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EDITORIAL

Prostate cancer diagnosis and treatment using multiparametric transrectal ultrasonography

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Introduction

Transrectal ultrasonography (TRUS) has versatile applications, such as diagnostic imaging of prostate cancer and benign prostatic hyperplasia (BPH), as well as navigation during prostate needle biopsy, high-intensity focused ultrasound (HIFU), and brachytherapy. Approaches with high diagnostic accuracy are being established by combining color Doppler that factors in blood flow information under grayscale ultrasound, with elastography that displays information about tissue elasticity inside the prostate. In addition, a TRUS navigation technique that improves treatment outcomes of radical prostatectomy by providing the surgeon with ultrasound images from within the prostate and images of the surrounding tissue in real time has been reported.

Multiparametric TRUS

Color/power Doppler

Rifkin classified abnormal Doppler flow signals from prostate cancer lesions into three types: diffuse flow, focal flow, and surrounding flow (Fig. 1) [1]. Kimura analyzed flow signal characteristics from the perspective of the zonal anatomy of the prostate gland (peripheral zone, central zone, anterior zone, transition zone) [2] and pointed out the importance of the contrast between grayscale images of the peripheral zone, where cancer develops the latest, and blood flow signals. He also presented a case with cancer in the anterior zone that was difficult to diagnose using blood flow signals.

The experience of the examiner is important as it is a qualitative assessment method regardless of analysis of flow signal patterns or zonal vascular anatomy. Therefore, analysis according to the amount of experience of the examiner using a large sample size is needed in order to assess the diagnostic accuracy of Doppler signals for prostate cancer.

Elastography

The Japan Society of Ultrasonics in Medicine has published elastography guidelines for prostatic diseases [3]. Elastography is mainly divided into strain imaging and shear wave imaging. Strain imaging is used to assess stiffness by displacing tissue by manual compression and measuring the distortion that occurs, while shear wave imaging is used to calculate the elasticity of tissue based on the propagation velocity of shear waves generated in the body.

Elastography is more sensitive than other methods like B-mode and Doppler ultrasound. In a randomized trial of B-mode and elastography in 353 patients, sensitivity was 15% for B-mode and 60.8% for elastography, which was much higher, while specificity was somewhat lower (92.3% vs 68.4%) [4]. Elastography has also been compared with radical prostatectomy specimens [3]. It was found that approximately 70–85% of patients were detected as compared with prostatectomy specimens. That detection rate is much better than the generally agreed upon detection rate with B-mode images (about 40%).

Nevertheless, some issues have been raised. In the case of strain imaging, which requires transrectal compression of the prostate gland, images are often unevaluable due to deviation of the compression point or inappropriate compression. Pallwein et al. [5] did not evaluate the prostatic inner gland using elastography. However, based on the evidence that there are many cancerous lesions present in the ventral prostate including the inner gland, biopsy of the ventral aspect cannot be ruled out. Another problem is the occurrence of artifacts resulting from calcification of tissue or increased stiffness of the inner gland due to BPH. With shear wave imaging, on the other hand, it is possible to calculate tissue

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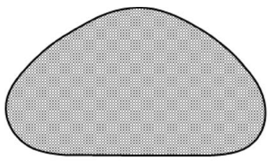
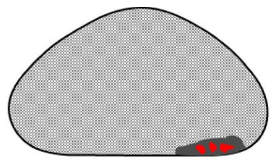
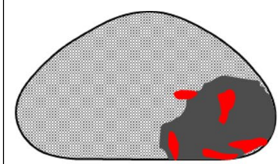
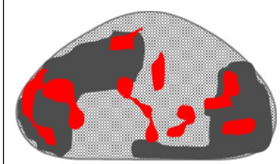
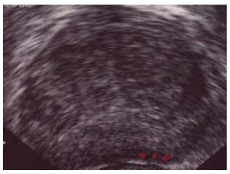
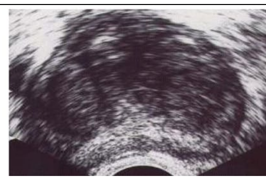
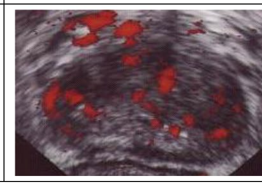
	DS0	DS1	DS2	DS3
Finding	No remarkable accumulation	Slight focal accumulation	Intense focal and/or surrounding accumulation	Diffuse accumulation
Schematic diagram				
Image				

Fig. 1 Assessment of blood flow images using power Doppler ultrasound

elasticity based on the propagation speed and display the kilopascal unit (kPa). Correas et al. [6] analyzed kPa in target cancerous lesions and Gleason score by area, and they concluded that the higher the Gleason score had significant relation with the increase in kPa.

There is a promising report that fusion of magnetic resonance imaging (MRI) and elastography clearly contributes to increased diagnostic accuracy of prostate cancer detection [7].

Contrast agents

Sato et al. [8] reported in 2011 that perflubutane (Sonazoid®), which was approved for the diagnosis of liver cancer in 2008, was also useful for the diagnosis of prostate cancer. In general, there are an increased number of microvessels in cancer tissue, and it is possible to depict the difference in microvessel density (MVD) between cancer and the surrounding tissue after intravenous injection of an ultrasonic contrast agent. This improves on the shortcoming of regular Doppler, i.e., the inability to identify microvessels. Contrast harmonic imaging (a method for imaging harmonic components generated when an ultrasonic contrast agent resonates and disintegrates) is used to create images of the phenomenon of ultrasonic waves reflecting and scattering on the surface of microbubbles generated by the contrast agent. Some shortcomings of this modality are as follows: (1) Identification is difficult in the transition zone as contrast enhancement is generally more pronounced there (greater inflow of contrast agent and early depiction) and (2) acoustic attenuation caused by calcification (prostatic calculi) within the prostate gland, which is also an intrinsic characteristic of ultrasound.

There have been reports in recent years that a technique using time intensity curve analyses [e.g., wash-in rate, time to peak (PT), time to appearance, peak intensity, area under the curve] during depiction of the contrast agent in a focused area with a suspected cancer lesion within the prostate gland is useful for diagnosis of the prostate and cancer aggressiveness [9, 10]. Research comparing focused area images and MRI images will be needed in the future.

Intervention use

Techniques that employ TRUS navigation in the radical treatment of prostate cancer are not limited to brachytherapy, which is a type of radiation therapy. TRUS has also been employed for surgical treatment (radical prostatectomy). The ultrasound anatomy associated with TRUS and longitudinal scanning is shown in Fig. 2. During laparotomy, the

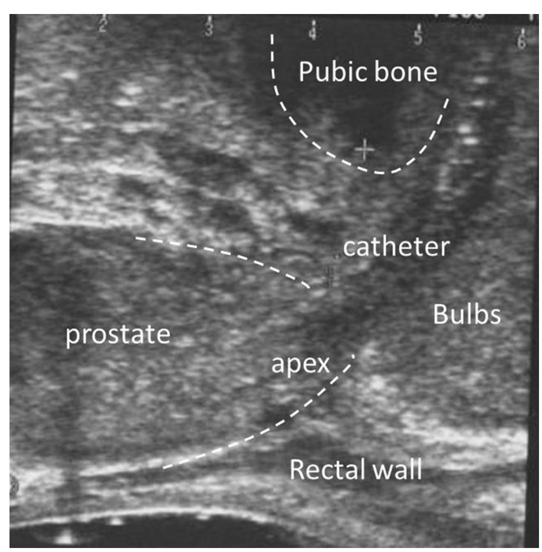


Fig. 2 Ultrasound anatomy (longitudinal scan)

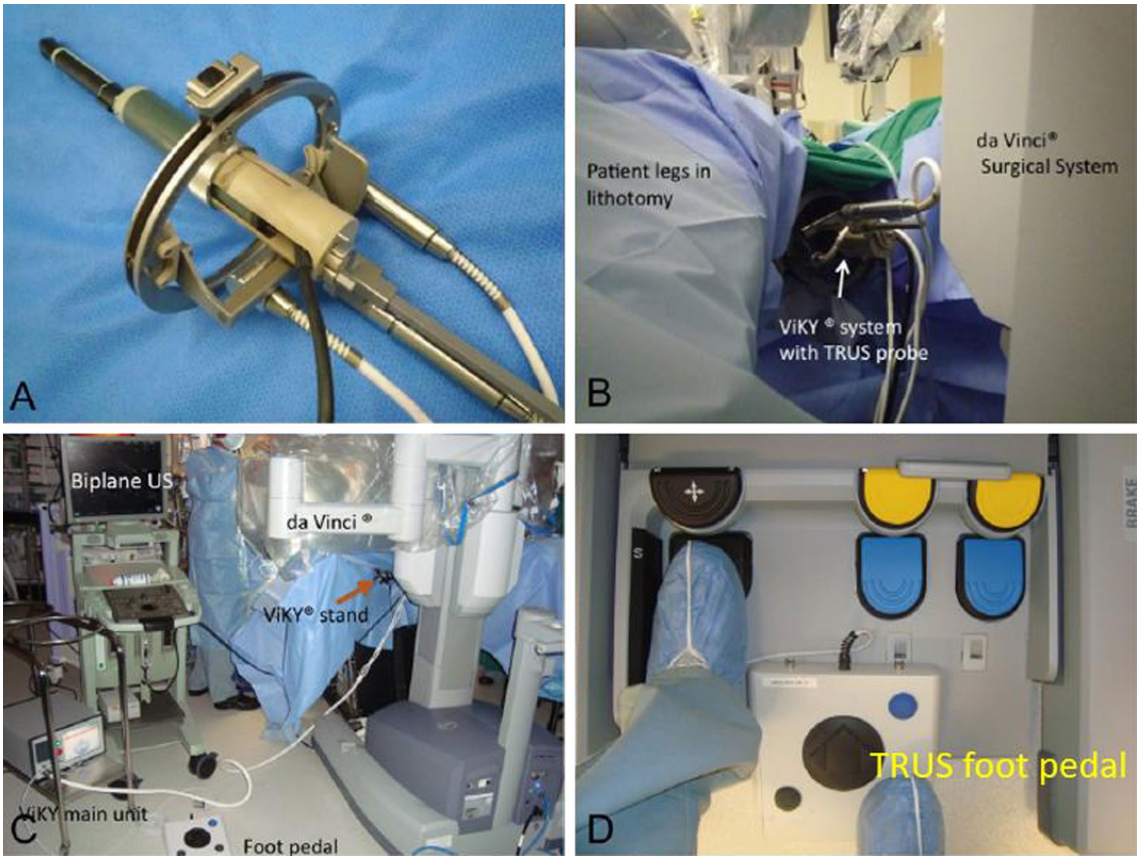


Fig. 3 Ultrasound navigation during robotic surgery. **a** The ultrasound probe is stabilized using one of the robotic arms. **b** The probe is stabilized with the patient in the lithotomy position. **c** The probe is wired to an ultrasound device, and image information is sent to the surgeon's console unit. **d** Inside the console: The yellow, blue, and black pedals located above are used to operate clamps in the body cavity, and the arrow pedal located below is an ultrasound scan pedal used by the surgeon to perform scans (modified the original figure in Ref. [10])

ultrasound operator provides the surgeon with images of the ultrasound anatomy or the movements of the acoustic shadows of clamps or suction tips currently being manipulated by the surgeon, using a biplane probe (5–7.5 MHz) that depicts transverse/longitudinal images. During robot-assisted (da Vinci) surgery, as the da Vinci device is situated between the thighs of the patient, it is possible to manipulate finger-type ultrasound probe setting to the patient's perineum and operate the ultrasound device from the side of the da Vinci device.

It is extremely important that the oncological and functional outcomes are guaranteed in endoscopic surgery including laparotomy and robot-assisted (da Vinci) surgery. Whether the surgical margin has been sufficiently secured is key to guaranteeing oncological control, while ensuring the membranous urethral length associated with accurate apical dissection in order to maintain continence [11] and confirming whether a neurovascular bundle-sparing procedure aimed at preservation of male function was properly performed are key to preservation of functional control.

Hung et al. [12] developed a system that allows the surgeon to intraoperatively manipulate via the console a probe inserted in the rectum during robot-assisted radical prostatectomy. This system was developed to compensate for the fact that the main robot unit is located between the patient's legs, leaving the ultrasound navigator with no room to work (Fig. 3).

MRI-TRUS fusion biopsy

MRI technical advances led to the spread of prostate biopsy based on MRI findings. Methods for performing target biopsy based on MRI information are (1) cognitive fusion, (2) MRI–MRI fusion (in-bore biopsy), and (3) MRI-TRUS fusion. MRI–MRI fusion is being performed in Japan, but its use is currently limited to a subset of institutions due to the cost of purchasing the equipment and the time it takes to perform a biopsy. MRI-TRUS fusion can be performed in a regular laboratory if the intraprostatic three-dimensional positioning is synchronized between the two imaging

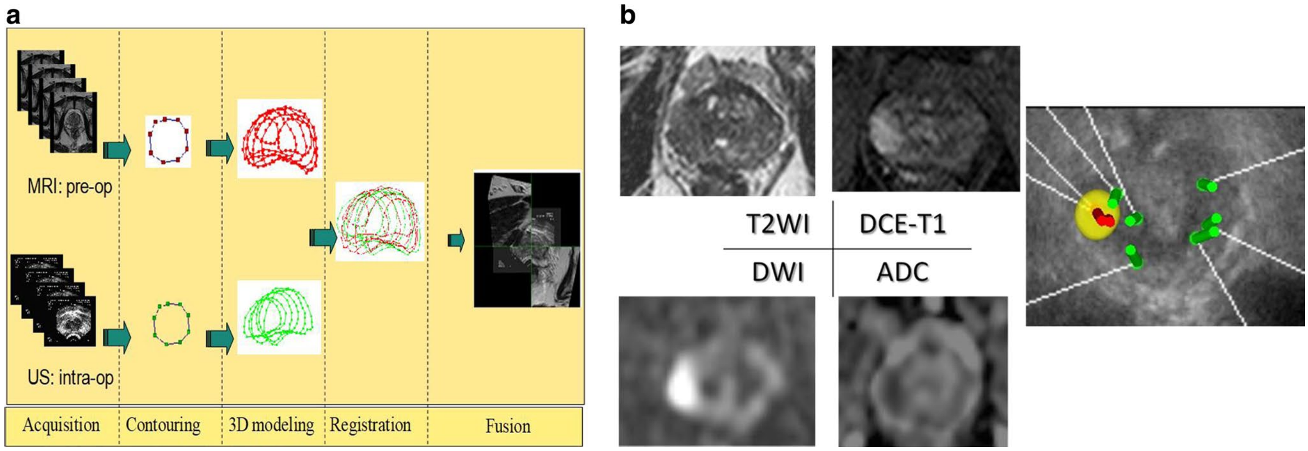


Fig. 4 MRI-US fusion biopsy. **a** MRI-US fusion technology using Urostation™ (Koelis). Registration is performed with marking of the entire surface of the prostate gland based on MRI and ultrasound 3D volume information. **b** Ultrasound-guided biopsy is performed by projecting the abnormal site (yellow) confirmed by multiparametric MRI onto the ultrasound image. The respective puncture routes are recorded, and cores positive for cancer are shown as red bars

modalities, and the biopsy time does not differ greatly from that of conventional systematic needle biopsy. The European Association of Urology as well as American Urological Association has been holding education seminars for several years, which has rapidly led to more widespread use. Artemis™ (Eigen), Urostation™ (Koelis), and HI-RVS (Hitachi) are examples of units that can be used for MRI-TRUS fusion. With the fusion of MRI and ultrasound images, target biopsy based on MRI findings allows for more accurate targeting than the so-called cognitive targeting where MRI information is used as a reference during ultrasound-guided biopsy.

A MRI-TRUS fusion biopsy system is shown in Fig. 4. With the application for fusion biopsy, new ablation (HIFU, cryoablation) devices that target only cancer lesions that should be treated and prostate organ-sparing targeted therapy using focal brachytherapy are expected to see more widespread use.

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