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# Sonoelastography of the prostate: Comparison with systematic biopsy findings in 492 patients

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**Abstract**

*Objective:* The aim of this study was to assess the value of sonoelastography (SE) for prostate cancer detection in comparison with systematic biopsy findings.
*Material and methods:* Four hundred and ninety two PSA screening volunteers (mean age: 61.9 ± 8.6) with an total PSA >1.25 ng/mL and a free to total PSA ration of <18% underwent SE of the prostate before 10 core systematic prostate biopsy. Tissue elasticity of the peripheral zone was investigated only. Tissue elasticity was displayed from red (soft) to green (intermediate) and to blue (hard). Only hard lesions (blue) were considered to be suspicious for prostate cancer. The peripheral zone of the prostate was divided in 3 regions on each side: base, mid-gland, apex. A different investigator performed systematic biopsy, and the biopsy findings were compared with the SE findings.
*Results:* In 125 of 492 patients (25.4%) systematic biopsy demonstrated prostate cancer. Cancer was detected in 321 of 2952 (11%) outer gland areas (74 in the base, 106 in the mid-gland, 141 in the apex). The Gleason score ranged from 3 to 10 (mean: 6.5). In SE 533 of 2952 (18.1%) suspicious areas were detected and 258 of these areas (48.4%) showed cancer. Most of the false-positive findings (275/533 areas; 51.6%) were associated with chronic inflammation and atrophy especially at the basal prostate areas. The sensitivity by entire organ was calculated with 86% and the specificity 72%. The analysis by outer gland areas showed the highest sensitivity in the apex (79%). The specificity by outer gland areas ranged between 85% and 93%. The correlation between SE findings and biopsy results was high ($p < 0.001$).
*Conclusion:* Sonoelastography findings showed a good correlation with the systematic biopsy 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 prostate cancer detection.


*Keywords:* Ultrasound; Sonoelastography; Prostate cancer

## 1. Introduction

Prostate cancer (PCa) shows an increasing incidence in the last years, and is the most common cancer in men [1]. The diagnosis is based on prostate specific antigen (PSA) testing, digital rectal examination (DRE) and ultrasound (US) guided biopsy. Based on the increasing incidence of PCa the number of prostate biopsies has also increased. Systematic biopsy with at least 8–10 cores is the method of choice. However this technique, based on gray-scale US imaging has shown several limitations. One limitation is that the chance that a hypoechoic area (the most common sign on gray-scale US for PCa) contains cancer varies between 17 and 57%, which leads to a low sensitivity and specificity of gray-scale US for PCa detection [2]. Another limitation is that even with increasing numbers of biopsy cores and more laterally directed biopsies the PCa detection rate cannot be increased even with 24 cores [3]. Therefore new techniques for cancer detection seem to be desirable.

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Sonoelastography (SE, strain imaging) is a new technique, which allows for assessment of tissue elasticity. Ophir et al. first described the principle of this technique in 1991 [4].

Pesavento et al. developed a fast cross-correlation technique that is the basis for real-time elastographical imaging [5]. This imaging modality is capable of visualizing displacements between US image pairs of tissue under "compression" [4,6].

Since most solid tumors differ with regards to their consistency from the deriving tissue, SE offers a novel tool in cancer detection [7]. New technical developments (e.g. for calculation of axial and lateral displacement of tissue structures under compression) allow for a better spatial resolution, a reduction of artefacts, and an increasing accuracy in using SE for routine examinations and first results have shown the usefulness of real-time SE for guiding prostate biopsy [8,9].

It has been shown that in a PSA screening population cancers originating from the inner gland (transition zone, TZ) are very rare, and therefore in this study only the outer gland (peripheral zone, PZ) was evaluated by means of SE [10].

Goals of our study were:

1. Comparison of biopsy results and SE findings: (a) for the entire prostate and (b) for the different outer gland areas in a PSA screening population.
2. Calculation of sensitivity and specificity for the SE findings in comparison to the results of systematic biopsy (the gold standard method).
3. Calculation of correlation between SE findings and (a) biopsy results, (b) the Gleason Score, and (c) the PSA values.

## 2. Material and methods

Included in this study were 492 patients (mean age: $61.9 \pm 8.6$) with increased PSA values (PSA screening criteria: $T_{PSA} > 1.25$ ng/mL), and a free-to-total ratio of <18% (mean: $6.8 \pm 7.1$) between March 2005 and February 2006. All patients were scheduled for a 10 core systematic biopsy, using a diplane endorectal probe (8808) attached to a BK US unit (Hawk, BK Medical, Copenhagen, Denmark). Systematic biopsy was performed by different experienced urologists (1–9 years of experience), who were blinded to the SE findings, as follows: 1 core from the base, 1 core from the mid-gland, 2 cores from the apex, and 1 core from the inner gland from each side of the prostate.

SE was performed by an experienced radiologist (7 years of experience) prior biopsy and we used a 7.5 MHz endocavity end-fire probe, attached to a Hitachi 8500 US unit. SE was done to evaluate the outer gland only [10].

The SE technique we used estimates displacement within corresponding A-lines, obtained by the evaluation of the cross correlation function of the RF-data set (unfiltered, high-frequency US data). 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) [11–13]. For real-time SE (up to 30 frames/s) the local strain was computed under slight compression and decompression of the prostate in the transverse plane.

After processing of the RF US data, the elastogram was shown side by side with conventional gray scale images on the screen of the US system. The applied force to the prostate was adjusted appropriately according to the visual indicator for compression seen on the video screen. This visual indicator was developed to decrease the interobserver variability and to ease the acquisition of real-time SE images. Multi-compression imaging is also used to improve the signal-to-noise-ratio (SNR) of the SE images [11–13] All images were recorded on DVD. The elasticity of the prostate tissue was displayed from red (soft) to green (intermediate) and to blue (hard). The color-coding is standardized and the same color-display was used in all patients. The diagnosis of PCa was based on the SE criteria described by Konig et al. [8].

(1) hard lesions were considered as suspicious for cancer;
(2) the strain image (elastogram) of the lesion was reproducible (after tilting of the US probe);
(3) a stiff lesion should have a diameter of at least 5 mm.

To compare the biopsy findings with the results of SE based on a topographic system, each prostate was divided in 6 areas of the outer gland (base, mid-gland, apex; on each side) [14]

Calcifications and other benign changes are more often found in the inner gland, which forces the SE technique to produce "stiffness-artefacts". On the other hand, the incidence of PCa in the outer gland is much higher than in the inner gland [10]. Therefore we defined to investigate the outer gland by SE for PCa detection only.

### 2.1. Statistical analyses

Patient characteristics were summarized with frequencies and percentages or with mean ± S.D.s, range, minimum and maximum values. To calculate the correlation between SE and systematic biopsy and between Gleason score and the 6 prostate areas we used the contingence coefficient. Normal distribution of PSA was tested with Kolmogorov–Smirnov. Kruskal–Wallis test was used to proof for significant differences between PSA and the SE findings, for each of the 6 outer gland prostate areas. Additionally the 95% confidence intervals (95% CI) have been computed for certain calculations. All reported $p$-values were 2-sided and an error level of 5% was used. Calculations were performed by using SPSS (Version 11.5) software.

## 3. Results

Mean prostate volume was $48.9 \pm 25.9$ mL. All prostates contained areas with soft and normal elasticity. Stiffer areas were suspected to be malignant and could reproducible be visualized on real-time SE as blue areas (Figs. 1–3). We found different patterns of increased stiffness, ranging from homogeneous dark blue areas to mosaic like or patchy patterns (Figs. 1–3). Glandular hyperplasia tended to be softer than stromal hyperplasia. Cystic lesions were illustrated with the softest area displayed in red, while the surrounding tissue framing the cystic lesion tended

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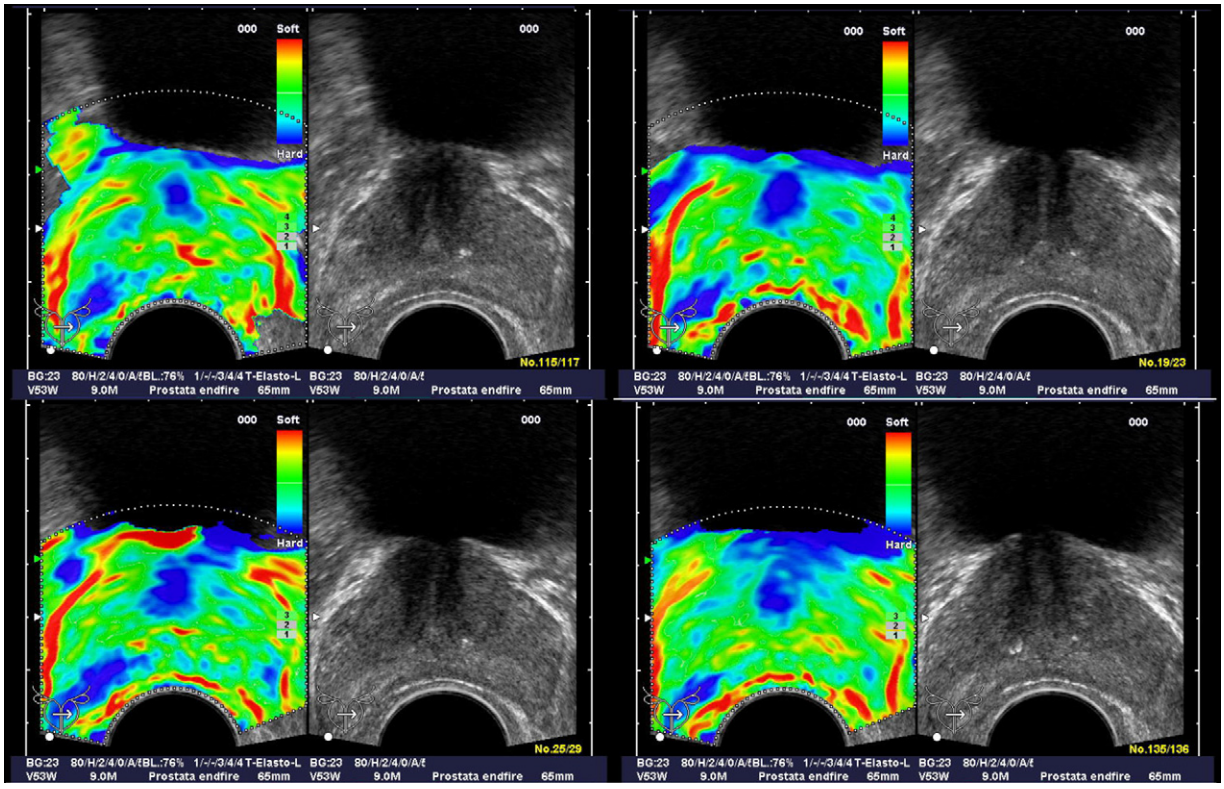


Fig. 1. Patient (picture series) with histologically confirmed prostate cancer in the right mid-gland of prostate. The elastographic examination showed a well-defined stiffer lesion. The peripheral zone on the left side showed normal stiffness.

to appear harder than the adjacent tissue. Prostatic stones were depicted as the hardest area displayed in blue.

### 3.1. Biopsy results and sonoelastography findings for the entire prostate

Systematic biopsy showed cancer in 125/492 patients (25.4%) with a Gleason Score from 3 to 10 (mean: 6.5; Table 1).

Analysis of SE for the entire prostate (only the outer gland) showed suspicious areas in 242 prostates (49.2%).

True positive were 146 (29.7%), false positive 91 (18.5%), true negative 233 (47.4%) and false negative 22 (4.5%) revealing a sensitivity of 0.86 (95% CI: 0.808–0.916) and a specificity of 0.72 (95% CI: 0.667–0.767). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) are shown in Table 2.

Table 1
Analysis of biopsy results and sonoelastography (SE) findings in 492 patients and 2952 outer gland areas

| Localization | Biopsy | SE rt.neg | SE fs.neg | SE fs.pos | SE rt.pos | SE total pos |
|---|---|---|---|---|---|---|
| Patients | 125/492 | 233 | 22 | 91 | 146 | 242 |
| Basal og areas rt | 32 | 422 | 17 | 33 | 20 | 53 |
| Mid og areas rt | 55 | 384 | 17 | 43 | 48 | 91 |
| Apical og areas rt | 66 | 361 | 17 | 51 | 63 | 114 |
| Basal og areas lt | 42 | 415 | 24 | 32 | 21 | 53 |
| Mid og areas lt | 51 | 375 | 17 | 57 | 43 | 100 |
| Apical og areas lt | 75 | 346 | 24 | 59 | 63 | 122 |
| Sum of og areas | 321 | 2303 | 116 | 275 | 258 | 533 |

og: outer gland, rt: right, fs: false, pos: positive, neg: negative, lt: left, mid: mid-gland.

### 3.2. Biopsy results and sonoelastography findings for the different outer gland areas

The pathohistological analysis of the outer gland areas showed following results: 321/2952 (10.9%) of outer gland areas were positive proven for cancer.

At the base 74 (7.5%; 32 right, 42 left) of all basal areas (=984) showed cancer.

At the mid-gland 106/984 (10.8%) areas (55 right, 51 left) showed cancer.

At the apex 141/984 (14.3%) areas (66 right, 75 left) showed cancer.

In the topographical analysis of the outer gland SE showed increased stiffness in 533/2952 areas (18.1%) and 258 (48.4%) of these areas showed cancer.

Table 2
Calculation of sensitivity, specificity, PPV, NPV and accuracy of SE for the entire prostate and the different outer gland areas

| | Patient | Base rt | Mid rt | Apex rt | Base lt | Mid lt | Apex lt |
|---|---|---|---|---|---|---|---|
| Sensitivity | 0.869 | 0.541 | 0.738 | 0.788 | 0.467 | 0.717 | 0.724 |
| Specificity | 0.719 | 0.927 | 0.899 | 0.876 | 0.928 | 0.868 | 0.854 |
| PPV | 0.616 | 0.377 | 0.527 | 0.553 | 0.396 | 0.430 | 0.516 |
| NPV | 0.914 | 0.961 | 0.958 | 0.955 | 0.945 | 0.957 | 0.935 |
| Accuracy | 0.770 | 0.898 | 0.878 | 0.862 | 0.892 | 0.850 | 0.831 |

rt: right, lt: left, mid: mid-gland.

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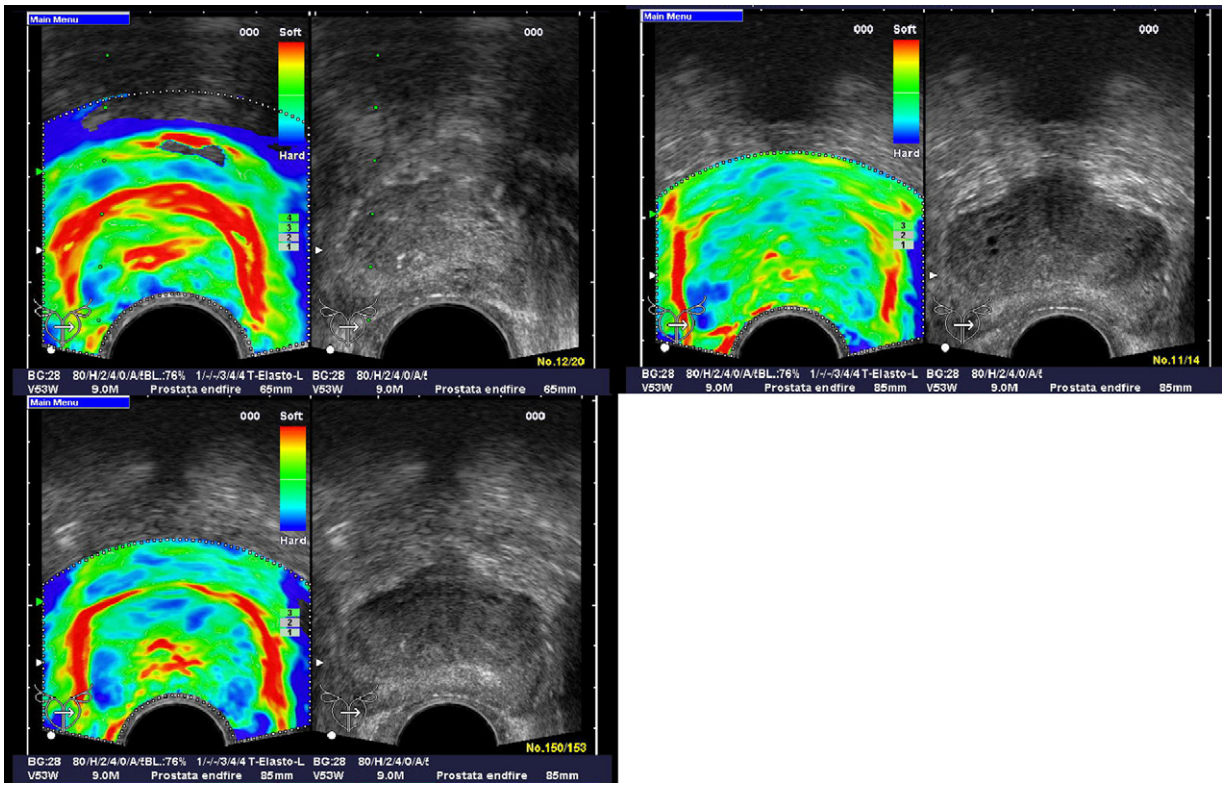


Fig. 2. Patient (picture series) with histologically confirmed focal prostate cancer in the peripheral zone of the right mid-gland. The lesion is elastographically well defined and slightly hypoechoic at the B-mode image. Stiffer areas were also visible in the left mid-gland (with mosaic-pattern-like appearance) and in the inner gland. These stiffness alterations were not clearly reproducible after tilting the ultrasound probe.

Most of the false-positive findings (275/533; 51.6%) were associated with chronic inflammation and atrophy especially at the base.

Analysis of SE for the different outer gland areas (Table 2) showed the lowest sensitivity for the base and the highest sensitivity for the apex.

The specificity (Table 2) was nearly equal for all areas.

The correlation between SE findings and biopsy results was significant (<0.001) with a contingency coefficient of 0.7 (Table 3).

We did not detect increased stiffness in 116/321 cancer areas (36.1%) in 22/125 patients (17.6%) with confirmed cancer.

Table 3
*p*-Value and contingence-coefficient showed a high correlation between SE findings in the different outer gland areas and histopathologic findings

| SE and h | | | | | |
|---|---|---|---|---|---|
| base rt | mid rt | apex rt | base lt | mid lt | apex lt |
| $p < 0.001$ | $p < 0.001$ | $p < 0.001$ | $p < 0.001$ | $p < 0.001$ | $p < 0.001$ |
| 0.707 | 0.704 | 0.707 | 0.694 | 0.687 | 0.695 |

SE: sonoelastography findings; h: histopathological findings; mid: mid-gland; rt: right; lt: left.

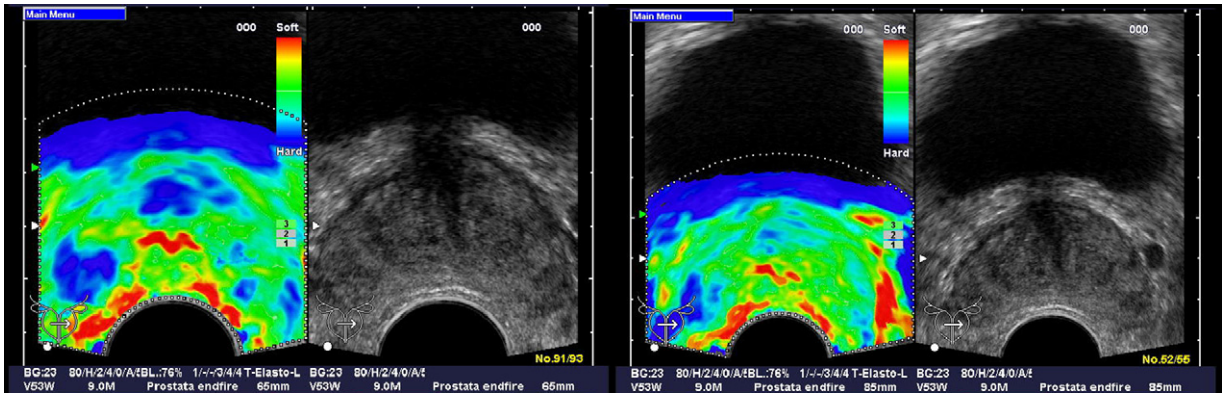


Fig. 3. Patient (picture series) with well defined and reproducible stiffer area on the right mid-gland presenting histologically confirmed focal prostate cancer. On the left side the patchy stiffness alterations could not be confirmed after tilting the ultrasound probe.

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Table 4
*p*-Value and contingence-coefficient between Gleason score and SE findings in the outer gland areas showed that these results are middle correlated

| | SE base rt | SE mid rt | SE apex rt | SE base lt | SE mid lt | SE apex lt |
|---|---|---|---|---|---|---|
| Gleason score | $p = 0.279$ | $p = 0.084$ | $p = 0.066$ | $p = 0.005$<br>0.435 | $p = 0.001$<br>0.461 | $p = 0.063$ |

SE: Sonoelastography findings; mid: mid gland; rt: right; lt: left.

Table 5
*p*-Values showed high significant differences between PSA values and the 4 groups (right positive, false positive, false negative, and right negative) of SE findings of the outer gland areas

| | base rt | mid rt | apex rt | base lt | mid lt | apex lt |
|---|---|---|---|---|---|---|
| PSA | $p = 0.003$ | $p < 0.001$ | $p = 0.001$ | $p < 0.001$ | $p = 0.001$ | $p < 0.001$ |

SE: sonoelastography findings; mid: mid gland; rt: right; lt: left.

### 3.3. Sonoelastography findings, gleason score and PSA

SE findings in the outer gland areas were middle correlated to the Gleason score (Table 4).

Real-time SE was capable of depicting 19/20 tumors (95.0%) with a Gleason score >7.

The detection rate for Gleason 6 cancer was 52/71 (73.2%) and for Gleason 7 cancer 21/23 (91.3%).

We found a highly significant difference between PSA values and the 4 groups (true positive, false positive, false negative, and true negative) of SE findings of the outer gland areas (Table 5).

## 4. Discussion

Prostate cancer is the most common cancer in men and since the "baby-boomer" generation will come to the age with higher risk for prostate cancer, it is expected that this will result in a significant further increase in incidence of PCa in the next years. Therefore, improvement of PCa detection is a main topic of diagnostic imaging. For this, PCa imaging is recently under strong efforts and cancer detection could be improved in the last decade mainly based on contrast-enhanced transrectal US and functional and structural endorectal MRI studies [14–19]. The results of MRI are promising, but, nevertheless, this method remains expensive and is not always available regarding the oncoming requirements. MR imaging-guided prostate biopsy enables the targeting of areas in the prostate that are suspicious for cancer and may hold promise for the evaluation of patients who have elevated PSA levels and negative findings at transrectal US-guided biopsy and in whom suspicious areas in the peripheral zone of the prostate are depicted on diagnostic MR images [19]. The detection rate of a malignant lesion in the prostate with the mentioned techniques ranges from 15% to 60% mainly dependent on the PSA value and stage of disease. But early detection is the key to successful PCa treatment.

US of the prostate is easy available but has a low sensitivity and specificity for PCa detection. Nevertheless, the US guided systematic (randomized) biopsy (sextant biopsy) of the prostate is still the "gold standard method of cancer diagnosis", but may miss cancers in up to 35% of cases [20]. Therefore further improvements with higher number of cores (up to 45; [21]) have been performed, however a recent study has shown that 24-core saturation prostate biopsy did not appear to offer benefit as an initial biopsy technique [3]. The authors concluded that these findings suggest that further efforts at extended biopsy strategies beyond 10–12 cores are not appropriate as an initial biopsy strategy. Therefore, other approaches are desirable to improve cancer detection. In our study we have used SE as a new approach for illustration of tissue elasticity.

Cancer tissue shows an increase in vessel density and cell density. The increase of cell density in tumors leads to a change of tissue elasticity, and Krouskop et al. described that there is a significant difference in stiffness between normal and neoplastic prostate and breast tissue [7]. For detection of changes in tissue elasticity, Ophir et al. developed 1991 an imaging technique based on static deformation and called it strain imaging [4,6]. This imaging modality is capable of visualizing displacements between ultrasound image pairs of tissue under compression. In order of time consuming calculations Pesavento et al. developed a fast cross-correlation technique, which enables a real-time elastographical imaging [4–6]. With ongoing technical advances SE was integrated in modern high-end US units [22,23]. The technical details of the elastographical algorithms of the US unit we have used are well described elsewhere [22,24]. Real time SE has already shown its promising value in the detection and differentiation of masses in the breast and thyroid gland [25,26]. Cochlin et al. introduced real-time elastography for the detection of prostate cancer in biopsy specimens. They reported that elastography had a sensitivity of 51% and a specificity of 83% for the detection of prostate cancer in individual patients and a sensitivity of 31% and a specificity of 82% for the detection of individually biopsied areas of the prostate [9]. In 2003, Sperandeo et al. 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 [27]. In 2005, Konig et al. also reported the efficacy of targeted prostate biopsy using real-time elastography. They could enhance PCa detection up to 84.1% [8].

In comparison to these studies we found an increase in sensitivity and specificity by patient including the outer gland only. In our PSA screening population (PSA cut-off is 1.25 ng/mL, which is much lower than the most common used cut-off of 4.0 ng/mL) SE showed by patient a sensitivity of 0.87 and specificity of 0.72 for cancer detection, which may make the SE an interesting tool for targeted biopsy. This may be explained by the higher number of patients and the technical advances in the last years, which allow for better evaluation of the prostate. The experienced examiner (it takes a mean of 3 months training to

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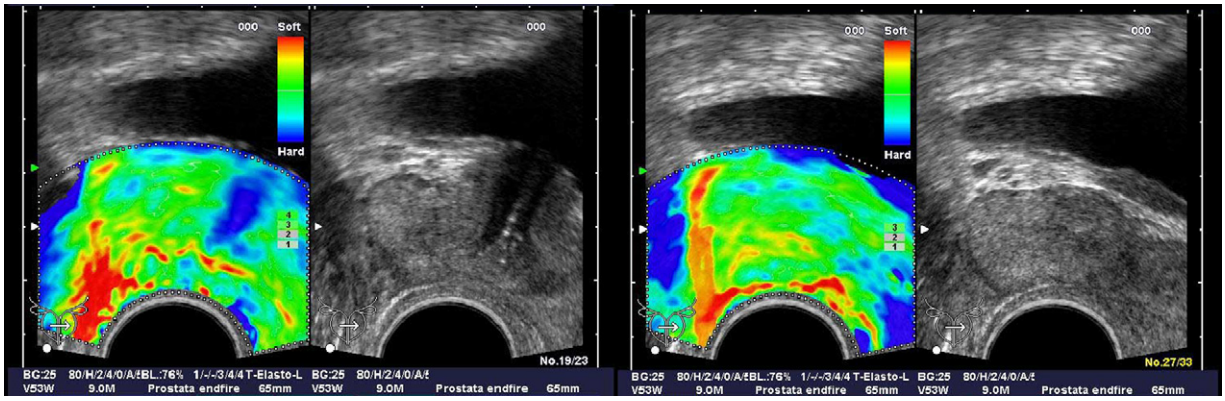


Fig. 4. Patient (picture series) with histologically confirmed chronic prostatitis with elevated PSA. In both elastograms the peripheral zone at the right base showed no reproducible stiffness alterations.

overcome the learning curve) can prove the reproducibility of stiffer areas after tilting of the US probe. The area-related analysis of peripheral zone showed the best sensitivity and specificity in the apex and the worst in the base. SE failed to visualize stiffness in 36.1% of outer gland areas in 22 of 125 patients only. This fact underlines the value of this method, but we have to consider that multifocal disease occurs in 70.4% of our patients, what is in line with the current literature, and SE failed to visualize this fact in 17% of patients. The Gleason score and the SE findings were only middle correlated. On the other hand SE showed an excellent detection rate in high-graded cancers with Gleason score 8 and more and so we think that our preliminary results show that SE is capable to detect most ”relevant“tumors especially in the apex and mid-gland.

We note some limitations; first is that the elastic 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 elasticity index (ongoing technical developments) maybe helpful in the future to determine clearly measurable thresholds between benign and malignant tissue alterations. Second, our study has used systematic biopsy as the gold standard, which has known limitations, and diagnosis was based on biopsy specimens. However, it is the method of choice for cancer detection. Therefore, real-time SE was performed without information on the actual distribution of prostate cancer. The fact that we included biopsy and SE results only from the outer gland maybe another limitation, but in a PSA screening population we have found that TZ cancer are very rare [10]. In 395 prostate cancers we found only one truly TZ-confined cancer (0.6%), which shows that TZ cancers are more or less irrelevant. Furthermore, in screening patients with cancer, who undergo radical prostatectomy, 88% are T2 cancers [10]. Since we are dealing with a PSA screening population (cut-off: 1.25 ng/mL), we found that hypoechoic areas are less common and the chance that a hypoechoic area contains cancer is as low as 4%, therefore we have not focused on targeting hypoechoic areas [10]. However a study comparing hypoechoic areas and elastography would be interesting. The main methodical limitation of SE is the increase of stiffness in chronic inflammatory tissue alterations (Fig. 4) with consecutive stromal hyperplasia and fibrosis.

There are also artefacts in the elastogram; some of them are of value like the “soft rim artefact” surrounding the prostate, which maybe can 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 [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. Tilting the US probe 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.

## 5. Conclusion

Our results demonstrate the potential and also limitation of SE for PCa detection. Especially in the apical areas we found promising results. Furthermore, real-time SE in conjunction with TRUS is a simple, non-invasive and relatively cheap technique. Since it may allow for targeted biopsy it can help to decrease the number of biopsy cores in men scheduled for biopsy. However further studies are necessary to evaluate if SE can play a role in general practice.

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