Three-Dimensional Sonoelastography for In Vitro Detection of Prostate Cancer

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ABSTRACT

PURPOSE: To prospectively evaluate the accuracy of 3D sonoelastography for detection of prostate cancer relative to gray scale sonography in vitro.

METHODS: Using an Institutional Review Board-approved, HIPAA compliant protocol with informal consent, 19 prostatectomy specimens from patients 46 to 70 years of age with biopsy proven prostate cancer were scanned in 3D using conventional B-scan and sonoelastography using vibrations above 100Hz. Step-sectioned whole-mount histology was utilized to create a 3D volume of the prostate and tumors within it. B-scan ultrasound images and regions of low vibration in the sonoelastography images (hard regions) were formatted in 3D. The lesions in the nineteen cases were analyzed as two groups: G1) pathology-confirmed tumors of 1.0 cc or greater; and G2) pathology-confirmed tumor size less than 1.0 cc. G1 cases were evaluated for B-scan ultrasound and sonoelastography vs. histology as a reference standard and were scored as either a True Positive, a False Positive, a True Negative, or a False Negative. G2 cases were evaluated for sonoelastography only. True positives required 3D lesion correlation between pathology and imaging data. Conventional definitions of accuracy and sensitivity were employed to calculate these statistics.

RESULTS: G1 (7 lesions with tumor volume 1.0 cc or greater): Sonoelastography: accuracy of 55%, sensitivity of 71%. B-scan: accuracy of 17%, sensitivity of 29%. Mean tumor size is 3.1cc +/- 2.1cc. G2 (22 lesions with tumor volume less than 1.0 cc). Mean tumor size is 0.32 cc +/- 0.21 cc. Sonoelastography: accuracy of 34%, sensitivity of 41%, false positives: 6.

CONCLUSIONS: Sonoelastography performed considerably better than gray scale sonography in the detection of prostate cancer tumors over 1 cc.

Key words: sonoelastography, prostate cancer, 3D imaging, elasticity, image fusion, ultrasound.

INTRODUCTION

Early and accurate detection of prostate cancer is an urgent priority, since it is the most prevalent male cancer and the second most frequent cause of male cancer deaths. New prostate cancer cases for 2004 are estimated at 230,110 and deaths are estimated at 29,900(1).

Current screening with serum prostate specific antigen (PSA) and digital rectal exam (DRE) followed by ultrasound-guided prostate biopsy have some significant shortcomings. Transrectal sonography (TRUS) identifies only 64% of cancers per gland (2) and 32-42% of cancers per lobe (3, 4). With random biopsy, up to 32% of cancers are missed when comparing biopsy results per lobe with prostatectomy specimens (3). These invisible cancers are as significant as TRUS-visible cancers (5). In PSA-screened populations, TRUS accuracy per patient was only 52%, due to the high number of false positives encountered (6). In this same group, DRE, which detects stiffness, was specific (82%) but insensitive (50%) for prostate cancer detection. DRE is limited anatomically to the posterior gland and cannot detect lesions confined anteriorly or in the transition zone where as many as 28% of cancers occur (7). Given the limitations in TRUS-guided prostate biopsy, a technique that improves imaging and biopsy yield of prostate cancer would be beneficial.

PSA screening commonly results in biopsy in men with serum PSA greater than 4 ng/ml, and greater than 2.5 ng/ml for younger men or those at high risk (8, 9). Biopsy is performed in 8-15% of men (10, 11) age 50-70 and yields 22% cancer (10). Those negative for cancer have repeat PSA and may be re-biopsied at 6-12 months, yielding another 12% with cancer (12). This incurs both increased costs and delays in diagnosis (10, 11, 12). Thus, improvements to TRUS and biopsy procedures are valuable.

DRE is used for prostate cancer screening because many cancers are palpably hard. Over the past 15-20 years, several research groups have investigated various imaging techniques called elasticity imaging, or elastography (13). This method takes advantage of the difference in the stiffness (shear modulus) between healthy and diseased tissue. Because many cancers have an elevated shear modulus, interest in estimating the elastic (mechanical) properties of tissue and in imaging hard tumors has grown over the past decade. Currently, techniques for elasticity imaging can be generally separated into five methods: magnetic resonance (MR) elastography (14), sonoelastography or vibration imaging (15), elastography or strain imaging (16), remote palpation (17), and transient elastography (18).

The purpose of our study was to prospectively evaluate the accuracy of 3D sonoelastographic imaging for detection of prostate cancer relative to gray scale sonography in vitro.

MATERIALS AND METHODS

Support for this study in the form of a loaned Logiq-7 B-scan imaging system was received from GE Medical Systems. The authors had control of all data and information submitted for publication.

Sonoelastography images are vibration amplitude images in which stiff regions (high elastic modulus) appear as areas of low vibration relative to the surrounding softer tissue which

transmits vibration more readily (19). Color Doppler is used to display the vibration differences, with high vibration displayed as bright green and low vibration as dark green. The Doppler image is an overlay on the gray scale image, which permits simultaneous co-registered image acquisition. A stiff lesion causes a local decrease in the vibration field which is displayed as a void or dark region in the color Doppler image.

Gland Selection and Reference Standard

Excised glands of prostate cancer patients were selected who met the following criteria: 1) scheduled for radical prostatectomy (so that 3D histology can be obtained as the reference standard); 2) palpable lesion reported on DRE, or at least one core that was 50% positive for tumor on pre-operative biopsy; and 3) not treated with hormonal or radiation therapy. The patients ranged from 46 to 70 years of age, with an average age of 60.5. This study was approved by our institutional review board, was HIPAA compliant, and informed consent for use the excised gland was obtained. Nineteen glands were selected during the period from 11/2001 through 8/2003.

These criteria did not include the prostate cancer cases where the tumor volume was estimated to be lower than roughly 1 cc and in others where the entire prostate and tumor had been treated by radiation or hormonal therapy, which alters the gland stiffness and the amount of residual tumor. This also eliminated rare cases where the tumor was so advanced as to leave questionable “normal” regions.

Scanning

The details of the scanning protocol and the blinded reading protocol were as follows. Specimens were obtained immediately after surgical excision, embedded in 3.4% agar gel, and imaged using a 3D protocol. Co-registered sonoelastography and B-scan images were acquired at 1 mm spacing using a linear 7MHZ probe (GE 739L) mounted on a motorized track (Velmex, Bloomsfield, NY). The images were obtained by LST and ZW, who have two years of experience with sonoelastography imaging. Vibration was performed from a source opposite the probe with frequencies of 100-300 Hz. A combination of frequencies (chords) was used to diminish artifacts (19). The highest frequency which adequately penetrated to give a uniform vibration field was chosen.

Pathology

After US imaging, the fresh prostate gland was weighed and measured for maximum dimension in all three planes from apex to base, transversely and anterior-posteriorly. The resection margins of the gland were inked with different colors representing each quadrant. A landmark device, consisting of two sets of four 3 mm diameter mating metal prongs was inserted into the specimen through the apex and the base to provide fiducial markers. After fixation, the gland was remeasured to assess shrinkage and sectioned into 4mm slices from the apex to the base and digitally photographed. The tissues from the petri dishes were transferred to cassettes after being photographed and were embedded in paraplast to make blocks that were sectioned 4-5 μ m thick and then placed on glass slides.

The microscopic whole mount sections were examined by one of the three pathologists in the team (PASA, GN, and PN, all with over five years experience in pathology), blinded to the sonoelastography results. The areas of carcinoma and benign nodular hyperplasia were outlined with two different color-marking pens, and the slides submitted for 3D volume reconstruction. Digital photographs of each gross prostate slice and its accompanying histology slide were processed in Adobe Photoshop (version 5.5) aligning each planar image by the puncture holes from the Landmark Device to generate the 3D reconstructions.

Reference Standard

B-scan transaxial 1mm ultrasound images were used to create a 3D image of the surface of the prostate. In each 2D slice the boundary of the gland was outlined by BP and ZW to segment the gland from the background. The sequence of boundary outlines were reconstructed in 3D and used as the reference standard for the true shape of the gland and as the baseline volume since the ultrasound images are unaffected by tissue fixation and cassette preparation.

Registration of the ultrasound and pathology volumes was achieved by identification of the prostate surface and the urethra, which is visible at the midgland level of the prostate anterior to the verumontanum. Registration accuracy was assessed by BP by measurement of urethral offset, and also by an overlap metric of intersection over union, applied to the whole gland (20). Fusion was achieved with an in-house correlative (21) program, and images viewed in IRIS Explorer (Numerical Algorithms Group, Downers Grove, IL), as described previously (21,22). The best 3D correlation maps the gray scale B-mode data into the histology frame of reference. The largest U/S detected sonoelastic or gray scale lesion respectively in each gland was compared with histology.

Scoring

Scoring of ultrasound and sonoelastography images was performed prospectively with blinding to knowledge of initial TRUS, DRE, or pathologic reports and findings. Scoring of B-scan ultrasound and sonoelastography images was performed independently by 2 separate observers (DJR, B-scan and LST, sonoelastography). Pathology reports and sections were reviewed (by PASA, GN, or PN) without knowledge of ultrasound or sonoelastography imaging results for tumor presence or absence, size and location. Locations, volumes, and types of adenomatous nodules (stromal or glandular) were recorded.

Sonoelastography images were considered positive for tumor when a contiguous localized 3D vibration deficit was present for more than 2mm craniocaudal. Sonoelastography imaging defects could be focal (well circumscribed with no vibration) or diffuse (poorly margined with green pixels [vibration] incompletely filling in the gray-scale image). B-Scan ultrasound images were considered positive for tumor when a discrete 3D hypoechoic nodule or region was identified or there was a local mass of any echogenicity disrupting the gland contour. Three-dimensional co-registered pathology, B-scan, and sonoelastic images were displayed as a 3D volume fusion with pathology lesions in red, sonoelastic lesions in green, and overlap between pathology and sonoelastography lesions as bright yellow. In addition, sequential transverse 2D images were examined. Pathology and sonoelastography lesion volumes, locations, and overlap measures were also recorded.

Statistical Analysis

The following definitions were used to record results within the 3D co-registered volumes. A True Positive (TP) is recorded for a local region of the prostate volume where a discrete lesion of pathology confirmed cancer has substantial (approximately 50%) or greater co-registration with a discrete sonoelastic or B-scan lesion. A False Positive (FP) is recorded for a local region of the prostate volume where a discrete sonoelastic or B-scan lesion has less than 50% co-registration with a pathology confirmed cancer. A False Negative (FN) is defined when a discrete cancer has no corresponding sonoelastic or B-scan lesion. A True Negative (TN) is recorded only if there is no cancer on pathology and no sonoelastic or B-scan lesion.

In the data analysis, the total number of identified lesions was defined as $N=TP+TN+FP+FN$; Accuracy as $(TP+TN)/N$; Sensitivity as $TP/(TP+FN)$ and positive predictive value; $PPV=TP/(TP+FP)$.

RESULTS

An example of a sonoelastic void is given on the right in Figure 1. This approach is also applicable to in vivo clinical examination as shown in Figure 2. The co-registration of B-scan surface, sonoelastographic lesions, and pathology lesions in 3D is given in Figure 3. A breakdown of the 3D co-registration into a sequence of stacked 2D slices (1 mm thickness) is shown in Figure 4.

Fig 1A - C. 2D transaxial images of a confirmed case of cancer in the mid-gland. Rectal surface is posterior. 1A – Histology is an H&E stain with the cancer (arrows) outlined in green by the pathologist. 1B – Gray scale US image in the same plane as A. The cancer is not visible. 1C – Sonoelastography image corresponding to B. There is a deficit in vibration (arrows), indicating an area of stiffer tissue.

Figure 2

Fig.2A - C: In vivo 2D sonoelastography co-registered with a histological slice. Images are all axial with rectal surface posterior. 2A – Histology slide shows cancer anterior and on the patients left, outlined in green. 2B – Gray scale image (center) is normal. 2C – Sonoelastography image corresponding to B has a dark vibration deficit (arrows) anteriorly and on the left, corresponding to the pathologically evident cancer (A). The sonoelastography image (right) show a vibration deficit (dark pixels) in the upper left in the same area as the histology slide (left) shows cancerous tissue, outlined in green by the pathologist. Note that the B-scan image in the center does not indicate cancer in that region.

Figure 3

Fig 3. 3D reconstruction of prostate cancer within the gland surface. The prostate surface (transparent blue) was reconstructed from B-scan data; tumor data from sonoelastography and histology are indicated by arrows. Apex, base, anterior, posterior, right, and left connotations are indicated on the figure.

Figure 4

Fig. 4: Four adjacent axial cross-sections (1 mm spacing between cross-sections) from a 3D fusion volume show the overlapping sonoelastography and histology tumor regions. The prostate surface was reconstructed from B -Scan data as white and histology data as yellow. The red region is the histology tumor and the green region is the sonoelastography tumor. The overlapping regions appear as yellow within the prostate. Rectal surface is posterior.

The results for both groups are shown in Table 1. The average tumor size for group G1 from histology was 3.0 cc, +/- 2.1cc. The average tumor size in this group, from sonoelastography, using the five true positives only was 2.8cc +/- 1.8 cc. The average size of the

five histology lesions to which they correspond was 3.7 cc $\pm$ 2.2 cc. The mean volume of the sonoelastic tumors in this group was 93% of the mean histology confirmed tumor volume. The mean lesion size of 22 histology confirmed lesions in group G2 were 0.32 cc $\pm$ 0.21 cc.

Table 1. Comparison of Sonoelastography and Histology

Series	TP	FP	TN	FN	Accuracy	Sensitivity	PPV
G1	5	2	0	2	55%	71%	71%
G2	9	6	1	13	34%	41%	60%

The ratio of intersection to union of whole gland volumes ranged from 0.69 to 0.82 (20,21) in this study. A complete description of the 3D image registration protocol has been published elsewhere (21).

Within the 19 prostates evaluated there were 29 discrete foci of cancer. These cancers ranged in volume from a maximum of 6.6 cm³ to under 0.1 cm³. One prostate was found to have no pathology confirmed cancer (within the limits of our 3mm sampling of pathology slices) and this prostate also had no sonoelastic lesions, producing one True Negative for the study.

In G1 (7 pathology confirmed focal lesions with tumor volume greater than or equal to 1cc) 7 sonoelastography lesions were scored as follows: TP=5 and FP=2. Because in two cases sonoelastography failed to match the pathologic tumor, for those glands FN=2, and TN=0 for this group. Thus, the sensitivity is 71%, the accuracy is 55%, and the positive predictive value is 71%. Similarly, gray scale (B-scan) ultrasound yielded TP=2, FP=5, FN=5, and TN=0. From this small sample we find that the accuracy is 2/12 or 17%, sensitivity is 2/7 or 29%, and PPV is 2/7 or 29%. The results are shown in Table 2.

Table 2. Comparison of B-scan Ultrasound and Histology

Series	TP	FP	TN	FN	Accuracy	Sensitivity	PPV
G1	2	5	0	5	17%	29%	29%

For G2 (22 pathology confirmed tumors less than 1cc), the sonoelastography results are: TP=9, FN=13, FP=6, and TN=1. Thus, the sensitivity is 41%, the accuracy is 34%, and the positive predictive value is 60%.

DISCUSSION

This study demonstrated that, on an examination of a whole gland for cancer, the sensitivity and accuracy of sonoelastography could be increased to levels of 71% and 55%, respectively, which is a major improvement over the levels that have been reported for conventional B-scan ultrasound. These results, however, are for a relatively small group of whole prostatectomy specimens (N=7) with a focal tumor of greater than 1.0 cm³.

The accuracy and sensitivity of sonoelastography was much poorer, however, for cases where the individual cancers were less than 1.0 cm³. Our previous work has shown that sonoelastography lesion image contrast diminishes with decreasing frequency (23, 24). Many of the tumors in group G2 are physically too small to generate sonoelastic contrast at the frequencies we are currently using. In addition, as the size of the cancer approaches 0.1 cm³, we lack an understanding of the mechanical and elastic properties of the tumor and if there is sufficient mechanical contrast compared to surrounding tissues to make a detectable void on a sonoelastic image. It is possible that very small tumor stiffness may not be the same as larger tumors, but could be considerably less, especially as compared to background tissue. Additional research into the biomechanical properties of prostate cancer is needed to provide the baseline data on this fundamental issue.

For group G1, B-scan values for prostate cancer detection are lower than other published studies (2, 3, 4) and this may be due to our stricter requirement of substantial 3D co-registration in order to qualify as a true positive. Comparison of in vitro transaxial scanning versus real-time biplanar transrectal ultrasound introduces another issue in that longer real-time imaging and imaging from more than one plane may improve lesion detection.

Another factor in the poor accuracy and sensitivity of both groups was the prevalence of false positives. Further analysis of the 3D images demonstrates that some of the false positive sonoelastic voids are due to calcifications or to regions of benign prostate hyperplasia (BPH) as confirmed by histology. It is reasonable to hypothesize that calcified regions will present as “hard” sonoelastic voids because these are easily visualized on B-scan, these are straightforward to eliminate in practice. However, not much is known about the elastic properties of BPH, either the stromal or glandular types. More information on this is needed, as the gray scale appearance of a BPH nodule also overlaps with cancer. Additional difficulties may be encountered in translating the current in vitro study to in vivo conditions, where patient motion and access constraints are present.

Finally, the comparison of volumes (3D sonoelastography versus pathology) is imprecise because of the coarse sampling of the whole specimens into 4-mm pathology specimens, as compared to 1mm ultrasound image acquisition. In addition, factors including tissue shrinkage and warping during preparation, and the need for manual outlining of the pathology slides, contribute to the imprecise volume estimates from pathology.

CONCLUSION

Three-dimensional sonoelastic imaging of prostate cancer currently shows promise for lesions greater than 1 cc, and is an improvement over gray scale sonography in vitro. False positives occur with calcifications (which can potentially be corrected by referencing the gray scale scan) and for adenomatous nodules, which currently cannot be distinguished from cancer by gray scale or elastography imaging. False negatives increase as tumor size decreases, and may be due to underestimates of tumor size by elastography and limited image contrast resolution at the frequencies applied. Future work will require better understanding of the mechanical properties of tissue, the stiffness differential between tumor and normal needed to provide image contrast and development of alternative vibration techniques to generate higher frequency shearwaves at depth.

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