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REVIEW

Ultrasound of the prostate

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Abstract

Ultrasound is a widely used imaging modality for evaluation of the prostate. The main topic of diagnostic imaging is an improvement of prostate cancer diagnosis. The current available systematic prostate biopsy is performed only under ultrasound guidance, but new imaging techniques allow prostate cancer visualization and therefore improved detection. Evolving methods such as contrast-enhanced colour Doppler imaging, contrast-specific ultrasound techniques and elastography may dramatically change the role of ultrasound for prostate cancer diagnosis. The purpose of this review is to provide an overview of ultrasound and its different techniques for imaging of the prostate and to discuss current trends and future directions.

Keywords: *Prostate cancer; biopsy; contrast enhanced; imaging; ultrasound.*

Introduction

Ultrasound (US) is a widely used and well-tolerated imaging modality for evaluation of the prostate. Recent technical advances in US applications have led to new aspects in the analysis of the prostate. Structural analysis is applied for measurement of prostate volume, study of echotexture, and illustration of tissue stiffness or elasticity. Functional analysis illustrates macrovascularity and microvascularity, which are indicators of tissue perfusion. The purpose of this review is to provide an overview of the use of US imaging techniques and to discuss current trends and future directions.

Prostate

The prostate gland produces and secretes an alkaline fluid, which energizes and protects the sperm during ejaculation. Commonly the prostate changes and enlarges with increasing age. Prostatitis, benign prostatic hyperplasia (BPH), and prostate cancer (PCa) are the most common types of prostate disease. PCa is the most common malignancy in men[1]. Transrectal ultrasound (TRUS) is a widely used imaging modality for prostate evaluation. The advantages of TRUS over other modalities are low costs, good availability, and ability to visualize the prostate in real time. Detection and delineation of prostate pathology with imaging remains a challenging endeavour.

Prostate anatomy

The prostate gland lies between the bladder neck and the urogenital diaphragm, just anterior to the rectum, an ideal position to be imaged via TRUS. The gland is traditionally described based on a pathologic zonal architecture. These divisions consist of the anterior fibromuscular stroma that is devoid of glandular tissue, transition zone, central zone, periurethral zone, and peripheral zone. The prostate is further divided into apex and base (directed upward to the inferior border of the bladder)[2]. The normal prostate gland has measures $3 \times 3 \times 5$ cm approximately or a volume of 25 ml. Seventy percent of all PCa are located in the peripheral zone, whereas 20% emerge from the transition zone and 10% in the central zone. The neurovascular bundle courses bilaterally along the posterolateral aspect of the prostate and is a preferential pathway of tumour spread.

Acute and chronic prostatitis

The prevalence of prostatitis ranges between 5% and 11%. Prostatitis occurs at any age and its incidence increases with age[3]. Acute bacterial prostatitis often begins with chills and fever, lower abdominal discomfort, perineal pain and burning on urination. In chronic bacterial prostatitis (when symptoms persist for at least 3 months) perineal pain and increased frequency of painful voiding are the most common symptoms. Acute or chronic bacterial prostatitis with confirmed or suspected infection should be distinguished from chronic pelvic pain syndrome (CPPS), according to the classification suggested by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The pathophysiology of prostatitis is not well understood. In patients with prostatitis, the activities of prostatic antibacterial factor are decreased and the pH is very alkaline. Bacteria (most commonly *Escherichia coli*) invade the prostate by an ascending urethral infection, by reflux of infected urine into prostatic ducts or by lymphatic/haematogenous spread[4]. Acute bacterial prostatitis appears in US as a hypoechoic rim around the prostate and colour Doppler shows an increased flow (Fig. 1)[5]. A prostate abscess appears sonographically as a hypoechogenic walled-off collection of fluid. In chronic bacterial prostatitis a diffuse increased enhancement of contrast agent may be found. US contrast agents show an increased perfusion of the prostate during acute and chronic infection, however they are not used in routine clinical practice since no studies regarding this issue have been performed[6].

Benign prostatic hyperplasia

More than 32 million men worldwide have symptoms related to BPH and BPH affects more than 50% of men over the age of 60 years and as many as 90% of men over the age of 70 years[5]. BPH is a benign disease of the prostate gland and consists of nodular hyperplasia of the fibrous, muscular, and glandular tissue within the periurethral and transition zones. The exact pathophysiology of BPH is still unknown but it is probably associated with hormonal changes that occur as men age. BPH appears in TRUS as an echogenic and non-mobile mass. TRUS is mainly used to assess prostate volume, which is crucial for therapeutic strategies. Prostate volume can be estimated by serial planimetry, orthogonal plane, rotational body (single plane, ellipsoid) and three-dimensional methods. Step-section planimetry is assumed to be the most accurate method of determining prostate volume, but it is time consuming and requires cumbersome special equipment. One-dimensional measurements are preferable in the clinic. The prolate ellipsoid formula, multiplying the largest anterioposterior (height), transverse (width) and cephalocaudal (length) prostate diameters by 0.524 ($H \times W \times L \times \pi/6$) is probably the most commonly used method, since it is rapid, reproducible, and has been shown to have high correlation with the actual prostate volume. The prolate spheroid formula $W \times W \times H \times \pi/6$ seems equally accurate, and has the advantage of requiring measurements in the transversal plane only[7].

Prostate cancer

PCa is the most common malignancy among men in western countries[1]. Furthermore, PCa is commonly asymptomatic at an early stage and most cancers are located in the peripheral zone. In patients who have elevated prostate-specific antigen (PSA) values PCa is suspected and therefore a digital rectal examination and TRUS-guided biopsy is performed. Imaging plays a

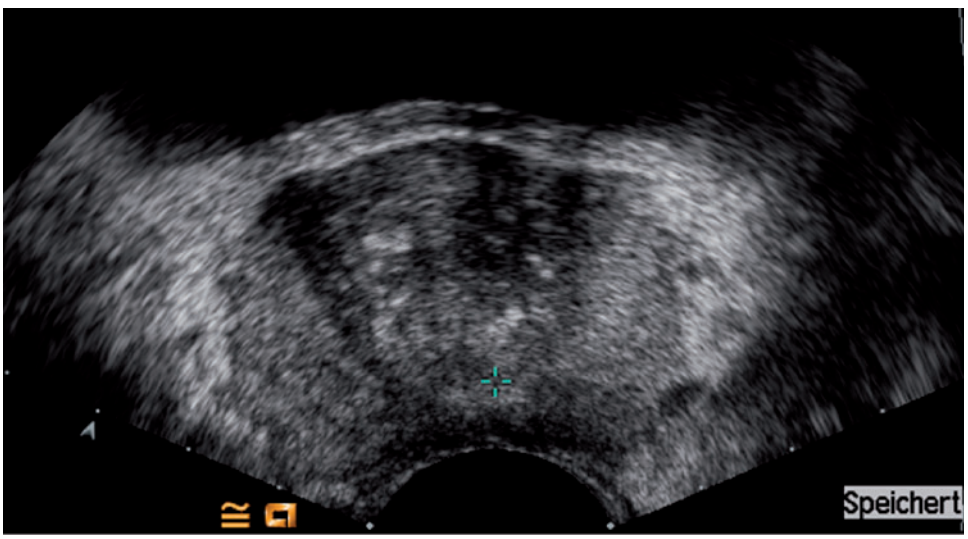

Figure 1 **Grey-scale US imaging of the prostate in a 55-year-old man who had a PSA level of 3.25 ng/ml showing no suspicious area.**

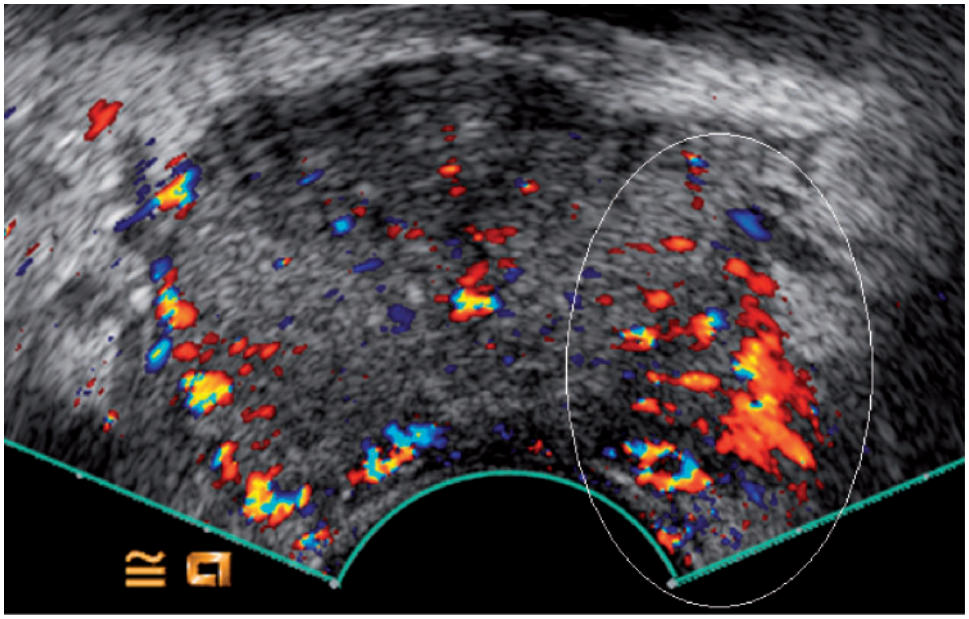

Figure 2 **Corresponding contrast-enhanced colour Doppler US showing clearly more enhancement of the left side (white ellipsoid). Targeted biopsy confirmed the presence of a Gleason score 3 + 4 cancer focus.**

central role in the detection, localization and staging of patients who have PCa[6].

Transrectal grey-scale imaging

Since its introduction in 1968 transrectal grey-scale imaging has improved by application of higher frequency probes and new signal reception techniques. The main use of grey-scale TRUS, however, is still the guidance of prostate biopsies. The classic PCa appears on TRUS as a hypoechoic nodule, however, this was in the pre-PSA era. Nowadays, because of the low PSA cut-off values, PCa is detected at an earlier stage, and many cancer foci appear isoechoic, and therefore cannot be detected by grey-scale TRUS[8].

In 1989, Hodge and associates introduced the TRUS-guided systematic sextant biopsy protocol. Since then many different protocols have been performed and nowadays at least 10–12 systematic biopsies of the peripheral zone are recommended as a first line strategy[9]. Oral or intravenous prophylactic antibiotics are state-of-the-art treatment. Optimal dosing and treatment time vary. Currently, quinolones are the drugs of choice, with ciprofloxacin superior to ofloxacin. The current consensus for local anaesthesia is the use of an US-guided peri-prostatic block. It does not make any difference whether the depot is apical or basal. Intrarectal instillation of a local anaesthetic is clearly inferior to peri-prostatic infiltration[10].

As a result of PSA screening with low PSA cut-off values, a stage migration has occurred toward less aggressive, organ-confined cancer[9]. Staging sensitivities in studies using grey-scale TRUS varied between 30% and 50% with specificities between 77% and 96%[11]. Three-dimensional TRUS aided in the assessment of extracapsular extension and seminal vesicle invasion[12].

Transrectal colour Doppler imaging

Colour Doppler imaging is well established to illustrate macrovascularity and therefore perfusion. PCa has an increased microvessel density compared with healthy prostatic tissue. Therefore, Doppler visualization of streaming blood within the vasculature may aid in detecting and localizing PCa (Fig. 2). In addition, the cancer grade correlates positively with the degree of Doppler signal[13]. Other studies have compared Doppler-guided and systematic biopsies with achieving a detection rate of up to 40%[14].

As a criterion for capsular penetration an increased capsular flow on colour Doppler imaging has been applied[2]. Another study that performed Doppler TRUS staging revealed a sensitivity of 59% for detecting locally advanced disease[15]. In addition, Doppler imaging also aids in differentiating fibrotic tissue from local recurrence of PCa[16].

Transrectal contrast-enhanced colour Doppler imaging

Contrast-enhanced US can be used for illustration of macrovascularity and microvascularity[17]. Microbubbles with a lipid or galactose shell filled with an inert gas and a diameter of 1–10 μm are administered intravenously. These microbubbles can be used as an echo enhancer for US, leading to visualization of blood flow in the microvessels. New contrast agents are constantly being developed. The most widely used ultrasound agents in PCa are

Levovist (Schering, Germany) and SonoVue (Bracco, Italy). Several different signal reception techniques can be applied for contrast agent detection (such as cadence-contrast pulse sequencing (CPS) or microvessel imaging (MVI) technology). The use of conventional Doppler imaging enhanced by microbubbles is the frequently reported in the literature.

Frauscher *et al.*[18] compared colour Doppler contrast-enhanced US targeted biopsy (CB) of the prostate using Levovist (Schering, Germany) with grey-scale ultrasound-guided systematic biopsy (SB). Two hundred and thirty male screening volunteers were included. The detection rate was 30%, including 24% by CB and 23% by SB. Cancer was detected by CB alone in 7% and by SB alone in 6% of the patients. The detection rate for CB cores (10% of cores) was significantly better than for SB cores (5% of cores). CB in a patient with cancer was 2.6-fold more likely to detect PCa than SB. CB detected as many cancers as SB with fewer than half the number of biopsy cores.

Mitterberger *et al.*[19] evaluated CB versus SB for the effect on Gleason score findings. The study included 690 men and SonoVue (Bracco, Italy) was used. PCa was identified in 221 of 690 subjects (32%) with a mean PSA of 4.6 ng/ml. PCa was detected in 180 subjects (26%) with CB, and in 166 patients (24%) with SB. The Gleason score of all 180 cancers detected by CB targeted biopsy was 6 or higher (mean 6.8). The Gleason score of all 166 cancers detected by SB ranged between 4 and 6 (mean 5.4). CB detected significantly higher Gleason scores compared with SB. Therefore CB techniques may allow identification of more aggressive cancers, which is important for defining prognosis and deciding adequate treatment.

In another prospective trial from Innsbruck, the previous findings were confirmed.[20] The chance to find cancer in a targeted biopsy (CB) core was significantly higher than in a random biopsy core (SB). Moreover, the total detection rate for five targeted biopsies alone was higher than for 10 random biopsies (Figs. 1–4).

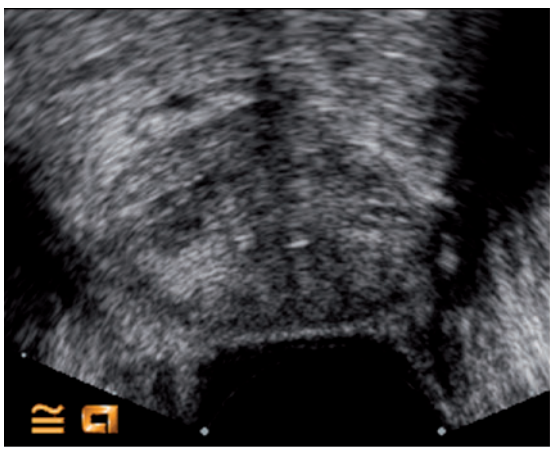

Figure 3 **Grey-scale US imaging of the prostate in a 57-year-old man who had a PSA level of 4.8 ng/ml showing no suspicious area.**

Transrectal contrast-specific US techniques

The development of contrast agent-specific US techniques have offered new potential for US in the detection of microvascularity, as found in the case of tumour vessels. These techniques use the non-linear properties of US contrast agents and therefore allow for a better axial and spatial resolution.

First results by Halpern *et al.*[21] have shown that this new technique allows for better PCa visualization and may allow for differentiation between benign and malignant prostatic tissue.

In another study Halpern *et al.*[22] assessed PCa detection and discrimination of benign from malignant prostate tissue with contrast-enhanced US using continuous harmonic imaging (CHI) and intermittent harmonic imaging (IHI), as well as continuous colour and power Doppler. Targeted biopsy cores were obtained from sites of greatest enhancement. PCa was detected in 363 biopsy cores from 104 of 301 subjects (35%). PCa was found in 15.5% (175 of 1133) of targeted cores and 10.4% (188 of 1806) of sextant cores ($P<0.01$). Among subjects with PCa, targeted cores were twice as likely to be positive. The authors concluded that the PCa detection rate of contrast-enhanced targeted cores is significantly higher compared with sextant cores. Contrast-enhanced transrectal sonography with IHI provides a statistically significant improvement in discrimination between benign and malignant biopsy sites. However, given the relatively low receiver operating characteristic areas, this technique may not be sufficient to predict which patients have benign versus malignant disease.

New ultrasound imaging techniques have been developed to better separate the information from bubble and tissue echoes. Cadence-contrast pulse sequencing (CPS) imaging is a low-power multipulse technique in which pulses with varied amplitude and phase are transmitted and the resulting echoes are summed. This imaging sequence results in substantial tissue suppression, allowing detection of the presence of small numbers of contrast agents retained in tissue. In addition, CPS can be used at a low mechanical index to prevent bubble destruction, which is a requirement for serial imaging of targeted contrast agents. By using CPS, certain sound sequences are transmitted that let the bubbles oscillate. The echoes of the contrast medium bubbles are separated from those of the tissue by using a special processing method. Thus, the inflow of contrast medium can be witnessed real-time on screen[23,24].

Aigner *et al.*[25] compared contrast-enhanced US using CPS technology with SB for detecting PCa in 44 men with suspicious PSA levels. Transrectal CPS images were taken with a low mechanical index (0.14). A microbubble contrast agent (SonoVue, Bracco, Italy) was administered

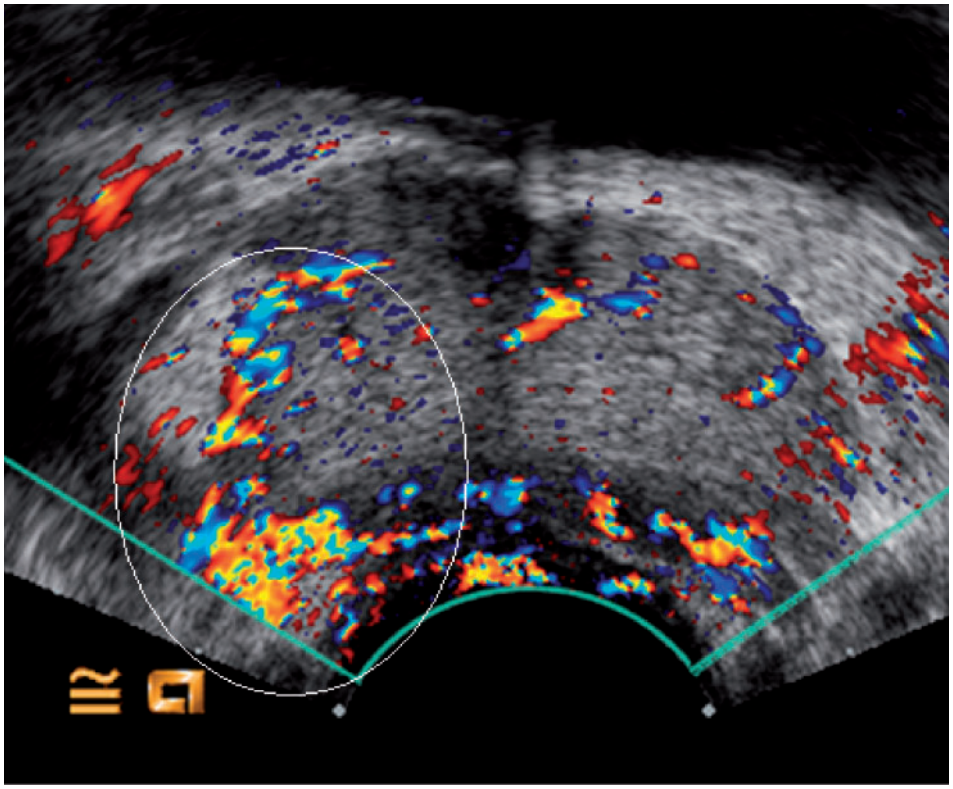

Figure 4 **Corresponding contrast-enhanced colour Doppler US showing clearly more enhancement of the right side (white ellipsoid). Targeted biopsy revealed a cancer focus with Gleason score 3 + 4.**

as a bolus, with a maximum dose of 4.8 ml. CPS was used to assess prostatic vascularity. Areas with rapid and increased contrast enhancement within the peripheral zone were defined as suspicious for PCa. Up to five CPS-targeted biopsies were taken and subsequently a 10-core SB was taken. PCa detection rates for the two techniques were compared. The results demonstrated that PCa was detected in 35 of 44 patients (80%), with a mean PSA level of 3.8 ng/ml. Lesions suspicious on CPS showed PCa in 35 of 44 patients (80%) and SB detected PCa in 15 of 44 patients (34%). CPS-targeted cores were positive in 105 of 220 cores (47.7%) and in 41 of 440 SB cores (9.3%). Aigner *et al.*[25] concluded that contrast-enhanced US using CPS enables excellent visualization of the microvasculature associated with PCa, and can improve the detection of PCa compared with SB. However, limitations in the series included that only CPS-positive cases were investigated, and CPS-targeted biopsy should be evaluated in a more extended biopsy scheme (Fig. 5).

In another study Seitz *et al.*[24] determined the ability of contrast-enhanced transrectal ultrasound (CE-TRUS) with CPS technology to identify PCa in 35 patients scheduled for radical prostatectomy and radical cystoprostatectomy. The US findings (CE-TRUS and B-mode TRUS) were correlated with step-section histology. Seitz *et al.*[24] found that CE-TRUS with CPS performed significantly better than B-mode TRUS for PCa detection. On a per patient basis, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for detecting PCa with CE-TRUS (with CPS) were 71%, 50%, 92%, and 18% in comparison with B-mode TRUS (sensitivity 45%, specificity 75%, PPV 93%, and NPV 18%). Seitz *et al.*[24] concluded that CE-TRUS with CPS detected PCa with a modest sensitivity and a high PPV in a selected patient cohort. However, future randomized-controlled multicenter studies are needed to further validate the value of CE-TRUS with CPS in the detection of PCa.

Real-time sonoelastography

Another newly implemented technique is real-time sonoelastography (RTE), which enables the illustration of distribution of tissue elasticity in one US slice[26]. This promising technique is calculated by post-processing algorithms and needs no contrast medium. RTE is therefore a real-time technique and shows different areas with different stiffness in a colour-coded image simultaneously with the B-mode or grey-scale image. RTE has been at the research stage for many years but has only recently come close to entering clinical practice and there is growing evidence through different published studies that RTE will further improve PCa detection.

Sperandeo *et al.*[27] reported the usefulness of elasticity imaging to differentiate malignant from benign lesions. They used tissue elasticity to detect cancer based on

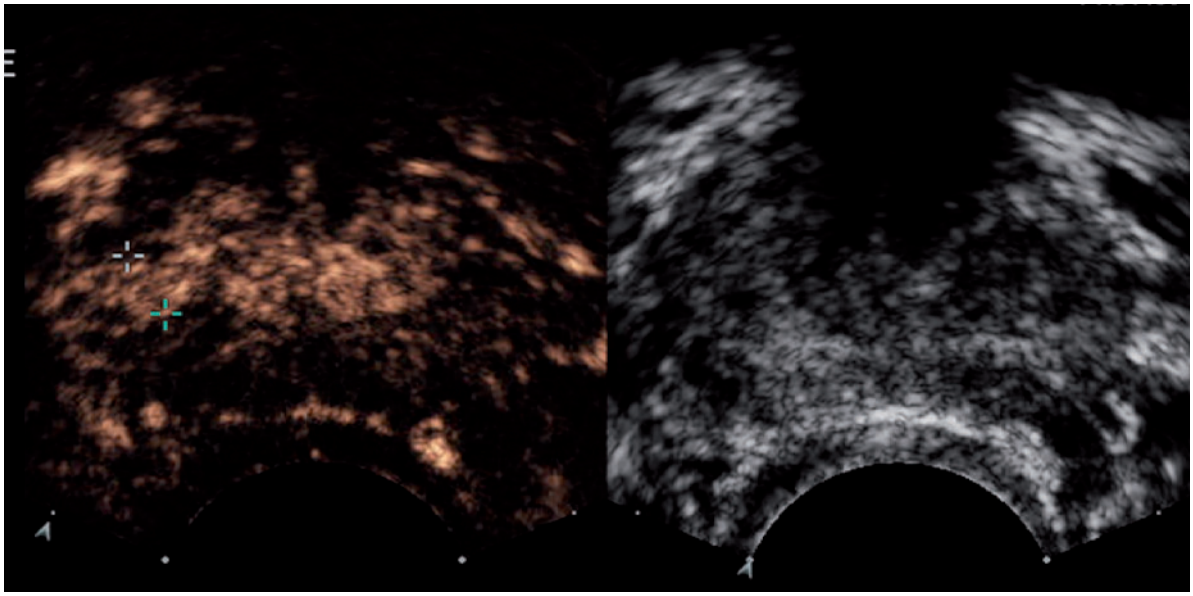

Figure 5 **US imaging of the prostate in a 60-year-old man who had a PSA level of 7.4 ng/ml. No abnormality was observed on grey-scale imaging (on the right side). Cadence-contrast pulse sequencing (CPS) imaging shows a rapidly enhancing lesion (18 s after bolus injection) on the right side (between crosslines). The enhancement is stronger than in the remaining prostate tissue. Three of five targeted cores were positive for cancer, whereas SB was negative.**

tissue deformation of grey-scale images under manual compression of the prostate with a transrectal probe. Sumura *et al.*[28] compared elastograms with the pathological findings of prostatectomy specimens. They reported that the detection rate of tumours even less than 1 ml volume was 73% and was 100% for tumours with a volume greater than 5 ml. They also reported that the detection rate of tumours located in the posterior gland (74%) was nearly equal to that of anterior tumours (75%). Tsutsumi *et al.*[29] found that the detection rate of tumours of the anterior part is higher compared with the posterior part of the prostate. Miyanaga *et al.*[30] reported that sonoelastography detected 93% of untreated PCas, which was significantly higher than the rate for DRE (59%) or TRUS (55%).

Salomon *et al.*[31] used elastography to determine the sensitivity and specificity for PCa detection in patients scheduled for radical prostatectomy. One hundred and nine patients with biopsy-proven localized PCa underwent elastography before radical prostatectomy. They found a sensitivity and specificity for detecting PCa of 75.4% and 76.6%, respectively. A total of 439 suspicious areas in elastography were recorded, and 451 cancerous areas were found in radical prostatectomy specimens. PPV, NPV, and accuracy for elastography were 87.8%, 59%, and 76%, respectively. Therefore they concluded that elastography can detect PCa foci within the prostate with good accuracy and has potential to increase US-based PCa detection.

Pallwein *et al.*[32] compared sonoelastography with SB findings of the prostate in 492 patients. In 125 of 492 patients (25%) SB demonstrated PCa. In sonoelastography, 533 of 2952 (18%) suspicious areas were detected and 258 of these areas (48%) showed cancer. Therefore they concluded that sonoelastography findings showed a good correlation with the SB results. The best sensitivity and specificity was found in the apex region. Sonoelastography seems to offer a new approach for differentiation of tissue stiffness of the prostate and may therefore improve PCa detection (Figs. 6 and 7).

Future developments

Contrast-specific US imaging techniques need specific three-dimensional acquisition for exact assessment of flow asymmetries, which would allow optimized PCa detection on the one hand, and may further allow minimal invasive therapies, or enable active surveillance in patients with diagnosis of PCa. New PCa-specific microbubbles are under development for exact detection and differentiation of PCa and benign prostatic tissue.

Ultrasound assessment with contrast agent dynamics (such as time–intensity curves) may allow an objective assessment of tumour vascularity and therefore improve PCa diagnosis.

Real-time elastography is limited because the compression is performed manually and is therefore not standardized. New techniques may allow for standardized compression and reduction in false-positive findings on elastography. Three-dimensional reconstructions will allow for a better assessment of the tissue stiffness difference within the prostate.

In addition, image fusion techniques, which allow for image fusion of MRI images into US units, and therefore enable US targeted biopsy into MRI suspicious lesions.

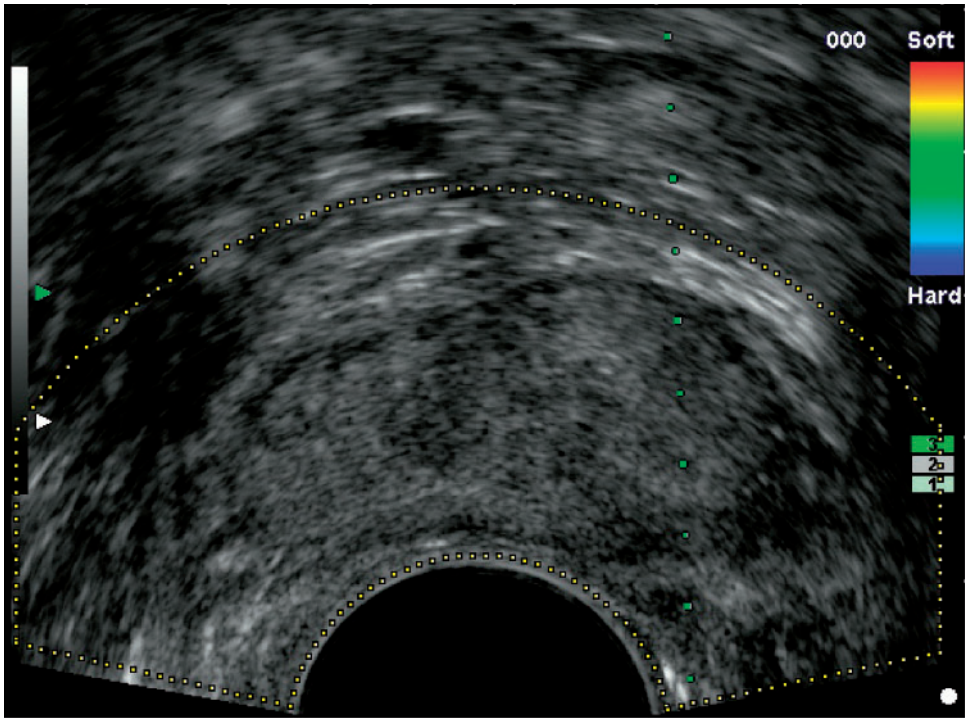

Figure 6 **Transverse transrectal grey-scale US image of prostate with no clear evidence for prostate cancer.**

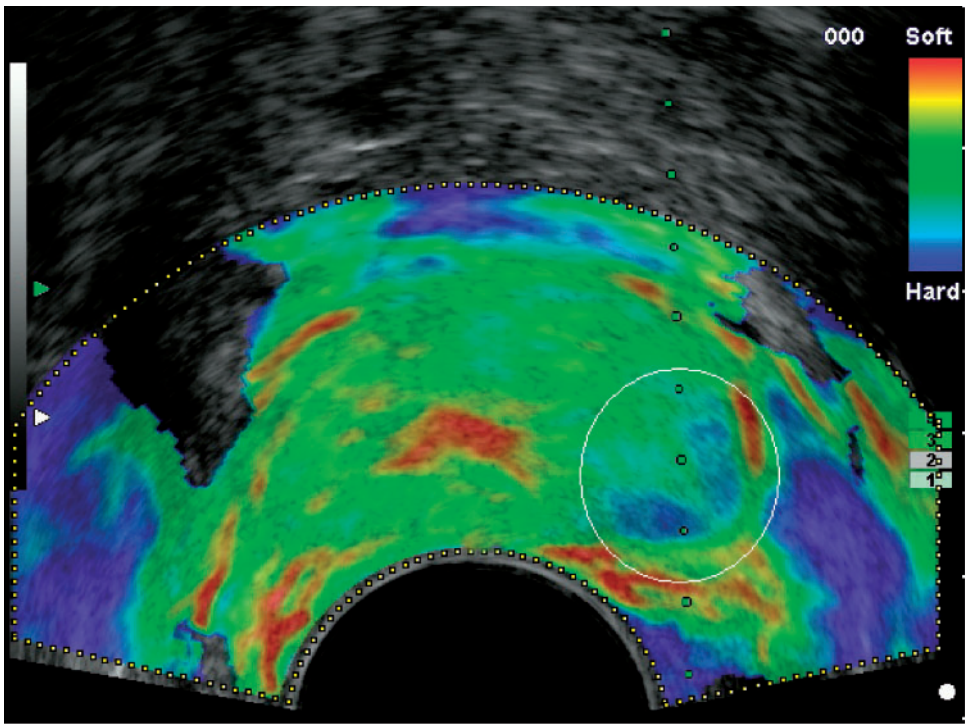

Figure 7 **Corresponding elastographic image of prostate. Elastogram shows a clearly visible stiffer area (blue colour) with suspicion of a prostate cancer on the left side of the prostate (white dot).**

Conclusion

Transrectal US-guided biopsy of the prostate with a minimum number of 10 biopsy cores of the peripheral zone remain the gold standard for PCa detection in the case of an elevated PSA or an abnormal DRE[9]. Contrast-enhanced targeted or real-time elastographically targeted biopsy can significantly increase PCa detection, especially the per core biopsy rate compared with SB[17]. Contrast-enhanced targeted US allows for detection of significantly higher Gleason score, which is important for PCa grading. Real-time elastography seems to offer new potential in PCa staging, compared with radical prostatectomy findings. Furthermore, new contrast-specific US techniques may further improve PCa diagnosis and may even avoid unnecessary biopsies in the future. However, both methods, contrast US and elastography, are still under clinical investigation and currently not used in standard clinical practice.

References

[1] Jemal A, Siegel R, Ward E, *et al.* Cancer statistics, 2008. CA Cancer J Clin 2008; 58: 71–96. doi:10.3322/CA.2007.0010. PMid:18287387.

[2] Ismail M, Gomella LG. Ultrasound for prostate imaging and biopsy. Curr Opin Urol 2001; 11: 471–7. doi:10.1097/00042307-200109000-00004. PMid:11493767.

[3] Krieger JN, Lee SW, Jeon J, *et al.* Epidemiology of prostatitis. Int J Antimicrob Agents 2008; 31(Suppl 1): S85–90. doi:10.1016/j.ijantimicag.2007.08.028. PMid:18164907.

[4] Grabe MB, Bishop MC, Bjerklund-Johansen M, *et al.* Guidelines on urological infections. 2009. http://www.uroweb.org.

[5] Futterer JJ, Heijmink SW, Spermon JR. Imaging the male reproductive tract: current trends and future directions. Radiol Clin North Am 2008; 46: 133–47, vii. doi:10.1016/j.rcl.2008.01.005. PMid:18328884.

[6] Pallwein L, Mitterberger M, Pelzer A, *et al.* Ultrasound of prostate cancer: recent advances. Eur Radiol 2008; 18: 707–15. doi:10.1007/s00330-007-0779-7. PMid:17938936.

[7] Eri LM, Thomassen H, Brennhovd B, *et al.* Accuracy and repeatability of prostate volume measurements by transrectal ultrasound. Prostate Cancer Prostatic Dis 2002; 5: 273–8. doi:10.1038/sj.pcan.4500568. PMid:12627211.

[8] Mitterberger M, Pelzer A, Colleselli D, *et al.* Contrast-enhanced ultrasound for diagnosis of prostate cancer and kidney lesions. Eur J Radiol 2007; 64: 231–8. doi:10.1016/j.ejrad.2007.07.027. PMid:17881175.

[9] Heidenreich A, Aus G, Bolla M, *et al.* EAU guidelines on prostate cancer. Eur Urol 2008; 53: 68–80. doi:10.1016/j.eururo.2007.09.002. PMid:17920184.

[10] Heidenreich A, Aus G, Bolla M, *et al.* [EAU guidelines on prostate cancer]. Actas Urol Esp 2009; 33: 113–26.

[11] May F, Treumann T, Dettmar P, *et al.* Limited value of endorectal magnetic resonance imaging and transrectal ultrasonography in the staging of clinically localized prostate cancer. BJU Int 2001; 87: 66–9. doi:10.1046/j.1464-410x.2001.00018.x. PMid:11121995.

[12] Mitterberger M, Pinggera GM, Pallwein L, *et al.* The value of three-dimensional transrectal ultrasonography in staging prostate cancer. BJU Int 2007; 100: 47–50. doi:10.1111/j.1464-410X.2007.06845.x. PMid:17433033.

[13] Tang J, Li S, Li J, *et al.* Correlation between prostate cancer grade and vascularity on colour Doppler imaging: preliminary findings. J Clin Ultrasound 2003; 31: 61–8. doi:10.1002/jcu.10139. PMid:12539246.

[14] Heijmink SW, Barentsz JO. Contrast-enhanced versus systematic transrectal ultrasound-guided prostate cancer detection: an overview of techniques and a systematic review. Eur J Radiol 2007; 63: 310–6. doi:10.1016/j.ejrad.2007.06.027. PMid:17719734.

[15] Sauvain JL, Palascak P, Bourscheid D, *et al.* Value of power Doppler and 3D vascular sonography as a method for diagnosis and staging of prostate cancer. Eur Urol 2003; 44: 21–30; discussion 30–1. doi:10.1016/S0302-2838(03)00204-5.

[16] Tamsel S, Killi R, Apaydin E, *et al.* The potential value of power Doppler ultrasound imaging compared with grey-scale ultrasound findings in the diagnosis of local recurrence after radical prostatectomy. Clin Radiol 2006; 61: 325–30; discussion 323–4. doi:10.1016/j.crad.2005.12.011. PMid:16546462.

[17] Pallwein L, Mitterberger M, Gradl J, *et al.* Value of contrast-enhanced ultrasound and elastography in imaging of prostate cancer. Curr Opin Urol 2007; 17: 39–47. doi:10.1097/MOU.0b013e328011b85c. PMid:17143110.

[18] Frauscher F, Klauser A, Volgger H, *et al.* Comparison of contrast enhanced colour Doppler targeted biopsy with conventional systematic biopsy: impact on prostate cancer detection. J Urol 2002; 167: 1648–52. doi:10.1016/S0022-5347(05)65171-3.

[19] Mitterberger M, Pinggera GM, Horninger W, *et al.* Comparison of contrast enhanced colour Doppler targeted biopsy to conventional systematic biopsy: impact on Gleason score. J Urol 2007; 178: 464–8; discussion 468. doi:10.1016/j.juro.2007.03.107. PMid:17561137.

[20] Mitterberger M, Horninger W, Pelzer A, *et al.* A prospective randomized trial comparing contrast-enhanced targeted versus systematic ultrasound guided biopsies: impact on prostate cancer detection. Prostate 2007; 67: 1537–42. doi:10.1002/pros.20639. PMid:17705242.

[21] Halpern EJ. Contrast-enhanced ultrasound imaging of prostate cancer. Rev Urol 2006; 8(Suppl 1): S29–37.

[22] Halpern EJ, Ramey JR, Strup SE, *et al.* Detection of prostate carcinoma with contrast-enhanced sonography using intermittent harmonic imaging. Cancer 2005; 104: 2373–83. doi:10.1002/cncr.21440. PMid:16240450.

[23] Stieger SM, Dayton PA, Borden MA, *et al.* Imaging of angiogenesis using cadence contrast pulse sequencing and targeted contrast agents. Contrast Media Mol Imaging 2008; 3: 9–18. doi:10.1002/cmmi.224.

[24] Seitz M, Gratzke C, Schlenker B, *et al.* Contrast-enhanced transrectal ultrasound (CE-TRUS) with cadence-contrast pulse sequence (CPS) technology for the identification of prostate cancer. Urol Oncol 2009; doi:10.1016/j.urolonc.2009.03.032.

[25] Aigner F, Pallwein L, Mitterberger M, *et al.* Contrast-enhanced ultrasonography using cadence-contrast pulse sequencing technology for targeted biopsy of the prostate. BJU Int 2009; 103: 458–63. doi:10.1111/j.1464-410X.2008.08038.x. PMid:19021610.

[26] Pallwein L, Aigner F, Faschingbauer R, *et al.* Prostate cancer diagnosis: value of real-time elastography. Abdom Imaging 2008; 33: 729–35. doi:10.1007/s00261-007-9345-7. PMid:18196315.

[27] Sperandeo G, Sperandeo M, Morcaldi M, *et al.* Transrectal ultrasonography for the early diagnosis of adenocarcinoma of the prostate: a new maneuver designed to improve the differentiation of malignant and benign lesions. J Urol 2003; 169: 607–10. doi:10.1016/S0022-5347(05)63965-1.

[28] Sumura M, Shigeno K, Hyuga T, *et al.* Initial evaluation of prostate cancer with real-time elastography based on step-section pathologic analysis after radical prostatectomy: a preliminary study. Int J Urol 2007; 14: 811–6. doi:10.1111/j.1442-2042.2007.01829.x. PMid:17760747.

[29] Tsutsumi M, Miyagawa T, Matsumura T, *et al.* The impact of real-time tissue elasticity imaging (elastography) on the detection of prostate cancer: clinicopathological analysis. Int J

Clin Oncol 2007; 12: 250–5. doi:10.1007/s10147-007-0669-7. PMid:17701002.

[30] Miyanaga N, Akaza H, Yamakawa M, *et al.* Tissue elasticity imaging for diagnosis of prostate cancer: a preliminary report. Int J Urol 2006; 13: 1514–8. doi:10.1111/j.1442-2042.2006.01612.x. PMid:17118027.

[31] Salomon G, Kollerman J, Thederan I, *et al.* Evaluation of prostate cancer detection with ultrasound real-time elastography: a comparison with step-section pathological analysis after radical prostatectomy. Eur Urol 2008; 54: 1354–62. doi:10.1016/j.eururo.2008.02.035. PMid:18374470.

[32] Pallwein L, Mitterberger M, Pinggera G, *et al.* Sonoelastography of the prostate: comparison with systematic biopsy findings in 492 patients. Eur J Radiol 2008; 65: 304–10. doi:10.1016/j.ejrad.2007.03.032. PMid:17524586.