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Award Number: DAMD17-99-1-9007

TITLE: Combining Clinical, Sonographic, and Elastigraphic Features to Improve the Detection of Prostate Cancer

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REPORT DATE: December 1999

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	December 1999	Annual (16 Nov 98 - 15 Nov 99)

4. TITLE AND SUBTITLE
Combining Clinical, Sonographic, and Elastigraphic Features to Improve the Detection of Prostate Cancer

5. FUNDING NUMBERS
DAMD17-99-1-9007

6. AUTHOR(S)
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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT ***(Maximum 200 Words)***
The ultimate goal of this project is to combine features derived from ultrasound (US) images, US radio-frequency (RF) data, tissue elasticity imaging, and clinical data such as PSA into a computerized system for displaying prostate images that indicate probable location(s) of cancer. This project proposed to begin by gathering RF data from in-vitro prostatectomy specimens in cross sectional planes 2mm apart. These data are used to calculate RF features such as scatterer size, and backscatter coefficient at each location in the gland. The data are also used to generate images and elastograms from which image texture features and tissue hardness features are computed. The features are then correlated with histology taken at the same tissue planes to determine which features and feature combinations most accurately predict the presence of cancer.

Despite administrative problems that delayed the start of the project by six months, we have brought the acquisition equipment on line, acquiring both RF and pathology data from the prostate glands of 26 patients. From the RF we produced the first elastograms ever from a gland NOT embedded in a gel block proving that acquisition of reliable strain data from a gland immersed in saline is possible. We also developed new standoff devices to improve data quality from the peripheral zone of the prostate and developed improved software for elastogram and RF feature calculation. The assembly of the pathology images into whole mount images corresponding to the scan planes obtained with ultrasound is well underway. Development of software for texture analysis and integration of existing software components awaits the arrival of a replacement postdoctoral fellow in January.

14. SUBJECT TERMS
Prostate Cancer, ultrasound, elastography, tissue characterization

15. NUMBER OF PAGES
13

16. PRICE CODE

CURITY CLASSIFICATION REPORT	CURITY CLASSIFICATION THIS PAGE	CURITY CLASSIFICATION ABSTRACT	ITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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Brian [illegible] 14 December 1999

PI - Signature Date

TABLE OF CONTENTS

INTRODUCTION

The ultimate goal of this project is to combine features derived from ultrasound (US) images, US radio-frequency (RF) data, tissue elasticity imaging, and clinical data such as PSA into a computerized system for displaying prostate images that indicate probable location(s) of cancer. Each of these different classes of features has been shown to be useful for prostate cancer detection. By combining those features in each class that perform best in a set of test cases, we hope to develop an accurate tool for detecting regions on the ultrasound image that a high probability for cancer. Eventually we hope these techniques will be used to rapidly identify high probability areas and mark them on the ultrasound image in real time or near real time.

This project began by gathering RF data from in-vitro prostatectomy specimens in cross sectional planes 2mm apart using a linear array transducer. These data are used to calculate RF features such as scatterer size, and backscatter coefficient at each location in the gland. The data are also used to generate images and elastograms from which image texture features and tissue hardness features are computed. The features will be correlated with histology taken at the same tissue planes to determine which features and feature combinations most accurately predict the presence of cancer. The various image, hardness, and RF features will then be combined with prior probability information derived from an AFIP 3D model of prostate occurrence and with clinical PSA values to produce a system that can accurately identify the presence of prostate cancer using ultrasound data.

After developing the techniques to perform identification of prostate cancer using the linear array scans, our plan is to migrate the technique to data from a curved array transducer and then finally to data from an endorectal prostate probe. We hope in the end to be able to demonstrate an in vitro system using an endorectal prostate probe that will be able to mark areas of high probability for cancer on each ultrasound image. This will prepare us for an in vivo study directed at developing an ultrasound system that can better direct biopsies of the prostate gland to areas of high likelihood for actual prostate cancer.

RESEARCH ACTIVITIES AND PROGRESS

Administrative Activities and Problems:

Delay in Start Date

The first year of this project has been one of overcoming administrative and personnel obstacles. Although the contract was awarded in November of 1998, University Administrative problems prevented me from gaining paid faculty status until 1 May 1999. I was therefore barred from using any of the project funds or even preparing to hire a research assistant until that date. In late May 1999, I was finally assigned research space in the orthopedics department and could begin setting up equipment I was to use for the project. Some minor remodeling was required but the remodeling and configuration of the research equipment was completed by early June 1999. Unfortunately, in the one-year period since the equipment had been moved to the University of Vermont from Georgetown University, some critical components had disappeared making it necessary for me to construct replacements. These components were completed by mid June 1999.

In May 1999, I moved immediately to hire a research assistant part time as called for in the proposal. This process was completed by early June. Training and final arrangements for obtaining radical prostatectomy specimens were completed by the third week of June and our first acquisition of prostate data at the University of Vermont occurred on 27 June 1999. Thus, the six-month delay in starting the project has placed data acquisition approximately six months behind schedule but I am optimistic that some of that lost time can be made up in the next year.

Personnel Issues

The delay in being allowed to begin work aggravated another important personnel problem. Rashidus Mia, the graduate student at George Washington University who was to be the postdoctoral fellow on this project, elected to leave GWU and pursue a career in industry. George Washington University has not been able to find an adequate replacement for him. Since this person is critical to the success of the program, I have decided to wait no longer for GWU. I have cancelled the subcontract and have made an agreement with the Department of Mechanical Engineering at the University of Vermont to provide a qualified replacement. This person (Dr. Zhe He) is a highly proficient computer programmer who did graduate work in opto-electronic engineering and comes highly recommended by Dr. Dryver Huston, chairman of the Department of Mechanical Engineering at the University of Vermont. Dr. Zhe will work under my direction and that of Dr. Huston. Drs. Robert Wagner and Keith Weir of the FDA will provide him with additional training on the specifics of this project to help get him going quickly on the tasks required of him. It is expected that Dr. Zhe will begin work in January 2000.

RESEARCH PROGRESS

Task 1 (Months 1-6): Collect RF data on 25 prostate glands with the linear array transducer. Develop a preliminary plan for data acquisition for tasks 5 and 7.

This part of the project has been completed. As of 26 November, RF data had been acquired from the prostate glands of 26 patients. During the first five of these, fine-tuning of the

acquisition process was underway and the elastographic data from these patients is therefore more limited than for the later patients.

Initially, the plan was to acquire the data with the anterior surface of the gland facing the transducer. This resulted in shadowing that interfered with visualization of the posterior part of the gland where the peripheral zone is located. Since the peripheral zone is a critical area for the development of prostate cancer, we decided to change the orientation of the gland so that the posterior surface was closest to the transducer. In doing this, other problems surfaced. One serious problem was that the first 3-4 mm of distance from the transducer yields inferior data due to reverberation artifacts and due to the wider beamwidth at that location. An ultrasound standoff was needed, but the standoff would have to be stiff enough to allow compression of the prostate gland while still being similar in density to the adjacent prostate gland so that a reverberation artifact would not appear within the prostate gland data.

This was accomplished by producing a plastic casting containing a cavity for the standoff gel (Figure 1). The casting is attached to the transducer and a block of solid gel cut from a commercial disposable gel pad (Aquaflex, Parker Laboratories) is inserted into the cavity (held in by friction) and is coupled to the transducer with standard ultrasound gel. The solid gel forms a surface stiff enough to use as a compressor during elastography RF acquisition, but without reverberation artifacts. To further minimize the effects of acoustic shadowing in the prostate gland, a 5MHz transducer rather than a 7.5MHz transducer is used. The 5 MHz transducer gives a lower resolution ultrasound image, but high quality RF data for elastography and for RF analysis.

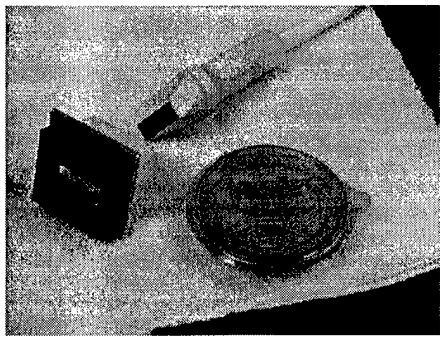


Figure 1: plastic standoff holder, transducer and gel pad

One possible serious issue was the lack of supporting tissue around the prostate gland during acquisition of the RF data for elastography. In all previous work on prostate, elastograms have been generated from data acquired from a prostate gland embedded in a gelatin block. The gelatin block provides support for the gland to prevent sideways movement, a flat surface against which to compress, and an automatic acoustic standoff.

It is impractical to embed a clinical prostate specimen in gel however since the pathologists must examine and ink the surface of the gland prior to preparing it for histologic sectioning. In addition, the gel would have to be completely removed for proper fixation of the prostate gland later in pathology. Also, the heat of the gel embedding process might alter the microscopic appearance of cells leading to errors in diagnosis. For these reasons, our project proposed scanning the glands in sterile saline without the normal supporting gel block but a big concern was whether a useful elastogram could be obtained at all by this method.

Figure 2 below shows that quality elastography IS possible using our technique. Some artifacts occur due to the contact of the flat compressor mainly with the center of the prostate gland but

we believe that this effect can be corrected for. Further software improvements will also better correct for lateral shift of the prostate leading to better stiffness data in the future.

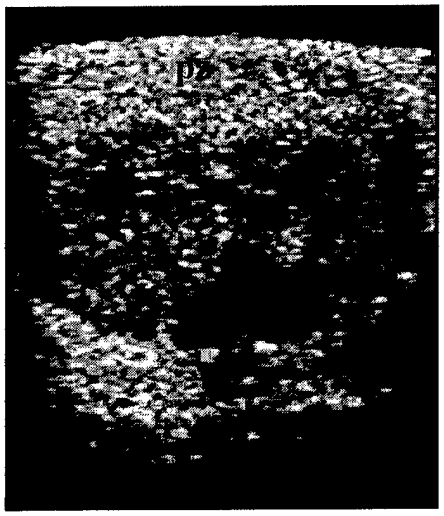


Figure 2a.

Figure 2b.

Figure 2: Large prostate gland with a prominent central zone on b-scan (a) and high-resolution elastography (b). Note that the central zone has a hardness similar to the peripheral zone (pz) and that the verumontanum/urethra (vu) appears as a bright focus on the elastogram. On the elastogram harder areas are dark and softer areas are bright.

Task 2 (months 1-6): Develop a methodology for registering optical pathology information with ultrasound data.

The process of taking pathology data and matching it to the corresponding ultrasound image and location involves several steps. The prostatectomy specimen is fixed in buffered formalin after the ultrasound scan is complete. This process stiffens the tissue so that less deformation occurs during sectioning. Then the surface of the gland is marked with inks of various colors. The gland is then sliced into multiple transverse sections with the plane of the sections being perpendicular to the posterior surface of the gland. This is simply achieved by placing the posterior surface down on the cutting table and cutting downward vertically. Every effort is made to slice the gland at 2mm intervals as are the ultrasound sections, but since the process is manual, the slices may be slightly thicker than 2mm. The slice thickness of the pathology specimens can be specified relative to the ultrasound sections by taking the ratio of the number of slices for each method, i.e. if 15 sections are made using ultrasound and 12 made at pathology, then the slice thickness of the pathology slices is 2mm x 15/12 = 2.5mm. Another key issue is how to determine which pathology slice corresponds to which ultrasound slice. This problem has been addressed by placing sutures on the surface of the gland at the plane of the first or second ultrasound slice. The ultrasound image in which the hyperechoic sutures appear is recorded on the ultrasound log sheet and the pathologist also records which slice contains the sutures during sectioning. This allows the two "stacks" of sections to be properly matched up against each other. Initially, four sutures delineating the plane of the scan were placed in the plane of the first

ultrasound section. Because of complaints that the sutures were hard too numerous and were causing damage to the microtome blades, the number has been reduced to two, both placed on the left side of the gland.

After the transverse sections are made in pathology, each section is further divided into quarters to that the tissue will fit on a standard microscope slide. This means that microscopic images from the quarter sections must be reassembled after staining. We have elected to handle this problem by taking digital photomicrographs of the section AFTER marking the locations of cancer cells with ink. A low power digital micrograph is then taken of appropriate slides of each section and the four images are reassembled digitally using commercial photo editing software. Because some distortion of the tissue occurs during processing, the sections may not fit perfectly together but the distortion is generally less then ± 2mm.

We plan to acquire some image warping software to allow us to correct for some of the distortions to enable us to fit the quarters together more precisely. We also plan to use this software to make the microscope images match even more closely to the ultrasound images. This will be done on the assembled histologic cross section by simply adjusting the shape of the histologic image of the gland to match the ultrasound image shape. No fiducial markers will be used since all of the candidates for marker materials would interfere with the sectioning of the gland or with microscope slide preparation.

Our plan for finding the ultrasound RF data to be classed as "cancer" is this:

1. After the histologic sections have been reassembled with ink marks on cancer areas, match each section to the corresponding "slice" of ultrasound data.
2. Superimpose the histologic image on the ultrasound image or elastogram to confirm that the images match with respect to shape, rotation and size. Mark out the same region on the ultrasound image that corresponds to the location of cancer on the histologic image and process only that RF data for texture features and RF features. We have software under development that can do this.
3. Evaluate the RF and texture features for features that seem to discriminate between cancer and normal tissue.
4. The same process will be carried out on the elastographic strain images to determine if strain values are useful for cancer detection.
5. Normal areas of the glands will be used to gather data about the RF, Texture, and strain values of normal prostatic tissue.

Although the basic methods for registering the ultrasound image and RF data with the pathology data have been developed as outlined above. We expect to have to make modifications as we examine more images and learn more about the appearances of tumors.

Task 3 (months 1-6): Use digital database of prostate cancer rate developed at Georgetown University and AFIP to establish a probability map of prostate cancer in a 3D domain.

To reveal the spatial pattern of localized prostate cancer distribution, a three-dimensional (3-D) statistical volumetric model, showing the probability map of prostate cancer distribution together with the anatomical structure of the prostate, has been developed from 70 digitally-imaged surgical specimens. Through an enhanced virtual environment with various visualization capabilities, this master model permits for the first time an accurate characterization and understanding of prostate cancer distribution patterns. The construction of the statistical volumetric model is characterized by mapping all of the individual models onto a generic prostate site model, in which a self-organizing scheme is used to decompose a group of contours representing multifold tumors into localized tumor elements. A crucial step in creating the master model is the development of an accurate multi-object and non-rigid registration/warping scheme incorporating various variations among these individual models in true 3-D. This is achieved with a multi-object based principle-axis alignment and an affine transform, and followed by a thin-plate spline interpolation driven by the surface based deformable warping dynamics. Based on the accurately mapped tumor distribution, a standard finite normal mixture is used to model the cancer volumetric distribution statistics. The process is graphically outlined in Figure 3 below:

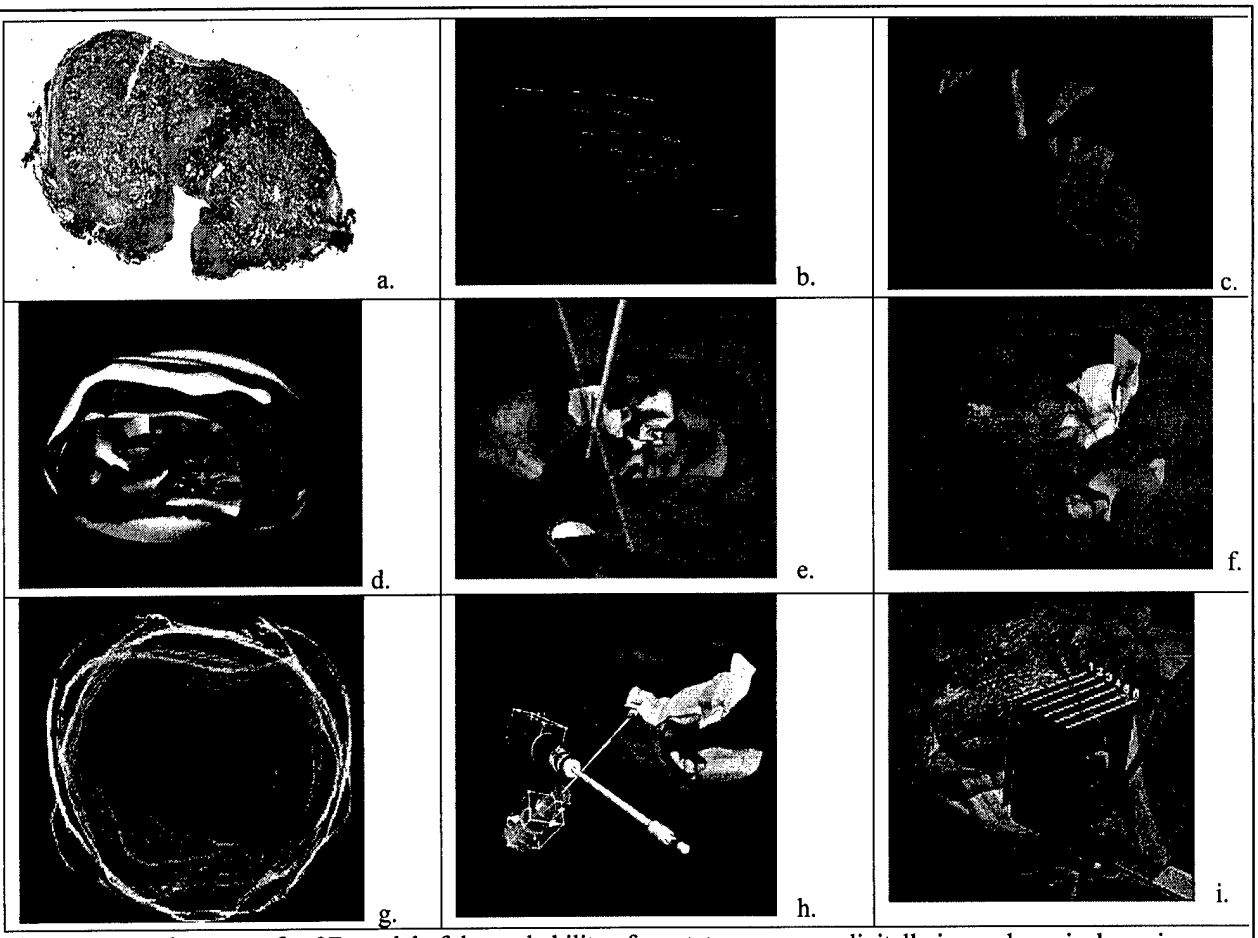


Figure 3. Development of a 3D model of the probability of prostate cancer. a. digitally imaged surgical specimens, b. decomposition of tumor contours, c. reconstruction of multifocal tumors, d. prostate site model in 3D computer graphics, e. TRUS based biopsy simulation virtual environment, f. display of multifocal tumor distribution, g. 3D statistical volumetric model of tumor spatial distribution -- data from this model will be used to calculate prior probabilities for the current study, h. biopsy planning, i. Model guided biopsy-- in our proposal actual ultrasound data with the added model data will be used.

Task 4 (months 1-9): Software development.

This task was largely to be the job of the postdoctoral fellow guided by Drs Wagner and Weir at the FDA and by Dr. Ophir for the elastography portion. Obviously, in view of Dr. Mia's departure from the project, progress will be limited in this area until he is replaced early next year. Still, some progress has been made. Software to read the Diasonics scanner RF data for calculation of RF features has been completed by Dr. Weir of the FDA. This software can calculate RF features for a subregion of the prostate that is selected by the user from an ultrasound image (Figure 3j). This is the software that will be used to gather regions of interest that match the areas marked as cancer on the histologic sections. Also, Dr. Ophir and his colleagues have completed more advanced software for elastogram calculation than was available at the time we made our initial proposal. An example of the difference in image quality is shown below in Figure 4.

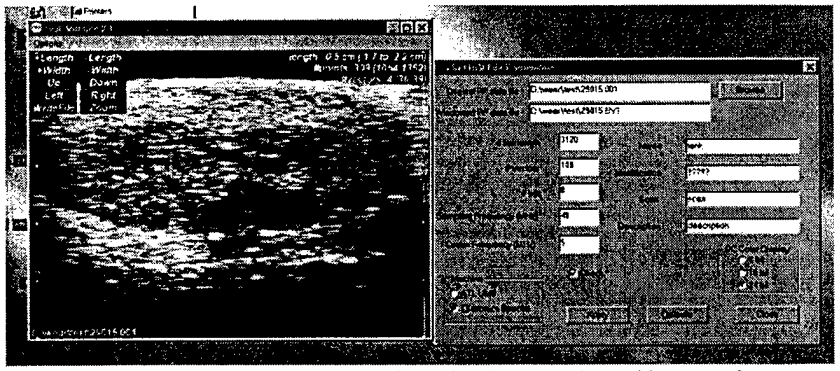
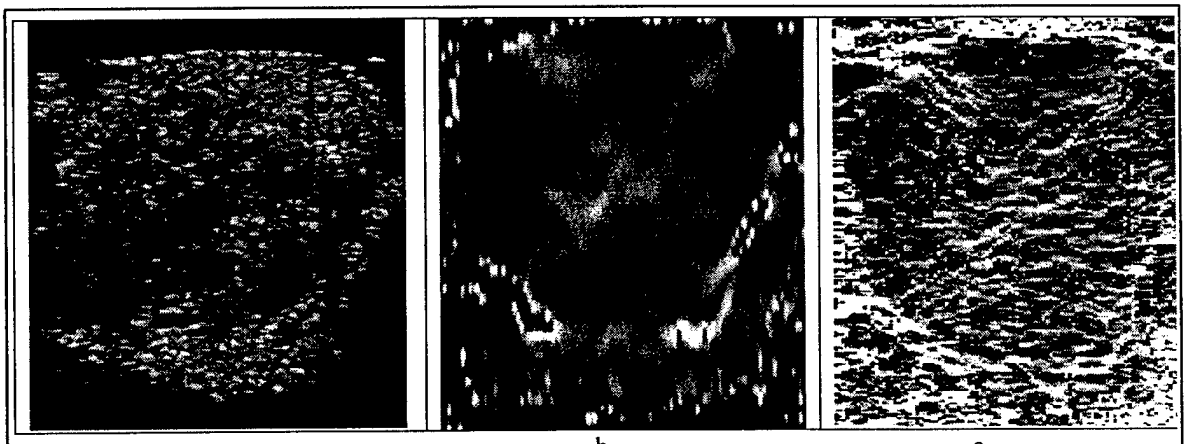


Figure 3j: Screen capture of software for selecting a region of interest for RF feature calculation. The yellow box represents the selected region of interest.



a. b. c.

Figure 4. Sonogram (a), elastogram (b) and high resolution elastogram (c) showing a hard area on the left hand side of the gland suspicious for cancer. The broad bright areas in the central gland in (b) are an artifact of the processing scheme used. The peripheral zone of the gland is at top.

Our tentative plan is to develop the "front end" software tying all three types of processing (image creation/texture analysis, RF feature generation, elastogram generation) together using the graphical user interface development environment of MATLAB. A sonogram representation of

the RF data will be displayed and the user may choose to process and obtain results from only a subregion, or the entire image may be processed with features calculated for all of the 2-4mm subregions in the image. For processing entire images, a batch mode will also be available. Later, after a subset of features have been selected for their ability to discriminate cancer from benign tissue, a batch mode will be added in which entire images are processed and subregions color "stained" according to the probability of cancer in each subregion. This work falls under Task 5.

This work is behind schedule but we are hopeful that it will proceed quickly once Dr. Mia's replacement is on board. Many of the software components have been constructed. It only remains to tie them together.

Task 5 (months 12-18): Data Fusion

Work on this task has not yet begun but will begin after the arrival of the postdoctoral fellow replacement in January.

Task 6 (months 7-18): More prostate data collection.

This segment of data collection has just begun. A few minor modifications to the acquisition protocol will be made in this phase. One prostate gland will be used to try larger compressions since little difference in the elastograms was noted at compressions from .3% to 2%, partly because of much of the compression stress being taken up by the gel pad. Compressions in the 2 – 4% range will be tried on the next prostate in addition to the normal acquisition.

Task 7 (months 11-22): Compute RF and texture features for all stage 1 acquisitions.

This phase has not yet begun because of the delay in completing the texture analysis software. The other components of this task involve development of neural network and Bayesian classifiers and this work will be delayed until the texture analysis software is available.

Task 8 and Task 9 (months 13-26 and 24-30): Acquire RF with a curved array transducer.

This is delayed until our results for the linear array are more complete. A new scanner with higher quality imaging may be used for this phase. That scanner (ATL 1000) will arrive in January.

KEY RESEARCH ACCOMPLISHMENTS

- Validated the method of obtaining RF data from excised prostate glands immersed in saline. The RF data is of sufficient quality to allow generation of high-resolution elastograms.
- Refined software for elastogram generation to increase spatial resolution and to correct for lateral decorrelation.
- Developed a method of registering ultrasound RF prostate cross-sections with cross-sectional images obtained in pathology. This system will allow correlation of ultrasound RF data with corresponding pathology with a spatial error of 2mm or less.

REPORTABLE OUTCOMES

None yet

CONCLUSIONS

Considering the late start of this project and the lack of key personnel in the early stages of the project, considerable progress has been made in acquiring and analyzing prostate radio frequency ultrasound data. We are still somewhat behind the targets set in the statement of work, but the rate of acquisition of prostate glands is increasing making it possible for us to "catch up" in the next nine months.

In particular, we have produced high quality elastograms from larger numbers of human prostates than has ever been achieved before. We also have software that can analyze the prostate data from selected subregions for RF features. We are in the process of identifying subregions containing cancer based on the correlated pathology sections so that we can build a database of feature values for benign and cancerous prostate tissue.

Having found a suitable replacement for Rashidus Mia, we ought to be able to quickly develop the software needed to complete the analysis of the RF data which will allow us to proceed to the key tasks of determination of the most discriminating feature combinations and development of Bayesian and neural network classifiers.