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14. ABSTRACT

Gland-sparing procedures that target specific areas of the prostate have been reported, using laser and HIFU techniques. These focal therapies require real-time visualization of the prostate during intervention, which is cumbersome to perform while the patient is in an MRI. Magnetic Resonance-Ultrasound (MR-US) fusion allows for specific targeting of the tumors in real-time during clinical interventions, outside of an MR suite. However, existing MR-US fusion exclusively utilizes TRUS. By utilizing a circumferentially wrapped catheter-based transducer, the entire prostate may be visualized at once; improving image registration and reducing motion errors. 3D TUUS imaging has been demonstrated in a phantom setting illustrating that the entire prostate gland can be visualized at once. This imaging advance may serve as a platform technology allowing the development of image guided focal prostate therapy.

15. SUBJECT TERMS

Ultrasound, prostate cancer, transurethral, MRI, image fusion

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1. **Introduction:**
   Curative therapies for prostate cancer (CaP) include surgical resection, irradiation, or ablation of the entire gland. Focal or site-specific treatment of CaP, while still early in investigation, requires an accurate real-time visualization of the prostate. An increasing body of literature documents the advantages of Magnetic Resonance-Ultrasound fusion for targeting specific tumors within the prostate. However, these approaches rely on transrectal ultrasound (TRUS), which suffers from registration and motion artifacts, as well as poor visualization of the anterior prostate. It is proposed that the use of a catheter-based transurethral ultrasound (TUUS) device has the ability to image the prostate in 3D with higher resolutions than TRUS. The overall objective of this proposal is to validate and clinically evaluate the use of 3D-TUUS in men undergoing needle-based interventions of the prostate. MR imaging will be used as the gold standard to compare TUUS and TRUS images. Achieving this goal will be facilitated by an FDA-approved radially-phased intravascular ultrasound device (Visions, Volcano Therapeutics), which will be clinically tested for use in the prostate. The results of this study demonstrate that TUUS prostate volume reconstruction is more accurate the TRUS with a percent difference of 8.07% and 54.72% when compared to MRI volume reconstruction, respectively.

2. **Keywords:**
   Ultrasound, MRI, image fusion, prostate cancer, transurethral

3. **Accomplishments:**
   a. **Major Goals of the Project**
      i. **Training and education development in prostate cancer research**
      ii. **Validate and refine 3D reconstruction accuracy of TUUS imaging**

Major Task 1: Training and educational development in prostate cancer research *(only applicable to training award mechanisms)*	**Months**	**UCLA**
Subtask 1: ARC Training and Certification Program	1-6	Completed
Subtask 2: Biweekly progress update meeting with mentor	1-24	Dr. Grundfest
Subtask 3: Biweekly meeting with co-mentor	1-24	Dr. Marks
Subtask 4: IRB Training	1-24	Completed
Subtask 5: Attend Urology Grand Rounds Weekly Conferences	1-24	Completed
Milestone(s) Achieved: Presentation of project results at a conference	24	*Presentation Cancelled*

Research-Specific Tasks:

Specific Aim 1: Validate and refine 3D reconstruction accuracy of TUUS imaging		**UCLA**

Subtask 1: Validation of the image reconstruction accuracy of MR and TUUS in phantoms	1-3	Completed
Subtask 2: Compare volume reconstruction accuracy to 3D TRUS	4-12	Completed
Milestone(s) Achieved: Validation of 3D TUUS reconstruction accuracy	12	Completed
Specific Aim 2: Validate MR-TUUS image registration error	10-21	UCLA
Milestone(s) Achieved: Validation of MR-TUUS image registration error with MRI and compared to 3D TRUS	21	Completed
Specific Aim 3: Pilot study to evaluate MR-TUUS fusion in brachytherapy needle placement	13-24	In Progress
Major Task 1: Develop planning software to track needle insertion		In Progress
Major Task 2: Determine error in needle placement		In Progress
Milestone(s) Achieved: Assessed the use of TUUS in needle guidance in brachytherapy	24	In Progress

b. Accomplished Goals

i. Implemented MRI/TRUS/TUUS prostate phantoms
ii. Imaged prostate phantoms using MRI, TRUS, and TUUS
iii. Submitted an IRB for pilot study
iv. Compared prostate volume accuracy between TUUS and TRUS
v. Compared prostate fiducials between TUUS and TRUS to MRI

During the reporting period of (29 September 2015 – 28 March 2017) biweekly

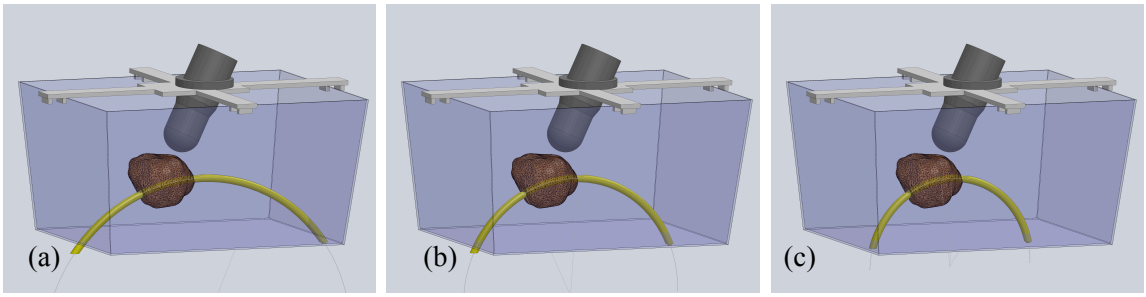

Figure 1: SOLIDWORKS CAD software prostate phantom model, (a) with 20 deg urethra bend, (b) 30 deg urethra bend, and (c) 40 deg urethra bend.

progress report meetings with my mentor Dr. Grundfest and co-mentor Dr. Marks were done. IRB and ARC training was completed, urology grand rounds weekly conferences have been attended. Research was conducted toward the aim of validating and refining 3D reconstruction accuracy of transurethral ultrasound (TUUS) imaging. To work towards accomplishing this goal three TUUS prostate phantoms with three prostatic urethra bend of 20 degrees, 30 degrees and 40 degrees were designed in SOLIDWORKS CAD software to develop a prostate phantom model (**Fig. 1**). The prostate is the same shape and size in all three images in Fig. 1, only the prostatic urethra bend is different. This was done to see the effect of the prostatic bend on TUUS imaging. These three angles of curvature were chosen around the mean prostatic urethra bend of 29.0 degrees with a standard deviation of 12.2 degrees [i]. The phantoms were designed for imaging with standard transrectal ultrasound (TRUS) probe, a TUUS probe, and MRI.

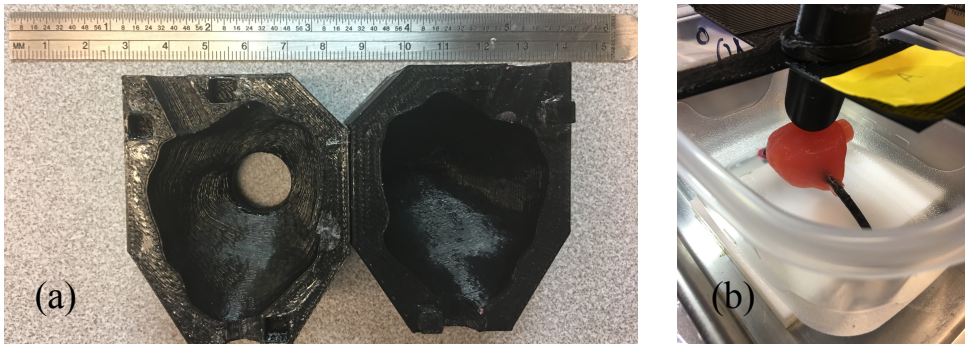

Figure 2: 3D printed prostate phantom mold (a), and pelvis phantom mold with prostate agar phantom in place (b).

The TUUS phantoms were prepared using a standard recipe [ii] for the prostate and the 3D printed mold designed in SOLIDWORKS. Figure 2 and 3 illustrates an example of the MRI/TUUS/TRUS prostate and pelvis phantom mold, and the phantom during and after fabrication. An FDA approved radially-phased 64-element array intravascular ultrasound (IVUS) device (Visions, Volcano Therapeutics) 8.2 French catheter and Volcano s5 imaging system were used for the TUUS imaging. A Siemens Avanto 1.5 Tesla MRI was used to image all the prostate phantoms.

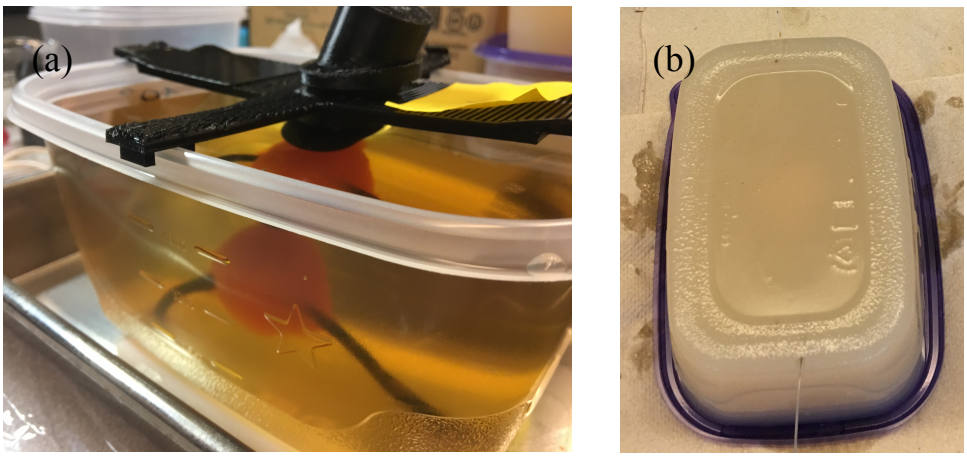

Figure 3: Complete prostate phantom immediately after pouring agar (a), and complete prostate phantom at room temperature with IVUS catheter in place (b).

The IVUS was electronically controlled to yield 2D images that were stitched to reconstruct a high quality 3D image of the prostate. The stitching of the images and 3D reconstruction for both the TUUS and MRI images was accomplished using a free DICOM medical imaging software called Horos. This software allows the user to view all the images and draw a polygon around the region of interest (ROI). Once all the ROIs are drawn the program constructs a 3D surface rendering using the ROIs and calculates the volume. The volumes calculated for each modality MRI and TUUS can be easily compared to each other. Figure 4 is an example of the ROI and the 3D volume construction. TRUS imaging was accomplished using a Hitachi Hi-Vision 5500 Ultrasound system with 7.5 MHz end-fire endorectal probe. 3D TRUS acquisition utilized an FDA-approved targeting and tracking system for prostate biopsy (Artemis, Eigen, Grass Valley, CA). This device employs digital video processing of conventional ultrasound images, which allows it to create a contemporaneous 3D reconstruction of the prostate and digitally record and store the biopsy sites for serial study and sampling. 3D reconstruction is completed by that system immediately after the ROIs are drawn.

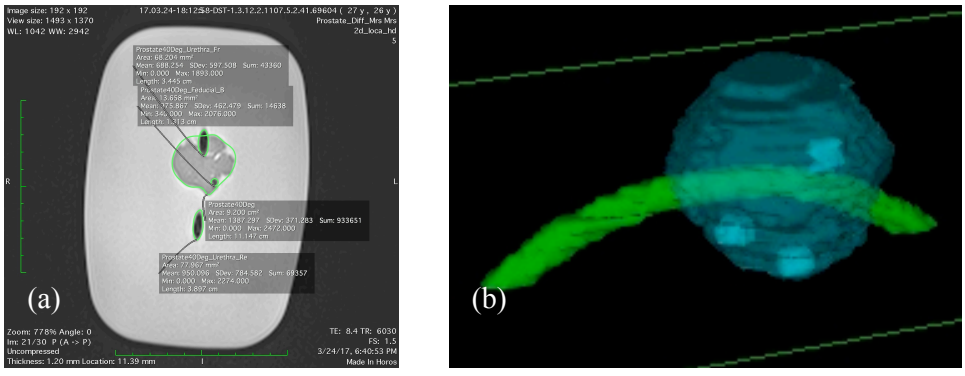

Figure 4: An example of ROIs for prostate, urethra, and fiducial (a), and 3D reconstruction of all the 2D images after all the ROIs have been drawn for each image (b).

All phantoms were scanned using the TUUS probe and the 3D TRUS probe and system and MRI. The volume reconstruction accuracy of TUUS and TRUS was compared with MRI, MRI being the ground truth. The average volume generated by the MRI images for the prostate was calculated to be 32.03cm^3 with a standard

deviation of 2.26 cm^3. For the TUUS and TRUS images the average volume was calculated to be 34.61 cm^3 with a standard deviation of 1.1 cm^3 and 49.55cm^3 with a standard deviation of 1.06 cm^3, respectively. When the TUUS and TRUS volumes are compared with MRI the percent difference between TUUS and MRI, and TRUS and MRI is 8.07% and 54.72%, respectively. This demonstrates that TUUS is significantly more accurate than TRUS when comparing prostate volumes. The three different bend radii's had a negligible effect on the TUUS imaging. The difference between TUUS volume reconstruction for the 20deg, 30 deg and 40deg was as low as 0.1cm^3 to as high as 0.4cm^3, this could also be attributed the user will draw the same ROI from day to day. When comparing the error between the fiducial marker locations between MRI and TUUS and MRI and TRUS, the percent error is 4.08%, and 9.59%, respectively. This also demonstrates that TUUS is significantly more accurate than TRUS when compared with MRI as the ground truth. These results warrant additional investigation in the future.

Recently, the approved IRB was up for renewal and due to changes in UCLA IRB renewal process and additional requirements that were not present when the IRB was first submitted and approved, the IRB has been held up. Due to this issue the pilot study was not performed but I'm currently working with IRB to resolve this issue, and will perform the pilot study with the help of Drs. Marks and Grundfest.

Challenges:
Some of the challenges that were encountered during this work are the stability of the phantoms over time, acquiring IVUS catheters, access to the imaging tools (TUUS imaging machine, TRUS imaging machine and MRI machine) needed for this research and scheduling time to use those tools. The tools needed to accomplish the research tasks outlined in the statement of work are used routinely for patients at UCLA Ronald Reagan hospital, which make it difficult to have physical access to the tools. Also at the beginning of this research period it took a considerable amount of time to get in contact with the appropriate persons to get permission to use the equipment and to develop a collaborative working relationship with the staff to get physical access to the equipment. In addition, it took a considerable amount of time to acquire samples of the IVUS catheters needed to perform the *in vitro* experiments Qty (3). The fabricated phantoms have a finite shelf life and after several weeks of storage the phantoms become unstable and degrade in size and elasticity. This requires scheduling time to use all three imaging machine within a short period of time which is challenging. Also the IVUS probes have a finite number of trials, usually between 4 to 6 trials per probe, this restricts the number of *in vitro* experiments that can be done, since I have a limited quantity of IVUS catheters. Many attempts were made to contact Volcano Corp. to acquire additional samples of the IVUS probes but these attempts were unfruitful.

IRB Approval for pilot Study

During this period an application titled "A study to determine accuracy of transurethral ultrasound (TUUS) imaging" was submitted to the UCLA institutional review board (IRB) for review. The application was approved by the UCLA IRB (IRB#15-000120). Currently the IRB is in the renewal process and due to changes in UCLA IRB renewal process and additional requirements that were not present when the IRB was first submitted and approved, the IRB has been held up. As soon as the IRB is reapproved I will be able to perform the pilot study in the third aim of this project.

c. **What opportunities for training and professional development has the project provided?**
This project has provided the opportunity for IRB training, training on the use of the Volcano Corp. IVUS imaging machine, training on the Artimus 3D TRUS machine, use of the Siemens MRI machine.

d. **How were the results disseminated to communities of interest?**
Nothing to Report

e. **What do you plan to do during the next reporting period to accomplish the goals?**
Nothing to Report.

4. **Impact**
   a. **What was the impact on the development of the principle discipline of the project?**
   Nothing to Report
   b. **What was the impact on other disciplines?**
   Nothing to Report
   c. **What was the impact on technology transfer?**
   Nothing to Report
   d. **What was the impact on society beyond science and technology?**
   Nothing to Report

5. **Changes/Problems:**
   a. **Changes in approach and reasons for change**
   Nothing to Report
   b. **Actual or anticipated problem or delays and actions or plans to resolve them**
   The approved IRB was recently up for renewal and due to changes in UCLA IRB renewal process and additional requirements that were not present when the IRB was first drafted and approved, the IRB has been held up. Due to this issue the pilot study has been put on hold. I have been working with the IRB staff to resolve this issue and provide the necessary information to get the IRB approved again. As soon as the IRB is approved again I will perform the pilot study with the help of Drs. Marks and Grundfest.
   c. **Changes that had significant impact on expenditures**
   Nothing to Report
   d. **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and or select agents**
   Nothing to Report

6. **Products:**
   Nothing to Report

7. **Participants & Other Collaborating Organizations:**
   a. **What individuals have works on the project?**
      Name: Dr. George Saddik Ph.D.
      Project Role: PI
      Research Identifier: UCLA ID# 104243711
      Nearest person month worked: 12
      Contribution to Project: N/A
      Funding Support: N/A
   b. **Has there been a change in the active other support of the PD/PI(s) or senior /key personnel since the last reporting period?**
      Nothing to Report
   c. **What other organizations were involved as partners?**
      Nothing to Report

8. **Special Reporting Requirements:**
   Nothing to Report

9. **Appendices:**
   a. **References:**

      i. David R. Holmes III, Brian J. Davis, Christopher C. Goulet, Torrence M. Wilson, Lance A. Mynderse, Keith M. Furutani, Jon J. Camp, Richard A. Robb, Shape analysis of the prostate: Establishing imaging specifications for the design of a transurethral imaging device for prostate brachytherapy guidance, *Journal of Brachytherapy*, 13 (2014) 465-470.
      ii. M. O. Culjat, D. Goldenberg, P. Tewari, and R. S. Singh, "A Review of Tissue Substitutes for Ultrasound Imaging," *Ultrasound in Medicine & Biology*, vol. 36, pp. 861-873, 6// 2010.

   b. **Prostate Phantom Recipe**
      i. Prostate:
      3.5 g Agar in 100 mL water, 3 4mm glass beads added at 40^{o}C
      Pelvis:
      3.5 g Agar and 4.5 g glass microbeads in 100 mL of water