Sonoelasticity Imaging of Prostate Cancer: In Vitro Results

PURPOSE: To compare sonoelasticity imaging versus ultrasound (US) in detection of prostate cancer.

MATERIALS AND METHODS: Sonoelasticity imaging and US were performed on 10 prostatectomy specimens in which cancer was detected at previous biopsy. Six patients had no palpable lesions at digital rectal examination. Specimens were imaged axially at the apex, middle, and base of the gland to correlate with location of pathologic sections. All images were interpreted blindly and prospectively, and results were compared with pathologic findings.

RESULTS: Sensitivity and specificity with sonoelasticity imaging were 85% and 84%, respectively, and 30% and 100% with standard US when compared with pathologic findings. Sixty-four percent of pathologically confirmed tumors detected at sonoelasticity imaging were isoechoic on conventional US images.

CONCLUSION: In this limited study, sonoelasticity imaging was more sensitive for tumor detection and more accurate for assessment of tumor location than was conventional US.

Index terms: Prostate, neoplasms, 844.32 • Prostate, US, 844.1298 • Ultrasound (US), experimental, 844.12984

Sonoelasticity imaging was initially developed by Lerner et al (1) to detect the relative stiffness of tissues on the basis of differential vibration characteristics. With sonoelasticity imaging, tissue is vibrated with a low-frequency source and tissue motion is detected and displayed as a color image superimposed on the conventional gray-scale ultrasound (US) image. Results of early studies in phantom and animal models confirmed that isoechoic lesions on grayscale images could be differentiated with sonoelasticity imaging because of their differing sensitivity to vibration (1). The theory of sonoelasticity imaging is based on the postulate that low-frequency vibrations are easily conducted through soft tissue and muscle; discrete stiff tumors, however, create a detectable disturbance in the vibration pattern. This theory was successfully applied to canine and human prostatectomy specimens with modified laboratory equipment (2). These early investigations demonstrated a clear correlation between vibration image deficits and areas of palpable stiffness. The current study was performed with specially modified, commercially available equipment to test the hypothesis that sonoelasticity imaging in vitro could enable detection of nonpalpable prostate cancer that appears normal at US.

MATERIALS AND METHODS
Ten specimens obtained at radical prostatectomy from patients with biopsy-proven adenocarcinoma were scanned with standard US and sonoelasticity imaging immediately after surgery. Preoperative diagnosis of carcinoma was made on the basis of histologic findings at transrectal US-guided biopsy in nine patients and transurethral prostatectomy in one. Transrectal US was performed by a urologist (R.D.M.), and findings were correlated with those obtained at digital rectal examination and with prostate-specific antigen (PSA) levels (Table 1). Biopsy specimens were obtained from six palpable hypoechoic lesions and random sextant biopsy specimens from three patients with normal transrectal US findings. Preoperative transrectal US findings and biopsy results were not available at the time of specimen scanning or image interpretation.

After prostatectomy, specimens were transported on ice and were scanned within 30 minutes of removal from the body. Specimens were placed prone in a clear plastic container lined with plastic wrap. The container was open like a doughnut interiorly to allow direct contact between the specimen and the vibration source anteriorly (Fig 1). Specimens were stabilized within a cutout gel standoff pad and surrounded with US gel for acoustic coupling.

Imaging was performed with a 7-MHz linear-array transducer clamped in position with a thin layer of gel on the perirectal surface so as not to dampen the acoustic vibration originating from the opposite side. US and sonoelasticity imaging locations were chosen by visually dividing the specimen into thirds and imaging in the axial plane, perpendicular to the gland, at the base, midportion, and apex; in addition, some lesions were confirmed in the longitudinal plane. Distance between images depended on gland size and was not controlled by an external stepping apparatus. Section thickness was dictated by the transducer face and the elevation plane thickness of the ultrasound beam at the focal zone. Images were recorded on laser film, color transparency, or paper. All imaging was performed with a commercially available instrument (Acuson 128XT; Acuson, Mountain View, Calif.).

Tissue vibration was accomplished by shear wave production from a cone-shaped source that lightly touched the dependent surface of the prostate. Vibration frequencies that were sampled ranged from 50 to 250 Hz, with a peak source amplitude of less than 0.1 mm. Special modified proprietary software was used to display vibration within tissue as a "green-tag" overlay on the image. That is, Doppler receiver parameters were set to a

Abbreviation: PSA = prostate-specific antigen.
green-tag function, which is based on an estimate of the standard deviation of the Doppler spectrum. Normal vibrating tissue above a threshold of approximately 0.02-mm displacement was identified as green, and nonvibrating tissue as gray-scale image. The current software version displays the green-tag function as an all-or-none function, without shading, to represent amplitude of vibration above a threshold. Areas of no gray-scale image (ie, shadows) also do not display a green-tag vibration image.

After imaging, specimens were transported on ice to the pathology department for sectioning. Glands were sectioned per routine protocol in 4-mm slices from apex to base. Each slice was divided into quarters, which were labeled left anterior, right anterior, left posterior, and right posterior; in addition, each slice was lettered alphabetically and subnumbered from apex to base (eg, apex = a1 and a2). Depending on the length of the prostate, as few as four or as many as 10 slices may be required. A single slide was prepared from the surface of each slab in each cassette. Pathologic results were obtained from departmental dictated reports and review of original sections in questionable areas. Tumor location and extent were recorded by a pathologist; tumor size and volume, however, were not. In addition, because pathologic sectioning followed US imaging, no direct correlation between precise tumor boundaries could be obtained.

US and sonoelasticity images were reviewed off-line and visually divided into anterior and posterior and right and left segments to best correspond to the pathologic cassettes. Because preoperative transrectal US was performed for biopsy only and imaging results were not recorded for each segment at each level, they could not be directly correlated with in vitro sonoelasticity and US images.

US images were scored as positive for tumor when a discrete hypoechoic nodule or region was identified (3-5). Sonoelasticity images were scored as positive for tumor when the nodule or region was detected by gray-scale imaging and did not fill in uniformly with the green-tag vibration signal. Sonoelasticity imaging defects could be focal (well circumscribed with no vibration) or diffuse (poorly marginated with green pixels [vibration] incompletely filling in the gray-scale image). Scoring of US and sonoelasticity images was performed blindly and prospectively (reader 1, D.J.R.) without knowledge of initial transrectal US, digital rectal examination, or pathologic reports and findings; a second blinded interpretation of sonoelasticity images was also performed (reader 2, K.J.P.). Separate statistical analyses were performed and a statistic obtained (6) to analyze interobserver variation. Pathologic reports and sections were reviewed by (M.A.H.) without knowledge of transrectal US, US, or sonoelasticity imaging results and scored for tumor presence or absence. At the time of composite review, 108 sonoelasticity images and US quadrant images were available to all reviewers and form the database for this study. US and sonoelasticity images were compared with pathologic findings for each section and each patient.

**RESULTS**

In this preselected population, sonoelasticity imaging yielded an 85% sensitivity and 84% specificity for car-

---

**Table 1**

Preoperative Diagnosis of Prostate Cancer

<table>
<thead>
<tr>
<th>Patient</th>
<th>PSA Level* (ng/mL)</th>
<th>Findings at Digital Rectal Examination</th>
<th>Findings at Transrectal US</th>
<th>Findings at US of Specimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9.4</td>
<td>Nodule, midline, mid gland to apex</td>
<td>Hypoechoic at site of digital rectal examination finding</td>
<td>Hypoechoic, midline apex to base</td>
</tr>
<tr>
<td>2</td>
<td>4.3</td>
<td>Nodule, left base of gland</td>
<td>Hypoechoic at site of digital rectal examination finding</td>
<td>Normal</td>
</tr>
<tr>
<td>3</td>
<td>13.4</td>
<td>Nodule, left mid gland</td>
<td>Hypoechoic bilaterally</td>
<td>Hypoechoic, right side</td>
</tr>
<tr>
<td>4</td>
<td>9.8</td>
<td>Normal</td>
<td>Hypoechoic, right base to apex and left mid gland peripheral zone</td>
<td>Normal</td>
</tr>
<tr>
<td>5</td>
<td>4.2</td>
<td>Indurated right lobe</td>
<td>Hypoechoic right lobe</td>
<td>Hypoechoic, apex, anterior</td>
</tr>
<tr>
<td>6</td>
<td>2.5</td>
<td>Normal</td>
<td>Transrectal US not performed, A2 carcinoma noted at examination of transrectal prostatectomy</td>
<td>Normal</td>
</tr>
<tr>
<td>7</td>
<td>12.2</td>
<td>Normal</td>
<td>Normal</td>
<td>Abnormal, right peripheral base to apex</td>
</tr>
<tr>
<td>8</td>
<td>8.9</td>
<td>Nodule, left mid gland</td>
<td>Abnormal peripheral zone at abnormal digital rectal examination site</td>
<td>Hypoechoic: right and left base to apex peripheral zone</td>
</tr>
<tr>
<td>9</td>
<td>6.7</td>
<td>Nodule, left mid gland</td>
<td>Abnormal peripheral zone at abnormal digital rectal examination site</td>
<td>Normal</td>
</tr>
<tr>
<td>10</td>
<td>10.1</td>
<td>Normal</td>
<td>Normal</td>
<td>Abnormal, left and right base posteriorly</td>
</tr>
</tbody>
</table>

*Monochromatic assay; normal = ≤ 4 ng/mL.

---

**Table 2**

Results of Sonoelasticity Imaging and US versus Examination of Pathologic Specimens

<table>
<thead>
<tr>
<th>Sonoelasticity Imaging</th>
<th>Reader 1</th>
<th>Reader 2</th>
<th>Mean</th>
<th>US</th>
</tr>
</thead>
<tbody>
<tr>
<td>True positive (n)</td>
<td>66</td>
<td>70</td>
<td>68</td>
<td>24</td>
</tr>
<tr>
<td>False positive (n)</td>
<td>21</td>
<td>25</td>
<td>23.5</td>
<td>29</td>
</tr>
<tr>
<td>False negative (n)</td>
<td>2</td>
<td>7</td>
<td>4.5</td>
<td>0</td>
</tr>
<tr>
<td>Sensitivity (TP/[TP + FN])</td>
<td>0.83</td>
<td>0.88</td>
<td>0.85</td>
<td>0.3</td>
</tr>
<tr>
<td>Specificity ([TN + FP])/TP**</td>
<td>0.93</td>
<td>0.75</td>
<td>0.84</td>
<td>1.0</td>
</tr>
<tr>
<td>Positive predictive value ([TP + FN])</td>
<td>0.97</td>
<td>0.91</td>
<td>0.94</td>
<td>1.0</td>
</tr>
<tr>
<td>Negative predictive value ([TN + FN])</td>
<td>0.65</td>
<td>0.68</td>
<td>0.66</td>
<td>0.33</td>
</tr>
<tr>
<td>Accuracy ([TP + FN]/([TP + FN] + [FP + FN]))</td>
<td>0.85</td>
<td>0.84</td>
<td>0.85</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Note.—FN = false negative; FP = false positive; TN = true negative; TP = true positive

*P < .0001 (Fisher Exact Test), extremely significant
**P = .115 (Fisher Exact Test), not significant.
yielded prostatic intraepithelial neoplasia in one segment, stromal and glandular hyperplastic nodules 8–10 mm in diameter in two, and diffuse stromal hyperplasia in four. Diffuse, nonnodular glandular hyperplasia was noted in review of some true-negative segments.

Sonoelastography images demonstrated focal nonvibrating nodules that correlated with those on standard gray-scale images (Fig. 2) and also showed diffuse infiltrative tumor not depicted on gray-scale images (Fig. 3). Although the vibration source was located on the anterior surface opposite the receiving transducer, both anterior and posterior tumor-containing segments were identified. Reader 1 correctly identified 18 anterior tumor segments on sonoelastography images, compared with 22 identified by reader 2. Both readers correctly identified tumor in 48 posterior segments. Sonoelastography imaging defects were observed through a broad range of frequencies, from 50 to 240 Hz (Fig. 4). Both readers agreed overall on findings in 88 of 108 sections. The κ statistic, calculated according to the method of Fleiss (6), was .56.

For each patient, and on the presumption that US abnormalities would direct biopsy, three of 10 specimens had no gray-scale findings for tumor, for a sensitivity of 70% for standard US. Preoperatively, abnormalities in these same three specimens at transrectal US correlated with those at digital rectal examination. Conversely, three patients with normal findings reported preoperatively at transrectal US had focal hypoechoic peripheral zone lesions at postoperative US of the specimen (Table 1). At sonoelastography imaging, tumor was detectable in some portion of all specimens, for 100% sensitivity in each patient.

**DISCUSSION**

Sonoelastography imaging offers a unique advantage over transrectal US and digital rectal examination because it combines and extends in a single examination features of both procedures. In addition to posterior and apical lesions, sonoelastography imaging enables detection of characteristic tumor stiffness in anterior, lateral, and superior regions of the prostate that are inaccessible at digital rectal examination. An isoechoic tumor noted at transrectal US may be detected because of its different vibration pattern. The standard features of transrectal US diagnosis are maintained, includ-
ing the ability to measure prostate volume to correlate with PSA levels and identification of discrete hypoechoic lesions and areas of asymmetry or capsular distortion to direct biopsy. Sixty-five percent of tumor-containing segments detected at sonoelastographic imaging were not identified at US; thus, sonoelastographic imaging offers substantial potential to improve prostate cancer detection and staging. Given the experience reported in the radiology and urology literature, these results are not surprising: Only 32%-42% of prostate carcinomas in each lobe were detectable at standard US (7,8). Even when directed and random biopsy procedures were performed (8), the number of prostate cancers undetected at transrectal US is substantial. In the series of 134 cancerous prostate lobes reported by Slonim et al (8), 78 (58%) demonstrated no hypoechoic lesion at standard transrectal US, and findings in 43 (32%) were false-negative when biopsy and prostatectomy results were compared. In the series of 153 patients reported by Daniels et al (9), carcinoma was detected in 37 (24%) sonographically and palpably normal prostate lobes when the contralateral lobe contained carcinoma. A method such as sonoelastographic imaging potentially could improve the false-negative biopsy rate by demonstration of vibration abnormalities in areas that appear normal at sonography. Inasmuch as US-guided biopsy may someday be used for triage and staging, segmental imaging that permits identification of bilateral disease and estimation of disease extent may be important in patient care.

Sensitivity of sonoelastographic imaging for tumor diagnosis was markedly improved over that of in vitro US (P < .001, extremely significant). This is due in part to low gray-scale sensitivity to tumor in individual segments, which made sensitivity of sonoelastographic imaging in our study more striking. Another limitation of in vitro imaging is distortion of normal anatomic relationships, which makes it difficult to detect tumor on the basis of gland asymmetry or capsular bulging. This may also have artificially lowered our findings of gray-scale sensitivity to tumor in individual segments. In addition, all of our patients had diffuse bilateral disease, which may account in part for the paucity of focal lesions detectable at US (8). False-negative findings at sonoelastographic imaging may have resulted from small amounts of tumor in the imaged segment, infiltrative tumor without enough fibrosis or stiffening to cause a change in vibration, or mismatch of imaging segments with pathologic sections, because our study protocol did not permit precise correlation but only a regional estimate of tumor presence or absence.

Hypoechoic lesions detected at transrectal US show low specificity for carcinoma unless accompanied by other indicators of carcinoma such as positive results of digital rectal examination or elevated PSA levels (10-12). Thus, sonoelastographic imaging has potential to improve the specificity of standard transrectal US biopsy by avoidance of sampling of hypoechoic regions at standard US that demonstrate a normal vibration pattern at sonoelastographic imaging. In the current study, false-positive results at sonoelastographic imaging included prostatic intraepithelial neoplasia, and stromal hyperplasia with 8-10-mm nodules that may have been stiff enough and large enough to disrupt the vibration pattern in two cases. Dense diffuse stromal hyperplasia also may have displaced enough glandular tissue to diminish vibration.

Some variation in sonoelastographic imaging results was noted between

Figure 4. Diffuse carcinoma demonstrated at multiple frequencies in a 69-year-old man with no palpable abnormality and a serum PSA level of 6.7 ng/mL. (a) Standard prone transverse US image obtained at the base of the prostate demonstrates somewhat heterogeneous echostructure. (b) Corresponding sonoelastographic image obtained at 50 Hz shows poor vibration diffusion, most pronounced posteriorly on the right (+). A second section of the base, obtained slightly caudal to a, shows a heterogeneous gray-scale pattern. (d) Corresponding sonoelastographic image obtained at 150 Hz documents absent bilateral posterior and right anterior vibration.
readers. The sensitivity of sonoelasticity imaging with both readers, however, was far superior to that of grayscale US in individual segments. Readers agreed on more than 80% of image interpretations; interobserver agreement with the κ statistic, however, was low. This was due in part to asymmetry of the sample, in which more than 60% of readings were positive because of the large number of tumor-containing segments present. This diminished the opportunity for observer disagreement, and the κ statistic was, therefore, based on a smaller chance group. In addition, sonoelasticity imaging is a new technique, and image interpretation is subjective.

Our results are preliminary because the vibration equipment is prototypical and the receiver-imaging aspects of sonoelasticity imaging have yet to be optimized and standardized, along with optimization of the vibration source and frequency. The relatively poor detection of tumor in the anterior segments raises the possibility of tissue saturation in proximity to the vibration source. These findings will require further investigation. In vivo application will require an adequate patient vibration source and receiver programs for use with endocavitary transducers. Then, with a mixed population with benign and malignant pathologic conditions, in vivo results must corroborate our in vitro experience before sonoelasticity imaging can be adapted for clinical use.

Acknowledgments: The authors thank Acuson Corporation for generous technical support in the development of this project and Beverly Pollet and Margaret Kowaluk for manuscript preparation.

References