Feasibility of vibro-acoustography with a quasi-2D ultrasound array transducer for detection and localizing of permanent prostate brachytherapy seeds: A pilot ex vivo study

Mohammad Mehrmohammadi

Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, Minnesota 55905

Azra Alizad

*Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, Minnesota 55905
and Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota 55905*

Randall R. Kinnick

Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, Minnesota 55905

Brian J. Davis

Department of Radiation Oncology, Mayo Clinic, Rochester, Minnesota 55905

Mostafa Fatemi^{a)}

Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, Minnesota 55905

(Received 20 February 2014; revised 15 June 2014; accepted for publication 7 August 2014; published 28 August 2014)

Purpose: Effective permanent prostate brachytherapy (PPB) requires precise placement of radioactive seeds in and around the prostate. The impetus for this research is to examine a new ultrasound-based imaging modality, vibro-acoustography (VA), which may serve to provide a high rate of PPB seed detection while also effecting enhanced prostate imaging. The authors investigate the ability of VA, implemented on a clinical ultrasound (US) scanner and equipped with a quasi-2D (Q2D) array US transducer, to detect and localize PPB seeds in excised prostate specimens.

Methods: Nonradioactive brachytherapy seeds were implanted into four excised cadaver prostates. A clinical US scanner equipped with a Q2D array US transducer was customized to acquire both US and C-scan VA images at various depths. The VA images were then used to detect and localize the implanted seeds in prostate tissue. To validate the VA results, computed tomography (CT) images of the same tissue samples were obtained to serve as the reference by which to evaluate the performance of VA in PPB seed detection.

Results: The results indicate that VA is capable of accurately identifying the presence and distribution of PPB seeds with a high imaging contrast. Moreover, a large ratio of the PPB seeds implanted into prostate tissue samples could be detected through acquired VA images. Using CT-based seed identification as the standard, VA was capable of detecting 74%–92% of the implanted seeds. Additionally, the angular independency of VA in detecting PPB seeds was demonstrated through a well-controlled phantom experiment.

Conclusions: Q2DVA detected a substantial portion of the seeds by using a 2D array US transducer in excised prostate tissue specimens. While VA has inherent advantages associated with conventional US imaging, it has the additional advantage of permitting detection of PPB seeds independent of their orientation. These results suggest the potential of VA as a method for PPB imaging that ultimately may allow US-based real-time intraoperative dosimetry. © 2014 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4893532>]

Key words: vibro-acoustography, ultrasound, quasi-2D, brachytherapy, prostate, intraoperative

1. INTRODUCTION

Prostate cancer is the most common cancer and second leading cause of cancer death in American men, claiming 29 720 lives in 2013.¹ Among various therapy procedures, permanent prostate brachytherapy (PPB) plays an important role in the management of localized prostate cancer.^{2,3} This technique is simple, cost-effective and takes a relatively short time to perform.³ Permanent prostate brachytherapy is performed by implanting radioactive pellets, also known as seeds, in and around the prostate as has been previously described.⁴ As

noted in the ESTRO guidelines on target delineation, a critical step in post-implant dosimetry is the identification of the seeds in the target region.^{5,6} Accurate intraoperative guidance of seed placement is a critical step in achieving an appropriate radiation dose for the optimal treatment of localized prostate cancer. Currently, transrectal ultrasound (TRUS) and computed tomography (CT) imaging are the major imaging modalities used in image guidance and post-implant dosimetry dosimetry.^{7–11} Different approaches relating to timing of planning and imaging in the preimplant, intraoperative, and post-implant settings have evolved and have been shown to be

effective.¹² In considering further evolution and potential improvement in image guidance during permanent brachytherapy, an ideal imaging system would include portability, with simultaneous accurate needle and seed imaging, as well as prostate anatomy.

With respect to the current status of intraoperative seed imaging capabilities, researchers have reported the various PPB seed detection rate by using TRUS.^{7,13,14} Some studies have reported that the PPB seed detection rate by using TRUS is approximately 50%.^{13,14} In any event, it is clear that the overall rate of seed identification by TRUS is unfortunately below that needed to perform TRUS-based intraoperative dosimetry. TRUS as an imaging modality is nevertheless essential for the procedure the way it is commonly undertaken because of its portability, low cost, and ability to image the prostate rapidly and accurately, along with needle position. As is well-known, the anatomical zones, and prostate tissue boundary are poorly visualized in CT images.^{15–17} Moreover, CT imaging is not capable of differentiating between the prostate tissue, periprostatic musculature, and venous plexus.⁵ Other approaches have been reported to achieve intraoperative dosimetry such as TRUS-fluoroscopic image fusion.^{18–20} More recently, magnetic resonance (MR) guided seed implantation has been reported and shown promising results in MR guided seed implantation^{21–23} and post-implant dosimetric assessment.²⁴ Vidakovic *et al.*²⁵ introduced a post-implant CT and MR image registration method which enhances the post-implant dosimetry by improving the definition of tissue structures and the seeds. Despite the notable advantages or MR, it must be noted that MR is costly and not readily available for this approach in all centers nor is it easily utilized for intraoperative dosimetry.

Vibro-acoustography (VA) is a novel ultrasound-based imaging technique, capable of visualizing both acoustic and mechanical properties of objects.^{26,27} In VA, ultrasound is employed to produce a localized low-frequency force to vibrate the tissue. In technical terms, such a force is called an “acoustic radiation force (ARF),” although it should be emphasized this is not ionizing radiation. Upon stimulating the tissue with ARF, the local vibration of tissue produces acoustic waves that convey information about the acoustical and mechanical properties of the stimulated spot detected by a hydrophone. The process is repeated through the entire volume of interest and the amplitude of the detected acoustic waves is then used to reconstruct an image which represents the acoustic and mechanical properties of the object.^{26,27} The low-frequency ARF is generated through interaction of two confocal ultrasound beams, at slightly different frequencies.^{26,27} As a result of such interaction, a localized ARF is generated within the focal region. The earlier VA prototype systems, consisted of a dual-element confocal US transducer with a center disk surrounded by a ring-shaped piezoelectric, driven with two continuous waves or tone bursts of different frequencies f and $f + \Delta f$.^{26,27} In this configuration, the VA images were obtained by mechanical raster-scanning of the probe over the object to make a “C-plane” (C-plane is a plane perpendicular to the ultrasound beams) image. By adjusting the distance between the object and the confocal VA probe, it was pos-

sible to image multiple planes at varying depths. Additional technical details of the confocal VA systems are described elsewhere.^{26–31}

The advantage of a confocal VA system is the perfect interaction and the symmetric spatial distribution of the ARF which is essential to provide high quality VA images. However, since the confocal VA probe must mechanically move to stimulate the tissue at each point within the imaging C-plane (i.e., raster scan in two directions), its frame rate and speed of data acquisition to generate an image maybe lower than clinically desired frame rates. More importantly, due to the large diameter of the confocal VA probe and the scanning mechanism, the implementation of a confocal VA in a transrectal configuration is fundamentally not feasible. To address the problem of long acquisition time and to take a step closer to development of a clinically desired system, VA was implemented on a clinical ultrasound scanner (GE Vivid 7, General Electric) equipped with a one-dimensional (1D) ultrasound array transducer.³² In this implementation, the scanning is done electronically along the length of the US array transducer (azimuth direction) and mechanically in the orthogonal direction. Although the implementation of VA using a 1D linear array transducer^{32,33} could potentially address the long scanning time and pave the way for future clinical utility for VA, it has certain limitations. While VA operating with a confocal probe provides an ARF with a symmetric spatial distribution in the focal plane,^{34,35} the 1D linear-array transducer produces an asymmetric ARF.³⁶ Therefore, objects and features can appear elongated or blurred in 1D VA images.^{32,33} As a result, although 1D VA can reveal larger objects and features in tissues, smaller objects such as PPB seeds cannot be well-visualized by using 1D array transducers. To solve the problem of asymmetric ARF while benefiting from a shorter acquisition time, there is a need to utilize a 2D ultrasound transducer. A simulation study of VA using a 2D reconfigurable array has been previously reported by our research group.³⁷ While a 2D reconfigurable array is potentially an ideal solution for clinical implementation of VA, we have recently developed a VA system using a Q2D (in technical term, it is called 1.75D array transducer) array transducer as an intermediate step toward a desired 2D VA system.^{36,38} This Q2D array US transducer has multiple rows of elements in elevation which can be electronically configured to optimally generate a close-to-symmetric ARF. Beam mixing and generating ARF by using a Q2D array US transducer is closer to the ideal confocal VA and thus can improve VA images as compared to a 1D linear array transducer.^{36,38}

Vibro-acoustography has shown promising results in various medical diagnostic applications ranging from detection of breast tumors^{29,31} and calcifications in arteries,²⁸ to exogenous objects such as brachytherapy seeds³⁹ and metal implants. Our research group has previously demonstrated the functionality of confocal VA in prostate imaging^{30,40} and detecting brachytherapy seeds in excised prostate specimens.^{39,41} Here, we investigate the utility of VA, implemented on a clinical ultrasound scanner and equipped with a Q2D array US transducer, to detect and localize PPB seeds within the prostate tissue. We name this new development

as “quasi-2D (Q2D) VA” method. Our results suggest that Q2DVA is capable of detecting seeds with a high sensitivity and detection rate. Moreover, seed detection with VA is shown to be independent of seed orientation, which is an important advantage of VA as compared to conventional TRUS imaging.

2. MATERIALS AND METHODS

2.A. Q2D VA/US system

The block diagram of the Q2DVA/US system is shown in Fig. 1(a). A clinical US scanner (GE Vivid 7, GE Healthcare Ultrasound Cardiology, Horten, Norway) was modified to perform both conventional B-scan ultrasound and Q2DVA. The modified system was able to transmit ultrasound beams at two different frequencies and generate the low-frequency ARF required for VA. The scanner drives a Q2D array US transducer, designed by GE and manufactured by Tetrad, a subsidiary of W. L. Gore (Englewood, CO). The Q2D array US transducer consisted of 840 piezoelectric elements in a form of a matrix of 70 columns $\times$ 12 rows [Fig. 1(b)]. Each piezoelectric element size was $900 \times 900 \mu\text{m}$. The Q2D array US transducer was designed for the operating frequencies between 5 and 8 MHz. Since the ultrasound scanner was capable of simultaneously driving 128 channels, a subset of the 12×12 elements were selected to form an “active” VA aperture³⁶ [Fig. 1(b)]. Out of the 144 elements within the selected square sub-aperture, 128 elements could be active at a time (i.e., driven by GE vivid 7 scanner). In our Q2DVA studies, the active aperture is divided into an exterior ring-shaped section (elements marked with dark gray color) around a center square shaped section (elements marked with light gray color). The black-colored elements are inactive elements in

this sub-aperture configuration. This configuration (we call this configuration “null-corner-center”) can closely simulate a dual-element confocal transducer where a ring-shaped piezoelectric surrounds a center disk.^{26,27} In the case shown in Fig. 1(c), the ring-shaped section, marked in dark gray, transmits the acoustic waves at $f_1 = 4.9480$ MHz and the central portion (light gray) transmits at $f_2 = 5.000$ MHz. These two beams intersect and generate a low frequency modulated ARF at $\Delta f = 51.5464$ kHz at the focal region. The spatial distribution of ARF by using the described configuration is studied by Urban *et al.*³⁶ During the scanning, a digitally controlled multiplexer was utilized to translate and steer the active aperture along the azimuthal direction and over the total aperture of the transducer. The probe is moved by a motorized linear axis [not shown in Fig. 1(a)] to mechanically scan the tissue and provide C-plane VA images. Several C-planes at various depths ranging from 15 to 40 mm (depends on the tissue specimen size) were scanned by controlling the distance between the Q2DVA probe and the tissue specimen. The Q2DVA images were acquired at multiple equally distanced imaging planes separated by 2.5 mm.

Upon applying the localized ARF, the acoustic emission due to the tissue vibrations was detected by a preamplified hydrophone (ITC-6050 C; ITC, Santa Barbara, CA) placed approximately 5 cm directly behind the left edge of the gel block containing the prostate tissue [Fig. 2(b)]. The hydrophone was outside the path of the ultrasound beams to prevent a direct interaction between the ultrasound beams and the hydrophone which can cause interference with acoustic emissions from the tissue (i.e., VA signal). The signals detected by the hydrophone were filtered by a band-pass (BP) filter (40–60 KHz bandwidth) and then digitized. The digitized signal was stored in a computer for VA image reconstruction and further post-processing.

FIG. 1. (a) Block diagram of the Q2DVA system consisting of a clinical ultrasound scanner equipped with a Q2D array US transducer. (b) The cross section of the Q2D array US transducer consisted of 12 rows and 70 columns of piezoelectric elements. The active subaperture consisted of 144 elements within a square of 12×12 elements is marked with the dotted black square. (c) The active subaperture element configuration consisted of a ring-shaped section, marked in dark gray, transmits the acoustic waves at f_1 and the central portion (light gray) transmits at f_2 .

FIG. 2. (a) Cross-section demonstration of seed-membrane experiments indicating the membrane, a seed, the direction of US beams in both VA and US, and the rotation directions. (b) Photograph of the experimental setup including the excised prostate tissue embedded in a gelatin cast, the hydrophone, and the Q2DVA probe.

2.B. Seed angular independency experiments

We have previously demonstrated the superior performance of a VA system in detecting metallic seeds at different angles with respect to the ultrasound beam^{41,42} by using a confocal dual-element probe.^{26,27} To further demonstrate the superior ability of Q2DVA compared to conventional B-mode, we performed a set of well-controlled experiments in which seeds were mounted on a latex membrane and were imaged at different angles between the incident US beams and their long axis [Fig. 2(a)]. Ten metallic brachytherapy seeds were mounted on a thin latex robber membrane. The distance between Q2D VA and US transducers were fixed to 50 mm for both Q2DVA and B-mode US imaging. A rotary stage [shown in Fig. 2(b)] was used to accurately control the angle between the seeds and the US beams direction. US and Q2DVA images were obtained at angles of 0°–40° at 5° increments.

Mounting the seeds on a membrane allowed us to accurately control the experimental parameters, such as the exact location of the seed and the angle between the seeds and the incident US beam(s). Such accuracy could not be achieved with seeds implanted within prostate tissue. However, to demonstrate the feasibility of angle-independent Q2DVA imaging of implanted seeds, one of the prostate specimens with implanted seeds was imaged at different angles between 0° and 20° with both US and Q2DVA.

2.C. Tissue specimen preparation

Preliminary Q2DVA studies were performed on four prostate specimens excised from human cadavers. All tissue specimen handling and imaging procedures were performed under a protocol approved by the institutional review board (IRB) at the Mayo Clinic. Tissue samples were fixed in 10% formaldehyde solution to prevent potential contamination. Nonradioactive metallic brachytherapy seeds, used for training purposes, with sizes of 4.5 mm long and 0.8 mm (Mick Radio-Nuclear Instruments, Inc., Mt. Vernon, NY) in diameter were implanted using 18 G (1.3 mm diameter), 20 cm long brachytherapy implant needles (Bard, Inc., New Providence, NJ). Seeds were implanted in the prostate specimen at an orientation that mimics *in vivo* brachytherapy seed implantation supervised by a practicing radiation oncologist with seed implant experience (Dr. Brian J. Davis, Department of Radiation Oncology, Mayo Clinic, Rochester, MN).⁴³ Depending on the size of the prostate specimen, ranging from 20 to 35 cc, different numbers of seeds ranging from 13 to 30 seeds were implanted. While this number of seeds is low compared to a typical prostate implant, it was viewed as satisfactory for the purposes of our study. A plastic tube was inserted into the urethra for better identification and handling of the tissue. To better simulate the *in vivo* situation where the prostate tissue is surrounded by other soft tissues, prostate specimens were cast into tissue mimicking gelatin blocks made out of 10% (v/v) gelatin from porcine skin (Sigma-Aldrich G2500 Type A, 300 bloom, Saint Louis, MO) after dummy seed implantation. Consistent with other prior studies, condensed milk was added to the gelatin mixture in order to increase acoustic attenuation and thus better simulate the acoustic properties of soft tissues.⁴⁴ The specimen was placed into gel blocks such that the entrance of the urethra into the prostate (bladder side) was oriented superiorly and the exit of the urethra was oriented inferiorly, in an approximate cranial to caudal direction (top to bottom). The blocks of gelatin containing the implanted prostate specimens were placed in the water tank for Q2DVA and US studies as shown in Fig. 2(b).

2.D. CT imaging

Upon completion of the Q2DVA scans, the prostate specimens embedded into gel blocks were imaged using a CT scanner (LightSpeed RT16, GE Healthcare). CT imaging of the samples was performed at 120 kvp and with 2.5 mm helical slice width. The helical multislice CT images of tissue specimens were used to reconstruct 3D volumetric images in order to better visualize the seeds and to enable counting the number of seeds for comparison with Q2DVA images. CT results served as the gold standard in this study for evaluating the performance of VA in PPB seed detection.

2.E. Image reconstruction, processing, and seed detection

The amplitude of the acoustic emissions, picked up by the hydrophone was used to form the VA images. A band-pass

filter (SR650, Stanford Research Systems, SR650, Sunnyvale, CA), with the pass-band of 40–60 KHz was used to suppress the noise mixed with the acoustic emissions at Δf . Finally, the total number of seeds were counted and compared with CT images serving as the reference.

3. RESULTS

Figure 3 represents an example of a Q2DVA image, obtained from a prostate tissue sample and at a 27.5 mm deep C-plane. The presence and location of metallic seeds are clearly revealed with a large imaging contrast compared to the tissue background. Moreover, the prostate tissue boundary, periprostatic tissue, and the location of the urethra is well visualized in the Q2DVA image. The speckle-free nature of VA images makes it possible to visualize the prostate tissue boundary and structures, as well as the implanted metallic seeds. It must be noted that the seeds are implanted at various tissue depths (i.e., distance from the Q2DVA probe). Due to the spatial distribution of the ARF in the axial direction and around the focal plane, the Q2DVA probe stimulates a finite size slice of the tissue at each focal depth. As a result, all seeds located within the stimulated region of the tissue appear in the C-plane VA image. Since the maximum stimulation energy is focused at the focal plane, the seeds closer to the focal plane appear with a clear contrast (brighter than the background). However, the seeds that are located slightly out of the focal plane can still be stimulated and thus be imaged [Fig. 3(b)—marked with solid line arrows] with a lower contrast. In our study, the tissue specimens were imaged at different depths to ensure Q2DVA imaging of the whole specimen volume.

Figure 4 shows the Q2DVA images of a prostate tissue sample, obtained by adjusting the focal plane at various depths. Figures 4(a)–4(d) represent Q2DVA images at depths of 20, 25, 30, and 35 mm, respectively. Although each seed can appear in more than one imaging plane, the imaging contrast changes depending on the depth from the prostate surface

FIG. 3. An example of a C-scan Q2DVA image of a prostate tissue containing implanted seeds and at a depth of 27.5 mm. The prostate tissue boundaries are clearly outlined (solid white line). The urethra and periprostatic tissue are also delineated (dashed and dotted lines, respectively). The seeds are clearly visualized as small bright line-shape structures (marked with dashed arrows). The blurred line-shape structures (marked with solid line arrows) indicate the seeds which are located out of the focal plane.

FIG. 4. (a)–(d) Q2DVA images of a seed-implanted prostate tissue sample at depths of 20, 25, 30, and 35 mm, respectively. The seed marked with the white arrow shows the best contrast at the imaging depth of 30 mm, indicating the approximate depth of the seed. (e) Scout CT image of the casted prostate tissue after implanting the seeds. Twenty-two seeds can be counted in the imaged prostate specimen.

of the seed. For example, the seed marked with a white arrow in Fig. 4(a) appears with an enhanced contrast in Fig. 4(c) indicating that it is located approximately 30 mm deep. Therefore, the depth information of the seeds can also be revealed through analyzing the VA signal strength of each seed at various depths. Analyzing Q2DVA images at all imaging depths leads to identification of 20 seeds within the prostate specimen. The scout CT image of the same sample [Fig. 4(e)] reveals the presence of 22 seeds in this tissue samples. Therefore, Q2DVA images could visualize nearly all of the

FIG. 5. Comparison between Q2DVA and CT imaging in detecting the implanted PPB seeds in four excised prostate specimens.

implanted seeds in this prostate specimen. Moreover, the tissue boundary and tissue structures are well-visualized in Q2DVA images and at all imaging depths.

To further evaluate the ability of Q2DVA in detecting PPB seeds, all four tissue samples were imaged at multiple equally distanced parallel imaging planes. Upon reconstruction of VA images, the number of seeds was counted in each tissue specimen (blinded to CT data) and the results were compared to the number of seeds detected in the CT images. The graph shown in Fig. 5 represents the summary of comparison between Q2DVA and CT in detecting PPB seeds. The Q2DVA images could detect a large ratio (74%–92%) of the implanted seeds compared to the CT (gold standard). Overall, 86% of PPB seeds were detected by Q2DVA using the Q2DVA probe.

To demonstrate angular independency of Q2DVA in detecting PPB seeds, Q2DVA and US images of the seeds mounted on membranes were compared. Since VA images are acquired on a C-plane and US images are on a B-mode plane, consecutively acquired B-mode US images (step size of 200 μm) were used to form a three-dimensional (3D) volumetric US images. The results of Q2DVA and 3D reconstructed US at three different angles of 0°, 20°, and 40° are shown in Fig. 6. At 0°, the US beam(s) are perpendicular to the long axis of the seeds and therefore the maximum backscatter signal is picked up in US imaging. Therefore at 0°, both Q2DVA and US can clearly visualize the seeds with a high contrast. However, by rotating the seeds-mounted membrane [i.e., increasing the angle between incident US beam(s) and the line perpendicular to the seed], the US echo intensity decreases and thus the US image of the seed loses contrast. The two ends of the seeds act as a point source scattering a relatively strong echo almost at all angles. The seeds are still visible in the US image at 20° rotation but by increasing the rotation angle beyond 20°, the middle parts of the seeds fade and only the two ends of the seeds are visualized as two bright points. This effect is clearly shown in 3D US image at 40°. On the other hand, the seeds are consistently uniform and clearly visible in the Q2DVA images.

To better demonstrate the comparison between Q2DVA and 3D US images of seeds at different angles, the Q2DVA images were compared to the US images on a plane parallel to the surface of the membrane (similar to C-plane). This approach allows comparing the intensity and contrast of the

FIG. 6. Q2DVA and 3D rendered B-mode US images of metallic seeds mounted on a thin membrane and at 0°, 20°, and 40° angle between the long axis of the seeds and the US incident beam(s). The 3D US blocks are reconstructed from consecutively acquired B-mode and were rendered in 3D blocks for better demonstration. The 3D blocks are rotated to provide the best view of the seeds.

FIG. 7. (a) Normalized Q2DVA intensity for a sample seed mounted on a membrane and at different angles. (b) Normalized B-mode US intensity (on an imaging plane parallel to the rotated membrane) at different rotation angles.

seeds on similar C-planes. For simplicity, a region of interest including one of the seeds was selected in all VA images. The intensity of the VA image was normalized to its maximum within the region of interest. Then the normalized VA signal amplitude is plotted along a line that passes through the seed along its long axis. The same procedure was repeated for the US projection images of the seeds on the 2D plane parallel to the membrane surface. The results for both Q2DVA and US are shown in Fig. 7. Figure 7(a) clearly indicates that the contrast of the seed does not change at different angles. Moreover, the continuity of the high intensity region associated with the seed indicates that the total seed is clearly visualized in VA. It must be noted that the length of the rotated seeds in VA images are shorter than the seed imaged at 0° . However, this is due to the fact that the projection of the angled seeds is shorted on Q2DVA C-plane and is an expected result. On the other hand, the normalized US signal intensities shown in Fig. 7(b) clearly indicate the signal loss for the middle parts of

the seeds at angles larger than 20° . These results indicate the superior ability of Q2DVA in detecting seeds tilted at an angle and as compared to the ability of conventional ultrasound to detect such seeds.

To further quantify the ability of Q2DVA and US in detecting seeds at various angles, contrast to noise ratio (CNR) of the seed along with the long axis are defined as follows:

$$\text{CNR} = 20 \log \left(\frac{M_{\text{seed}} - M_{\text{background}}}{\frac{1}{2}(M_{\text{seed}} + M_{\text{background}})} \right), \quad (1)$$

where M_{seed} and $M_{\text{background}}$ are the mean intensities of the signals from the seeds and the background. Table I includes the CNR results of both Q2DVA and US for a selected seed at different angles. The significant drop in CNR of US images at angles of 30° – 40° indicates the visibility of the seeds is drastically affected by their orientation. However, VA provides almost constant CNR over such a wide range of rotation

TABLE I. CNR (dB) values for a sample metallic seed imaged by both Q2DVA and US and at angles between 0° and 40° .

Rotation angle	0	5	10	15	20	25	30	35	40
Q2DVA	36.74	33.61	36.76	39.18	37.10	32.38	35.81	37.52	35.36
US	27.58	23.35	20.49	17.71	14.93	7.80	2.32	1.08	1.89

angles which indicates there is no significant influence associated with the angular rotation of the seeds.

To demonstrate the angular independency of Q2DVA in detecting PPB seeds and in an actual prostate tissue specimen, a tissue sample was imaged at different angles ranging from 0° to 20° . “ 0° ” represents the condition in which the acoustic beams are perpendicular to the seed axis, or in other words, the seed axis is parallel to the imaging plane (C-plane). The orientation of the tissue samples (caste in gel blocks) including metallic seeds are shown in Fig. 8(a). The rotation of the seeds was controlled using a rotation stage shown in Fig. 2. The Q2DVA images of the prostate tissue sample and within a region of interest containing two PPB seeds are shown in Figs. 8(b)–8(e). Rotation of the seeds with respect to the probe (or imaging plane) may cause a part of the seed to be placed out of the focus of the ARF. As a result, at higher angles of rotation, a part of the seed may be out of the scanning plane and appear in adjacent imaging planes. To address this issue, the Q2DVA images were acquired at two different depths of 37.5–40 mm. Although no contrast enhancement or other image enhancement techniques was used to modify the reconstructed Q2DVA images, both seeds are clearly apparent at all angles between 0° and 15° . At 20° , the seed marked with the solid arrow is still clearly visualized. However, the second seed (marked with a dotted arrow) is not completely visualized due to the fact that the far end of the seed is not placed in the focal zone of the ARF and thus is not excited enough to generate the distinct VA signal.

4. DISCUSSION

Our results demonstrate several noticeable advantages of VA using a Q2D US probe in detecting PPB seeds. Compared

to TRUS imaging, Q2DVA can visualize PPB seeds with a high contrast, without speckles, and independent of their angular orientation. Although the resolution of Q2DVA images in the axial (depth) direction depends on the focus of the ARF, the seeds appear with the highest imaging contrast in the imaging plane closest to their actual depth. Moreover, the prostate tissue structures are visualized by Q2DVA images. The latter advantage of Q2DVA can be significant in clinical practice where it is important to determine the location of the PPB seeds in different zones of the prostate tissue. It must be noted that the presence of large calcifications in the prostate can affect the ability of Q2DVA to detect PPB seeds by blocking the ultrasound beams and thus the ARF. However, the presence of such large calcium buildups can also affect the efficiency of TRUS.

The resolution of the Q2DVA images is determined by the spatial distribution of the ARF and is in submillimeter range. The Q2DVA probe provides a symmetric distribution of ARF, similar to the confocal VA system. Therefore, the qualities of acquired VA images are comparable to the ones obtained by using the confocal VA probe and as a result, large ratios of implanted seeds were visualized with a high contrast. While no complex image processing procedure was applied to VA images in this study, it is possible to develop an automated “seed extraction” algorithm that can find seed-shaped objects in VA images and remove the redundant seeds which appear in more than a single plane based on *a priori* information of the ARF distribution in the axial direction. One possibility of further investigation, which includes automatic identification of brachytherapy seeds from VA data, could be undertaken in a manner similar to that reported by Brinkmann and Kline⁴⁵ used in seed identification and sorting of CT data, and as adapted for use with metallic objects of varying density and

FIG. 8. (a) The scheme showing the rotation of seed-implanted prostate samples to demonstrate the angular dependency of Q2DVA. (b)–(f) Q2DVA images of the prostate specimen in a selected region of interest containing two seeds (marked with dotted and solid arrows). The images in panels (b)–(f) represent Q2DVA images obtained when the angle between imaging plane and the surface of the transducer was set to 0° , 5° , 10° , 15° , and 20° , respectively.

size.⁴⁶ Likewise, *a priori* knowledge of needle position could also be used to facilitate seed position in VA applications in a manner similar to that reported by Wen *et al.*⁴⁷ and could also be used as a basis for incorporation into a VA-based intraoperative dosimetry method.

The utilization of the Q2DVA probe makes data acquisition faster compared to confocal VA. The C-plane scanning time is directly proportional to the number of pixels in Q2DVA images. The minimum time required to acquire a VA signal at each pixel location using the Q2D system is 2 ms. In this study, acquiring each C-plane Q2DVA images with 192×265 pixels, requires a minimum time of 101.8 s. For *in vivo* applications, the scanning time will depend on how fast the motor can rotate the transrectal probe. We estimate that the whole prostate VA scanning (assuming imaging at 5–8 planes) can be performed in 5–15 min.

In terms of clinical utility, implementation of VA with a Q2D probe is a significant step toward clinical use of the VA for *in vivo* applications of prostate imaging. The confocal VA configuration cannot be used in clinical settings due to the physical size of the confocal probe and the need for a two-axis scanning mechanism.^{26,27,39} However, a Q2DVA probe with smaller sized elements can fit into a transrectal case with a rotational scan capability and thus be utilized for *in vivo* Q2DVA. It should be emphasized, however, that the results presented here, while encouraging and of interest toward advancing the technology associated with prostate imaging and brachytherapy, are *ex vivo* and may not perfectly represent an *in vivo* application.

One of the most difficult problems of TRUS in imaging PPB seeds after implantation is the angular dependency. Since TRUS imaging is based on detecting the acoustic echoes reflected from the surface of the seeds, the performance of TRUS in detecting seeds is highly affected by the orientation of the seed. In practice, implanting brachytherapy seeds is associated with slight changes in the orientation of the seeds, and may also depend on whether seeds are implanted in loose or stranded form. Therefore, the performance of conventional TRUS in detecting PPB seeds is limited such that TRUS-based post-implant dosimetry is difficult and not routinely performed. However, VA due to its unique signal generation mechanism is not sensitive to the orientation of the seeds. The VA signal is generated as long as enough ARF excites the seed regardless of its orientation. Our results clearly indicated the angular independency of Q2DVA in detecting PPB seeds at a wide range of rotated angles while conventional B-mode US (even after 3D rendering) was not capable of clearly identifying the seeds at angles larger than 20° .

Shadowing is a major problem for any US or acoustic-based imaging modality. The same limitation applies to VA too. However, VA has a significant advantage over conventional pulse-echo US imaging. In pulse-echo US, if a barrier blocks the US beam, both pulse and echo must pass through the barrier and thus the signal degrades significantly. However, in VA, the acoustic emission by tissue can bypass the blocking part due to multiple tissue paths to the receiver (hydrophone). Moreover, the lower frequency of the acoustic emission (kHz range) allows bypassing the smaller blocking

units such as seeds. Therefore, the effect of beam blocking is less severe in VA compared to traditional US imaging. However, the presence of large calcium blocks in prostate tissue, could affect VA as it does to US imaging.

Since VA and US share common hardware (US scanner and transducer), we envision the utilization of VA as a complementary modality for TRUS imaging. In 1983, Holm *et al.*⁴⁸ reported on the use of TRUS as a means to guide permanent prostate brachytherapy. The use of TRUS greatly increased the accuracy of the procedure because it is an excellent modality of real-time prostate imaging, particularly with respect to identification of the prostate margin, adjacent critical organs, and brachytherapy needles. Design and development of a Q2DVA probe that can be fit into a transrectal case, would enable clinicians to benefit from the advantages of both TRUS and VA modalities. We envision with implementation of Q2D transrectal VA or by utilizing reconfigurable array ultrasound technology^{37,49,50} to develop a fully 2D transrectal US probe. The high quality of VA images of PPB seeds could thus provide an intraoperative platform to enhance the seed implant procedure in practice. Further evaluation of the *in vivo* utility of VA for imaging PPB seeds is a subject of ongoing and planned studies. Conceivably, a transrectal Q2D probe could operate in TRUS mode for needle guidance during the needle placement and seed implantation portion of the procedure. Such a probe could also serve as a tool for intraoperative prostate brachytherapy dosimetry, particularly as technical improvements are made and the proportion of seeds detected approaches 100%. The goal of performing intraoperative dosimetry is to gain immediate feedback regarding the dosimetric quality of an implant. For I-125 dosimetry it is suggested that the ideal time for post-implant dosimetry is 30 days following the procedure.⁵¹ Nonetheless, the American Brachytherapy Society updated guidelines from 2012 recommend that patients undergo post-implant CT based dosimetry within 60 days of the procedure.⁵² This includes same day ("Day 0") dosimetry as an acceptable option. Ohashi *et al.*⁵³ have re-examined this issue and compared immediate postoperative dosimetry to Day 30 dosimetry and found only small differences between the two. In addition, in a survey of brachytherapy practitioners by Buyyounouski *et al.*,⁵⁴ 37% of respondents who perform LDR brachytherapy performed Day 0 post-implant dosimetry and 73% Day 30 post-implant dosimetry (10% both Day 0 and Day 30). Consequently, it would be of use to have a rapid, portable, and intraoperative means of performing Day 0 intraoperative dosimetry.

5. CONCLUSIONS

We have demonstrated the feasibility of using VA with a Q2D array US transducer in detection and localization of PPB seeds in excised prostate tissue. In comparison with CT as a gold-standard method of seed detection, Q2DVA images revealed a large fraction of implanted seeds in imaged prostate specimens. In contrast to TRUS imaging, Q2DVA demonstrated a capability of imaging PPB seeds independent of their orientation. Implementation of Q2DVA on a transrectal ultrasound probe could lead to the development and utilization of

combined TRUS and VA to provide more clinically useful information with the ultimate goal of achieving intraoperative VA-based dosimetry.

ACKNOWLEDGMENTS

This study was supported by NIH Grant Nos. P50-CA91956-P2 and P50-CA91956-10DR1 from the National Cancer Institute. The authors are grateful to Dr. James F. Greenleaf and Dr. Matthew W. Urban for their helpful discussions, Dr. Christopher Deufel for help with CT imaging of tissue specimens, to Thomas Kinter for computer support, and to Jennifer Milliken for administrative support. Mayo Clinic and the corresponding authors (M.F.) have financial interests associated with the technology used in this research; the technology has been licensed in part to industry.

- ^{a)} Author to whom correspondence should be addressed. Electronic mail: fatemi.mostafa@mayo.edu; Telephone: (507)284-0608; Fax: (507)266-0361.
- ¹ R. Siegel, D. Naishadham, and A. Jemal, "Cancer statistics, 2013," *CA: Cancer J. Clin.* **63**, 11–30 (2013).
- ² I. Norderhaug, O. Dahl, P. Å. Høisæter, R. Heikkilä, O. Klepp, D. R. Olsen, I. S. Kristiansen, H. Wæhre, and T. E. Bjerklund Johansen, "Brachytherapy for prostate cancer: A systematic review of clinical and cost effectiveness," *Eur. Urol.* **44**, 40–46 (2003).
- ³ H. Ragde, G. L. Grado, B. Nadir, and A. A. Elgamal, "Modern prostate brachytherapy," *CA: Cancer J. Clin.* **50**, 380–393 (2000).
- ⁴ A. P. Dicker, G. Merrick, L. Gomella, R. K. Valicenti, and F. Waterman, *Basic and Advanced Techniques in Prostate Brachytherapy* (CRC Press, Boca Raton, FL, 2005).
- ⁵ C. Salembier, P. Lavagnini, P. Nickers, P. Mangili, A. Rijnders, A. Polo, J. Venselaar, P. Hoskin, and GEC ESTRO PROBATE Group, "Tumour and target volumes in permanent prostate brachytherapy: A supplement to the ESTRO/EAU/EORTC recommendations on prostate brachytherapy," *Radiother. Oncol.* **83**, 3–10 (2007).
- ⁶ D. Ash, A. Flynn, J. Battermann, T. de Reijke, P. Lavagnini, and L. Blank, "ESTRO/EAU/EORTC recommendations on permanent seed implantation for localized prostate cancer," *Radiother. Oncol.* **57**, 315–321 (2000).
- ⁷ B. H. Han, K. Wallner, G. Merrick, W. Butler, S. Sutlief, and J. Sylvester, "Prostate brachytherapy seed identification on post-implant TRUS images," *Med. Phys.* **30**, 898–900 (2003).
- ⁸ Y. Su, B. J. Davis, K. M. Furutani, M. G. Herman, and R. A. Robb, "Seed localization and TRUS-fluoroscopy fusion for intraoperative prostate brachytherapy dosimetry," *Comput. Aided Surg.* **12**, 1277–1287 (2007).
- ⁹ Y. Su, B. J. Davis, M. G. Herman, and R. A. Robb, "Prostate brachytherapy seed localization by analysis of multiple projections: Identifying and addressing the seed overlap problem," *Med. Phys.* **31**, 1277–1287 (2004).
- ¹⁰ D. B. Fuller, H. Jin, J. A. Koziol, and A. C. Feng, "CT-ultrasound fusion prostate brachytherapy: A dynamic dosimetry feedback and improvement method. A report of 54 consecutive cases," *Brachytherapy* **4**(3), 207–216 (2005).
- ¹¹ S. Nag, W. Bice, K. DeWynngaert, B. Prestidge, R. Stock, and Y. Yu, "The American Brachytherapy Society recommendations for permanent prostate brachytherapy postimplant dosimetric analysis," *Int. J. Radiat. Oncol., Biol., Phys.* **46**, 221–230 (2000).
- ¹² A. Polo, C. Salembier, J. Venselaar, and P. Hoskin, "Review of intraoperative imaging and planning techniques in permanent seed prostate brachytherapy," *Radiother. Oncol.* **94**, 12–23 (2010).
- ¹³ Y. Su, B. J. Davis, M. G. Herman, A. Manduca, and R. A. Robb, "Examination of dosimetry accuracy as a function of seed detection rate in permanent prostate brachytherapy," *Med. Phys.* **32**, 3049–3056 (2005).
- ¹⁴ B. Davis, W. LaJoie, K. McGee, S. Geyer, B. King, T. Wilson, L. Mynderse, M. Herman, and R. Robb, "Seed identification rates as a function of imaging modality in permanent prostate brachytherapy using CT-MR-TRUS image fusion," *Proc. Am. Brachyther. Soc.* **2002**, 42 (2002).
- ¹⁵ B. Al-Qaisieh, D. Ash, D. M. Bottomley, and B. M. Carey, "Impact of prostate volume evaluation by different observers on CT-based post-implant dosimetry," *Radiother. Oncol.* **62**, 267–273 (2002).
- ¹⁶ D. F. Dubois, B. R. Prestidge, L. A. Hotchkiss, J. J. Prete, and W. Bice, "Intraobserver and interobserver variability of MR imaging- and CT-derived prostate volumes after transperineal interstitial permanent prostate brachytherapy," *Radiology* **207**, 785–789 (1998).
- ¹⁷ W. R. Lee, M. Roach, J. Michalski, B. Moran, and D. Beyer, "Interobserver variability leads to significant differences in quantifiers of prostate implant adequacy," *Int. J. Radiat. Oncol., Biol., Phys.* **54**, 457–461 (2002).
- ¹⁸ L. Gong, P. S. Cho, B. H. Han, K. E. Wallner, S. G. Sutlief, S. D. Pathak, D. R. Haynor, and Y. Kim, "Ultrasonography and fluoroscopic fusion for prostate brachytherapy dosimetry," *Int. J. Radiat. Oncol., Biol., Phys.* **54**, 1322–1330 (2002).
- ¹⁹ I. B. Tutar, L. Gong, S. Narayanan, S. D. Pathak, P. S. Cho, K. Wallner, and Y. Kim, "Seed-based transrectal ultrasound-fluoroscopy registration method for intraoperative dosimetry analysis of prostate brachytherapy," *Med. Phys.* **35**(3), 840–848 (2005).
- ²⁰ M. Moradi, S. S. Mahdavi, E. Dehghan, J. R. Lobo, S. Deshmukh, W. J. Morris, G. Fichtinger, and S. E. Salcudean, "Seed localization in ultrasound and registration to C-arm fluoroscopy using matched needle tracks for prostate brachytherapy," *IEEE Trans. Biomed. Eng.* **59**, 2558–2567 (2012).
- ²¹ A. D'Amico, R. Cormack, C. Tempany, S. Kumar, G. Topulos, H. Kooy, and C. N. Coleman, "Real-time magnetic resonance image-guided interstitial brachytherapy in the treatment of select patients with clinically localized prostate cancer," *Int. J. Radiat. Oncol., Biol., Phys.* **42**, 507–515 (1998).
- ²² M. Muntener, A. Patriciu, D. Petrisor, D. Mazilu, H. Bagga, L. Kavoussi, K. Cleary, and D. Stoianovici, "Magnetic resonance imaging compatible robotic system for fully automated brachytherapy seed placement," *Urology* **68**, 1313–1317 (2006).
- ²³ S. J. DiBiase, K. Hosseinzadeh, R. P. Gullapalli, S. C. Jacobs, M. J. Naslund, G. N. Sklar, R. B. Alexander, and C. Yu, "Magnetic resonance spectroscopic imaging-guided brachytherapy for localized prostate cancer," *Int. J. Radiat. Oncol., Biol., Phys.* **52**, 429–438 (2002).
- ²⁴ T. Ohashi, T. Momma, S. Yamashita, K. Nagatsuma, K. Kanai, K. Kitagawa, S. Takahashi, T. Hanada, A. Yoroze, and N. Shigematsu, "Impact of MRI-based postimplant dosimetric assessment in prostate brachytherapy using contrast-enhanced T1-weighted images," *Brachytherapy* **11**, 468–475 (2012).
- ²⁵ S. Vidakovic, H. S. Jans, A. Alexander, and R. Sloboda, "Post-implant computed tomography-magnetic resonance prostate image registration using feature line parallelization and normalized mutual information," *J. Appl. Clin. Med. Phys.* **8**, 21–32 (2006).
- ²⁶ M. Fatemi and J. F. Greenleaf, "Ultrasound-stimulated vibro-acoustic spectrography," *Science* **280**, 82–85 (1998).
- ²⁷ M. Fatemi and J. F. Greenleaf, "Vibro-acoustography: An imaging modality based on ultrasound-stimulated acoustic emission," *Proc. Natl. Acad. Sci. U.S.A.* **96**, 6603–6608 (1999).
- ²⁸ A. Alizad, M. Fatemi, R. A. Nishimura, R. R. Kinnick, E. Rambod, and J. F. Greenleaf, "Detection of calcium deposits on heart valve leaflets by vibro-acoustography: An *in vitro* study," *J. Am. Soc. Echocardiogr.* **15**, 1391–1395 (2002).
- ²⁹ A. Alizad, M. Fatemi, L. E. Wold, and J. F. Greenleaf, "Performance of vibro-acoustography in detecting microcalcifications in excised human breast tissue: A study of 74 tissue samples," *IEEE Trans. Med. Imaging* **23**, 307–312 (2004).
- ³⁰ A. Alizad, M. Mehrmohammadi, F. G. Mitri, B. J. Davis, T. J. Sebo, L. A. Mynderse, R. R. Kinnick, J. F. Greenleaf, and M. Fatemi, "Application of vibro-acoustography in prostate tissue imaging," *Med. Phys.* **40**, 022902 (10pp.) (2013).
- ³¹ A. Alizad, D. H. Whaley, M. W. Urban, R. E. Carter, R. R. Kinnick, J. F. Greenleaf, and M. Fatemi, "Breast vibro-acoustography: Initial results show promise," *Breast Cancer Res.* **14**(5), R128 (2012).
- ³² M. W. Urban, C. Chalek, R. R. Kinnick, T. M. Kinter, B. Haider, J. F. Greenleaf, K. E. Thomenius, and M. Fatemi, "Implementation of vibro-acoustography on a clinical ultrasound system," *IEEE Trans. Ultrason. Ferroelectr. Freq. Control* **58**, 1169–1181 (2011).
- ³³ G. T. Silva, J. F. Greenleaf, and M. Fatemi, "Linear arrays for vibro-acoustography: A numerical simulation study," *Ultrason. Imaging* **26**, 1–17 (2004).
- ³⁴ S. Chen, M. Fatemi, R. Kinnick, and J. F. Greenleaf, "Comparison of stress field forming methods for vibro-acoustography," *IEEE Trans. Ultrason. Ferroelectr. Freq. Control* **51**, 313–321 (2004).

- ³⁵G. T. Silva, S. Chen, A. C. Frery, J. F. Greenleaf, and M. Fatemi, "Stress field forming of sector array transducers for vibro-acoustography," *IEEE Trans. Ultrason. Ferroelectr. Freq. Control* **52**, 1943–1951 (2005).
- ³⁶M. W. Urban, P. Garigipati, P. Peers, K. E. Thomenius, M. Fatemi, and P. Debevec, "A beamforming study for implementation of vibro-acoustography with a 1.75-D array transducer," *IEEE Trans. Ultrason. Ferroelectr. Freq. Control* **60**, 535–551 (2013).
- ³⁷H. A. Kamimura, M. W. Urban, A. A. Carneiro, M. Fatemi, and A. Alizad, "Vibro-acoustography beam formation with reconfigurable arrays," *IEEE Trans. Ultrason. Ferroelectr. Freq. Control* **59**, 1421–1431 (2012).
- ³⁸M. W. Urban, M. Fatemi, and A. Alizad, "Beamforming for vibro-acoustography using a 1.75 D array transducer," *J. Acoust. Soc. Am.* **127**, 1828–1828 (2010).
- ³⁹F. Mitri, B. Davis, M. Urban, A. Alizad, J. Greenleaf, G. Lischer, T. Wilson, and M. Fatemi, "Vibro-acoustography imaging of permanent prostate brachytherapy seeds in an excised human prostate-Preliminary results and technical feasibility," *Ultrasonics* **49**, 389–394 (2009).
- ⁴⁰F. G. Mitri, B. J. Davis, A. Alizad, J. F. Greenleaf, T. M. Wilson, L. A. Mynderse, and M. Fatemi, "Prostate cryotherapy monitoring using vibroacoustography: Preliminary results of an *ex vivo* study and technical feasibility," *IEEE Trans. Biomed. Eng.* **55**, 2584–2592 (2008).
- ⁴¹F. Mitri, B. Davis, J. Greenleaf, and M. Fatemi, "*In vitro* comparative study of vibro-acoustography versus pulse-echo ultrasound in imaging permanent prostate brachytherapy seeds," *Ultrasonics* **49**, 31–38 (2009).
- ⁴²J. Mamou, S. Ramachandran, and E. J. Feleppa, "Angle-dependent ultrasonic detection and imaging of brachytherapy seeds using singular spectrum analysis," *J. Acoust. Soc. Am.* **123**, 2148–2159 (2008).
- ⁴³B. J. Davis, R. R. Kinnick, M. Fatemi, E. P. Lief, R. A. Robb, and J. F. Greenleaf, "Measurement of the ultrasound backscatter signal from three seed types as a function of incidence angle: Application to permanent prostate brachytherapy," *Int. J. Radiat. Oncol., Biol., Phys.* **57**, 1174–1182 (2003).
- ⁴⁴J. Browne, K. Ramnarine, A. Watson, and P. Hoskins, "Assessment of the acoustic properties of common tissue-mimicking test phantoms," *Ultrasound Med. Biol.* **29**, 1053–1060 (2003).
- ⁴⁵D. H. Brinkmann and R. W. Kline, "Automated seed localization from CT datasets of the prostate," *Med. Phys.* **25**, 1667–1672 (1998).
- ⁴⁶B. J. Davis, D. H. Brinkmann, J. J. Kruse, M. G. Herman, W. N. LaJoie, D. J. Schwartz, T. M. Pisansky, and R. W. Kline, "Selective identification of different brachytherapy sources, ferromagnetic seeds, and fiducials in the prostate using an automated seed sorting algorithm," *Brachytherapy* **3**, 106–112 (2004).
- ⁴⁷X. Wen, S. Salcudean, and P. D. Lawrence, "Detection of brachytherapy seeds using 3-D transrectal ultrasound," *IEEE Trans. Biomed. Eng.* **57**, 2467–2477 (2010).
- ⁴⁸H. H. Holm, N. Juul, J. F. Pedersen, H. Hansen, and I. Stoyer, "Transperineal 125 seed implantation in prostatic cancer guided by transrectal ultrasonography," *J. Urol.* **130**, 283–286 (1983).
- ⁴⁹C. G. Woychik, A. T. Byun, R. Fisher, K. Thomenius, L. Der-Song, X. Zhuang, O. Oralkan, S. Vaithilingam, and B. T. Khuri-Yakub, "Multi-row linear cMUT array using cMUTs and multiplexing electronics," *Proceeding of IEEE International Ultrasonics Symposium*, pp. 2696–2699 (2009).
- ⁵⁰J. Song, S. Jung, Y. Kim, K. Cho, B. Kim, S. Lee, J. Na, I. Yang, O.-K. Kwon, and D. Kim, "Reconfigurable 2D cMUT-ASIC arrays for 3D ultrasound image," *Proc. SPIE 8320, Medical Imaging 2012: Ultrasonic Imaging, Tomography, and Therapy*, 83201A (2012).
- ⁵¹F. M. Waterman, N. Yue, B. W. Corn, and A. P. Dicker, "Edema associated with I-125 or Pd-103 prostate brachytherapy and its impact on post-implant dosimetry: An analysis based on serial CT acquisition," *Int. J. Radiat. Oncol., Biol., Phys.* **41**, 1069–1077 (1998).
- ⁵²B. J. Davis, E. M. Horwitz, W. R. Lee, J. M. Crook, R. G. Stock, G. S. Merriker, W. M. Butler, P. D. Grimm, N. N. Stone, and L. Potters, "American Brachytherapy Society consensus guidelines for transrectal ultrasound-guided permanent prostate brachytherapy," *Brachytherapy* **11**, 6–19 (2012).
- ⁵³T. Ohashi, A. Yorozu, K. Toya, S. Saito, T. Momma, H. Nagata, M. Kosugi, N. Shigematsu, and A. Kubo, "Comparison of intraoperative ultrasound with postimplant computed tomography–dosimetric values at Day 1 and Day 30 after prostate brachytherapy," *Brachytherapy* **6**, 246–253 (2007).
- ⁵⁴M. K. Buyyounouski, B. J. Davis, B. R. Prestidge, T. G. Shanahan, R. G. Stock, P. D. Grimm, D. J. Demanes, M. Zaider, and E. M. Horwitz, "A survey of current clinical practice in permanent and temporary prostate brachytherapy: 2010 update," *Brachytherapy* **11**, 299–305 (2012).