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Leo Pallwein
Michael Mitterberger
Peter Struve
Wolfgang Horninger
Friedrich Aigner
Georg Bartsch
Johann Gradl
Matthias Schurich
Florian Pedross
Ferdinand Frauscher

Comparison of sonoelastography guided biopsy with systematic biopsy: impact on prostate cancer detection

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L. Pallwein (✉) · P. Struve · F. Aigner · J. Gradl · M. Schurich · F. Frauscher
Department of Radiology 2/ Uroradiology,
Medical University Innsbruck,
Anichstrasse 35,
6020 Innsbruck, Austria
e-mail: leo.pallwein@i-med.ac.at

M. Mitterberger · W. Horninger · G. Bartsch
Department of Urology,
Medical University Innsbruck,
Innsbruck, Austria

F. Pedross
Department of Medical Statistics,
Information and Health Economics,
Medical Universit Innsbruck,
Innsbruck, Austria

Abstract A prospective study was performed to determine the value of sonoelastography (SE) targeted biopsy for prostate cancer (PCa) detection. A series of 230 male screening volunteers was examined. Two independent examiners evaluated each subject. One single investigator performed ≤5 SE targeted biopsies into suspicious regions in the peripheral zone only. The stiffness of the lesion was displayed by SE and color-coded from red (soft) to blue (hard). Hard lesions were considered as malignant and targeted by biopsy. Subsequently, another examiner performed ten systematic biopsies. Cancer detection rates of the two techniques were compared. Cancer was detected in 81 of the 230 patients (35%), including 68 (30%) by SE targeted biopsy and in 58 (25%) by systematic biopsy. Cancer was detected by targeted biopsy alone in 23 patients (10%) and by systematic biopsy alone in 13 patients (6%). The detection rate for SE targeted biopsy cores (12.7% or 135 of 1,109 cores) was significantly better than for systematic biopsy cores (5.6% or 130 of 2,300 cores, $P<0.001$). SE targeted biopsy in a patient with cancer was 2.9-fold more likely to detect PCa than systematic biopsy. SE targeted biopsy detected more cases of PCa than systematic biopsy, with fewer than half the number of biopsy cores in this prostate-specific antigen screening population.

Keywords Prostate · Ultrasound · Sonoelastography

Introduction

Transrectal gray-scale ultrasound (US)-guided biopsy is the standard method for diagnosing prostate cancer (PCa) in patients with elevated prostate-specific antigen (PSA) and/or abnormal digital rectal examination (DRE). Due to an increase in the incidence of PCa, it is expected that in the United States 1.9 million biopsies will be performed in 2006. To improve PCa detection, various biopsy strategies have been devised to increase the diagnostic yield of prostate biopsy: sampling of visually abnormal areas, more lateral placement of biopsies, anterior biopsies, and obtaining an increased number of cores, with up to 45 biopsy cores. Unfortunately, several studies have shown that systematic biopsy still misses a considerable number of PCas. Therefore new strategies for PCa detection have been investigated. It is known that increased microvascularity accompanies cancer growth [1]. Neovascularity may thus be detectable by color Doppler US imaging due to abnormal blood flow patterns in larger feeding vessels [2]. This may present a valid approach to increasing diagnostic yield.

Other study groups described an increased cell density in neoplastic tissue [3]. This leads to an increased stiffness of tumor tissue, which can be evaluated by digital examination. However, DRE is examiner-dependent and is limited to the posterior part of the prostate [4]. Some hard nodules detected by DRE might actually indicate the presence of benign changes in the prostate, e.g., benign prostatic hyperplasia (BPH), inflammatory changes or calcifications.

Ophir et al. [5, 6] described the principles of elastography ("strain imaging") in 1991. This imaging

method is capable of visualizing displacements between US image pairs of tissue under axial compression. In order to reduce time-consuming calculations, Pesavento et al. [7] developed a fast cross sectional technique that is based on real-time elastographical imaging. Since most solid tumors differ with regard with their consistency from the deriving tissue, elastography may offer a new tool for cancer detection. The usefulness of real-time elastography for targeting of prostate biopsy had been reported previously [8, 9].

We performed a prospective study to determine whether a limited biopsy approach with real-time sonoelastography (SE) targeted biopsy of the prostate would detect PCa as well as gray-scale US-guided systematic biopsy with a larger number of biopsy cores.

Materials and methods

Between February 2006 and July 2006 we investigated 230 patients (mean age: 62.3±8.0 years) with a total PSA of 1.25 ng/ml or greater and free-to-total PSA less than 18% who were scheduled for prostate biopsy. From all patients an informed consent was received. Study exclusion criteria were clinical prostatitis within 1 month of biopsy and active urinary tract infection. The evening before biopsy all participants began a 5-day course of a fluoroquinolone antibiotic or appropriate alternative antibiotic if there was a fluoroquinolone allergy. A cleansing enema was administered on the morning of biopsy. Men with a prosthetic device, such as an artificial joint or mechanical heart valve, or the diagnosis of mitral valve prolapse with regurgitation and/or valve thickening received additional prophylactic antibiotic coverage with amoxicillin and/or gentamycin before biopsy. Patients were instructed not to ingest anticoagulant agents for at least 10 days before biopsy. Biopsies were obtained with the patient in the lithotomy position. DRE was not part of the screening process in this study. In each patient biopsy was performed by two independent examiners.

First, one investigator performed SE targeted biopsies into suspicious (stiffer) regions of the peripheral zone only. The maximum number of targeted biopsies was limited to five per patient [10]. We used a US system, EUB 8500 (Hitachi Medical, Tokyo, Japan), with a 7.5-MHz end-fire transrectal probe for this study. Sonoelastographic images were generated by the use of the so-called "Extended Combined Autocorrelation Method". This method allows the reconstruction of the tissue elasticity of the examined structures on the basis of the three-dimensional finite element model. Furthermore, this technique enables accurate estimation of the tissue elasticity distribution and adequate compensation of sideslips [11]. Real-time SE was performed by slight compression and decompression of the prostate, which was manually induced by the investigator using a transrectal US probe to apply force to the prostate. The force was adjusted appropriately according to a visual indicator for compression seen on the video screen. The visual indicator was developed to decrease the interobserver variability and to ease the skill acquisition for real-time SE. After processing the radio-frequency US data, the elastogram was shown side by side with conventional gray-scale images on the screen of the US system. The displacement estimates are used to determine the tissue strain as well as to reconstruct the Young's modulus (estimation of time shifts between corresponding A-lines) [11–14]. Regions with varying hardness are compressed differently and the local strain is computed and displayed. Real-time SE computes and displays the local strain with more than 30 frames/s. The strain is computed by the determination of local displacements between two consecutive images. The stiffness of the lesion was displayed from red (soft) to green (intermediate) and blue (hard). The diagnosis of PCa was based on the SE criteria described by Konig et al. [8]:

1. Hard (blue) lesions were considered as malignant;
2. The strain image of the lesion was reproducible (after tilting of the US probe).

Subsequently, another examiner (blinded to the results of SE) performed ten systematic prostate biopsies using a biplane endorectal probe (8808) attached to a US unit (Hawk, BK Medical, Copenhagen, Denmark). Systematic biopsy was performed as follows: one core from the base, one core from the mid-gland, two cores from the apex, and one core from the inner gland (transition zone) from each side of the prostate. Biopsies were obtained without regard to prostate B-mode US appearance.

Biopsies were obtained transrectally using an 18-gauge biopsy needle. Each biopsy core was reviewed by a pathologist and reported either as cancer with an assigned Gleason score, prostatic intraepithelial neoplasia, inflammation or benign prostatic tissue. Pathology results were reviewed to determine the number of patients diagnosed with PCa.

To compare the systematic biopsy findings with the results of SE targeted biopsy based on a topographic system, each prostate was divided into eight areas: six in the outer gland and two in the inner gland. However, the inner gland findings (one biopsy each side) were not included in our results, because a recent study has shown that the majority of cancers originate in the outer gland [15].

Statistical analysis

Patient characteristics were summarized with frequencies and percentages or with mean, ±SD, range, minimum and maximum values. To show significance between systematic biopsy and targeted biopsy, McNemar's test was used. Sensitivity for the SE targeted biopsy was

calculated in comparison with systematic biopsy (the "gold standard" method). To proof for significant differences of distribution of Gleason scores between systematic biopsy and targeted biopsy the Wilcoxon's rank sum test was performed. Additionally, the 95% confidence intervals (95% CI) have been computed for certain characteristics. All reported *P* values were two-sided and an error level of 5% was used.

All calculations were performed by using SPSS (version 11.5) software.

Results

Overall, cancer was detected in 81 of the 230 patients (35%). The mean prostate volume in all patients was 49±29 ml (Table 1).

PCa detected by patient

PCa was found by SE targeted biopsy in 68 patients (30%) and systematic biopsy in 58 patients (25%). Cancer was detected by SE targeted biopsy alone in 23 patients (10%) and by systematic biopsy alone in 13 (6%) patients. Sensitivity for cancer detection was 84% (68 of 81 cases) for SE targeted biopsy and 72% (58 of 81 cases) for systematic biopsy (Table 1).

Although PCa detection was slightly higher for SE targeted biopsy compared with the systematic approach, analysis by patient demonstrated no statistically significant difference in the overall cancer detection rate in the two arms of our study (30% versus 25%; McNemar's test $P=0.134$).

PCa detected by core

PCa detection rate for SE targeted biopsy was 135 of 1,109 cores (12.7%), and for systematic biopsy 130 of 2,300 cores (5.6%). The cancer detection rate per core was significantly higher for the SE targeted approach versus the systematic approach (McNemar's test: $P<0.001$). SE targeted biopsy in a patient with cancer was 2.9-fold more likely to detect PCa than systematic US-guided biopsy (Table 2).

Table 2 Numbers and sites of cores containing cancer detected by targeted biopsy alone or systematic biopsy alone

	SE targeted biopsy	Systematic biopsy
Apex	61 cores (22%)	49 cores (28%)
Mid-gland	45 cores (23%)	45 cores (34%)
Basis	29 cores (45%)	36 cores (38%)
Sum	135 cores	130 cores

The Gleason score in all 68 patients diagnosed by SE targeted biopsy varied between 6 and 9. Mean Gleason score of cancers detected by SE targeted biopsy alone was not higher than the score of cancers detected by systematic biopsy alone (6.6±0.8 versus 6.6±0.9; Table 1). No significant differences of distribution of Gleason scores were found between systematic biopsy and targeted biopsy (Wilcoxon rank sum test: $P=0.109$). However, real-time SE was capable of detecting all cancers with a Gleason score >7 (Fig. 1), 92% of cancers with Gleason score 7 (Fig. 2), and 79% of cancers with a Gleason score 6 (Fig. 3, Table 1).

Table 2 lists numbers and sites of PCa detected by targeted biopsy alone or systematic biopsy alone. Dividing the prostate into six outer gland areas (base right, mid-gland right, apex right, base left, mid-gland left, apex left), SE targeted biopsy found cancer in 61 cores at the apex (45%), in 45 cores at the mid-gland (33%), and in 29 cores at the base (22%). Systematic biopsy found cancer in 49 apical cores (38%), in 45 mid-gland cores (34%), and in 36 basal cores (28%). Therefore, in comparison with systematic biopsy the detection rate of SE targeted biopsy is slightly better in the apical areas (45% versus 38% of positive cores).

Multifocal disease occurs in 57% of our patients and SE failed to visualize this fact in 15% of our patients.

A total of 91 patients (40%) without cancer but with stiffer areas on SE were diagnosed with inflammatory prostate disease by histopathological examination (Fig. 4). Diffuse and focal inflammatory changes of the prostate were a major reason for false-positive findings on SE imaging. High- and low-grade prostatic intraepithelial neoplasia (PIN) was diagnosed in 11 (5%) and two (0.8%) patients, respectively. The 11 men with high grade PIN were scheduled for repeat biopsy within 3 to 6 months.

Table 1 Biopsy results for the combined, the systematic (gold standard method of cancer diagnosis), and the SE targeted approach

	Combined biopsy	Systematic biopsy	SE targeted biopsy
Gleason 6	$n=56$	$n=39$ (64%)	$n=44$ (79%)
Gleason 7	$n=13$	$n=9$ (69%)	$n=12$ (92%)
Gleason 8	$n=9$	$n=7$ (78%)	$n=9$ (100%)
Gleason 9	$n=3$	$n=3$ (100%)	$n=3$ (100%)
Sum	$n=81$	$n=58$	$n=68$

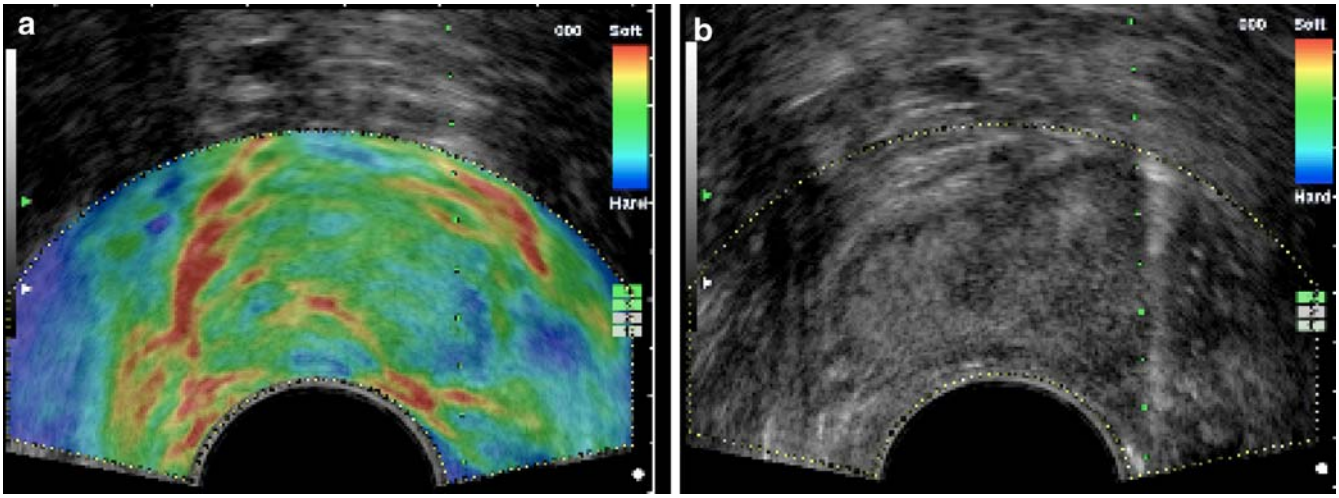

Fig. 1 SE (*left image*) showing stiffer (*blue*) areas in a patient with confirmed multifocal prostate cancer on the left side. The B-mode image shows the needle guidance into this stiff area, revealing a Gleason 8 cancer

Discussion

PCa is the most common form of cancer affecting men in the Western world. It is expected that in the future there will be a further increase in the incidence of PCa, largely because of the general aging of the population. Therefore, PCa detection is a main topic of diagnostic imaging, while screening for PCa is still controversial. PCa imaging is recently under strong efforts. Contrast-enhanced US and functional and structural endorectal magnetic resonance imaging (MRI) have both shown promise [2, 16]. The detection rate of PCa with the mentioned techniques ranges from 15% to 60%, mostly dependent on the PSA value and stage of disease. However early detection is the key to successful PCa treatment.

Nevertheless, systematic (or random) sextant biopsy of the prostate, which was the gold standard method of cancer diagnosis for many years, may miss cancers in up to 35% of cases [18–20]. Therefore, further improvements with a higher number of cores (up to 45) have been performed. However, a recent study has shown that 24-core saturation prostate biopsy did not appear to offer benefit compared with an initial ten-core biopsy technique [21]. Naughton et al. [22] reported no increase in PCa detection when comparing six versus 12 biopsy cores. The authors concluded that these findings

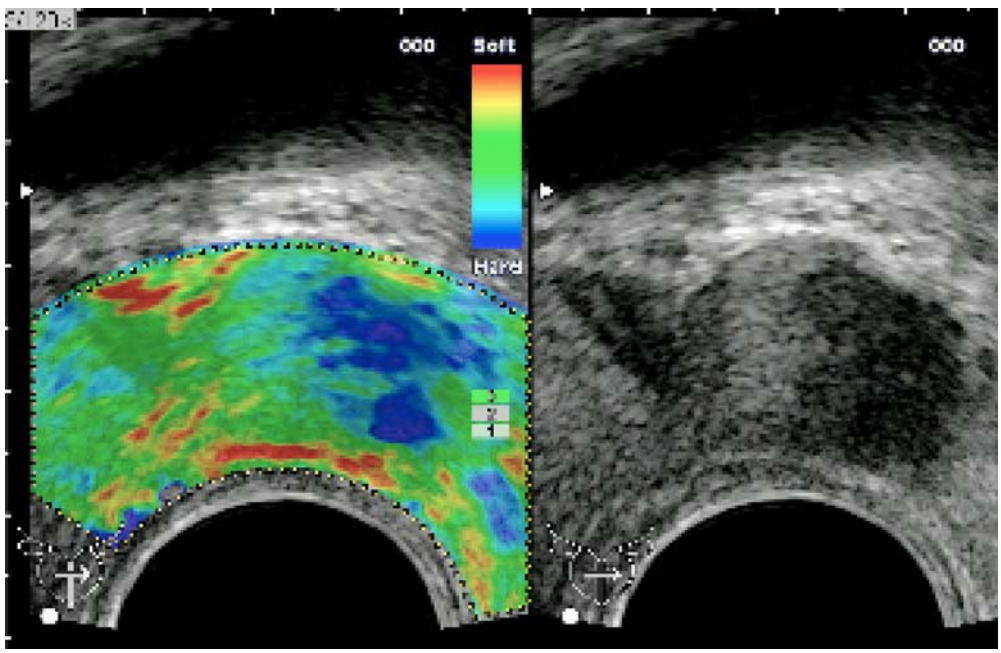

Fig. 2 SE (*left image*) showing a stiffer area (*blue*) on the left side of the prostate, suspicious for prostate cancer. Histology revealed a Gleason 7 cancer

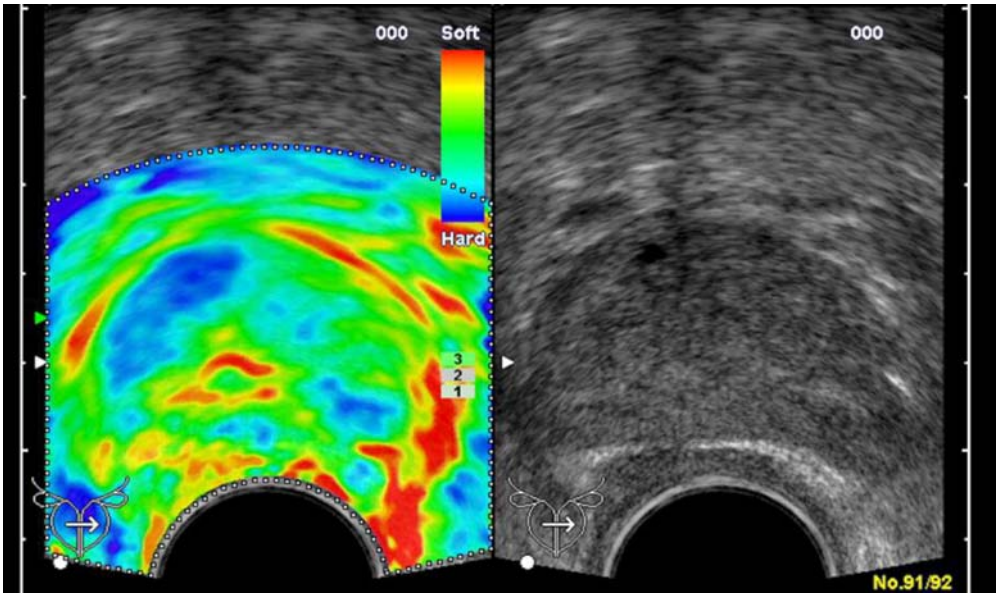

Fig. 3 SE (*left image*) of the mid-gland showing stiffer areas (*blue*) suspicious for multifocal prostate cancer in the left outer gland and in the right outer gland. Histology demonstrated bilateral Gleason 6 cancers

suggest that further efforts at extended biopsy strategies beyond ten to 12 cores are not appropriate as an initial biopsy strategy. Transrectal US of the prostate is easily available, and even with its low sensitivity and specificity, nearly 90% of cancers are detected by US guided systematic biopsy [1, 17]. However, new approaches are desirable to improve cancer detection to further improve detection as well as sensitivity and specificity.

Studies have shown that adding targeted biopsies from hypoechoic areas can improve PCa detection [23]. However, the review article by Heijmink et al. [24] showed that targeting hypoechoic lesions achieves high sensitivity but has low specificity. Furthermore, hypoechoic lesions are becoming less pathognomonic in the PSA screening era [25].

Moreover, some studies have shown that adding biopsies from the transition zone (TZ), can improve cancer detection. Pelzer et al. [15] assessed the value of TZ biopsies in a PSA screening population and found in 395 men with PCa only one true TZ cancer (0.6%). Their results show that TZ biopsies do not improve PCa detection rate and are therefore unnecessary in patients participating in a PSA screening program. Therefore, we feel comfortable that we did not investigate the TZ by SE.

Cancer tissue shows an increase in vessel density and cell density [3, 15]. The increased vascularization can be visualized with contrast enhanced US, and Frauscher et al. [2] used this for a targeted approach during biopsy of prostate areas with increased vascularization and could

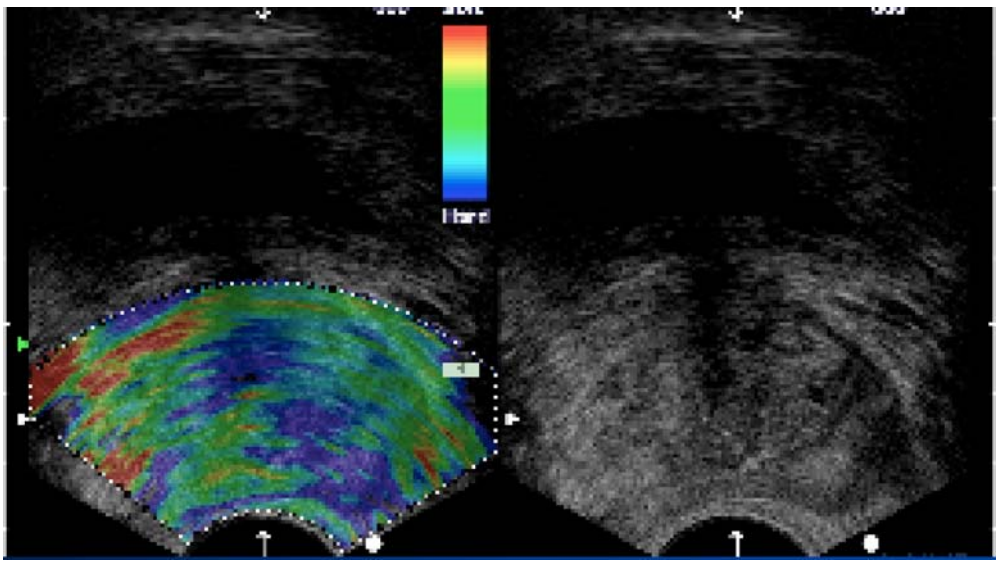

Fig. 4 SE (*left image*) of the mid-gland shows stiffer areas (*blue*) in the left outer gland. Histopathological examination demonstrated chronic prostatitis

thus significantly improve the cancer detection rate. The increase of cell density in tumors leads to a change of tissue elasticity. Krouskop et al. [3] described that there is a significant difference in stiffness between normal and neoplastic prostate and breast tissue. For detection of changes in tissue elasticity, in 1991 Ophir et al. [5, 6] developed an imaging technique based on static deformation and called it strain imaging. This imaging modality is capable of visualizing displacements between US image pairs of tissue under "compression". In order to reduce time-consuming calculations, Pesavento et al. [7] developed a fast cross-correlation technique, which enables a real-time elastographical imaging. With ongoing technical advances, elastography was integrated in modern high-end US units [11–14, 26]. Real-time SE has already shown its promising value in the detection and differentiation of masses in the breast and thyroid gland [27, 28]. Cochlin et al. [9] introduced real-time elastography for the detection of PCa in biopsy specimens. They reported that elastography had a sensitivity of 51% and a specificity of 83% for the detection of PCa in individual patients and a sensitivity of 31% and a specificity of 82% for the detection of individually biopsied areas of the prostate. In 2003, Sperandeo et al. [29] reported the usefulness of "elasticity" imaging to differentiate malignant from benign lesions. They used tissue elasticity to detect cancer based on tissue deformation of gray-scale images under manual compression of the prostate with a transrectal probe. In 2005, Konig et al. [8] also reported the efficacy of targeted prostate biopsy using real-time elastography. They could enhance PCa detection up to 84.1%. We have found a similar sensitivity of 84% for PCa detection using SE, by investigating the outer gland only.

Technical advances in SE in recent years enable better evaluation of the prostate. The experienced examiner, who needs at least 3–6 months training with SE, can prove the reproducibility of stiffer areas by repeating the examination of a suspicious area after tilting the US probe. However, new developments, which allow for an objective measurement of tissue elasticity, may reduce interobserver-variability and further improve the value of SE.

In our series of 230 men, SE targeted biopsy was able to detect PCa in 68 patients (30%). The detection rate was slightly higher compared with systematic gray-scale US (58 patients or 25%). However, SE failed to detect 13 cancers (5.6%). Several factors may have contributed to these results. Changes of BPH often demonstrate increased stiffness, which cannot be differentiated from malignant tissue. The pressure on the outer gland in BPH can produce a mosaic pattern, such as stiffness artefacts. Most of the false-positive findings (91 patients' areas; 40%) were associated with inflammatory disease and atrophy, especially at the basal prostatic areas.

The mean Gleason score for cancers detected by systematic biopsy was not significantly different to the mean Gleason score of all cancers detected by SE targeted biopsy. No significant differences of distribution of Gleason scores were found between systematic biopsy and targeted biopsy (Wilcoxon rank sum test: P=0.109). However, real-time SE was capable of detecting 12/12 cases (100%) of cancers with a Gleason score of 8 or higher and 12/13 cases (92%) of cancers with Gleason score 7. Therefore, based on our results, SE imaging was more likely to detect "clinically significant" PCas in our series.

Based on our analysis of individual biopsy cores the detection rate of SE targeted biopsy (12.7% or 135 of 1,109 cores) was significantly better than the rate of systematic biopsy (5.6% or 130 of 2,300 cores, P<0.001). In patients with PCa, a stiffer region in the peripheral zone detected by SE was 2.9-times as likely to contain cancer compared with a systematic biopsy core. Therefore, SE targeted biopsy seems to be able to improve cancer detection by reducing the number of needed biopsy cores.

The calculated sensitivity (84%) for the SE targeted biopsy is promising. SE failed to visualize stiff lesions in only 13 patients with proven cancer. This fact underlines the high sensitivity of this method, but we have to consider that multifocal disease occurs in 57% of our patients, what is in line with the current literature, and SE failed to visualize this fact in 15% of patients.

We note several limitations. First, all SE examinations were done by a single investigator. Therefore we do not have data on inter-and intraobserver-variability.

Second, we have used an endfire probe, which does not allow for scanning perpendicularly to the prostate surface, and may therefore have some disadvantages in performing prostate biopsy, and sampling prostate tissue. However, SE is currently only available on the endfire probe. Only the endfire probe allows for real-time SE targeted biopsies, which is not possible with a transverse side-fire probe, such as the one used in the study by Konig et al. [8].

Third, the elasticity coefficient is an absolute value, but the strain value is a relative index that may change with tissue composition, tissue structure, and alteration of the compression force. Quantification systems of the tissue elasticity (ongoing technical developments) may be helpful in the future to determine clearly measurable thresholds between benign and malignant tissue alterations.

Fourth, our study has used systematic biopsy as the gold standard, despite its known limitations, and diagnosis was based on biopsy specimens.

Fifth, our study did not compare SE targeted with gray-scale US targeted biopsy of hypoechoic lesions. However, as stated above, targeting hypoechoic areas is of limited value in a PSA screening population.

Sixth, we have used only one US system. Therefore, is has to be investigated if these results can be reproduced with different US systems and different elastographic modes.

Finally, there are also artefacts in the elastogram, some of which are of value like the "soft rim artefact" surrounding the prostate, which may helpful in case of extracapsular extension. Other artefacts, like the "halo-sign," were not delineable in most cases of cancer and seem to be questionable in their value [8]. SE was able to illustrate tissue elasticity adequately to a depth of approximately 5 cm, but we think that in case of BPH and in the lateral part of the elastograms multiple "stiffness-artefacts" are detectable. Repetition of the examination of a suspicious area after tilting the US probe is essential, and should be helpful to overcome these "lateral stiffness artefacts", but the "deep stiffness artefacts" with increasing depth of US waves will remain a major limitation of this promising method.

Conclusion

Our results demonstrate the usefulness of SE for detection of PCa in our PSA screening population. Real-time SE is a unique imaging modality, which allows for non-invasive assessment of tissue elasticity. Furthermore, real-time SE in conjunction with transrectal US is a simple, noninvasive and relatively cheap technique. Since it allows for targeted biopsy, the number of biopsy cores per patient can be reduced, which may reduce patient morbidity and lower costs. Further studies are necessary to evaluate if SE can evolve into clinical practice.

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