Ultrasound modalities and quantification

Ultrasound modalities and quantification: developments of multiparametric ultrasonography, a new modality to detect, localize and target prostatic tumors

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Purpose of review
An imaging tool providing reliable prostate cancer (PCa) detection and localization is necessary to improve the diagnostic pathway with imaging targeted biopsies. This review presents the latest developments in existing and novel ultrasound modalities for the detection and localization of PCa.

Recent findings
The ultrasound modalities that were very promising on introduction (HistoScanning and Doppler) have shown a wane in performance when tested in larger patient populations. In the meantime, novel ultrasound modalities have emerged in the field of PCa detection. Modalities, such as shear wave elastography (SWE) and contrast-enhanced ultrasound (CEUS) show very promising results. SWE produces an absolute elasticity measure and removes the need for manual compression of the tissue. The former allows comparison between scans and patients, the latter reduces the interoperator variability. Quantification of CEUS enables easily interpretable and accurate imaging of the microvascular changes associated with clinically significant prostate tumors.

Summary
The novel ultrasound modalities of SWE and CEUS imaging open the door for taking targeted biopsies based on the detection and localization of PCa by these novel modalities. This potentially improves PCa detection wherein significantly reducing the number of biopsy cores.

Keywords
contrast-enhanced ultrasound imaging, prostate cancer, shear wave elastography, TransRectalUltraSound

INTRODUCTION

The current standard to diagnose prostate cancer (PCa) is grayscale TransRectal UltraSound (TRUS-) guided systematic biopsies [1]. Grayscale TRUS is not sensitive or specific enough for targeted biopsies and systematic biopsy procedures significantly miss and undergrade tumors [2]. An imaging tool providing reliable PCa detection and localization is necessary to improve the diagnostic pathway [3] and unlock the potential of emerging focal treatment options such as high intensity focused ultrasound (HIFU), cryotherapy and irreversible electroporation (IRE) [4].

Encouraging results have been reported by studies using multiparametric MRI (mpMRI) for the detection of PCa in expert centers. However, issues of costs, availability of MRI and reproducibility of these results outside of expert centers inhibit widespread adoption for now [5]. Various ultrasound modalities have been developed for PCa including Doppler techniques, contrast-enhanced ultrasound (CEUS) and sonoelastography [5]. Recent meta-analyses show improved results of CEUS and

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KEY POINTS

- CEUS quantification improves PCa detection and may decrease the operator dependency by analyzing and processing information from ultrasound data not visible with the bare eye and providing easy-to-read parametric output.
- During external validation with HistoScanning in large patient groups initial results could not be reproduced. Large external validation trials for C-TRUS are not available yet.
- SWE is superior over conventional elastography because of device-regulated compression and an absolute output value, allowing for interpatient and intrapatient comparison of results. The results of the first clinical trials are encouraging.
- CEUS quantification develops quickly and initial results show that very high sensitivities and specificities can be achieved.

elastography over conventional grayscale TRUS [6▪,7▪].

Quantification techniques are being developed for different ultrasound modalities [8,9]. These software-based tools use either the raw or video data to extract parameters that help differentiate malignant from benign tissue. Several features of the quantification techniques potentially enable them to increase the sensitivity for the detection of PCa. An important advantage is that quantification techniques can display differences that are normally too subtle to distinguish with the human eye. Parameters or even the probability of tumor presence can be displayed in easily interpretable color-coded maps, potentially decreasing operator dependency. In this review, we will provide an overview of the latest advances in the different ultrasound quantification techniques that are aimed at aiding detection and localization of PCa.

HistoScanning

HistoScanning is a technology that uses statistical features in the raw ultrasound data to distinguish malignant from benign tissue. Braeckman *et al.* [10] presented the first results on detection of PCa using HistoScanning in a small population of 14 patients scheduled for radical prostatectomy. They detected PCa with 100% sensitivity. In a subsequent study, Braeckman *et al.* [11] presented sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 100, 81, 80 and 100%, respectively, for lesions at least 0.5 ml. Simmons *et al.* [12] screened 51 patients with PCa, scheduled for radical prostatectomy. For lesions at least 0.2 ml they reported values for sensitivity, specificity, PPV and NPV of 90, 72, 82 and 83%, respectively. In the latest study in 198 patients, the performance values for lesions at least 0.5 ml dropped to 40, 73, 33 and 79%, respectively [13▪]. Finally, HistoScanning was compared with TRUS-guided biopsies and transperineal template prostate biopsies [14▪]. In the first case the cancer detection rates were 62.5% (TRUS-biopsies) and 38.1% (HistoScanning). In the second comparison the detection rates were 54.4% (transperineal template prostate biopsies) and 14% (HistoScanning). The methodology of HistoScanning seems to lack robustness, the sensitivity and specificity reduced significantly after implementing the technique in other centers.

Computerized-TransRectal UltraSound

Computerized-TransRectal UltraSound (C-TRUS) was first mentioned in 1990 [15] as a technology to distinguishing malignant from benign tissue using an artificial neural network. The input neurons consisted of six statistical features derived from the grayscale ultrasound images. The output neurons of the neural network indicated the tissue as benign/malignant and the Gleason grade. The neural network connecting the input and output neurons has at first been trained using 53 samples chosen from five patients [16]. In the remaining 500 samples, C-TRUS showed a sensitivity and specificity of 79 and 99%, respectively. In the latest study, Strunk *et al.* [17] combined C-TRUS with mpMRI in a population of 20 patients with elevated prostate-specific antigen (PSA). C-TRUS detected suspicious lesions in 20/20 patients whereas mpMRI detected suspicious lesions in 17/20 patients. In merely 11/19 patients PCa was found by targeted biopsies. This implies a PPV of 58% for C-TRUS targeted biopsies. The robustness of C-TRUS still remains to be established in larger populations.

Doppler TransRectal UltraSound

In 1989, color Doppler TRUS entered the armamentarium of ultrasound quantification techniques [18]. Doppler imaging quantified the vasculature in the prostate to detect and localize prostate tumors based on the development of neovessels around the tumor (angiogenesis). Halpern and Strup [19] compared grayscale ultrasound, color Doppler and power Doppler in the detection of PCa. They concluded that Doppler ultrasound did not reveal PCa with sufficient accuracy to avoid systemic biopsies.

Sauvain *et al.* [20▪] investigated the value of power Doppler TRUS in the detection of low-risk

PCa. In a study of 243 patients scheduled for prostate biopsies with a PSA level less than 10 ng/ml and negative digital rectal examination, 106 patients presented cancer. The authors found a 45% sensitivity and 74% specificity in diagnosing low-risk cancers. Tsai *et al.* [21] measured parameters such as the end-diastolic blood flow velocity (EDV) and the resistive index at each neurovascular bundle site. In a group of 292 patients EDV and resistive index showed comparable diagnostic performance [area under the curve (AUC) = 0.687 and 0.657, respectively]. These were less than that of PSA (AUC = 0.812). At a cutoff value of 4.5 ml/s EDV showed a 65.5% sensitivity and 66.7% specificity. The sensitivity and specificity of resistive index was 71.5 and 60.3%, respectively, at a cutoff of 0.71. The potential of Doppler TRUS for detecting PCa appears to be hampered. This is probably the result of the limited resolving power of Doppler TRUS.

(Shear wave) elastography

Ophir *et al.* [22] have coined the term elastography in 1991. Elastography is based on the principle that soft tissue deforms more than hard tissue when pressure is applied. Lesions in prostatic tissue can then be identified as regions with different stiffness values [23▪]. A recently published meta-analysis of seven studies compared elastography with radical prostatectomy specimens and found a pooled sensitivity and specificity of 72 and 76%, respectively [7▪]. With shear wave elastography (SWE), two shear waves are created by focusing a pushing beam at different depths (see Fig. 1). The propagation of these shear waves is related to the local elastic properties. With SWE, quantitative elasticity (Young's modulus in kPa) maps of the tissue are constructed. A major advantage of SWE is that no pressure needs to be applied by the operator to induce deformation of the prostatic tissue.

Only a limited amount of data are available for SWE. Correlating SWE and sextant biopsy results in 53 men, Barr *et al.* [24▪▪] found a 96% sensitivity, a 96% specificity, a PPV of 69% and an NPV of almost 100% using a cutoff of 37 kPa. Young's modulus was significantly higher in areas with malignant tissue compared with areas with atypia or inflammation. In a similar study among 50 patients, Ahmad *et al.* [25] found sensitivities and specificities of 90 and 88% in patients with PSA less than 20 ng/ml and 93 and 93% in patients with PSA more than 20 ng/ml. They did not mention the cutoff used, but based on the estimated stiffness in benign (74.9 ± 47.3 kPa) and malignant tissue (133.7 ± 57.6 kPa), it can be expected to be much higher than that used by Barr *et al.* The data of Ahmad *et al.* also suggest a relationship between Young's modulus and the Gleason grade. In a third study of 87 patients, Woo *et al.* [26] found a sensitivity of 43%, a specificity of 80.8%, a PPV of 13.5% and an NPV of 94.8% at a cutoff value of 43.9 kPa. They also showed a linear trend between Young's modulus and the Gleason grade and significantly higher stiffness values in aggressive tumor. Finally, in a study of 60 patients scheduled for radical prostatectomy, Boehm *et al.*

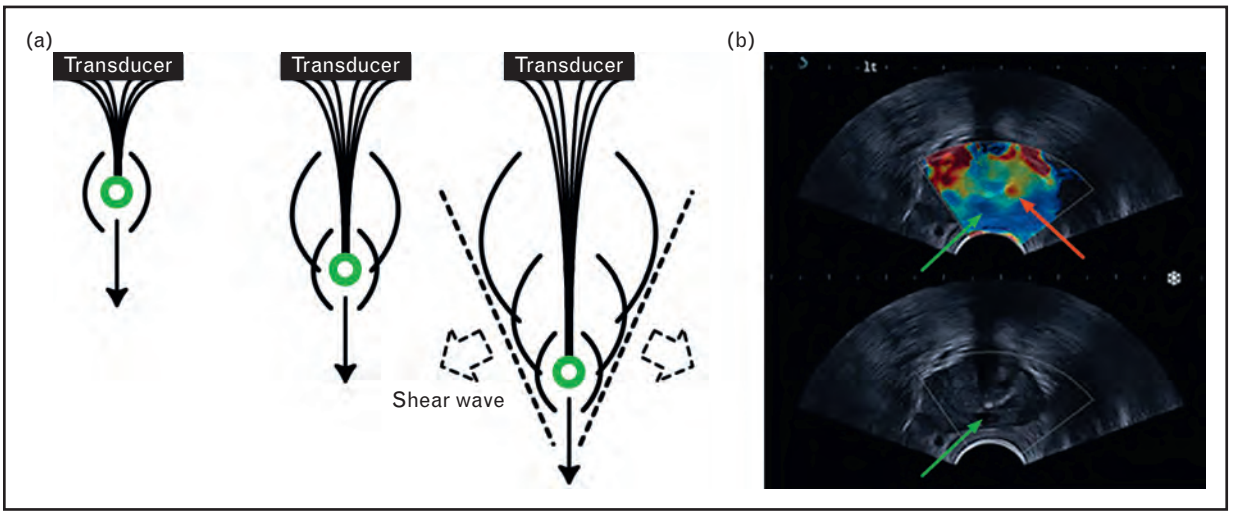

FIGURE 1. (a) Schematic representation of the physical principles of shear wave generation in biological tissue. (b) Comparison of ultrasound and shear wave elastography (SWE). This patient presented with a hypoechoic nodule on ultrasound (black lesion with arrow). SWE was preformed, and the nodule was found to be of low stiffness (G20 kPa). Note the blue area with a green arrow. However, another lesion was found with a high stiffness (75 kPa) and was found on biopsy to be PC with Gleason grade 7. Note the red lesion with a red arrow.

[27▪] showed an 81% sensitivity, a 69.1% specificity and an AUC of 0.692 at a cutoff of 50 kPa. They could not show a relation between the Young's modulus and the Gleason grade. The evidence for SWE thus comes from three well designed biopsy studies and an important first comparison between radical prostatectomy specimens and SWE imaging of the entire prostate, not just typical regions. All studies did demonstrate that the Young's modulus of PCa is significantly higher than that of benign prostatic tissue. Although the cutoff value for an adequate distinction between PCa and benign tissue is still undetermined.

Contrast-enhanced ultrasound

In CEUS, a highly echogenic intravascular ultrasound contrast agent (UCA) is used. UCAs consist of gas-filled microbubbles that are stabilized by a protein or lipid shell. These microbubbles have a diameter of 2–8 μm, allowing them to pass through the microvasculature [28,29]. UCAs were first used in combination with Doppler ultrasound imaging, whereas the microbubbles functioned as additional scatterers in the bloodstream. One drawback of this method is the high-mechanical index used by Doppler ultrasound, causing premature bursting of the bubbles [9]. Newer CEUS techniques exploit the oscillations of the microbubbles that occur under low-mechanical index ultrasound. These nonlinear oscillations can be separated from the linear tissue reflections using techniques such as harmonic imaging, pulse inversion, amplitude modulation and contrast pulse sequencing, allowing visualization and quantification of blood flow [9].

PCa tumors require increased blood supply provided by angiogenesis to progress beyond the size of 2 mm and develop into a clinically significant tumor [30▪▪]. The angiogenic vessels are small and typically exhibit an irregular, tortuous architecture and altered, leaky, endothelial lining causing irregular blood flow. It is these alterations in tumor vascularity and microvascular flow patterns that are targeted by CEUS and associated quantification techniques. In a 2013 meta-analysis (16 studies, including 2624 patients) on the diagnostic performance of CEUS, Li *et al.* [6▪] found a pooled sensitivity and specificity of 70 and 74%, respectively. As the different enhancement patterns between benign and malignant tissue may be subtle, the learning curve is considerable and the potential of human interpretation is limited. Goossen *et al.* [31] attempted to quantify perfusion by measuring contrast-enhanced power Doppler ultrasound enhancement patterns in 29 patients scheduled for radical prostatectomy. They plotted time–intensity curves (TICs) by assessing how many pixels in a given region-of-interest (ROI) were enhanced as a function of time after UCA injection. By assessing the time to maximal enhancement they were able to correctly identify the side of the major tumor focus in 78% of the patients. In 2010, Zhu *et al.* [32] found that shorter arrival time and time to maximum enhancement correlated with higher tumor grade in the biopsy results of 103 patients.

One of the UCA manufacturers (Bracco Suisse SA, Geneva, Switzerland) is developing dedicated software (VueBox) to extract and analyze perfusion characteristics from CEUS imaging for use in various organs including the liver [33]. This software allows plotting of perpixel TICs and parametric maps extracted from the TICs (Fig. 2). Using a prototype of this software, Jung *et al.* [34▪] noted suspicious and unsuspicious sectors in the CEUS recordings of 20 patients scheduled for radical prostatectomy. Twenty-nine and 25 of the 34 tumor foci could be identified by evaluating the mean transit time (time between 50% levels of wash-in and wash-out phase of the TIC) and rise time (time range of UCA influx), respectively. Thirty tumors were found by assessing early enhancement, resulting in an 88% sensitivity and a 100% specificity.

In the current version of this prototype software, probability maps for PCa presence can be generated based on histograms of wash-in-rate values (maximum slope of the TIC) calculated in small ROI around each pixel. Statistical measures such as the mode and SD are determined from the histograms. Correlation with histopathology specimens revealed that PCa can be differentiated from benign tissue based on mode and SD values [35].

Instead of quantifying perfusion parameters, Mischi *et al.* [36▪▪] focus on the dispersion kinetics of the UCA as the injected bolus moves through the prostate, a method called contrast-ultrasound dispersion imaging (CUDI). The rationale behind this approach is that on the microvascular level, the properties of the angiogenic microvasculature associated with malignancy on perfusion are unpredictable. The high microvessel density and arteriovenous shunts promote increased perfusion whereas the tortuosity, aberrant endothelial lining and higher interstitial pressure in tumors have a negative effect on perfusion. Dispersion on the other hand is predictably lower because of the less efficient, irregular structure of the angiogenic microvascular network within the malignant tissue. Originally, Kuenen *et al.* [37] used a mathematical model to estimate a parameter (κ) related to dispersion by analysis of each pixel's TIC. They performed a pilot study using five datasets from four patients comparing this method with a malignant ROI and a benign

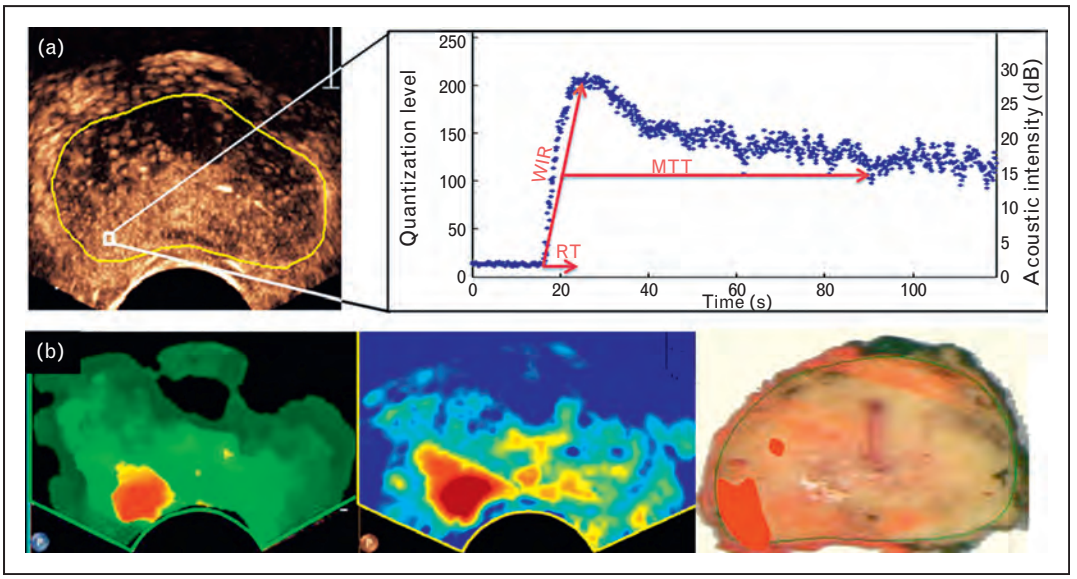

FIGURE 2. (a) Example of a time–intensity curve (TIC) for a given pixel. WIR, wash-in-rate; MTT, mean transit time; RT, rise time. (b) Left: example of a probability map (red indicates a high suspicion) generated by dedicated software under the development of Bracco Suisse SA that analyzes the dispersion of WIRs among neighboring pixels. Middle: contrast-ultrasound dispersion imaging (CUDI) map indicating a region of similarly shaped TIC's, suspicious for prostate cancer (PCa) presence (marked red). Right: histopathological examination of the same plane confirmed PCa presence in the right peripheral zone (marked red).

ROI determined by histopathological examination after radical prostatectomy. They found a perpixel sensitivity and specificity of 81 and 84%, respectively. In 2012, the benefits of including the available spatial information were explored. This method is based on the observation that low UCA dispersion within an area correlates with more similarly shaped TIC's for the pixels within that area. In their initial validation, Mischi *et al.* [36▪▪] used the preoperative scans and histopathological examination of five prostates to assess whether they could discriminate benign from malignant tissue by evaluating the coherence between TICs as a measure of similarity. The maximum AUC was 0.82. In two subsequent publications, Kuenen *et al.* [38▪,39▪] describe a refinement of the coherence method and a new method that evaluates the correlation between the TICs. The results of validations in a dataset of 12 patients were AUCs of 0.88 and 0.89, respectively. Additionally, the authors demonstrated the progress made by using the same dataset to compare the new methods with the initial coherence method described by Mischi *et al.* [36▪▪] (AUC = 0.82) and the original method requiring the mathematical model [37] (AUC = 0.70). The validation dataset was then expanded to 43 planes in 24 patients from two centers showing a comparable performance, with AUC of 0.88 [40]. The latest work by this research group, by Mischi *et al.* [41] presents a new similarity measure called mutual information analysis and a clinical validation in 26 datasets from 15 patients resulting in an AUC of 0.92. The small time interval between subsequent publications on new methods and major refinements of existing methods (months rather than years) reflects the rapidly ongoing developments in CEUS quantification. Currently all available evidence comes from small datasets that are mostly acquired in a single center. Moreover, the studies often correlate predefined benign and malignant areas of the prostate with imaging instead of classifying the entire prostate (divided in sectors) with imaging. For definitive establishment of the value of these techniques and their uptake in routine clinical practice, large, well designed validation trials are therefore still needed.

FUTURE

Validation of ultrasound quantification techniques in large multicenter studies opens the door toward targeted biopsies instead of the regular 12–16 systematic biopsies. The parametric maps derived from CEUS and/or SWE need to be fused with real-time TRUS to identify suspected regions and immediately take targeted biopsies. An interesting prospect is the combination of ultrasound techniques and the first steps toward 'multiparametric ultrasound' have been undertaken and show improved results [42▪,43].

Reliable and easy-to-interpret ultrasound-based imaging makes it possible to take targeted biopsies in a single session, by the (office-based) urologist, wherein achieving improved detection and grading compared with systematic biopsies. Furthermore, cost-effective imaging for the targeting of (focal) treatment and follow-up would be made possible.

CONCLUSION

The recent developments in ultrasound quantification techniques, such as for CEUS and SWE, provide a realistic opportunity to make systematic biopsies obsolete.

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Conflicts of interest

P.F. is Bracco Suisse SA, Geneva, Switzerland employee. The remaining authors have no conflicts of interest.

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