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TITLE: Non-uniformly Sampled MR Correlated Spectroscopic Imaging in Breast Cancer And Non-linear Reconstruction

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14. ABSTRACT: Magnetic Resonance Imaging (MRI) is an excellent anatomical tool to image tissue non-invasively. Dynamic contrast enhanced MRI (DCE-MRI) has excellent sensitivity but with varying specificity. MR Spectroscopy (MRS) enables biochemical characterization non-invasively of metabolites. Three major hypotheses are: (1) Accelerated 5-dimensional (5D) echo-planar imaging based correlated spectroscopic imaging (EP-COSI) acquisition produces multi-slice based multi-voxel two-dimensional (2D) MRS in a clinically feasible time. (2) Incorporating non-uniform under sampling (NUS) for spectral/spatial sampling into the 5D EP-COSI data acquisition and the group sparsity (GS)-based reconstruction will reduce the total acquisition time by at least a factor of 12. (3) ADC values derived from the multi-slice DWI data will correlate negatively with choline groups and positively with lipids quantified by the EP-COSI technique. Three goals are proposed: i) NUS schemes will be combined with 5D EP-COSI sequence. ii) GS- based CS reconstruction schemes will be developed for accelerated acquisition and optimized to reconstruct the NUS EP-COSI data with better reliability . iii) Alterations in metabolite and lipid levels will be correlated with ADC changes in breast cancer patients compared to healthy women which will improve the diagnostic accuracy. The study patient cohort will include 50 patients with malignant breast carcinoma, 20 patients with benign breast tumor and 20 healthy women.					
15. SUBJECT TERMS Dynamic contrast enhanced (DCE) MRI, MR Spectroscopy (MRS), echo-planar imaging based correlated spectroscopic imaging (EP-COSI), five-dimensional (5D), two-dimensional (2D), apparent diffusion coefficient (ADC)					
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1. Introduction: Breast cancer death rates are higher than those for any other cancer, besides lung cancer in US. More than 232,670 new cases are diagnosed annually (1). Diagnostic accuracy and effective therapeutic management of the breast tumor remain significant medical challenges, hence early detection, diagnosis, and timely treatments are essential to successful health care (2-6). Currently, histological classification from biopsy specimens is generally used as the gold standard to determine malignancy. Hence, optimal imaging methods will enable predicting whether a tumor is going to behave in a benign or aggressive fashion. The proposed Breakthrough Step I grant application will focus on three specific goals: 1) To implement and optimize the NUS based 5D EP-COSI sequence on a 3T Prisma MRI scanner to accelerate the acquisition by an order of magnitude. 2) To develop GS- and total variation (TV)- based CS reconstruction schemes for accelerated acquisition and optimized to reconstruct the NUS EP-COSI data with better fidelity. 3) To record changes in metabolite and lipid levels will be correlated with ADC changes in breast cancer patients compared to healthy women to improve the diagnostic accuracy. Next to lung cancer, breast cancer is the leading cause of death in women in the US. Improving the specificity of malignant and benign tumors using accelerated MRI techniques will be a major outcome. Compressed sensing (CS)-based multi-dimensional magnetic resonance spectroscopic imaging (MRSI) will significantly increase the speed of data acquisition with minimal discomfort for breast cancer patients leading to improved diagnostic accuracy and early detection. In this proposal, we will develop a novel technique for identifying breast cancers more robustly and with greater accuracy than methods currently available.

2. Keywords: Dynamic contrast enhanced (DCE) MRI, MR Spectroscopy (MRS), echo-planar imaging based correlated spectroscopic imaging (EP-COSI), five-dimensional (5D), two-dimensional (2D), apparent diffusion coefficient (ADC). Group sparsity (GS), compressed sensing (CS), total variation (TV)

3. Accomplishments:

Three major goals are the following: 1) To further optimize a novel five-dimensional (5D) technology called accelerated echo-planar based correlated spectroscopic imaging (EP-COSI) on a 3T Prisma MRI/MRS scanner (using the Siemens IDEA compiler running on the latest VD13D platform). 2) To implement and optimize non-linear reconstruction methods such as group sparsity and total variation. 3) To record i) the 5D NUS EP-COSI data, and ii) DWI and to evaluate ADC maps in the malignant and benign breasts, and healthy women and to correlate the MRSI findings with that of DWI in differentiating benign from malignant breast cancers, and to calculate specificity, sensitivity and accuracy of multi-voxel based 2D MRS and DWI data to differentiate benign from malignant tumors.

What was accomplished Under these goals:

To accomplish the above mentioned goals, we proposed the following ten tasks:

Task 1: To implement and evaluate a novel five-dimensional (5D) technology called accelerated echo-planar based correlated spectroscopic imaging (EP-COSI) on a 3T Prisma MRI/MRS scanner (using the latest Siemens IDEA compiler running on the latest VE11 platform). (**Months 1-6**).

The 5D EP-COSI sequence as shown in Fig.1 was implemented using three different platforms (VE11A, VE11B and VE11C): top row: the analog-to-digital converter (ADC); 2nd row: the radio-frequency (RF) wave forms used to the slice localization along 3 spatial dimensions; 3rd through 5th rows represent X, Y and Z gradient wave forms.

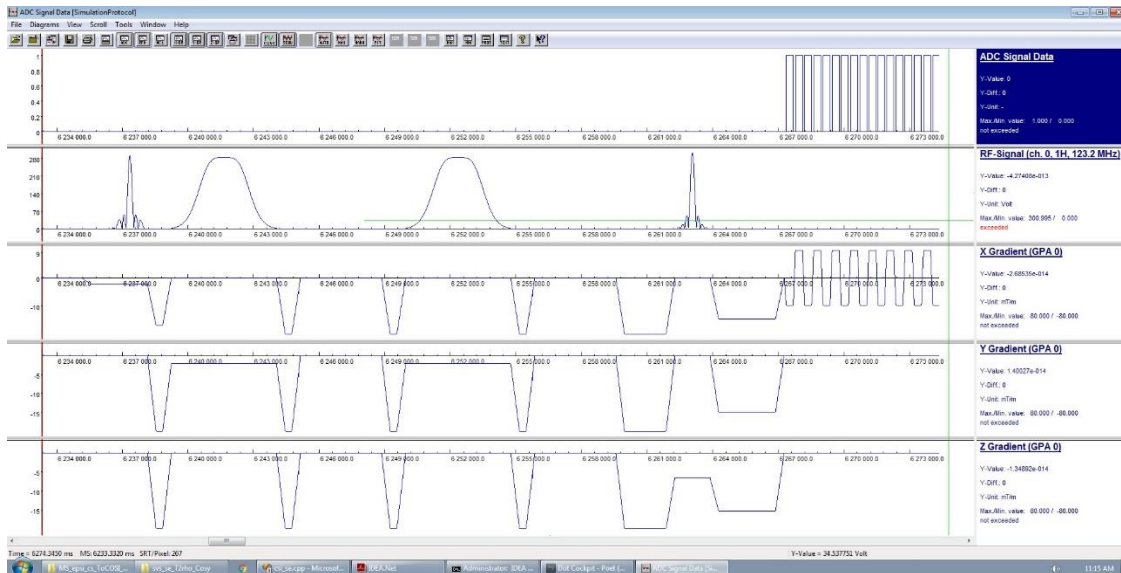


Fig.1. The 5D EP-COSI sequence showing the ADC, RF and gradient waveforms.

Task 2: To evaluate the accelerated 5D EP-COSI data using a breast phantom containing two concentric spheres, the inner one containing several metabolites (choline and ethanolamine groups, creatine, lactate and more amino acids) which have been reported in breast tissues surrounded by the outer phantom containing corn oil to mimic fatty tissues known to be in breast tissues, and to optimize the echo speed-factor and other acquisition parameters using the phantom (**Months 1-6**).

As shown in Fig.2, we prepared a corn oil phantom (left) containing saturated and unsaturated lipids to mimic infiltrating fat in the breast tissue and a quad phantom (right) containing N-acetylaspartate, lactate, creatine and choline. Eight slices from the oil phantom localized by the 5D EP-COSI sequence is shown on the left and similarly, 8 slices from the quad phantom on the right side. Extracted 2D COSY spectra from the corn oil and lactate are also shown.

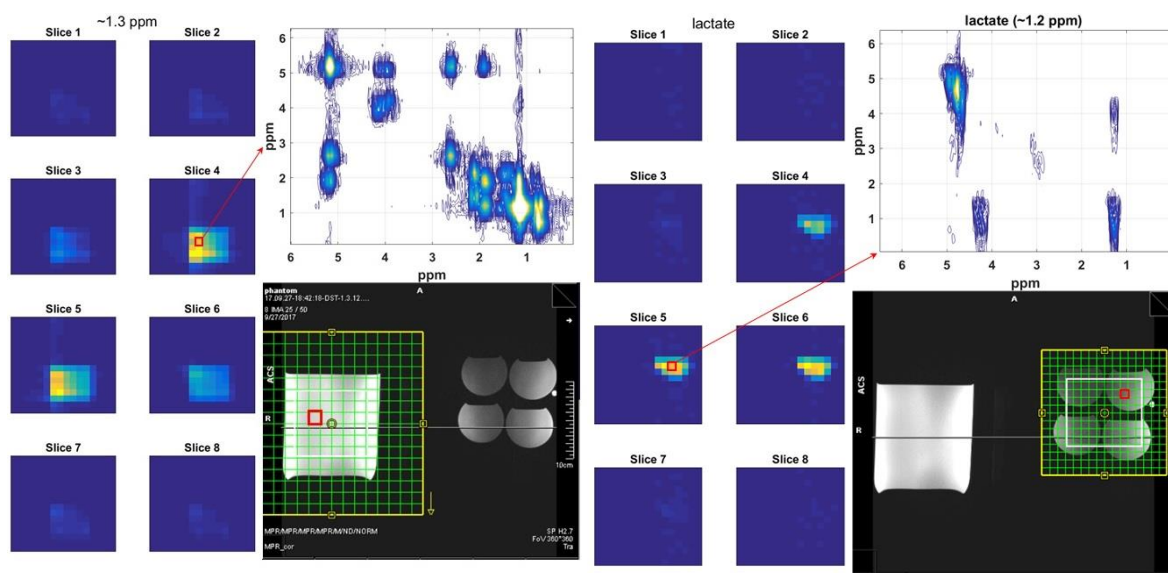


Fig.2. A corn oil and a quad phantom containing metabolites are shown.

Task 3: To implement and optimize non-linear reconstruction methods (group sparsity and total variation). (Months 3-9).

Using the above corn oil and the metabolite (quad) phantoms, the undersampled data at 8X and 12X were reconstructed using two different non-linear reconstruction methods: 1) total variation and 2) group sparsity (GS). The GS method was able to retain the fidelity even at higher acceleration schemes (12X and 16X).

Task 4: To continue to evaluate/optimize the accelerated 5D EP-COSI data using the breast phantom containing two concentric spheres, to optimize the echo speed-factor and other acquisition parameters using the phantom (Months 7-18).

We have purchased a spherical flask containing two layers in which the corn oil will be inside one layer and breast metabolites (choline, phosphoryl and glycerylphosphoryl choline, uridine phosphate) from Sigma-Alrich. We plan to acquire the 5D EP-COSI data to investigate the contamination of lipids (corn oil)..

Task 5: To record the 5D EP-COSI spectra in the fatty, glandular and ductal areas of healthy breasts. Twenty healthy female volunteers (25-70 years old) with no previous history of breast cancer will be investigated. (Months 9-36).

As shown in Fig.3, the accelerated (8X) 5D EP-COSI data was acquired in a healthy subject and the reconstructed data using TV and GS are shown. The chemical shift multi-slice images were of good quality using both reconstruction methods.

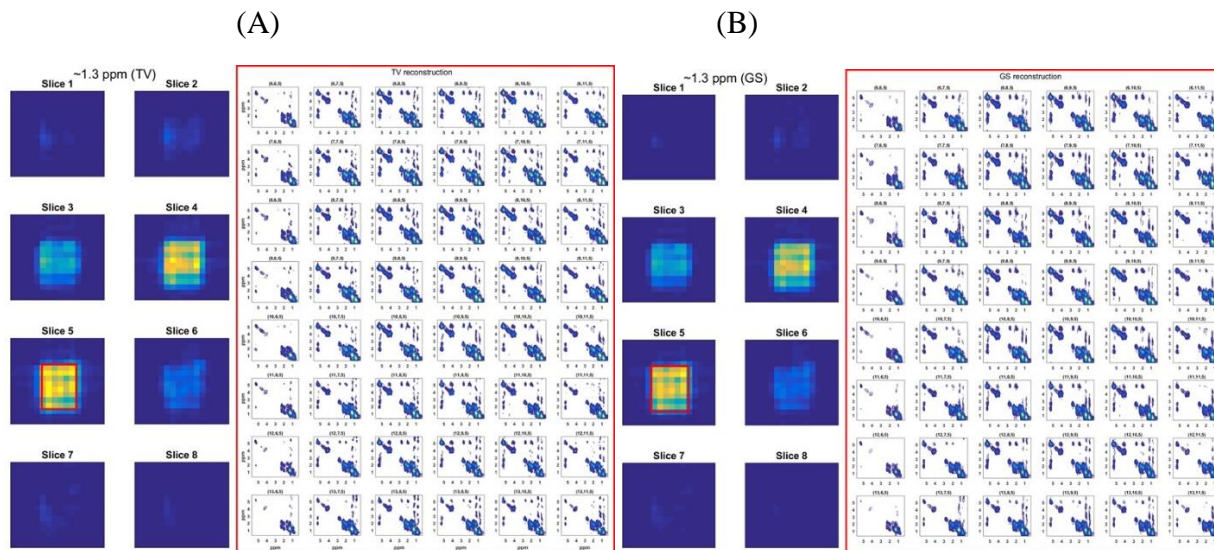


Fig.3. Accelerated 5D EP-COSI data acquired in a healthy volunteer and reconstructed using TV (A) and GS (B)

Eighteen healthy women (age range of 26-64 years) have been screened for the MRI scans. One subject declined to continue with the scan due to claustrophobia. Hence, the 5D EP-COSI data have been successfully scanned in 17 healthy using the Siemens 3T Skyra MRI scanner currently running on the VE11C platform.

Task 6: To record multi-slice DWI in twenty healthy breasts, and to calculate the ADC maps. (Months 9-36).

Diffusion weighted MRI data have been successfully recorded in 17 healthy subjects using the Siemens 3T Skyra MRI scanner currently running on the VE11C platform.

Task 7: To record the 5D EP-COSI spectra in twenty patients with benign breast tumor (fibroadenoma, proliferative fibrocystic change and papillomas) (Months 9-36).

The 5D EP-COSI and diffusion weighted MRI data have been successfully scanned in 15 benign breast cancer subjects using the Siemens 3T Skyra MRI scanner currently running on the VE11C platform. Shown in Fig.4 are results from a benign breast cancer subject.

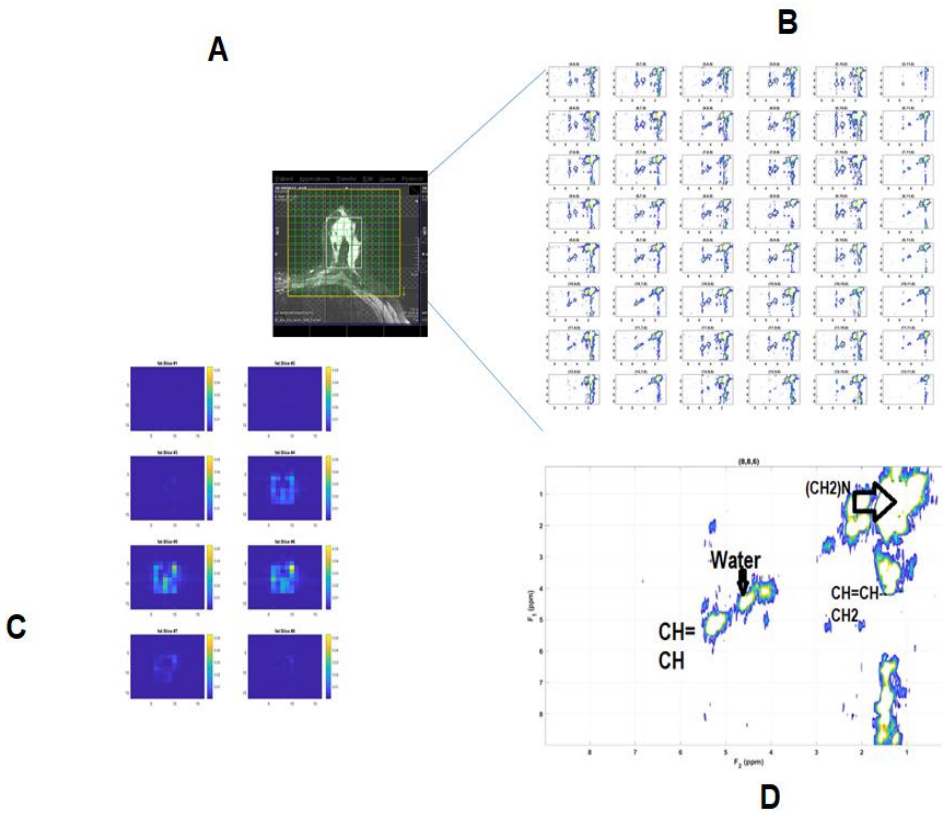


Fig.4. Accelerated (8X faster) 5D EP-COSI data acquired in a 32 yo benign (fibroadenoma) breast cancer subject and reconstructed using GS: A) Axial MRI showing the FOV covered by 5D EP-COSI. B) Multi-voxel COSY spectra over the volume localized by the 5D EP-COSI sequence. C) 8 Slice-chemical shift Images of the polymethylene (CH₂)_N resonance at 1.4ppm. D) 2D COSY spectrum extracted from the location (8,8) of the 6th slice .

Task 8: To record the 5D EP-COSI spectra in fifty patients with biopsy-proven breast cancer (ductal carcinoma and invasive lobular cancer) (Months 9-36).

Twenty six malignant breast cancer patients have been investigated so far. The 5D EP-COSI acquisition was terminated in two malignant breast cancer patients either due to multiple clips from biopsy or subject's refusal to continue with the scan.

Results from a 41 y.o. malignant breast cancer patient is shown in Fig.5.

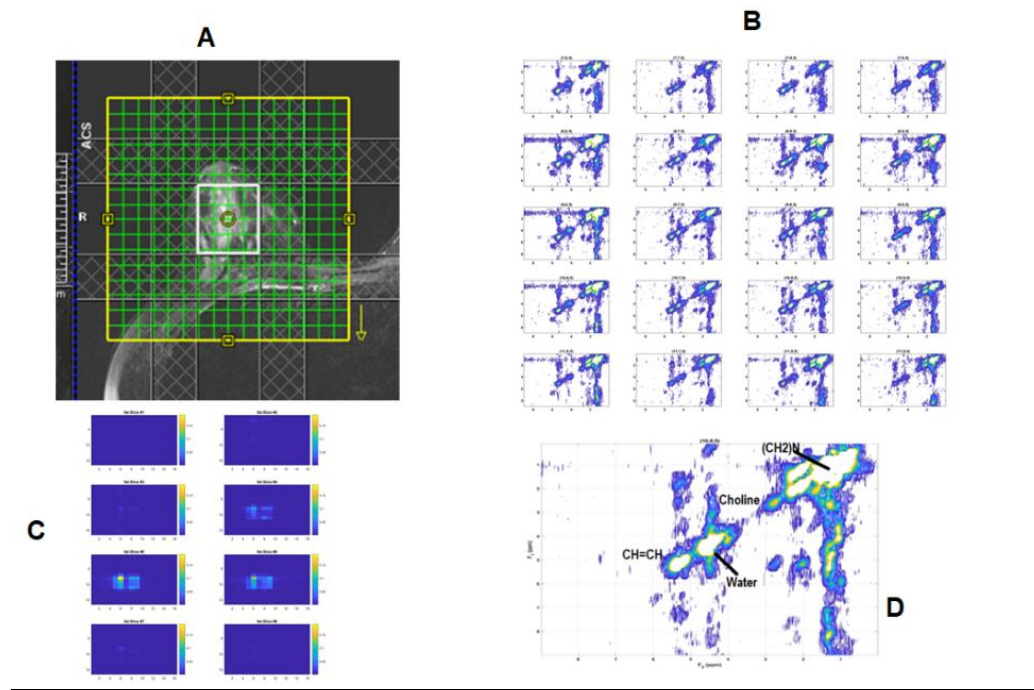
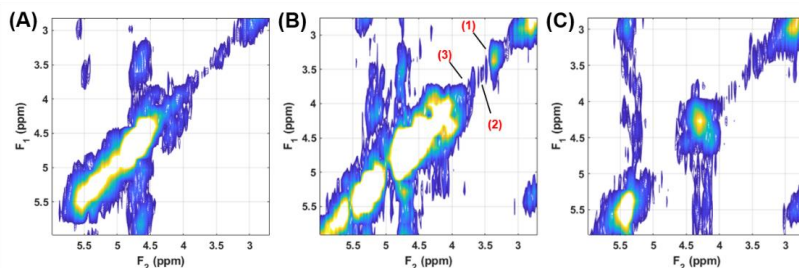


Fig.5. Accelerated 5D EP-COSI data (8X faster) acquired in a 41 yo malignant breast cancer patient (grade 3, invasive ductal carcinoma and ductal carcinoma in situ) and reconstructed using GS: A) Axial MRI showing the field of view (FOV) covered (yellow boundary) and the 3 spatial dimensions localized by the white box. B) Multi-voxel COSY spectra (1cm x1cm x1.5cm) over the volume localized by the 5D EP-COSI sequence. C) 8 Slice-chemical shift Images of the polymethylene (CH₂)_N resonance at 1.4ppm . D) 2D COSY spectrum extracted from the location (10,8) of the 5th slice .

Shown in Fig.6 through Fig.7 are new preliminary results acquired in malignant and benign breast cancer patients using 5D EP-COSI.

Figure 6: Extracted COSY spectra from voxels within the tumor regions of 3 malignant patients (A) – (C). The F₁-F₂ ppm range is expanded to within 2.7 – 6 ppm. The peak regions labeled (1), (2), and (3) are those corresponding to metabolites such as choline, taurine and myo-inositol/glycine.



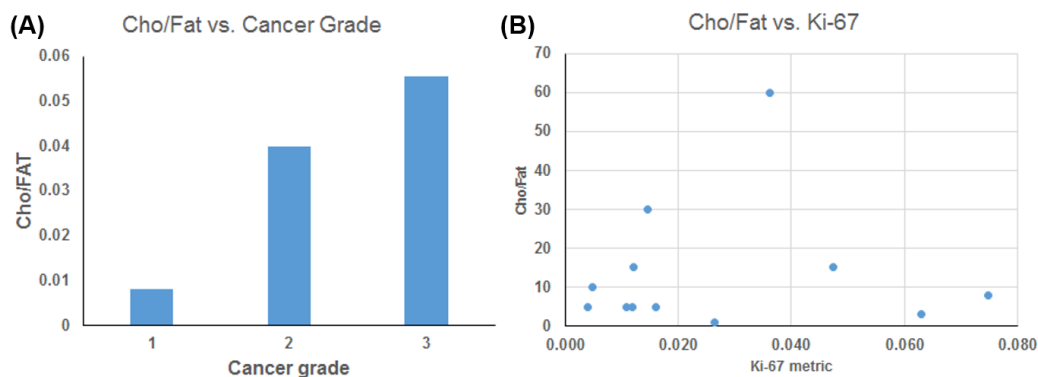
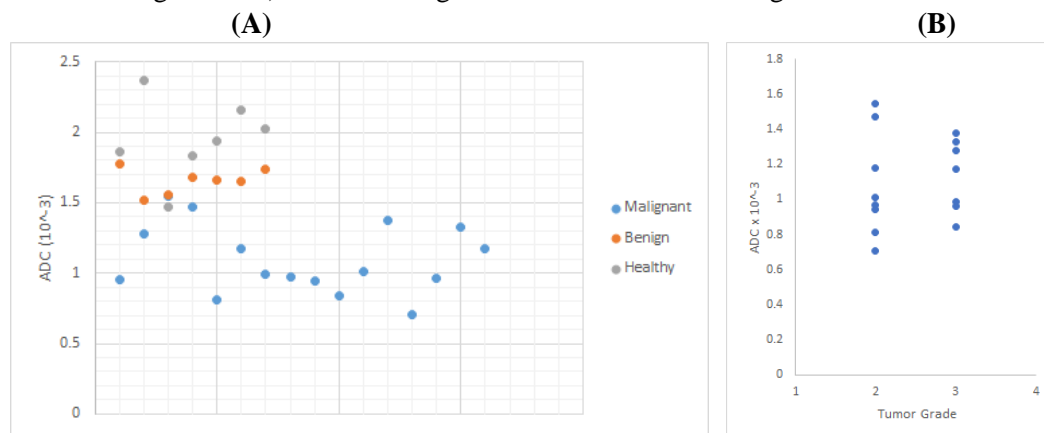


Figure 7. (A) Mean choline-to-fat ratio (Cho/Fat) as a function of cancer grade (B) Cho/Fat and the relationship to the Ki-67 metric, which indicates the degree of severity of the malignant cancer, with 1 being the most severe.

Task 9: To record multi-slice DWI in fifty malignant patients with biopsy-proven breast cancer and twenty benign breast cancer, and to calculate the ADC maps. (Months 9-36).

DWI was also recorded in twenty six malignant breast cancer patients and we have been quantifying the apparent diffusion coefficient (ADC) using the DWI data. Shown in Fig.8 are ADC values in 3 subject groups (A) and ADC values with respect to tumor grades (B) in malignant patients.

Figure.8: A) ADC (10^{-3} mm²/sec) values quantified in malignant and breast cancer patients, and healthy women using DWI. B) Plots showing ADC values versus tumor grades.



Task 10: To correlate the accelerated 5D EP-COSI findings with that of DWI in differentiating benign from malignant breast cancers, and to calculate specificity, sensitivity and accuracy of the MRSI and DWI data in differentiating benign from malignant tumors. (Months 12-36).

We have studied a total of 26 malignant and 15 benign breast cancer patients and seventeen healthy women successfully. Both 5D EP-COSI and DWI data have been recorded, and post-processing of the entire data is being analyzed now.

Major Activities: 1) Our continuation renewal application was submitted to the UCLA IRB office in May 2019 and the renewal application was approved by the UCLA IRB in the early May/June; a copy of the continuation approval was submitted to HRPO in August. 2) The 5D EP-COSI and DWI data were recorded in 9 malignant and 10 benign breast cancer patients and ten healthy subjects during the 3rd year.

Significant Results/Key Outcomes: After testing the 5D EP-COSI sequence in 17 healthy women, we have scanned a total of 26 malignant and 15 benign breast cancer patients so far. One subject declined to continue with the scan due to claustrophobia. The 5D EP-COSI and diffusion weighted MRI were scanned using the Siemens 3T Skyra MRI scanner currently running on the VE11C platform.

What Opportunities for training and professional development has the project provided?: Mr. Andres Saucedo, a Ph.D. student working in the group of Dr. Thomas, has received the required safety training to run the MRI and MR spectroscopy protocol. He has recorded MRI, DWI and 5D EP-COSI in 26 malignant and 15 benign breast cancer patients, and 17 healthy women using the 3T MRI scanner (Siemens Skyra).

How were the results disseminated to communities of interest: Nothing to Report

What do you plan to do during the next reporting period to accomplish the goals?: We will continue to screen more malignant and benign breast cancer patients. After screening the subjects for MRI safety and other related issues, they will be scanned using the 3T Skyra MRI scanner equipped with a dedicated breast coil. A manuscript including the 5D EP-COSI data will be prepared in 2020.

4. Impact:

What was the impact on the development of the principal disciplines of the project?: Nothing to Report

What was the impact on other disciplines? Nothing to Report

What was the impact on technology transfer? Nothing to Report

What was the impact on society beyond science and technology? Nothing to Report

5. Changes/Problems: Nothing to Report

6. Products:

Publications, Conference papers and Presentations: Two abstracts were presented as ePoster presentations at the 2019 International Society of Magnetic Resonance in Medicine, May 11-26, Montreal, Canada:

- 1) Saucedo A, et al. "Detection of Choline, Glycine and Myo-inositol in Malignant Breast Cancer *In-vivo* Using Multi-dimensional Spectroscopic Imaging"

2) Saucedo et al. “Apparent Diffusion Coefficient Using Diffusion Weighted MRI and Biochemical Correlates in Human Breast Cancer”

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name	M. Albert Thomas Ph.D.
<u>Project Role</u>	<u>P.I.</u>
<u>Researcher Identifier</u>	0000-0001-9037-2585
<u>Nearest person month worked</u>	<u>12 months</u>
<u>Contribution to Project</u>	<u>Design of the project and supervision of the MRI data acquisition and pos-processing</u>
<u>Funding Support</u>	<u>Dr. Thomas is currently funded by NIH and VA Merit grant also</u>
Name	Melissa Joines M.D.
<u>Project Role</u>	<u>Co.I.</u>
<u>Researcher Identifier</u>	None
<u>Nearest person month worked</u>	<u>12 months</u>
<u>Contribution to Project</u>	<u>Study Subject Recruitment and review of MRI</u>
<u>Funding Support</u>	<u>None</u>
Name	Stephanie Lee-Felker M.D.
<u>Project Role</u>	<u>Co.I.</u>
<u>Researcher Identifier</u>	None
<u>Nearest person month worked</u>	<u>12 months</u>
<u>Contribution to Project</u>	<u>Study Subject Recruitment and review of MRI</u>
<u>Funding Support</u>	<u>None</u>
Name	Manoj Sarma
<u>Project Role</u>	<u>Co-I</u>
<u>Nearest person month worked</u>	<u>4 months</u>
<u>Contribution to Project</u>	<u>Sequence Development and Data Processing</u>
<u>Funding Support</u>	<u>Partly funded by NIH grants also</u>
Name	Andres Saucedo M.S.
<u>Project Role</u>	<u>Graduate Student Researcher</u>
<u>Research Identifier</u>	None
<u>Contribution to Project</u>	<u>Data Acquisition and Post-processing</u>
<u>Funding support</u>	<u>funded by the current DOD grant</u>
Name	Stephanie Gilbert B.S.
<u>Project Role</u>	<u>Study Coordinator</u>
<u>Nearest person month worked</u>	<u>3 months</u>
<u>Contribution to Project</u>	<u>IRB protocol renewal/amendment, recruitment</u>
<u>Funding Support</u>	<u>Radiology Departmental funds</u>

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

What other organizations were involved as partners? Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS: Nothing to Report

9. Appendices: Nothing to Report.