultrasound is still under evaluation and can sensitize prostate biopsy [29–31].

Prostate cancer is a stiff lesion, and this feature plays a major role during DRE [32,33]. A technique able to map tissue elasticity would therefore be useful in detecting and locating cancer areas within the prostate. Two ultrasound elastography techniques have been developed, based on different approaches: the first one entails the use of the quasi-static method, and the second uses the transient shear wave technique [34].

In this article, we present a review of these two techniques, describing the following points:

- how these techniques are applied in the framework of prostate cancer;
- interpretations of elastography results;
- performance of these two techniques for the detection and characterisation of prostate cancers;
- practical advices for using these techniques in the clinical environment;
- and finally their limitations.

Quasi-static elastography

Method

Soft tissues tend to exhibit higher strain (deformation) than stiffer areas when compression is applied. Quasi-static ultrasound elastography (or strain elastography) of the prostate is based on the analysis of tissue deformation in a region, generated by inducing a mechanical stress (compression of the tissue by the transrectal transducer

itself); the deformation is then supposed to be uniform in space and intensity [35–40]. A water-filled balloon may be placed between the probe and the rectal wall to improve the homogeneity of the deformation [41]. A speckle comparison, before and after compression, yields to a colour map of local tissue deformation or strain called elastogram. Tissue stiffness is estimated by visualizing the differences in strain between adjacent regions. Therefore, no quantitative elasticity analysis is available. The stiffness colour scale is automatically distributed from the lowest to the highest strain found in the image plane, and this is why the size and position of the stiffness box may induce some variability. The ROI should cover the entire prostate gland and the surrounding tissues. Semi-quantitative information can be derived by measuring strain ratio between two ROI (usually one considered “normal” and the other “abnormal”). The strain for each pixel is colour coded (or grey scale coded) and displayed as overlay on the B-mode image (Fig. 1).

Interpretation

Quasi-static elastography requires slight compressions and decompressions, which are induced by the transrectal probe. A quality index may help in ensuring appropriate speed and pressure. Stiff tissues exhibit a reduced strain, while soft tissues have an increased strain. Hypoechoic hard lesions are highly suspicious for malignancy (Fig. 2).

Shear wave elastography (SWE)

Method

Unlike quasi-static elastography, SWE requires no compression on the rectal wall to produce elastograms. SWE is based on the measurement of shear wave velocity propagating through the tissues [42]. This technique provides a

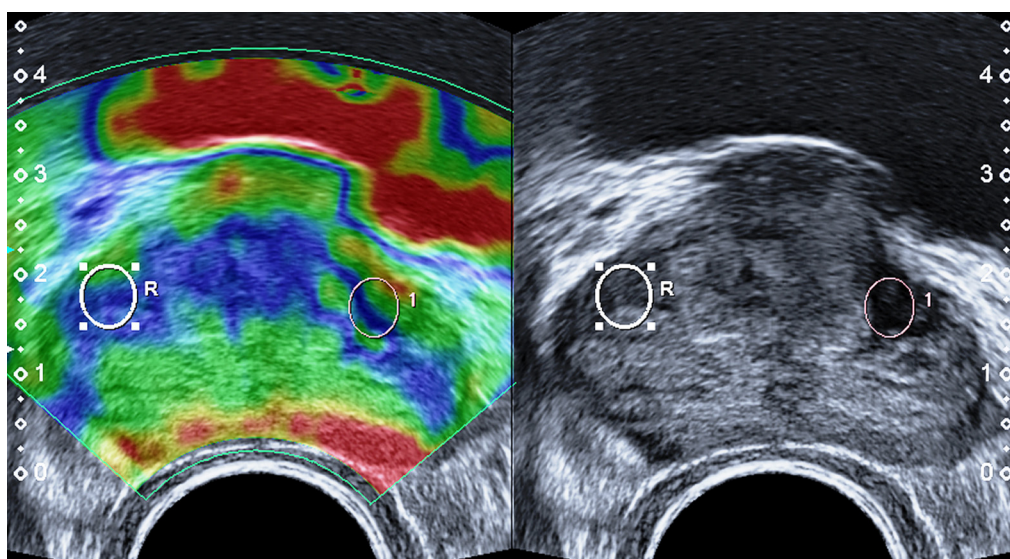


Figure 1. The transrectal transducer is used as a compression device and applies cycles of compression and decompression. A speckle comparison, before and after the compression, allows calculation of local tissue deformations and display/code them as a two-dimensional colour map called an elastogram.

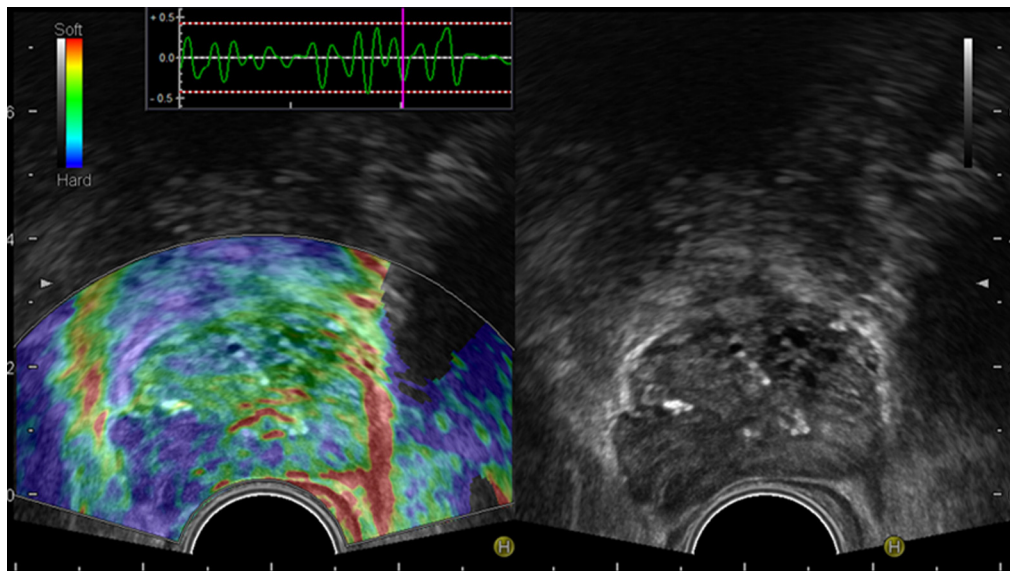


Figure 2. Patient with a PSA of 22 ng/mL, quasi-static elastography of the prostate. The cancer shows little deformation and is shown coded as blue-violet (showing the hard tissue in this system). The lesion is likely to invade the prostate capsule and extend to the peri-prostatic space both in B-mode and in elastography (Courtesy Ellison Bibby—Hitachi Medical Systems).

quantitative map of soft tissues elastic properties in real time, displayed either in kilopascal or in meter per second. SWE basic principle relies on two successive steps: first, a shear wave is remotely induced by the endorectal transducer in the prostate, using the acoustic radiation force of a focused ultrasonic beam, and second, the shear wave propagation is captured by imaging the prostate. The shear modulus (i.e. stiffness) is derived by measuring the shear wave propagation velocity (c.f. J.L. Gennisson article). The shear wave speed (in meter per second) or the Young's modulus (in kilopascal) is color-coded for each pixel and displayed as an overlay on the image in B-mode (Fig. 3).

Interpretation

Optimized settings include maximizing penetration and setting up an appropriate scale (70 to 90 kPa). The ROI can only cover half of the gland in a transverse plane, so each side of the prostate is scanned separately and stored digitally from base to apex for further review and stiffness measurements. For each plane, the transducer is maintained in a steady-state position during 2 to 4 seconds until stabilization of the signals. Stiff tissues are colour-coded in red, while soft tissues appear in blue. Hypoechoic stiff lesions are suspicious for malignancy. The elasticity values (mean, standard deviation, min and max) are then calculated for each ROI. The ratio between the mean values of two ROIs placed in a suspicious region and in the adjacent normal peripheral zone can be calculated.

In young patients without prostate disease, the entire prostate exhibits a similar soft appearance with elasticity values below 30 kPa (Fig. 3). In benign prostate hypertrophy, the peripheral zone remains soft and homogeneous, while the central and transition zones become heterogeneous and hard, with increased values (particularly in the presence of macro-calcifications) (Fig. 4). Typical peripheral zone benign

nodules are soft (< 35 kPa), while cancer nodules are stiffer (> 35 kPa).

Performance of elastography in detecting and characterizing prostate cancer

Several studies point evidence that elastography provides useful additional information to conventional TRUS for PCA detection. Three different applications have been identified: firstly, characterization of abnormal regions detected by B-mode imaging, colour Doppler US or MRI; secondly, detection of lesions not seen with any imaging technique; and thirdly, biopsy targeting. SWE allows continuous scanning of the prostate from base to apex to detect stiff regions, and provide quantitative elasticity values of nodules and stiffness ratio between nodules and adjacent prostate tissue.

Most studies report a significant improvement in prostate cancer identification with quasi-static elastography, including guidance for targeted biopsies [36,37,39,40,43]. However, there are still some controversies and some recent studies reported an inability to differentiate prostate cancer from chronic prostatitis [44] or that quasi-static elastography was less accurate than randomized biopsies for identifying prostate cancer (Fig. 5) [45]. Improvement in biopsy guidance is often reported in the literature [46–48], but some well-designed studies did not confirm such results [45,49].

SWE is a more recent technique and there are few reports to date. The best stiffness cut-off value to differentiate benign from malignant lesions was found to be 35 and 37 kPa in two independent studies [50,51]. In both of these studies, the lowest performance for SWE in terms of sensitivity, specificity, positive and negative predictive values were 63,

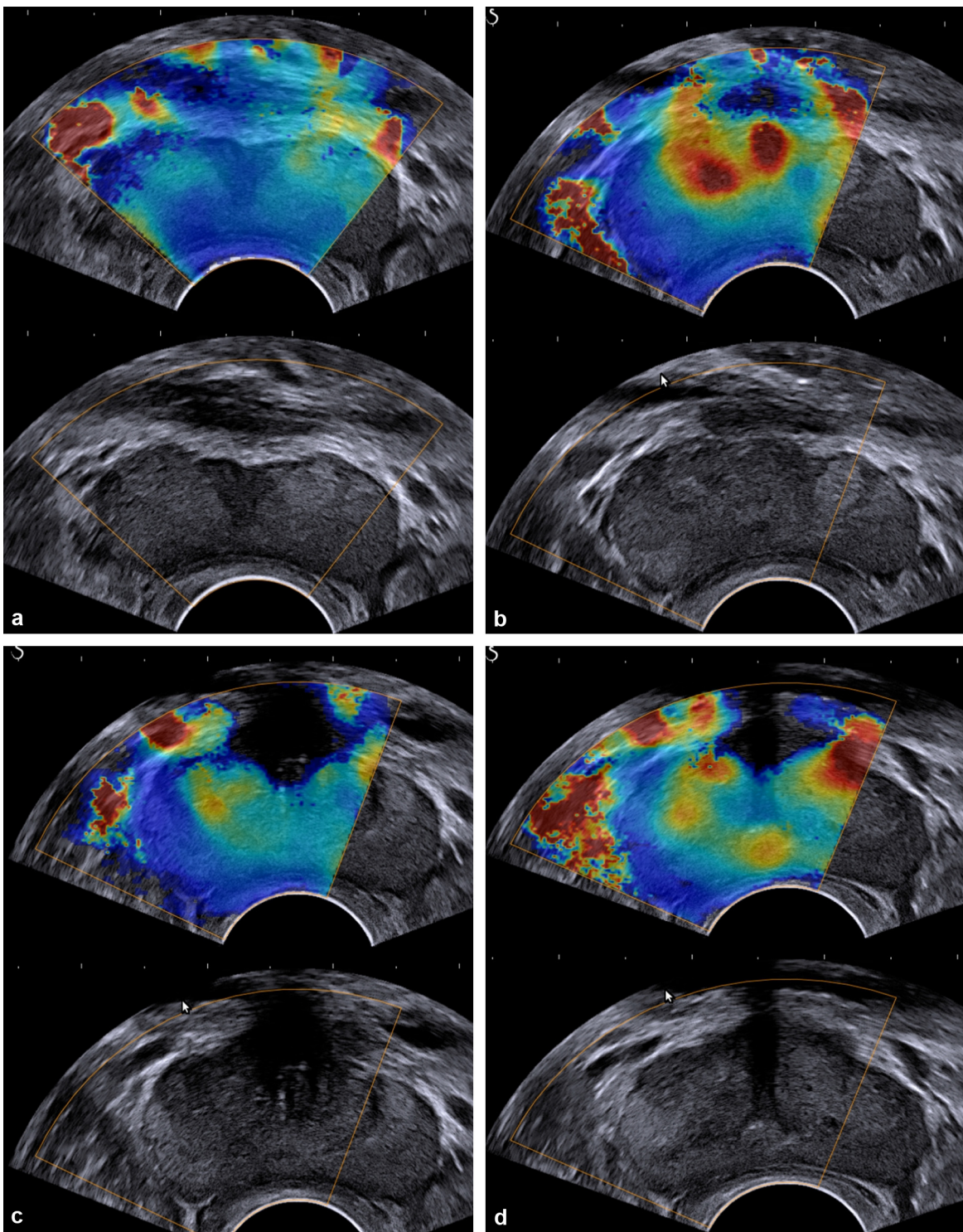


Figure 3. A 32-year-old man, infertility, presenting with early benign prostate hypertrophy. Shear wave elastography with sections from the base to the apex (a, b, c, d) shows a very homogeneous and very soft peripheral zone, coded in blue, with mean elastography values below 10 kPa (the elasticity scale varies from 0 to 70 kPa). The central and transitional zones are already heterogeneous and contain nodules with increased hardness.

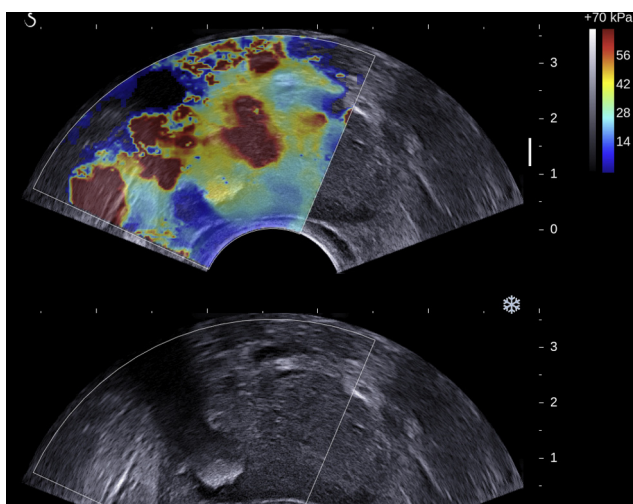


Figure 4. A 58-year-old man with a PSA of 4.6 ng/mL. A large calcification, clearly visible on B-mode imaging in the right mid-prostate, induced a focal increase in stiffness. This calcification cannot be confused with a parenchymal nodule, and it is not a SWE false positive.

91, 69,4 and 91%, respectively (Fig. 6). The shear wave elasticity ratio performed better, presumably because it takes into account the increased stiffness of the peripheral zone from calcifications and chronic prostatitis. The ratios between the nodule and the adjacent peripheral gland tissue for benign and malignant lesions were 1.5 ± 0.9 and 4.0 ± 1.9 ($p < 0,002$), respectively [50].

Prostate elastography may be recommended to increase diagnostic confidence in the detection of prostate cancer (characterization of a focal abnormal area, detection of a stiff region not seen with other imaging techniques) and to increase the positive predictive biopsy rate.

Practical advice for carrying out prostate elastography

No specific preparation is required for either quasi-static or SWE (apart from an enema for some teams). Elastography

imaging is conducted after a complete, high quality TRUS examination in the transverse and sagittal planes, in order to measure prostate volume, identify suspicious areas in the peripheral gland and analyse the peri-prostatic space (including the seminal vesicles).

Prostate elastography is recommended only if the user has adequate training and experience with the system and the ultrasound elastography technique used. He should also be familiar to prostate TRUS and US guided biopsies.

No study has compared the quasi-static and SWE techniques. SWE does, however, appear easier to carry out and requires less training, because no manual compression is required, and because this method is less subject to operator variability. However, experience and knowledge of the limitations of both techniques are essential for both methods.

Limitations and artifacts

Both elastography techniques have limitations. For the quasi-static technique, they include the lack of uniform compression over the entire gland, the intra and inter-operator dependency, the penetration issues in large prostate glands, the level of training, and the artefacts due to slippage of the compression plane that can occur in up to 32% of the images [43]. This artifact is reduced with training and balloon interposition.

SWE also has a number of limitations including the minimal pressure applied to the transducer (an end-fire transducer requires bending to image the prostate), the slow frame rate (one image per second), the limited size of the ROI (only half of the prostate gland is covered) (Figs. 3, 4, 6 and 7), to the delay to achieve image stabilization for each plane acquisition and the signal attenuation in large prostates making the evaluation of the anterior transitional zone difficult or impossible (Fig. 7).

Both techniques are also subject to the same intrinsic limitations: not all cancers are stiff, and all stiff lesions are not cancerous (calcifications, fibrosis...). Elasticity information must always be combined with the results of the transrectal US B-mode, and with the results of other imaging techniques such as MRI.

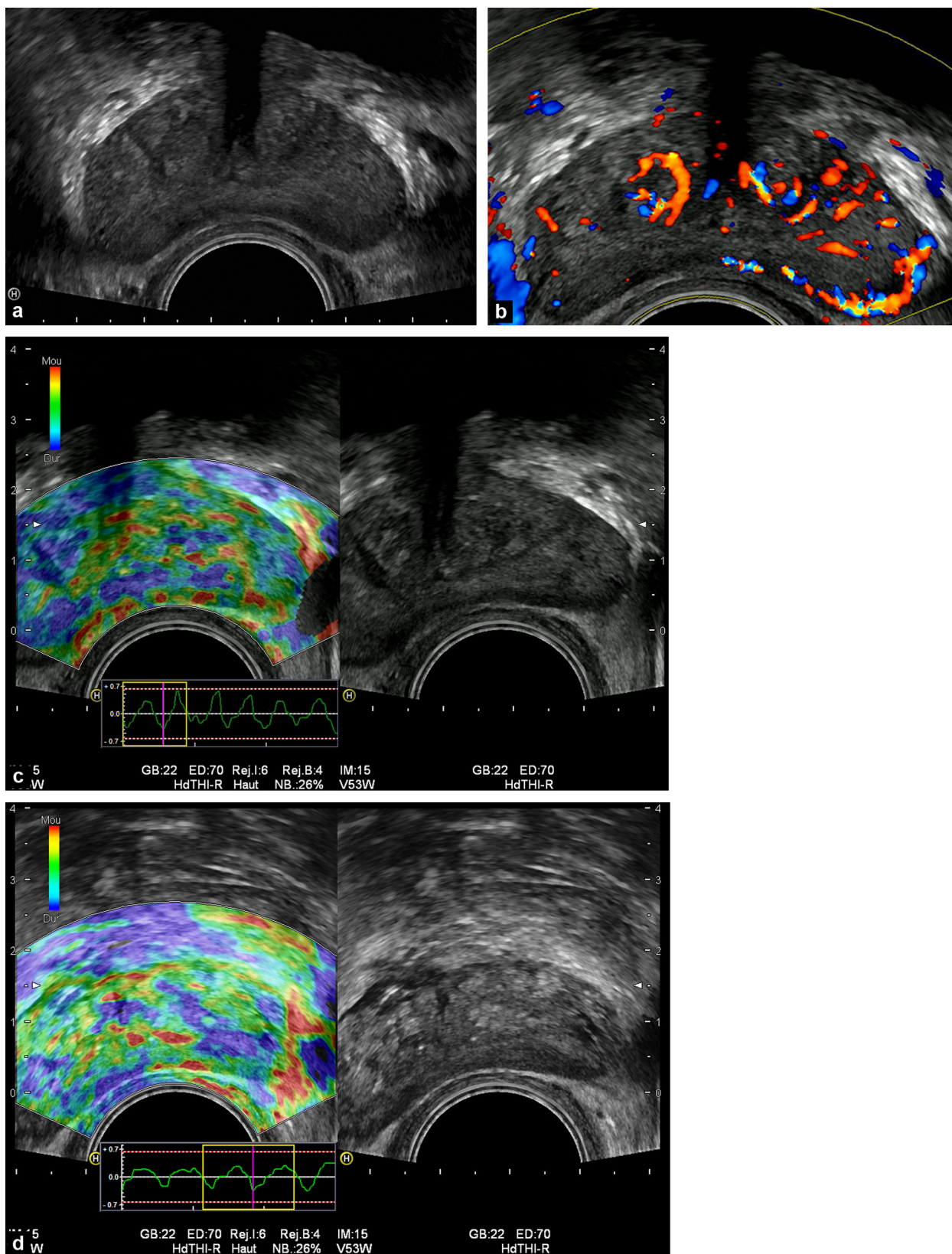


Figure 5. A 65-year-old patient, with an increasing and high PSA at 12 ng/mL. The first series of biopsies was carried out 18 months earlier and revealed a 2 mm micro-focus of cancer Gleason 6. The patient was placed under active surveillance. In B-mode (a) and colour Doppler US (b), there was no focal abnormality and particularly no peripheral hypoechoic area with increased vascularity. Quasi-static elastography was difficult to interpret in the absence of focal increased stiffness area; only some small poorly delineated stiff areas were seen without B-mode abnormal changes. All 15 samples (systematic posterior and anterior biopsies) came back positive with tumour lengths of 11 to 21 mm and a Gleason score of 7.

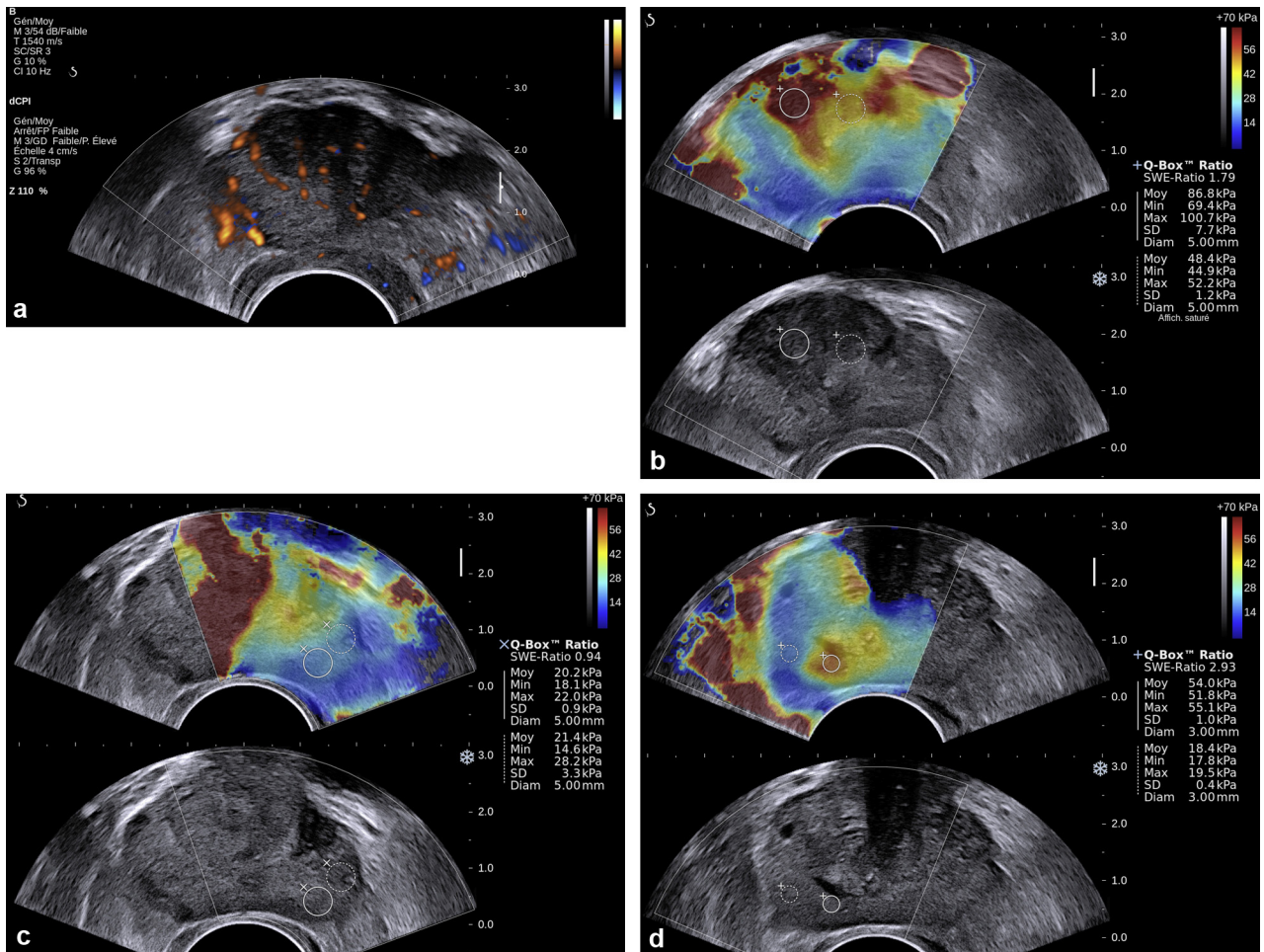


Figure 6. A 57-year-old man with PSA values of 6.6 ng/mL and abnormal rectal examination results, this is the second series of prostate biopsies. A focal nodule was detected at TRUS as hypoechoic and hypervascular, as well as at MP-MRI (T2, DCE and diffusion) at the anterior right base (a). SWE showed an increased stiffness (mean value of 87 kPa) (b), while in comparison the left side of the prostate exhibited normal stiffness values (c). The three samples taken in stiff focal lesion revealed an adenocarcinoma Gleason 6 measuring 7 mm. Another peripheral nodule located in the right paramedian base was detected only with SWE, as it was isoechoic to normal prostate parenchyma. This lesion was not seen at MP-MRI. This stiff lesion exhibited high elasticity value of 54 kPa and a ratio of 1.8 (d). This nodule was also biopsied, revealing another Gleason 7 cancer, measuring 11 mm (longer than the lesion seen at MP-MRI and B-mode TRUS).

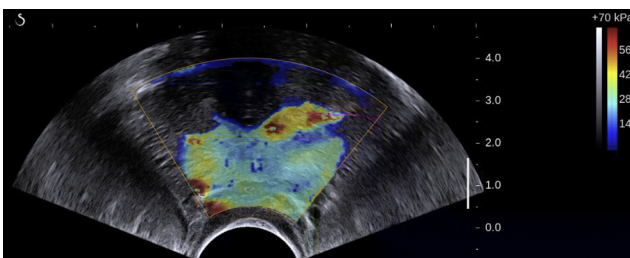


Figure 7. A 53-year-old man with PSA values of 5.5 ng/mL and a prostate volume of 88 mL. As the prostate was very large, shear wave elastography did not allow analysis of the anterior part of the gland because this region was too far away from the transducer (attenuation effect).

Conclusion

Ultrasound elastography brings in a new parameter – tissue stiffness – which provides additional information for

detecting prostate cancer and guiding biopsies. Elastography provides greater sensitivity for detecting prostate cancer and exhibits a high negative predictive value, ensuring that few cancers are missed in the peripheral zone of the prostate. Elastography should become an additional method of examination of the prostate to complement traditional transrectal ultrasound imaging and MRI, and this method could eventually become as routinely used as colour Doppler. However, this technique does require a learning curve (mainly for quasi-static technique as the operator is the one inducing tissue deformation by applying alternative pushes with the transducer), so that the user becomes familiar with the characteristics and limitations of the technique used, in order to produce a correct diagnosis.

In the future, elastography should include volumetric elastography of the prostate (3D), which will only be possible with shear wave techniques, and volumetric fusion with other imaging methods such as MRI. These new techniques should improve guiding capabilities in order to target biopsies to the most suspicious zones. Better detection

of prostate cancer and assessment of its aggressiveness remain essential for developing focal treatment to improve patients' quality of life.

Disclosure of interest

Professor Correas is a speaker, expert and member of the scientific board of Toshiba MS and Philips US, and speaker and expert for the companies SuperSonic Imagine and General Electric.

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