Contrast-enhanced ultrasound for prostate cancer imaging

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Prostate cancer is the number one non-skin malignancy of males in Western countries. In the U.S.A. and European Union combined, more than 500,000 men are diagnosed with prostate cancer each year, and more than 90,000 die of it [1,2]. In the U.S., 1 in 6 men will be diagnosed with prostate cancer in their lifetime, and 1 in 32 will die of it [3,4].

Survival times have considerably improved over the last years. However, a conclusive diagnosis still requires multicore biopsies, and treatment very frequently involves severe impairments of quality of life, including problems with urinary, bowel, and sexual function.

Looking at the full care-cycle that prostate cancer patients go through in developed countries from diagnosis to therapy to follow-up (Figure 1), a number of gaps stand out:

- Need for an accurate screening test, to avoid unnecessary biopsies
- Need for targeted instead of blind biopsies, in order to reduce false negatives and to improve grading and staging
- Need for accurate grading, staging and prognosis, in order to a) reduce side effects by enabling active surveillance and treating only relevant cases and b) avoid recurrence as a result of understaging and inappropriate treatment
- Need for targeted therapies (focal local treatment, targeted systemic therapies), in order to reduce both side-effects and recurrence.

In essence, these gaps point to two major deficiencies in the current care of prostate cancer. First, the lack of an accurate screening test, which gives rise to concerns both about missing relevant cases [7] and about overdiagnosis and overtreatment [8]. Secondly, and this sets prostate cancer apart from most other cancers, there is no widely available and reliable imaging method for local tumors.

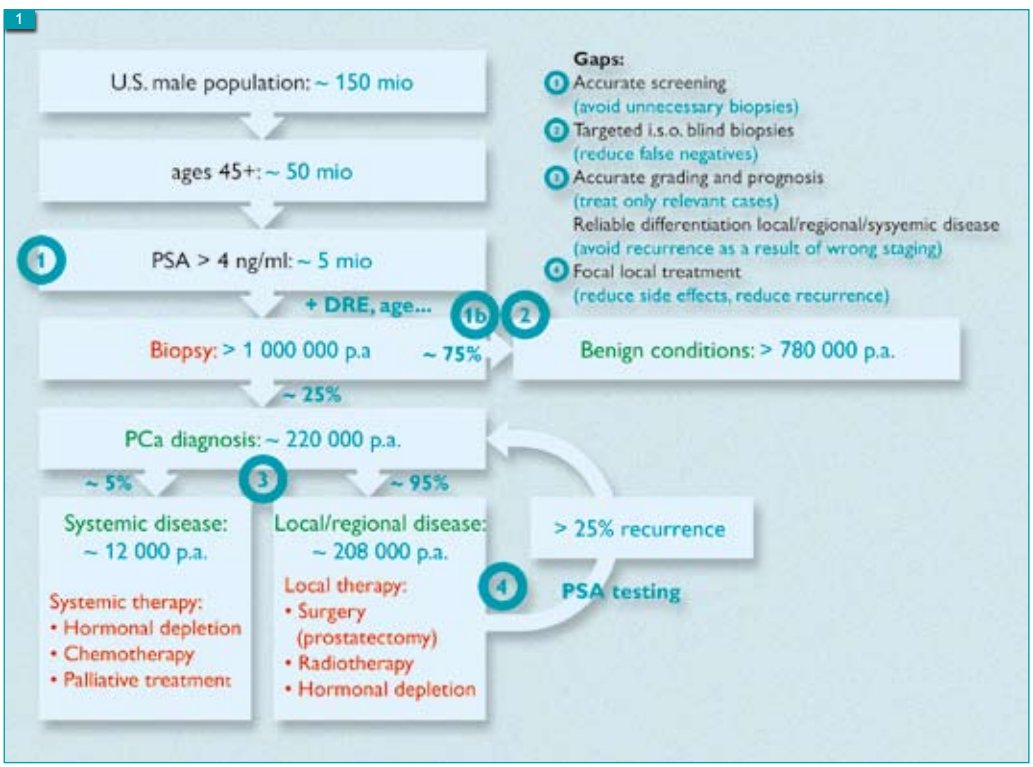

Figure 1: United States Prostate Cancer Patient Flow (2006) and gap analysis [1, 4, 5, 6].
PSA: Prostate Specific Antigen
DRE: Digital Rectal Examination
PCa: Prostate Carcinoma.

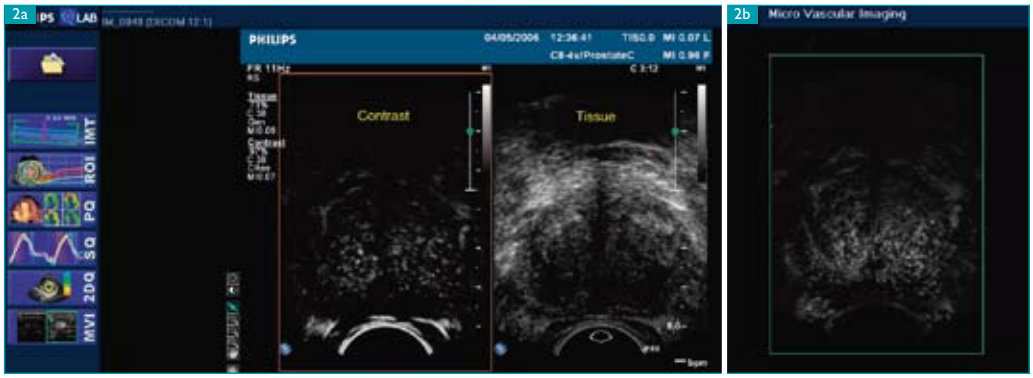

Figure 2. CEUS imaging.

Figure 2a. Contrast-only and tissue-only simultaneous imaging.

Figure 2b. Maximum Intensity Projection over time: Micro-Vascular Imaging (MVI).

Decisions on patient care are typically based on rather limited pieces of information on the localization, extent and grade of malignant tissue. Apart from digital rectal examination, systematic biopsy sampling, indirect indications based on prostate specific antigen level in the serum or shape alterations of the prostate, and bone metastasis imaging in late-stage disease, prostate cancer diagnosis and therapy are essentially blind [9].

Potential applications of imaging of prostate cancer include diagnosis, grading, staging (either directly or indirectly by image-guided biopsies) as well as therapy guidance, therapy monitoring, and follow-up.

One property of the disease that complicates imaging is that, in contrast to many other neoplasms, malignant prostate lesions do not generally present as a solitary round mass. Rather, prostate cancer is most often multifocal and tends to grow along the capsule of the gland in an oblong shape [10]. On the microscopic level, prostate malignancy is typically characterized by a loss of the glandular architecture, increased cellular density, and altered microvasculature. Relevant predictors of clinically significant disease include tumor volume, tumor grade (as ranked by the Gleason score), and microvessel density [11]. Prognosis and volume of high-grade disease are linked [12], which underscores the importance of spatial mapping as delivered by imaging methods.

Looking towards available medical imaging methods [14], conventional grayscale transrectal ultrasonography is the standard for guiding biopsies to the organ, but has limited value in identifying malignant foci. Magnetic resonance (MR) imaging and its combination with MR spectroscopy is helpful for evaluating the extent of local disease, but due to cost so far has a limited role. Computed tomography (CT) and radionuclide bone scans are reserved for the evaluation of advanced disease. Radionuclide imaging with targeted antibodies and positron emission tomography (PET) is utilized for clarification of the lymph node status and for localizing relapse after radical therapy.

This article presents a new approach to imaging localized prostate cancer: contrast-enhanced ultrasonography. The method is based on the visualization of microvessel density by micro-bubble contrast agents and suitable ultrasound techniques [15].

Contrast-enhanced ultrasonography is a new approach to imaging localized prostate cancer.

Pilot study: preliminary results

Until recently, contrast-enhanced ultrasonography (CEUS) has not been used for prostate cancer imaging. To establish the value of this approach a cooperation was initiated between Philips Medical Systems and the Department of Urology, AMC, Amsterdam, and a pilot project was defined.

In this pilot project, patients scheduled for a radical prostatectomy underwent a CEUS investigation. The CEUS imaging was compared with the histology as obtained after removal of the prostate. The goal of the pilot study was to describe features and characteristics as found with CEUS that correlate with malignant tissue as found in the histology.

Materials and methods

The procedure was explained to patients scheduled for a radical prostatectomy, and after patients gave their informed consent, 30 patients underwent CEUS of the prostate between March 2006 and March 2007. For the investigations a Philips iU22 ultrasound system was used, with a C8-4v endocavity probe. The software installed on the system enabled contrast specific imaging with simultaneous display of a contrast-only and a tissue-only image (Figure 2a).

A Philips iU22 ultrasound system with a C8-4v endocavity probe was used for the investigations.

One phial of the contrast agent Sonovue (Bracco) was prepared according to the directions for use. Using a syringe pump (BR-INF 100, Bracco) a continuous infusion of 4.8 ml contrast agent was administered, with an infusion rate between 1.3 and 1.5 ml per minute. In this way, the available

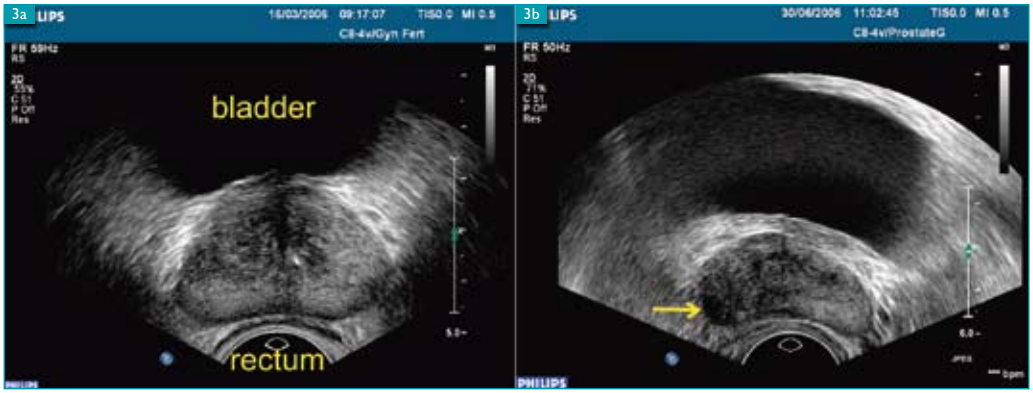

Figure 3. Grayscale imaging of the prostate.

Figure 3a. Normal prostate.

Figure 3b. Suspicious hypoechoic lesion (arrow).

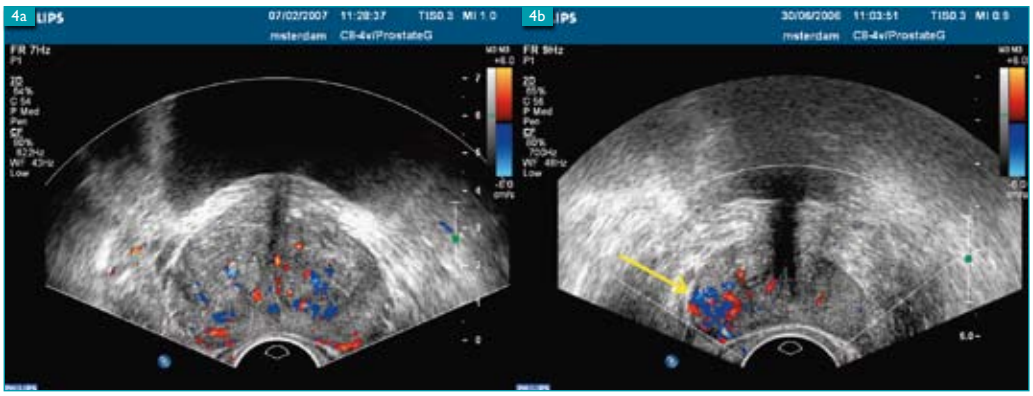

Figure 4: Color Doppler imaging of the prostate.

Figure 4a. Normal prostate.

Figure 4b. Suspicious lesion.

time for CEUS imaging was approximately 4 minutes.

Before the contrast was administered, the prostate was examined by grayscale ultrasound, and in most cases with color Doppler imaging. Then, the contrast infusion was started. A minimum of four transverse scanning planes were chosen. The first plane was selected based on the information available from previous biopsies and on the grayscale ultrasound. Then, three planes in the apex, mid-prostate and base were selected.

Destruction-replenishment curves were recorded in the four scan planes. Microbubbles in the scan plane were destroyed using a short period of high mechanical index (MI) imaging, after which the inflow of the microbubbles in the scan plane was visualized and recorded.

To be able to judge the value of new imaging modalities, it is necessary to compare the imaging with the gold standard: the histology of the tissue. For this reason, the study comprised patients scheduled for a radical prostatectomy, and in March 2007 the histology of 19 patients was known.
The removed prostate was sliced into 4 mm transverse planes. Each slice was photographed and microscopically examined. After the histological examination, the tumor outlined was delineated on the macroscopic photograph.

Using off-line post-processing software (QLAB, Philips), the stored clips were analyzed with a Maximum Intensity Projection (over time) analysis algorithm: Micro-Vascular Imaging (MVI) (Figure 2b). Perfusion patterns were identified, characterized and described by two readers in consensus.

Results and discussion

An example of a grayscale image of the prostate is shown in Figure 3a. The location of the probe in the rectum is at the bottom of the image. At the top, the bladder is visible as a "black hole". In between, there is a high-resolution image of the prostate. A second example is shown in Figure 3b. On the left-hand side of this image, a hypoechoic lesion can be seen within the prostate (arrow). Hypoechoic lesions are a possible indication for malignant tissue. However, the sensitivity and specificity of grayscale imaging for prostate cancer detection are low. Studies report sensitivities of 33-90% and associated specificities of 74-30% [16,17].

Color Doppler imaging of the prostate is shown in Figure 4a. Because of the presence of small vessels and slow blood flow in the prostate, the sensitivity of color Doppler imaging for detecting blood flow in the prostate is low. Figure 4b shows the same prostate as in Figure 3b. In this case an increased Doppler signal is visible on the left side of the image, which is an indication for the presence of a tumor. However, the sensitivity

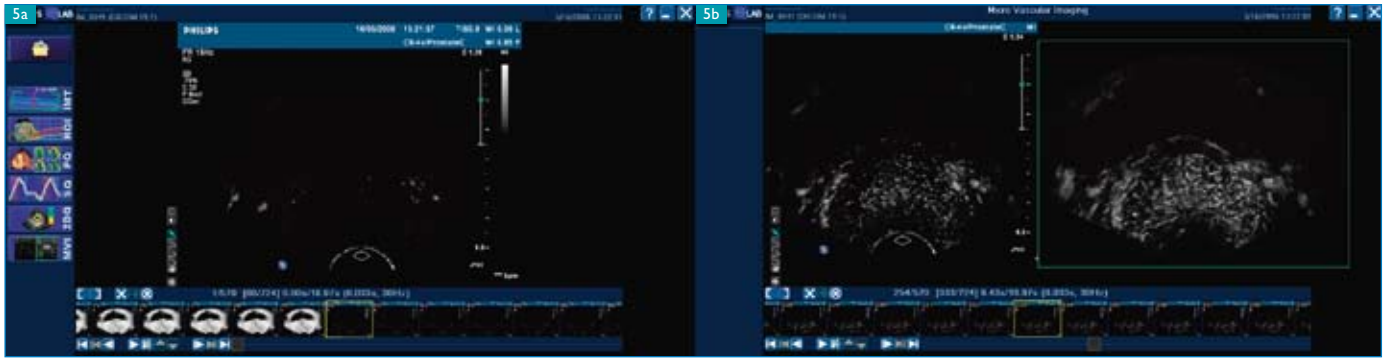

Figure 5. MVI imaging. Figure 5a. First frame after short period of high MI. Figure 5b. Approximately 8 seconds after the period of high MI; left panel: prostate filled with microbubbles, right panel: MVI image built up during the approx. 8 seconds.

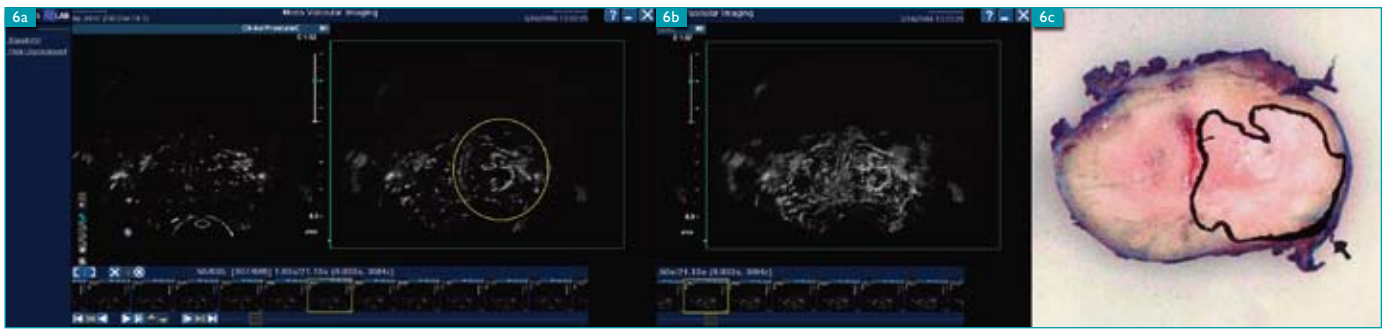

Figure 6. MVI imaging. Figure 6a. Suspicious lesion (early phase) Figure 6b. Suspicious lesion (later phase) Figure 6c. Corresponding histology slice

and specificity of color Doppler for prostate cancer detection are also low. It has been stated that color Doppler ultrasound adds only minor information to gray-scale imaging [18,19].

The diagnostic accuracy of grayscale and/or Doppler imaging are too low. To increase the sensitivity of Doppler techniques, research was initiated over the last decade to investigate the use of contrast enhanced power and color Doppler techniques [20,21]. It was demonstrated that contrast enhanced power Doppler can increase the diagnostic accuracy as compared with non-contrast imaging; however, the increase was not large enough for a significant clinical improvement. Contrast enhanced color Doppler has been used to guide biopsies, and studies showed that this contrast technique can be used to improve biopsy strategies.

In the pilot project reported here, a far more advanced contrast specific imaging technique was used [15]. It was expected that with this technique detailed (micro-)vascular imaging would become possible.

N.B. Ultrasound is a real-time imaging modality. The development of the MVI image over time gives the observer additional information that is not present in static images. The movement of bubbles, the intensity over time etc. will also give the observer additional information that helps in detecting abnormalities. Most of the examples presented here are far more obvious in real time than in the printed static images.

Figure 5 shows an example of MVI. Figure 5a is a screen-capture of QLAB. The image shows the first frame after a short period of high MI scanning. The small "white" frames just before the selected frame show the last high MI scanning frames. Figure 5b is a frame approximately eight seconds after the high MI period. In the left-hand panel the prostate, now filled with microbubbles, can be seen (compare with Figure 5a). The right-hand panel shows the MVI analysis: a maximum intensity projection over the (approximately) eight seconds. This image shows a very detailed picture of the vasculature of the prostate. In general, we found that normal tissue shows perfusion in the form of the spokes of a wheel, as can be seen in this MVI image.

A clear disturbance of such a spoked wheel perfusion can be seen in Figure 6a and 6b, acquired at different times after high MI bubble destruction. Increased and disturbed perfusion is visible in the image on the right-hand side of the prostate. The mid-line of the prostate is shifted to the left, and the capsule of the prostate looks irregular. Figure 6c shows the corresponding

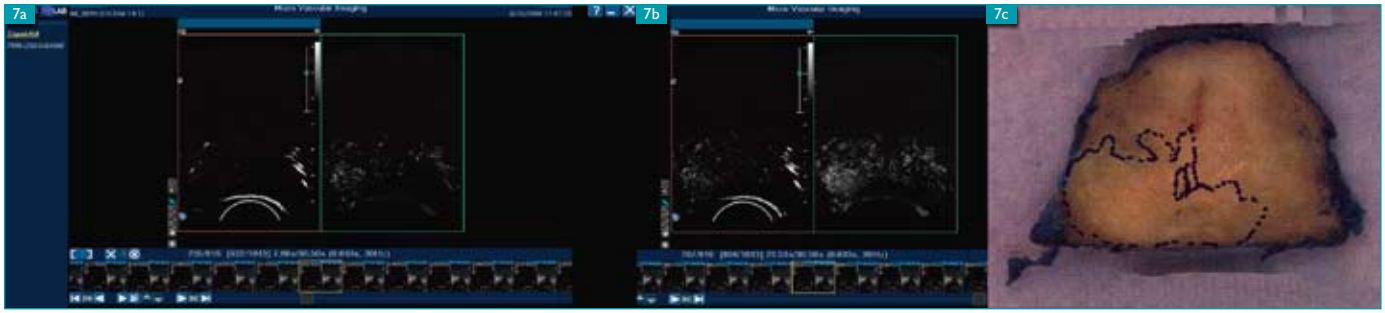

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Figure 7. MVI imaging.

Figure 7a. Suspicious lesion (early phase)

Figure 7b. Suspicious lesion (later phase)

Figure 7c. Corresponding histology slice.

slice of the histology. There is a clear correlation between imaging and histology.

Figure 7a shows the MVI of the same prostate as that shown in Figures 3b and 4b. In this prostate, a faster enhancement and diffuse perfusion is visible in the area of the tumor found in the histology. Thus in this case grayscale, color Doppler and CEUS all detected the malignant tissue.

All imaging sessions of patients with known histology were reviewed, and grayscale, Doppler and CEUS images were compared with the histology:

- Grayscale: in 9/19 cases a suspicious lesion in the imaging corresponded with malignancy in the histology; in one of these cases there was also a suspicious lesion in an area that contained no malignancy
- Doppler: in 7/17 the suspicious lesion in color Doppler corresponded with an area of malignancy. In one other case Doppler imaging indicated the wrong location.
- CEUS: in 17/19 cases suspicious lesions could be seen that correlated with the location of the tumor as found in histology. In seven of these cases suspicious lesions were also shown in areas that contained no malignancies.

In conclusion, we found:

- CEUS examination was successful in all patients. No side effects occurred.
- CEUS in its present form can show the (micro) perfusion of prostate tissue in great detail.
- There is a correlation between abnormal perfusion patterns and malignant tissue.

A well-known aspect of prostate cancer is its different histological appearances. This study shows that CEUS is sensitive enough to detect different perfusion patterns in malignant areas. A benign prostate, in general, shows a spoked-wheel perfusion. We found 4 major characteristics that correlate with malignancy:

- Early enhancement
- Increased enhancement
- Diffuse enhancement
- Abnormal perfusion patterns as compared to the "spoked-wheel".

Because this CEUS technique visualizes perfusion of tissue, it can also be helpful in the follow-up of ablative treatments. Figure 8 shows the effects on perfusion after cryoablation of the prostate. As cryoablation kills (tumor) cells, perfusion should be absent in the treatment areas. From the Figure it can be seen that, as a result of cryoablation, "black" contrast areas are present, indicating the absence of perfusion and thus the destruction of tissue. The exact value of CEUS for this application and the use during angiogenesis inhibitor treatment is now under investigation in the AMC.

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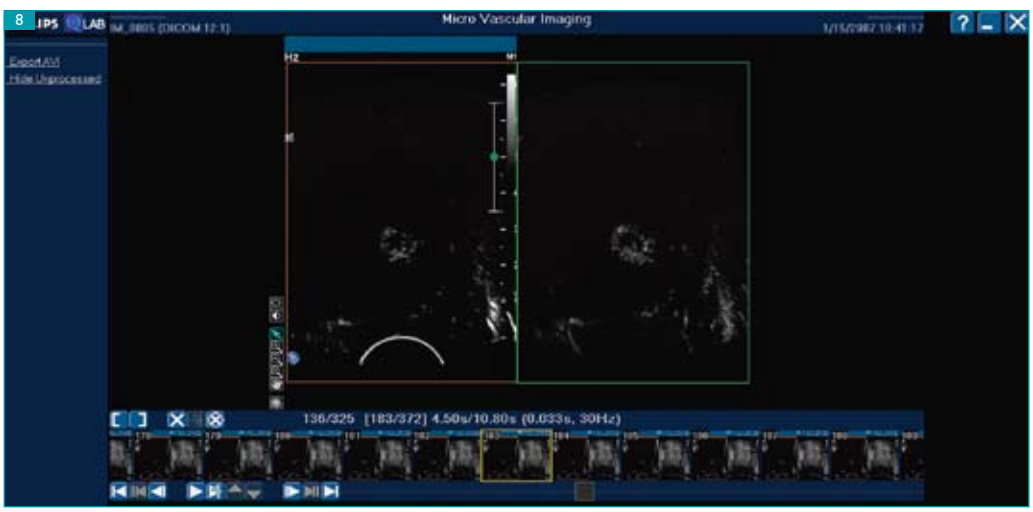
Figure 8: MVI of prostate cancer treated with cryoablation ("freezing"). During the treatment, the tissue is frozen to temperatures below -40° C by needles inserted into the prostate. The urethra is protected by a warming catheter. The "white spot" in the middle is perfusion still present around the urethra. The rest of the prostate is (almost) completely black, indicating destruction of tissue.



Future of CEUS

In this pilot project we correlated CEUS imaging with histology. Based on a subjective analysis, we found that different perfusion characteristics do correlate with malignant tissue. These promising results of the pilot study demonstrate that CEUS in its current form has the potential to improve diagnosis of prostate cancer, and could play an important role in the prostate cancer care-cycle. Further prospective (multi-center) studies are needed to determine the exact additional clinical value.

There are some limitations related to the presented pilot study. First of all, two readers not blinded for histology, in consensus, described the characteristics of abnormal perfusion. Secondly, all patients were known to have prostate cancer. Another limitation is that we used a subjective analysis. We tried to subjectively describe the CEUS characteristics that could indicate malignant tissue. Furthermore, only a limited number of scan planes were examined with CEUS, due to the 2D-technique used and the limited time available. This means that only selected parts of the prostate have been examined with CEUS. And last but not least, the correlation between imaging and histology was performed by selecting the most probable histology slice that corresponded with the scan plane.

Our research is now focusing on solving these limitations, by improving technology, developing objective analysis algorithms, improving correlation between imaging and histology by e.g. image fusion, and application of these techniques in all patients with suspected prostate cancer ■

▶ Changes in perfusion characteristics detected with CEUS correlate with malignant tissue.

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