Transrectal contrast enhanced ultrasound for diagnosis of prostate cancer

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TOPIC PAPER

Transrectal contrast enhanced ultrasound for diagnosis of prostate cancer

M. H. Wink · J. J. M. C. H. de la Rosette · C. A. Grimbergen · H. Wijkstra

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Abstract The diagnosis of prostate cancer is based on histology. Prostate biopsies are obtained based on the triad of prostate specific antigen (PSA), digital rectal examination (DRE) and transrectal ultrasound. Because prostate biopsies still have a large percentage of negative outcomes, patient selection and biopsy direction need improvement. This paper describes the recent improvements in prostate cancer imaging, especially contrast-enhanced transrectal ultrasound.

Keywords Ultrasonography · Diagnostic imaging · Contrast media · Microbubbles · Prostate · Prostatic neoplasms

Prostate cancer detection

One in six men is confronted with prostate cancer during his life. This will result in approximately 234.460 new cases and 27.350 deaths in the US in 2006 [29]. Diagnosis of prostate cancer is made based on histological biopsy results. The decision whether or not to take biopsies is dependant on prostate specific antigen levels (PSA), digital rectal examination (DRE) and transrectal ultrasound findings (TRUS). However, the value of each of these investigations is limited. The sensitivity of sextant biopsies based on this triad is reported to be 50–85% [39]. The optimal PSA cut-off level is not yet determined, neither is the optimal amount of biopsies obtained for diagnosis [28, 49]. Several studies state a detection rate in repeat biopsies after initial negative sextant biopsy technique of 10–25% [10, 17]. To enhance sensitivity various extensive biopsy protocols have been evaluated, comparing the golden standard, the sextant biopsies, with up to 21 biopsies in one session. All of these state an increase in detection up to 41%. There seems to be no difference in clinical significance between the cancers found in the sextant and the extensive biopsy protocols. A recent systematic review stated that the optimal balance between detection and complication rate is found in a protocol in which 12 biopsies are obtained [12].

To improve the diagnostic accuracy of these biopsies, it is important to improve the sensitivity and specificity of the investigations based on which the biopsies are obtained. A meta-analysis shows that the PSA-isoforms can reduce the number of unnecessary biopsies, without lowering the detection rate [43]. However, optimal thresholds are not yet determined. DRE is a subjective investigation with a great inter-observer variability [50]. A combination of DRE and PSA displays a higher positive predictive value of positive biopsies than PSA alone [1]; however, this may not be true for the lower PSA ranges [2]. Since the widespread use of PSA leads to early detection of prostate cancer and thus considerably smaller tumour volumes [8, 30], better visualization of the tumour would increase diagnostic accuracy.

TRUS on its own has a low diagnostic accuracy for detection and staging [52]. Adding targeted biopsies in patients with visible lesions on B-mode TRUS to a random biopsy protocol might increase sensitivity for detection of prostate cancer [37]. Colour and power Doppler techniques

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M. H. Wink · J. J. M. C. H. de la Rosette · H. Wijkstra (✉)
Department of Urology (G4-105),
Academic Medical Center, Meibergdreef 9,
1105 AZ Amsterdam, ZO, The Netherlands
e-mail: H.Wijkstra@amc.uva.nl

C. A. Grimbergen
Department of Medical Physics,
Academic Medical Center, Meibergdreef 9,
1105 AZ Amsterdam, ZO, The Netherlands

increase the sensitivity of TRUS, but cannot avoid the necessity of random biopsies [24, 33].

Imaging techniques in the diagnosis of prostate cancer

The visualization of prostatic tumours encounters many limitations. Correlation between ultrasound findings and the presence of malignant tissue is not straightforward. Because of the high incidence of the disease, much research has been and is done to improve visualization of these tumours. Other imaging modalities, such as positron emission tomography (PET), CT and MRI are being evaluated as well as new ultrasound technologies.

CT

CT currently offers no prominent additional value in the diagnosis of prostate cancer, except for staging of the pelvic and distant metastases. The reported sensitivity for lymph node disease, even in patients with PSA levels exceeding 25 ng/ml is around 30% [16]. MRI is replacing CT for this indication.

MRI

In 2000, Wefer et al. [53] stated that endorectal MRI can detect just as much prostate cancers as sextant biopsies. Since biopsies are still required for confirmation and grading, the clinical additional value is not yet known. MRI is mainly used for determining the volume and local extent of prostate cancer. A meta-analysis by Engelbrecht et al. shows a large heterogeneity in local staging performance of MRI. The maximum joint sensitivity and specificity numbers for the detection of extracapsular disease was 71% [14]. The localization and characterization of prostatic tumours can be further improved with new MRI technologies, such as MR spectroscopy, three-dimensional MRI and dynamic contrast-enhanced MRI [19, 45]. Hara et al. [27] stated that detection and precise staging using dynamic MRI is possible. Patients with moderate to high risk of extracapsular extension could benefit from pre-operative endorectal MRI. The accuracy of three Tesla MRI for local staging is reported to be 94% in experienced hands [20]. However, MRI, certainly with the latest techniques, is not widely available for regular patient care and is still a relatively expensive investigation. It can play a role in high-risk patients with negative biopsies or expected extra-capsular extension.

PET

PET is in use for medical purposes since the mid-1980s and can visualize prostate cancer [7]. For the localization and detection of organ-confined prostate cancer, however, it is not a useful imaging tool [15, 35]. PET could be of value in the evaluation of lymph nodes and determining the site of local recurrence in case of a PSA rise after therapy [6]. Recently, Reske et al. found that PET–CT could localize prostate cancer in patients with biopsy proven prostate cancer with a sensitivity of 81%. Furthermore, in patients with recurrent prostate cancer, this modality seems promising for the detection of local recurrences and lymph node disease [15, 46].

TRUS

Because TRUS is performed in every patient for guidance of random biopsies, improvement of this imaging modality could be of great value to increase the detection rate and to decrease the number of biopsies necessary to detect prostate cancer in a patient. Furthermore, the ability to define the extent of the tumour would be of great value in the choice of therapy and prediction of outcome of this therapy.

Ultrasound in general and TRUS specifically underwent many technical improvements during the last decade. Because TRUS is still part of the diagnostic process of prostate cancer all over the world, this paper will focus on the developments of this imaging modality from regular grey-scale ultrasound to contrast specific imaging techniques. Sensitivity and specificity of TRUS are low and new techniques were and are necessary to improve accuracy.

Loch describes a computerized supported TRUS analysis to improve the detection rate of TRUS. This technique detected clinically relevant prostate carcinomas that were missed by random biopsies. The specificity of regular TRUS imaging could be improved by computerized analysis, thus eliminating the differences among observers [36].

Because malignancy is associated with changes in vascular perfusion due to expansive growth and increased need of oxygen and nutrients, new imaging techniques aim at visualization of blood flow and discrimination between different patterns of perfusion. For the imaging of blood flow, movement- detecting techniques, such as colour and power Doppler, were developed. These techniques on their own, however, did not improve the detection rate [23]. The development of microbubbles, contrast media specifically for ultrasound use, has led to more sensitive perfusion imaging.

Contrast-enhanced TRUS (CEUS)

Contrast agents

Contrast agents for CT and MRI investigations are readily available and widely in use. In 1968, enhancement of US

signals with air bubbles was first described [22]. Since then, various US contrast agents have been developed, all gas bubbles with different shells for stabilisation. CEUS is developed for and mainly used in echocardiography.

Microbubbles are highly compliant to sound waves and are compressed and subsequently enlarged in response to ultrasound waves in the frequency of the transmitted wave. In very low acoustic power ultrasound, the reaction of these bubbles is linear, comparable to the reaction of tissue. When higher powers are applied the reaction of the bubbles is non-linear and very high acoustic powers disrupt the microbubbles. This shortens the half-life of the contrast agent and minimizes the time available for the examination.

The non-linear behaviour of the bubbles has been used to increase the sensitivity of the contrast detection and to emphasize the difference between tissue and contrast. The developments in CEUS techniques and the value for the diagnosis of prostate cancer will be described below.

Doppler

In the beginning of CEUS, microbubbles were used to enhance B-mode and Doppler US. Fundamental grey-scale imaging can only be enhanced when very high concentrations of bubbles are present in large vessels and are not valuable for prostate imaging because of low blood volumes.

Power Doppler CEUS (PDCEUS) examinations have been investigated for use in prostatic ultrasound. The extra reflectors of US signals in the blood flow after the administration of microbubbles enhance the Doppler signal. The sensitivity of PDCEUS in biopsy controlled studies is reported between 65 and 93% [4, 26, 41, 44]. However, specificity is still relatively low and clinical additional value is disputable [31].

In patients that underwent PDCEUS before radical prostatectomy the correlation between imaging and histology was studied. Goossen et al. [21] demonstrated that time enhancement curves derived from the PDCEUS signal could localize prostate cancer in either the right or the left lobe in 78% of the patients. Furthermore, a correlation was found between microvessel density, which is associated with tumour growth, and enhancement during three-dimensional PDCEUS [48]. Three-dimensional PDCEUS proved to be the best independent predictor for diagnosis of prostate cancer [51].

When the visualization of prostate cancer improves, biopsies can be precisely targeted so that random biopsies are not necessary. The group from Innsbruck stated that colour Doppler CEUS targeted biopsies can detect as many prostate cancers as random biopsies do, but with fewer cores per patient. However, the combination of both increases the detection rate [18, 40].

Non-linear imaging techniques

These techniques use the non-linear behaviour of microbubbles in an ultrasound field. Because tissue reflects acoustic waves mainly in a linear way and microbubbles mainly display non-linear backscatter, specific detection of these harmonic signals increase the specificity of CEUS. In harmonic B-mode imaging one frequency is transmitted and another frequency can be received. This way, emphasis lies on the reflections of bubbles and echoes from normal tissue are somewhat, but not totally, suppressed.

Various bubble detection methods using harmonic imaging techniques have been developed to improve the contrast-to-tissue ratio. Some of these have been described for prostate cancer diagnosis. Halpern et al. discussed the first experiences with two different harmonic imaging techniques correlated with biopsy results. Harmonic pulse inversion imaging is a technique in which two opposite pulses are sent, whose fundamental reflections cancel out each other so that the harmonic reflections remain. Using this technique and a constant infusion of microbubbles an increased sensitivity for the detection of prostate cancer was found compared to grey-scale TRUS [26]. One year later, a study was presented using wide-band harmonic imaging. Images were correlated with histology after laparoscopic prostatectomy. Cancers in the outer gland of the prostate were identified in 48%, compared to 24% using unenhanced imaging. The same group recently published their results with Doppler, continuous harmonic and intermittent harmonic imaging in a biopsy controlled study in 301 patients. This last technique uses intermittent scanning with a variable delay between the scans. This way, the microbubbles can advance in the microvasculature without being destroyed by the acoustic waves. It was stated that a targeted biopsy core during intermittent harmonic imaging was twice as likely to contain carcinoma than a random core in a patient with prostate cancer [25].

Figure 1 shows an example of a transrectal CEUS investigation using harmonic imaging. The un-enhanced image (a) shows a slightly inhomogeneous peripheral zone, without a clear tumour location. After the administration of contrast, increased enhancement can be observed in the right side of the peripheral zone (b). This area proved to be the largest tumour location with a Gleason grade 7. In the rest of the prostate some locations of prostatic intraepithelial neoplasia and small focus of Gleason 6 adenocarcinoma were found after radical prostatectomy. Off-line analysis of the time-enhancement curves showed a quick wash-in and -out of contrast in the tumour area with a high peak of maximum

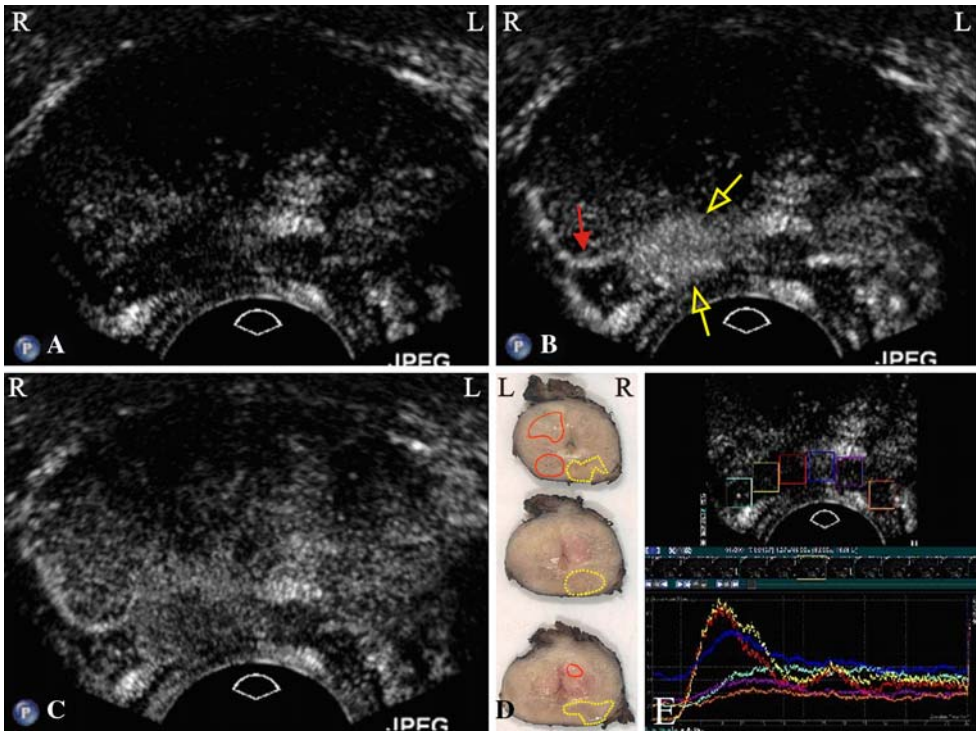

Fig. 1 Harmonic CEUS in a patient with biopsy proven prostate cancer. **a** Baseline harmonic image before contrast administration. **b** After the administration of a bolus of microbubbles (Sonovue, Bracco) a fast enhancement of an area in the right side of the peripheral zone of the prostate can be observed (yellow arrows). Furthermore, the red arrow indicates a "feeding vessel" to the suspicious area. **c** After some time, the rest of the prostate shows enhancement, while a quick washout of microbubbles is seen in the suspicious area. **d** The laparoscopic radical prostatectomy specimen. In yellow the main tumor area (Gleason 7), in red some areas of prostatic intraepithelial neoplasia and small foci of Gleason 6 adenocarcinoma. The area of abnormal enhancement corresponds to the main tumor site. **e** Time enhancement curves of the patient in figure 1. Regions of interest (ROI) are placed throughout the entire peripheral zone of the prostate and time-intensity curves are constructed. The yellow, red and in part the blue ROIs and corresponding curves show a faster and more intense enhancement and faster washout of contrast than the curves corresponding to the other ROIs

enhancement (c). Compared to other regions in the prostate a clearly different time-intensity curve can be seen. Image processing techniques enable objective analysis of CEUS images and further research in this field is a necessity.

Recently, even more specific imaging techniques have been introduced. One of them is contrast pulse sequence (CPS) imaging. In this technique, series of pulses with different amplitudes and phases are transmitted from the ultrasound probe [42]. A contrast-only and a tissue-only image are created which can be evaluated simultaneously. This technique has been studied in the evaluation of hepatic and renal tumours with great success [3, 38]. It has been used, but not yet described, for TRUS imaging of the prostate. Preliminary results from our institution show that the blood flow of the prostate can be visualized in detail using this technique. Another new technology is micro-vascular imaging (MVI), a post-processing technique that selectively visualizes the signals from the microbubbles as they progress in time with suppression of background signals. An example of this technique is given in Fig. 2. The first data using this technique in our institution are now under investigation. Various (abnormal) flow patterns can be detected and will be correlated to histology concerning localization and staging.

Treatment monitoring

Because of the detailed imaging of perfusion, CEUS could be of value in the follow-up of minimally invasive and medical treatment modalities. These treatments usually influence the perfusion of the prostate. In 2002, CEUS monitoring of hormonal treatment was described. A decrease in CEUS signal was observed over time [11]. The effects of HIFU could also be visualized in a study in which patients underwent a radical prostatectomy after HIFU treatment of a part of the prostate. The areas without perfusion could be demarcated and treatment effect could be assessed using a three-dimensional power Doppler technique [47]. Currently, using contrast specific CEUS techniques, studies are ongoing regarding the monitoring of anti-angiogenetic treatment and the visualization of treatment effect of cryoablation for prostate carcinoma.

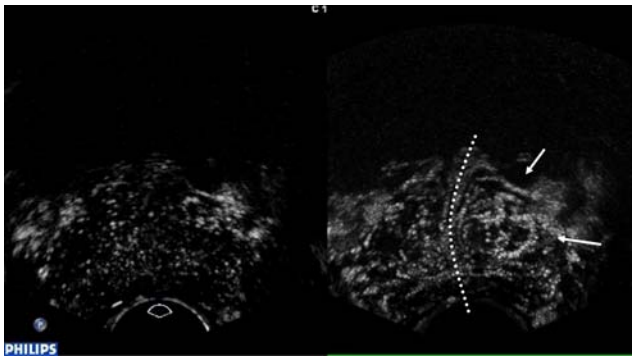

Fig. 2 Micro vascular imaging (MVI). An example of a post-processed image produced with MVI. This technique uses background subtraction and displays all new contrast signals as they progress in time. On the left the regular contrast specific CEUS image, on the right MVI. In the right side of the MVI-image (the left side of the prostate), an area with increased and inhomogeneous enhancement is seen (arrows), which corresponds to the histological tumor location after radical prostatectomy. Furthermore, there is a slight asymmetry towards the left side of the image (line)

Future developments

Contrast-only images as provided by CPS CEUS and MVI will probably improve the evaluation of the enhancement patterns. As described above, image processing such as time-enhancement curves will improve objective evaluation of CEUS images. After the administration of microbubbles an enhancement curve can be created and after disruption of the bubbles in the ultrasound field a reperfusion curve can be made. This allows repeated evaluation of enhancement patterns. Software for these analyses is usually provided on the ultrasound device [34]. All contrast specific imaging software now only available on the high-end scanners, will probably come available on less expensive devices such as regularly used in urological practice.

Besides technical improvements, new microbubble agents are constantly under way. Each contrast agent has its own properties and behaves differently in an acoustic wave [5]. Recently, targeted microbubbles have been investigated. Labelled with different antigens, bubbles can be targeted against, for example, inflammation and angiogenesis [13]. Especially the last target can possibly enable selective imaging of tumour tissue [54].

Furthermore, microbubbles have been shown to be able to carry drugs and genes and are therefore agents capable for drug delivery. Microbubbles, loaded with pharmaceutical agents can be brought into the blood stream and destructed by ultrasound in the target area for therapy. This way, higher doses of medicine can be administered locally [9]. In experimental settings, gene transfer using microbubbles and ultrasound has been described as an efficient method for gene therapy [32].

Conclusion

Transrectal CEUS improves sensitivity, but not specificity, of TRUS and targeted biopsies during CEUS increase the detection rate of prostate biopsies. However, because targeted biopsies miss a significant percentage of cancers, random biopsies are still a necessity. New contrast specific imaging techniques will probably improve CEUS of the prostate. The goal of future research is to visualize and localize prostate cancer to make random biopsies avoidable. This way, less biopsies will be needed and staging and grading of prostate cancer will improve. Furthermore, experiments with targeted imaging with labelled microbubbles will possibly make tumour specific imaging available in the future.

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