IMAGING MODALITIES IN FOCAL THERAPY: MULTIPARAMETRIC ULTRASOUND

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Summary.- OBJECTIVES: Prostate cancer (PCa) is the most common form of cancer among men in the US and the second most common cause of death. It has been observed that an increasing number of newly diagnosed patients exhibit low-risk features and that overtreatment with radical prostatectomy is a growing problem. The feasibility of focal therapy as an organ-sparing alternative, however, depends on the reliability of imaging techniques to identify, localize and monitor clinically relevant PCa lesions. The aim of this review is to investigate the potential of multiparametric ultrasound (mpUS) for focal therapy.

METHODS: We briefly introduce the most common focal therapies and thoroughly discuss the ability of available ultrasound modalities to localize PCa and reflect tissue properties. The imaging requirements of the focal therapies are studied to put the performance of the US techniques into perspective.

RESULTS: We found that transrectal greyscale echography, Doppler sonography, elastography, contrast-enhanced ultrasonography and computerized ultrasound have been studied for the purpose of prostate imaging. Several of these modalities are already frequently used in current clinical practice; to add to the diagnostic process of PCa, to guide and monitor the application of focal therapy or to perform follow-up after treatment. Despite their capability to detect a large fraction of the PCa lesions, none of these modalities is currently considered sufficiently accurate for stand-alone tumour detection and localization. However, although there are only few studies reporting on a combined use of different ultrasound modalities, the results of an mpUS approach seem promising.

CONCLUSION: Several US modalities have been successfully applied as a viable alternative to monitor tissue destruction during and after treatment. In view of the advantages of US and the promising results of a multiparametric approach in PCa detection and localization, researchers are urged to further investigate mpUS for therapeutic purposes.

Keywords: Prostate cancer. Ultrasonography. Multiparametric ultrasound. Focal therapy. Tumour localization.

Resumen.- OBJETIVOS: El cáncer de próstata es la forma de cáncer más común en hombres en los EEUU y la segunda causa más frecuente de muerte. Se ha observado que un número creciente de pacientes de nuevo diagnóstico presentan características de bajo riesgo y que el sobretratamiento con prostatectomía radical es...
According to recent statistics, prostate cancer (PCa) is the most prevalent form of cancer among American men, accounting for 26% of the new cases and nearly 10% of the cancer-related deaths each year (1). The introduction of the prostate-specific antigen (PSA) blood test led to a rapid increase of the yearly number of PCa diagnoses in the last decade of the 20th century. As a consequence, the percentage of patients with an early-stage, low-risk disease has grown dramatically (2).

Currently, PSA assessment and digital rectal examination (DRE) are utilized as early-diagnostic tools. Due to the low positive predictive value of these techniques, there is a high risk of over-diagnosis (3). We therefore fully rely on systematic biopsy for the definitive diagnosis of PCa, even though there are some concerns with this procedure: an increasing number of patients with complications leading to hospitalization has been reported (4) and malignancies are found in a large fraction of the negative-biopsy patients that underwent repeat biopsy (5). Transrectal ultrasound (TRUS) imaging is frequently employed to assist in diagnosis or guide needle-biopsies (6), but no imaging technique currently has sufficient negative predictive value to alleviate the need for systematic biopsy.

Patients diagnosed with prostate cancer are most commonly treated with prostatectomy. Although a lower mortality was observed for patients undergoing prostatectomy versus watchful waiting in a follow-up study of two decades (7), it has been reported that over-treatment is a growing problem due to the increasing portion of the PCa cases with low-risk features (2). Moreover, some cancers are not likely to become life-threatening during the lifetime of the patient. Since there is a substantial risk of side-effects as a result of radical prostatectomy (urinary incontinence, erectile dysfunction and bowel toxicity, etc.), there is a growing demand for focal therapy (8).

It remains difficult, however, to identify patients who should be referred for focal therapy (9). Apart from the classic PCa risk stratification criteria (e.g. Gleason score, cancer volume and PSA level) and the general health of the patient (e.g. life expectancy and comorbidity), the cancer topography is of major importance to decide whether a patient qualifies for focal treatment (10). The fact that PCa is generally a multifocal disease of which the clinically significant foci are difficult to detect thus emphasizes the need for highly accurate imaging tools. The focal, organ-sparing approach requires a very accurate localization of the malignancies for the diagnosis, targeting of treatment and guidance. Moreover, it is always combined with active surveillance of the (untreated parts of the) prostate afterwards (9,10).

In this paper, we review the potential of ultrasonic imaging modalities in focal therapy of the prostate. The latest guidelines on focal therapy still...
define transperineal template mapping biopsies as the gold standard for patient characterization (11). Since this procedure involves the removal of 80.7 cores on average (9), the first aim of dedicated imaging technology is to reduce biopsy-related complications. Secondly, more accurate visualization is expected to improve the effectiveness of focal treatment.

The most recent guidelines for trials refer to multiparametric magnetic resonance imaging (mpMRI) as the main tool to select suitable patients (12). Indeed, promising specificities (82%-92%) and negative predictive values (65%-94%) were reported in mpMRI studies (i.e. T2-weighted MRI in combination with diffusion weighted imaging and/or dynamic contrast-enhanced MRI) (13). It is in view of this, that we would like to consider a multiparametric ultrasound (mpUS) approach. A recent review on the subject reveals that mpUS is not widely studied yet, but that early results are encouraging (14). Apart from its value as a real-time imaging tool during the treatment itself, mpUS might serve as a cost-effective and safe diagnostic tool to select patients for focal therapy and to plan the treatment procedure.

2. MODALITIES IN FOCAL THERAPY

Focal therapy includes lesion-targeted therapy, hemiablative therapy, or subtotal gland therapy, sparing at least one neurovascular bundle of the prostate. We briefly discuss the most applied techniques used: high-intensity focused ultrasound, cryotherapy, photodynamic therapy, radiation therapy, focal interstitial laser thermotherapy and irreversible electroporation. The main principles of these techniques are explained, along with the imaging requirements they pose for effective treatment.

2.1. High-intensity focused ultrasound

In High-intensity Focused Ultrasound (HIFU) tightly focused ultrasound waves of high intensity (i.e. >5 W/cm²) are used to selectively ablate cancerous tissue due to coagulation necrosis and cell disruption, which occurs at temperatures above 56°C (15). Currently, three transrectal HIFU devices are commercially available: Ablatherm and FocalOne (EDAP TMS, Lyon, France) as well as Sonablate (SonaCare Medical, Charlotte, NC, USA). These devices contain treatment and imaging transducers within one probe, which enables visualization during treatment. Unfortunately, TRUS does not always show a precise delineation between treated and untreated regions (10). Since one of the cell destruction mechanisms is coagulation necrosis, tissue perfusion carries substantial information about the results of the induced treatment. Another piece of information that HIFU could benefit from is the temperature distribution during treatment. Assessment of HIFU performance showed that it is a successful treatment of local prostate cancer with a low morbidity, low PCa-specific mortality rate and high metastasis free survival rate (15). Moreover, technological improvements in the device resulted in decreasing rates of incontinence. The advantages of HIFU are that it can be repeated and that it can be used as a residual therapy after radiation therapy.

2.2. Cryotherapy

Cryotherapy involves the destruction of tissue via freezing, which requires a temperature lower than -40°C imposed for at least three minutes. This is achieved with a cryogen, that is, a gaseous or liquid freezing agent, which is transperineally delivered with cryoneedles (15). The first application of cryotherapy for PCa was reported in 1964. However, first-generation devices were associated with high patient morbidity (10). Current generation’s cryosurgery involves ultrasound guidance during treatment, urethral warmers as well as active thawing of tissue subsequently to its freezing, which results in more precise treatment and reduction of secondary tissue damage (15). Recent reports show encouraging results: a study performed between 2002 to 2011 on 73 patients with low-intermediate risk tumour showed tumour recurrence in 12 patients in the untreated lobe of the prostate, and 1 in the treated. Continence was completely preserved in all patients and 86% were documented to have potency sufficient for intercourse (16). In another case study cryotherapy was used as salvage treatment in prostate cancer recurrence after radiotherapy (17). No cancer-related deaths were exhibited in a 33.5 months follow-up and incontinence and erectile dysfunction were observed in 13% and 86% of patients, respectively. On the whole, cryotherapy could benefit from real-time temperature maps, as well as perfusion information.

2.3. Photodynamic therapy

Photodynamic therapy uses a drug (photosensitizer) that can be activated by light of a specific wavelength within the photosensitizer’s absorbance band. When the drug is activated it forms reactive species with oxygen, which damage the cells in the irradiated volume either directly (tissue photosensitizer) or with the induction of vascular stasis (vascular photosensitizer) (10). Tissue photosensitizers take time to accumulate in the tissue. Some of them concentrate preferentially in the tumour region (15). The tissue photosensitizer and light are administered
in two separate sessions with several days in between. Moreover, this type of photosensitizer is washed out of the body slowly. Vascular photosensitizers are activated while they are in the vasculature; therefore the drug and light are administered in the same session, and the drug is washed out of the body fast. Examples of photosensitizers are Cremophor, which was used earlier, and a more recent development TOOKAD Soluble. Generally, low-power laser light is directed to the treatment site through fibres using the transperineal approach. An important limitation of PDT is that some prostate cancer cell lines (PC3, DU145) that survive light insult proliferate, migrate, and invade faster than before, emphasizing that non-optimal PDT can cause tumour recurrence (18). In addition to PSA testing and examination, further MRI and ultrasound studies are recommended to assess the treatment effects.

2.4. Radiation treatment

2.4.1 Brachytherapy

Brachytherapy is a technique in which a radioactive material is either temporarily or permanently implanted at the tumour location or in its close proximity. The placement of implants is performed transperineally, conventionally under ultrasound guidance. Temporary implants usually involve the placement of a catheter or slide, which is then filled with radioactive material. These types of implants are used for fractioned therapy, when the dose is administered in several fractions. Permanent implants are usually shaped as needles or seeds and are installed permanently in the prostate (10).

There are two types of brachytherapy according to the intensity of irradiation: low dose (iodine-125, palladium-103), or high dose (iridium-192, cobalt-60). The latter technique is more promising: a number of studies provide evidence for the efficacy of dose escalation in prostate cancer, and mature results from randomized trials show that control of disease improves with increasing radiation dose (19).

2.4.2 External beam therapy

External beam therapy (EBT), also called external radiation therapy, is a method for delivering one or several X-ray beams to the tumour area. Beams are generated outside the patient (usually by a linear accelerator) and are targeted at the tumour site. These X-rays can deposit a specified radiation dose in the area of the tumour to destroy the cancer cells and, with careful treatment planning, spare the surrounding normal tissue (10). Sometimes EBT is combined with brachytherapy: a randomized trial showed that the relapse-free survival was significantly higher for the patient group that was exposed to EBT and high dose brachytherapy compared to the group exposed to EBT alone (20). EBT is usually performed under surveillance of computed tomography (CT) (10).

2.5. Interstitial laser thermotherapy

During focal interstitial laser thermotherapy (ILT), radiant energy is delivered to the target tissue via transperinially inserted MRI-compatible quartz fibres of 300 to 600 μm in diameter. This energy is absorbed by tissue, heating it up and causing coagulative necrosis. Irreversible protein damage occurs quasi-instantaneously at around 60°C, whereas temperatures between 42°C and 60°C require a longer heating period for tissue destruction (10). One of the recent studies showed that 7 out of 9 patients had no cancer recurrence 6 months after a MR-guided ablation procedure, while 2 had a Gleason 6 grade cancer due to suboptimal targeting (21). This underlines the need for accurate imaging. As for morbidity, average urinary and sexual function scores were not significantly affected by the treatment. Therefore, ILT proves to be effective, when the treatment planning is performed correctly. ILT could benefit from temperature monitoring, as well as perfusion visualization.

2.6. Irreversible electroporation therapy

Electroporation is the process in which electric pulses are used to create nanopores in the cell membrane, allowing surrounding molecules to enter the cell. Depending on the electric field magnitude, pulse duration and number of pulses the induced electroporation can be reversible or irreversible. In the latter case, the cells die due to their inability to maintain homeostasis (10). Irreversible electroporation (IRE) therapy makes use of transperineally inserted electrodes at the margin of the tumour area to induce this cell death mechanism. Angiodynamics Nanoknife System (Angiodynamics, Latham, NY) is the first available technological platform performing IRE. Typically, 90 pulses of 3000 V, lasting from 20 to 100 μ, are delivered to the patient. Treatment planning is based on preplanning ultrasound and MRI. Electrode placement is generally conducted under TRUS guidance and follow-up performed with mpMRI and with contrast-enhanced ultrasonography (CEUS) (22). Initial results are promising in terms of preservation of potency and continence due to high sparing capabilities of this technique. Suspicious residual disease was only reported in 6 of the 34 treated patients (23).
3. ULTRASOUND MODALITIES

3.1. Greyscale transrectal ultrasound

Since the 1980s, transrectal ultrasound (TRUS) has been used to assist in the diagnosis and treatment of PCa, mainly to evaluate the disease, to guide needle-biopsies or to assist in the application of focal therapy (6). As the development of TRUS-guided biopsies coincided with the widespread introduction of PSA testing, its contribution to the advances in PCa diagnoses and treatment is easily underestimated (10). TRUS-guided biopsy in TRUS suspicious lesions, for instance, is highly recommended in most diagnostic guidelines (5).

Despite undergoing many improvements since its first application in PCa, greyscale TRUS images alone are not considered a reliable diagnostic tool to detect PCa. Although predominantly hypoechoic, a large fraction of the prostate malignancies are found to be isoechoic (6). It has been estimated that only about 60% of the lesions is visible on greyscale TRUS scans and, accordingly, the use of this modality for PCa diagnosis was reported to have positive predictive values from 53% to 91% in trade-off with negative predictive values ranging from 11% to 79% (14). An additional problem of greyscale TRUS is that other prostatic diseases and abnormalities (e.g. benign prostate hyperplasia and prostatitis) also appear as hypoechoic, which drastically reduces the sensitivity and positive predictive value of the diagnosis (6).

In the past few years several computer-aided diagnosis techniques have been developed to eliminate the differences among observers and retrieve diagnostic information from the TRUS images that is difficult to find with the human eye. These methods perform spectral analysis on the returning echoes for tissue characterization. An artificial neural network approach called C-TRUS achieved an accuracy of 79% in detecting pathology-confirmed PCa lesions (24). Since then, the technique has not only been evaluated at site, but also in a multicentre study, showing that the technique is able to detect some clinically relevant tumours even when systematic biopsy returned negative (25). In addition, a computer-aided diagnosis program called HistoScanning™ was developed. Although small sample results were promising, retrospective analyses revealed that HistoScanning™ did not have a sufficiently high reliability in tumour detection and did not recommend its use in routine clinical practice (26).

Although MRI is the main modality for the preplanning in focal therapy, real-time TRUS has been successfully practiced during most therapeutic procedures. Being more cost-effective and practical, also taking into account the expensive MRI-compatible equipment, the insertion of needles, fibres, etc., is usually US-guided. It also allows clinicians to correct the protocol when the prostate deforms due to the insertion of the transducer or swelling during treatment. Most HIFU-devices provide real-time TRUS monitoring and fuse these images digitally with pre-acquired MR data (10,15). There have been tests assessing the real-time treatment effect of HIFU by looking at the change in US backscattered signals (27). In follow-up, TRUS images are mostly used to measure the shrinking of the prostate (10).

3.2. Elastography

Elasticity is a valuable characteristic of biological tissues. Being the main quantity assessed during DRE, the fact that prostatic carcinoma is generally stiffer than healthy tissue has been used for centuries. It has also been observed that the elasticity scales with tumour grade (i.e. Gleason score) and that a stiffness measure might be used to distinguish PCa from other abnormalities in the prostate such as benign prostate hyperplasia, which generally has a higher elasticity (i.e. lower stiffness) (28).

It is possible to assess the tissue stiffness using ultrasound, but since the bulk modulus governing ultrasound propagation is almost homogeneous over all tissue, special protocols are required to map the elasticity. We distinguish quasi-static methods, in which the stress is manually delivered to the tissue, and dynamic methods, in which shear waves are produced (28). In both techniques tissue displacement is assessed to estimate the strain.

Quasi-Static Elastography (QSE) such as strain elastography is easier to implement, but it is limited to superficial organs and does not allow comparison between patients as its elasticity estimations are relative. Since the stress is applied by gentle, cyclic compressions of the clinician, this method has the drawback of being highly operator-dependent and exhibiting a considerable learning curve, just like DRE (28). After promising clinical results of QSE in the first decade of this century (29), meta-analysis on the accuracy of QSE revealed an appreciable specificity (60%-95%) and sensitivity (71%-82%) (30). Analysis on its use in targeted biopsy (31) and its value for real-time diagnosis (32) found similar specificity (79%-76%), but lower sensitivity (62%-72%), and emphasized the lack of standardized protocols. As for Shear Wave Elastography (SWE), the transrectal ultrasound probe is used to generate a shear wave by the acoustic radiation force of a focused beam. This wave travels more slowly through the body than
regular US signals and ultrasonic assessment of its propagation speed allows us to approximate the Young’s modulus of tissue (28). The evaluation of this technique for the localization of PCa is still in an early phase, but the available studies indicate that SWE yields both a higher sensitivity (90%-96%) and specificity (88%-96%) (14).

The performance of QSE was found inferior to MRI in the visualization of the treatment effect immediately after HIFU treatment (33), but the potential of SWE is still under investigation (10).

3.3. Doppler sonography

Doppler sonography visualizes (blood) flow in tissue by analysis of the Doppler shift in the spectrum of the echo data. Traditionally, colour Doppler ultrasonography (CDU) and power Doppler ultrasonography (PDU) are distinguished. In CDU, the velocity and direction of the flow are shown in shades of red and blue, normally, to representing (angle-dependent component of the) flow toward and away from the transducer. PDU depicts the power of the Doppler signal, which usually correlates with number of cells (scatterers) moving in the sample volume. Therefore, it is not sensitive to aliasing and less dependent on the measurement angle than CDU (34).

Exploiting the fact that PCa displays angiogenesis before developing to clinical significance, an observable increase in vascularization has been suggested as an indicator of PCa (35). However, studies indicate that feasibility of Doppler imaging in PCa diagnosis is rather limited, which is attributed to its inability to detect the small flows in microvasculature (34). The application of contrast-enhanced Doppler imaging (36) or the use of high-frequency Doppler to increase the sensitivity for smaller flows (37) were not found to have increased added value for targeted biopsies. Moreover, none of these studies saw a demonstrable benefit from PDU over CDU (34,36,37). Nevertheless, the value of Doppler, especially PDU or its three-dimensional application, was demonstrated in a number of more recent studies (14).

Reported use of Doppler imaging in focal therapy include multiple studies on cryoablation, in which colour Doppler was used to select areas with abnormal flow for biopsy prior to and after treatment (9). Moreover, contrast-enhanced Doppler has been used to monitor the affected tissue volume after HIFU treatment (38).

3.4. Contrast-enhanced ultrasound

Alternatively, one can assess the PCa-characteristic proliferation of neovasculature using CEUS, which is even able to visualize flows below the resolution of PDU. To this end, microbubble contrast agents (CAs) are intravenously injected. These CAs do not leave the blood stream, pass through the circulation and enhance the acoustic signal in the microvessels, allowing a very accurate visualization of the perfusion. CAs are particularly well imaged by harmonic imaging techniques and, as already mentioned, also contrast-enhanced Doppler can be performed. In dynamic CEUS, microbubble bursting is prevented by using low-energy US pulses (39). On the other hand, microbubble bursting can also be exploited by the so-called flash-replenishment imaging. Here, after bubble destruction with a high-energy ultrasound pulse, CA refilling of the (micro)vessels is visualized to estimate perfusion (36).

Some promising studies have been published on the use of CEUS to detect PCa (14). A meta-analysis on CEUS, in which the latest results are not included, demonstrated its value in the PCa diagnostic process, but concluded that the technique did not have a sufficiently high accuracy to replace systematic biopsy (40). Another systematic review reported that it is the combination of CEUS-targeted and systematic biopsies that has the most favourable detection rate (41).

In addition, instead of looking at the perfusion itself, dispersion characteristics have been hypothesized to be a good measure for the crucial changes as a result of angiogenesis. In contrast-ultrasound dispersion imaging (CUDI), the local dispersion kinetics of the CA bolus is assessed; either by fitting the time-intensity curves of each pixel by a convective dispersion model (42) or by similarity analysis (43). Both methods yield promising results.

CEUS recordings have been mentioned in many therapeutic modalities as a way to verify tissue destruction. Real-time CEUS monitoring was applied before, during and after ILT, depicting treatment effect in good correspondence with MRI scans (44). In the follow-up of HIFU as well as IRE treatment, CEUS was reported to be a promising tool to visualize viable and devascularized regions (22,45). However, the interference of microbubbles with HIFU should be investigated before allowing immediate repeat of this procedure after CEUS. CEUS has been hypothesized to be a good alternative to gadolinium-enhanced T1-weighted MRI in cryotherapy and PDT as well (10).

4. MULTIPARAMETRIC ULTRASOUND

The limited accuracy of individual ultrasound techniques in localizing PCa lesions is mainly
due to the fact that prostatic carcinomas manifest themselves in very different ways depending on the grade, topography, size and focality. Some are recognizable by increased stiffness (elastography), high perfusion (CEUS), high flows (Doppler), increased microvascularity (dispersion imaging) or anatomical abnormalities (TRUS and computerized TRUS). It has been hypothesized that a combination of these techniques would not only allow us to avoid missing tumours that are undistinguishable in one or the other of these modalities, but also to discriminate malignancies from other diseases that mimic the appearance of PCa in certain US scans. Moreover, it might even allow us to estimate the grade and aggressiveness of the lesions since the different features relate to different stages in the development of PCa.

To this date, however, only few studies looked at the combination of US modalities in PCa localization (14). Based on the results of histopathological examination, the combined greyscale TRUS and CEUS mapping increased the PCa detection rate to 80% compared to 62% and 40% for CEUS and greyscale TRUS alone (46). CEUS scanning of PCa regions that were appointed as suspicious based on real-time QSE led to a decrease in histologically-confirmed false positives, improving the positive predictive value from 65% to 90% (47). Promising results were also reported for a combination of real-time QSE and CEUS for targeted biopsies, showing a higher detection rate than the individual modalities or what can be expected from systematic biopsies (48).

Alternatively, the combination of greyscale TRUS, PDU and CEUS was also shown to increase the over-all PCa detection performance in a 10-biopsy protocol in 150 patients; enhancing the detection rate at cancer sites from 51%, 48% and 73%, respectively, to 82% (49). Similarly, the combination of greyscale TRUS, CDU and QSE for targeted biopsy was found to have superior detection rate compared to the single techniques, with systematic biopsy as reference (50).

Not only the US modalities that are taken into account are different, these studies report on varying study set-ups, imaging settings and outcomes to evaluate the mpUS performance. This makes it difficult to compare the studies and draw general conclusions on the feasibility of mpUS in focal therapy. However, many authors note that the modalities detect different tumours (49) and all of them report general increase in detection rate. Researchers are therefore urged to study mpUS in a more systematic, comprehensive and rigorous fashion. Perhaps, the procedure could be improved by developing a scoring system like in mpMRI or using a computer learning classification algorithm (14). Since learning algorithms might even differentiate between high-risk and low-risk PCa, this would be especially beneficial in patient referral for focal therapy and the planning of treatment.

5. CONCLUSION

A survey on the use of ultrasonic imaging techniques in focal therapy revealed that the entire spectrum of US modalities is widely applied for patient selection, treatment planning, guidance, monitoring and follow-up. Most focal therapies require transperineal intervention, which is usually performed under TRUS guidance. Even though MRI is clearly favoured for treatment planning and patient selection, the actual procedure often relies on ultrasonography as a result of its cost-effectiveness and compatibility with therapeutic devices. The method of monitoring the treatment parameters (temperature, oxygen, perfusion, etc.) varies among therapeutic modalities. For example, MR thermometry is mentioned for both cryotherapy and ILT. Many studies found the use of ultrasound, especially CEUS for the imaging hypovascularized zones, not to be inferior to MRI to measure treatment effect. Moreover, with the development MRI-TRUS fusion techniques, the use of both mpMRI and mpUS is expected to grow compared to systematic biopsy (26).

Though all ultrasonic modalities have been thoroughly studied for their value in the diagnostic procedure of PCa, none of the methods has been shown sufficiently accurate to replace systematic biopsy yet. A recent systematic review on targeted biopsies concluded that there is no clear favourite modality, not even mpMRI, to select biopsy regions based on the detection rate (41). However, the field of prostate imaging is rapidly evolving and increases in the detection performance are expected. For US modalities, especially the advances in three-dimensional imaging, shear-wave elastographic technology and contrast-enhanced image processing are followed with particular interest.

Despite promising first results, there is little literature on a systematic multiparametric approach of US modalities in the localization of prostate tumours. Therefore, it is difficult to speculate about the value of mpUS in focal therapy. Regarding the advantages of ultrasound over MRI (i.e. being more cost-effective, wider available, less time-consuming, more practical, more suitable for perioperative use and more easily combined with therapeutic devices), the frequent use of US modalities in current focal procedures, the introduction of MRI-TRUS fusion and its enhanced performance in multiparametric fashion, we expect
that mpUS will become an increasingly interesting modality in focal therapy.

6. ACKNOWLEDGEMENTS

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7. ABBREVIATIONS

CA Contrast Agents
CDU Colour Doppler Ultrasonography
CEUS Contrast-Enhanced Ultrasound
CT Computed Tomography
CUDI Contrast Ultrasound Dispersion Imaging
DRE Digital Rectal Examination
HIFU High-Intensity Focused Ultrasound
ILT Interstitial Laser Thermotherapy
IRE Irreversible Electroporation
(mp)MRI (multiparametric) Magnetic Resonance Imaging
(mp)US (multiparametric) Ultrasound
PCa Prostate Cancer
PSA Prostate-Specific Antigen
PDU Power Doppler Ultrasonography
QSE Quasi-Static Elastography
SWE Shear-Wave Elastography
TRUS Transrectal Ultrasound

REFERENCES AND RECOMMENDED READINGS

(*of special interest, **of outstanding interest)


