Value of Real-Time Elastography Targeted Biopsy for Prostate Cancer Detection in Men With Prostate Specific Antigen 1.25 ng/ml or Greater and 4.00 ng/ml or Less

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Purpose: We assessed the prostate cancer detection rate of real-time elastography targeted biopsy in men with total prostate specific antigen 1.25 ng/ml or greater and 4.00 ng/ml or less.

Materials and Methods: Real-time elastography using an EUB 8500 Hitachi ultrasound system (Hitachi Medical, Tokyo, Japan) was done in 94 men with a mean age of 57.4 years (range 35 to 77) with increased prostate specific antigen between 1.25 ng/ml or greater and 4.00 ng/ml or less (mean 3.20, range 1.30 to 4.00) and a free-to-total prostate specific antigen ratio of less than 18%. Real-time elastography was done to evaluate peripheral zone tissue elasticity and hard areas were defined as suspicious. Targeted biopsies with a maximum of 5 cores were done in suspicious areas, followed by 10-core systematic biopsy. We analyzed the cancer detection rate of real-time elastography and systematic biopsy.

Results: Cancer was found in 27 of 94 patients (28.7%). Real-time elastography detected cancer in 20 patients (21.3%) and systematic biopsy detected it in 18 (19.1%). Positive cancer cores were found in real-time elastography targeted cores in 38 of 158 cases (24%) and in systematic cores in 38 of 752 (5.1%) (chi-square test $p < 0.0001$). The cancer detection rate per core was 4.7-fold greater for targeted than for systematic biopsy.

Conclusions: Real-time elastography targeted biopsy allows prostate cancer detection in men with prostate specific antigen 1.25 ng/ml or greater and 4 ng/ml or less with a decreased number of cores compared with that of systematic biopsy.

Key Words: prostate, prostatic neoplasms, prostate-specific antigen, elasticity imaging techniques, biopsy

Abbreviations and Acronyms

DRE = digital rectal examination
MRI = magnetic resonance imaging
NPV = negative predictive value
PCa = prostate cancer
PPV = positive predictive value
PSA = prostate specific antigen
RTE = real-time elastography
TZ = transition zone

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PROSTATE cancer is the most common cancer in men in the Western world. The American Cancer Society estimated 192,280 new cases and 27,360 PCa related deaths in 2009.[1] The most common strategy of PCa detection is based on PSA, DRE and transrectal ultrasound guided systematic biopsy.[2–4] Unfortunately these approaches have unsatisfactory diagnostic accuracy.[3,5,6] Thus, imaging modalities able to visualize PCa are currently undergoing intensive research.

One imaging method to detect PCa is RTE. The technique of elastographic imaging is based on the fact that cancer tissue has greater cell and

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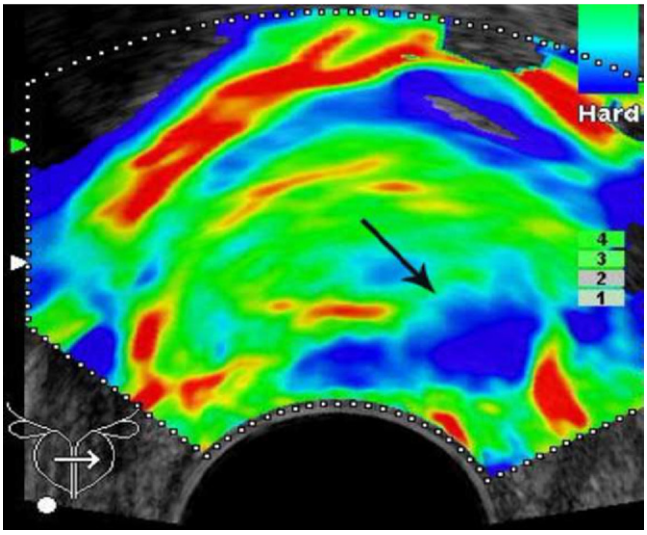

Figure 1. At hard area at left apex (blue area, arrow) histology revealed Gleason score 7 (3 + 4) cancer.

vessel density, resulting in greater tissue stiffness.[7] The technique allows tissue elasticity assessment by compression and decompression in real time. In preliminary studies RTE has enabled cancer detection, ie of the breast, thyroid and prostate.[7] Therefore, this technique has become more interesting for suspected PCa. Salomon et al reported that RTE had 76% diagnostic accuracy for cancer detection compared with that of radical prostatectomy specimens.[8]

The optimal cutoff value for PSA to allow optimal cancer detection is still under debate. In our Tyrolean screening program we use a cutoff of 1.25 ng/ml and noted a significant decrease in PCa related mortality.[9] Also, Thompson et al found cancer in 15.2% of men with PSA 4.00 ng/ml or less.[10] Thus, we assessed the value of RTE targeted biopsy for PCa detection in men with PSA 1.25 ng/ml or greater and 4.00 ng/ml or less.

MATERIALS AND METHODS

Patients

Included in our study were 94 PSA screening volunteers with a mean age of 57.4 years (range 35 to 77) scheduled for prostate biopsy based on total PSA 1.25 ng/ml or greater and 4.00 ng/ml or less, and a free-to-total PSA ratio of less than 18%.[9] All patients provided informed consent and the study received local ethical review board approval. Study exclusion criteria for prostate biopsy were described previously.[11] DRE was not included in our screening program. A total of 79 patients (84%) underwent an initial biopsy session and 15 (16%) underwent repeat biopsy sessions. Ten (9.4%), 2 (2%) and 3 patients (3%) had undergone 1 to 3 previous biopsies, respectively, within the last 36 months.

RTE Targeted Biopsy

We used an EUB 8500 Hitachi ultrasound unit with a 7.5 MHz end fire transrectal probe to assess tissue elasticity. Elastograms were obtained by slight prostate compression and decompression. Hard areas were considered PCa suspicious and seen as blue areas (fig. 1). These areas were reproducible using a previously described approach.[12] Red and green areas were defined as normal prostate tissue.

Elastography was done to evaluate the peripheral zone only since most cancers originate from this zone.[13] Up to 5 targeted cores were obtained from the hard outer gland areas under RTE guidance using an 18 gauge needle. The peripheral zone was divided into 6 areas, including base right, mid gland right, apex right, base left, mid gland left and apex left. Based on these sites we evaluated PCa detection for each technique. For per core PCa detection analysis we excluded TZ cores.

Systematic Biopsy

Systematic biopsy was done at the same session by a different investigator blinded to RTE results. A 10-core approach was used. Cores were obtained from the base (1), mid gland (1), apex (2) and TZ (1) at each side of the prostate. Transrectal ultrasound was done in a standardized way independent of grayscale findings.[14]

Analysis

Pathological. Each biopsy core was numbered, assigned to a sextant and reviewed by a pathologist (fig. 2). Results were reported as cancer with an assigned Gleason score or as atrophy, benign prostatic hyperplasia, adenomyomatosis, prostatitis or normal findings.

Statistical. Patient characteristics are shown as the incidence and percent or the mean ± SD, range, minimum and maximum. Sensitivity, specificity, PPV and NPV were calculated on a per patient and per core (per sextant) basis. Since targeted biopsy was done in the peripheral zone only, TZ cores were excluded from data analysis for per core (per sextant) PCa detection.

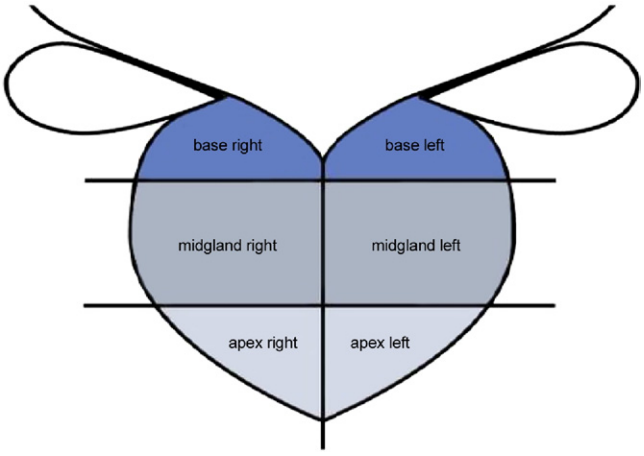

Figure 2. Prostate zone anatomy. Peripheral zone is divided into base, mid gland and apex at each site. Study did not focus on inner gland.

We used the McNemar chi-square to compare the RTE detection rate by patient with the systematic biopsy detection rate. The Kolmogorov-Smirnov test was used to test for normality in the positive biopsy rate per core. Subsequently differences between unpaired groups were evaluated by ANOVA when normally distributed, or the Kruskal-Wallis test when not normally distributed. All reported p values are 2-sided and an error level of 5% was used. The p value was adjusted with the Sidak correction. Calculations were made using SPSS®, version 16.0.

RESULTS

Cancer was detected in 27 of the 94 men (28.7%) with a mean age of 57.4 years (range 35 to 77), a mean PSA of 3.20 ng/ml (range 1.30 to 4.00) and a mean prostate volume of 42.10 ml (range 18 to 112).

PCa Detection

By patient. RTE detected cancer in 20 patients (21.3%) and systematic biopsy detected cancer in 18 (19.1%) (table 1). Cancer was detected by RTE targeted biopsy alone in 9 patients and by systematic biopsy alone in 7 (9.6% vs 7.4%, McNemar chi-square 0.25, p = 0.8). On RTE 51 of the 94 men (54.3%) had suspicious findings and 43 had normal findings. Of the 51 patients with suspicious findings on RTE PCa was correctly diagnosed in 20 (39%). In 4 men with suspicious findings RTE failed to detect cancer and 3 with normal RTE findings had PCa on systematic biopsy. This resulted in 74% sensitivity, 60% specificity, 39% PPV and 93% NPV by patient.

By core. RTE targeted cores were cancer positive in 38 of 158 cases (24%) and systematic cores were cancer positive in 38 of 752 (5.1%). The cancer detection rate per core was higher for the RTE targeted approach than for the systematic approach. The probability that a targeted core was cancer positive was 4.7-fold greater than for a systematic core. Gleason score in all 20 patients diagnosed by RTE targeted biopsy was between 5 and 7. The mean Gleason score in RTE targeted vs systematic biopsies was not significantly different (6.20 vs 6.17, p = 0.109, table 1). However, RTE detected all cancers with a Gleason score of 7 and 67% with a score of 6 (table 1).

We analyzed 6 outer gland areas, including base right, mid gland right, apex right, base left, mid gland left and apex left. RTE targeted biopsy revealed cancer in 15 cores (39%) at the apex, in 16 (42%) at the mid gland and in 7 (18%) at the base. Systematic biopsy revealed cancer in 13 cores (34%) at the apex, in 15 (39%) at the mid gland and in 10 (26%) at the base (table 2). A total of 31 patients (33%) without cancer but with stiffer areas on RTE were diagnosed with atrophy (6), benign prostatic hyperplasia (9), adenomyomatosis (4) or prostatitis (12). RTE negative findings with benign results on systematic biopsy included atrophy in 10 cases, hyperplasia in 15, adenomyomatosis in 5 and prostatitis in 8.

Table 1. *Combined, systematic and RTE targeted approach biopsy results*

Gleason	No. Combined	No. Systematic (%)	No. RTE (%)
5	1	0	1 (100)
6	21	15 (71)	14 (67)
7	5	3 (60)	5 (100)
Totals	27	18	20

Table 2. *Cores containing cancer detected by RTE targeted and systematic biopsy*

Site*	No. RTE Cores (%)	No. Systematic Cores (%)
Overall	158	752
Apex	15 (39)	13 (34)
Mid gland	16 (42)	15 (39)
Base	7 (18)	10 (26)
Totals	38 (24)	38 (5.1)

* TZ cores were excluded from data analysis.

PSA Subgroup Analysis

In the PSA range of 1.25 to 2.00 ng/ml cancer was found in 1 of 9 cases (11%). This cancer was detected by targeted biopsy with RTE but not with systematic biopsy. Mean patient age was 50 years (range 40 to 58), mean PSA was 1.7 ng/ml (range 1.30 to 2.00) and mean prostate volume was 33.5 ml (range 18 to 50). In the PSA range of 2.01 to 3.00 ng/ml cancer was found in 7 of 26 cases (27%). Targeted biopsy detected 6 cancers and systematic biopsy detected 5. Mean patient age was 54 years (range 43 to 75 years), mean PSA was 2.6 ng/ml (range 2.10 to 3.00) and mean prostate volume was 36.5 ml (range 18 to 65). In the PSA range between 3.01 and 4.00 ng/ml cancer was found in 19 of 59 cases (32%). Targeted biopsy and systematic biopsy detected 13 cancers. Mean patient age was 60 years (range 35 to 77), mean PSA was 3.6 ng/ml (range 3.00 to 4.10) and mean prostate volume was 45.5 ml (range 20 to 112).

Cancer detection was significantly different between groups 1 and 2 vs 3 ($p < 0.001$). Subgroup analysis showed no significant differences for age (p = 0.436) and volume (p = 0.781) between groups 1 and 2. Age and volume analysis showed a significant difference between groups 1 and 3 (p = 0.004 and 0.014), and 2 and 3 (p = 0.021 and 0.001, respectively). PCa was most often found in PSA group 3.

DISCUSSION

PCa was found in 28.7% of men with PSA 1.25 ng/ml or greater and 4.00 ng/ml or less. By biopsy core

analysis showed a clear benefit for the RTE targeted approach, by which PCa detection could be improved with a decreased number of cores. On by patient analysis RTE targeted biopsy detected cancer in 20 and systematic biopsy in 18 ($p = 0.8$). Targeted cores detected cancer 4.7 times more often than systematic cores.

This study shows that RTE can improve PCa detection. Previous studies have shown the potential of this technique. In the current series in men with PSA 1.25 ng/ml or greater and 4.00 ng/ml or less RTE revealed suspicious areas in 51 (54.3%).[8,12,15] Suspicious areas were defined as areas with greater tissue stiffness based on greater cell and vessel density,[7] which appears as a blue area on RTE. An important issue when evaluating a suspicious area is reproducibility. We used the approach described by König et al.[12] In our group of 94 men 43 did not show suspicious findings on RTE, representing 42% of the study population. In these men with normal RTE cancer was found by systematic biopsy in 3. Gleason score in these 3 cases was 6 or less. Based on a small number of cases our data suggest that RTE may be useful to avoid biopsy.

Of the 51 patients with suspicious RTE findings 20 were diagnosed with cancer. Unfortunately we noted a considerable number of false-positive findings on RTE (PPV 39%). Nonetheless, sensitivity was 74% and NPV was 93%, comparable to that of Salomon et al.[8] Sensitivity data on biopsy findings are comparable with those of Pallwein et al, who compared elastography with whole mount prostate specimens.[16] Although comparison with systematic biopsy is not the ideal gold standard, we are comfortable with this approach since systematic biopsy is the technique used worldwide to diagnose PCa.

MRI enables PCa detection in the peripheral zone and the TZ. We did not study the TZ with RTE. However, currently available MRI data are based on patients with PSA 4.00 ng/ml or greater. Thus, to our knowledge the true value of MRI for TZ cancer detection in a population with low PSA (4.00 ng/ml or less) is not yet known. Studies have shown high NPV when using T2-weighted MRI, MRI spectroscopy and dynamic contrast enhanced MRI.[17] Thus, based on the high NPV it was stated that when MRI is negative, the presence of PCa is low. When comparing the NPV of MRI (greater than 90%) and NPV of RTE, we found almost comparable the results. RTE may be a new, valuable technique but in the presence of normal findings the possibility of cancer is low. Direct comparison of RTE and MRI would be desirable since the data were acquired on the 2 imaging techniques in different populations.

Based on the study by Thompson et al, who found a considerable number of relevant cancers in the PSA group 4.00 ng/ml or less,[10] we investigated RTE in men with low PSA. Since DRE is not part of our screening program, we did not study men with PSA 1.25 ng/ml or less. This cutoff, defined in the Tyrolean PSA screening program, can decrease PCa related mortality.[9] Furthermore, Holmström et al reported that PSA less than 1.00 ng/ml can be used to rule out PCa.[18] Since this statement is based on this series only, further studies are desirable to determine whether PSA less than 1.00 ng/ml can definitively exclude PCa.

Recent studies showed that cancer detection can be improved by increasing the number of cores on systematic biopsy.[19] Unfortunately this is associated with considerable cost. Saturation biopsy is associated with an additional cost of approximately $5,000 per patient.[20] Studies have shown that 24-core biopsy has no advantage compared with 12-core biopsy.[21,22] Also, saturation biopsy has the disadvantage of PCa over diagnosis.[23] Thus, this approach is still under debate.

In our study RTE showed improved cancer detection with a decreased number of cores (table 3). We believe that image targeted biopsy has great potential for diagnosing PCa, especially when the number of biopsy cores needed for cancer diagnosis can be decreased. This may have a significant impact on patient morbidity associated with biopsy.

RTE has a high 93% NPV and may have the benefit of sparing patients from prostate biopsy when using PSA as the indication. Since in 2007 approximately 2 million prostate biopsies were done in the United States and approximately 220,000 cancers were detected, this approach seems inadequate for PCa detection since a great number of men underwent biopsy without having PCa. Also, systematic biopsy may miss relevant cancer in 35% of cases.[24] RTE may be a new imaging tool that can decrease the number of men who undergo biopsy. Further multicenter studies are desirable to determine whether these results can be reproduced in different populations and in different countries.

Our series has several limitations. Ultrasound is generally an investigator dependent technique, as is RTE. We do not have data on intra-observer and interobserver variability. Subjective estimation of

Table 3. *Patients with cancer, and cancer positive RTE targeted and systematic cores in 3 PSA subgroups*

PSA (ng/ml)	No. Cores/Total No. (%)		No. Pts/Total No. (%)
	RTE	Systematic	
1.25–2.00	1/17 (5.8)	0/72	1/9 (11)
2.01–3.00	7/23 (30.4)	7/208 (0.03)	7/26 (27)
3.01–4.00	30/118 (25.4)	31/472 (0.07)	19/59 (32)
Totals	38/158 (24)	38/752 (5.1)	27/94 (28)

electrographic colors is an important limitation and new quantification systems are desirable to achieve more objective, reliable parameters.

CONCLUSIONS

RTE enables cancer detection in the PSA group between 1.25 ng/ml or greater and 4.00 ng/ml or less. By core analysis showed improved PCa detection for RTE targeted cores compared with that of systematic cores. Overall cancer detection was not significantly different for RTE and systematic biopsy. In this low PSA group 28.7% of cases showed cancer. RTE seems to be a new tool that allows targeted biopsy and, thus, may decrease the number of patients scheduled for prostate biopsy in the future.

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